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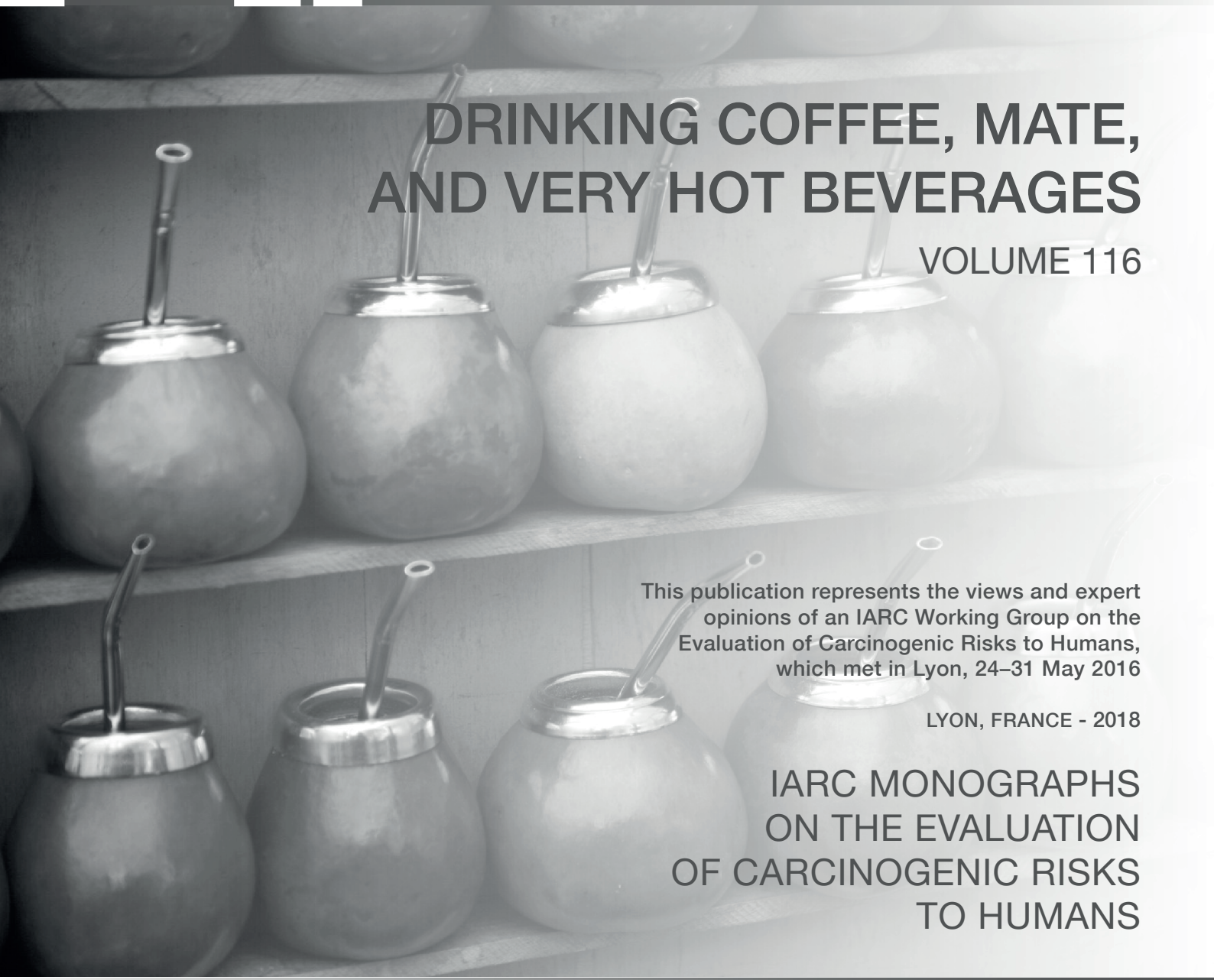

DRINKING COFFEE, MATE, AND VERY HOT BEVERAGES

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

2. CANCER IN HUMANS

2.1 Cancer of the bladder

2.1.1 Cohort studies

See Table 2.1, Fig 2.1, Fig. 2.2, and Fig. 2.3.

This section summarizes the results of the Working Group's review of prospective cohort studies that reported on the association between drinking coffee and the risk of cancer of the bladder. One study that reported on bladder cancer mortality as an end-point (Snowdon & Phillips, 1984) was excluded, as the role of coffee in cancer etiology cannot be distinguished from its role in cancer progression or response to treatment. Also excluded are three studies, two of the same cohort, that did not report estimates of association (Schulte et al., 1985, 1986; Whittemore et al., 1985).

When reviewing the available studies, the Working Group considered two important criteria in evaluating how informative each was. One was appropriate adjustment for tobacco smoking, given that this is an important bladder cancer risk factor and is often reported to be correlated with coffee drinking. The other was consideration of sensitivity analyses excluding patients diagnosed too close to the start of the cohort; patients with bladder cancer might be likely to change their coffee drinking habits, which might lead to bias in the analyses. Studies that conducted such sensitivity analyses and adjusted for tobacco smoking were therefore considered to be the most informative, and are discussed first. Studies that adjusted for smoking but did not conduct sensitivity analyses, as well as one study that did neither, are then discussed. Overall, studies with a large sample size are considered more informative as measures of association will tend to be more precise; we therefore discuss larger studies first, followed by smaller studies.

In the following paragraphs the cohort studies that were considered the most informative by the Working Group are described. These studies were given more weight in the evaluation.

In the Netherlands Cohort Study (Zeegers et al., 2001), 569 incident cases of cancer of the urinary bladder were identified. Among men, the relative risk for the highest level of intake (≥ 7 cups/day) compared with the lowest (0 to < 2 cups/day) was 1.33 (95% CI, 0.94–1.90), with an estimate per 1 cup/day of coffee of 1.04 (95% CI, 1.00–1.09). The test for trend was not statistically significant (*P* for trend, 0.06). Among women, the relative risk for the highest level (≥ 5 cups/day) was 0.36 (95% CI, 0.18–0.72), with an estimate per 1 cup/day of 0.83 (95% CI, 0.72–0.96). A statistically significant test for trend (*P* for trend, < 0.01) was reported. Sensitivity analyses excluding cases diagnosed in the first 1–2 years of follow-up did not change results. [The limitations of this study were the lack of consideration of coffee drinking history and lack of stratification by smoking status.]

Table 2.1 Cohort studies on cancer of the bladder and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeegers et al. (2001) Netherlands, 1986 (enrolment), 1992 (follow-up)	3500, Netherlands Cohort Study, men and women (aged 55–69 yr), case–cohort approach Exposure assessment method: FFQ (non-validated coffee questions, self-administered, frequency and amount), caffeinated coffee only (low consumption of decaffeinated)	Urinary bladder: ~96% TCC	*Coffee consumption among men (cups/day)*			Age, numbers of cigarettes/day, years of cigarette smoking	Strengths: prospective, large number of cases, detailed questionnaire including 19 beverages, both men and women included, complete follow-up data Limitations: no drinking history; no follow-up information
			0 to < 2	23	0.89 (0.51–1.54)		
			2 to < 3	32	0.72 (0.45–1.13)		
			3 to < 4	61	1.27 (0.87–1.87)		
			4 to < 5	119	1.00		
			5 to < 6	72	0.98 (0.68–1.4)		
			6 to < 7	91	1.25 (0.89–1.76)		
			≥ 7	93	1.33 (0.94–1.90)		
			Per 1 cup/day	NR	1.04 (1.00–1.09)		
			Coffee consumption among women (cups/day)				
			0 to < 2	11	1.23 (0.56–2.73)		
			2 to < 3	13	0.84 (0.4–1.76)		
			3 to < 4	20	1.00		
			4 to < 5	17	0.44 (0.22–0.86)		
			≥ 5	17	0.36 (0.18–0.72)		
			Per 1 cup/day	NR	0.83 (0.72–0.96)		
Ros et al. (2011) 10 European countries, 1992–2000 (enrolment), follow-up varied by country	233 236 (67 914 men and 165 322 women), EPIC, subjects aged 25–70 yr Exposure assessment method: validated FFQ, frequency and amount considered	Urinary bladder: UCC	*Coffee consumption (mL/day)*			Age, sex, centre, smoking status, duration of smoking, lifetime intensity of smoking, energy intake from fat and non-fat sources	Strengths: prospective large cohort, extensive set of potential confounders, possible to distinguish between low- and high-risk urothelial bladder cancers Limitations: no history of coffee drinking, no information about type of coffee studied, results not stratified by sex or smoking, no follow-up information on exposure
			T1: < 429 (men), 250 (women)	133	1.00		
			T2: 429–874 (men), 250–469 (women)	179	1.11 (0.88–1.41)		
			T3: ≥ 875 (men), ≥ 500 (women)	201	1.11 (0.85–1.43)		
			Continuous for every 100 mL increase (observed)	380	1.00 (0.98–1.03)		
			Trend test *P* value, 0.5				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Michaud et al. (1999) USA, 1986 (enrolment), 1996 (last follow-up)	47 909; HPFS, male health professionals aged 40–75 yr in all 50 states, predominantly white Exposure assessment method: validated FFQ by mail, regular and decaffeinated coffee, frequency/serving size assessed	Urinary bladder: 90% TCC	*Decaffeinated coffee consumption*			Geographic region, age, pack-years of smoking, current smoking status, energy intake, intake of fruits and vegetables, intake of all other beverages (water, milk, juice, soda, lemonade, tea, alcohol)	Strengths: prospective, follow-up information every 2 yr Limitations: restricted to mostly white professional men in USA (no women included), no history of intake
			< 1 cup/mo	106	1.00		
			1 cup/mo–6 cups/wk	65	0.94 (0.69–1.29)		
			1–3 cups/day	72	1.20 (0.87–1.65)		
			≥ 4 cups/day	9	0.83 (0.41–1.66)		
			Trend test *P* value, 0.47				
			Coffee consumption				
			Per 240 mL of daily intake	252	0.93 (0.85–1.02)		
			< 1 cup/mo	75	1.00		
			1 cup/mo–6 cups/wk	56	0.97 (0.68–1.37)		
			1–3 cups/day	98	1.00 (0.73–1.37)		
			≥ 4 cups/day	23	0.79 (0.48–1.30)		
			Trend test *P* value, 0.56				
Nagano et al. (2000) Japan, 1979–1981 (enrolment), 1980–1993 (follow-up)	38 540 atomic bomb survivors, Life Span Study (men and women) Exposure assessment method: frequency only by self-administered questionnaire	Urinary bladder	*Coffee consumption frequency (times/wk)*			Age, sex, radiation dose, smoking status and cigarettes/day, education level, BMI, calendar time	Strengths: prospective Limitations: modest numbers, not representative of all Japanese population, no information on serving sizes, consumption history, or types of coffee
			0	25	1.00		
			1–4	32	0.73 (0.43–1.25)		
			≥ 5	32	0.90 (0.52–1.56)		
			Trend test *P* value, 0.78				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jacobsen et al. (1986) Norway, 1964 (enrolment), 1967 (questionnaire), follow-up until 1978	16 555; two cohorts of Norwegian men (population sample and brothers of migrants to the USA); spouses and siblings of individuals enrolled in a case–control study of gastrointestinal cancer were included Exposure assessment method: validated self-administered questionnaire with follow-up	Urinary bladder	*Coffee consumption (cups/day): men only* ≤ 2 > 7 Trend test *P* value, 0.88	 20 10	 1.00 0.98 (NR)	Age, residence, smoking status, cigarettes/day	Strengths: prospective, sensitivity analyses considering time between diagnosis and baseline Limitations: no assessment of duration of coffee drinking, unclear reference period for coffee intake, coffee type only coffee (decaffeinated/instant not commonly consumed)
Stensvold & Jacobsen (1994) Norway, 1977–1982 (enrolment), follow-up until 1990	43 973 men and women aged 35–54 yr participating in cardiovascular screening programme Exposure assessment method: validated self-administered FFQ	Urinary bladder: ICD-7, 181	*Coffee consumption (cups/day): men* ≤ 4 5–6 ≥ 7 Per 2 cup/day increase *Coffee consumption (cups/day): women* ≤ 4 5–6 ≥ 7 Per 2 cup/day increase	 13 8 19 NR 3 5 5 NR	 1.00 0.70 1.50 1.13 (0.87–1.49) 1.00 2.10 2.40 1.22 (0.73–2.05)	Age, cigarettes per day, county of residence	Strengths: population-based, included participants in different parts of Norway Limitations: no assessment of duration of coffee intake or type of coffee/preparation method, modest sample size

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sugiyama et al. (2017) Japan, 1990–2007 (Miyagi), 1994–2008 (Ohsaki)	73 346 (38 646 Miyagi, 34 700 Ohsaki) men and women aged 40–79 yr, cohorts were pooled for analyses Exposure assessment method: validated self-administered FFQ	Urinary bladder: ICD-O-3 C67–67.9	*Coffee consumption (cups/day)*			Sex, age, BMI, history of hypertension, diabetes mellitus, myocardial infarction, stroke, job status, years of education, smoking status and cigarettes/ day, alcohol consumption, green tea consumption, time spent walking	Strengths: prospective, large cohorts, use of population-based registries Limitations: no history of drinking coffee assessed, no follow-up information (only baseline), no information on brewing or type of coffee, no occupational exposures assessed, very few cases
			Never	63	1.00		
			Occasionally	130	1.22 (0.90–1.66)		
			1–2	65	0.88 (0.61–1.26)		
			≥ 3	16	0.56 (0.32–0.99)		
			Trend test *P* value, 0.04				
		Urinary bladder: ICD-O-3 C67–67.9	*Coffee consumption (cups/day) stratified by smoking: never smokers*				
			Never	19	1.00		
			Occasionally	35	1.46 (0.82–2.58)		
			1–2	13	0.97 (0.47–2.01)		
			≥ 3	2	0.62 (0.14–2.72)		
			Coffee consumption (cups/day) stratified by smoking: former or current smokers				
			Never	38	1.00		
			Occasionally	83	1.22 (0.83–1.81)		
			1–2	48	0.95 (0.61–1.47)		
			≥ 3	13	0.61 (0.32–1.17)		

Table 2.1 (continued)

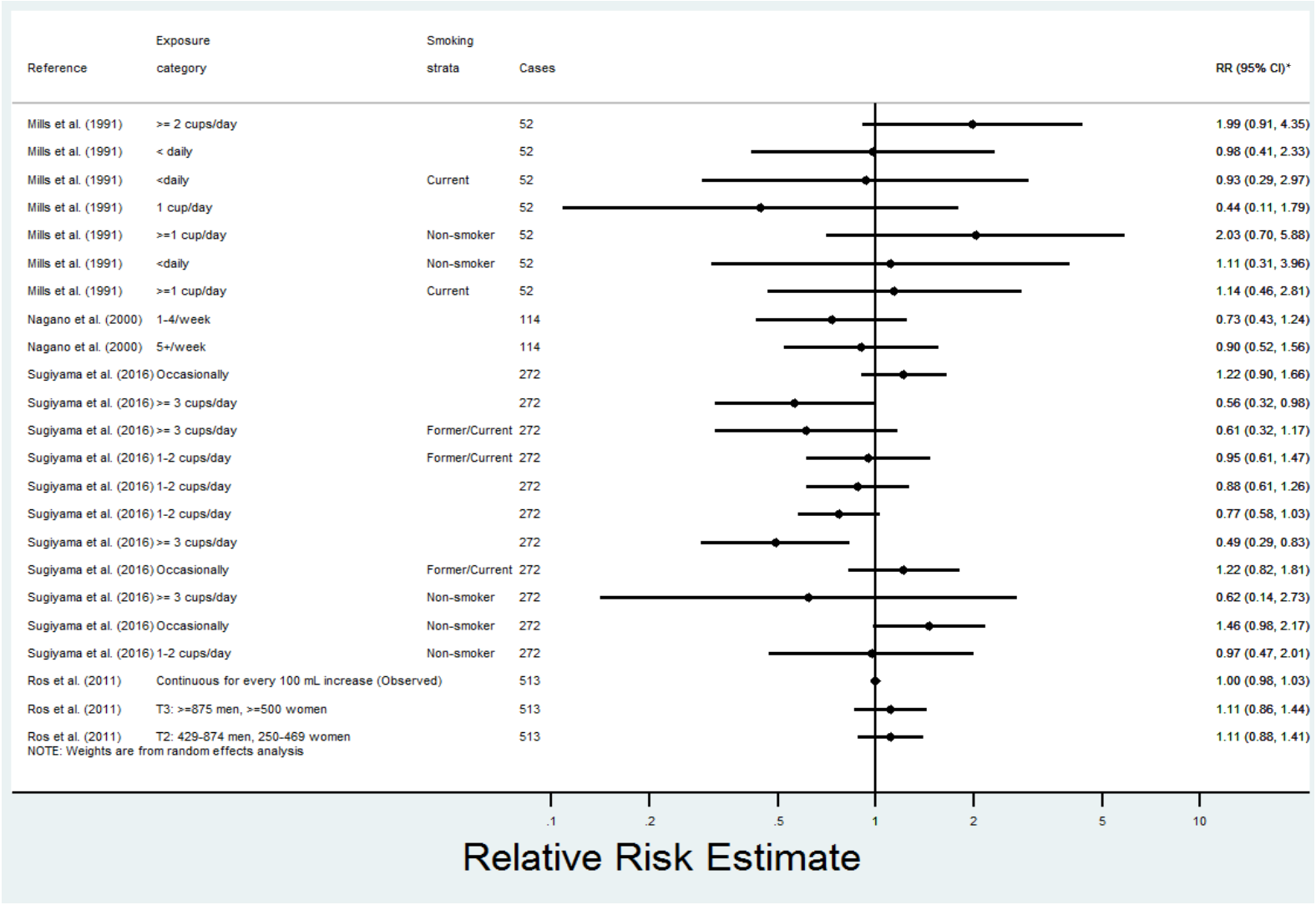
Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kurahashi et al. (2009) Japan 1990, 1993 (enrolment), 2005 (follow-up)	133 084 (65 660 men, 67 424 women), JPHC, 104 440 residents of 11 public health centre areas across Japan of age 40–69 yr included Exposure assessment method: validated, self-administered questionnaire assessing frequency/amount (no decaffeinated coffee considered)	Urinary bladder	*Coffee consumption among men*			Age, area of recruitment, smoking status/ pack-years, alcohol drinking, green tea	Decaffeinated coffee is rare in Japan; no other cancers reported in this paper Strengths: prospective, catchment area includes most of the country, stratification by sex and smoking Limitations: no assessment of drinking history, modest numbers (especially for stratified analyses)
			Almost never	50	1.00		
			1–4 times/wk	52	1.26 (0.84–1.88)		
			1–2 cups/day	43	1.53 (0.98–2.37)		
			≥ 3 cups/day	19	1.37 (0.75–2.51)		
			Trend test *P* value, 0.09				
			Coffee consumption among women				
			Almost never	19	1.00		
			1–4 times/wk	15	1.03 (0.51–2.07)		
			≥ 1 cup/day	8	0.55 (0.23–1.33)		
			Trend test *P* value, 0.23				
			Coffee frequency among men stratified by smoking status				
			Among never smokers				
			Almost none	6	1.00		
			1–4 times/wk	9	1.89 (0.67–5.32)		
			≥ 1 cup/day	11	2.48 (0.88–7.05)		
			Among former smokers				
			Almost none	13	1.00		
			1–4 times/wk	13	1.25 (0.58–2.71)		
			≥ 1 cup/day	16	2.09 (0.96–4.54)		
			Among current smokers				
			Almost none	29	1.00		
			1–4 times/wk	30	1.11 (0.65–1.9)		
			≥ 1 cup/day	33	1.13 (0.65–1.97)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chyou et al. (1993) Hawaii (Oahu), 1965–1968 (enrolment), 15 years of follow-up	7355 Japanese men born during 1900–1919 (no other criteria mentioned) Exposure assessment method: 24-hour recall questionnaire (no decaffeinated coffee considered)	Urinary bladder	*Coffee consumption (cups/wk)* ≤ 1 2–4 ≥ 5 Trend test *P* value, 0.174	 5 5 86	 1.00 3.52 (1.02–12.2) 2.07 (0.84–5.12)	Age, pack-years smoking	Strengths: prospective, good assessment of cancers Limitations: modest sample size, only assessed past 24 hours of intake not long-term history of drinking, few criteria listed for study eligibility, only men
Mills et al. (1991) USA (California), 1974 (recruitment), 1976 (survey), 1982 (end of follow-up)	34 198 non-Hispanic white members of Seventh-day Adventist church in California, > 25 yr old Exposure assessment method: self-administered 51-item FFQ and lifestyle questionnaire (no decaffeinated coffee considered)	Urinary bladder: 92% TCC	*Coffee intake frequency (cups/day)* Never < 1 1 ≥ 2 Trend test *P* value, 0.13 *Coffee frequency among never smokers (cups/day)* Never < 1 ≥ 1 *Coffee frequency among past/current smokers (cups/day)* Never < 1 ≥ 1	 26 7 2 12 NR NR NR NR NR	 1.00 0.98 (0.41–2.31) 0.44 (0.11–1.83) 1.99 (0.91–4.34) 1.00 1.11 (0.31–3.95) 2.03 (0.70–5.87) 1.00 0.93 (0.29–2.96) 1.14 (0.46–2.80)	Age, sex, smoking	Strengths: prospective, men and women included Limitations: no assessment of duration of coffee drinking, population studied does not traditionally drink coffee so intake of coffee might be a proxy for other changes from traditional Adventist lifestyle

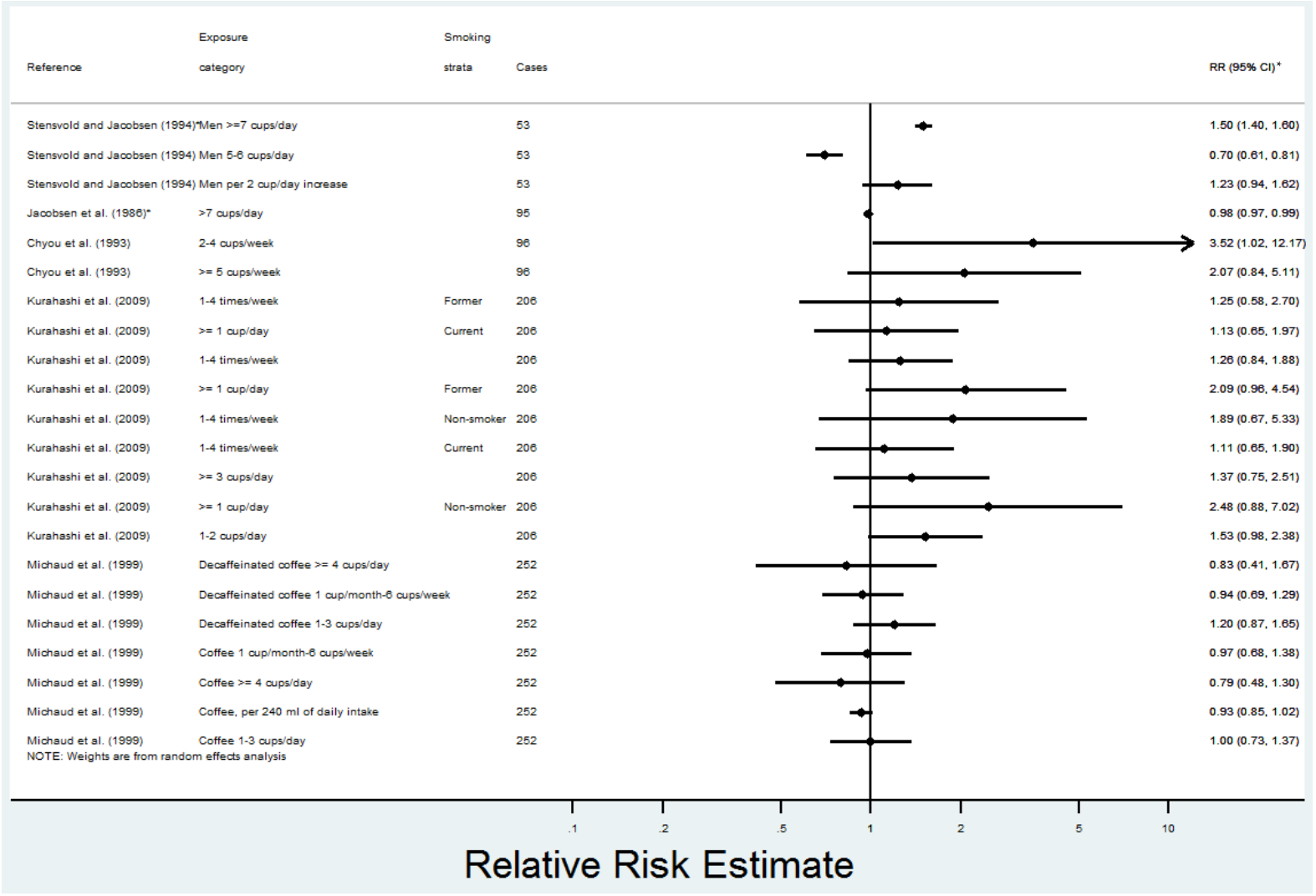
BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; ICD-7, International Classification of Disease - Revision 7; ICD-O-3, International Classification of Disease – Oncology Revision 3; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NR, not reported; TCC, transitional cell carcinoma; UCC, urothelial cell carcinoma; wk, week(s); yr, year(s)

Fig. 2.1 Relative risk estimate for coffee and bladder cancer cohorts: both sexes



* CIs were forced to display on the plot
Compiled by the Working Group

Fig. 2.2 Relative risk estimate for coffee and bladder cohorts: men only



* CIs were forced to display on the plot
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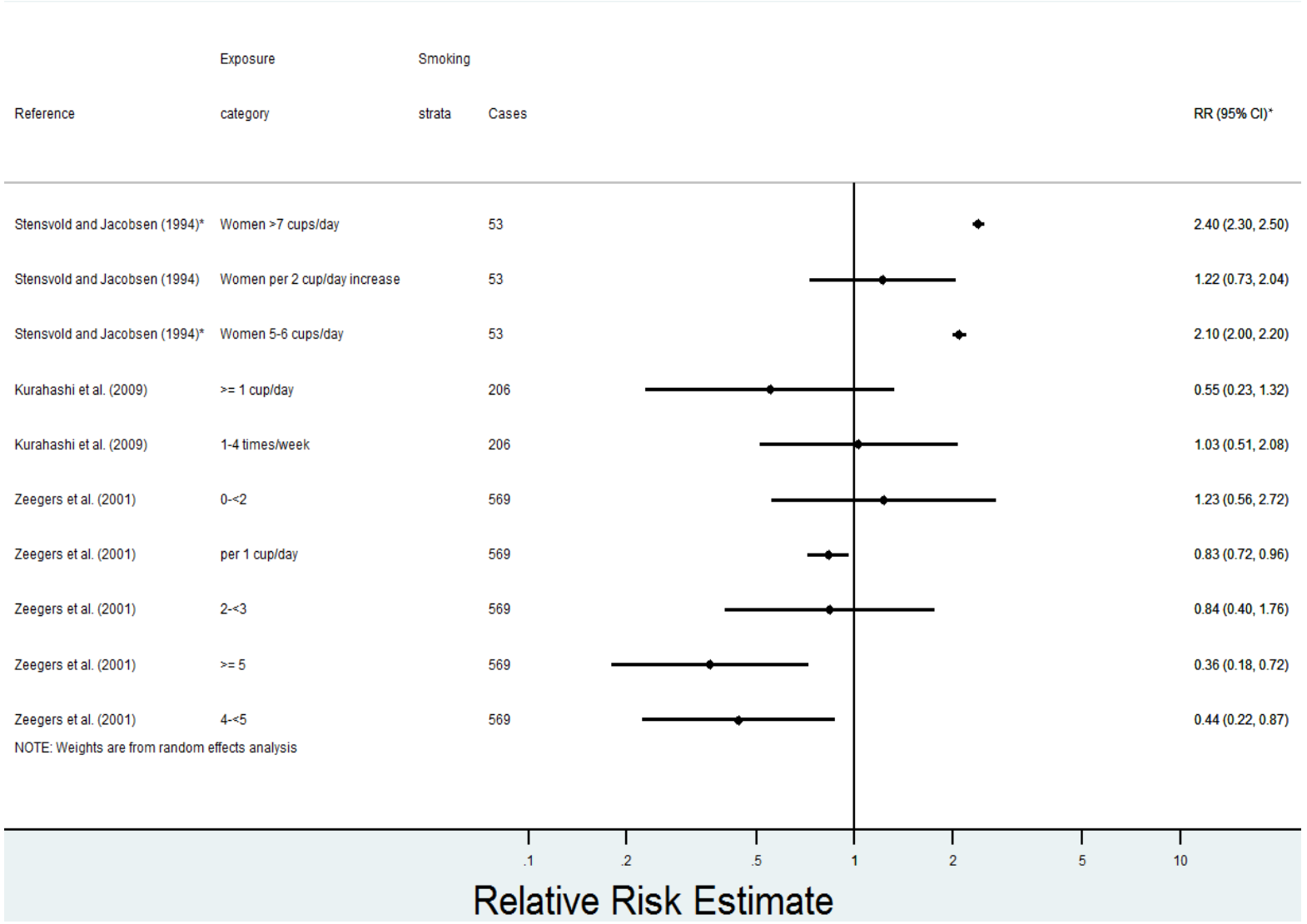
Fig. 2.3 Relative risk estimate for coffee and bladder cohorts: women only



* CIs were forced to display on the plot
Compiled by the Working Group

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 513 incident cases were identified during 1992–2000 (Ros et al., 2011). The relative risk for every 100 mL of coffee increase was 1.0 (95% CI, 0.98–1.03). The relative risk for the highest level of coffee intake (≥ 875 mL/day for men and ≥ 500 mL/day for women) compared with the lowest level (< 429 mL/day for men and < 250 mL/day for women) was 1.11 (95% CI, 0.85–1.43, *P* for trend, 0.5). Sensitivity analyses excluding cases diagnosed within 2 years of recruitment did not change results. Stratification of cases by high (≥ T1, CIS, WHO grade 3) or low (Ta grade 1, Ta grade 2) risk of progression also yielded comparable results. [Limitations noted were: stratified results by smoking were conducted and mentioned but estimates not shown; a lack of consideration of coffee-drinking history; and no follow-up data on coffee drinking.]

In the Health Professionals Follow-up Study (HPFS) (Michaud et al., 1999) 252 incident cases of bladder cancer were identified during 1986–1996. The relative risk for the highest level of caffeinated coffee intake (≥ 4 cups/day) compared with the lowest (< 1 cup/month) was 0.79 (95% CI, 0.48–1.30), with no evidence of dose–response and trend (*P* for trend, 0.56). Similarly, for decaffeinated coffee the relative risk for the highest level of coffee (≥ 4 cups/day) compared with the lowest (< 1 cup/month) was 0.83 (95% CI, 0.41–1.66), with no evidence of dose–response and trend (*P* for trend, 0.47). Sensitivity analyses excluding cases diagnosed during the first 3 years of the study did not change findings. [A weakness was the lack of consideration of coffee-drinking history.]

In the Life Span Study of atomic bomb survivors in Japan (Nagano et al., 2000), 114 incident cases of bladder cancer were identified between 1979 and 1983 (83 men and 31 women). The relative risk for the highest level of intake (> 5 times/week) compared with never drinkers was 0.90 (95% CI, 0.52–1.56), with no evidence of dose–response or trend (*P* for trend, 0.78). Sensitivity analyses excluding cases diagnosed during the first 2 years after a postal survey (a total of 96 cases) yielded the same results. [A weakness of this study was the limited assessment of coffee consumption with no quantity/serving, history of intake, or follow-up data provided.]

In a study that included 94 bladder cancer cases diagnosed within two Norwegian cohorts of men (Jacobsen et al., 1986), the relative risk for the highest level of intake (> 7 cups/day) compared with the lowest (≤ 2 cups/day) was 0.98. No confidence intervals were provided. Similar estimates were obtained for women, although no adjustment for smoking was possible among them. Excluding cases diagnosed in the first 4 years of the cohorts yielded comparable results. [Weaknesses of this study were the lack of assessment of coffee-drinking history, no follow-up data regarding coffee, and no stratification of results by smoking. Even though decaffeinated coffee or instant coffee were not assessed, it was indicated that these were rarely consumed at the time of the study.]

In the Norwegian National Health Screening Service for cardiovascular disease (Stensvold & Jacobsen, 1994) a total of 53 incident cases of cancer of the bladder (40 men and 13 women) were identified. Among men the relative risk per 2 cups/day increase in coffee drinking was [1.13 (95% CI, 0.87–1.49)]; among women the corresponding relative risk was [1.22 (95% CI, 0.73–2.05)] [the paper reports coefficients for these estimates, which were exponentiated here]. Analyses using tertiles of coffee intake are presented without confidence intervals. Sensitivity analyses for the first 2 years of diagnoses in cohort were performed. [A main weakness was the modest sample size, particularly for women, and lack of consideration of duration of coffee intake.]

In the following, cohort studies that reported results for coffee intake but were given less weight by the Working Group are described.

A study that combined data from the Miyagi Cohort Study and the Ohsaki Cohort Study in Japan, including 272 bladder cancer cases, was reported (Sugiyama et al., 2017). The relative risk for the highest consumption level (≥ 3 cups/day) compared with never drinkers was 0.56 (95% CI, 0.32–0.99; *P* for trend, 0.04). When stratifying individuals by smoking status, the relative risks for the same comparisons were 0.62 (95% CI, 0.14–2.72) for never smokers and 0.61 (95% CI, 0.32–1.17) for former or current smokers, with a test of interaction *P* = 0.99. Interaction analyses were also performed for sex, age, body mass index (BMI), diabetes, and alcohol; no evidence of effect modification was obtained for any of these variables. [The number of cases was small for stratified analyses, especially among never smokers.]

In the Japan Public Health Center-based Prospective (JPHC) study 206 (164 men and 42 women) bladder cancer cases were identified (Kurahashi et al., 2009). Among men, the hazard ratio for the highest category of coffee intake (≥ 3 cups/day) compared with those who consumed almost no coffee was 1.37 (95% CI, 0.75–2.51; *P* for trend, 0.09). [No evidence of a dose–response relationship was observed.] Among women the hazard ratio for the highest category of intake (≥ 1 cup/day) compared with almost none was 0.55 (95% CI, 0.23–1.33; *P* for trend, 0.23). Among never smoking men, the hazard ratio for the highest category (≥ 1 cup/day) compared with almost no coffee drinking was 2.48 (95% CI, 0.88–7.05), 2.09 (95% CI, 0.96–4.54) among former smokers, and 1.13 (95% CI, 0.65–1.97) among current smokers. A test of interaction was not statistically significant. [The main weaknesses were the modest sample size among never smokers, and the lack of coffee-drinking history and follow-up exposure data.]

In a prospective study conducted in Hawaii, 96 men with bladder cancer were identified (Chyou et al., 1993). The relative risk for high (≥ 5 cups/week) compared with low (≤ 2 cups/week) intake was 2.07 (95% CI, 0.84–5.12; *P* for trend, 0.174). There was no evidence of a dose–response relationship. A previous study reported on a subset of these men (Nomura et al., 1986). [A limitation of this study was the fact that coffee intake was assessed via 24 hour recalls, which may not be representative of long-term coffee drinking. The numbers of cases in lower-intake categories were very small.]

A total of 52 bladder cancer cases were identified within the Seventh-day Adventist Church Cohort study conducted in California (Mills et al., 1991). The relative risk for the highest level of intake (≥ 2 cups/day) compared with never drinkers was 1.99 (95% CI, 0.91–4.34; *P* for trend, 0.13) with little evidence of a dose–response relation. Analyses stratifying by smoking status showed that the relative risk for the highest category (≥ 1 cup/day) compared with never drinkers was 2.03 (95% CI, 0.70–5.87) among never smokers and 1.14 (95% CI, 0.46–2.80) among past or current smokers. [Key limitations were overall small numbers (especially among never smokers with only 25 cases), an unclear definition of smoking variables in regression, and a concern for potential underreporting of tobacco consumption.]

In the Iowa Women's Health Study 112 incident bladder cancer cases were identified between 1986 and 1998 among postmenopausal women (Tripathi et al., 2002). The relative risk for the highest frequency of coffee intake (≥ 4 times/day) compared with the lowest (never or < 1 time/month) was 1.59 (95% CI, 0.95–2.68). [Since it was not clear whether smoking was included as a confounder, the Working Group decided not to include this study for final evaluation.]

2.1.2 Case–control studies

See Table 2.2.

The Working Group identified 64 case–control studies that reported on associations

Table 2.2 Case–control studies on cancer of the bladder and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cole (1971) USA (Massachusetts), 1966–1968	Cases: 470 population-based, pathology logs of hospitals in the area were used Controls: 500 population-based using residents lists, matched to cases by sex and year of birth Exposure assessment method: interviewer-administered questionnaire, frequency and amount of coffee, unclear validation	Urinary bladder: TCC and SCC	*Coffee intake among men (cups/day)*			Age, cigarette smoking (cigarettes smoked/day), occupation	Also presented analyses stratified by age and sex, although numbers were very small; among men the association was stronger for older men, and among women it was stronger for women aged 60–74 yr Strengths: population-based, adequate sample size, consideration of occupational exposures Limitations: no information on drinking history or types of coffee consumed, no confidence intervals shown for RR in dose–response analyses, small numbers for some stratified analyses
			< 1	29	1.00		
			1	86	1.34 (NR)		
			2–3	146	1.18 (NR)		
			≥ 4	84	1.31 (NR)		
			≥ 1 vs < 1	316	1.24 (0.80–1.93)		
			Coffee intake among women (cups/day)				
			< 1	9	1.00		
			1	19	1.60 (NR)		
			2–3	50	3.76 (NR)		
			≥ 4	22	2.19 (NR)		
			≥ 1 vs < 1	100	2.58 (1.30–5.10)		
			Coffee intake among non-smokers without high-risk occupations (cups/day)				
			< 1	10	1.00		
			1	31	2.18 (NR)		
			2–3	37	1.84 (NR)		
			≥ 4	12	2.60 (NR)		
Fraumeni et al. (1971) USA (New Orleans), 1958–1964	Cases: 493; NR see Dunham et al. (1968) Controls: 527; NR see Dunham et al. (1968) Exposure assessment method: Questionnaire; see Dunham et al. (1968)	Urinary bladder	*Daily consumption coffee (cups/day)*			Age, cigarette smoking	Strengths: both white and black subjects Limitations: no confidence intervals shown for most estimates
			Any amount vs none	NR	1.50		
			Daily consumption of coffee among white men (cups/day)				
			0 (reference)	5	1.00		
			1–2	85	1.40 (NR)		
			3–4	76	1.96 (NR)		
			≥ 5	99	1.66 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fraumeni et al. (1971) (cont.)			*Daily consumption of coffee among black men (cups/day)*				
			0 (reference)	6	1.00		
			1–2	23	2.13 (NR)		
			3–4	27	2.90 (NR)		
			≥ 5	13	2.10 (NR)		
			Daily consumption of coffee (cups/day)				
			Any daily amount vs none (all men)	323	1.95 (NR)		
			Any daily amount vs none (white men)	260	1.78 (NR)		
			Any daily amount vs none (black men)	63	2.10 (NR)		
			Daily consumption of coffee among white women (cups/day)				
			0 (reference)	14	1.00		
			1–2	45	0.70 (NR)		
			3–4	29	0.47 (NR)		
			≥ 5	24	0.32 (NR)		
			Trend test *P* value, 0.04				
			Daily consumption of coffee among black women (cups/day)				
			0 (reference)	2	1.00		
			1–2	27	10.00 (NR)		
			3–4	10	4.58 (NR)		
			≥ 5	8	2.30 (NR)		
			Trend test *P* value, 0.04				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fraumeni et al. (1971) (cont.)			*Daily consumption of coffee among all women (cups/day)*				
			Any daily amount vs none (all women)	147	1.19 (NR)		
			Daily amount vs none (white women)	98	0.51 (NR)		
			Daily amount vs none (black women)	45	5.65 (NR)		
			Trend test *P* value, 0.04				
			Daily consumption coffee (cups/day)				
			Never smokers (blacks)	NR	1.00		
			Ever smokers (blacks)	NR	3.56 (NR)		
			Never smokers (whites)	NR	1.00		
			Ever smokers (whites)	NR	0.67 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simon et al. (1975) USA (Massachusetts, Rhode Island), 1965–1971	Cases: 135 hospital-based Controls: 390 hospital-based, identified via discharge lists of same hospitals as cases, free of urinary tract problems (no selection made related to other diseases) Exposure assessment method: mailed questionnaire, validation unclear (both regular and decaffeinated coffee considered)	Urinary bladder	*Coffee consumption among non- and light smokers (cups/day)* 0 to < 1 ≥ 1 *Coffee consumption among moderate to heavy smokers (cups/day)* 0 to < 1 ≥ 1	 9 76 1 45	 1.0 1.7 (0.8–3.5) 1.0 3.7 (0.6–23.6)	None	Strengths: Assessed coffee drinking strength and history Limitations: hospital-based, controls not excluded based on non-urinary tract disease that may also affect coffee drinking (GI diseases), small numbers in stratified analyses, no estimates provided adjusting for smoking, women only

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mettlin & Graham (1979) USA (Buffalo, New York), 1957–1965	Cases: 569 hospital-based Controls: 1025 hospital-based, admitted to same hospital as cases with non-neoplastic complaints, no matching performed Exposure assessment method: questionnaire, validation unclear, administered in person, frequency/amount of coffee	Urinary bladder: ICD-188	*Coffee consumption among men (cups/day)*			Cigarettes smoked/ day	Same patient population as described by Bross & Tidings (1973) Strengths: adequate sample size with large number of controls Limitations: hospital-based, no drinking history, controls may include patients with disorders that affect coffee drinking, number of women for smoking stratified analyses was small (not presented here)
			< 1	24	1.00		
			1	56	1.38 (NR)		
			2	73	1.16 (NR)		
			3	76	2.11 (NR)		
			> 3	124	1.64 (NR)		
		Urinary bladder	*Coffee consumption among women (cups/day)*				
			< 1	15	1.00		
			1	25	0.83 (NR)		
			2	34	1.03 (NR)		
			3	13	1.25 (NR)		
			> 3	24	0.81 (NR)		
			Coffee consumption among men and women (cups/day)			Sex, cigarettes smoked/day	
			< 1	39	1.00		
			1	81	1.15 (NR)		
			2	107	1.11 (NR)		
			3	89	1.82 (NR)		
			> 3	148	1.30 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mettlin & Graham (1979) (cont.)			*Coffee consumption among light-smoking (< half a pack/day) men (cups/day)*			Cigarettes smoked/ day	
			< 1	16	1.00		
			1	28	1.28 (0.58–2.82)		
			2	34	0.98 (0.46–2.09)		
			3	30	2.18 (0.97–4.93)		
			> 3	26	1.40 (0.62–3.15)		
			Coffee consumption among light-smoking (< half a pack/day) women (cups/day)				
			< 1	14	1.00		
			1	24	0.80 (0.33–1.93)		
			2	30	0.93 (0.40–2.19)		
			3	12	1.17 (0.40–3.47)		
			> 3	15	0.66 (0.25–1.74)		
Wynder & Goldsmith (1977) USA (various states), 1969–1974	Cases: 732 hospital-based, from 17 hospitals in New York (majority), Houston, Los Angeles, Miami, Birmingham, New Orleans, Virginia Controls: 732 hospital-based, patients without history of tobacco-related conditions, matched to cases by sex, race, hospital status, age at diagnosis Exposure assessment method: questionnaire, in-person interview, frequency and amount	Urinary bladder	*Coffee (cups/day)*			Smoking	Strengths: adequate numbers, includes cases from various regions of the USA Limitations: controls may include patients with diseases that affect coffee intake, few details of statistical analyses, no history of coffee drinking considered
			None/ occasionally	NR	1.0		
			1–3	NR	1.4 (0.8–2.3)		
			4–6	NR	1.9 (1.0–3.6)		
			≥ 7	NR	2.0 (0.8–4.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) Canada (Nova Scotia, Newfoundland, British Columbia), 1974–1976	Cases: 632 population-based, identified through cancer registries Controls: 632 population-based, neighbourhood controls, matched to cases by age and sex Exposure assessment method: interviewer-administered questionnaire	Urinary bladder	*Lifetime average total coffee for men (cups/day)*			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, diabetes, education, aspirin, artificial sweetener	Strengths: coffee drinking history and coffee types, included men and women, comprehensive consideration of confounders Limitations: small numbers for stratified analyses
			Never drinker	NR	1.0		
			1–2	NR	[1.6 (1.0–2.6)]		
			3–4	NR	[1.3 (0.7–2.3)]		
			> 4	NR	[1.5 (0.8–2.8)]		
			Lifetime average total coffee for women (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes	
			Never drinker	NR	1.0		
			1–2	NR	[0.7 (0.3–1.5)]		
			3–4	NR	[1.7 (0.6–4.8)]		
			> 4	NR	[1.3 (0.4–4.1)]		
			Lifetime average instant coffee for men (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, education, aspirin, artificial sweetener, regular coffee	
			Never drinker	NR	1.0		
			1–2	NR	[1.5 (1.0–2.3)]		
			3–4	NR	[1.7 (0.9–3.3)]		
			> 4	NR	[1.5 (0.7–3.1)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) (cont.)			*Lifetime average instant coffee for women (cups/day)*			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes, regular coffee	
			Never drinker	NR	1.0		
			1–2	NR	[1.1 (0.5–2.5)]		
			3–4	NR	[1.2 (0.3–5.1)]		
			> 4	NR	[1.2 (0.2–5.5)]		
			Lifetime average regular coffee for men (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, education, aspirin, artificial sweetener, instant coffee	
			Never drinker	NR	1.0		
			1–2	NR	[2.0 (1.1–3.4)]		
			3–4	NR	[1.5 (0.8–2.7)]		
			> 4	NR	[1.8 (1.0–3.5)]		
			Lifetime average regular coffee for women (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes, instant coffee	
			Never drinker	NR	1.0		
			1–2	NR	[0.4 (0.2–8.0)]		
			3–4	NR	[0.7 (0.2–14)]		
			> 4	NR	[0.7 (0.2–16)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) (cont.)			*Lifetime average instant coffee for non-smoking women (cups/day)*			NR	
			≤ 2	NR	1.0		
			> 2	NR	1.4 (0.4–4.4)		
Morrison et al. (1982) USA (Boston), UK (Manchester), Japan (Nagoya), 1976–1978	Cases: 1666 population-based, identified through hospitals Controls: 2229 population-based, randomly identified, matched to cases by age and sex Exposure assessment method: questionnaire (no information about validation) administered in person	Urinary bladder	*Coffee (cups/day): all studies combined*			Age, sex, study area, cigarette smoking	Strengths: large sample size, comprehensive exposure assessment, consideration of occupational exposure and other confounders Limitations: not all analyses are shown, no confidence intervals provided for most of the estimates
			< 1	514	1.0		
			> 1	903	1.0 (0.8–1.2)		
			Coffee (cups/day): Boston study, men only				
			< 1	23	1.0		
			1	98	0.8 (NR)		
			2	95	0.7 (NR)		
			3	82	0.9 (NR)		
			4	41	0.8 (NR)		
			5	19	0.8 (NR)		
			≥ 6	65	1.5 (NR)		
			Coffee (cups/day): Boston study, women only				
			< 1	20	1.0		
			1	59	0.8 (NR)		
			2	38	0.6 (NR)		
			3	19	1.7 (NR)		
			4	12	0.9 (NR)		
			5	10	0.7 (NR)		
			≥ 6	7	1 (NR)		
			Coffee (cups/day): Manchester study, men only				
			< 1	224	1.0		
			1	85	1.1 (NR)		
			2	40	0.9 (NR)		
			3–4	27	0.9 (NR)		
			≥ 5	12	0.8 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Morrison et al. (1982) (cont.)			*Coffee (cups/day): Manchester study, women only*				
			< 1	79	1.0		
			1	46	1.4 (NR)		
			2	8	0.4 (NR)		
			3–4	14	1.2 (NR)		
			≥ 5	5	1 (NR)		
			Coffee (cups/day): Nagoya study, men only				
			< 1	116	1.0		
			1	43	1.0		
			2	38	1.2		
			3–4	20	1.3		
			≥ 5	7	1.9		
			Coffee (cups/day): Nagoya study, women only				
			< 1	52	1.0		
			1	11	0.7		
			> 2	2	0.7		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) USA (10 geographical regions), 1977–1978	Cases: 2982 population-based, identified through SEER cancer registries Controls: 5782 population-based, identified through RDD or Medicare records, frequency matched to cases on age, sex, and geographical distribution Exposure assessment method: interviewer-administered questionnaire, different types of coffee and frequency of drinking assessed	Urinary bladder	*Coffee drinking history*			Sex, age, race, geographic area, tobacco history (based on cigarettes/day and smoking status)	Strengths: large sample size, thorough confounding assessment, years of coffee drinking assessed Limitations: modest numbers in some stratified analyses, small number in reference group
			Never drinker	98	1.0		
			Ever drinker	2809	1.4 (1.1–1.8)		
			Men: never drinker	58	1.0		
			Men: ever drinker	2139	1.6 (1.2–2.2)		
			Women: never drinker	40	1.0		
			Women: ever drinker	670	1.2 (0.8–1.7)		
			Coffee consumption (cups/wk) among men				
			≤ 7	397	1.0		
			7.1–14	389	0.9 (0.8–1.1)		
			41.1–21	381	1.0 (0.8–1.2)		
			21.1–35	493	1.1 (0.9–1.3)		
			35.1–49	195	1.0 (0.8–1.3)		
			49.1–63	109	1.2 (0.9–1.6)		
			63.1–155	148	1.5 (1.1–1.9)		
			Coffee consumption (cups/wk) among women				
			≤ 7	164	1.0		
			7.1–14	161	0.9 (0.7–1.2)		
			41.1–21	110	0.8 (0.6–1.1)		
			21.1–35	133	0.9 (0.7–1.2)		
			35.1–49	49	0.7 (0.5–1.1)		
			49.1–63	21	0.9 (0.5–1.7)		
			63.1–155	26	0.8 (0.4–1.4)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) (cont.)			*Coffee drinking status by smoking status among men*				
			Non-smokers	NR	–		
			Never drinkers	159	1.0		
			Ever drinkers	NR	1.5 (0.9–2.5)		
			Past smokers	NR	–		
			Never drinkers	62	1.0		
			Ever drinkers	NR	1.4 (0.8–2.6)		
			Smokers	NR	–		
			Never drinkers	56	1.0		
			Ever drinkers	NR	2.1 (1.2–3.9)		
			Coffee drinking high/low by smoking status among men				
			Non-smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	21	4.2 (1.7–10.0)		
			Past smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	208	1.3 (1–1.8)		
			Smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	302	1.2 (1–1.6)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) (cont.)			*Coffee drinking status by smoking status among women*			Sex, age, race, geographical area, amount of tobacco	
			Non-smokers	NR	–		
			Never drinkers	121	1.0		
			Ever drinkers	NR	0.9 (0.6–1.5)		
			Past smokers	NR	–		
			Never drinkers	13	1.0		
			Ever drinkers	NR	3.0 (0.8–12.0)		
			Smokers	NR	–		
			Never drinkers	27	1.0		
			Ever drinkers	NR	1.3 (0.6–2.9)		
			Coffee drinking high/low by smoking status among women				
			Non-smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	24	0.4 (0.2–1.5)		
			Past smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	25	1.7 (0.7–4.2)		
			Smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	67	1 (0.6–1.7)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sturgeon et al. (1994) USA (10 geographical regions), 1977–1978	Cases: 1860; see Hartge et al. (1983) Controls: 3934; see Hartge et al. (1983) Exposure assessment method: questionnaire; see Hartge et al. (1983)	Urinary bladder: TCC	*Coffee consumption (cups/wk) by tumour grade*			Age, sex, cigarette use (status and cigarettes/day), history of urinary infections, history of bladder stones, artificial sweetener, family history of urinary tract cancer, high-risk occupation, race, education	Same study as Hartge et al. (1983) Strengths: large sample size, thorough confounding assessment, years of coffee drinking assessed, very comprehensive and thorough analyses Limitations: modest numbers for stage and grade combined analyses
			Grade I, consumption < 50	326	1.0		
			Grade I, consumption ≥ 50	49	1.3 (0.9–1.8)		
			Grade II, consumption < 50	578	1.0		
			Grade II, consumption ≥ 50	87	1.3 (1.0–1.7)		
			Grade III/IV, consumption < 50	562	1.0		
			Grade III/IV, consumption ≥ 50	61	1.4		
			RR for coffee (cups/wk) by tumour stage				
			Non-invasive, consumption < 50	983	1.0		
			Non-invasive, consumption ≥ 50	147	1.4 (1.1–1.7)		
			Invasive overall, consumption < 50	522	1.0		
			Invasive overall, consumption ≥ 50	68	1.2 (0.9–1.6)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sturgeon et al. (1994) (cont.)			*RR for coffee (cups/wk) by tumour grade and stage*				
			Non-invasive low grade, consumption < 50	668	1.0		
			Non-invasive low grade, consumption ≥ 50	109	1.4 (1.1–1.8)		
			Non-invasive high grade, consumption < 50	156	1.0		
			Non-invasive high grade, consumption ≥ 50	15	1.3 (0.7–2.2)		
			Invasive low grade, consumption < 50	197	1.0		
			Invasive low grade, consumption ≥ 50	23	1.0 (0.6–1.5)		
			Invasive high grade, consumption < 50	293	1.0		
			Invasive high grade, consumption ≥ 50	43	1.4 (1.0–2.0)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kantor et al. (1988) USA (10 geographical regions), 1977–1978	Cases: 2915; see Hartge et al. (1983) Controls: 5782; see Hartge et al. (1983) Exposure assessment method: questionnaire; see Hartge et al. (1983)	Urinary bladder: SCC	*Coffee consumption (cups/wk)*			Sex, age, cigarette smoking	Strengths: consideration of tumour subtypes, large sample size for TCC Limitations: very small numbers for SCC and adenocarcinoma, small number in reference group (never drinkers)
			0–7	9	1.0		
			8–21	12	0.9 (0.3–2.2)		
			22–49	13	1.4 (0.5–3.5)		
			50–63	3	2.1 (0.4–10.8)		
			≥ 64	2	1.1 (0.1–6.6)		
		Urinary bladder: adenocarcinomas	*Coffee consumption (cups/wk)*				
			0–7	5	1.0		
			8–21	13	2.1 (0.7–6.9)		
			22–49	11	2.8 (0.8–9.5)		
			50–63	1	2.7 (0.1–48.7)		
			≥ 64	2	5.2 (0.5–58.1)		
			Trend test *P* value, 0.049				
		Urinary bladder: TCC	*RR for coffee (cups/wk)*				
			0–7	625	1.0		
			8–21	932	1.0 (0.9–1.1)		
			22–49	761	1.1 (0.9–1.2)		
			50–63	110	1.4 (1.0–1.8)		
			≥ 64	153	1.5 (1.1–1.9)		
			Trend test P value, < 0.01				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rebelakos et al. (1985) Greece (Athens), 1980–1982	Cases: 300 hospital-based Controls: 300 hospital-based, different hospitals from cases (majority traumatic fractures or conditions) Exposure assessment method: interviewer-administered questionnaire (no information about validation), amount and duration recorded	Urinary bladder: 93% TCC	*Coffee consumption (cups/day): men and women*			Age, sex, smoking status	Strengths: proper adjustment Limitations: moderate size, but too small for stratified analyses by sex (few women), no consideration of drinking history, no mention of other confounders other than age and smoking, different types of coffee not specified
			0	25	1.0		
			1	62	1.2 (0.8–2.2)		
			2	150	1.7 (1.0–2.8)		
			3	36	2.7 (0.9–8.2)		
			≥ 4	24	0.7 (0.2–2.7)		
			> 2 vs < 2 (including 0)	210	1.7 (1.2–2.3)		
			Coffee consumption (cups/day): men				
			0	15	1.0		
			1	41	1.1 (0.5–2.3)		
			2	133	1.5 (0.8–2.7)		
			3	32	4.0 (1.2–13.4)		
			≥ 4	22	0.5 (0.1–2.5)		
			> 2 vs < 2 (including 0)	187	1.7 (1.2–2.4)		
			Coffee consumption (cups/day): women				
			0	10	1.0		
			1	21	2.0 (0.9–5.0)		
			2	15	2.1 (0.9–5.0)		
			3	0	0.0 (0.0–0.0)		
			≥ 4	2	2.0 (0.2–23.6)		
			> 2 vs < 2 (including 0)	17	1.6 (0.8–3.2)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Claude et al. (1986) Germany (Lower Saxony), 1977–1982	Cases: 431 hospital-based Controls: 431 hospital-based, identified in urology ward and for older individuals from elderly homes in town, matched to cases 1:1 by age and sex Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated) of coffee considered	Urinary bladder	*Consumption of ground coffee (cups/day): men*			Smoking	Strengths: adequate numbers Limitations: hospital-based, possible bias due to selection of hospital-based controls with urological diseases, duration of intake not considered
			0	NR	1.00		
			1–2	NR	1.42 (0.70–2.80)		
			3–4	NR	1.39 (0.70–2.60)		
			> 4	NR	2.29 (0.40–11.60)		
			Drinker vs non-drinker	NR	1.57 [(0.60–3.80)]		
			Consumption of ground coffee (cups/day): women				
			0	NR	1.00		
			1–2	NR	1.26 (0.80–2.00)		
			3–4	NR	1.89 (0.50–6.60)		
			> 4	NR	2.18 (0.50–10.00)		
			Drinker vs non-drinker	NR	0.99 [(1.00–1.00)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kunze et al. (1992) Germany (Lower Saxony), 1977–1985	Cases: 675 hospital-based Controls: 675 hospital-based, identified in urology ward, matched by age and sex (64% of men had hyperplasia of the prostate, 73% women had lower urinary infections) Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated) of coffee considered	Urinary bladder: lower urinary tract cancers, majority bladder but also others	*Coffee consumption (cups/day): women* 0 1–2 3–4 ≥ 5 *Coffee consumption (cups/day): men* 0 1–2 3–4 ≥ 5	 NR 47 60 24 NR 168 205 102	 1.0 1.4 (0.7–3.0) 2.4 (1.0–5.4) 2.7 (0.9–7.8) 1.0 1.3 (0.8–2.0) 1.5 (0.95–2.3) 2.0 (1.2–3.3)	Smoking status, pack-years	Extension of a study reported by Claude et al. (1986), so includes patients reported in this previous study Strengths: adequate numbers Limitations: hospital-based, possible bias due to selection of hospital-based controls with urological diseases, no history of coffee drinking considered

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jensen et al. (1986) Denmark (Copenhagen), 1979–1981	Cases: 371 population-based Controls: 771 population-based, matched to cases by sex, age, and residential area Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated, instant) of coffee considered, drinking history and amount	Urinary bladder: majority TCC	*Coffee consumption*			Age, smoking status, lifetime cigarette exposure (pack-years)	Strengths: adequate sample size, comprehensive questionnaire Limitations: no information on validation of questionnaire, modest numbers for reference category for stratified analyses by sex
			Men per L/day	NR	[1.1 (0.9–1.4)]		
			Women per L/day	NR	[1.1 (0.7–1.9)]		
			Coffee consumption (mL/day): men				
			0	15	1.0		
			1–499 (0–2 cups)	69	0.9 (0.5–1.9)		
			500–999 (2–4 cups)	90	0.8 (0.4–1.6)		
			1000–1499 (4–6 cups)	56	0.9 (0.4–1.8)		
			≥ 1500 (> 6 cups)	50	1 (0.5–2.1)		
			Trend test *P* value, 0.83				
			Coffee consumption (mL/day): women				
			0	4	1.0		
			1–499 (0–2 cups)	20	1.9 (0.6–6.7)		
			500–999 (2–4 cups)	33	1.2 (0.4–3.5)		
			1000–1499 (4–6 cups)	15	1.6 (0.4–6.0)		
			≥1500 (> 6 cups)	13	2.7 (0.7–10.9)		
			Trend test *P* value, 0.37				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kabat et al. (1986) USA (various states), 1976–1983	Cases: 152; see Wynder & Goldsmith (1977) Controls: 492; see Wynder & Goldsmith (1977) Exposure assessment method: questionnaire; see Wynder & Goldsmith (1977)	Urinary bladder	*Brewed coffee consumption (cups/day): men*			None	Strengths: focus on non-smokers (important given the strong confounding effect of smoking), large catchment area across the USA Limitations: hospital-based controls (which may introduce bias if they had diseases that affect coffee intake), small numbers for some of the coffee drinking categories
			None/occasional	40	1.00		
			1–2	18	0.91 (0.48–1.71)		
			3–4	15	1.38 (0.69–2.79)		
			5–6	3	1.38 (0.34–5.59)		
			≥ 7	0	0.46 (0.03–8.47)		
			Brewed coffee consumption (cups/day): women				
			None/occasional	40	1.00		
			1–2	24	1.51 (0.84–2.72)		
			3–4	8	0.81 (0.35–1.88)		
			5–6	2	0.66 (0.14–3.10)		
			≥ 7	2	2.43 (0.41–14.34)		
			Decaffeinated coffee consumption (cups/day): men				
			None/occasional	60	1.00		
			1–2 cups/day	14	1.07 (0.54–2.11)		
			3–4 cups/day	2	0.40 (0.09–1.71)		
			≥ 5 cups/day	0	0.27 (0.02–4.10)		
			Decaffeinated coffee consumption (cups/day): women				
			None/occasional	62	1.00		
			1–2	9	0.50 (0.24–1.07)		
			3–4	5	0.73 (0.26–2.01)		
			≥ 5	0	0.58 (0.03–11.82)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Piper et al. (1986) USA (New York), 1975–1980	Cases: 165 population-based, identified through cancer registry Controls: 165 population-based, identified through RDD, paired to cases by strata defined by age and residence Exposure assessment method: telephone questionnaire, no information about validation, regular coffee only	Urinary bladder	*Coffee consumption (cup-years) among women* Non-drinker 1–50 51–100 ≥ 101	 NR NR NR	 1.0 0.9 (0.5–2.3) 1.9 (0.8–4.6) 2.1 (0.7–6.3)	Race, level of education, smoking (pack-years), phenacetin drugs use, bladder infection, thyroid uptake procedure	Strengths: population-based, adequate control for confounders Limitations: narrow focus on young women, no history of coffee drinking studied
Iscovich et al. (1987) Argentina (La Plata), 1983–1985	Cases: 117 hospital-based, 60% of registered cases for catchment area Controls: 117 hospital-based (16% digestive system problems, 17% heart disease, 12% hypertension), 2:1 ratio: one recruited from same hospitals, another from the neighbourhood of the case Exposure assessment method: in-person questionnaire, coffee frequency and amount considered	Urinary bladder	*Coffee consumption (cups/day)* 0 1 2 ≥ 3 Trend test *P* value, < 0.05	 35 24 16 24	 1.00 1.08 (NR) 4.45 (NR) 12 (NR)	Age, average cigarettes smoked	Strengths: case recruitment comparable to a population-based study Limitations: modest numbers, use of hospital-based controls that included disorders that may affect coffee intake (thus leading to potential biases that may inflate ORs), no confidence intervals presented, no history of coffee drinking considered

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciccone & Vineis (1988) Italy (Torino), 1978–1983	Cases: 512 hospital-based Controls: 594 hospital-based, patients with urological or surgical conditions (~20% from 'other surgical departments'; no other information provided), no information on matching to cases Exposure assessment method: in-person questionnaire (unclear validation), coffee history and frequency of intake	Urinary bladder	*Current consumption (cups/day): men*			Age, smoking status, lifelong use of cigarettes, high-risk occupations	Strengths: stratification by smoking Limitations: hospital-based (therefore concern about bias introduced), very small numbers for stratified analyses
			Non-drinker	88	1.0		
			1	93	0.8 (0.5–1.3)		
			2	122	1.0 (0.7–1.5)		
			3	122	1.2 (0.8–1.8)		
			≥ 4	87	0.8 (0.5–1.2)		
			Consumption (cups/day) 10 yr before diagnosis: men				
			Non-drinker	39	1.0		
			1	65	1.2 (0.7–2.1)		
			2	97	1.5 (0.9–2.5)		
			3	104	1.1 (0.7–1.8)		
			≥ 4	139	1.1 (0.6–1.8)		
			Current consumption (cups/day): women			Age, smoking status, lifelong use of cigarettes	
			Non-drinkers	8	1.0		
			1	17	1.4 (0.5–3.8)		
			2	12	1.0 (0.4–3.0)		
			3	8	0.7 (0.2–2.2)		
			≥ 4	7	0.8 (0.2–2.6)		
			Consumption (cups/day) 10 yr before diagnosis: women				
			0–1	16	1.0		
			2	13	0.9 (0.4–2.3)		
			3	8	0.5 (0.2–1.5)		
			≥ 4	15	1.4 (0.6–3.5)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciccone & Vineis (1988) (cont.)			*Current consumption (cups/day): non-smoking men*			Age, high-risk occupations	
			Non-drinker	3	1.0		
			1	6	1.1 (0.2–5.4)		
			2	5	1.9 (0.4–9.3)		
			3	5	4.4 (0.8–25.1)		
			Consumption (cups/day) 10 yr before diagnosis: non-smoking men			Age, smoking, high-risk occupations	
			Non-drinker	2	1.0		
			1	4	1.6 (0.2–10.4)		
			2	5	2.7 (0.4–17)		
			≥ 3	5	4.9 (0.8–31.6)		
			Current consumption (cups/day): non-smoking women			Age	
			Non-drinker	7	1.0		
			1	11	1.1 (0.4–3.3)		
			2	7	0.9 (0.3–3.2)		
			≥ 3	6	0.5 (0.1–1.5)		
		Urinary bladder: no information provided on histological types	*Consumption (cups/day) 10 yr before diagnosis: non-smoking women*				
			0–1	12	1.0		
			2	6	0.9 (0.3–2.6)		
			3	5	0.7 (0.2–2.2)		
			≥ 4	8	1.5 (0.6–3.5)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Risch et al. (1988) Canada (South Central Ontario), 1979–1982	Cases: 835 population-based, identified through hospital registries or regional tumour registry Controls: 781 population-based identified from population listings, matched by sex, birth year, area of residence Exposure assessment method: questionnaire, in-person interview (no information about validation), different types (ground, instant, instant decaffeinated, espresso) of coffee considered, frequency and lifetime use considered	Urinary bladder	*Ever coffee drinking of total coffee: men*			Lifetime smoking history (pack-years), history of diabetes	Strengths: large sample size, comprehensive questionnaire, consideration of non-smokers, different types of coffee and lifetime use Limitations: sample size not shown for different strata in analyses, no tests for trend shown
			Ever drinker	NR	0.86 (0.59–1.25)		
			Ever drinker, non-smokers	NR	1.69 (0.30–9.59)		
			Ever drinker, non-user of artificial sweetener	NR	0.64 (0.38–1.06)		
			Ever coffee drinking of total coffee: women				
			Ever drinker	NR	1.87 (1.03–3.40)		
			Ever drinker, non-smokers	NR	2.05 (0.69–6.15)		
			Ever drinker, non-user of artificial sweetener	NR	2.55 (1.05–6.22)		
			Average consumption of total coffee (cups/day): men				
			None	NR	1.00		
			> 1–3	NR	1.04 (0.76–1.41)		
			> 3–6	NR	1.15 (0.82–1.62)		
			> 6	NR	0.91 (0.58–1.44)		
			Total lifetime intake	NR	0.95 (0.85–1.06)		
			Average consumption of total coffee (cups/day): women				
			None	NR	1.00		
			> 1–3	NR	0.96 (0.57–1.61)		
			> 3–6	NR	1.85 (0.98–3.50)		
			> 6	NR	1.11 (0.46–2.71)		
			Total lifetime intake	NR	1.16 (0.88–1.53)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Risch et al. (1988) (cont.)			*Ever drinker of ground coffee: men*				
			Ever	NR	1.02 (0.78–1.33)		
			Total lifetime intake	NR	0.95 (0.85–1.08)		
			Ever drinker of ground coffee: women				
			Ever	NR	1.15 (0.75–1.76)		
			Total lifetime intake	NR	1.11 (0.83–1.48)		
			Ever drinker of instant coffee: men				
			Ever	NR	0.93 (0.74–1.18)		
			Total lifetime intake	NR	0.94 (0.83–1.07)		
			Ever drinker of instant coffee: women				
			Ever	NR	0.97 (0.65–1.47)		
			Total lifetime intake	NR	0.95 (0.73–1.25)		
			Ever drinker of instant decaffeinated coffee: men				
			Ever	NR	1.12 (0.83–1.51)		
			Total lifetime intake	NR	0.91 (0.76–1.10)		
			Ever drinker of instant decaffeinated coffee: women				
			Ever	NR	1.5 (0.90–2.52)		
			Total lifetime intake	NR	1.2 (0.87–1.67)		
			Ever drinker of espresso coffee: men				
			Ever	NR	1.64 (0.96–2.79)		
			Total lifetime intake	NR	1.29 (0.96–1.74)		
			Ever drinker of espresso coffee: women				
			Ever	NR	1.50 (0.59–3.78)		
			Total lifetime intake	NR	1.75 (0.91–3.39)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Slattery et al. (1988a) USA (Utah), 1977–1983	Cases: 332 population-based, cases identified through population-based cancer registry Controls: 686 population-based, identified through RDD or social security administration roster (Medicare), frequency matched by age and sex Exposure assessment method: questionnaire, in-person survey, lifetime coffee (only caffeinated)	Urinary bladder	*Caffeinated coffee (cups/wk)*			Smoking status (never, ex, current)	Possible overlap with Slattery et al. (1988b) Strengths: population-based, cases identified via registry Limitations: very unique population with majority of Mormons (distinctive coffee drinking and smoking habits)
			Never drinkers	NR	1.00		
			1–15	NR	1.32 (0.88–2.00)		
			16–30	NR	0.80 (0.50–1.26)		
			> 30	NR	1.28 (0.76–2.17)		
			Caffeinated coffee (cups/wk): never smokers			None	
			Never drinkers	NR	1.00		
			1–15	NR	1.42 (0.69–2.90)		
			16–30	NR	1.36 (0.55–3.35)		
			> 30	NR	1.50 (0.39–2.17)		
			Caffeinated coffee (cups/wk): smokers				
			Never drinkers	NR	1.00		
			1–15	NR	1.36 (0.88–2.10)		
			16–30	NR	0.88 (0.56–1.39)		
			> 30	NR	1.54 (0.98–2.44)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Slattery et al. (1988b) USA (Utah), 1977–1983	Cases: 419 population-based, identified through population-based cancer registry Controls: 889 population-based, identified through RDD or social security administration roster (Medicare), 2:1 ratio of controls to cases, frequency matched by age, sex Exposure assessment method: questionnaire, in-person survey, lifetime coffee (only caffeinated)	Urinary bladder	*Consumption of caffeinated coffee, number of 8 oz servings (~1 cup)/wk*			Age, sex, diabetes, bladder infections, cigarette smoking (smoking status, pack-years)	Strengths: population-based, cases identified via registry Limitations: very unique population with majority of Mormons (distinctive coffee drinking and smoking habits)
			0	164	1.00		
			1–20	99	1.23 (0.88–1.72)		
			21–40	93	1.05 (0.73–1.51)		
			> 40	58	1.60 (1.00–2.56)		
			Consumption of caffeinated coffee, number of 8 oz servings (~1 cup)/wk				
			0	354	1.00		
			≥ 1	62	1.04 (0.73–1.48)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Clavel & Cordier (1991) France 1984–1987	Cases: 781 hospital-based Controls: 781 hospital-based controls, identified in same hospitals as cases (non-cancer, no symptoms of bladder cancer), matched by sex, age, place of residence Exposure assessment method: in-person questionnaire, different types (regular, instant, caffeinated, decaffeinated) of coffee considered, history of consumption (average daily consumption since age 18)	Urinary bladder	*Average daily coffee consumption (cups/day): men and women*			Age, hospital, residence, smoking status	Strengths: large sample size, several types of coffee studied Limitations: hospital-based, 21% of controls had gastrointestinal disease and 30% men with heart disease problems (which may affect coffee intake), sample sizes too small for stratified analyses (too many cells with number of subjects < 10), no combined analyses shown
			0	12	1.00		
			1–4	488	1.24 (0.56–2.74)		
			5–7	61	1.46 (0.6–3.51)		
			> 7	27	2.94 (1.06–8.15)		
			Average daily coffee consumption (cups/day): non-smoking women			Age, hospital, residence	
			0	3	1.00		
			1	7	1.00		
			2	16	0.99 (0.34–2.93)		
			3	13	1.51 (0.48–4.74)		
			> 3	15	2.29 (0.59–8.86)		
			Average daily coffee consumption (cups/day): non-smoking men				
			0	1	1.00		
			1	3	0.97 (0.08–11.43)		
			2	9	2.93 (0.31–30.35)		
			≥ 3	29	5.10 (0.59–43.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
D'Avanzo et al. (1992) Italy (Milan), 1985–1990	Cases: 555 hospital-based from Milan and Pordenone Controls: 855 hospital-based, recruited in same hospitals as cases (no urological and non-cancer patients, no specific diseases excluded were listed) Exposure assessment method: validated in-person questionnaire, regular and decaffeinated coffee	Urinary bladder	*Regular coffee duration of drinking (yr), both sites combined*			Age, sex, education level, smoking (status, cigarettes/ day), alcohol, occupation	Same design as La Vecchia et al. (1989a) so probably some overlap of cases Strengths: validated questionnaire, consideration of duration of drinking Limitations: possible bias introduced by use of hospital-based controls, many of whom may have had disease that affect coffee intake
			Non-drinkers	71	1.0		
			< 30	219	1.2 (0.9–1.7)		
			≥ 30	267	1.4 (0.9–2.2)		
			Trend test *P* value, < 0.05				
			Regular coffee drinking status, both sites combined				
			Non-drinkers	71	1.0		
			Drinkers	484	1.3 (1.0–1.8)		
			Trend test *P* value, > 0.05				
			Regular coffee drinking frequency (cups/day), both sites combined				
			Non-drinkers	71	1.0		
			1	126	1.2 (0.8–1.7)		
			2	167	1.4 (0.9–2.0)		
			3	109	1.5 (1.0–2.2)		
			≥ 4	82	1.4 (0.9–2.2)		
			Trend test *P* value, > 0.05				
			Decaffeinated coffee drinking status, both sites combined				
			Non-drinkers	519	1.0		
			Drinkers	39	1.5 (0.9–2.4)		
			Trend test *P* value, > 0.05				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nomura et al. (1991) USA (Hawaii), 1977–1986	Cases: 261 population-based, identified at 7 hospitals Controls: 522 population-based, identified from state survey, matched to cases by sex, ethnic group, age, residence Exposure assessment method: validated in-person questionnaire, frequency and quantity of coffee (regular, decaffeinated, brewed, instant, and all combinations of these) considered	Urinary bladder	*Coffee consumption, all types (cup-years): men*			Pack-years of smoking	Strengths: validated and thorough coffee drinking assessment, including years of consumption Limitations: no adjustment for race, analyses of different coffee types not adjusted for each other
			Non-drinker	7	1.0		
			Drinker	188	0.8 (0.3–2.0)		
			1–49	34	0.6 (0.2–1.6)		
			50–109	74	0.9 (0.4–2.3)		
			≥ 110	80	1.0 (0.4–2.7)		
			Trend test *P* value, 0.12				
			Coffee consumption, regular ground (cup-years): men				
			Non-drinker	10	1.0		
			Drinker	185	0.9 (0.4–2.0)		
			1–39	46	0.9 (0.4–2.0)		
			40–89	58	0.9 (0.4–2.1)		
			≥ 90	81	1.0 (0.4–2.3)		
			Trend test *P* value, 0.72				
			Coffee consumption, instant (cup-years): men				
			Non-drinker	106	1.0		
			Drinker	89	1.0 (0.7–1.4)		
			1–14	37	0.8 (0.5–1.3)		
			≥ 15	52	1.2 (0.8–1.9)		
			Trend test *P* value, 0.26				
			Coffee consumption, instant decaffeinated (cup-years): men				
			Non-drinker	144	1.0		
			Drinker	51	1.3 (0.8–2.0)		
			1–4	26	1.5 (0.8–2.6)		
			≥ 5	25	1.1 (0.6–1.9)		
			Trend test *P* value, 0.82				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nomura et al. (1991) (cont.)			*Coffee consumption, all types (cup-years): women*				
			Non-drinker	6	1.0		
			Drinker	60	0.8 (0.3–2.6)		
			1–49	24	0.9 (0.3–2.9)		
			50–109	24	0.9 (0.2–2.9)		
			≥ 110	12	0.5 (0.5–2.1)		
			Trend test *P* value, 0.26				
			Coffee consumption, regular ground (cup-years): women				
			Non-drinker	9	1.0		
			Drinker	57	0.7 (0.2–1.9)		
			1–39	20	0.7 (0.2–2.1)		
			40–89	29	0.8 (0.3–3.6)		
			≥ 90	8	0.3 (0.1–1.0)		
			Trend test *P* value, 0.02				
			Coffee consumption, instant (cup-years): women				
			Non-drinker	32	1.0		
			Drinker	34	1.8 (0.9–3.3)		
			1–14	22	1.8 (0.9–3.7)		
			≥ 15	12	1.6 (0.6–4.0)		
			Trend test *P* value, 0.46				
		Urinary bladder: 98% bladder cancer, 83% of which were SCC or TCC	*Coffee consumption, instant decaffeinated (cup-years): women*				
			Non-drinker	53	1.0		
			Drinker	13	0.6 (0.3–1.2)		
			1–4	7	0.5 (0.2–1.4)		
			≥ 5	6	0.6 (0.2–1.6)		
			Trend test *P* value, 0.3				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Escolar Pujolar et al. (1993) Spain (Cadiz, Barcelona, Madrid, Guipuzkoa, Bizcaya), 1983–1986	Cases: 497 hospital-based but with good population coverage, 51% identified using registries Controls: 1113, ~50% hospital-based (excluding urological, diabetes, heart or circulatory, cancer of respiratory or upper gastrointestinal tract), matched for sex, age, province of residence; other ~50% were population-based controls identified from electoral rolls Exposure assessment method: in-person questionnaire, unclear validation, coffee (regular, instant, decaffeinated) history/ frequency considered	Urinary bladder	*Coffee consumption status and frequency (cups/wk): men*			Smoking (cigarettes/day), occupation, consumption of artificial sweeteners, age, province of residence Smoking status, consumption of artificial sweeteners, age, province of residence	Strengths: adequate sample size, comprehensive assessment of coffee drinking (taking into account frequency, amount, and duration), stratification by smoking Limitations: use of hospital-based controls may introduce bias, very small numbers for stratified analyses by smoking
			Non-drinker (reference)	34	1.00		
			Ex-drinker	42	1.22 (0.69–2.15)		
			Current drinker	362	0.96 (0.62–1.49)		
			Drinker	404	0.98 (0.64–1.52)		
			2–7	138	0.99 (0.63–1.57)		
			8–14	130	0.95 (0.59–1.51)		
			≥ 15	135	1.02 (64.0–1.63)		
			Coffee consumption status and frequency (cups/wk): women				
			Non-drinker (reference)	5	1.00		
			Ex-drinker	6	0.87 (0.20–3.77)		
			Current drinker	48	0.98 (0.31–3.14)		
			2–7	17	1.02 (0.29–3.58)		
			8–14	24	1.14 (0.34–3.85)		
			≥ 15	13	0.71 (0.20–2.56)		
			Coffee lifelong consumption in cups (thousands): women				
			0	3	1.00		
			1–10	6	1.47 (0.29–7.58)		
			10–20	13	1.80 (0.41–7.90)		
			20–30	9	2.03 (0.43–9.70)		
			30–40	10	1.47 (0.31–6.89)		
			≥ 40	12	1.39 (0.31–6.25)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Escolar Pujolar et al. (1993) (cont.)			*Coffee consumption status and frequency (cups/wk): non-smoking men*			Smoking (cigarettes/day), occupation, consumption of artificial sweeteners, age, province of residence	
			Non-drinker	3	1.00		
			Ex-drinker	1	0.61 (0.06–6.26)		
			Current drinker	24	2.78 (0.78–9.87)		
			Drinker	25	2.41 (0.68–8.46)		
			2–7	10	2.22 (0.57–8.66)		
			8–14	10	3.11 (0.79–12.27)		
			≥ 15	5	1.87 (0.41–8.47)		
			Coffee lifelong consumption in cups (thousands): men				
			0 cups	28	1.00		
			1–10	70	1.09 (0.63–1.87)		
			10–20	86	0.91 (0.54–1.54)		
			20–30	69	1.11 (0.65–1.90)		
			30–40	52	0.99 (0.56–1.74)		
			≥ 40	128	1.14 (0.69–1.90)		
			Coffee lifelong consumption in cups (thousands): non-smoking men				
			0 cups	3	1.00		
			1–10	5	1.74 (0.38–7.95)		
			10–20	6	2.42 (0.55–10.66)		
			20–30	5	2.67 (0.57–12.45)		
			30–40	4	3.67 (0.70–19.25)		
			≥ 40	5	2.08 (0.44–9.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) USA (west New York), 1979–1985	Cases: 351 hospital-based, recruited at most hospitals in the area (Buffalo, Niagara Falls, Rochester) Controls: 855 population-based neighbourhood controls in same counties as cases Exposure assessment method: in-person questionnaire, validated for some of the factors via telephone recalls, coffee (regular, decaffeinated, instant, perk) frequency only	Urinary bladder: TCC	*Coffee consumption (cups/day)*			Age, education, cigarette smoking (pack-years), other liquids, sodium, carotene, calories	Strengths: adequate sample size, use of population-based controls, hospital-based cases with ample catchment area (comparable to population-based cases) Limitations: no history of coffee consumption recorded, patients too ill to participate or deceased were not included, many controls declined to participate because the survey was too long
			0–1	60	1.0		
			2	62	1.3 (0.8–2.0)		
			3–4	114	1.6 (1.1–2.3)		
			≥ 5	115	2.1 (1.3–3.2)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) for non-smokers aged > 65 yr				
			0–1	NR	1.0		
			2	NR	2.3		
			3–4	NR	3.3		
			≥ 5	NR	6.4		
			Trend test *P* value, 0.02				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) (cont.)			*Coffee consumption (cups/day) by coffee type: men*			Age, education	
			0–1, any type	60	1.0		
			2–4 decaffeinated, instant	25	1.8 (1.0–3.2)		
			≥ 5 decaffeinated, instant	2	0.4 (0.9–1.8)		
			2–4 decaffeinated, perk	8	1.0 (0.5–2.4)		
			≥ 5 decaffeinated, perk	7	2.8 (1.0–7.8)		
			2–4 regular, instant	29	1.5 (0.9–2.5)		
			≥ 5 regular, instant	19	1.6 (0.9–3.0)		
			2–4 regular, perk	114	1.5 (1.0–2.1)		
			≥ 5 regular, perk	87	2.5 (1.7–3.8)		
			Coffee consumption (cups/day) among those aged < 65 yr			Age, education, cigarette smoking pack-years, other liquids, sodium, carotene, calories	
			0–1	NR	1.0		
			2	NR	1.3 (0.7–2.7)		
			3–4	NR	1.4 (0.7–2.6)		
			≥ 5	NR	1.9 (1.0–3.7)		
			Trend test *P* value, 0.03				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) (cont.)			*Coffee consumption (cups/day) among those aged > 65 yr*				
			0–1	NR	1.0		
			2	NR	1.3 (0.7–2.2)		
			3–4	NR	1.7 (1.0–2.8)		
			≥ 5	NR	2.2 (1.2–4.1)		
			Trend test *P* value, < 0.01				
			Coffee consumption (cups/day) among non-smokers aged < 65 yr				
			0–1	NR	1.0		
			2	NR	0.6		
			3–4	NR	1.0		
			≥ 5	NR	1.6		
			Trend test *P* value, 0.08				
Momas et al. (1994) France (Herault district), 1987–1989	Cases: 219 population-based, identified via cancer registry Controls: 792 population-based selected via electoral rolls Exposure assessment method: in-person or mailed questionnaire, duration and changes in coffee intake	Urinary bladder	*Lifelong coffee drinking (cups)*			Lifelong tobacco smoking (cigarettes equivalent), spice consumption, age, occupation, residence, vegetable consumption, lifelong alcohol drinking, birthplace, saccharin	Strengths: population-based study, consideration of coffee duration Limitations: very small numbers for reference category used, only considered lifelong coffee intake (not frequency)
			< 365	8	1.0		
			365–25 000	36	1.6 (0.6–3.8)		
			25 001–60 000	59	1.6 (0.6–3.8)		
			> 60 000	58	4.1 (1.7–10.0)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bruemmer et al. (1997) USA (Washington), 1987–1990	Cases: 262 population-based cases identified via cancer registry (SEER) Controls: 405 population-based, identified via RDD Exposure assessment method: telephone interview questionnaire, coffee (regular, decaffeinated) frequency and amount of intake considered only	Urinary bladder: invasive or non-invasive (in situ or papillary)	*Coffee consumption (cups/day): women*			Age, county, smoking status (never, former, current)	Pack-years was not found to be a confounder, so it was not added Strengths: population-based, consideration of decaffeinated Limitations: modest numbers (especially for women), no consider of duration of intake or amounts, participants < 65 yr
			None	11	1.0		
			≤ 3	21	0.5 (0.2–1.2)		
			> 3–6	20	0.5 (0.5–1.3)		
			> 6	8	0.6 (0.2–1.9)		
			Trend test *P* value, 0.46				
			Coffee consumption (cups/day): men				
			None	24	1.0		
			≤ 3	50	1.1 (0.5–2.1)		
			> 3–6	77	1.7 (0.9–3.4)		
			> 6	51	1.2 (0.6–2.3)		
			Trend test *P* value, 0.38				
			Decaffeinated coffee consumption: women				
			≤ 1 cup/mo	39	1.0		
			> 1 cup/mo – 1 cup/wk	12	1.6 (0.7–3.6)		
			> 7 cups/wk	9	2.1 (0.8–5.3)		
			Trend test *P* value, 0.08				
			Decaffeinated coffee consumption: men				
			≤ 1 cup/mo	148	1.0		
			> 1 cup/mo – 1 cup/wk	31	1.4 (0.8–2.6)		
			> 7 cups/wk	23	0.9 (0.5–1.8)		
			Trend test *P* value, 0.85				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Donato et al. (1997) Italy (Brescia), 1991–1992	Cases: 172 hospital-based Controls: 578 hospital-based identified from three hospitals (prostate adenoma, urolithiasis, obstructive uropathy), male controls were age-matched (not possible for women) Exposure assessment method: in-person validated questionnaire, coffee quantity and frequency considered	Urinary bladder	*Coffee consumption status and frequency:* women			Age, residence, education, date of interview, smoking (lifetime cigarettes smoked), alcohol	Strengths: good representation of underlying case population Limitations: hospital-based controls (not clear if the diseases included may affect coffee intake), very tiny numbers for stratified analyses by sex (women)
			Non-drinker	2	1.0		
			Ex-drinker	0	–		
			Current drinker	35	5.2 (1.0–30.4)		
			1–2 cups/day	27	4.3 (0.8–23.9)		
			3–4 cups/day	8	4.9 (0.7–33.0)		
			Coffee consumption status and frequency: men				
			Non-drinker	7	1.0		
			Ex-drinker	6	2.7 (0.7–10.3)		
			Current drinker	122	2.6 (1.1–6.1)		
			1–2 cups/day	66	2.3 (0.9–5.6)		
			3–4 cups/day	44	2.8 (1.1–7.4)		
			≥ 5 cups/day	11	4.5 (1.2–16.8)		
			Trend test *P* value, > 0.1				
Pohlabeln et al. (1999) Germany (Hesse), 1989–1992	Cases: 300 hospital-based Controls: 300 hospital-based (identified from same hospitals as cases), matched to cases on sex, age, area of residence Exposure assessment method: questionnaire, in-person interview, coffee frequency and amount considered	Urinary bladder	*Coffee amount: men and women*			Smoking status and pack-years	With more thorough adjustment for smoking, weaker ORs were observed for coffee intake. Restricting analyses to urinary bladder yielded similar results. Strengths: thorough adjustment by smoking, stratification by smoking Limitations: hospital-based (therefore concerns about potential bias), very small number of women
			Heavy consumption	NR	1.52 (0.39–5.93)		
			Coffee frequency (cups/day): men				
			≤ 1	53	1.00		
			2–4	128	1.51 (0.95–2.39)		
			≥ 5	58	1.59 (0.87–2.91)		
			Coffee frequency (cups/day): women				
			≤ 1	11	1.00		
			2–4	40	1.28 (0.50–3.31)		
			≥ 5	10	1.25 (0.29–5.30)		
			Coffee frequency (cups/day): non-smokers			NR	
			≤ 1	8	1.00		
			2–4	15	2.29 (0.82–6.36)		
			≥ 5	1	0.69 (0.07–6.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Geoffroy-Perez & Cordier (2001) France, 1984–1987	Cases: 765 hospital-based Controls: 765 hospital-based (free of cancer, respiratory diseases, and bladder cancer symptoms), matched to cases based on hospital, sex, age, area of residence Exposure assessment method: questionnaire, in person interview, drinking history, frequency and amounts	Urinary bladder	*Frequency of coffee intake (mL/wk): men*			Age, centre, place of residence, smoking status, pack-years	Strengths: large sample size, duration of drinking was taking into account Limitations: concern about controls with disease that may affect coffee intake (GI diseases, cardiovascular)
			≤ 1050	83	1.00		
			1051–2050	116	1.45 (0.97–2.16)		
			2051–2400	133	1.54 (1.04–2.28)		
			2401–2800	127	1.62 (1.08–2.40)		
			> 2800	134	1.42 (0.94–2.14)		
			Trend test *P* value, 0.14				
			Frequency of coffee intake (mL/wk): women			Age, centre, place of residence, smoking status	
			≤ 1150	20	1.00		
			1151–2100	38	1.40 (0.63–3.12)		
			2101–2600	28	1.25 (0.53–2.98)		
			> 2600	19	0.74 (0.28–1.96)		
			Trend test *P* value, 0.63				
			Frequency of coffee intake (mL/wk): non-smoking women			Age, centre, place of residence	
			≤ 1100	13	1.00		
			1101–2100	25	1.67 (0.66–4.21)		
			2101–2550	9	1.11 (0.35–3.51)		
			> 2550	19	1.28 (0.45–3.63)		
			Trend test *P* value, 0.69				
			Frequency of coffee intake (mL/wk): non-smoking men				
			≤ 1050	7	1.00		
			1051–2050	8	1.41 (0.43–4.65)		
			2051–2600	28	3.78 (1.36–10.47)		
			> 2600	11	2.49 (0.73–8.49)		
			Trend test *P* value, 0.02				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Woolcott et al. (2002) Canada, 1992–1994	Cases: 927 population-based, identified via registry Controls: 2494 hospital-based, identified through RDD, frequency matched to cases on age and sex distribution of the combined case series (bladder, colon, rectum) Exposure assessment method: mailed questionnaire, coffee (brewed, iced) considered	Urinary bladder: ICD-9 188	*Coffee frequency (cups/day) for all individuals*			Age, sex, education level, smoking (ever, current, cumulative, intensity), energy intake, calcium, fibre, beer	Strengths: population-based, large sample size Limitations: controls were matched to other cancer cases, few cases were non-smokers
			< 1	150	1.00		
			1–2	320	1.03 (0.81–1.32)		
			3–4	278	0.88 (0.68–1.13)		
			≥ 5	165	1.06 (0.79–1.42)		
			Trend test *P* value, 0.76				
			Coffee frequency (cups/day): never smokers				
			< 1	NR	1.00		
			1–2	NR	1.46 (0.91–2.35)		
			3–4	NR	1.25 (0.73–2.13)		
			≥ 5	NR	1.84 (0.80–4.22)		
			Trend test *P* value, 0.23				
			Coffee frequency (cups/day): ever smokers				
			< 1	NR	1.00		
			1–2	NR	0.90 (0.67–1.20)		
			3–4	NR	0.77 (0.58–1.03)		
			≥ 5	NR	0.92 (0.66–1.27)		
			Trend test *P* value, 0.39				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Radosavljević et al. (2003) Serbia, 1997–1999	Cases: 130 hospital-based Controls: 130 hospital-based (no urological malignancies or diseases that change diet), same hospital as cases, matched 1:1 by sex, age, place of residence Exposure assessment method: FFQ, unclear validation and administration, patterns of consumption and changes in diet in the past 10 yr considered	Urinary bladder: 93% TCC	*Coffee intake* *Coffee intake*	NR NR	1.46 (1.05–2.01) 1.55 (1.24–1.94)	Smoking soda, spirit, mineral water, skim milk, yogurt, frequency of daily urination Smoking	Limitations: hospital-based, concern about controls; units of coffee intake not clear
Ugnat et al. (2004) Canada (British Columbia, Alberta, Saskatchewan, Manitoba), 1994–1997	Cases: 549 population-based controls identified as part of a larger population-based study (NECSS) Controls: 1099 population-based matched to cases by distribution of age, identified randomly from health insurance plan lists or RDD Exposure assessment method: mailed questionnaire, unclear validation	Urinary bladder	*Coffee consumption* < 1 cup/mo ≥ 1 cup/mo – ≤ 1 cup/day 2–3 cups/day ≥ 4 cups/day Trend test *P* value, 0.0001 *Coffee frequency (cups/day): non-smokers* < 4 > 4	 34 89 214 210 NR NR	 1.00 1.13 (0.69–1.83) 1.56 (0.99–2.46) 1.77 (1.11–2.82) 1.00 6.17 (1.73–21.96)	Age, province, education, pack-years of smoking, tea NR	Strengths: population-based, adequate sample Limitations: no consideration of duration of intake of coffee, not clear if test of trend corresponds to adjusted or unadjusted model

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wakai et al. (2004) Japan (Nagoya), 1994–2000	Cases: 124 hospital-based cases identified from database of outpatients Controls: 620 hospital-based, randomly selected from outpatients in database without cancer, matched by age, sex, year of visit Exposure assessment method: self-administered questionnaire but checked by interviewer, frequency of coffee intake	Urinary bladder: 90% TCC	*Coffee consumption (cups/day)* Almost never Occasionally 1 2 ≥ 3 Trend test *P* value, 0.68	 26 23 28 26 21	 1.00 0.93 (0.52–1.66) 0.82 (0.47–1.44) 1.07 (0.59–1.94) 1.14 (0.58–2.23)	Age, sex, year of first visit, pack-years cigarette smoking	Less than 3% of cases drank high levels of coffee Limitations: hospital-based, (therefore potential for bias among controls depending on cause of outpatient visit), no lifetime consumption of coffee considered, few confounders considered
De Stefani et al. (2007) Uruguay, 1996–2000	Cases: 255 hospital-based Controls: 501 hospital-based (excluding diseases related to tobacco, alcohol or recent changes in diet), identified at same hospital as cases, frequency matched by age, sex, and residence Exposure assessment method: in-person questionnaire, coffee drinking history considered	Urinary bladder: TCC	*Coffee with milk (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, 0.01 *Pure coffee consumption (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, 0.03 *Total coffee consumption (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, < 0.01	 135 70 24 135 22 15 135 84 36	 1.0 1.5 (1–2.2) 1.9 (1–3.7) 1.0 1.6 (0.8–3.1) 2.0 (0.9–4.4) 1.0 1.5 (1.1–2.2) 2.1 (1.2–3.6)	Age, sex, residence, urban/rural status, family history of bladder cancer, BMI, occupation, smoking status, years since quitting smoking, number of cigarettes smoked per day, mate, soft drinks, milk, tea	Some overlap in patients between this study and that by Balbi et al. (2001) Limitations: data regarding drinking history mentioned but not provided

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Covolo et al. (2008) Italy (Brescia), 1997–2000	Cases: 197 hospital-based Controls: 211 hospital-based, identified at same hospital as cases (patients with urological non-neoplastic diseases), frequency matched to cases on age, period of recruitment, and hospital Exposure assessment method: in-person questionnaire, coffee (with milk, cappuccino, decaffeinated) lifetime consumption	Urinary bladder	*Coffee consumption (cups/day)* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): heavy smokers* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): non-smokers* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): light smokers* Non-drinkers 1–3 > 3	 26 125 77 12 86 27 5 10 2 9 29 17	 1.00 0.76 (0.41–1.41) 1.25 (0.59–2.67) 1.00 1.45 (0.56–3.70) 1.46 (0.49–4.36) 1.00 0.42 (0.01–1.77) 0.35 (0.04–2.99) 1.00 0.47 (0.16–1.35) 3.04 (0.77–11.97)	Age, education, PAHs and AA exposure, cumulative lifetime smoking (pack-years)	Genotype data also collected: GSTM1, GSTT1, GSTP1, NAT1, NAT2, SULTIA1, XRCC1–3, XPD. Combined estimates of genotypes and coffee were presented, but no tests of interaction. Strengths: Lifetime history of coffee use Limitations: Hospital-based controls (therefore concern about possible bias introduced by changes in coffee consumption), very small numbers in stratified analyses by smoking, very modest sample size for GxE interaction analyses

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jiang et al. (2008) USA (Los Angeles), 1987–1999	Cases: 1586 population-based, identified via cancer registry (SEER) Controls: 1586 population-based, identified via neighbourhoods of cases, matched to cases by age, sex, and race Exposure assessment method: in-person questionnaire, both regular and decaffeinated coffee considered	Urinary bladder	*Coffee consumption (cups/day)* 0 < 1 1–2 3–4 5–6 ≥ 7 Trend test *P* value, 0.052	 129 49 501 467 226 210	 1.00 1.15 (0.71–1.85) 1.04 (0.78–1.38) 1.21 (0.89–1.64) 1.19 (0.95–1.68) 1.38 (0.95–2.00)	Level of education, use of NSAIDs, intake of carotenoids, years as hairdresser/ barber, cigarette smoking status, duration of smoking, intensity of smoking, age, sex, race	Strengths: population-based, large sample size Limitations: no long-term history of consumption of coffee, only recent (2 yr before diagnosis)
Villanueva et al. (2009) Spain (Barcelona, Valles/Bages, Alicante, Tenerife, Asturias), 1998–2001	Cases: 1219 hospital-based Controls: 1271 hospital-based, identified from same hospitals as cases (disease unrelated to bladder cancer risk factors), individually matched to cases by sex, age and residence Exposure assessment method: questionnaire, computer-assisted interview, coffee assessment included age started and stopped drinking, and average intake per day during adult life	Urinary bladder	*Coffee consumption (cups/day)* Never Ever 1 2 3 ≥ 4 Trend test *P* value, 0.082 *Coffee consumption (cups/day): current smokers* Never Ever 1 2 3 ≥ 4 Trend test *P* value, 0.559	 120 1016 336 303 223 154 46 468 130 143 105 90	 1.00 1.25 (0.95–1.64) 1.24 (0.92–1.66) 1.11 (0.82–1.51) 1.57 (1.13–2.19) 1.27 (0.88–1.81) 1.00 1.20 (0.72–2.01) 1.14 (0.65–2.00) 1.20 (0.68–2.09) 1.39 (0.77–2.53) 1.13 (0.61–2.09)	Age, sex, area, intensity of smoking (cigarettes/day)	Strengths: large sample size, large representation of hospitals in this area, coffee drinking history Limitations: hospital-based controls could induce bias if they altered coffee drinking due to disease (does not seem likely in this case)

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villanueva et al. (2009) (cont.)			*Coffee consumption (cups/day): former smokers*				
			Never	34	1.00		
			Ever	423	1.85 (1.16–2.95)		
			1	152	1.92 (1.16–3.17)		
			2	128	1.62 (0.97–2.70)		
			3	94	2.36 (1.36–4.11)		
			≥ 4	49	1.57 (0.86–2.90)		
			Trend test *P* value, 0.176				
			Coffee consumption (cups/day): never smokers				
			Never	40	1.00		
			Ever	125	0.85 (0.53–1.35)		
			1	54	0.91 (0.53–1.56)		
			2	32	0.61 (0.34–1.10)		
			3	24	1.06 (0.53–2.13)		
			≥ 4	15	1.23 (0.55–2.76)		
			Trend test *P* value, 0.961				
Wang et al. (2013a) USA (Houston, Texas), 1999–ongoing	Cases: 1007 hospital-based Controls: 1299 clinic-based, identified at clinics in the area for annual health check-ups Exposure assessment method: in-person questionnaire, coffee (regular, decaffeinated) frequency and amount	Urinary bladder: TCC	*Frequency of all coffee intake (servings/day)*			Age, sex, ethnicity, energy intake, smoking status	Assessed polymorphisms in UGT enzymes Strengths: large sample size Limitations: no lifetime history of coffee assessed
			Never	155	1.00		
			0.1–1.9	271	1.13 (0.87–1.47)		
			≥ 2	581	1.14 (0.90–1.46)		
			Trend test *P* value, 0.336				
			Frequency of regular coffee intake (servings/day)				
			Never	288	1.00		
			0.1–1.9	235	0.91 (0.72–1.15)		
			≥ 2	484	0.92 (0.74–1.13)		
			Trend test *P* value, 0.426				
			Frequency of decaffeinated coffee intake (servings/day)				
			Never	717	1.00		
			0.1–1.9	94	1.75 (1.28–2.41)		
			≥ 2	196	1.37 (1.09–1.73)		
			Trend test *P* value, 0.001				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Turati et al. (2015) Italy (Aviano, Pordenone, Milan, Naples, Catania), 2003–2014	Cases: 690 hospital-based Controls: 655 hospital-based (with acute, non-neoplastic diseases unrelated to smoking and alcohol or long-term diet changes) identified from same network of hospitals as cases, matched by study centre, sex, and age Exposure assessment method: in-person questionnaire, coffee (regular, cappuccino, decaffeinated) frequency of consumption, age at starting and quitting, changes in drinking during life, and average lifetime coffee drinking estimated	Urinary bladder	*Average lifetime coffee drinking (cups/day)*			Age, sex, study centre, year of interview, smoking (status and cigs/day among current smokers)	Strengths: thorough exposure assessment Limitations: use of hospital-based controls, although it is noted that most diseases among controls seem unrelated to coffee intake
			0 to < 1	57	1.00		
			1 to < 2	142	1.30 (0.83–2.03)		
			2 to < 3	166	0.90 (0.58–1.38)		
			3 to < 4	149	1.16 (0.74–1.82)		
			≥ 4	176	1.73 (1.08–2.77)		
			1 cup/day increase	NR	1.06 (0.99–1.14)		
			Trend test *P* value, 0.049				
			Coffee drinking status				
			Never	30	1.00		
			Ex	42	1.21 (0.61–2.40)		
			Current	618	1.25 (0.74–2.10)		
			Lifetime coffee drinking (1 cup/day increase) by age			Age, sex, study centre, year of interview, tobacco smoking, education, alcohol, BMI, family history of bladder cancer, history of cystitis	
			Age < 65 yr	NR	1.09 (0.99–1.21)		
			Age > 65 yr	NR	1.05 (0.95–1.16)		
			Lifetime coffee drinking (1 cup/day increase) by sex				
			Men	NR	1.05 (0.98–1.14)		
			Women	NR	1.14 (0.90–1.45)		
			Lifetime coffee drinking (1 cup/day increase) by smoking status				
			Never smokers	NR	1.18 (0.96–1.46)		
			Ex-smokers	NR	1.07 (0.97–1.19)		
			Current smokers	NR	1.03 (0.92–1.15)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Turati et al. (2015) (cont.)			*Duration of coffee drinking (yr)*			Age, sex, study centre, year of interview, smoking (status and cigarettes/day among current smokers)	
			≤ 35	146	1.00		
			36–44	172	1.13 (0.79–1.63)		
			45–51	174	1.17 (0.79–1.72)		
			≥ 52	185	1.20 (0.80–1.79)		
			10-yr increase	NR	1.03 (0.95–1.13)		
			Coffee drinking frequency (cups/day)				
			0 to < 1	99	1.00		
			1 to < 2	128	1.13 (0.77–1.68)		
			2 to < 3	161	0.86 (0.60–1.24)		
			3 to < 4	146	1.15 (0.78–1.69)		
			≥ 4	156	1.28 (0.85–1.94)		
			1 cup/day increase	NR	1.03 (0.96–1.10)		
			Trend test *P* value, 0.305				
			Age at starting drinking (yr)				
			< 20	267	1.00		
			≥ 20	380	1 (0.78–1.28)		

AA, aromatic amines; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; GI, gastrointestinal; ICD, International Classification of Disease; mo, month(s); NECSS, Canadian National Enhanced Cancer Surveillance System; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; RDD, random-digit dialling; RR, relative risk; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology and End Results; TCC, transitional cell carcinoma; UGT, UDP-glucuronosyltransferase; vs, versus; wk, week(s); yr, year(s)

between coffee intake and risk of cancer of the bladder. In reviewing the literature, the Working Group considered the following criteria when determining which studies would be informative for evaluation of the association between risk of bladder cancer and coffee consumption.

1. Sample size, which impacts statistical power. As there were a large number of studies published on this topic, the Working Group focused its review on studies had a minimum of 100 cases.
2. Case and control selection: hospital-based versus population-based control selection. Depending on the inclusion criteria for hospital controls, these individuals may have diseases that could potentially lead to modification in coffee intake, making them less representative of the underlying population to which the cases should be compared, and therefore result in selection biases. In particular, studies that included hospital-based controls with gastrointestinal diseases and cardiovascular disorders were considered potentially problematic. The Working Group considered whether studies had specifically listed which diseases were included among hospital-based controls, or provided some indication that diseases that may affect coffee intake had been excluded. The Working Group gave more weight to population-based studies.
3. Adjustment for potential confounding factors, in particular tobacco smoking. Given that smoking is a strong risk factor for bladder cancer and tends to be highly correlated with coffee intake in many populations, the Working Group considered only studies that evaluated smoking variables as possible confounders. Although adjustment for other confounders was also favourably considered and noted (e.g. occupational exposure), none of the other risk factors were deemed as important as tobacco smoking.

Based on the criteria described above, of the 64 studies identified: seven studies were excluded due to having a case sample size of < 100 (Sullivan, 1982; Mommsen et al., 1983a; González et al., 1985; Restrepo et al., 1989; Bento & Barros, 1997; Lu et al., 1999; Kobeissi et al., 2013); one study was excluded because no potential confounders were considered (Demirel et al., 2008); four studies were excluded because risk estimates were not reported (Morgan & Jain, 1974; Mommsen et al., 1983b; Wynder et al., 1985; Akdaş et al., 1990); one study was excluded because smoking was not adjusted for (Bravo et al., 1986); one study was excluded because no units were provided for the estimates of association (Boada et al., 2015); and five studies were excluded because they included cases and controls already included in other studies (Bross & Tidings, 1973; Mettlin & Graham, 1979; Marrett et al., 1983; Ohno et al., 1985; La Vecchia et al., 1989a).

The Working Group organized studies for discussion into four main groups defined in Sections 2.1.2 (a)–(d). Given that studies with larger sample sizes are likely to be more informative, larger studies are described first followed by studies with smaller sample sizes.

(a) Population-based studies

The population-based case–control studies that reported results for coffee intake and were considered informative by the Working Group are described in the following. These studies were given more weight in the evaluation than those described in Section 2.1.1 (b)–(d).

Hartge et al. (1983) conducted a study in the USA (2982 cases, 5782 controls) that reported a positive association between ever drinking coffee and risk of bladder cancer among men (OR, 1.6; 95% CI, 1.2–2.2), women (OR, 1.2; 95% CI, 0.8–1.7) and for both combined (OR, 1.4; 95% CI, 1.1–1.8). When various levels of coffee consumption were considered, the only statistically significant association was for men drinking over 63 cups of coffee per week (OR, 1.5; 95%

CI, 1.1–1.9) [equivalent to roughly 9 cups/day]. No dose–response relationship was evident for either men or women. Similarly, there was no association with duration of coffee drinking. When stratifying men by smoking status, no differences in the magnitude of estimates were observed when comparing ever drinkers to never drinkers. However, when comparing drinkers of large quantities to drinkers of smaller quantities (≤ 49 cups/week), a stronger significant positive association was observed among never smokers [numbers of subjects were smaller and confidence intervals very wide], whereas positive associations of smaller magnitude were observed among past or current smokers. Results were less pronounced among women, and none of the estimates was statistically significant. A subsequent study by Kantor et al. (1988) reported estimates by subtyping cases by three histological types; significant trends for positive associations with risk of adenocarcinomas or transitional cell carcinomas (TCC) for men and women combined were reported, although only the estimate for the highest intake (> 64 cups/week) versus lowest (0–7 cups/week) was statistically significant for TCC (OR, 1.5; 95% CI, 1.1–1.9; *P* for trend, < 0.01 [numbers for adenocarcinomas were extremely low (32 cases)]. There was no evidence of trend or statistically significant point estimates for squamous cell carcinomas [numbers were too small to interpret]. Another extension of the study by Sturgeon et al. (1994) considered subtypes of cases defined by tumour stage and grade. Positive associations of similar magnitude were observed for high versus low intake of coffee among non-invasive and invasive bladder cancer, as well as when stratifying cases by grade (I, II, or III/IV). Even though some of the estimates were statistically significant in some strata and not others, all estimates were of comparable magnitude.

Morrison et al. (1982) reported a study that combined data from three population-based case–control studies in Boston, USA (587 cases, 528 controls), Manchester, UK (541 cases, 725 controls), and Nagoya, Japan (289 cases, 586 controls) for a total of 1666 cases and 2229 controls. On pooling the three studies, there was no association for drinking ≥ 1 cup/day versus less (OR, 1.0; 95% CI, 0.8–1.2). Results stratifying by study area did not show consistent evidence of a dose–response relationship [confidence intervals for estimates were not reported for any of the study-specific results].

Jiang et al. (2008) conducted a study in Los Angeles County, California, USA (1586 cases, 1586 controls). They reported a positive association for heavy coffee drinking (≥ 7 cups/day) versus non-drinkers with an odds ratio of 1.38 (95% CI, 0.95–2.00). There was weak evidence of a dose–response relationship (*P* for trend, 0.052). [The limitations included a lack of consideration of coffee-drinking history; only coffee consumption from 2 years before diagnosis was considered.]

A population-based study was performed in Ontario, Canada (Woolcott et al., 2002) involving 927 cases and 2494 controls. No associations were noted when considering all individuals combined; positive associations were however observed among never smokers, although the estimates were not statistically significant and there was no consistent dose–response trend. No evidence of positive associations was observed among ever smokers. [The limitations of this study include the fact that controls were recruited for multiple cancers and matching for bladder cancer might not be optimal. Further, only 15% of cases were non-smokers ($n = 139$), which limits power for smoking-stratified analyses.]

Risch et al. (1988) (835 cases, 781 controls) reported that ever drinkers of coffee had an odds ratio of 0.86 (95% CI, 0.59–1.25) in men and 1.87 (95% CI, 1.03–3.4) in women. Restricting analyses to non-smokers yielded positive associations for both men and women, but neither was statistically significant. Analyses that considered several categories of frequency of coffee intake showed little evidence for a dose–response

relationship or association for men or women. Similarly, estimates were close to null when considering ground, decaffeinated, or instant coffee. For total lifetime intake or ever intake of espresso coffee, positive associations were noted for both men and women; neither reached statistical significance, however, with a lifetime intake odds ratio of 1.29 (95% CI, 0.96–1.74) for men and 1.75 (95% CI, 0.91–3.39) for women. [No tests for trend were presented. Smoking adjustment only included pack-years of smoking, raising concerns about residual confounding.]

Howe et al. (1980) reported on a study based in Nova Scotia, Newfoundland, and British Columbia in Canada, involving 632 cases and 632 controls. A non-statistically significant positive association between the highest level of lifetime average consumption (> 4 cups/day) of total coffee and risk of bladder cancer when compared with never drinkers was reported (OR, 1.5; 95% CI, 0.8–2.8 for men and OR, 1.3; 95% CI, 0.4–4.1 for women). No tests of trend were presented, and there was no evidence of a dose–response relationship. Separate risk estimates are also presented for instant coffee and regular coffee, for men and women individually. A positive association was reported for regular coffee for men (> 4 cups/day vs never drinkers: OR, 1.8; 95% CI, 1.0–3.5), but there was weak evidence of a dose–response relationship. Analyses restricted to non-smokers were conducted only among women and an odds ratio of 1.4 (95% CI, 0.4–4.4) was reported for a lifetime average of > 2 cups/day compared with ≤ 2 cups/days. [Numbers were very small for some of the cells in stratified analyses. All odds ratios and confidence intervals were estimated by the Working Group.]

Ugnat et al. (2004) (549 cases, 1099 controls) conducted a population-based case–control study in Canada (British Columbia, Alberta, Saskatchewan, and Manitoba provinces) and reported a positive association with high intake of coffee (≥ 4 cups/day vs < 1 cup/month: OR, 1.77; 95% CI, 1.11–2.82; *P* for trend, < 0.001), with evidence of a dose–response relationship. [It is unclear from the publication if the test for trend corresponds to the unadjusted or adjusted estimates.] It is mentioned in the text that a positive association was found among non-smokers (≥ 4 cups/day vs < 1 cup/month: OR, 6.17; 95% CI, 1.73–21.96). [The number of cases in these analyses was not reported. Further, the low response rates of cases and controls raise some concern about possible bias introduced by responders. Only pack-years for smoking adjustment were considered, raising concern about residual confounding.]

Cole (1971) (470 cases, 500 controls) conducted a population-based case–control study in Massachusetts, USA. Positive associations between coffee intake and risk of bladder cancer were reported (> 4 cups/day vs < 1 cup/day: OR, 1.31 for men and 2.19 for women) [no confidence intervals or a test for trend were presented], with weak evidence for a dose–response trend. The odds ratio for drinking > 1 cup/day versus < 1 cup/day was 1.24 (95% CI, 0.8–1.93) among men and 2.58 (95% CI, 1.30–5.10) among women. When restricting analyses to non-smokers without high-risk occupational exposure and comparing the highest intake (> 4 cups/day) to the lowest (< 1 cup/day), an odds ratio of 2.6 for men and women combined was reported [no confidence intervals were provided, and the reference category comprised only 10 cases].

Jensen et al. (1986) (371 cases, 771 controls) conducted a population-based case–control study in Copenhagen, Denmark and reported no association between coffee intake and risk of bladder cancer; per L/day of coffee intake, odds ratios were 1.1 (95% CI, 0.9–1.4) for men and 1.1 (95% CI, 0.7–1.9) for women. Analyses considering quintiles showed estimates close to 1 for men, with no evidence of dose–response or trend (*P* for trend, 0.83). In contrast, positive associations were reported among women for all categories in comparison to never drinkers with an odds ratio of 2.7 (95% CI, 0.7–10.9) for the

highest category (> 1500 mL/day or > 6 cups), but there was no evidence of a dose–response relationship and the trend was not statistically significant (*P* for trend, 0.37). [It was noted that the reference category for this analysis among women had only 4 cases and the highest category had only 13 cases.] No differences in age at which coffee drinking started or in duration of coffee drinking were observed between cases and controls, and changes over time of the quantity of coffee consumed were similar for both cases and controls; however, no estimates were shown.

Slattery et al. (1988a) reported the results of a population-based case–control study conducted in Utah, USA (332 cases, 686 controls). A non-statistically significant positive association with caffeinated coffee (> 30 cups/week vs 1–15 cups/week OR, 1.28; 95% CI, 0.76–2.17) was reported, without evidence of a dose–response relationship. Different models adjusting for different smoking variables yielded comparable results, with the exception of a model that adjusted for 'years stopped smoking' that yielded null results (> 30 cups/week vs 1–15 cups/week OR, 1.07; 95% CI, 0.62–1.85). Another paper published on the same study (Slattery et al., 1988b) with slightly larger numbers also reported a non-statistically significant association with no consistent dose–response relationship (> 40 servings/week vs never drinkers OR, 1.6; 95% CI, 1.00–2.56). In this study there was no evidence of an association between consumption of decaffeinated coffee and risk of bladder cancer. [It was noted in the study that a substantial proportion of the Utah population belongs to the Mormon church, which forbids the consumption of coffee and tea as well as alcohol and tobacco; there is therefore the potential for underreporting of both coffee and smoking, which might lead to bias and residual confounding.]

Bruemmer et al. (1997) reported on a population-based study in Washington, USA (262 cases, 405 controls). The odds ratio comparing the highest category of regular coffee intake (> 6 cups/day) with non-drinkers was 1.2 (95% CI, 0.6–2.3) for men and 0.6 (95% CI, 0.2–1.9) among women. There was no evidence of a dose–response relationship and no statistically significant trends. When considering decaffeinated coffee, the comparable odds ratios were 0.9 (95% CI, 0.5–1.8) for men and 2.1 (95% CI, 0.8–5.3) for women [there were only 9 cases in the highest intake category]. There was no evidence of a trend among men; there was however a suggestion of a trend among women with an estimate of 1.6 (95% CI, 0.7–3.6; *P* for trend, 0.08) for the middle category. [The Working Group noted that this study only included men and women of age up to 65 years and the models only adjusted for smoking status, raising concerns over residual confounding.]

Nomura et al. (1991) reported on a study conducted in Hawaii, USA (261 cases, 522 controls). For 'cup-years' of coffee consumed among men, estimates of association for all types of coffee combined or for regular ground coffee were around 1.0 with no evidence of a dose–response relationship or trend. For both regular and decaffeinated instant coffee, some estimates were > 1 but there was no evidence of a dose–response relationship. Among women, for all types of coffee combined and regular ground coffee there were inverse associations for the highest intake categories (regular ground coffee OR, 0.3; 95% CI, 0.1–1.0 for > 90 cup-years compared with non-drinkers), but the trend was only statistically significant for regular ground coffee ($P = 0.02$). [The number of cases in the highest intake category was 8 and there were 9 non-drinkers.] For regular instant coffee and decaffeinated instant coffee some of the estimates were either > 1.0 or < 1.0; none were statistically significant however, and there was no evidence of a dose–response relationship or trend. [There was no evidence that different coffee types were mutually adjusted, and there was no adjustment for race even though this was a multiethnic study.

Adjustment for smoking only included pack-years, raising concerns about potential residual confounding.]

Momas et al. (1994) reported on a study conducted in the Herault district, France (219 cases, 792 controls). They reported an odds ratio for lifelong coffee drinking of 4.1 (95% CI, 1.7–10.0) for > 60 000 cups compared with < 365 cups. Whereas estimates for lower strata were smaller, there was no clear dose–response relationship. [No estimates of trend were reported. It was also noted that the reference category had only 8 cases and that adjustment for smoking only included lifelong smoking (cigarettes equivalent), raising concerns about residual confounding.]

Piper et al. (1986) reported results from a population-based case–control study of bladder cancer in women (aged 20–49 years) conducted in New York State (165 cases, 165 controls). The odds ratio for drinking more than 101 cup-years compared with non-drinkers was 2.1 (95% CI, 0.7–6.3). [No test for trend estimate or counts for each exposure level were presented. Adjustment for smoking only included pack-years, raising concerns about residual confounding.]

(b) Hospital-based case-control studies that used population-based controls

Hospital-based case–control studies that used population-based controls and reported results for coffee intake are discussed in the following. The Working Group considered these studies to be slightly less informative than those described in Section 2.1.2 (a) above, and they were correspondingly given less weight in the evaluation.

Escolar Pujolar et al. (1993) reported findings from a study conducted in Spain (497 cases, 1113 controls). They reported no evidence of association between frequency of coffee consumption and risk of bladder cancer among men, with all estimates close to 1.0. The highest versus lowest intake level odds ratio among women was 0.71 (95% CI, 0.20–2.56), but there was no evidence of a dose–response trend. When considering lifelong consumption in number of cups, the odds ratio for 40 000 cups versus none was 1.14 (95% CI, 0.69–1.9) for men and 1.39 (95% CI, 0.31–6.25) for women. Analyses restricted to non-smoking men or women showed positive associations, although neither were significant [the numbers of cases for many of the strata among men were < 10, and all of the strata among women were < 10]. [The Working Group noted that very small numbers were employed in the stratified analyses by smoking. Smoking adjustment may not have been adequate, as only cigarettes/day for men and smoking status for women were considered.]

Vena et al. (1993) reported results from a study carried out in western New York, USA (351 hospital-based cases, 855 population-based controls). When comparing the highest intake category (≥ 5 cups/day) to the lowest (0–1 cup/day) they reported an odds ratio of 2.1 (95% CI, 1.3–3.2), and there was evidence of a dose–response relationship with a significant trend (*P* for trend, <0.001). When restricting analyses to non-smokers there was also evidence of a positive association, and among those > 65 years old there was evidence of a dose–response relationship and a significant trend (*P* for trend, 0.02). Positive associations were also noted for decaffeinated instant, decaffeinated perk, regular instant, and regular perk, although these analyses were only adjusted for age and education. [Among the weaknesses of this study were the low response rates which, combined with the fact that deceased subjects or those too ill to participate were not included, raises concerns about possible bias. Many of the controls declined to participate, which could also introduce a bias. Many of the strata evaluated had very small numbers. Subject numbers for analyses stratifying by smoking status were not shown. Adjustment for smoking only considered pack-years which might not be adequate, raising concerns about residual confounding.]

(c) Hospital-based case-control studies that excluded diseases that may affect coffee intake

Hospital-based case–control studies that used hospital-based controls and reported results for coffee intake are described in the following. The Working Group considered these studies less informative than those described in Sections 2.2.1 (a) and (b) above, and so were given less weight in the evaluation.

Villanueva et al. (2009) reported on a hospital-based study conducted in Spain (1219 cases, 1271 controls). The odds ratio for the highest level of consumption (≥ 4 cups/day) compared with never drinkers was 1.27 (95% CI, 0.88–1.81; *P* for trend, 0.082) and there was no consistent dose–response relationship. They also reported estimates stratified by smoking status; the odds ratios for the highest intake versus never drinkers were > 1.0 among never, former, and current smokers, but there was no consistent dose–response relationship for any of the groups and none of the trend tests were significant. [Smoking adjustment only included smoking intensity, so residual confounding cannot be ruled out.]

Wang et al. (2013a) reported on a hospital-based case–control study conducted in Houston, Texas, USA (1007 cases, 1299 controls). When comparing the highest intake level of all types of coffee combined (> 2 servings/day) with never drinkers, the odds ratio was 1.14 (95% CI, 0.9–1.46; *P* for trend, 0.336). There was no evidence for a dose–response relationship. When considering decaffeinated coffee only, the comparable odds ratio was 1.37 (95% CI, 1.09–1.73; *P* for trend, 0.001); however, there was no evidence of a dose–response relationship, with the middle category estimate being larger than the highest category. Estimates for regular coffee only were no near 1.0. [Controls were individuals attending clinics for annual check-ups; there is therefore concern that their coffee-drinking habits are not representative of the underlying population. Adjustment for smoking only included smoking status, raising concerns about residual confounding.]

Turati et al. (2015) reported on a hospital-based study conducted in Italy (690 cases, 655 controls). When considering the average lifetime intake, the odds ratio for the highest versus the lowest category was 1.73 (95% CI, 1.08–2.77) and 1.06 for a 1 cup/day increase (95% CI, 0.99–1.14). There was no consistent evidence of a dose–response trend, and the trend test *P* value was 0.049. Estimates for current drinking did not show statistically significant associations or evidence of a dose–response relationship. However, when analyses were restricted to non-smokers there was an odds ratio of 1.18 (95% CI, 0.96–1.46), whereas estimates were around 1.0 among ex-smokers or current smokers. Comparable analyses performed with lifetime coffee drinking showed similar odds ratios (close to 1.0) across the three categories of smoking. There was no significant association observed between years of drinking or age at which coffee drinking began.

Rebelakos et al. (1985) conducted a study in Greece (300 cases, 300 controls) and reported that drinking > 2 cups/day compared with < 2 cups/day had an odds ratio of 1.7 (95% CI, 1.2–2.3). Results stratifying by sex showed estimates of similar magnitude, although they were only significant among men. Analyses comparing cups/day to never drinkers showed no evidence of a dose–response relationship. [The Working Group noted that sample size among women was very small (these analyses were therefore underpowered) and that adjustment for smoking only considered smoking status, raising concerns about residual confounding.]

De Stefani et al. (2007) conducted a hospital-based study in Uruguay (255 cases, 501 controls) and reported an odds ratio for the highest intake (≥ 7 cups/week) and intermediate intake of coffee (1–6 cups/week) compared with never drinkers of 2.1 (95% CI, 1.2–3.6) and 1.5 (95% CI, 1.1–2.2), respectively, with a *P* for

trend of <0.01. Similar estimates were observed when considering pure coffee or coffee with milk. [Diseases among controls were listed; it is unclear whether some of them could affect coffee intake, raising concerns about possible bias in estimates.]

(d) Hospital-based case-control studies that used controls with diseases that may affect coffee intake, or where no information was provided

Hospital-based case–control studies that used hospital-based controls and included diseases that may have affected coffee intake, or studies for which it is not clear if other diseases were considered (raising concerns about biased estimates), are described in the following. The Working Group considered these studies to be less informative than those described in Sections 2.1.2 (a)–(c) above, and gave them little weight in the evaluation.

Clavel & Cordier (1991) conducted a hospital-based study in France (781 cases, 781 controls), reporting positive associations for all individuals combined and for non-smoking men and women separately. [All analyses were conducted using never drinkers as the reference, and subject numbers for this category are < 10 for both men and women non-smokers (1 and 3, respectively); all estimates are therefore very unstable. Adjustment for smoking was performed using smoking status only, which may lead to residual confounding. More than 50% of controls had a disease that may affect coffee intake, leading to biased estimates.]

Geoffroy-Perez & Cordier (2001) reported on a hospital-based study conducted in France (765 cases, 765 controls). When comparing the highest intake category with the lowest, they reported an odds ratio of 1.42 (95% CI, 0.94–2.14) among men and 0.74 (95% CI, 0.28–1.96) among women. There was no evidence for a dose–response trend for either men or women. When restricting analyses to non-smokers, positive associations were observed for both men and women without consistent evidence of a dose–response relationship. [For analyses of non-smokers, the reference category had 7 cases for men and 13 cases for women. Control subjects had conditions that could affect coffee drinking habits (approximately 20% had gastrointestinal diseases and close to 30% had cardiovascular diseases), leading to concerns about possible selection bias.]

Kunze et al. (1992) reported on a hospital-based study carried out in Germany (675 cases, 675 controls) which found an odds ratio for the highest category of intake (> 5 cups/day) compared with never drinkers of 2.0 (95% CI, 1.2–3.3) for men and 2.7 (95% CI, 0.9–7.8) for women. There was also some evidence of a positive dose–response relationship, but no test for trend was provided. A previous report was published by Claude et al. (1986), reporting on a subset of these patients. [A main limitation of this study was the use of controls with urological diseases, such as hyperplasia of the prostate in men and urinary infections in women, which may affect their liquid intake and possibly introduce a bias in the estimates.]

Wynder & Goldsmith (1977) reported findings from a hospital-based study conducted in the USA (732 cases, 732 controls). Compared with individuals with no or occasional intake, the odds ratio for those who consumed ≥ 7 cups/day was 2.0 (95% CI, 0.8–4.9). [No definition of the smoking variable used for controlling confounding was provided. Controls with diseases that may affect coffee intake were not excluded, raising concerns about bias.] An expanded study (Kabat et al., 1986) included some of these cases as well as additional cases recruited later (152 cases, 492 controls). No association between consumption of brewed coffee or decaffeinated coffee and risk of bladder cancer was observed for either sex, with all estimates being very close to unity and based on very small numbers. [The Working Group noted the very small numbers for stratified analyses, the same

concerns as for the parent study by Wynder & Goldsmith (1977).]

Mettlin & Graham (1979) reported results from a hospital-based study performed in the USA (569 cases, 1025 controls) which showed that consumption of ≥ 3 cups/day compared with < 1 cup/day was associated with an odds ratio of 1.30 for men and women combined [no confidence intervals were provided]. The corresponding results for men and women separately were 1.64 and 0.81. Among men classified as relatively light smokers (< half a pack/day) there was still a positive association, whereas for women classified as relatively light smokers there was a slight inverse association. Neither estimate was statistically significant, and there was no evidence of a dose–response relationship [no definition of diseases among controls]. A previous report by Bross & Tidings (1973) reported on the same patients in this study.

D'Avanzo et al. (1992) reported results from a hospital-based study performed in Italy (555 cases, 855 controls). The odds ratio for the highest intake level of regular coffee (≥ 4 cups/day) compared with non-drinkers was 1.4 (95% CI, 0.9–2.2; *P* for trend, > 0.05), with no evidence of a dose–response relationship. Coffee drinking for ≥ 30 years compared with no coffee drinking yielded an odds ratio of 1.4 (95% CI, 0.9–2.2), whereas drinking coffee for < 30 years had an odds ratio of 1.2 (95% CI, 0.9–1.7; *P* for trend, < 0.05). [The strengths of this study include consideration of drinking history.] A non-statistically significant positive association was also reported for decaffeinated ever drinking versus never drinking. [No specific diseases excluded from controls were listed, raising concerns about possible bias.]

Ciccone & Vineis (1988) reported on a hospital-based study in Italy (512 cases, 594 controls); none of the estimates were statistically significant. Analyses stratifying by smoking were presented, but subject numbers were very small. [No information was provided about the conditions of the controls.]

Fraumeni et al. (1971) reported on a study conducted in the USA (493 cases, 527 controls), a reanalysis of a previous study conducted by Dunham et al. (1968). A positive association was found for black men and women (statistically significant in women only), without evidence of a dose–response relationship. Positive associations were seen for white and black men, but neither was statistically significant. Overall, there was no consistent dose–response relationship [no confidence intervals were presented].

Pohlabeln et al. (1999) conducted a hospital-based study in Germany (300 cases, 300 controls). When comparing the highest intake level of coffee (≥ 5 cups/day) with the lowest (≤ 1 cup/day), the odds ratios were 1.59 (95% CI, 0.87–2.91) for men and 1.25 (95% CI, 0.29–5.30) for women. There was no evidence of a dose–response relationship, as estimates for the middle category (2–4 cups/day) were either higher than or similar to the highest category. No test for trend was provided. They also reported analyses among non-smokers, but numbers were too small to be meaningful. [Among male controls, 41% had prostatic adenoma and 30% had kidney stones. Among women, 13% had urinary infections and 62% had kidney stones. The Working Group considered that it is feasible that patients with prostate adenoma may have changed coffee-drinking habits due to increased urination, raising concerns about possible bias.]

Covolo et al. (2008) reported on a hospital-based study carried out in Italy (197 cases, 211 controls). Comparing the highest level of coffee intake (> 3 cups/day) with non-coffee drinkers resulted in an odds ratio of 1.25 (95% CI, 0.59–2.67). There was no evidence of a dose–response relationship and no test for trend presented. Results were also stratified by smoking, but numbers of non-smokers were too small to be meaningful. Interactions were presented for the examined polymorphisms in metabolism enzymes, but no details of test of interaction were presented. [The Working Group was concerned

about bias introduced by patient controls, as well as the small numbers in many categories.]

Donato et al. (1997) reported on another hospital-based study in Italy (172 cases, 578 controls). Among men, the odds ratio for comparing the lowest (1–2 cups/day), intermediate (3–4 cups/day), and highest intake level (≥ 5 cups/day) with non-drinkers were 2.3 (95% CI, 0.9–5.6), 2.8 (95% CI, 1.1–7.4), and 4.5 (95% CI, 1.2–16.8), respectively, without a statistically significant trend (*P* for trend, >0.1). Among women, the estimates for the lowest (1–2 cups/day) and highest (3–4 cups/day) coffee intake levels compared with non-coffee drinkers were 4.3 (95% CI, 0.8–23.9) and 4.9 (95% CI, 0.7–33.0), respectively. [Numbers for some of the categories were very small, in particular non-drinkers. Controls included several benign urological diseases (prostate adenoma, urolithiasis, obstructive uropathy), and it is not clear if these disorders affect coffee intake. Prostate adenoma could affect coffee intake, raising concerns about bias in the results.]

Simon et al. (1975) conducted a hospital-based study in the USA (135 cases, 390 controls) and reported non-statistically significant positive associations among non-smokers/light smokers and also among moderate–heavy smokers. [Subject numbers for this analysis were very low.]

Radosavljević et al. (2003) conducted a hospital-based study in Serbia (130 cases, 130 controls) and reported an odds ratio for coffee intake of 1.46 (95% CI, 1.05–2.01). [The units associated with the reported odds ratios are not clear from the paper. The smoking variable used was not defined, so there is concern over residual confounding. It is not clear if the diseases among controls may have influenced coffee intake, leading to bias.]

Wakai et al. (2004) reported results from a study conducted in Japan (124 cases, 620 controls). The odds ratio for comparing the highest level of coffee intake (≥ 3 cups/day) with the lowest (almost never) was 1.14 (95% CI, 0.58–2.23). There was no evidence of a dose–response trend and the trend test was not statistically significant.

Iscovich et al. (1987) conducted a hospital-based study in Argentina with 117 cases and 234 controls (117 hospital and 117 neighbourhood). The odds ratios for consumption of 1 cup/day, 2 cups/day or ≥ 3 cups/day compared with non-drinkers were 1.08, 4.45, and 12, respectively. [No confidence intervals or test for trend were provided. Hospital controls included patients with digestive system problems (16%), heart disease (17%), and hypertension diseases (12%), all of which could affect coffee drinking and lead to bias.]

2.1.3 Meta-analyses and pooled analyses

Sala et al. (2000) conducted a pooled analyses of coffee intake and bladder cancer among non-smokers that included ten case–control studies carried out in Europe, including Rebelakos et al. (1985), Jensen et al. (1986), Ciccone & Vineis (1988), Clavel & Cordier (1991), Kunze et al. (1992), Escolar Pujolar et al. (1993), Donato et al. (1997), and Pohlabeln et al. (1999), discussed in Section 2.1.2 above. These ten studies involved a total of 564 cases and 2929 controls. The pooled odds ratio from comparing the highest intake level (≥ 10 cups/day) with never drinkers was 1.8 (95% CI, 1.0–3.3), with no evidence of a dose–response relationship or a significant trend. When stratifying studies by types of controls among studies that used hospital-based controls, the odds ratio was 3.2 (95% CI, 1.4–7.3) with a *P* for trend of 0.05. Among studies that used population-based controls, the odds ratio was 0.7 (95% CI, 0.2–2.0) with a *P* for trend of 0.3 [the number of cases in the highest category among population-based controls was 4]. Similar estimates were observed when further stratifying by sex although, among women, the odds ratio for population-based controls was > 1.0. Analyses taking into account duration of consumption in years (six studies) showed an

odds ratio for the longest duration compared with never drinkers of 0.9 (95% CI, 0.6–1.2).

Wu et al. (2015) conducted a meta-analysis that included 25 case–control (15 419 cases and 23 585 controls) and five prospective studies (753 cases and 236 343 controls). The overall pooled odds ratio for all studies was 1.33 (95% CI, 1.19–1.48), and heterogeneity was present (P = 0.008; I^2 = 38.4%). For case–control studies, the combined odds ratio was 1.37 (95% CI, 1.22–1.53) and also showed heterogeneity (P = 0.017; I^2 = 37.1%). For cohort studies the corresponding odds ratio was 1.10 (95% CI, 0.78–1.54) with less heterogeneity (P = 0.112; I^2 = 44%). Subgroup analyses were performed for various characteristics, such as type of control (hospital, population, or both). The meta-analysis odds ratio for studies that used hospital-based controls (20 studies) was 1.44 (95% CI, 1.21–1.72); for studies that used population-based controls (12 studies), the meta-analysis odds ratio was 0.98 (95% CI, 0.63–1.52). While studies based in Europe or America had comparable meta-analysis odds ratios of approximately 1.3, studies from Asia had an odds ratio of 1.0 (95% CI, 0.7–1.4). [Of the 11 cohort studies with data available, Wu et al. (2015) only included 4; there are also 6 other studies that were published during the period considered in this meta-analysis that were not included.]

2.2 Cancer of the pancreas

The Working Group reviewed all of the pertinent cohort studies (including nested case–control or case–cohort studies), case–control studies, and pooled and meta-analyses that assessed the association between coffee consumption and cancer of the pancreas.

Studies were excluded if statistical analyses were not adjusted for smoking, since it is an important potential confounder (Jick & Dinan, 1981; Kessler, 1981; Goldstein, 1982; Heuch et al., 1983; Snowdon & Phillips, 1984; Hsieh et al., 1986; Jacobsen et al., 1986; Mack et al., 1986; Norell et al., 1986; Wynder et al., 1986; Raymond et al., 1987; Pfeffer et al., 1989; Mizuno et al., 1992; Kalapothaki et al., 1993; Gullo et al., 1995; Kokic et al., 1996; Mori et al., 1999). We also excluded studies that did not provide sufficient information regarding risk estimates associated with coffee intake (Kinlen & McPherson, 1984; Baghurst et al., 1991, Chan et al., 2009).

If the 14 cohort studies included in a pooled analysis by Genkinger et al. (2012) are counted individually, then evidence from 20 individual cohort studies is available. In addition, 22 case–control studies were available that controlled for smoking, 14 of which were population-based and 8 hospital-based. For the reviewed studies, detailed information is presented in Table 2.3 for cohort studies and Table 2.4 for case–control studies.

2.2.1 Cohort studies

See Table 2.3.

A nested case–control analysis of a cohort study investigated pancreatic cancer mortality in a follow-up of 50 000 male former college students (Whittemore et al., 1983). There were 84 deaths from pancreatic cancer. Data on coffee and tea consumption and other variables were collected during a physical examination at the college. No statistically significant association with coffee consumption was noted; after adjustment for smoking, age, college, and class year the relative risk was 1.1 (95% CI, 0.7–1.9) when comparing those drinking ≥ 2 cups/day with those drinking < 2 cups/day.

In a Hawaiian cohort study of the association between cancer incidence and coffee consumption, 7355 Japanese men were followed for a minimum of 14 years from the time of collection of a 24-hour dietary recall during 1965–1968 (Nomura et al., 1986). This is an update of an earlier study by the same group (Nomura et al., 1981). Incidence rates were adjusted for age or

Table 2.3 Prospective cohort studies on cancer of the pancreas and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Whittemore et al. (1983) USA, 1962–1966 (enrolment), mortality until 1978	50 000 (84 cases): college alumni, male students who entered Harvard University during 1916–1950 or University of Pennsylvania during 1931–1940 Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)* < 2 ≥ 2	 60 24	 1.0 1.1 (0.7–1.9)	Age, smoking, college, class year	Strengths: nested case–control with 4 controls per case, matched on birth year Limitations: fatal cancer only, small number of cases, limited exposure information
Nomura et al. (1986) USA (Hawaii), 1965–1968 (enrolment), incidence until July 1983	7355 (21 cases): Japanese men born during 1900–1919 on Hawaiian Island of Oahu, aged 45–68 yr at baseline Exposure assessment method: 24-hour diet recall	Pancreas	*Current coffee drinking (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.41	 2 7 7 5	 1.00 1.16 2.08 1.63	Age, smoking	Strengths: prospective design Limitations: very small number of cases, intake based on 24-hour recall, limited confounder information
Hiatt et al. (1988) USA, 1978–1984 (enrolment), incidence 6 yr	122 894 (49 cases): members (men and women) of the Kaiser Permanente Medical Care Program in Northern California who had a multiphasic health check-up during 1978–1984, mean age at baseline 41 yr Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)* 0 < 1 1–3 ≥ 4	 NR NR NR NR	 1.0 0.8 (0.3–2.6) 0.9 (0.4–2.1) 0.7 (0.2–1.9)	Age, sex, ethnicity, smoking, alcohol consumption, diabetes, blood glucose	Strengths: prospective design Limitations: short follow-up, small number of cases

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mills et al. (1988) USA, 1976 (enrolment), mortality 1976–1982 (6 yr)	34 198 (40 cases), non-Hispanic white Californian Seventh-day Adventists, men and women, aged ≥ 25 yr Exposure assessment method: questionnaire	Pancreas	*Coffee drinking status*			Age, smoking, sex, consumption of meat and eggs	Strengths: prospective design Limitations: fatal cancer only, low number of cases due to short follow-up, only dichotomous exposure to coffee (few heavy coffee drinkers), generalizing findings to general population limited
			Not current	NR	1.00		
			Current	NR	2.21 (0.61–7.99)		
Friedman & van den Eeden (1993) USA, incidence 1964–1988	175 000 (450 cases, 2687 controls in nested case–control analysis), members (men and women) of the Kaiser Permanente Medical Care Program in Northern California Exposure assessment method: questionnaire, focusing on large volumes of consumption	Pancreas	*Current coffee drinking (cups/day)*			Age, sex, smoking, race, examination site, date of first check-up	Part of substantial multiple-comparison analysis Strengths: large cohort study, with relatively large number of cases Limitations: very limited exposure information (single coffee intake question of "Do you usually drink over 6 cups of coffee per day?")
			≤ 6	NR	1.00		
			> 6	NR	0.95 (0.73–1.22)		
			Trend test *P* value, 0.672				
Zheng et al. (1993) USA, 1966 (enrolment), mortality 1966–1986 (20 yr)	17 633 (57 cases), white men aged ≥ 35 yr, policy holders of the Lutheran Brotherhood Life Insurance Society (LBS) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day)*			Age, smoking, alcohol consumption	Strengths: prospective design Limitations: fatal cancer only, small number of cases
			< 3	21	1.0		
			3–4	18	0.6 (0.3–1.2)		
			5–6	12	0.7 (0.4–1.6)		
			≥ 7	5	0.9 (0.3–2.4)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shibata et al. (1994) USA, 1981–1985 (enrolment), incidence 1981–1990 (9 yr)	13 979 (65 cases), men and women, mean age at entry (standard deviation) 75.0 yr (men) and 73.8 yr (women) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day)* < 1 1 2–3 ≥ 4	 7 16 35 5	 1.00 1.82 (0.75–4.43) 1.67 (0.74–3.77) 0.88 (0.28–2.80)	Age, sex, smoking	Strengths: prospective design Limitations: upper–middle socioeconomic class considered only, small number of cases, limited confounder information
Stensvold & Jacobsen (1994) Norway, 1977–1982 (enrolment), incidence until 1990 (average 10.1 yr)	42 973 (41 cases) men and women aged 35–54 yr, living in three counties in different parts of Norway, participating in a cardiovascular screening programme organized by the National Health Screening Service Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): women* ≤ 4 ≥ 5 *Current coffee drinking (cups/day): men* ≤ 4 5–6 ≥ 7	 6 9 9 9 8	 1.0 1.2 1.0 1.0 0.6	Age, smoking, residence	Strengths: prospective design, sex-specific analyses Limitations: small number of pancreas cancer cases overall, and sex-specific, very few subjects drinking 0–1 cups/day, limited confounder information, multiple comparisons (15 cancer sites analysed)

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Harnack et al. (1997) USA, 1986 (enrolment), incidence 1986–1994 (9 yr)	33 976 (66 cases) women living in Iowa aged 55–69 yr (Iowa Women's Health Study), 99% of cohort was white Exposure assessment method: FFQ	Pancreas	*Coffee (cups/wk)*			Age, smoking	Comparison of results in never smokers with total cohort suggests residual confounding by smoking. Updated version of this study (with inverse association) is reported in pooled analysis of Genkinger et al. (2012) Strengths: population-based cohort, validated FFQ (from NHS), prospective design precludes recall bias, separate results for never smokers Limitations: low number of cases, limited confounder information
			≤ 7	11	1.00		
			8–17.5	20	1.91 (0.92–40.00)		
			> 17.5	35	2.15 (1.08–4.30)		
			Trend test *P* value, 0.03				
			Coffee consumption (cups/wk): never smokers			Age	
			≤ 7	10	1.00		
			8–17.5	11	1.36 (0.58–3.20)		
			> 17.5	17	1.74 (0.80–3.80)		
			Trend test *P* value, 0.17				
Michaud et al. (2001) USA, 1980 (NHS enrolment), 1986 (HPFS enrolment), 1980–1996 (NHS incidence), 1986–1998 (HPFS, incidence)	88 799 in NHS (158 female cases), 47 794 in HPFS (130 male cases) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): women*			Age, sex, smoking, BMI, diabetes, cholecystectomy, energy intake, period	Strengths: validated FFQ (from NHS), large cohorts with detailed information, able to control for multiple confounders Limitations: limited to health professionals
			0	39	1.00		
			< 1	10	0.72 (0.36–1.44)		
			1	14	0.71 (0.38–1.30)		
			2–3	52	0.88 (0.58–1.34)		
			> 3	43	0.88 (0.56–1.38)		
			Trend test *P* value, 0.92				
			Current coffee drinking (cups/day): men				
			0	47	1.00		
			< 1	36	1.04 (0.67–1.61)		
			1	10	0.48 (0.24–0.95)		
			2–3	31	0.89 (0.56–1.40)		
			> 3	6	0.37 (0.16–0.88)		
			Trend test *P* value, 0.04				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Michaud et al. (2001) (cont.)			*Current coffee drinking (cups/day)*				
			0	86	1.00		
			< 1	46	0.94 (0.65–1.36)		
			1	24	0.60 (0.38–0.94)		
			2–3	83	0.88 (0.65–1.21)		
			> 3	49	0.62 (0.27–1.43)		
			Trend test *P* value, 0.35				
Isaksson et al. (2002) Sweden 1961 (enrolment), 1969–1997 (incidence, 16 yr median)	21 884 (131 cases), Swedish Twin Registry cohort: male and female same-sexed twin pairs born during 1886–1925 and both living in Sweden in 1961 Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)*			Age, sex, smoking	Strengths: 90% of the pancreas tumours were histologically confirmed Limitations: no incidence data in period 1961–1969, limited dietary and confounder information
			0–2	29	1.00		
			3–6	95	0.91 (0.60–1.38)		
			≥ 7	7	0.39 (0.17–0.89)		
Lin et al. (2002) Japan, 1988–1990 (enrolment), mortality until 1997 (8.1 yr average)	110 792, JACC (46 465 men and 64 327 women), inhabitants of 45 areas throughout Japan aged 40–79 yr at baseline Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking: men*			Age, smoking pack-years	According to authors, the association between coffee consumption and pancreatic cancer risk was similar for non-smokers and current smokers (data not shown) Strengths: large cohort study with relatively large number of cases Limitations: fatal cancer only, no data on histological confirmation, small proportion drinking larger amounts of coffee with very few drinking > 4 cups/day, limited confounder information
			0	35	1.00		
			1–2 cups/mo	12	0.74 (0.37–1.49)		
			1–4 cups/wk	19	0.58 (0.32–1.08)		
			1 cup/day	8	0.59 (0.26–1.33)		
			2–3 cups/day	11	0.75 (0.36–1.59)		
			≥ 4 cups/day	5	3.19 (1.22–8.35)		
			Trend test *P* value, 0.79				
			Current coffee drinking: women				
			0	27	1.00		
			1–2 cups/mo	12	1.27 (0.64–2.54)		
			1–4 cups/wk	11	0.74 (0.36–1.50)		
			1 cup/day	9	0.94 (0.44–2.01)		
			2–3 cups/day	2	0.31 (0.07–1.33)		
			≥ 4 cups/day	1	1.8 (0.24–13.66)		
			Trend test *P* value, 0.21				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Stolzenberg-Solomon et al. (2002) Finland, 1985–1988 (enrolment), incidence until 1997 (10.2 yr median)	27 111 (163 cases), participants ATBC, smoking men aged 50–69 yr residing in southwestern Finland, randomized to receive supplements or placebo Exposure assessment method: FFQ	Pancreas	*Coffee consumption (g/day)* ≤ 321.4 450 624.9 878.6 > 878.6 Trend test *P* value, 0.62	 NR NR NR NR NR	 1.00 1.48 (0.89–2.46) 1.12 (0.61–2.03) 1.72 (1.01–2.86) 0.95 (0.54–1.68)	Age, smoking years	Strengths: detailed and validated FFQ Limitations: male smokers only, few people with low intake of coffee
Khan et al. (2004) Japan, mortality 1984–2002 (mean 13.8 yr for men, 14.8 yr for women)	3158 (25 fatal cases), subjects aged ≥ 40 yr using the resident registries of Hokkaido, Japan (1524 men and 1634 women) Exposure assessment method: questionnaire	Pancreas	*Coffee drinking: men* Non/occasional ≥ several times/wk Coffee drinking: women Non/occasional ≥ several times/wk	 NR NR NR NR	 1.0 0.6 (0.2–2.2) 1.0 0.2 (0–1.8)	Age, smoking Age, health status, health education, health screening, smoking	Limitations: no data on histological confirmation, very small number of cases, fatal cases only, limited control for confounders

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Luo et al. (2007) Japan, incidence 1990–2003 (mean 11 yr)	102 137 (233 cases), JPHC Study, conducted in 11 public health centre-based areas throughout Japan among residents aged 40–69 yr (48 783 men and 53 354 women) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking: men*			Age, sex, smoking, BMI, physical activity, alcohol, diabetes, cholelithiasis, study area, green tea	Strengths: large number of incident cases Limitations: no data on histological confirmation, relatively few people with high coffee intake
			Rarely	54	1.0		
			1–2 cups/wk	30	1.0 (0.6–1.5)		
			3–4 cups/wk	15	0.8 (0.5–1.5)		
			1–2 cups/day	25	0.7 (0.4–1.1)		
			≥ 3 cups/day	11	0.6 (0.3–1.1)		
			Trend test *P* value, 0.04				
			Current coffee drinking: women				
			Rarely	38	1.0		
			1–2 cups/wk	16	0.9 (0.5–1.7)		
			3–4 cups/wk	14	1.7 (0.9–3.1)		
			1–2 cups/day	24	1.3 (0.8–2.3)		
			≥ 3 cups/day	6	1.3 (0.5–3.3)		
			Trend test *P* value, 0.2				
			Current coffee drinking: men and women combined				
			Rarely	92	1.0		
			1–2 cups/wk	46	1.0 (0.7–1.4)		
			3–4 cups/wk	29	1.1 (0.7–1.7)		
			1–2 cups/day	49	0.9 (0.6–1.3)		
			≥ 3 cups/day	17	0.8 (0.4–1.3)		
			Trend test *P* value, 0.4				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nilsson et al. (2010) Sweden, incidence 1992–2007 (median 6 yr)	64 603 (74 cases), prospective cohort study from the VIP, subjects aged 40–60 yr at start Exposure assessment method: FFQ	Pancreas	*All coffee (cups/day)*			Age, sex, smoking, BMI, education, physical activity	Strengths: distinction between filtered and boiled coffee Limitations: small number of cases, no data on histological confirmation
			< 1	5	1.00		
			1–3	41	1.18 (0.47–3.02)		
			≥ 4	28	1.50 (0.57–3.92)		
			Coffee intake, filtered method (cups/day)				
			< 1	23	1.00		
			1–3	38	0.85 (0.50–1.44)		
			≥ 4	13	0.88 (0.44–1.76)		
			Coffee intake, boiled method (cups/day)				
			< 1	42	1.00		
			1–3	24	1.68 (1.01–2.81)		
			≥ 4	8	2.51 (1.15–5.50)		
Nakamura et al. (2011) Japan, mortality 1992–1997 (5 yr)	30 826 (14 241 men and 16 585 women; 52 fatal cases) residents of Takayama, Gifu Prefecture, Japan, aged ≥ 35 yr Exposure assessment method: FFQ	Pancreas	*Current coffee drinking: men*			Age, smoking, BMI, diabetes	Limitations: small number of cases, only fatal cases, no histological confirmation, low coffee intake levels
			Never	14	1.00		
			> 1 cup/mo to 4–6 cups/wk	11	0.67 (0.29–1.55)		
			≥ 1 cup/day	8	0.44 (0.15–1.29)		
			Trend test *P* value, 0.08				
			Current coffee drinking: women				
			Never	9	1.00		
			> 1 cup/mo to 4–6 cups/wk	5	0.62 (0.2–2)		
			≥ 1 cup/day	4	0.68 (0.17–2.78)		
			Trend test *P* value, 0.71				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Genkinger et al. (2012) USA, Canada, Netherlands, Sweden, Australia, incidence 1980–2005 (varies by cohort)	853 894 (317 828 men, 536 066 women) and 2185 cases (1047 men, 1138 women); pooling of 14 prospective cohort studies (including ATBC, BCDDP, CNBSS, CPS-II, CTS, COSM, HPFS, IWHS, MCCS, NLCS, NYSC, NHS, PLCO, SMC) Exposure assessment method: FFQ	Pancreas	*Coffee consumption (g/day): men and women*			Age, smoking, alcohol consumption, diabetes, BMI, energy intake, year of enrolment	When the case definition was limited to adenocarcinomas (n = 1554), no statistically significant association was observed with intake of coffee. Strengths: large size with high number of cases, enabling analyses of broad exposure range and possibility to evaluate effect modification Limitations: none
			0	149	1.00		
			0.01 to < 150	135	1.16 (0.84–1.6)		
			150 to < 400	316	1.01 (0.82–1.25)		
			400 to < 900	738	1.08 (0.89–1.31)		
			≥ 900	257	1.10 (0.81–1.48)		
			Continuous for 237 g/day increase	1595	1.01 (0.97–1.04)		
			Trend test P value, 0.71				
			Coffee consumption (g/day): men				
			0	54	1.00		
			0.01 to < 150	79	1.53 (1.03–2.26)		
			150 to < 400	163	1.02 (0.73–1.43)		
			400 to < 900	411	1.15 (0.84–1.58)		
			≥ 900	130	0.95 (0.67–1.36)		
			Continuous for 237 g/day increase	837	0.98 (0.95–1.01)		
			Trend test P value, 0.06				
			Coffee consumption (g/day): women				
			0	95	1.00		
			0.01 to < 150	56	0.87 (0.53–1.43)		
			150 to < 400	153	1.00 (0.76–1.32)		
			400 to < 900	327	1.04 (0.8–1.34)		
			≥ 900	127	1.18 (0.71–1.98)		
			Continuous for 237 g/day increase	758	1.04 (0.97–1.11)		
			Trend test P value, 0.5				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bidel et al. (2013) Finland, incidence 1972–2006 (mean 18 yr)	60 041 (29 159 men and 30 882 women; 235 cases) from six geographic areas of Finland, random sampling of the population aged 25–74 yr, stratified by area, sex, and 10-year age group Exposure assessment method: mailed, self-administered questionnaire	Pancreas	*Current coffee drinking (cups/day): men*			Age, smoking, study year, education, alcohol consumption, physical activity, diabetes, tea, BMI	Coffee cup size was small (100 mL) Strengths: prospective design with long follow-up (precluding recall bias), sex-specific analyses possible, wide range of coffee intake analysed
			0	9	1.00		
			1–2	14	0.72 (0.30–1.71)		
			3–4	32	0.76 (0.35–1.67)		
			5–6	38	0.64 (0.29–1.41)		
			7–9	20	0.72 (0.31–1.68)		
			≥ 10	16	0.80 (0.30–1.95)		
			Trend test *P* value, 0.91				
			Current coffee drinking (cups/day): women				
			0	3	1.00		
			1–2	11	1.30 (0.36–4.77)		
			3–4	33	1.29 (0.39–4.31)		
			5–6	40	1.21 (0.36–4.07)		
			7–9	16	1.52 (0.42–5.43)		
			≥ 10	3	0.71 (0.14–3.63)		
			Trend test *P* value, 0.88				
Bhoo-Pathy et al. (2013) 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK), 1992–2000 (enrolment), follow-up varied by country (mean 11.6 years)	477 312 (865 cases), EPIC cohort Exposure assessment method: FFQ	Pancreas	*Total coffee: country-specific quartiles*			Age, sex, centre, and age at diagnosis, height, weight, smoking status, history of diabetes, education, physical activity, energy intake, red meat, processed meat, alcohol, tea, soft drink, fruit, and vegetable intake	Median total coffee intake ranged from 92 mL/day in Italy to 900 mL/day in Denmark. Decaffeinated coffee also showed no association. Strengths: large study size and number of cases, with large variation in coffee intake, coffee intake calibrated with 24-hour recall Limitations: method and source of follow-up not described for most countries
			Non-drinker	52	1.09 (0.8–1.5)		
			Q1 (ref)	237	1.00		
			Q2	214	1.11 (0.92–1.34)		
			Q3	196	0.99 (0.81–1.21)		
			Q4	166	1.07 (0.86–1.33)		
			Continuous for 100 mL/day increase	865	1.00 (0.97–1.02)		
			Trend test *P* value, 0.925				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guertin et al. (2016) USA, enrolment (NA), follow-up incidence until 2006	457 366 (1541 cases with exocrine pancreas cancer); NIH-AARP Diet and Health Study, participants aged 50–71 yr residing in one of six US states or two metropolitan areas Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): men*			Age, smoking, diabetes, race/ ethnicity, BMI, highest level of education, alcohol consumption, health status, use of nutritional supplements, current marital status, physical activity, history of cardiovascular disease, family history of cancer, energy intake, nutrient density-adjusted intakes of fruits, vegetables, folate, protein, saturated fat, total fat	The association did not differ by tobacco smoking or self-reported history of diabetes. Strengths: large study size and number of cases
			0	71	1.00		
			< 1	153	1.14 (0.86–1.52)		
			1	146	1.02 (0.76–1.35)		
			2–3	427	1.05 (0.81–1.36)		
			4–5	142	1.06 (0.79–1.43)		
			≥ 6	54	1.21 (0.84–1.75)		
			Trend test *P* value, 0.55				
			Current coffee drinking (cups/day): women				
			0	58	1.00		
			< 1	81	0.91 (0.65–1.28)		
			1	112	1.12 (0.82–1.55)		
			2–3	218	1.01 (0.75–1.35)		
			4–5	53	0.89 (0.60–1.3)		
			≥ 6	26	1.38 (0.85–2.22)		
			Trend test *P* value, 0.53				

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BCDDP, Breast Cancer Detection Demonstration Project; BMI, body mass index; CNBSS, Canadian National Breast Screening Study; CI, confidence interval; COSM, Cohort of Swedish Men; CPS-II, Cancer Prevention Study; CTS, California Teacher's Study; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women's Health Study; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; JPHC, Japan Public Health Center-based Prospective; MCCS, Melbourne Collaborative Cohort Study; mo, month(s); NA, not available; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health–Association of American Retired Persons; NLCS, Netherlands Cohort Study; NR, not reported; NYSC, New York State Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; VIP, Västerbotten Intervention Project; wk, week(s); yr, year(s)

both age and smoking, using the entire cohort as the standard population. No significant association was reported between coffee drinking and risk of pancreatic cancer after adjusting for smoking (*P* for trend, 0.41). [The Working Group noted the very low number of cases; in addition, dietary information was based on a single 24-hour recall.]

A cohort study in northern California investigated a 6-year follow-up of pancreatic cancer incidence among 122 894 men and women who had completed a questionnaire collecting data on coffee, tea, smoking, and alcohol use during 1978–1984 (Hiatt et al., 1988). There were 49 cases of pancreatic cancer. A multivariate analysis identified no increased pancreatic cancer risk associated with increasing coffee consumption.

A cohort study (Mills et al., 1988) of 34 198 non-Hispanic, white Californian Seventh-day Adventists followed participants for 6 years after their completion of a questionnaire determining exposure to several risk factors, including coffee consumption, in 1976. Forty deaths from pancreatic cancer were reported. Multivariate analyses using the Cox proportional hazards model resulted in a relative risk for current coffee consumption versus no coffee consumption, adjusted for age, sex, and smoking, of 2.21 (95% CI, 0.61–7.99). [The Working Group noted that the distribution of coffee drinking in this population is unusual because there are few drinkers of larger quantities of coffee; only 17–18% of the population drank ≥ 2 cups/day.]

Friedman & van den Eeden (1993) conducted a nested case–control study within the Kaiser–Permanente cohort study, consisting of people who had received multiphasic health check-ups in the San Francisco Bay Area. Measurement of coffee intake was limited to one yes-or-no question in a questionnaire focusing on heavy consumption: "Do you usually drink over 6 cups of coffee per day?" As part of an exploratory analysis of 779 characteristics, coffee intake was also analysed. After multivariate adjustment, drinking > 6 cups/day of coffee was not associated with increased pancreatic cancer risk (RR, 0.95; 95% CI, 0.73–1.22).

Via the Lutheran Brotherhood Life Insurance Society (LBS) cohort, Zheng et al. (1993) studied risk factors for pancreatic cancer mortality in a cohort study of 17 633 white men in the USA who responded to a mailed questionnaire in 1966 and were followed up until 1986 for mortality. After 20 years of follow-up, 57 fatal pancreatic cancer cases were identified. Coffee consumption at baseline (current coffee drinking) was measured using a food frequency questionnaire (FFQ). Coffee was not related to pancreatic cancer mortality; the relative risk for those drinking ≥ 7 cups/day was 0.9 (95% CI, 0.3–2.4) compared with those drinking < 3 cups/day.

Shibata et al. (1994) examined risk factors for pancreatic cancer in a cohort study of 13 979 men and women resident within a retirement community in USA. After 9 years of follow-up, 65 incident cases of pancreatic cancer were identified. Coffee consumption at baseline was measured using a FFQ. Coffee was not related to pancreatic cancer risk; the relative risk for those drinking ≥ 4 cups/day compared with those drinking < 1 cup/day was 0.88 (95% CI, 0.28–2.80).

As part of a larger study on coffee drinking and cancer incidence, Stensvold & Jacobsen (1994) studied a cohort of 21 735 men and 21 238 women aged 35–54 years. The study population participated in a cardiovascular screening in three counties in Norway during 1977–1982. After an average follow-up period of 10.1 years, 41 incident cases were identified. Data on coffee habits at baseline were based on information from a self-administered FFQ. No statistically significant association was found between coffee drinking and incidence of cancer of the pancreas. In men, the relative risk for those drinking ≥ 7 cups/day compared with ≤ 4 cups/day was 0.6 (no confidence interval given) [coffee consumption is high in Norway]. In women, the relative

risk for those drinking ≥ 5 cups/day compared with those drinking ≤ 4 cups/day was 1.2. [The Working Group noted that the reference group could include individuals who consumed significant amounts of coffee.]

Harnack et al. (1997) examined the relationship between coffee consumption and pancreatic cancer incidence in the Iowa Women's Health Study cohort. Data were available from 33 976 women aged 55–69 years in 1986 who responded to a mailed questionnaire and who were followed until 1994 (9 years) for cancer incidence. Coffee intake at baseline was estimated using a validated FFQ. The relative risk for those drinking ≥ 17.5 cups/week compared with those drinking ≤ 7 cups/week was 2.15 (95% CI, 1.08–4.30; *P* for trend, 0.03). Among never smokers, the relative risk for the same consumption levels was not statistically significant at 1.74 (95% CI, 0.80–3.80; *P* for trend, 0.17). [The Working Group noted that an updated version of this study with a longer follow-up, but with an inverse association, is reported in the pooled analysis of Genkinger et al. (2012).]

Michaud et al. (2001) used data on coffee intake from semiquantitative FFQs administered at baseline in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), and in subsequent follow-up questionnaires. In both the NHS and HPFS, repeated measurements for coffee intake were accounted for in the analysis. The HPFS included 44 794 men, while there were data available on 88 799 women from the NHS. Results revealed a significant inverse association in men (RR for those drinking > 3 cups/day compared with those drinking 0 cups/day was 0.37; 95% CI, 0.16–0.88; *P* for trend, 0.04), and no association in women (RR, 0.88; 95% CI, 0.56–1.38; *P* for trend, 0.92). No associations between decaffeinated coffee or caffeine intake and pancreatic cancer, overall or by sex, were evident. [Data from the NHS and HPFS were included in the pooled analysis of Genkinger et al. (2012).]

Isaksson et al. (2002) studied the association between coffee consumption and pancreatic cancer incidence in a cohort study of twins established in 1958 and followed up by the Swedish Twin Registry. At 1961 (baseline), self-administered questionnaires regarding lifestyle factors were mailed. The analysis included 12 204 women and 9680 men who responded to these questionnaires. For those who consumed ≥ 7 cups/day compared with those who reported ≤ 2 cups/day, the relative risk of pancreatic cancer was 0.39 (95% CI, 0.17–0.89). [The Working Group noted that no incidence follow-up data were available for the period 1961–1969.]

Lin et al. (2002) evaluated the association between coffee consumption and pancreatic cancer mortality in a large-scale prospective cohort study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study). At baseline, a self-administered questionnaire was used to estimate coffee consumption. During the follow-up period (mean 8.1 years), 225 pancreatic cancer deaths were identified. Overall, coffee intake was not associated with fatal pancreatic cancer. While the relative risks were inverse for those drinking up to 3 cups/day of coffee compared with non-consumers of coffee (0 cups/day), the corresponding relative risk was positive and statistically significant (RR, 3.19; 95% CI, 1.22–8.35) for men who consumed ≥ 4 cups/day of coffee. A similar, but less-pronounced pattern of risks was observed among women. [The Working Group noted that, there was only limited control for confounders.]

Stolzenberg-Solomon et al. (2002) examined the association between coffee and exocrine pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study cohort in Finland among 27 111 male smokers aged 50–69 years. Coffee intake was estimated with a self-administered FFQ given at baseline (1985–1988). Compared with those drinking ≤ 321.4 mL/day of coffee, the relative risk for those drinking > 878.6 g/day was 0.95 (95% CI,

0.54–1.68; *P* for trend, 0.62). [The Working Group noted that coffee consumption was not very low in the reference group. Data from this study were included in the pooled analysis of Genkinger et al. (2012).]

Khan et al. (2004) studied the association between coffee drinking and pancreatic cancer mortality in a cohort study (1984–2002) in Hokkaido, Japan, among 1524 men and 1634 women aged 40 years and over at the beginning of the study period. Baseline coffee consumption was assessed with a questionnaire. During follow-up until 2002, 25 fatal cases were detected. There was no significant association between coffee drinking and the incidence of pancreatic cancer in men or women. [The Working Group noted the extremely low number of cases in sex-specific analyses.]

Luo et al. (2007) examined the association between coffee drinking and the risk of pancreatic cancer in a large population-based cohort study in Japan (JPHC study). A total of 233 incident cases of pancreatic cancer were identified. Baseline coffee consumption was assessed with a FFQ. Coffee drinking was not significantly associated with the risk of pancreatic cancer in men and women combined (*P* for trend, 0.4). Among men, but not among women, there was a significant trend towards lower risk with increasing coffee intake; the relative risk for ≥ 3 cups/day versus rarely drinking coffee was 0.6 (95% CI, 0.3–1.1; *P* for trend, 0.04).

Nilsson et al. (2010) investigated total, filtered, and boiled coffee consumption in relation to the risk of incident cancer in a prospective cohort study from the ongoing, population-based Västerbotten Intervention Project (VIP) established in 1985 in Sweden. Consumption of filtered and boiled coffee was assessed using a FFQ. Total and filtered coffee were not associated with risk of pancreatic cancer, but boiled coffee was positively associated with a relative risk of 2.51 for ≥ 4 cups/day versus < 1 cups/day (95% CI, 1.15–5.50; *P* for trend, 0.006). When coffee intake was modelled as a continuous variable, there was significant heterogeneity between filtered and boiled coffee (*P* for trend, 0.013) with an elevated risk for boiled coffee.

Nakamura et al. (2011) evaluated the association between coffee consumption and risk of death from pancreatic cancer in a prospective cohort study in Takayama, Japan. Coffee intake was estimated with a self-administered FFQ distributed at baseline. There was no significant association between intake of coffee and the risk of pancreatic cancer death; when comparing subjects drinking ≥ 1 cup/day versus never drinkers of coffee, the relative risk was 0.44 (95% CI, 0.15–1.29; *P* for trend, 0.08) among men and 0.68 (95% CI, 0.17–2.78; *P* for trend, 0.71) among women. [The Working Group noted the very small numbers of cases in sex-specific analyses.]

Genkinger et al. (2012) performed a pooled analysis of primary data from 14 cohort studies as part of the Prospective Studies of Diet and Cancer Pooling Project, a large international consortium. These studies included: the ATBC; Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP); Canadian National Breast Screening Study (CNBSS); Cancer Prevention Study II Nutrition Cohort (CPS II); California Teachers Study (CTS); Cohort of Swedish Men (COSM); Health Professionals Follow-up Study (HPFS); Iowa Women's Health Study (IWHS); Melbourne Collaborative Cohort Study (MCCS); the Netherlands Cohort Study (NLCS); New York State Cohort (NYSC); Nurses' Health Study (NHS); Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; and Swedish Mammography Cohort (SMC). Baseline coffee consumption was measured with FFQs as applied in each of the cohorts. Estimated coffee intake levels were converted into grams/day to avoid heterogeneity due to different cup sizes between countries. Coffee consumption was not associated with pancreatic cancer risk overall, and there was no indication of a dose–response association in categorical or

continuous analyses. When comparing intake of ≥ 900 g/day with 0 g/day, the pooled relative risk was 1.10 (95% CI, 0.81–1.48) with a *P* value of 0.08 in a test for between-study heterogeneity. There was no indication of a differential association by sex (*P* value, 0.69 in test for between-study heterogeneity due to sex). The pooled relative risks among women were 1.18 (95% CI, 0.71–1.98; *P* value in test for between-studies heterogeneity, 0.01) and among men 0.95 (95% CI, 0.67–1.36; *P* value in test for between-studies heterogeneity, 0.83). Although not statistically significant, a suggestion of heterogeneity due to differences in the percentage of current smokers in the female cohorts was present (*P* value for between-studies heterogeneity, 0.12). Expressed per increment of 237 mL/day, the pooled relative risk was 1.01 (95% CI, 0.97–1.04) for women and men combined with a *P* value for between-studies heterogeneity of 0.05. The large size of the pooled analysis also permitted evaluation of the effect of modification by other variables; however, there was no evidence of interaction by evaluated lifestyle or cohort characteristics. Among never smokers (525 cases), the relative risk was 1.04 (95% CI, 0.95–1.15) per 237 mL/day. [The large size of this pooled analysis of individual data with a high number of cases enabled analyses of broad exposure ranges and the possibility of evaluating effect modification.]

Bidel et al. (2013) examined the association between coffee and pancreatic cancer in a cohort study in six areas in Finland among 29 159 men and 30 882 women aged 25–74 years at baseline. Coffee intake was estimated with a self-administered questionnaire. Incident cancer cases were identified through the country-wide Finnish Cancer Registry. Coffee consumption was not associated with an increased risk of pancreatic cancer in men, women, or both sexes combined. The hazard ratio of pancreatic cancer incidence for ≥ 10 cups/day of coffee compared with non-drinkers was 0.80 (95% CI, 0.30–1.95; *P* for trend, 0.91) for men, and 0.71 (95% CI, 0.14–3.63; *P* for trend, 0.88) for women, and 0.82 (95% CI, 0.38–1.76; *P* for trend, 0.95) for men and women combined.

Bhoo-Pathy et al. (2013) analysed the relationship between coffee intake and pancreatic cancer in the EPIC cohort conducted in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. The cohort included 477 312 participants without cancer who completed a FFQ during 1992–2000 and were followed up for cancer incidence. Estimated coffee intake from the FFQ was calibrated with a 24-hour recall. Median total coffee intake ranged from 92 mL/day in Italy to 900 mL/day in Denmark. Consumption of total coffee, caffeinated, and decaffeinated coffee intake were not associated with risk of pancreatic cancer. For total coffee, the hazard ratio of pancreatic cancer risk for the highest versus the lowest quartile of consumption was 1.07 (95% CI, 0.86–1.33; *P* for trend, 0.925). Hazard ratios for caffeinated and decaffeinated coffee were similar. Continuous analyses for increments of 100 mL/day did not show any increase or decrease in risk of pancreatic cancer for all coffee types. No material changes in risk estimates were observed when beverages were grouped using EPIC cohort-wide categories instead of country-specific intake. Associations between coffee intake and pancreatic cancer were generally similar across subgroups as defined by sex, age group, smoking status, and BMI categories.

Guertin et al. (2016) used data from the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study. At baseline, participants were aged 50–71 years and resided in one of six US states or two metropolitan areas. For this analysis, 457 366 participants (275 328 men and 182 038 women) with non-missing data on coffee intake and smoking were included. Cancer cases were identified by linkage of the NIH-AARP cohort to 11 state cancer registries and the National Death

Index. Intakes of coffee and predominant type of coffee consumed were assessed with a FFQ. Although models adjusted only for age and sex suggested a statistically significant higher risk of pancreatic cancer with higher coffee intake, the association was substantially attenuated after extensive adjustment for smoking. Adjustment for additional covariates did not appreciably alter risk estimates. In the fully adjusted model, the hazard ratio of pancreatic cancer risk for men drinking ≥ 6 cups/day of coffee versus 0 cups/day was 1.21 (95% CI, 0.84–1.75; *P* for trend, 0.55); for women, the corresponding hazard ratio was 1.38 (95% CI, 0.85–2.22; *P* for trend, 0.53). The association did not vary with tobacco smoking or self-reported history of diabetes.

2.2.2 Case–control studies

See Table 2.4.

(a) Population-based case–control studies

Severson et al. (1982) based their study on 22 cases aged 40–79 years from a registry that was part of the Surveillance, Epidemiology and End Results (SEER) Program in Seattle, Washington, USA during 1977–1980, and on a random population sample of controls (n = 485). Next of kin were interviewed for most of the cases (20), whereas personal interviews were obtained for controls. The odds ratio for current versus not current coffee drinking was 1.0 (95% CI, 0.2–4.5). [This study was published as a letter, which contained few details.]

In the study of Gold et al. (1985), 201 cases (94 men, 107 women) with pancreatic cancer from 16 hospitals in Baltimore, Maryland, USA were included in a matched analysis. Of the 201, 25% had a personal interview. Two control groups were used: a matched hospital series (for age, race, sex, hospital, date of admission) from which patients with other cancers were excluded; and a population-based group that was chosen by random-digit dialling (RDD), matched by age, race, sex, and telephone exchange, and interviewed by telephone. Participation was about 50% of eligible individuals in both control series. No significant associations were found between pancreatic cancer and coffee drinking when using hospital- or population-based controls. The relative risks for those drinking ≥ 3 cups/day versus 0 cups/day, while controlling for smoking status, were 1.68 (95% CI, 0.71–3.95) when using population controls and 1.52 (95% CI, 0.68–3.43) with hospital controls.

A small study by Gorham et al. (1988) of 30 cases and 47 controls was based only on death certificates in Imperial County, California, USA, during 1978–1984. Controls were matched for age, sex, race, and year of death; cancer patients were excluded. The estimated relative risk for pancreatic cancer mortality associated with consumption of ≥ 3 cups/day compared with < 3 cups/day of coffee was 2.7, which dropped to 1.9 and was non-significant after adjustment for smoking. [The Working Group noted that only 30 of 51 deaths from pancreatic cancer were included; hospital records were not examined.]

A case–control study in the USA involved 212 cases identified from death certificates and 220 population-based controls contacted by RDD and matched to cases by age within 5 years (Olsen et al., 1989). Family members (usually widow or spouse) were interviewed on the case's use of cigarettes, alcohol, coffee, and other dietary factors 2 years before the death of the patient or before interview for controls. Coffee intake was not associated with pancreatic cancer mortality (OR for ≥ 7 cups/day versus < 1 cup/day, 0.60; 95% CI, 0.27–1.27.

Farrow & Davis (1990) conducted a case–control study with 148 cases and 188 controls among married men in Washington State, USA. Cases residing in three counties of Washington State, aged 20–74 years at diagnosis, were identified from the SEER Program. Population-based controls, matched to cases by age, were contacted by RDD. Information about each

Table 2.4 Case–control studies on cancer of the pancreas and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacMahon et al. (1981b) USA, 1974–1979	Cases: 367 admitted to one of 11 hospitals Controls: 644 hospital-based, other patients treated in same hospitals as cases (excluding diseases of biliary tract, pancreas, CVD, diabetes, respiratory or bladder cancer, peptic ulcer) Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day)* 0 1–2 ≥ 3 Trend test *P* value, 0.001	 20 153 194	 1.0 1.8 (1.0–3.0) 2.7 (1.6–4.7)	Age, sex, smoking	Strengths: comparable catchment area of cases and controls Limitations: many controls had gastrointestinal problems and may therefore have reduced their coffee intake, response rates moderate, interviewers not blinded for case/control status
Severson et al. (1982) USA, 1977–1980	Cases: 22 from SEER registry in Seattle, aged 40–79 yr at diagnosis Controls: 485 population-based, randomly selected from population in which cases arose, aged 40–79 yr Exposure assessment method: interview	Pancreas	*Coffee drinking status* Not current Current	 NR NR	 1.0 1.0 (0.2–4.5)	Age, sex, smoking	Strengths: population-based study Limitations: very small number of cases, cases information from two living patients and 20 from next-of-kin because of death, limited exposure information
Wynder et al. (1983) USA, 1977–1981	Cases: 275 aged 20–80 yr, admitted to 17 hospitals in 6 major cities Controls: 7994 hospital-based controls, matched on age, race, sex, room status from same hospital as cases (diseases, some cancers, not associated with tobacco) Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day): men* 0 1 2 3–5 ≥ 6 *Coffee consumed (cups/day): women* 0 1 2 3–5 ≥ 6	 26 15 34 50 28 25 19 25 36 17	 1.00 0.80 (0.40–1.48) 1.10 (0.68–1.95) 1.00 (0.59–1.59) 1.00 (0.59–1.79) 1.0 0.90 (0.48–1.64) 0.90 (0.51–1.59) 0.90 (0.53–1.50) 1.00 (0.52–1.83)	Age, smoking Age, smoking	Strengths: relatively large series with detailed control for smoking Limitations: hospital-based controls, reduced response rates in cases and controls

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kinlen & McPherson (1984) UK, 1952–1954	Cases: 216 aged > 40 yr, derived from an earlier study by Stocks (1957) conducted in 1952–1954 in greater Liverpool area and north Wales Controls: 432 hospital-based, cancer controls from Stocks study (excluding smoking-related and GI tract cancer, and ovarian cancer), matching on sex, age, residence area Exposure assessment method: interview	Pancreas	*Coffee drinking status: men* Never Weekly Daily *Coffee drinking status: women* Never Weekly Daily	 69 22 18 55 29 23	 1.00 0.87 (0.48–1.54) 0.93 (0.49–1.76) 1.00 1.28 (0.71–2.28) 0.86 (0.86–1.58)	Age, tea, smoking Age, smoking, tea	Strengths: adjustment for tea Limitations: hospital-based, little information about cases, no information about response rates, limited exposure information
Gold et al. (1985) USA, 1978–1980	Cases: 201 from 16 major hospitals in Baltimore area Controls: 201 population-based, matched by age, race, sex and telephone exchange, plus 201 hospital-based (other cancers excluded) controls matched for age, race, sex, hospital, date of admission Exposure assessment method: interview (often with next of kin)	Pancreas	*Coffee consumed (cups/day): population controls* 0 1–2 ≥ 3 *Coffee consumed (cups/day): hospital controls* 0 1–2 ≥ 3	 18 91 88 18 91 88	 1.00 1.37 (0.59–3.18) 1.68 (0.71–3.95) 1.00 1.43 (0.65–3.14) 1.52 (0.68–3.43)	Age, sex, smoking	Strengths: relatively large case series with two types of control groups Limitations: large difference in proportion of proxy interviews between cases (75%) and controls (0%), different response rates between cases and controls

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Falk et al. (1988) USA, 1979–1983	Cases: 363 incident cases from hospitals in Louisiana Controls: 1234 admitted to same hospital as cases, matched on sex, age, race Exclusions: chronic conditions (cancers, diabetes, CVD, digestive diseases, respiratory diseases) suspected to be related to lifestyle or diet Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day): women*			Age, smoking, alcohol consumption, intake of fruit, income	Strengths: questionnaire instead of interview Limitations: hospital-based, interview for 50% of cases and 13% of controls through next of kin (potential for recall bias)
			0	32	1.00		
			1–2	58	0.67		
			3–4	35	0.69		
			5–7	15	0.96		
			≥ 8	20	0.92		
			Coffee consumed (cups/day): men				
			0	34	1.00		
			1–2	64	0.66		
			3–4	34	0.53		
			5–7	23	0.67		
			≥ 8	48	1.39		
Gorham et al. (1988) USA, 1978–1984	Cases: 30 fatal pancreatic cancer cases identified from death certificates in Imperial County, California Controls: 47 controls identified from death certificates (excluding deaths from cancer), matching on age, sex, race and year of death Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day)*			Age, smoking	Strengths: comparison of fatal cases with dead controls should lead to less information bias, interviewers blinded with respect to cause of death Limitations: only 30 of 51 deaths from pancreatic cancer were included, hospital records were not examined, information from next of kin, median length of time between death and date of interview was 6 yr in cases and controls
			< 3	7	1.0		
			≥ 3	16	1.9		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Clavel et al. (1989) France, 1982–1985	Cases: 161 cases (98 men) with diagnosed cancer of exocrine pancreas from public hospitals in Paris (102 of 161 cases histologically verified); mean age at diagnosis was 62 yr in men and 64 yr in women Controls: 268 hospital-based controls, matched on age, sex, hospital, interviewer; 129 controls had other cancers (excluding biliary, liver, stomach, oesophagus, respiratory and bladder cancers) and 139 had non-neoplastic disorders Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day): women* 0 1 2–3 ≥ 4 Trend test *P* value, 0.006 *Coffee consumed (cups/day): men* 0 1 2–3 ≥ 4 Trend test *P* value, 0.14	 4 24 29 6 6 35 44 15	 1.00 3.94 (0.85–18.22) 6.71 (1.47–30.65) 9.56 (1.29–70.71) 1.00 1.07 (0.30–3.88) 1.45 (0.41–5.04) 2.08 (0.49–8.86)	Age, ethnicity, education, alcohol consumption, smoking	Unusually high risks were seen in women and in persons who had never drank alcohol. Strengths: study of interaction with alcohol Limitations: hospital–based, interviewers not blinded, proportion of subjects born outside France was higher among cases than controls (but was adjusted for in analyses), possible interview bias in study period due to widely publicized study by MacMahon et al. (1981b)
Cuzick & Babiker (1989) UK, 1983–1986	Cases: 216 cases (30% histologically verified) from Leeds, London, Oxford Controls: 279, mix of hospital-based (212) and population-based (67) controls from same three areas Exposure assessment method: questionnaire	Pancreas	*Coffee consumed currently (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.23 *Coffee consumed 10 yr previously (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.43	 97 77 19 23 117 69 18 12	 1.00 0.87 0.63 1.37 1.00 0.93 0.85 0.77	Age, smoking, sex	Strengths: analyses of coffee consumption 10 yr previously Limitations: mostly hospital-based

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Olsen et al. (1989) USA, 1980–1983	Cases: 212 aged 40–84 yr identified from death certificates in Minneapolis–St Paul area Controls: 220 population-based white men contacted by RDD, matched to cases by age within 5 yr Exposure assessment method: FFQ	Pancreas	*Coffee consumed (cups/day)* < 1 1–3 4–6 ≥ 7	 29 60 74 49	 1.00 0.50 (0.26–1.00) 0.72 (0.37–1.45) 0.60 (0.27–1.27)	Age, smoking, education, diabetes, meat intake, intake of vegetables	Strengths: dead cases are compared with dead controls, comparable information more likely Limitations: information obtained from next of kin
Farrow & Davis (1990) USA, 1982–1986	Cases: 148 men from SEER, Washington State, aged 20–74 yr Controls: 188 population-based controls contacted by RDD, matched to cases by age Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day)* 0 1–2 3–5 ≥ 6	 18 27 55 62	 1.0 0.7 (0.3–1.7) 1.0 (0.4–2.2) 1.1 (0.5–2.4)	Age, smoking, race, education, energy-adjusted intake of protein and calcium	Strengths: surrogate interviews for all cases and controls, comparable information more likely Limitations: information obtained from next of kin, interviews were held 2.0–4.5 yr after the diagnosis

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jain et al. (1991) Canada, 1983–1986	Cases: 249 diagnosed in 20 hospitals in Toronto Controls: 505 population-based, matched by sex and age from population lists Exposure assessment method: diet history interview	Pancreas	*Lifetime coffee consumption (cup-years)* 0 ≤ 39 40–110 ≥ 110 Continuous for 100 cup-years	 25 69 76 76 229	 1.00 0.94 (0.47–1.89) 0.90 (0.45–1.79) 0.90 (0.44–1.81) 0.96 (0.77–1.19)	Age, sex, smoking, residence, proxy/ direct interview, energy intake, fibre	Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) also showed no evidence of an effect. Strengths: relatively large study with dietary history interview; lifetime history estimates of coffee, tea and alcohol consumption Limitations: low response rates, interview 3 mo after diagnosis with high case fatality rate, different proportions of cases and controls interviewed by proxy (possibly leading to bias), 194 of 249 cases interviewed by proxy (62% with spouse, 31% with daughters and sons, and 7% with others), 194 of 505 controls interviewed by proxy (72% with spouse, 19% with daughters and sons, and 9% with others)
Ghadirian et al. (1991) Canada, 1984–1988	Cases: 179 aged 35–79 yr, diagnosed in 19 hospitals located in greater Montreal Controls: 239 population-based matched for age, sex, and place of residence selected randomly from RDD Exposure assessment method: questionnaire, interviews	Pancreas	*Cumulative lifetime coffee consumption* Quintile 1 Q2 vs Q1 Q3 vs Q1 Q4 vs Q1 Q5 vs Q1 Trend test *P* value, 0.53	 NR NR NR NR NR	 1.00 0.44 0.82 0.51 0.55 (0.19–1.62)	Age, sex, smoking, education, respondent type	Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) also showed no evidence of an effect. Strengths: lifetime coffee drinking and coffee drinking patterns (e.g. with meals) were studied Limitations: large difference in proportion of interviews by proxy between cases (75%) and controls (17%)

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bueno de Mesquita et al. (1992) Netherlands, 1984–1987	Cases: 176 aged 35–79 yr in central part of the Netherlands Controls: 487 population-based controls aged 35–79 yr from municipal population registries in the same area, frequency matched to the age-and-sex distribution of the cases Exposure assessment method: interviewer-administered questionnaire on lifetime frequency	Pancreas	*Cumulative lifetime coffee consumption (L)* < 6 193 < 9 012 < 11 840 ≥ 11 840 Trend test *P* value, 0.06	 26 23 17 24	 1.00 0.72 (0.36–1.43) 0.37 (0.18–0.79) 0.58 (0.28–1.20)	Age, sex, smoking, respondent type, energy intake, intake of vegetables, tea	The suggestion of an inverse dose–response relationship with the lifetime consumption of coffee was not present in the analysis of direct responders only. Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) showed no evidence of an association. Strengths: lifetime coffee drinking Limitations: possible selection bias due to relatively large difference in response rate between cases and controls and different proportion of proxy interviews between cases (42%) and controls (29%)
Lyon et al. (1992) USA, 1984–1987	Cases: 149 with pancreatic adenocarcinoma or carcinoma, from Utah Cancer Registry, aged 40–79 years Controls: 363 population-based controls, frequency matched to the distribution of cases by age, sex, and county of residence at the time of diagnosis Exposure assessment method: questionnaire, telephone interview with proxies	Pancreas	*Cumulative lifetime coffee consumption (cups)* 0–2000 2001–50 000 ≥ 50 000 Trend test *P* value, < 0.001	 38 44 40	 1.00 1.34 (0.78–2.29) 2.38 (1.16–4.85)	Age, sex, smoking, religion	Strengths: for all cases and controls, surrogate interviews were held with next of kin (comparable information more likely) Limitations: non-response rate among controls was higher than among cases, surrogate information obtained from next of kin (information less reliable)

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zatonski et al. (1993) Poland, 1985–1988	Cases: 110 identified through hospitals and the Cancer Registry located in the Opole Voivodeship Oncological Clinic Controls: 195 population-based controls from same area, frequency matched on age, sex, place of residence Exposure assessment method: interviewer-administered questionnaire on lifetime frequency of the consumption of specific beverages per age period	Pancreas	*Cumulative lifetime coffee consumption (L)* 0 < 417 < 1916 ≥ 1916 Trend test *P* value, 0.042	 58 17 18 16	 1.00 0.61 (0.30–1.23) 0.63 (0.30–1.30) 0.48 (0.22–1.02)	Age, sex, smoking, education	Strengths: substantial proportion of never drinkers of coffee Limitations: large difference in proportion of proxy interviews between cases (71%) and controls (0%) leading to information bias, few subjects drinking large amounts of coffee
Partanen et al. (1995) Finland, 1984–1987	Cases: 662 identified at the Finnish Cancer Registry Controls: 1770 from Finnish Cancer Registry (1014 stomach, 441 colon, 315 rectum cancer) Exposure assessment method: questionnaire, mail questionnaire, coffee use 20 yr before diagnosis considered, obtained from next of kin	Pancreas	*Coffee consumed 20 yr previously (cups/day)* None/ occasional 1–3 4–6 > 6	 24 104 273 91	 1.00 0.83 (0.50–1.38) 0.96 (0.59–1.56) 0.71 (0.41–1.20)	Age, sex, smoking	Consumption of coffee is high in Finland, with few people who never or occasionally drink coffee. ORs were lower (but NS) when rectum cancers were used as controls only, as opposed to colon cancer controls only (OR close to 1). Strengths: size, surrogate interviews were held with next of kin for all cases and controls (comparable information more likely) Limitations: use of cancer controls possibly related to coffee consumption, surrogate information obtained from next of kin (information less reliable), response rates in cases or controls were not provided

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nishi et al. (1996) Japan, 1987–1992	Cases: 141 pancreas cancer diagnosed at Sapporo Medical University and its affiliated hospitals Controls: 282 population-based controls from Hokkaido, matched for sex, age and place of residence Exposure assessment method: cases interviewed and controls received a questionnaire	Pancreas	*Coffee consumed (cups/day): men*			Age, smoking	Reports a U-shape curve, with extra meta-analyses. Strengths: population-based Limitations: cases were interviewed but controls received a questionnaire (possibly leading to information bias), limited control for confounders
			0	NR	1.00		
			Occasionally	NR	0.18 (0.07–0.43)		
			1–2	NR	0.53 (0.27–1.07)		
			≥ 3	NR	0.93 (0.44–1.96)		
			Coffee consumed (cups/day): women				
			0	NR	1.00		
			Occasionally	NR	0.53 (0.20–1.38)		
			1–2	NR	0.70 (0.31–1.58)		
			≥ 3	NR	1.37 (0.46–4.14)		
Silverman et al. (1998) USA, 1986–1989	Cases: 436 among 30–79-year-old residents of areas covered by cancer registries in Atlanta, Detroit, and 10 New Jersey counties Controls: 2003, random sample from general population, frequency matched on age, race, sex, and study area Exposure assessment method: interview (sometimes with next of kin) with FFQ	Pancreas	*Coffee consumed (cups/day): men*			Age, race, study area, smoking, alcohol consumption, diabetes, BMI, energy intake, cholecystectomy, income	Strengths: size, high proportion of direct interviews
			≤ 1	53	1.0		
			2	57	1.1 (0.7–1.7)		
			3	31	1.0 (0.6–1.7)		
			4–5	23	0.8 (0.4–1.4)		
			≥ 6	28	0.9 (0.5–1.7)		
			Non-drinker (reference)	26	1.0		
			Ever	192	0.9 (0.5–1.4)		
			Coffee consumed (cups/day): women				
			≤ 1	65	1.0		
			2	52	1.0 (0.7–1.6)		
			3	26	0.7 (0.4–1.1)		
			4–5	32	1.0 (0.6–1.7)		
			≥ 6	15	1.0 (0.5–2.2)		
			Non-drinker (reference)	23	1.0		
			Ever	190	1.4 (0.9–2.4)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (2000) Canada, 1994–1997	Cases: 583 aged 30–76 yr from eight provincial cancer registries confirmed Controls: 4813 population-based, frequency matched on age and sex Exposure assessment method: FFQ	Pancreas	*Coffee consumed: men*			Age, province of residence, smoking, alcohol consumption, energy intake, fat intake	Proxy interviews for 24% of cases but 0% of controls. Strengths: large study Limitations: large difference in proportion of proxy interviews between cases and controls, leading to information bias
			< 3 cups/mo	34	1.00		
			1–6 cups/wk	33	1.23 (0.71–2.13)		
			1 cup/day	33	0.70 (0.40–1.22)		
			2–3 cups/ day	124	1.11 (0.72–1.71)		
			≥ 4 cups/day	91	1.23 (0.78–1.97)		
			Coffee consumed (cups/day): women			Age, province of residence, smoking, alcohol consumption, energy intake, fat intake, number of live births	
			< 3 cups/mo	43	1.00		
			1–6 cups/wk	29	0.90 (0.52–1.57)		
			1 cup/day	40	1.00 (0.61–1.65)		
			2–3 cups/ day	85	0.81 (0.53–1.33)		
			≥ 4 cups/day	55	1.02 (0.63–1.66)		
Turati et al. (2011a) Italy, 1983–2008	Cases: 688, pooling of data from two hospital-based case–control studies in Milan (362 cases, 1983–1992) and Pordenone (326 cases, 1992–2008) Controls: 2204, hospital-based controls (admitted to the same hospitals as cases for acute conditions other than neoplasia or diseases of the digestive tract), frequency matched with cases by age and sex Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day)*			Age, sex, smoking, year of enrolment, education, BMI, alcohol consumption, diabetes	Includes results from La Vecchia et al. (1987) by pooling two case–control studies. No heterogeneity by age, sex, smoking, other covariates. No association with decaffeinated coffee. Strengths: large pooled study with investigation of effect modifiers Limitations: hospital-based controls
			0	78	1.00		
			≤ 1	171	1.41 (1.02–1.94)		
			≤ 2	199	1.29 (0.94–1.77)		
			≤ 3	133	1.23 (0.88–1.72)		
			> 3	107	1.46 (1.02–2.10)		
			Continuous for 1 cup/ day	610	1.05 (0.98–1.11)		
			Trend test *P* value, 0.232				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Azeem et al. (2013) Czech Republic, 2006–2009	Cases: 309 (180 men, 129 women) from three hospitals in three regions Controls: 220 (123 men, 97 women) population-based, matched on age, sex, health status and region Exposure assessment method: questionnaire, interview, measurements of anthropometric data	Pancreas	*All types of coffee consumed*			Age, sex, smoking, BMI, education, physical activity, alcohol consumption, tea	Limitations: interviewers were not blinded, no indication of the cancer diagnosis method, response rates unknown
			0–1 cup/wk	53	1.00		
			> 1 cup/wk – 2 cups/day	202	1.02 (0.60–1.75)		
			≥ 3 cups/day	38	0.78 (0.36–1.66)		

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FFQ, food frequency questionnaire; GI, gastrointestinal; mo, month(s); NR, not reported; NS, not significant; OR, odds ratio; RDD, random-digit dialling; SEER, Surveillance, Epidemiology and End Results; vs, versus; wk, week(s); yr, year(s)

man's consumption of coffee and other exposures was collected in a telephone interview with his wife. Coffee was not significantly associated with pancreatic cancer risk; the odds ratio for ≥ 6 cups/day versus 0 cups/day was 1.1 (95% CI, 0.5–2.4). [The Working Group noted that the deliberate use of surrogate interviewees enhanced comparability of information of cases and controls; nevertheless, both could have suffered from misclassification. This problem may have been aggravated as a result of the long period (2–4.5 years) between the times of diagnosis and interviews with spouses, who were required to recall exposure details of more than 3 years before diagnosis.]

Jain et al. (1991) described results obtained in a population-based case–control study carried out in Toronto, Canada, as part of the IARC-SEARCH programme. A quantitative diet history was used to estimate the lifetime consumption of different types of coffee for 249 cases and 505 controls. A total of 194 cases were interviewed by proxy. A proxy control was obtained for each case interviewed by proxy. Odds ratio estimates for quartiles of coffee consumption or per 100 cup-years increment showed no evidence of an association between coffee intake and pancreatic cancer risk. The odds ratio for ≥ 110 cup-years versus 0 cup-years was 0.90 (95% CI, 0.44–1.81). The odds ratio for an increment of 100 cup-years was 0.96 (95% CI, 0.77–1.19). Further analysis by type of coffee (regular, instant, caffeinated, and decaffeinated) also showed no evidence of an association.

Ghadirian et al. (1991) described results from another Canadian case–control study that was part of IARC-SEARCH. A total of 179 cases, aged 35–79 years, were diagnosed in 19 hospitals located in Greater Montreal. Population-based controls (239) matched for age, sex, and place of residence were selected by the RDD method or randomly from the telephone directory. There was an inverse association (*P* for trend, 0.53) between cumulative lifetime coffee consumption in quintiles and pancreatic cancer risk (Q5 vs Q1 OR, 0.55; 95% CI, 0.19–1.62). Similar results were evident in analyses by type of coffee consumed. The authors noted that proxy respondents reported higher amounts of total coffee intake compared with direct respondents for all subjects combined. [The Working Group noted a large difference in proportion of interviews by proxy between cases (75%) and controls (17%), leading to possible information bias.]

Bueno de Mesquita et al. (1992) conducted a case–control study on pancreatic cancer and coffee consumption in the Netherlands as part of IARC-SEARCH. Pancreatic cancer cases (alive or dead) were 35–79 years of age, newly diagnosed between 1984 and 1987, and living in the central part of the Netherlands at the time of diagnosis of cancer of the exocrine pancreas. Population-based controls were obtained from municipal population registries in the area and matched to the age–sex distribution of the cases. A quantitative diet history was used to estimate the lifetime consumption of total coffee and of different types of coffee for 176 cases and 487 controls. The results for lifetime drinking of coffee indicated an inverse dose–response association between coffee intake and risk of pancreatic cancer, with the test for trend approaching statistical significance (*P* for trend, 0.06). The odds ratio for ≥ 11 840 L coffee per life versus < 6193 L coffee per life was 0.58 (95% CI, 0.28–1.20). The suggestion of an inverse dose–response relationship with the lifetime consumption of coffee was not present in the analysis of direct responders only. [The Working Group noted that possible selection bias may have occurred due to relatively large differences in the response rate between cases and controls. The different proportions of proxy interviews between cases and controls (42% versus 29%) could also contribute to information bias.]

Lyon et al. (1992) conducted a population-based case–control study of 149 cases of cancer of the exocrine pancreas (excluding

insulinomas) and 363 controls in Utah, USA. All information was obtained from proxy respondents for cases and controls. Pancreatic cancer risk increased with the amount of coffee drunk with an odds ratio of 2.38 (95% CI, 1.16–4.85) for those having at least 50 000 lifetime cups (*P* for trend, < 0.001) compared with those having 0–2000 lifetime cups. Positive associations were also observed for users of regular and decaffeinated coffee, but were stronger in magnitude for users of decaffeinated coffee than users of regular coffee. [The Working Group noted many limitations of this study. The non-response rate among controls (23%) was higher than among cases (12%), which might have led to selection bias. Since all information was obtained from proxy respondents, it is possible that there was a difference in the type of proxy respondents available for the cases compared with the controls. Approximately 5% more spouses were available as proxies for the controls than for the cases, whereas about 7% more children or children's spouses were available as proxies for the cases than for the controls, possibly resulting in information bias.]

Zatonski et al. (1992) conducted a case–control study on the association between pancreatic cancer and coffee consumption in Poland as part of IARC-SEARCH. Of the 110 cases, 32 were interviewed directly and a proxy interview was available for 78. All 195 controls were interviewed directly following the very low acceptance rate among proxy controls found in a pilot study. Lifetime coffee drinking was estimated for total coffee and different types of coffee. Compared with never drinkers of coffee, the odds ratio of risk of pancreatic cancer for ≥ 1916 L of coffee per life was 0.48 (95% CI, 0.22–1.02). A significant trend test (*P* for trend, 0.042) was observed, which remained when the analyses were limited to directly interviewed subjects only and when consumption of tea was additionally adjusted for. [The Working Group noted a large difference in the proportion of proxy interviews between cases and controls, which may have led to information bias.]

Nishi et al. (1996) conducted a case–control study in Hokkaido, Japan, employing 141 cases with cancer of the pancreas and 282 controls (2 for each case) matched for sex, age, and place of residence. This is an update of an earlier study by Goto et al. (1990). To estimate coffee intake, cases were interviewed by a trained interviewer while a 'self-rating questionnaire' was distributed to the controls. Consumption of coffee was not significantly associated with risk of pancreatic cancer; the odds ratio for ≥ 3 versus 0 cups/day was 0.93 (95% CI, 0.44–1.96) among men and 1.37 (95% CI, 0.46–4.14) among women. [The Working Group noted that cases were interviewed but controls received a questionnaire, possibly leading to information bias. There was also limited control for confounders.]

Silverman et al. (1998) conducted a population-based case–control study of pancreatic cancer diagnosed in Atlanta, Detroit, and in 10 New Jersey counties, USA, from August 1986 to April 1989. Reliable dietary histories were obtained for 436 patients and 2003 general-population control subjects aged 30–79 years. Men who were regular coffee drinkers experienced no overall increased risk, whereas women who were regular drinkers had a non-significant 40% increased risk of pancreatic cancer as compared with non-drinkers of coffee. Among coffee drinkers, neither a gradient in risk with increasing amount of coffee consumed or increased risk with any amount of consumption was observed for either men or women.

Villeneuve et al. (2000) conducted a population-based case–control study of pancreatic cancer diagnosed in eight Canadian provinces as part of the Canadian National Enhanced Cancer Surveillance System (NECSS) project. Cases (n = 583) aged 30–76 years were identified from eight provincial cancer registries. Population-based controls (4813), frequency-matched for age and sex, were selected from health insurance

plans using stratified random sampling or RDD, depending on province. Coffee intake was estimated using a FFQ. Among cases, 24% were proxy interviews with next of kin; among controls the corresponding percentage was 0. Coffee intake was not significantly associated with pancreatic cancer risk in either men or women. The odds ratio for ≥ 4 cups/day versus < 3 cups/month in men was 1.23 (95% CI, 0.78–1.97); in women the respective association was 1.02 (95% CI, 0.63–1.66). [The Working Group noted a large difference in proportion of proxy interviews between cases and controls, which may have led to information bias.]

Azeem et al. (2013) conducted a population-based case–control study (529 subjects, 303 men and 226 women, period of study 2006–2009) of lifestyle factors and risk of pancreatic cancer in the Czech Republic. Newly diagnosed cases of pancreatic cancer (n = 309) were recruited from three hospitals. [The Working Group noted that no information on how the diagnosis of pancreatic cancer was established was provided.] Controls (n = 220) were a population-based sample of individuals from the same regions as cases. After adjustment for other factors, no trend was observed with respect to the amount of coffee consumption for ≥ 3 cups/day compared with 0 to ≤ 1 cup/week (OR, 0.78; 95% CI, 0.36–1.66).

(b) Hospital-based case–control studies

MacMahon et al. (1981a, b; the latter study was reported in a letter) reported on a case–control study of 367 (216 men, 151 women) subjects with cancer of the pancreas (excluding islet cell tumours) under 80 years of age identified in 11 hospitals in Boston and Rhode Island, USA, and 644 controls who had been at hospital for other diseases at the same time as the cases. Each case and control pair was interviewed personally by the same physician. Compared with non-drinkers of coffee, the relative risks for those drinking 1–2 cups/day and ≥ 3 cups/day were 1.8 (95% CI, 1.0–3.0) and 2.7 (95% CI, 1.6–4.7), respectively (P for trend, 0.001). Elevated relative risks were also reported among men and women separately, but these estimations were not adjusted for smoking. [The Working Group noted that many controls had gastrointestinal problems, meaning that subjects may have reduced their coffee intake to relieve symptoms. For this reason, the Working Group judged that the observed positive associations might have been spurious effects due to selection bias.]

A study (part of a larger study of tobacco-related cancers in six US cities) of 275 histologically verified cases (153 men, 122 women) aged 20–80 years, interviewed during 1977–1981, and of 7994 hospital controls reported null associations between risk of pancreatic cancer and coffee intake (Wynder et al., 1983). Controls were patients with diseases not related to tobacco. Personal interviews were carried out within 6 months of diagnosis. The study found no association between coffee consumption and pancreatic cancer. [The Working Group noted that the low response rate among cases and controls may have resulted in selection bias.]

Kinlen & McPherson (1984) re-evaluated data from the case–control study of Stocks (partly reported by Stocks, 1957) collected from hospitals in north-western England and north Wales during 1952–1954, including 216 cases (109 men, 107 women) aged > 40 years. These were compared with 432 controls who were patients with other cancers in the original study matched for age, sex, and area of residence; patients with cancers of the lung, bladder, mouth, pharynx, oesophagus, gastrointestinal tract, and ovary were excluded. No association between pancreatic cancer risk and coffee consumption was found either before or after adjustment for smoking.

A case–control study by Falk et al. (1988), based on 363 incident cases (203 men, 160 women) and 1234 hospital controls, was carried out in Louisiana, USA. Control subjects were matched for hospital, age, sex, and race. Patients with cancer, diabetes, circulatory disorders, and

digestive or respiratory diseases were excluded from the pool of potential controls. Direct interviews were carried out with 50% of cases and 50% were with next of kin. For controls, direct interviews were with 13%. No association was found between coffee drinking (any amount) and risk of pancreatic cancer for men or women after adjusting for age, residence, smoking, alcohol, fruit consumption, diabetes, and income. [The Working Group noted the high proportion of proxy interviews, especially among controls.]

Clavel et al. (1989) conducted a hospital-based interview study in Paris, France, with 161 cases of cancer of the pancreas (98 men, 63 women) during 1982–1985. There were 268 hospital controls, 129 of which had other cancers (excluding biliary, liver, stomach, oesophagus, respiratory, and bladder cancers) and 139 of which had non-neoplastic disease. All were matched to cases for age, sex, hospital, and interviewer. None of the cases and about 5% of controls refused to participate. After adjustment for education, alcohol, and smoking, a non-significant trend for pancreatic cancer was observed among men with a relative risk of 2.08 for ≥ 4 cups/day compared with 0 cups/day (95% CI, 0.49–8.86). In women, the respective trend was statistically significant and the corresponding relative risk was 9.56 (95% CI, 1.29–70.71). [The Working Group noted that unusually high relative risks were seen in women and in persons who had never drunk alcohol, possibly due to interview bias from publicity about the topic.]

A study of 216 cases of cancer of the pancreas (123 men, 93 women) and 279 controls was carried out in the UK during 1983–1986 (Cuzick & Babiker, 1989) based on personal interviews. The controls included 212 hospital controls without cancers or other chronic medical conditions, and the remaining 67 were population-based controls. The study reported essentially null associations between pancreatic cancer risk and coffee consumption, although a slightly elevated risk was seen in cases whose current consumption was ≥ 5 cups/day (RR, 1.4) as compared with 0 cups/day. This trend disappeared when coffee consumption approximately 10 years before the interview was examined.

Partanen et al. (1995) conducted a case–control study using pancreatic cancer deaths as cases and patients with cancers other than that of the pancreas as controls during 1984–1987 in Finland, a country with very high coffee consumption. Cases and controls were identified from the Finnish Cancer Registry: 662 endocrine pancreas cancer cases and 1770 controls (1014 stomach, 441 colon, and 315 rectum cancer). Using a mail questionnaire, data on coffee consumption 20 years before diagnosis were obtained from next of kin. There was no association between coffee consumption and pancreatic cancer mortality; the odds ratio for those drinking > 6 cups/day compared with never/occasional coffee drinkers was 0.71 (95% CI, 0.41–1.20). Odds ratios were lower (but non-significant) when rectum cancers were used as controls only, as opposed to colon cancer controls only (ORs close to 1).

Turati et al. (2011a) performed a pooled analysis of two earlier case–control studies from northern Italy, conducted between 1983 and 2008, including a total of 688 cases of cancer of the pancreas and 2204 hospital controls with acute, non-neoplastic diseases. The first study, conducted during 1983–1992 in Milan, included 362 incident cases of pancreatic cancer (229 men, 133 women) and 1552 controls and is an update of an earlier study by La Vecchia et al. (1987) and Soler et al. (1998). The second study, conducted between 1992 and 2008 in Milan and Pordenone, northern Italy, included 326 incident cases (174 men, 152 women) and 652 controls, frequency-matched with cases by age and sex (Rossi et al., 2010). In both studies, controls were admitted to the same network of hospitals as cases for a wide spectrum of acute conditions other than neoplasia or diseases of the digestive tract. Less than 5% of cases and controls refused to participate in the interview. Cases

and controls were interviewed using a structured questionnaire regarding frequency of coffee consumption. Compared with non-drinkers of coffee, the odds ratio for coffee drinkers was 1.34 (95% CI, 1.01–1.77). The odds ratio for those drinking > 3 cups/day was 1.46 (95% CI, 1.02–2.10) compared with coffee non-drinkers. However, there was no trend in risk of pancreatic cancer with respect to dose (cups/day) (*P* for trend, 0.232). The odds ratio for an increment of 1 cup/day was 1.05 (95% CI, 0.98–1.11). There was no heterogeneity in the apparent associations in strata defined by age, sex, and other covariates, including tobacco smoking. No association emerged for drinkers of decaffeinated coffee compared with non-drinkers of decaffeinated coffee (OR, 0.87; 95% CI, 0.60–1.26).

2.2.3 Meta-analyses

Meta-analyses of cohort studies on the association between coffee consumption and cancer of the pancreas were conducted by Dong et al. (2011), Yu et al. (2011), and Ran et al. (2016); these meta-analyses included studies that did not adjust for smoking, however, and also excluded several studies. Because of the shortcomings of these meta-analyses, the Working Group focused on the more rigorous meta-analysis by Turati et al. (2012).

Turati et al. (2012) conducted a meta-analysis on the association between coffee consumption and pancreatic cancer risk, using data from case–control and cohort studies that were published until March 2011. They identified 37 case–control and 17 cohort studies (10 594 cases) as eligible for meta-analysis. Random-effects models were used. When only smoking-adjusted studies were considered, 22 case–control studies and 15 cohort studies were suitable for meta-analysis. Among the smoking-adjusted studies, Turati et al. estimated pooled relative risks of pancreatic cancer for high versus low coffee consumption of 1.10 (95% CI, 0.92–1.31) for case–control studies, 1.04 (95% CI, 0.80–1.36) for cohort studies, and 1.08 (95% CI, 0.94–1.25) for all studies, with significant between-study heterogeneity ($P = 0.002$). This heterogeneity was not explained by study design, sex, or geographic location. The summary relative risk was 1.00 (95% CI, 0.83–1.19) for men and 1.15 (95% CI, 0.94–1.41) for women when combining all smoking-adjusted studies (*P* heterogeneity between sexes, 0.312). Per increment of 1 cup/day of coffee based on the smoking-adjusted studies, the summary relative risk was 1.04 (95% CI, 1.00–1.09) for case–control studies and 1.00 (95% CI, 0.95–1.05) for cohort studies. The authors estimated a weak positive association between coffee consumption and pancreatic cancer risk when combining case–control studies that were not adjusted for tobacco, which can be attributed to residual confounding by smoking.

2.3 Cancer of the liver

A total of 14 cohort and 11 case–control studies that examined the association between coffee consumption and the risk of cancer of the liver were available for review by the Working Group.

Regarding the cohort studies, seven were conducted in Japan, three in the US, three in Europe, and one in Singapore. Among these 14 cohort studies, 11 focused on incidence (Inoue et al., 2005, 2009; Shimazu et al., 2005; Hu et al., 2008; Ohishi et al., 2008; Johnson et al., 2011; Lai et al., 2013; Aleksandrova et al., 2015; Bamia et al., 2015; Petrick et al., 2015; Setiawan et al., 2015) and 3 focused on mortality (Kurozawa et al., 2004, 2005; Wakai et al., 2007). Inoue et al. (2005, 2009) reported findings from the same prospective cohort study, but the latter study (Inoue et al., 2009) reported the results from a subcohort with information on hepatitis C virus (HCV) and hepatitis B virus (HBV) status. Kurozawa et al. (2004, 2005) and Wakai et al. (2007) also reported results derived from the same study population; the latter (Wakai

et al., 2007) used a nested case–control analysis. Likewise, Bamia et al. (2015) and Aleksandrova et al. (2015) reported results derived from the same population; the latter used a nested case–control study analysis. Johnson et al. (2011) and Lai et al. (2013) reported results for both cohort and nested case–control analysis. Petrick et al. (2015) reported results from a pooled analysis of the cohort studies. One pooled analysis of US cohorts analysed the risk by histological subtypes, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma (Petrick et al., 2015).

Case–control studies were conducted in various countries: three studies in Italy, one in Greece, one in Italy and Greece, two in Japan, and one each in Serbia, the Republic of Korea, Hong Kong Special Administrative Region, and India. All studies except one (Tanaka et al., 2007) were hospital-based. Tanaka et al. (2007) included both population-based and hospital-based control groups.

The Working Group also reviewed seven meta-analyses of coffee drinking and cancer of the liver.

A cohort study (Kurozawa et al., 2004) reporting coffee consumption and risk of hepatocellular carcinoma (HCC) mortality by sex and age group has been excluded from this review; the results were derived from univariate analysis with no adjustment for other risk factors, and the results controlling for confounding factors were reported in another paper by Kurozawa et al. (2005). One case–control study (Kanazir et al., 2010) was also excluded from this review because it did not adjust for any covariates.

2.3.1 Cohort studies

See Table 2.5.

Inoue et al. (2005) investigated the association between coffee consumption and incidence of HCC among 90 452 Japanese (43 109 men and 47 343 women) aged 40–69 years at baseline in the JPHC-based prospective study, which began during 1990–1994. Information on coffee drinking was obtained by self-reported questionnaire at baseline. After adjusting for potential confounders, those who consumed coffee on a daily basis had a lower risk of HCC than non-drinkers (HR, 0.49; 95% CI, 0.36–0.66). The risk decreased with the amount of coffee consumed; compared with non-drinkers, the hazard ratio for drinking 1–2 cups/day was 0.52 (95% CI, 0.38–0.73), for 3–4 cups/day 0.48 (95% CI, 0.28–0.83), and for ≥ 5 cups/day 0.24 (95% CI, 0.08–0.77). The *P* value for trend was < 0.001. The inverse association persisted when the participants were stratified by age, smoking, alcohol intake, green vegetable intake, green tea intake, and history of chronic liver disease. Similar associations were observed when the analysis was restricted to HCV+ or HBV+ cases. [The strengths of this study were its prospective design and large scale. Limitations included the facts that consumption was self-reported, changes in coffee consumption were not considered, and the HCV/HBV status of controls was not available.]

Kurozawa et al. (2005) examined the association between coffee drinking and HCC mortality in the JACC Study. In total, 110 688 men and women aged 40–79 years were grouped by coffee intake categories. Information on habitual coffee consumption was obtained by self-reported questionnaire at baseline. On adjusting for potential confounders, including history of diabetes, liver diseases, and alcohol consumption, the hazard ratio of HCC mortality for drinkers of ≥ 1 cups/day of coffee compared with non-coffee drinkers was 0.50 (95% CI, 0.31–0.79); the hazard ratio for drinkers of < 1 cup/day was 0.83 (95% CI, 0.54–1.25). [The strengths of this study were its large scale and prospective design. Limitations included the absence of HCV and HBV markers.]

Shimazu et al. (2005) examined the association between coffee consumption and the risk of cancer of the liver in a pooled analysis of

Table 2.5 Cohort studies on cancer of the liver and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) Japan, 1990–1994 to 2001	90 452 (43 109 men and 47 343 women), JPHC Study subjects aged 40–69 yr, 11 public health centre-based areas, residential register Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption: men and women*			Sex, age, study area, smoking, alcohol drinking, green vegetable intake, green tea drinking	Strengths: prospective, large scale Limitations: self-report, change not considered, HCV, HBV status of controls unknown
			Almost never	161	1.00		
			1–2 days/wk	65	0.75 (0.56–1.01)		
			3–4 days/wk	36	0.79 (0.55–1.14)		
			Almost everyday	72	0.49 (0.36–0.66)		
			1–2 cups/day	54	0.52 (0.38–0.73)		
			3–4 cups/day	15	0.48 (0.28–0.83)		
			≥ 5 cups/day	3	0.24 (0.08–0.77)		
			Trend test *P* value, < 0.001				
			Coffee consumption: men				
			Almost never	116	1.00		
			1–2 days/wk	43	0.74 (0.52–1.05)		
			3–4 days/wk	27	0.76 (0.50–1.16)		
			Almost everyday	59	0.49 (0.35–0.69)		
			1–2 cups/day	45	0.55 (0.38–0.80)		
			3–4 cups/day	11	0.41 (0.21–0.77)		
			≥ 5 cups/day	3	0.27 (0.09–0.87)		
			Trend test *P* value, < 0.001				
			Coffee consumption: women				
			Almost never	45	1.00		
			1–2 days/wk	17	0.77 (0.43–1.37)		
			3–4 days/wk	9	0.89 (0.43–1.84)		
			Almost everyday	13	0.48 (0.25–0.92)		
			1–2 cups/day	9	0.43 (0.20–0.90)		
			3–4 cups/day	4	0.89 (0.31–2.59)		
			≥ 5 cups/day	0	–		
			Trend test *P* value, 0.042				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) (cont.)			*Coffee consumption: HCC with HCV+, men and women combined*				
			Almost never	86	1.00		
			1–2 days/wk	26	0.59 (0.38–0.91)		
			3–4 days/wk	15	0.66 (0.38–1.16)		
			Almost everyday	37	0.57 (0.37–0.86)		
			1–2 cups/day	29	0.64 (0.41–0.99)		
			3–4 cups/day	6	0.42 (0.18–0.99)		
			≥ 5 cups/day	2	0.34 (0.08–1.41)		
			Trend test *P* value, 0.005				
			Coffee consumption: HCC with HBV+, men and women combined (60 cases)				
			Almost never	24	1.00		
			1–2 days/wk	9	0.66 (0.31–1.43)		
			3–4 days/wk	9	1.14 (0.52–2.47)		
			Almost everyday	18	0.60 (0.31–1.18)		
			1–2 cups/day	12	0.56 (0.26–1.21)		
			3–4 cups/day	5	0.81 (0.30–2.22)		
			≥ 5 cups/day	1	0.39 (0.05–2.98)		
			Trend test *P* value, 0.231				
			Coffee consumption: no history of CLD				
			Almost never	NR	1.00		
			1–2 days/wk	NR	0.85 (0.59–1.24)		
			3–4 days/wk	NR	1.15 (0.76–1.74)		
			Almost everyday	NR	0.45 (0.3–0.67)		
			1–2 cups/day	NR	0.46 (0.29–0.72)		
			3–4 cups/day	NR	0.52 (0.26–1.05)		
			≥ 5 cups/day	NR	0.15 (0.02–1.05)		
			Trend test *P* value, < 0.001				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) (cont.)			*Coffee consumption: history of CLD*				
			Almost never	NR	1.00		
			1–2 days/wk	NR	0.79 (0.48–1.30)		
			3–4 days/wk	NR	0.44 (0.18–1.11)		
			Almost everyday	NR	0.91 (0.58–1.41)		
			1–2 cups/day	NR	0.99 (0.61–1.61)		
			3–4 cups/day	NR	0.71 (0.31–1.67)		
			≥ 5 cups/day	NR	0.76 (0.18–3.16)		
			Trend test *P* value, 0.432				
Kurozawa et al. (2005) Japan, 1988–1990, follow-up until 1999	110 688 (46 399 men, 64 289 women), JACC Study, subjects aged 40–79 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)*			Age, sex, education, history of diabetes and liver disease, smoking and alcohol habits	Strengths: large-scale, prospective design Limitations: absence of HCV and HBV markers
			All subjects				
			Non-drinkers	103	1.00		
			< 1	57	0.83 (0.54–1.25)		
			≥ 1	98	0.50 (0.31–0.79)		
			Trend test *P* value, 0.007				
			Coffee consumption (cups/day): men			Age, education, history of diabetes and liver disease, smoking and alcohol habits	
			Men				
			Non-drinkers	66	1.00		
			< 1	41	0.91 (0.57–1.45)		
			≥ 1	71	0.49 (0.28–0.85)		
			Trend test *P* value, 0.007				
			Coffee consumption (cups/day): women				
			Non-drinkers	37	1.00		
			< 1	16	0.64 (0.27–1.51)		
			≥ 1	27	0.51 (0.20–1.31)		
			Trend test *P* value, 0.141				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kurozawa et al. (2005) (cont.)			*Coffee consumption (cups/day): with history of liver diseases*			Age, sex, education, history of diabetes, smoking and alcohol habits	
			Non-drinkers	62	1.00		
			< 1	35	0.94 (0.53–1.66)		
			≥ 1	54	0.44 (0.22–0.88)		
			Trend test *P* value, 0.028				
			Coffee consumption (cups/day): without history of liver diseases				
			Non-drinkers	41	1.00		
			< 1	22	0.79 (0.44–1.41)		
			≥ 1	44	0.61 (0.32–1.16)		
			Trend test *P* value, 0.113				
Shimazu et al. (2005) Japan (Miyagi): (1) 1984–1992 and (2) 1990–1997	Cohort 1: 22 404 (10 588 men and 11 816 women), aged ≥ 40 yr Cohort 2: 38 703 (18 869 men, 19 834 women), aged 40–64 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day): cohort 1*			Age, sex, history of liver disease, alcohol consumption, smoking status	Strengths: prospective, large scale Limitations: no information on HBV and HCV infection status, DCO cases possibility of misclassifying secondary metastasis to liver, former drinkers not distinguishable from non-drinkers
			Never	29	1.00		
			Occasionally	25	0.56 (0.33–0.97)		
			≥ 1	16	0.53 (0.28–1.00)		
			Trend test *P* value, 0.038				
			Coffee consumption (cups/day): cohort 2				
			Never	12	1.00		
			Occasionally	21	1.05 (0.52–2.16)		
			≥ 1	14	0.68 (0.31–1.51)		
			Trend test *P* value, 0.3				
			Coffee consumption (cups/day): pooled				
			Never	41	1.00		
			Occasionally	46	0.71 (0.46–1.09)		
			≥ 1	30	0.58 (0.36–0.96)		
			Trend test *P* value, 0.024				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wakai et al. (2007) Japan, 1988–1990	Cases: 96 of HCC mortality, identified from death certificates Controls: 420 HCV+ and 3024 HCV– controls, matched for age, sex, HCV-antibody seropositivity Exposure assessment method: questionnaire; rank correlation $r^2 = 0.79$	Liver/HCC	*Coffee consumption (cups/day): total*			Area, smoking and drinking habits, history of diabetes mellitus and liver diseases	Strengths: nested case–control design (as part of JACC) Limitations: mortality not incidence, coffee intake at baseline only
			Total				
			Non-drinkers	44	1.00		
			< 1	34	0.77 (0.45–1.32)		
			≥ 1	18	0.49 (0.25–0.96)		
			Trend test *P* value, 0.038				
			Coffee consumption (cups/day): HCV-Ab-positive				
			Non-drinkers	28	1.00		
			< 1	23	0.91 (0.41–2.04)		
			≥ 1	9	0.31 (0.11–0.85)		
			Trend test *P* value, 0.031				
			Coffee consumption (cups/day): HCV-Ab-negative				
			Non-drinkers	16	1.00		
			< 1	11	0.65 (0.29–1.46)		
			≥ 1	9	0.75 (0.29–1.92)		
			Trend test *P* value, 0.45				
Hu et al. (2008) Finland, 1972–2006	60 323; seven independent cross-sectional surveys in six geographic areas Exposure assessment method: questionnaire	Liver/HCC	*Daily coffee consumption (cups/day)*			Adjusted for age, sex, study year, alcohol consumption, education, smoking, diabetes, and CLD	Strengths: large-scale population-based, prospective, long follow-up (19.3 yr) Limitations: self-report only at baseline, impossible to assess caffeine intake, no data on HBV or HCV, residual confounding
			Total	128	–		
			0–1	20	1.00		
			2–3	30	0.66 (0.37–1.16)		
			4–5	33	0.44 (0.25–0.77)		
			6–7	28	0.38 (0.21–0.69)		
			≥ 8	17	0.32 (0.16–0.62)		
			Trend test *P* value, 0.003				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hu et al. (2008) (cont.)			*Daily coffee consumption (cups/day): men (82 cases)*				
			0–1	16	1.00		
			2–3	21	0.68 (0.35–1.31)		
			4–5	17	0.35 (0.18–0.71)		
			6–7	15	0.31 (0.15–0.63)		
			≥ 8	13	0.28 (0.13–0.61)		
			Trend test *P* value, 0.001				
			Daily coffee consumption (cups/day): women (46 cases)				
			0–1	4	1.00		
			2–3	9	0.62 (0.19–2.04)		
			4–5	16	0.60 (0.20–1.82)		
			6–7	13	0.58 (0.19–1.82)		
			≥ 8	4	0.41 (0.10–1.70)		
			Trend test *P* value, 0.82				
Ohishi et al. (2008) Japan, 1969–2002	Cases: 224 HCC identified from Hiroshima and Tissue Registry and Nagasaki Cancer Registry Controls: 644 matched from the cohort by sex, age, city, time of serum storage, method for serum storage and radiation exposure Exposure assessment method: questionnaire	Liver/HCC	*Coffee intake frequency*			Hepatitis virus infection, alcohol consumption, smoking, BMI, diabetes mellitus, radiation dose of the liver	Strengths: prospective, nested case–control, HCV and HBV infection considered Limitations: severity of liver fibrosis could not be considered
			Never	187	1.00		
			Daily	37	0.40 (0.16–1.02)		
			Trend test *P* value, 0.055				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2009) Japan, 1993–2006	18 815; JPHC Cohort II Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day): total (110 cases)*			Sex, age, area, smoking, alcohol drinking, green tea intake, BMI, history of diabetes, serum ALT, HCV and HBV infection status	Strengths: prospective analysis with blood samples Limitations: relatively small number of cases
			Almost never	67	1.00		
			< 1	35	0.67 (0.42–1.07)		
			1–2	18	0.49 (0.27–0.91)		
			≥ 3	6	0.54 (0.21–1.39)		
			Trend test *P* value, 0.025				
			Coffee consumption (cups/day): HCV+ and/or HBV+ (92 cases)				
			Almost never	43	1.00		
			< 1	28	0.55 (0.33–0.93)		
			1–2	15	0.47 (0.24–0.93)		
			≥ 3	6	0.61 (0.23–1.62)		
			Trend test *P* value, 0.036				
			Coffee intake (cups/day): HCV+ (80 cases)				
			Almost never	38	1.00		
			< 1 cup/day	24	0.56 (0.32–0.99)		
			1–2 cups/day	12	0.40 (0.18–0.88)		
			≥ 3 cups/day	6	0.78 (0.28–2.15)		
			Trend test *P* value, 0.065				
Johnson et al. (2011) Singapore, 1993–1998 to 2006	63 257 Chinese aged 45–74 yr Exposure assessment method: 165-item FFQ	Liver/HCC	*Coffee consumption (cups/day)*			Age, sex, dialect group, years of recruitment, BMI, education, consumption of alcohol beverages, cigarette smoking, black tea and green tea intake, and history of diabetes	Strengths: prospective with blood samples (in part) Limitations: lack of HBV and HCV status for all participants, participants not examined for liver damage at baseline; relatively small number of cases
			Non-drinkers	69	1.00		
			0 to < 1	38	0.94 (0.63–1.40)		
			1 to < 2	149	1.17 (0.87–1.56)		
			2 to < 3	92	0.78 (0.56–1.07)		
			≥ 3	14	0.56 (0.31–1.00)		
			Trend test *P* value, 0.05				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Johnson et al. (2011) Singapore, 1993–1998 to 2006	Cases: 92 HCC by national cancer registry Controls: 276 individually matched by sex, dialect group, age at enrolment, date of baseline interview and date of biospecimen collection (± 6 mo) Exposure assessment method: 165-item FFQ	Liver/HCC	*Coffee consumption (cups/day)* Non-drinkers 0 to < 1 1 to < 2 2 to < 3 ≥ 3 Trend test *P* value, 0.71	 17 11 34 28 2	 1.00 0.77 (0.26–2.29) 0.84 (0.38–1.85) 1.32 (0.56–3.14) 0.23 (0.05–1.21)	Age, sex, dialect group, years of recruitment, BMI, education, consumption of alcohol beverages, cigarette smoking, black tea and green tea intake, history of diabetes, and HBV/ HCV infection status	Case–control analysis of a subset of the cohort Strengths: nested case–control, prospective HBV and HCV information available Limitations: participants were not examined for liver damage at baseline, relatively small number of cases
Lai et al. (2013) Finland, 1985–1988, follow-up to December 2009	27 037; ATBC study male smokers aged 50–69 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)* Never drinker > 0 to < 1 1 to < 2 2 to < 3 3 to < 4 ≥ 4 Unit change (per cups/day) Trend test *P* value, 0.0007	 9 36 60 47 22 20 NR	 1.00 1.35 (0.65–2.82) 0.73 (0.48–1.12) 0.52 (0.33–0.82) 0.45 (0.26–0.78) 0.53 (0.30–0.95) 0.82 (0.73–0.93)	Intervention arm, age, BMI, education, marital status, history of diabetes, smoking, alcohol consumption, serum cholesterol	Strengths: prospective study, long follow-up Limitations: HCV/ HBV status available for subset only

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lai et al. (2013) (cont.)			*Coffee consumption, filtered method (cups/day)*			Type of coffee, ATBC intervention arm, age, BMI, education, marital status, history of diabetes, smoking, alcohol consumption, serum cholesterol	
			> 0 to < 1	16	1.00		
			1 to < 2	34	0.80 (0.44–1.47)		
			2 to < 3	26	0.54 (0.29–1.03)		
			3 to < 4	9	0.34 (0.15–0.78)		
			≥ 4	12	0.61 (0.28–1.34)		
			Unit increase (per cups/day)	NR	0.82 (0.69–0.98)		
			Trend test *P* value, 0.03				
			Coffee consumption, boiled method (cups/day)				
			> 0 to < 1	7	1.00		
			1 to < 2	10	0.60 (0.23–1.57)		
			2 to < 3	5	0.25 (0.08–0.80)		
			3 to < 4	7	0.60 (0.21–1.75)		
			≥ 4	4	0.40 (0.12–1.40)		
			Unit increase (per cups/day)	NR	0.85 (0.65–1.11)		
			Trend test *P* value, 0.19				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bamia et al. (2015) Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, UK) 1992–2000 to 2004–2008	486 799; EPIC Study Exposure assessment method: questionnaire	Liver/HCC	*Coffee intake, quintiles (mL/day)*			Sex, diabetes, education, BMI, smoking, physical activity, alcohol intake, energy intake, tea intake	Stratified for age at recruitment and centre. Strengths: cohort design, multicentre coverage to examine variable range of intake across European countries, validated questionnaire, relatively long follow-up Limitations: modest number of HCC cases, lack of data on brewing methods
			Q1 (M: 0–83.3; F: 0–60)	47	1.00		
			Q2 (M: 83.3–200.4; F: 60–191.9)	49	0.85 (0.56–1.29)		
			Q3 (M: 200.5–476.9; F: 191.9–375)	38	0.63 (0.39–1.02)		
			Q4 (M: 477.2–830.4; F: 375–580.2)	36	0.49 (0.29–0.82)		
			Q5 (M 831.3–4500; F: 580.3–6250)	31	0.28 (0.16–0.50)		
			Trend test *P* value, < 0.001				
Petrick et al. (2015) USA, 1992–1995, 2007–2010 or variable	1 212 893; Liver Cancer Pooling Project (LCPP), USA-based NCI cohort consortium comprising NIH-AARP, AHS, USRTS, PLCO, WHS, CPS-II, IWHS, BWHS, WHI Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)*			Sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P*-value for trend of continuous variables	Strengths: large sample size allowed stratifying by caffeine content of coffee and sex, histological subtype of liver cancer (HCC and ICC) Limitations: number of ICC limited
			Non-drinker	85	1.00		
			Ever	650	1.00 (0.79–1.27)		
			> 0 to < 1	138	1.24 (0.94–1.64)		
			1 to < 2	149	1.16 (0.88–1.52)		
			2–3	255	0.89 (0.68–1.15)		
			> 3	97	0.73 (0.53–0.99)		
			Continuous	NR	0.90 (0.85–0.94)		
			Trend test *P* value, < 0.0001				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Coffee consumption (cups/day): men (530)*			Age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P*-value for trend of continuous variable	
			Non-drinker	40	1.00		
			Ever	490	1.21 (0.87–1.69)		
			> 0 to < 1	113	1.57 (1.09–2.25)		
			1 to < 2	103	1.35 (0.93–1.95)		
			2–3	195	1.06 (0.75–1.51)		
			> 3	79	0.93 (0.63–1.37)		
			Continuous (cups/day)	NR	0.90 (0.86–0.96)		
			Trend test *P* value, 0.0004				
			Coffee consumption (cups/day): women (205)				
			Non-drinker	45	1.00		
			Ever	160	0.78 (0.56–1.10)		
			> 0 to < 1	25	0.79 (0.47–1.33)		
			1 to < 2	46	1.01 (0.66–1.53)		
			2–3	60	0.71 (0.48–1.06)		
			> 3	18	0.46 (0.26–0.81)		
			Continuous (cups/day)	NR	0.87 (0.79–0.96)		
			Trend test *P* value, 0.004				
			Caffeinated coffee (cups/day)			Sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P* value for trend of continuous variables	
			Non-drinker	85	1.00		
			Ever	379	1.00 (0.77–1.28)		
			> 0 to < 1	58	1.22 (0.87–1.73)		
			1 to < 2	85	1.19 (0.87–1.62)		
			2–3	174	0.95 (0.72–1.26)		
			> 3	62	0.71 (0.50–1.01)		
			Trend test *P* value, 0.002				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Decaffeinated coffee (cups/day)*				
			Non-drinker	85	1.00		
			Ever	204	1.16 (0.88–1.53)		
			0	63	1.00		
			> 0 to < 1	58	1.33 (0.92–1.91)		
			1 to < 2	51	1.38 (0.95–2.02)		
			2–3	64	0.97 (0.67–1.40)		
			> 3	21	0.92 (0.55–1.54)		
			Trend test *P* value, 0.1				
		Liver and bile ducts: ICC	*Coffee consumption (cups/day)*				
			Non-drinker	33	1.00		
			Ever	199	0.93 (0.63–1.37)		
			> 0 to < 1	36	1.15 (0.70–1.89)		
			1 to < 2	33	0.79 (0.48–1.30)		
			2–3	85	0.93 (0.61–1.42)		
			> 3	40	1.00 (0.61–1.63)		
			Continuous, cups/day	NR	1.00 (0.92–1.08)		
			Trend test *P* value, 0.9				
			Caffeinated coffee (cups/day)				
			Non-drinker	33	1.00		
			Ever	119	0.91 (0.60–1.37)		
			0	33	1.00		
			> 0 to < 1	17	1.32 (0.71–2.43)		
			1 to < 2	15	0.59 (0.32–1.10)		
			2–3	57	0.91 (0.58–1.43)		
			> 3	30	1.08 (0.63–1.83)		
			Trend test *P* value, > 0.99				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Decaffeinated coffee (cups/day)*				
			Non-drinker	33	1.00		
			Ever	56	0.95 (0.59–1.53)		
			0	18	1.00		
			> 0 to < 1	15	1.17 (0.58–2.35)		
			1 to < 2	10	0.94 (0.43–2.07)		
			2–3	20	1.11 (0.56–2.17)		
			> 3	6	1.03 (0.39–2.70)		
			Trend test *P* value, 0.6				
Setiawan et al. (2015) USA, 1993–1996, 18 yr follow-up	162 022; multiethnic cohort (MEC) study, Hawaii and California Exposure assessment method: questionnaire	Liver/HCC	*Regular coffee (cups/day)*			Age, sex, ethnicity, education, BMI, alcohol intake, smoking status, diabetes	Strengths: prospective, long follow-up time, multiethnic and large sample size, confounder adjustment Limitations: coffee assessment by single self-report, lack of information on liver disease other than HCC, no information on HBV/HCV status
			Never	119	1.00		
			< 1	111	1.14 (0.88–1.48)		
			1	137	0.87 (0.67–1.11)		
			2–3	67	0.62 (0.46–0.84)		
			≥ 4	17	0.59 (0.35–0.99)		
			Trend test *P* value, 0.002				
			Decaffeinated coffee (cups/day)				
			Never	287	1.00		
			< 1	128	0.87 (0.70–1.08)		
			≥ 2	21	0.86 (0.55–1.34)		
			Trend test *P* value, 0.2				

Ab, antibody; AHS, Agricultural Health Study; ALT, alanine transaminase; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; CLD, chronic liver disease; CPS-II, Cancer Prevention Study-II; DCO, death certificate only; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; IWHS, Iowa Women's Health Study; JACC Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective; LCPP, Liver Cancer Pooling Project; M, male; MEC, multiethnic cohort; mo, month(s); NIH-AARP, National Institutes of Health–American Association of Retired Persons; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; USRTS, United States Radiologic Technologists Study; WHI, Women's Health Initiative; WHS, Women's Health Study; wk, week(s); yr, year(s)

data available from two cohort studies based in Miyagi, Japan. A self-administered questionnaire regarding the frequency of coffee consumption and other health habits was distributed to 22 404 women and men in Cohort 1 and 38 703 subjects in Cohort 2. After adjustment for age, sex, history of liver disease and diabetes, alcohol consumption, and smoking status, the pooled hazard ratios (95% CI) of drinking coffee occasionally and ≥ 1 cups/day compared with never were 0.71 (0.46–1.09) and 0.58 (0.36–0.96) (*P* for trend, 0.024). [The strengths of this study were its prospective design and large scale. Limitations included: the lack of information regarding HBV and HCV infection status; death certificate only (DCO) cases meant it was possible to misclassify secondary metastasis as cancer of the liver; and former drinkers were not distinguished from non-drinkers.]

Wakai et al. (2007) examined HCC mortality in relation to coffee consumption and anti-HCV antibody (Ab) seropositivity. This study was carried out in Japan as a nested case–control study as part of the JACC Study previously reported by Kurozawa et al. (2005). The analyses involved 96 HCC mortality cases with serum samples. Among 39 242 subjects donating blood samples at baseline, controls were matched for age, sex, and HCV-Ab seropositivity. Habitual coffee consumption was assessed by self-reported questionnaire at baseline. Coffee drinking was significantly associated with a decreased risk of death from HCC. After adjustment, including for history of diabetes and liver disease, odds ratios (95% CI) for daily coffee drinkers versus non-drinkers were 0.49 (0.25–0.96), 0.31 (0.11–0.85), and 0.75 (0.29–1.92) for total subjects, HCV-Ab-positive subjects and HCV-Ab-negative subjects, respectively. The increased risk observed among HCV-Ab-positive individuals with significant trend (*P* for trend, 0.031) was not observed among HCV-Ab-negative individuals. [The main strength of this study was its nested case–control design. Limitations included the consideration of mortality and not incidence, and coffee intake was only recorded at baseline.]

Hu et al. (2008) examined the single and joint associations of coffee consumption and serum gamma-glutamyltransferase (GGT) with the risk of primary cancer of the liver. The study cohort included 60 323 Finnish subjects who were aged 25–74 years and free from any cancer at baseline. Information on coffee consumption was collected using mailed self-administered questionnaires. After adjustment for risk factors including alcohol consumption, diabetes, and chronic liver disease at baseline and during follow-up, and BMI, hazard ratios (95% CI) of liver cancer in participants who drank 2–3, 4–5, 6–7, and ≥ 8 cups/day of coffee compared with none were 0.66 (0.37–1.16), 0.44 (0.25–0.77), 0.38 (0.21–0.69), and 0.32 (0.16–0.62) (*P* for trend, 0.003). Further adjustment for serum GGT in subgroup analysis did not substantially affect the results. This inverse association between coffee consumption and liver cancer risk persisted in analyses stratified by several risk factors. [The main strengths of this study were its large-scale, population-based, prospective design and long follow-up (19.3 years). Limitations included consideration of coffee consumption at baseline only, a lack of data on HBV or HCV, and residual confounding.]

Ohishi et al. (2008) conducted a nested case–control study using sera stored before HCC diagnosis in the longitudinal cohort of Japanese atomic bomb survivors, considering the joint effect (synergism) of HBV and HCV infections. The study included 224 incident HCC cases and 644 controls who were matched to cases on sex, age (± 2 years), city, and time (± 2 years) and method of serum storage, and were counter-matched on radiation dose. Information on daily coffee drinking was obtained from a survey in 1978. After adjustment for HBV and HCV infections, alcohol consumption, smoking habits, BMI, and diabetes mellitus, the odds ratio of HCC for daily coffee drinking compared with

never drinking coffee was 0.4 (95% CI, 0.16–1.02; *P* for trend, 0.055). [The strengths of this study were its prospective, nested case–control design and the fact that HCV and HBV infection status was considered. The main limitation was that severity of liver fibrosis could not be considered.]

Inoue et al. (2009) examined whether coffee consumption was associated with a reduced risk of liver cancer by hepatitis virus infection status in the JPHC Study Cohort II. This study was a subcohort analysis of Inoue et al. (2005), with HCV and HBV infections determined by analyses of blood samples. Hazard ratios of liver cancer for different levels of coffee consumption compared with almost-never drinkers were estimated after adjusting for risk factors including smoking status, ethanol intake, BMI, history of diabetes, and HCV and HBV infection status. Increased coffee consumption was associated with a reduced risk of liver cancer in all subjects; multivariate-adjusted hazard ratios (95% CI) for < 1, 1–2, and ≥ 3 cups/day were 0.67 (0.42–1.07), 0.49 (0.27–0.91), and 0.54 (0.21–1.39), respectively. A similar trend in the hazard ratios was observed in those with HCV and/or HBV infection. [The Working Group considered the strengths of this study to be its prospective analysis with blood samples as well as consideration of HCV and HBV infection status. Its main limitation was the relatively small number of cases.]

Johnson et al. (2011) examined the association between coffee consumption and the risk of developing HCC of the liver within the Singapore Chinese Health Study, a prospective cohort of 63 257 Chinese men and women aged 45–74 years (a relatively high-risk population for developing HCC). Data on coffee consumption were collected through in-person interviews at baseline during 1993–1998. A total of 362 cohort participants had developed HCC by 2006. High levels of coffee consumption were associated with reduced risk of HCC. Compared with non-drinkers, individuals who consumed coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, and ≥ 3 cups/day had a reduced risk of HCC with hazard ratios (95% CI) of 0.94 (0.63–1.40), 1.17 (0.87–1.56), 0.78 (0.56–1.07), and 0.56 (0.31–1.00), respectively (*P* for trend, 0.05). All results were adjusted for age at recruitment, sex, dialect group, year of recruitment, BMI, level of education, consumption of alcoholic beverages, cigarette smoking, frequency of black and green tea intake, and history of diabetes.

This study also provided results from the subset of the cohort who provided blood samples at baseline. A total of 92 cases of HCC of the liver and their controls matched for age, date of interview, and date of blood sample collection were analysed. On adjustment for HBV and HCV infection status, in addition to the factors previously indicated, the odds ratios of HCC and high consumption of coffee in the subset were similar to those based on the entire cohort, although not all odds ratios were statistically significant. Odds ratios (95% CI) of the risk of HCC for individuals who consumed coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, and ≥ 3 cups/day compared with non-drinkers were 0.77 (0.26–2.29), 0.84 (0.38–1.85), 1.32 (0.56–3.14), and 0.23 (0.05–1.21), respectively (*P* for trend, 0.71). [The strength of this study was its prospective nature and use of blood samples for part of the cohort. Its limitations included a lack of HBV and HCV status for all cohort participants, participants in the cohort were not measured for the amount of liver damage present at baseline, and the relatively small number of cases.]

Lai et al. (2013) evaluated the association between coffee intake and incident cancer of the liver and chronic liver disease mortality in 27 037 Finnish male smokers, aged 50–69 years, in the ATBC Study. Coffee consumption was recorded at baseline by FFQ and subjects were followed up for 24 years for incident liver cancer. Adjusted hazard ratios (95% CI) for the association between coffee intake and incident liver cancer, compared with never drinkers, were 1.35 (0.65–2.82), 0.73 (0.48–1.12), 0.52 (0.33–0.82),

0.45 (0.26–0.78), and 0.53 (0.30–0.95) for drinking coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, 3 to < 4, and ≥ 4 cups/day, respectively (*P* for trend, 0.0007). Inverse associations persisted in those without diabetes, among HBV- and HCV-negative subjects, and in analyses stratified by age, BMI, alcohol consumption, and smoking dose. The study observed similar associations for those drinking boiled or filtered coffee. This study also provided results among those with information on HBV and HCV using 155 cases of cancer of the liver and 770 controls. The association was not appreciably different when adjusted for HBV and HCV infection status. [The strengths of this study were its prospective nature and long follow-up. However, it was not reported whether the coffee consumed was caffeinated or decaffeinated.]

Bamia et al. (2015) investigated the association between coffee consumption and risk of HCC in the EPIC study. Information on coffee intake was obtained through centre-specific questionnaires on cups per day, week, or month. Hazard ratios for HCC incidence in relation to categories of coffee intake in mL/day were estimated, adjusting for risk factors including self-reported diabetes, ethanol intake, BMI, energy intake, and tea intake. Compared with the lowest quintile (Q1), coffee consumers in the higher quintiles had lower hazard ratios (95% CI) of 0.85 (0.56–1.29), 0.63 (0.39–1.02), 0.49 (0.29–0.82), and 0.28 (0.16–0.50) for quintiles Q2, Q3, Q4, and Q5, respectively (*P* for trend, < 0.001). There was no compelling evidence of heterogeneity of these associations across strata of important HCC risk factors, including HBV or HCV infection status, in a nested case–control analysis. The inverse, monotonic associations of coffee intake with risk of HCC were apparent for caffeinated (*P* for trend, 0.009) but not decaffeinated coffee (*P* for trend, 0.45), but this information was only available for about one third of the study subjects. [The strengths of this study included its cohort design, multicentre coverage to examine a variable range of intake across European countries, a validated questionnaire, and a relatively long follow-up. Its limitations were the modest number of HCC cases and a lack of data on brewing methods.]

Aleksandrova et al. (2015) also used the EPIC population to evaluate the potential mediating roles of inflammatory, metabolic, liver injury, and iron metabolism biomarkers on the association between coffee intake and risk of HCC using a nested case–control study design. The association between cancer of the liver and coffee consumption was similar to that reported by Bamia et al. (2015), who also provided evidence that this association was mediated by biomarkers of inflammation and hepatocellular injury.

Petrick et al. (2015) investigated whether caffeine is responsible for the inverse association between coffee and cancer of the liver. Through the Liver Cancer Pooling Project, a consortium of US-based cohort studies, data from 1 212 893 individuals (860 cases of HCC and 260 cases of intrahepatic cholangiocarcinoma (ICC)) in 9 cohorts were pooled. Hazard ratios and confidence intervals were estimated adjusting for sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, and alcohol intake. Higher coffee consumption was associated with a lower risk of HCC; the hazard ratio for consumption of > 3 cups/day of coffee compared with a non-drinker was 0.73 (95% CI, 0.53–0.99; *P* for trend, < 0.0001). When considering men and women separately, a reduced risk for consumption of > 3 cups/day of coffee compared with a non-drinker was notable among women (HR, 0.46; 95% CI, 0.26–0.81; *P* for trend, 0.004) compared with men (HR, 0.93; 95% CI, 0.63–1.37; *P* for trend, 0.0004). The associations were stronger for caffeinated coffee; the hazard ratio for consumption of > 3 cups/day of coffee compared with a non-drinker was 0.71 (95% CI, 0.50–1.01; *P* for trend, 0.002) for caffeinated coffee compared with 0.92 (95% CI, 0.55–1.54; *P* for trend, 0.1) for decaffeinated coffee. There was no association between coffee consumption and ICC. [The Working Group

noted that the large sample size allowed stratification by caffeine content of coffee and sex. An additional strength of the study was consideration of the histological subtype of liver cancer (HCC and ICC). The number of cases of ICC was however limited and no data on HBV/HCV status were provided.]

Setiawan et al. (2015) evaluated the association between coffee intake and HCC of the liver in 162 022 African-American, Native Hawaiian, Japanese-American, Latino, and white subjects in the US Multiethnic Cohort (MEC) of Hawaii and California assembled in 1993–1996. During an 18-year follow-up period, there were 451 incident cases of HCC. Compared with non-coffee drinkers, those who drank 2–3 cups/day had a 38% reduction in risk for HCC (HR, 0.62; 95% CI, 0.46–0.84); those who drank ≥ 4 cups per day had a 41% reduction in HCC risk (HR, 0.59; 95% CI, 0.35–0.99) ($P < 0.002$). The inverse associations were similar regardless of the participants' ethnicity, sex, BMI, smoking status, alcohol intake, or diabetes status. [The strengths of this study included its prospective design, the long follow-up time, its multiethnicity, and the large sample size. Limitations included coffee assessment by a single self-report, a lack of information on liver disease other than HCC, and no information on HBV and HCV infection status.]

2.3.2 Case–control studies

See Table 2.6.

(a) Population-based case–control studies

Tanaka et al. (2007) conducted a case–control study recruiting 209 incident cases of HCC and three different control sets (1308 community controls, 275 hospital controls, and 381 patients with chronic liver disease without HCC), all of whom were aged 40–79 years and residents of Saga Prefecture, Japan. A questionnaire survey obtained information on coffee use during the previous 1–2 years and 10 years before, and plasma HBV surface antigen (HBsAg) and HCV-Ab were tested for all but the community controls. After adjustment for sex, age, heavy alcohol use, smoking status, and HBV and HCV markers (except for community controls), coffee use during the previous 1–2 years was associated with a decreased HCC risk using any of the control groups. For coffee use 10 years before, comparison between HCC cases and either community controls or chronic liver disease (CLD) patients revealed a decreased risk. Against community controls, adjusted odds ratios (95% CI) for occasional use, 1–2 cups/day, and ≥ 3 cups/day compared with no use were 0.33 (0.22–0.48), 0.27 (0.15–0.48), and 0.22 (0.11–0.43), respectively (P for trend, < 0.001). Against CLD controls, the equivalent odds ratios (95% CI) were 0.86 (0.55–1.34), 0.62 (0.32–1.21), and 0.53 (0.25–1.12), respectively. No significant trend was observed using hospital patients as controls. [The strengths of this study include the multiple centres and multiple types of controls (community, hospital, and CLD). Limitations include the possible decrease of coffee use among HCC cases due to their advanced liver disease, and the fact that caffeine and unfiltered coffee intake could not be evaluated due to uncommon use.]

(b) Hospital-based case–control studies

La Vecchia et al. (1989b) investigated the association between coffee drinking and the risk of digestive tract neoplasms including cancer of the liver in a hospital-based case–control study; 151 cases of liver cancer and 1944 control subjects admitted for acute, non-digestive tract disorders in general hospitals from the Greater Milan area, Italy, during 1983–1988 were included. Information on coffee consumption was collected by interview using a standard questionnaire. There was no significant or consistent association between coffee intake and liver cancer. The multivariate odds ratio for consumption of 2 cups/day and ≥ 3 cups/day compared

Table 2.6 Case–control studies on cancer of the liver and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
La Vecchia et al. (1989b) Italy, 1983–1988	Cases: 151 (115 men, 36 women) histologically confirmed cases Controls: 1944 (1334 men, 610 women) patients admitted for acute, non-digestive tract disorders Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day)* 0–1 2 ≥ 3 Trend test *P* value, 0.09	 71 39 41	 1.00 0.79 (NR) 0.78 (NR)	Age, sex, social class, education, marital status, smoking, alcohol consumption	Strengths: multicentre network, well-defined catchment area Limitations: hospital-based, no virus infection status adjustment
Kuper et al. (2000a) Greece, 1995–1998	Cases: 333 (283 men, 50 women) HCC cases Controls: 360 (298 men, 62 women) hospitalized for eye, ear, nose, throat, or orthopaedic conditions (matched for sex and 5-year age band) Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/wk)* All subjects Non-drinkers < 20 ≥ 20 *Coffee consumption for subjects with virus information (330) (cups/wk)* Non-drinkers < 20 ≥ 20 Trend test *P* value, 0.75 *Coffee consumption for subjects without both HBsHg and anti-HCV (82) (cups/wk)* Non-drinkers < 20 ≥ 20 Trend test *P* value, 0.66	 333 36 230 67 NR NR NR NR NR NR	 – 1.0 0.9 (0.5–1.5) 0.7 (0.4–1.2) 1.0 1.1 (0.5–2.6) 0.9 (0.4–2.5) 1.0 1.9 (0.6–5.9) 1.7 (0.5–5.9)	Age and sex Age, sex, year of schooling, HBsAg, and anti-HCV Age and sex	Strengths: virus infection status considered Limitations: hospital-based

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gallus et al. (2002) Italy and Greece, 1984–1997 (Italy), 1995–1998 (Greece)	Cases: 834 (661 men, 173 women) Controls: 1912 (1439 men, 473 women), Italian patients with acute non-neoplastic conditions (matched for area and hospital) and Greek patients hospitalized for eye, ear, nose, throat or orthopaedic conditions (matched for sex and 5-year age band) Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day): Greece and Italy combined*			Age, sex, education, tobacco smoking, alcohol drinking, BMI, history of diabetes and hepatitis	Analysis of data from La Vecchia et al. (1989b) and Gallus et al. (2002) Strengths: participation almost complete (< 5% refuse interview), confounding factors considered Limitations: hospital-based, change of exposure after hospital admission
			Non-drinkers	129	1.0		
			Drinkers	705	1.0 (0.7–1.3)		
			1	231	1.2 (0.9–1.6)		
			2	292	1.0 (0.7–1.3)		
			≥ 3	178	0.7 (0.5–1.0)		
			Trend test *P* value, 0.015				
			Duration (yr): Greece and Italy combined				
			Non-drinkers	705	1.0		
			< 30	161	1 (0.7–1.4)		
			30–39	243	1 (0.7–1.4)		
			≥ 40	294	1 (0.7–1.3)		
			Trend test *P* value, 0.864				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gelatti et al. (2005) Italy, 1994–2003	Cases: 250 (204 men, 46 women), first diagnosis of HCC admitted to two major hospitals Controls: 500 (408 men, 92 women) admitted for other than liver disease, matched with age, sex, date of hospital admission Exposure assessment method: questionnaire, interview	Liver/ HCC	*Coffee consumption (cups/day)*			Adjusted for HBV, HCV, alcohol intake, sex, age	Strengths: virus infection adjusted and stratified Limitations: hospital-based
			0	44	1.0		
			1–2	119	0.8 (0.4–1.3)		
			3–4	69	0.4 (0.2–0.8)		
			≥ 5	18	0.3 (0.1–0.7)		
			Coffee consumption (cups/day) by HBV infection				
			HBV–, 1–2	129	1.0		
			HBV–, > 2	61	0.5 (0.3–0.8)		
			HBV+, 1–2	35	16.4 (7.1–38.2)		
			HBV+, > 2	25	7.3 (3.3–16.1)		
			Coffee consumption (cups/day) by HCV infection				
			HCV–, 1–2	92	1.0		
			HCV–, > 2	53	0.6 (0.4–0.9)		
			HCV+, 1–2	70	38.2 (18.2–80.1)		
			HCV+, > 2	34	9.0 (4.5–17.8)		
Ohfuji et al. (2006) Japan, 2001–2002	Cases: 73 primary HCC diagnosis by histopathologic examination or imaging study from the hospital record Controls: 253, ratio of 1:1–5 matching for age (± 2 yr), sex, the date of first hospital visit Exposure assessment method: questionnaire	Liver/ HCC	*Frequency of consumption (cups/day) before identification of liver disease*			Duration from first identification of liver disease, BMI at first identification of liver disease, disease severity at first hospital visit, family history of liver disease, interferon therapy, smoking, alcohol drinking, other caffeine-containing beverage	Strengths: both cases and controls were HCV infection positive Limitations: hospital-based, selection bias (all subjects were HCV+), timing of HCV infection was known for 65% of subjects, imperfect memory of distant past history of coffee consumption
			Non-drinker	25	1.00		
			< 1	19	0.61 (0.18–2.03)		
			≥ 1	29	0.38 (0.13–1.12)		
			Trend test *P* value, 0.171				
			Frequency of consumption (cups/day) after identification of liver disease				
			Non-drinker	27	1.00		
			< 1	25	0.57 (0.20–1.67)		
			≥ 1	21	0.19 (0.05–0.71)		
			Trend test *P* value, 0.032				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Montella et al. (2007) Italy, 1999–2002	Cases: 185 (149 men, 36 women) incident HCC who had not yet received any cancer treatment at study entry Controls: 412 (281 men, 131 women) from same hospitals for acute, non-neoplastic diseases unrelated to diet Exposure assessment method: FFQ administered by trained interviewer	Liver/ HCC	*Coffee consumption (cups/wk)*			Age, sex, centre, education, smoking habits, maximal lifetime alcohol intake, HCV/HBV status	Strengths: virus infection status considered, minimal information bias due to same interviewer under similar setting between cases and controls Limitations: hospital-based, recall and selection bias, change of coffee consumption not considered
			Abstainers	27	2.28 (0.99–5.24)		
			< 14	67	1.00		
			14–20	50	0.54 (0.27–1.07)		
			21–27	27	0.57 (0.25–1.32)		
			≥ 28	14	0.43 (0.16–1.13)		
			Trend test *P* value, 0.02				
			Decaffeinated coffee consumption (never/ ever)				
			Never	174	1.00		
			Ever	11	0.72 (0.21–2.50)		
			Coffee consumption (cups/wk) for HCV–/HBV– (38 cases)				
			Abstainers	9	2.09 (0.72–6.07)		
			< 14	13	1.00		
			14–20	7	0.63 (0.22–1.82)		
			≥ 21	9	0.38 (0.13–1.09)		
			Trend test *P* value, < 0.01				
			Coffee consumption (cups/wk) for HCV+/HBV+ (147 cases)				
			Abstainers	18	2.64 (0.59–11.93)		
			< 14	54	1.00		
			14–20	43	0.58 (0.21–1.52)		
			≥ 21	32	0.84 (0.23–3.01)		
			Trend test *P* value, 0.15				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tanaka et al. (2007) Japan, 2001–2004	Cases: 209 from two large hospitals Controls: 1308 community control, 275 hospital control, 381 CLD control Exposure assessment method: questionnaire, interview	Liver/ HCC	*Coffee consumption (cups/day) during previous 1–2 yr: community controls*			Sex, age, heavy alcohol drinking, smoking status	Strengths: multicentre study, multiple types of controls (community, hospital, CLD) Limitations: possible decrease of coffee use among HCC cases due to their advanced liver disease
			None	135	1.00		
			Occasional	53	0.31 (0.21–0.46)		
			1–2	15	0.11 (0.06–0.21)		
			≥ 3	6	0.10 (0.04–0.24)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) during previous 1–2 yr: hospital controls			Sex, age, heavy alcohol drinking, smoking status, HBsAg, anti-HCV	
			None	135	1.00		
			Occasional	53	0.42 (0.19–0.95)		
			1–2	15	0.23 (0.08–0.68)		
			≥ 3	6	1.08 (0.22–5.35)		
			Trend test *P* value, 0.03				
			Coffee consumption (cups/day) during previous 1–2 yr: CLD controls				
			None	135	1.00		
			Occasional	53	0.86 (0.55–1.35)		
			1–2	15	0.42 (0.21–0.84)		
			≥ 3	6	0.29 (0.11–0.75)		
			Trend test *P* value, 0.001				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tanaka et al. (2007) (cont.)			*Coffee consumption (cups/day) during previous 10 yr: community controls*			Sex, age, heavy alcohol drinking, smoking status	
			None	127	1.00		
			Occasional	53	0.33 (0.22–0.48)		
			1–2	17	0.27 (0.15–0.48)		
			≥ 3	12	0.22 (0.11–0.43)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) during previous 10 yr: hospital controls			Sex, age, heavy alcohol drinking, smoking status, HBsAg, anti-HCV	
			None	135	1.00		
			Occasional	53	0.99 (0.42–2.32)		
			1–2	15	0.95 (0.31–2.89)		
			≥ 3	6	2.59 (0.58–11.56)		
			Trend test *P* value, 0.47				
			Coffee consumption (cups/day) during previous 10 yr: CLD controls				
			None	135	1.00		
			Occasional	53	0.86 (0.55–1.34)		
			1–2	15	0.62 (0.32–1.21)		
			≥ 3	6	0.53 (0.25–1.12)		
			Trend test *P* value, 0.05				
Leung et al. (2011) China, Hong Kong SAR, 2007–2008	Cases: 109 HCC by review of medical record Controls: 125 HBV carriers at the same hospital Exposure assessment method: questionnaire, face-to-face interview	Liver/ HCC	*Coffee consumption (times/wk)*			Age, sex, cigarette smoking, alcohol use, tea consumption, and physical activity	Strengths: HBV carriers Limitations: hospital-based
			No	81	1.00		
			Yes	28	0.54 (0.30–0.97)		
			< 1	86	1.00		
			1–3	11	0.58 (0.24–1.36)		
			≥ 4	12	0.41 (0.19–0.89)		
			Trend test *P* value, 0.02				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jang et al. (2013) Republic of Korea, 2007–2008	Cases: 258 HCC Controls: 480 health-check examinee (HCE), 626 CLD Exposure assessment method: questionnaire	Liver/ HCC	*Lifetime amount (cups): HCE (480 cases)*			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol consumption	Strengths: results from endemic area, multiple control (HCE and CLD), virus infection status considered Limitations: hospital-based
			≤ 20 000	54	1.00		
			> 20 000	204	0.56 (0.33–0.95)		
			Lifetime amount (cups): CLD (258 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol drinking amount, chronic liver disease (none, HCV, HBV, both HCV and HBV)	
			≤ 20 000	54	1.00		
			> 20 000	204	0.55 (0.36–0.85)		
			Lifetime amount (cups): patients without HBV (83 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol consumption	
			≤ 20 000	NR	1.00		
			> 20 000	NR	0.47 (0.23–0.94)		
			Lifetime amount (cups): patients with HBV (170 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol drinking amount, HBV status	
			≤ 20 000	NR	1.00		
			> 20 000	NR	0.64 (0.36–1.14)		
Patil et al. (2014) India (Mumbai), 2009–2011	Cases: 141 HCC patients, consecutive recruitment Controls: 240 patients with CLD of viral etiology, consecutive recruitment Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day)*			Age, alcohol consumption, ALT level, ferritin level, family income, sex, tobacco consumption	Strengths: viral infection positive only, ferritin level considered Limitations: hospital-based
			Never	105	1.00		
			Ever	36	2.00 (1.05–3.83)		
			≤ 2	20	1.00		
			> 2	3	0.37 (0.10–1.34)		

ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; DM, diabetes mellitis; FFQ, food frequency questionnaire; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCE, health-check examinee; HCV, hepatitis C virus; NR, not reported; SAR, Special Administrative Region; wk, week(s); yr, year(s)

with 0–1 cups/day were 0.79 and 0.78, respectively [confidence intervals were not reported]. The inverse exposure–response trend was not significant (*P* for trend, 0.09). [The multicentre network and well-defined catchment area were the strengths of this study, while limitations included the hospital-based design and lack of adjustment for virus infection status.]

Kuper et al. (2000a) conducted a hospital-based case–control study in Greece. Blood samples and questionnaire data were obtained from 333 incident cases of HCC of the liver during 1995–1998, as well as from 360 controls matched for sex and age (± 5 years) who were hospitalized for eye, ear, nose, throat, or orthopaedic conditions in Athens. Information on coffee consumption was collected by interview. Hepatitis B surface antigen (HBsAg) and antibodies to HCV (anti-HCV) were tested for the study participants. Coffee intake was not associated with HCC risk after controlling for age, sex, year of schooling, and HBV and HCV infection status. Compared with non-drinkers, odds ratios (95% CI) for consumption of < 20 cups/week and ≥ 20 cups/week were 1.1 (0.5–2.6) and 0.9 (0.4–2.5), respectively. [Consideration of virus infection status was a strength of this study, while its main limitation was its hospital-based design.]

Gallus et al. (2002) analysed the association between coffee consumption and HCC of the liver in the two preceding case–control studies conducted in Italy and Greece (La Vecchia et al., 1989b; Kuper et al. 2000a). Compared with non-drinkers, the multivariate odds ratio (95% CI) adjusting for age, sex, education, tobacco smoking, alcohol drinking, BMI, and history of diabetes and hepatitis was 0.7 (0.5–1.0) for drinkers of ≥ 3 cups/day (*P* for trend, 0.015). Duration (years) of coffee consumption was not associated with risk of HCC. [The strengths of this study were an almost-complete participation rate (< 5% refused interviews) and consideration of confounding factors. It was limited by its hospital-based design.]

Gelatti et al. (2005) conducted a hospital-based case–control study in an area of northern Italy. A total of 250 cases of HCC of the liver and 500 controls, hospitalized for any reason other than neoplasms and liver and alcohol-related diseases, were recruited during 1994–2003. Lifetime history of coffee consumption was assessed using a standardized questionnaire. Coffee consumption in the decade before the interview was associated with a reduced risk of HCC with a clear inverse dose–response relationship. With respect to non-drinking subjects, the odds ratio (95% CI) was 0.3 (0.1–0.7) for ≥ 5 cups/day. [The strengths of this study included adjustment and stratification for virus infection. The hospital-based study design was a limitation.]

Ohfuji et al. (2006) conducted a hospital-based case–control study in Japan to assess the association between coffee and HCC of the liver, in which both 73 cases and 253 controls were patients with chronic type C liver disease. A self-administered questionnaire was used to assess coffee consumption. The effect of coffee intake was estimated separately for before and after first identification of liver disease. Coffee drinking on a daily basis (≥ 1 cup/day) revealed lowered odds ratios as compared with non-drinkers both before first identification of liver disease (OR, 0.38; 95% CI, 0.13–1.12; *P* for trend, 0.171) as well as after disease identification (OR, 0.19; 95% CI, 0.05–0.71; *P* for trend, 0.032). Odds ratios were adjusted for time from the first identification of liver disease, BMI, smoking, alcohol drinking, consumption of other caffeine-containing beverages, and clinical characteristics. The inverse association persisted after excluding subjects who reported a reduction in the frequency of coffee intake after first identification of liver disease. [The strength of this study was that both cases and controls were HCV positive. Limitations included: hospital-based design, generalizability (all subjects were HCV-positive), missing

information on the timing of HCV infection (known for only 65% of subjects), and imperfect recall of distant past coffee consumption.]

Montella et al. (2007) conducted a hospital-based case–control study in Italy that included 185 incident, histologically confirmed cases of HCC aged 43–84 years that were identified during 1999–2002. Controls were 412 subjects admitted to the same hospital networks as the cases for acute, non-neoplastic diseases unrelated to diet. Coffee consumption was assessed using a validated FFQ. Compared with people who drank < 14 cups/week of coffee, the adjusted risk of HCC decreased for increasing levels of consumption with odds ratios (95% CI) of 0.54 (0.27–1.07) for 14–20 cups/week, 0.57 (0.25–1.32) for 21–27 cups/week, and 0.43 (0.16–1.13) for ≥ 28 cups/week (*P* for trend, 0.02). An increased risk was observed among abstainers of coffee relative to people who drank < 14 cups/week of coffee (OR, 2.28; 95% CI, 0.99–5.24). Inverse associations were observed across strata of HCV and HBV infections and alcohol drinking. A non-significant inverse association was observed with consumption of decaffeinated coffee (OR, 0.72; 95% CI, 0.21–2.50). [The strengths of this study were the consideration of hepatitis infection status, and minimal information bias due to the same interviewer being used under a similar setting between cases and controls. The hospital-based design was a limitation.]

Leung et al. (2011) examined whether coffee has a protective effect in chronic HBV carriers, a group at high risk of developing liver cancer, in a hospital-based case–control study in Hong Kong Special Administrative Region, China. A total of 234 HBV chronic carriers (109 HCC cases and 125 controls) were recruited from a core hospital during 2007–2008. Data collection included review of medical records and face-to-face interview. On adjusting for age, sex, cigarette smoking, alcohol use, tea consumption, and physical activity, coffee drinking significantly reduced the risk of HCC (OR, 0.54; 95% CI, 0.30–0.97) compared with non-drinkers. The study also observed a significant dose–response association (*P* for trend, 0.02), with a reduced risk for moderate drinkers (≥ 4 times/week) of 59% (OR, 0.41; 95% CI, 0.19–0.89) compared with those with no coffee habit (< 1 time/week). [The main strength of this study was the use of HBV carriers to control for confounding by infection status. The hospital-based design was a limitation.]

Jang et al. (2013) performed a hospital-based case–control study in the Republic of Korea to determine the association between lifetime coffee consumption and the risk of HCC development in a HBV-prevalent region. A total of 1364 subjects – 258 HCC patients, 480 health-check examinees (control group 1, HCE), and 626 patients with chronic liver disease other than HCC (control group 2, CLD) – were interviewed on smoking, alcohol consumption, and coffee drinking using a standardized questionnaire. HBV e-antigen (HBeAg) status and serum HBV DNA levels were measured in patients infected with HBV. After adjustment for risk factors, including the presence of hepatitis virus (except for HCE) and lifetime alcohol drinking/smoking, a high lifetime consumption of coffee (> 20 000 cups) compared with a low lifetime coffee consumption (≤ 20 000 cups) was associated with a reduced risk of HCC using both HCE and CLD control groups, yielding odds ratios (95% CI) of 0.56 (0.33–0.95) and 0.55 (0.36–0.85), respectively. The high coffee consumption was not associated with a significantly increased risk of HCC; among patients with HBV, the odds ratio was 0.64 (95% CI, 0.36–1.14) after adjustment for HBeAg status, serum HBV DNA level, and antiviral therapy. [The strengths of this study included the fact that results were obtained from a hepatitis endemic area with consideration of infection status, the use of multiple controls (HCE and CLD). Limitations included its hospital-based design

and the potential for selection bias with CLD controls.]

Patil et al. (2014) analysed the association between coffee consumption and HCC of the liver in an Indian population that was HCV and/or HBV positive. The study enrolled 141 patients with HCC and 240 patients with HBV or HCV infection-related CLD. After adjusting for alcohol consumption, ALT level, ferritin level, and other covariates, ever compared with never consumption of coffee was associated with an increased risk of HCC (OR, 2.00; 95% CI, 1.05–3.83) in patients with hepatitis-related CLD. [The strengths of the study included the use of HBV- and/or HCV-positive subjects and the consideration of ferritin level. Limitations included the hospital-based design, the fact that controls were patients with CLD, and the categories of coffee consumption being only never or ever.]

2.3.3 Meta-analyses

Seven meta-analyses of the association between cancer of the liver and coffee drinking have been published (Bravi et al., 2007a, 2009, 2013, 2017; Larsson & Wolk, 2007; Yu et al., 2011; Sang et al., 2013). The most recent and comprehensive meta-analyses are summarized here.

Bravi et al. (2013) conducted a meta-analysis of epidemiological studies that examined the association between liver cancer and coffee consumption. A PubMed/MEDLINE search from 1966 to September 2012 was performed to identify case–control or cohort studies that examined the association between coffee consumption and cancer or HCC of the liver. The summary relative risks for any, low, and high consumption of coffee versus no consumption were obtained from the results for eight cohort and eight case–control studies. The summary relative risk for any coffee consumption versus no consumption was 0.60 (95% CI, 0.50–0.71; I^2, 73.9%; $P < 0.001$) from 16 studies that included a total of 3153 HCC cases. The findings were similar for the case–control (RR, 0.56; 95% CI, 0.42–0.75, I^2, 74.1%; P for trend, < 0.001) and the cohort studies 0.64 (RR, 0.64; 95% CI, 0.52–0.78; I^2, 69.1%; P for trend, 0.002). Compared with no coffee consumption, the summary relative risk was 0.72 (95% CI, 0.61–0.84; I^2, 58.4%; P for trend, 0.003) for low consumption and 0.44 (95% CI, 0.39–0.50; I^2, 0.0%; P for trend, 0.495) for high consumption. The relative risk was 0.80 (95% CI, 0.77–0.84) for an increment of 1 cup/day of coffee. The inverse association between coffee and HCC risk was consistent regardless of subject sex, alcohol consumption, or history of hepatitis or liver disease. Several cohort studies reported after 2013 were not included in this meta-analysis.

Bravi et al. (2017) recently conducted an updated meta-analysis of prospective studies, including results from the recent cohort studies which were not included in the previous meta-analysis by Bravi et al. (2013), by performing a PubMed/MEDLINE and Embase search of articles published up to June 2015 on cohort studies. Twelve cohort studies (2154 cases in total) were included in this meta-analysis. Compared with no consumption, the summary relative risks for HCC by random-effect model were 0.66 (95% CI, 0.55–0.78) for regular, 0.78 (95% CI, 0.66–0.91) for low, and 0.50 (95% CI, 0.43–0.58) for high coffee consumption, with a significant heterogeneity ($P < 0.001$ for I^2-statistic). The summary relative risk for an increment of 1 cup/day was 0.85 (95% CI, 0.81–0.90). This meta-analysis supported the inverse association between coffee consumption and the risk of HCC.

2.4 Cancer of the breast in women

A total of 23 cohort and 22 case–control studies that investigated the association between coffee intake and of cancer of the breast in women were available for review by the Working Group. All but one of the cohort studies investigated

incident breast cancer; the remaining study considered breast cancer mortality. Four of the case–control studies investigated breast cancer in women with known status regarding *BRCA1/BRCA2* mutations. Four meta-analyses of the above-indicated studies, published from 2009 to 2013, are also included in this review.

Thirteen (twelve case–control and one cohort) studies were excluded for the following reasons.

The studies by Lawson et al. (1981), Lubin et al. (1981), and Franceschi et al. (1995) were excluded because coffee and tea (and decaffeinated coffee in Franceschi et al., 1995) were examined as one combined exposure; the association between coffee and risk of breast cancer could not be separated from those of the other beverages.

The study by Mansel et al. (1982) was excluded as the study design and analysis were unclear.

The studies by Lê (1985), Rohan & McMichael (1988), Smith et al. (1994), Zhang et al. (2007), and Ayari et al. (2013) were excluded as no measure of relative risk for coffee intake in relation to risk of breast cancer was reported.

The study by Pozner et al. (1986), which examined caffeine and coffee intakes in women with breast cancer to determine whether they influence cell differentiation in tumours, was excluded since, as described in the previous *IARC Monographs* evaluation (Volume 51; IARC, 1991), this study is difficult to group with other studies of etiology.

The study by Männistö et al. (1999), which used the association between coffee consumption and breast cancer risk as an illustration paradigm when investigating a methodological issue, was excluded because of the influence of recall bias in previous knowledge of health status.

The study by Shirlina et al. (2015), which investigated nutritional risk factors in association with breast cancer in the Russian Federation, was excluded as the full text (in Russian) could not be obtained.

A cohort study by Jacobsen et al. (1986), investigating the association between coffee and cancer incidence using two Norwegian cohorts, was excluded due to the small number of breast cancer cases in women (38/2891) and a lack of adjustment for reproductive factors or smoking.

2.4.1 Cohort studies

See Table 2.7.

(a) Incident cancer of the breast

Vatten et al. (1990) studied the association between coffee consumption and breast cancer incidence using a cohort of 14 593 Norwegian women (aged 35–51 years) who participated in a health screening examination for cardiovascular disease (National Health Screening Service) between 1974 and 1977. Age-adjusted incidence rate ratios (IRR) in relation to breast cancer risk indicated an overall inverse, non-statistically significant association between daily intake of coffee and risk of breast cancer. There was an indication or effect modification of the association by BMI (P-interaction = 0.02). The risk of breast cancer for coffee consumption of ≥ 5 cups/day compared with ≤ 2 cups/day yielded an incidence rate ratio of 0.5 (95% CI, 0.3–0.9; P for trend, 0.02) for BMI < 24. For BMI ≥ 24, an equivalent comparison yielded an incidence rate ratio of 2.1 (95% CI, 0.8–5.2; P for trend, 0.09). [The limitations of this study included the small number of cases and lack of information/adjustment for risk factors (apart from age) for breast cancer incidence (i.e. reproductive history, hormones, smoking).]

Høyer & Engholm (1992) studied the association between serum lipids and breast cancer risk, reporting also for coffee intake, in a cohort of 5207 Danish female participants (aged 30–80 years) recruited in the Glostrup Population Studies between 1964 and 1986. Participants were representative of urban and suburban Danes with respect to social class, housing, education, occupational conditions, and job categories (participation rate 78.5%). During the 4–26 years of

Table 2.7 Cohort studies on cancer of the breast and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Snowdon & Phillips (1984) USA, 1960–1980	23 912 (176 BC deaths) among white Seventh-day Adventists (aged ≥ 30 yr in 1960) Exposure assessment method: self-administered questionnaire	Breast	*Coffee consumption (cups/day)*			Age, sex, meat consumption, smoking	Breast cancer mortality Strengths: dietary questionnaire was used by the ACS study; record linkage for identification of cases Limitations: particular characteristics of studied population may have resulted in reporting bias, coffee consumption rare, number of events small (as cancer mortality and not incidence is the endpoint), no adjustment for important risk factors (therefore residual confounding)
			< 1	131	1.0		
			1	19	1.1 (0.7–1.8)		
			≥ 2	26	0.9 (0.6–1.3)		
			Trend test *P* value, 0.62				
Vatten et al. (1990) Norway, 1974–1977 (enrolment), 12 yr follow-up	14 593 (152 BC cases) among Norwegian women (aged 35–51 yr) who participated in National Health Screening Service Exposure assessment method: FFQ	Breast	*Coffee consumption (cups/day)*			Age	Strengths: comprehensive definition of cases, validation of questionnaire for coffee intake Limitations: small number of cases, possibility of information bias, no information/adjustment for important risk factors (e.g. reproductive or smoking), assessment of coffee at baseline only
			≤ 2	27	1.0		
			3–4	62	0.9 (0.6–1.4)		
			5–6	42	0.8 (0.5–1.3)		
			≥ 7	21	0.8 (0.5–1.4)		
			Trend test *P* value, 0.37				
Høyer & Engholm (1992) Denmark, 1964–1986 (enrolment), 1964–1986 (follow-up, 4–26 yr)	5207 (51 BC cases) among Danish women participants (aged 30–80 yr) Exposure assessment method: standardized questionnaires in all cohorts at baseline	Breast	*Coffee consumption (cups/day)*			Possibly for social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol, smoking (not clear)	Minimum analysis and focus on coffee intake since main exposure was serum lipids. Strengths: random sample of the general population, linkage to cancer registry (regarded as virtually complete) Limitations: most probably RR are crude
			≤ 2	NR	1.0		
			3–6	NR	1.4 (0.6–3.4)		
			≥ 7	NR	1.7 (0.7–4.3)		
			Trend test *P* value, > 0.20				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Folsom et al. (1993) USA, 1986 (enrolment), 1990 (follow-up)	34 388 (580 BC cases) among women aged 55–69 yr in 1986 participating in the IWHS Exposure assessment method: FFQ, regular coffee and caffeine intakes over the previous year assessed	Breast	*Coffee consumption among postmenopausal women*			Age, waist/hip ratio, number of live births, age at first live birth, age at menarche, family history of BC, family history (including family waist/ hip ratio and number of live births)	Caffeine was the main exposure of interest. Strengths: use of a large cohort, the comprehensive identification of cases, and validated Harvard semi-quantitative FFQ questionnaire for assessment of exposures Limitations: short follow-up period and therefore small number of cases, caffeine and not coffee was the main exposure of interest (and therefore examined in more detail)
			Never or < 1 time/mo	183	1.00		
			1 time/mo – 4 times/wk	78	0.87 (0.66–1.14)		
			5–7 times/wk	77	0.96 (0.73–1.27)		
			2–3 times/ day	136	0.98 (0.78–1.23)		
			≥ 4 times/ day	106	1.02 (0.79–1.30)		
			Trend test *P* value, 0.6				
Stensvold & Jacobsen (1994) Norway, 1977–1982	21 238 women resident in three Norwegian counties aged 35–54 yr Exposure assessment method: validated FFQ for coffee consumption	Breast	*Coffee consumption (cups/day)*			Age, cigarettes per day, county of residence	Strengths: comprehensive definition of cases, validation of questionnaire for coffee intake Limitations: small number of cases, possibility of information bias, no information/adjustment for important risk factors for BC incidence (i.e. reproductive), assessment of coffee only at baseline, no CI reported
			≤ 2	22	1.0		
			3–4	69	1.1 (NR)		
			5–6	77	1.4 (NR)		
			≥ 7	43	1.2 (NR)		
			Per category increment	211	1.07 (0.94–1.22)		

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Key et al. (1999) Japan, 1969–1970 and 1979–1980 (enrolment), follow-up until 1993	34 759 (427 BC cases) women in Hiroshima and Nagasaki, participants of the Radiation Effects Research Foundation's Life Span Study Exposure assessment method: non-validated dietary questionnaire	Breast	*Coffee consumption (times/wk)*			Attained age, calendar period, city of residence, age at the time of the bombing, radiation dose	Strengths: comprehensive identification of cases and adequate statistical analyses Limitations: major exposure studied was soya foods so coffee intake was not examined in detail, special characteristics of the studied populations, use of a non-validated dietary questionnaire, lack of information regarding potentially important confounders
			≤ 1	151	1.00		
			2–4	71	1.03 (0.78–1.37)		
			≥ 5	122	1.19 (0.93–1.52)		
			Unknown	83	1.11 (0.84–1.46)		
			Trend test *P* value, 0.258				
Michels et al. (2002) Sweden, 1987–1990 (enrolment), follow-up for 9.5 yr	59 036 (1271 BC cases) among women aged 40–76 yr participating in the large population-based SMC cohort Exposure assessment method: self-administered semi-quantitative FFQ, assessing diet over the 6 mo before recruitment	Breast	*Coffee consumption*			Age, family history of BC, height, BMI, education, parity, age at first birth, alcohol consumption, total caloric intake	Strengths: population with high coffee intakes, high response rates, comprehensive endpoint ascertainment, FFQ validated for coffee intake Limitations: assessment of coffee only at baseline
			≤ 1 cup/wk	76	1.00		
			2–4 cups/wk	33	0.81 (0.54–1.22)		
			1 cup/day	185	0.99 (0.75–1.28)		
			2–3 cups/day	763	0.94 (0.79–1.12)		
			≥ 4 cups/day	214	0.94 (0.75–1.28)		
			Trend test *P* value, 0.91				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Suzuki et al. (2004) Japan Cohort 1: 1984 (enrolment), 9 yr follow-up (111 267 person-years) Cohort 2: 1990 (enrolment), 7 yr follow-up (151 882 person-years)	14 409 (103 BC cases) in Cohort 1 and 20 595 (119 BC cases) in Cohort 2, comprising women aged > 40 yr participating in two population-based prospective cohort studies in Japan Exposure assessment method: self-administered validated questionnaires covering recent or usual consumption	Breast	*Coffee consumption* Never Occasionally ≥ 1 cup/day Trend test *P* value, 0.44	 NR NR NR	 1.00 0.78 (0.53–1.13) 0.81 (0.55–1.18)	Age, type of health insurance, age at menarche, menopausal status, age at first birth, parity, mother's history of BC, smoking, alcohol drinking, BMI	Green tea was the main exposure. Strengths: based on two cohort studies in Japan Limitations: small number of cases, coffee not the main exposure so not examined in detail
Hirvonen et al. (2006) France, 1994 (enrolment), 6.6 yr median follow-up	4396 (95 BC cases) apparently healthy women aged 35–60 yr at recruitment, participating in a controlled, primary-prevention trial of vitamins and minerals (SU.VI.MAX) Exposure assessment method: questionnaire; computerized 24-hour dietary record every 2 mo	Breast	*Tertiles of coffee intake (mL/day)* 0–111 112–252 ≥ 253 Trend test *P* value, 0.71	 30 32 33	 1.00 1.07 (0.64–1.79) 1.10 (0.66–1.84)	Age, smoking, menopausal status, oral contraception use, family history of BC, number of children	Strengths: close monitoring and efficient detection of BC cases due to frequent examination of participants (every year) Limitations: some reproductive factors as well as HRT and randomized treatment not adjusted for limited generalizability

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ganmaa et al. (2008) USA (11 states), 1976 (enrolment), follow-up during 1980–2002	85 987 (5272 BC cases) women aged 30–55 yr, recruited in the NHS Exposure assessment method: FFQ, coffee (caffeinated or decaffeinated) assessed in 1980, 1984, 1986, 1990, 1994, 1998, through a validated (for coffee) FFQ, assessing consumption over the previous year	Breast	*All coffee consumption: cumulatively averaged and updated*			Age, smoking status, BMI, physical activity, height, history of benign breast disease, family history of BC, weight change since age 18, age at menarche, parity, age at first birth, alcohol intake, total energy intake, age at menopause, postmenopausal hormone use	Strengths: validated (for coffee) FFQ, substantial number of cases, ability to examine BC by ER/PR status, detailed assessment and repeated measures of coffee intakes, comprehensive statistical analysis, ability to extensively adjust for potential confounders Limitations: selected cohort of nurses
			< 1 cup/mo	837	1.00		
			1 cup/mo – 4.9 cups/wk	745	1.01 (0.92–1.12)		
			5 cups/wk –1.9 cups/ day	1335	0.92 (0.84–1.01)		
			2–3.9 cups/ day	1718	0.93 (0.85–1.02)		
			≥ 4 cups/day	637	0.92 (0.82–1.03)		
			Trend test *P* value, 0.14				
Ishitani et al. (2008) USA, 1992 (enrolment), average follow-up of 10 yr	38 432 (1188 BC cases) among female US health professionals, aged ≥ 45 yr when recruited to the WHS Exposure assessment method: questionnaire; coffee consumption over the year before recruitment, the validated FFQ from the Nurses' Health Study was used	Breast	*Coffee (caffeinated and decaffeinated) (cups/day)*			Age and randomized treatment, as well as, for: alcohol consumption, BMI, family history of BC, history of hysterectomy, bilateral oophorectomy, smoking status, history of benign breast disease, age at menarche, parity, age at first birth, physical activity, total energy intake, multivitamin use, age at menopause, menopausal status, and postmenopausal hormone use	Strengths: validated FFQ, the substantial number of cases, the ability to examine BC by ER/PR status, comprehensive statistical analysis, ability to extensively adjust for potential confounders, long follow-up Limitations: selected cohort of health professionals (not expected to bias the results), the lack of repeated measures of coffee intake
			Almost never	274	1.00		
			< 1	145	0.97 (0.79–1.18)		
			1	166	0.98 (0.81–1.19)		
			2–3	405	1.05 (0.89–1.22)		
			≥ 4	191	1.08 (0.89–1.3)		
			Trend test *P* value, 0.27				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Larsson et al. (2009) Sweden, 1987–1990 (enrolment), mean follow-up until 2009 (17.4 yr; 1 071 164 person-years)	61 433 (2952 BC cases) women aged 40–76 years from the SMC, study design and BC cases ascertainment described by Michels et al. (2002) Exposure assessment method: as in Michels et al. (2002), plus 1997 self-administered FFQ to assess long-term effect of diet on BC risk	Breast	*Coffee consumption (cups/day)*			Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of BC, intakes of alcohol, tea, total energy	Strengths: as for Michels et al. (2002), repeated measures for coffee intake, follow-up resulted in a substantial number of BC cases, information on ER/PR status available for majority of cases Limitations: possibility of information bias
			< 1	251	1.00		
			1	486	1.05 (0.90–1.23)		
			2–3	1723	0.97 (0.84–1.11)		
			≥ 4	492	1.02 (0.87–1.2)		
			Trend test *P* value, 0.74				
Wilson et al. (2009) USA, 1991 (enrolment), 14 yr (945 764 person-years) of follow-up	90 628 (1179 BC cases) premenopausal women aged 26–46 yr Exposure assessment method: FFQ, similar assessment as for Ganmaa et al. (2008)	Breast	*Coffee consumption: quintiles of servings/day*			Age, calendar year, BMI, height, oral contraceptive use, parity and age at first birth, age at menarche, family history of BC, history of benign breast disease, smoking, physical activity, animal fat, glycaemic load, alcohol intake, total energy intake	Premenopausal BC was the end-point of interest. Acrylamide intake was the main exposure studied. Strengths: similar to those reported for Ganmaa et al. (2008) Limitations: similar to those reported for Ganmaa et al. (2008), lack of detailed examination of coffee in relation to BC risk since acrylamide was the exposure studied
			1st quintile	270	1.00		
			2nd quintile	155	1.11 (0.91–1.36)		
			3rd quintile	230	0.97 (0.81–1.16)		
			4th quintile	266	1.01 (0.85–1.21)		
			5th quintile	258	0.92 (0.77–1.11)		
			Trend test *P* value, 0.28				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boggs et al. (2010) USA (all regions), 1995 (enrolment), follow-up until 2007 (12 yr)	52 062 (1268 BC cases) African-American women aged 21–69 yr at enrolment in the BWHS Exposure assessment method: validated FFQ, self-administered at baseline in 1995 and in 2001	Breast	*Coffee consumption* Never or < 1 cup/mo < 1 cups/day 1 cups/day 2–3 cups/day ≥ 4 cups/day Trend test *P* value, 0.9	 592 357 148 122 49	 1.00 0.98 (0.85–1.12) 0.91 (0.76–1.09) 0.94 (0.77–1.15) 1.03 (0.77–1.39)	Energy intake, age at menarche, BMI at age 18, family history of BC, education, geographic region, parity, age at first birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, intake of alcohol, tea, decaffeinated coffee	Strengths: population-based sample, extended follow-up, repeated measures of coffee intake, advanced statistical analysis with time-varying covariates for exposures and potential confounders, control for a large number of BC risk factors Limitations: results not generalizable to populations other than African-American women
Nilsson et al. (2010) Sweden (Västerbotten), 1992–2007 (enrolment), follow-up until 2007 (median follow-up 6.6 yr)	32 178 (587 cases) women recruited in the VIP Exposure assessment method: semi-quantitative FFQ	Breast	*Boiled coffee (occasions/day)* < 1 1–3 ≥ 4 Trend test *P* value, 0.247 *Total/boiled/brewed coffee intakes (occasions/day)* < 1 1–3 ≥ 4 *Filtered coffee intake (occasions/day)* < 1 1–3 ≥ 4	 433 141 14 58 367 163 159 328 101	 1.00 1.02 (0.84–1.23) 0.52 (0.30–0.88) 1.00 1.06 (0.80–1.40) 0.92 (0.68–1.25) 1.00 1.00 (0.83–1.21) 1.01 (0.79–1.31)	Sex, age, BMI, smoking, education, recreational physical activity	Method of coffee preparation was the main interest of the study. Discrepancies in tables and figures regarding the number of women and BC cases Strengths: country with very high consumptions of coffee, method of coffee preparation considered, case ascertainment through high-quality national cancer registry Limitations: low participation rates (57% and 67%), but minimal evidence of systematic differences in the social and demographic characteristics of participants and non-participants, age used as a proxy marker for menopausal status

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Iwasaki et al. (2010) Japan, Cohort I enrolled in 1990, Cohort II enrolled in 1993, follow-up until 31/12/2006 (average 13.6 yr)	53 793 women (581 cases) aged 40–69 yr, participants in JPHC Study Exposure assessment method: questionnaire, assessments at baseline and after 5 years (1995–1998)	Breast	*Coffee consumption*			Age, area, age at menarche, menopausal status at baseline, age at menopause for postmenopausal women, number of births, age at first birth, height, BMI, alcohol intake among regular drinkers, smoking, leisure time physical activity, exogenous hormone use, family history of BC, intakes of green tea, oolong tea, and black tea	Green tea consumption was the main exposure Strengths: population-based, comprehensive case ascertainment Limitations: relatively low consumption of coffee in this population, relatively small number of cases, unusual analysis, not particularly detailed analysis of coffee
			< 1 cup/wk	161	1.00		
			1–4 cups/wk	180	1.15 (0.91–1.46)		
			1–2 cups/day	173	1.12 (0.87–1.43)		
			≥ 3 cups/day	63	1.22 (0.87–1.71)		
			Trend test *P* value, 0.26				
Fagherazzi et al. (2011) France, 1990 (enrolment), follow-up until June 2005 (median 11 yr)	67 703 (2868 BC cases) French women aged 40–65 yr at recruitment, insured by the national health insurance system Exposure assessment method: self-administered questionnaire assessing using diet over previous year	Breast	*Coffee consumption (cups/day)*			Age, baseline variables (total energy intake, ever use of oral contraceptives, age at menarche, age at menopause, number of children, age at first pregnancy, history of BC in the family and years of schooling), time-dependent variables (current use of postmenopausal hormone therapy, postmenopausal women only), personal history of benign breast disease, menopausal status, BMI	Strengths: substantial number of cases, case ascertainment through pathology reports Limitations: selection of teachers may reduce generalizability of results, lack of repeated measures for coffee consumption
			Non-consumer	410	1.00		
			≤ 1	491	1.02 (0.91–1.15)		
			1.1–3	1133	0.98 (0.85–1.11)		
			> 3	834	1.02 (0.9–1.16)		
			Trend test *P* value, 0.79				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gierach et al. (2012) USA, 1995–1996 (enrolment), follow-up until 2006	198 404 (9915 cases) female residents of eight US states aged 50–71 yr when recruited in NIH-AARP Exposure assessment method: 124-item food FFQ assessing diet over the past year	Breast	*Coffee consumption*			Age at entry, race/ ethnicity, education, BMI, smoking status and dose, alcohol, proportion of total energy from fat, age at first live birth, menopausal HRT use, history of breast biopsy, family history of breast cancer in a first-degree relative	Results did not vary by BMI or history of benign breast biopsy, or by clinical features of the tumour. No evidence of an association between breast cancer risk and either caffeinated or decaffeinated coffee Strengths: large size, availability of extensive information on potential confounding factors, examination of associations for many clinical features of breast tumours Limitations: coffee was assessed only at baseline
			Never	1138	1.00		
			≤ 2 cups/wk	1114	1.06 (0.97–1.15)		
			3–6 cups/wk	662	1.00 (0.91–1.10)		
			1 cup/day	1833	1.02 (0.94–1.09)		
			2–3 cups/day	3951	1.02 (0.95–1.09)		
			≥ 4 cups/day	1217	0.98 (0.91–1.07)		
			Trend test *P* value, 0.38				
Oh et al. (2015) Sweden, 1991–1992 (enrolment), follow-up until 2012 (856 529 person-years)	42 099 (1395 BC cases) women aged 30–49 yr in the Swedish WLH study, a random sample of women residing in the Uppsala Health Care Region in Sweden Exposure assessment method: validated FFQ for coffee/tea intakes, diet during previous year assessed	Breast	*Coffee consumption (cups/day)*			Age, BMI, duration of breastfeeding, alcohol consumption, smoking status, education, physical activity	Similar patterns of associations were observed for pre- and postmenopausal BC Strengths: population-based sample, extended follow-up, examination of the studied association by ER/PR status Limitations: coffee assessed only at baseline
			0	99	0.86 (0.69–1.08)		
			1–2	338	1.00		
			3–4	537	0.87 (0.76–1.00)		
			≥ 5	421	0.81 (0.70–0.94)		
			Per 1 cup/day increment	1395	0.97 (0.94–0.99)		
			Trend test *P* value, 0.009				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bhoo-Pathy et al. (2015) 10 European countries, 1992–2000 (enrolment), follow-up until 2010	335 060 (10 198 BC cases) female participants aged 25–70 yr in the EPIC cohort study Exposure assessment method: self- or interviewer-administered validated country-specific questionnaires (usually FFQs)	Breast	*Coffee consumption (total, caffeinated, decaffeinated): postmenopausal*			Age at menarche, ever use of oral contraceptives, age at first delivery, ever breastfeeding, smoking status, education, physical activity, alcohol, height, weight, energy intake from fat and non-fat sources, total saturated fat and fibre intakes, tea intake, ever use of postmenopausal hormones	Strengths: substantial numbers of BC cases (even for premenopausal BC), multi-country design ensuring variation in coffee consumption, comprehensive statistical analysis Limitations: selected cohorts (volunteers in most countries), lack of repeated assessments of coffee consumption (possibly important after 10-year follow-up)
			No	732	1.02 (0.94–1.12)		
			Low	2296	1.00		
			Moderately low	1979	0.97 (0.91–1.03)		
			Moderately high	2267	0.97 (0.92–1.03)		
			High	1860	0.95 (0.89–1.01)		
			Per 100 mL/day increment	9134	0.99 (0.98–0.99)		
			Trend test *P* value, 0.055				
			Coffee consumption (total, caffeinated, decaffeinated): premenopausal			Age at menarche, ever use of oral contraceptives, age at first delivery, ever breastfeeding, smoking status, education, physical activity, alcohol, height, weight, energy intake from fat and non-fat sources, total saturated fat and fibre intakes, tea intake	
			No	81	1.08 (0.83–1.4)		
			Low	246	1.00		
			Moderately low	234	1.23 (1.02–1.48)		
			Moderately high	251	1.11 (0.93–1.34)		
			High	252	1.15 (0.96–1.39)		
			Per 100 mL/ day increment	1064	1 (0.98–1.03)		
			Trend test *P* value, 0.272				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hashibe et al. (2015) USA, 1992 and 2001 (enrolment), follow-up until 2011	50 563 (1703 BC) women in PLCO Cancer Screening Trial Exposure assessment method: validated questionnaire recording coffee consumption over the previous year	Breast	*Coffee consumption: (cups/day)* < 1 1–1.9 ≥ 2 Trend test *P* value, 0.64 Per 1 cup/day increment	 599 276 828 1703	 1.00 0.95 (0.82–1.10) 0.97 (0.87–1.08) 0.98 (0.95–1.01)	Age, sex, race, education, cigarette pack-years, alcohol drinking frequency	Strengths: prospective design, detailed tobacco smoking adjustments, large sample size Limitations: lack of longitudinal data on exposure, lack of adjustment on reproductive factors, no specific focus on BC
Lukic et al. (2016) Norway, 1991–1992, 1996–1997, 2003, and 2004 (enrolment), follow-up from 1996–2013	91 767 (3277 cases) participants of NOWAC cohort Exposure assessment method: FFQs at each follow-up visit from 1998, recording (type of) coffee consumption over the previous year	Breast	*All types of coffee consumption (cups/day)* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 7 > 7 Trend test *P* value, 0.06	 626 1106 1363 182	 1.00 0.93 (0.84–1.02) 0.91 (0.82–1.00) 0.87 (0.71–1.06)	Menopausal status, smoking status, education, BMI, physical activity level, alcohol consumption, number of children age at first birth, use of HRT, maternal history of breast cancer	Strengths: prospective design, large sample size, random sample from the general population, high levels of coffee consumption, complete follow-up, validated FFQ, repeated measurements of coffee consumption and confounders, thorough analysis and use of multiple imputation Limitations: relatively low response rate

ACS, American Cancer Society; BC, breast cancer; BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ER(+/–), estrogen receptor (positive/negative); FFQ, food frequency questionnaire; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health – American Association of Retired Persons; NOWAC, Norwegian Women and Cancer; NR, not reported; PR(+/–), progesterone receptor (positive/negative); RR, relative risk; SMC, Swedish Mammography Cohort; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; VIP, Västerbotten Intervention Project; WHS, Women's Health Study; WLH, Women's Lifestyle and Health; wk, week(s); yr, year(s)

follow-up, 51 incident cases of breast cancer were identified by linkage to the Danish Cancer Registry. There was a positive, albeit not statistically significant, association between highest (≥ 7 cups/day) coffee consumption and breast cancer risk (HR, 1.7; 95% CI, 0.7–4.3; *P* for trend, > 0.20) compared with lowest coffee consumption (≤ 2 cups/day). [It is not clear whether this risk estimate was adjusted for the same factors as the association between serum lipids (the main exposure) and breast cancer risk (social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol consumption, and smoking). The strength of this study was its linkage to a cancer registry which is regarded as virtually complete; the subjects were therefore a representative sample. Limitations included the small number of cases and the limited interest in the association between coffee consumption and risk of breast cancer.]

Folsom et al. (1993) investigated the association between caffeine intake and the incidence of postmenopausal breast cancer in the Iowa Women's Health Study. Among 34 388 women aged 55–69 years in 1986 who were followed for 5 years (up to 1990), 580 incident breast cancer cases were identified by matching with the Iowa Health Registry, part of the National Cancer Institute's SEER Program. Hazard ratios of coffee intakes in relation to breast cancer incidence were adjusted for age, waist/hip ratio, and a large number of reproductive and family history variables. Smoking was apparently not accounted for. There was no apparent association between breast cancer occurrence and regular coffee or caffeine intake. [The limitations of this study included the short follow-up period and correspondingly low number of cases.]

Stensvold & Jacobsen (1994) analysed data from Norwegian residents in three counties who accepted an invitation to participate in a cardiovascular screening programme organized by the National Health Screening Service during 1977–1982. After an average of 10 years of follow-up, 211 breast cancer cases out of 21 238 women were identified through linkage to the Norwegian Cancer Registry and to the Norwegian Central Bureau of Statistics. Coffee intake was assessed through a validated FFQ enquiring about usual consumption in cups/day. Hazard ratios for breast cancer risk in association with coffee intakes of ≤ 2, 3–4, 5–6, and ≥ 7 cups/day were 1.0, 1.1, 1.4, and 1.2 respectively, after adjustment for age, cigarettes per day, and county of residence. [No confidence intervals were reported for these associations.] The estimated hazard ratio for an increment of 1 cup/day was 1.07 (95% CI, 0.94–1.22). No interaction by BMI was evident. [The strengths of this study included the comprehensive definition of cases and the validated FFQ for coffee intake. Limitations included the small number of cases, minimal confounding adjustment (i.e. not for reproductive history), and no confidence intervals reported for categories of exposure.]

The association between soya, as well as other foods and beverages (including coffee), and breast cancer risk was investigated in a prospective study of 34 759 women in Hiroshima and Nagasaki (Japan) by Key et al. (1999). The women were survivors of the atomic bombing in the Radiation Effects Research Foundation's Life Span Study who had completed at least one of two similar mail surveys sent out in 1969–1970 (survey 1) and 1979–1980 (survey 2). A null association between breast cancer risk and coffee intake was apparent in analyses adjusted for age, calendar time, city, and radiation dose, but not other established risk factors. [The strengths of this study were the comprehensive identification of cases and adequate statistical analyses. Limitations included: a lack of detailed analysis for coffee intake (since the major exposure was soya); a lack of generalizability of results due to the distinct population studied; the use of a non-validated dietary questionnaire; and the lack of information regarding potentially important confounders for breast cancer.]

Michels et al. (2002) studied the association between coffee, tea, and caffeine consumption and breast cancer incidence among 59 036 women (aged 40–76 years) during 1987–1990 in the population-based Swedish Mammography Cohort. Information on coffee drinking was obtained through a self-administered semiquantitative FFQ, validated for coffee/tea intakes, assessing diet over the 6 months before recruitment. During 508 267 person-years of follow-up, 1271 histologically confirmed cases of invasive breast cancer were identified by linkage with the regional cancer registries. Hazard ratios for the studied association were adjusted for several variables, but not for smoking. Coffee consumption was not associated with breast cancer incidence, overall or in subgroups by BMI and age at enrolment. [The strengths of the study included: use of a population with high coffee intake; the selection of, practically, all female residents of two cities in Sweden aged 40–76 years; validation of the FFQ for coffee consumption; and ascertainment of outcome through linkage to a cancer registry.]

In a subsequent paper based on the Swedish Mammography Cohort, Larsson et al. (2009) used data from 61 433 women to investigate the association between coffee, tea, and caffeine intake and breast cancer risk, overall as well as by estrogen/progesterone receptor (ER/PR) status. At least some of the participants included in the study by Michels et al. (2002) apparently coincide with the women included in the Larsson et al. (2009) study. Diet was assessed with a baseline FFQ (see description in study by Michels et al., 2002), but also used information gathered in 1997 in a second self-administered FFQ (to assess long-term effect of diet on breast cancer risk). Mean follow-up in 2009 was 17.4 years (1 071 164 person-years), during which 2952 incident cases of invasive breast cancer were ascertained; information on ER/PR status was also obtained for the majority of the cases. Null associations between coffee intake and breast cancer, overall as well as within ER-negative/PR-negative, ER-positive/PR-negative, and ER-positive/PR-positive breast cancer, were estimated after adjusting for various potential confounders, but not for smoking. The association did not differ by menopausal status, postmenopausal hormone use, or BMI. [A strength of this study was the repeated measures of coffee intake.]

Suzuki et al. (2004) investigated the association between risk of breast cancer and consumption of green tea and other beverages, including coffee by pooling data from two population-based prospective cohort studies of women in Japan. Women of age > 40 years were recruited in 1984 and 1990, and completed self-administered validated questionnaires covering recent or usual consumption of beverages including coffee. Hazard ratios of breast cancer risk associated with consumption of coffee in each cohort, as well as after pooling the respective data, were adjusted for potential confounders including somatometry, reproductive history, and smoking. Inverse, but not statistically significant, associations between risk of breast cancer and consumption of coffee were observed. Compared with women who never drank coffee, the pooled multivariate hazard ratios (95% CI) were 0.78 (0.53–1.13) for those drinking coffee occasionally and 0.81 (0.55–1.18) for those drinking ≥ 1 cups/day (*P* for trend, 0.44). [The limitations of this study were the small number of cases and the lack of detailed examination of coffee intake (since green tea was the exposure of interest).]

Coffee intake and risk of breast cancer was examined in a study by Hirvonen et al. (2006) in 4396 apparently healthy French women participating in the double-blind, placebo-controlled, French Supplémentation en Vitamines et Minéraux Antioxydants Study (SU.VI.MAX) of primary prevention of cardiovascular diseases with vitamin and mineral supplements. Women were aged 35–60 years at recruitment (1994) and were followed up for a median of 6.6 years. Assessment of diet (including coffee)

was performed through self-administration of a computerized 24-hour dietary record every 2 months (i.e. 6 times per year). Women who completed at least three 24-hour dietary records during the first follow-up year were included in the analysis. Hazard ratios for the studied association were adjusted for some potential confounders, but not for randomization arm. Results revealed no association between coffee consumption and breast cancer risk. [The strength of this study was the close monitoring and efficient detection of breast cancer cases due to frequent examination of participants (every year). Limitations included the fact that some reproductive factors (i.e. age at menarche/menopause), as well as hormone replacement therapy (HRT) and randomized treatment, were not adjusted for. The results may also have limited generalizability due to the eligibility criteria for participation in the clinical trial.]

Ganmaa et al. (2008) analysed data from 85 987 female participants (aged 30–55 years), recruited in 1976 in the Nurses' Health Study and followed up from 1980 to 2002 (1 715 230 person-years). Intake of coffee (and other beverages) was repeatedly assessed in 1980, 1984, 1986, 1990, 1994, and 1998 through a FFQ validated for coffee intake, assessing consumption over the previous year. Models were adjusted for an exhaustive number of potential confounders, mostly detailed for reproductive history and somatometry. Hazard ratios for breast cancer risk associated with caffeinated and decaffeinated coffee suggested inverse associations which were not statistically significant. There was no evidence for modification of the indicated associations by BMI. [The strengths of this study included: the large number of cases (long follow-up); repeated measures of coffee intakes, enabling comprehensive statistical analysis; validation of the FFQ for coffee; and extensive adjustment for potential confounders.]

In another study, Ishitani et al. (2008) studied the association between coffee/caffeine and incidence of breast cancer using data from 38 432 female US health professionals, aged ≥ 45 years in 1992 when recruited to the randomized clinical trial of the Women's Health Study (low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease). Hazard ratios for breast cancer in relation to coffee and caffeine consumption were adjusted for a large number of potential confounders, as well as for randomized treatment. Intakes of coffee (and of decaffeinated coffee) were not associated with overall risk of breast cancer. Among women with a history of benign breast disease, an increased risk of breast cancer was seen for consumption of ≥ 4 cups/day of coffee (adjusted HR, 1.35; 95% CI, 1.01–1.80; *P* for trend, 0.08; *P*-interaction, 0.05). No modifications by BMI, menopausal status, or postmenopausal hormone use were evident. [The advantages of this study were the large number of cases and close monitoring. Limitations included the lack of repeated measures of coffee intake, and selective inclusion of participants fulfilling the eligibility criteria for the randomized study.]

Wilson et al. (2009) reported on coffee intake in relation to premenopausal breast cancer risk in a study focusing mainly on acrylamide intake. Data from 90 628 premenopausal women, aged 26–46 years when they participated in the US-based Nurses' Health Study (NHS) II study in 1991, were used. Questionnaires and validation methods for assessment of coffee intake were similar to those used by Ganmaa et al. (2008), as were methods for case ascertainment. Relative risks for coffee, stratified for age and calendar year, were estimated and further adjusted for many potential confounders. Null associations between coffee intake (assessed in quintiles) and risk of breast cancer were evident in this study. [The study was limited by the lack of detailed examination of coffee in relation to breast cancer risk, since the effect of exposure to acrylamide was the main focus.]

Boggs et al. (2010) prospectively examined the relation of coffee consumption to the risk of breast

cancer among 52 062 African-American women from all regions of the USA, aged 21–69 years at enrolment (1995), in the Black Women's Health Study. A validated FFQ was self-administered at baseline in 1995 and in 2001 to assess dietary intakes. Hazard ratios for the studied association were adjusted for many potential confounders. Intake of coffee was not associated with risk of breast cancer overall, or by menopausal status or hormone receptor status (assessed in a subsample of the initial cohort). [This study had many strengths, including: use of a population-based sample; the extended follow-up; repeated measures of coffee intake; advanced statistical analysis with time-varying covariates for exposures/potential confounders; and extensive adjustment for potential confounders, minimizing residual confounding. It was limited by the specific population of African-American women who were examined.]

Nilsson et al. (2010) investigated whether consumption of filtered or boiled coffee is associated with a risk of developing cancer overall via the population-based Västerbotten Intervention Project (VIP). Data on diet were collected during 1992–2007 for 32 178 women aged > 29 years through a semiquantitative FFQ. Subjects were followed up for a median of 6 years and 587 breast cancer cases were identified by linking the VIP database with the regional cancer registry. Hazard ratios for cancer risk with respect to total, brewed, or boiled coffee consumption were adjusted for sex, age, BMI, smoking, education, and recreational physical activity. For breast cancer, a decreased risk was observed overall in women drinking boiled coffee at a frequency of ≥ 4 times/day compared with < 1 time/day (HR, 0.52; 95% CI, 0.30–0.88), but with no indication of a trend (*P* for trend, 0.247). Total and filtered coffee were not associated with breast cancer risk overall, but there was evidence for effect modification with age/menopausal status. Among women < 49 years of age, both total and filtered coffee intakes were associated with increased risk; the hazard ratio (95% CI) for a consumption frequency of ≥ 4 times/day versus < 1 time/day was 1.69 (0.96–2.98; *P* for trend, 0.015) for total coffee and 1.76 (1.04–3.00; *P* for trend, 0.045) for filtered coffee. An opposite tendency was seen in women > 55 years of age; the hazard ratio (95% CI) for a consumption frequency of ≥ 4 times/day versus < 1 time/day was 0.60 (0.39–0.93; *P* for trend, 0.006) for total coffee and 0.64 (0.44–0.94; *P* for trend, 0.045) for filtered coffee. [The strengths of this study included: use of a population with very high levels of coffee consumption; investigation of the association between the method of preparing coffee and cancer risk; population-based data collection, and comprehensive case-ascertainment. It was however limited by the low participation rates for the enrolment period examined and the lack of information on menopausal status (age is used as a proxy marker) and other reproductive history variables. The Working Group also noted a discrepancy between data reported in the tables and the abstract of this paper.]

Iwasaki et al. (2010) used data from two cohorts participating in a Public Health Center-based Prospective Study, undertaken in municipalities supervised by 11 public health centres in Japan to investigate whether green tea was associated with a risk of breast cancer. Coffee intake was used as a potential confounder in the indicated association, but relative risk estimates for breast cancer were also reported for coffee consumption. Recruitment began between 1990 and 1993; 53 793 participating women (aged 40–69 years at recruitment) completed a self-administered questionnaire on beverage intakes at baseline and most (43 639) completed a second more detailed questionnaire 5 years after baseline. Analysis was conducted separately for the baseline–2006 period and for the 1995–1998 to 2006 period to account for the different questionnaires used for the assessment of exposures. Adjustment was performed for a large number of potential confounders, including family history of

breast cancer and intakes of different types of tea. Adjusted hazard ratios (95% CI) for breast cancer risk associated with coffee intakes of < 1 cup/week, 1–4 cups/week, 1–2 cups/day, and ≥ 3 cups/day were 1.00, 1.15 (0.91–1.46), 1.12 (0.87–1.43), and 1.22 (0.87–1.71) (*P* for trend, 0.26) using the baseline data analysis. The respective hazard ratios for the 5-year follow-up data analysis were apparently similar. [Particular strengths of this study included its population-based design and comprehensive case-ascertainment. It was however limited by the relatively low consumption of coffee in this population and the difficult-to-follow statistical analysis.]

Data from the Etude Epidémiologique auprès des Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort were analysed by Fagherazzi et al. (2011). The study population was composed of 67 703 French women of age 40–65 years at recruitment (1990); the women were mainly teachers and insured by the national health insurance system. Usual diet over the previous year was assessed using a detailed validated dietary history questionnaire, self-administered in 1993. After a median follow-up of 11 years (707 137 person-years) to June 2005, 2868 cases of invasive breast cancer were diagnosed. Coffee consumption was not associated with risk of breast cancer, either overall or by menopausal or ER/PR status. [The strengths of this study included the substantial number of cases, case-ascertainment through pathology reports, and time-dependent confounding variables. Limitations included the lack of repeated measures for diet and therefore coffee consumption.]

Gierach et al. (2012) evaluated the association between coffee intake and incident breast cancer in 198 404 female residents of 8 US states aged 50–71 years when recruited in the NIH-AARP Diet and Health Study cohort. Assessment of coffee consumption was made via a validated FFQ questionnaire. By linking with a state cancer registry and mortality index, 9915 primary incident breast carcinomas were identified in 2006. Hazard ratios for breast cancer associated with coffee intake were adjusted for an exhaustive list of potential confounders, including family history of breast cancer. Effect modification by BMI, HRT use, smoking, alcohol, history of breast biopsy, family history of breast cancer, ER/PR status, stage at diagnosis, tumour grade, and histologic type was also examined. The association of coffee intake with breast cancer risk was essentially null, and results did not vary with BMI or history of benign breast biopsy. In analyses by type of tumour, no clear patterns emerged in the relationships between coffee intake and risk of any of the tumour characteristics. [The strengths of this study were its coverage of eight US states, the large number of subjects, the availability of extensive information on potential confounding factors, and the examination of associations for many clinical features of breast tumours. It was however limited by a lack of repeated assessment of coffee intake.]

Oh et al. (2015) studied the association between coffee, caffeine, and tea consumption and risk of breast cancer among 42 099 women participating in the Swedish Women's Lifestyle and Health (WLH) study during 1991–1992. Coffee consumption (cups/day) was assessed through a postal validated FFQ. Follow-up lasted until 2012 (856 529 person-years), and 1395 breast cancer cases were identified via linkage to national registries. Increased coffee intakes were associated with decreased breast cancer risk: compared with women consuming 1–2 cups/day of coffee, those consuming 3–4 cups/day or ≥ 5 cups/day had relative risks (95% CI) of 0.87 (0.76–1.00) and 0.81 (0.70–0.94), respectively. There was an indication of a dose–response pattern in breast cancer risk: relative risk was 0.97 (95% CI, 0.94–0.99) for a 1 cup/day increase in coffee consumption. Similar patterns/estimates were observed for pre- and postmenopausal breast cancer. [The strengths of this study included: use of population-based samples, extended follow-up, and examination of the studied association by

ER/PR status. The list of factors adjusted for was quite limited, but this reflects the authors' decision to adjust for only those variables which were statistically significant. Coffee intake was only assessed at baseline, although consumption may have changed during the 10 years of follow-up.]

The association between coffee (and tea) consumption and risk of pre- and postmenopausal breast cancer was examined by Bhoo-Pathy et al. (2015), undertaken in the EPIC cohort study. [Of note, this study also includes data from the EPIC-Netherlands study that was previously published by Bhoo-Pathy et al. (2010)]. A total of 335 060 women aged 25–70 years, recruited during 1992–2000 from 10 European countries, were followed up until 2010; 10 198 incident breast cancer cases were identified. Diet was assessed with self- or interviewer-administered validated (for diet) country-specific questionnaires (usually FFQs). Total coffee intake was associated with a lower risk of postmenopausal breast cancer, with no indication for modification by ER/PR status. The hazard ratio of consuming high versus low quantities of coffee was 0.95 (95% CI, 0.89–1.01; *P* for trend, 0.055), and a 100 mL/day increment yielded a hazard ratio of 0.99 (95% CI, 0.98–0.99). [This study had the advantages of: a large number of breast cancer cases, even for premenopausal breast cancer; a multicountry design, ensuring variation in coffee and types of coffee consumption; and a comprehensive and exhaustive statistical analysis. It was however limited by a lack of repeated assessments of coffee consumption, which may be important after 10 years of follow-up.]

Hashibe et al. (2015) investigated the association between coffee intake and cancer using data from the PLCO Cancer Screening Trial, aimed at evaluating the effectiveness of cancer screening tests in reducing mortality. Between 1992 and 2001, 50 563 women were recruited at 10 centres across the USA (Alabama, Michigan, Colorado, Hawaii, Wisconsin, Minnesota, Pennsylvania, Utah, Missouri, and Washington DC) and followed up until 2011; a total of 1703 breast cancer cases were identified. Coffee intake was assessed with a validated questionnaire recording coffee consumption over the 12 months preceding enrolment. For breast cancer, a null association with coffee intake was observed in women drinking 1–1.9 cups/day or ≥ 2 cups/day of coffee compared with minimal consumption (0–1 cups/day), or for 1 cup/day increment. [This study had the advantage of a prospective design and large sample size. Limitations included a lack of longitudinal data on exposure, a lack of adjustment for reproductive factors, and a lack of specific focus on breast cancer.]

Results of a study on coffee consumption and risk of cancer, with a special interest in breast cancer, was published by Lukic et al. (2016). The authors used the Norwegian Women and Cancer (NOWAC) cohort which comprises random samples of Norwegian women aged 30–70 years. Enrolment was conducted between 1991 and 2004 and subjects were followed up from 1996 to 2013. Information on coffee consumption was obtained via FFQs at each follow-up visit from 1998, recording type of coffee consumption over the previous year. To account for missing values, multiple imputation was carried out. The estimated hazard ratios (95% CI) for breast cancer risk were 1.00, 0.93 (0.84–1.02), 0.91 (0.82–1.00), and 0.87 (0.71–1.06) for consumption of ≤ 1 cup/day, > 1 to ≤ 3 cups/day, > 3 to ≤ 7 cups/day, and > 7 cups/day, respectively (*P* for trend, 0.06). After excluding cases of breast cancer diagnosed during the first 2 years of follow-up, associations among coffee consumers of low and high–moderate quantities compared with the reference group reached statistical significance with a *P* for trend of 0.01. [The strengths of this study included its prospective design, large sample size, random sample from the general population, high levels of coffee consumption, complete follow-up via linkage to the Norwegian Cancer Registry, validated FFQ, repeated measurements of coffee consumption

and of confounders, thorough analysis, and the use of multiple imputation.]

(b) Fatal cancer of the breast

In an early cohort study, Snowdon & Phillips (1984) investigated the association between coffee intake and cancer mortality (including 176 breast cancer deaths), as identified during 1960–1980 (21-year follow-up) in 23 912 white Seventh-day Adventists (aged ≥ 30 years in 1960), a religious group with very low prevalence of coffee consumption. The number of cups of coffee consumed per day was recorded by self-administered questionnaires, identical to those used by the American Cancer Society Study. Hazard ratios for coffee consumption in relation to cancer mortality, overall and by site, adjusting for age, sex, meat consumption, and smoking history, indicated null associations for fatal breast cancer. [This study was limited by: (1) the possibility of reporting bias; (2) the fact that coffee consumption is rare in this population; (3) the number of events was small, as cancer mortality and not incidence was the end-point; and (4) no adjustment for important risk factors was made, perhaps resulting in residual confounding.]

2.4.2 Case–control studies

See Table 2.8.

A potential limitation of case–control studies included in this report is, in general, the possibility of recall bias regarding the self-reported coffee consumption. Additional limitations and strengths are noted for each study.

(a) Population-based case–control studies

Schairer et al. (1987) conducted a case–control study on methylxanthine consumption and breast cancer risk in participants in the Breast Cancer Detection Demonstration Project in the USA. Breast cancer cases were women diagnosed from June 1977 to November 1980. Control subjects were women who had not been recommended for, and had not undergone, surgical evaluation during screening participation, and who were similar to breast cancer cases regarding certain characteristics including age and screening centre. Response rates were high, at 73% and 90% for cases and controls. Home interviews were obtained for the 1510 cases and 1882 controls enquiring (among other items) for both seasonal and year-round consumption of methylxanthine-containing beverages, including brewed/instant coffee with caffeine and decaffeinated coffee. Although Schairer et al. (1987) mention adjustment for potential confounders, no further information was given on the actual factors adjusted for in the analysis. Neither instant nor brewed caffeinated coffee consumption was associated with increased risk of breast cancer. Consumers of ≥ 5 cups/day of instant coffee with caffeine had an odds ratio of 0.7 (95% CI, 0.3–1.3) compared with non-drinkers (*P* for trend, 0.04), suggestive of a negative association. [The strengths of this study include the detailed assessment of coffee at multiple levels of consumption and over a long period before diagnosis (therefore eliminating misclassification and recall bias). Limitations included the lack of information on adjusting variables, although the authors mentioned that adjustment did not materially alter the reported results.]

Ewertz & Gill (1990) examined the association between dietary factors, including coffee, and breast cancer risk in a case–control study in Denmark including 1474 breast cancer cases (aged < 70 years). The cases were diagnosed during a 1-year period (March 1983 to February 1984), as identified by the Danish Cancer Registry and the nationwide clinical trial of the Danish Breast Cancer Cooperative Group. The 1322 women in the control group were an age-stratified random sample from the general population selected from the Central Population Registry. Data on diet were collected by self-administered semiquantitative FFQs, mailed to the cases 1 year after diagnosis to assess diet during the

Table 2.8 Case–control studies on cancer of the breast and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lubin et al. (1985) Israel, 1975–1979 (enrolment), 1975–1979	Cases: 807 cases from Tel Aviv metropolitan area Controls: 738 surgical and 807 neighbourhood controls matched by age, country of origin, length of residence in Israel Exposure assessment method: questionnaire; face-to-face interviews on the frequency of consumption 1 year before interview and within the previous decade	Breast	*Past coffee consumption (cups/day): surgical controls* 0 1 2–3 ≥ 4 *Past coffee consumption (cups/day): neighbourhood controls* 0 1 2–3 ≥ 4	 129 159 308 142 141 176 335 155	 1.0 0.7 (0.4–1.1) 0.7 (0.4–1.0) 0.7 (0.4–1.1) 1.0 0.5 (0.3–0.9) 0.5 (0.2–0.9) 0.6 (0.2–0.9)	Age, country of origin, length of residence in Israel	Methylxanthines daily intake was a co-exposure Strengths: inclusion of two control sets, face-to-face interview for obtaining detailed information on exposure, accounting for present and past exposure Limitations: lack of adjustment for confounders other than the matching factors
Rosenberg et al. (1985) Eastern USA, 1975–1982	Cases: 2651 first primary BC inpatients aged 30–69 yr from hospitals Controls: two control groups of patients aged 30–69 yr when admitted to the same hospitals. 1st group: 1501 women with acute non-malignant conditions (trauma or infections); 2nd group: 385 women with selected malignancies (malignant melanoma, lymphoma and leukaemia) Exposure assessment method: questionnaire; nurse-interviewers collected information on consumption of caffeinated and decaffeinated coffee during the several months before admission	Breast	*Coffee consumption (cups/day)* 0 1–2 3–4 ≥ 5 *Coffee consumption (cups/day)* 0 1–2 3–4 ≥ 5	 493 1015 721 413 493 1015 721 413	 1.0 1.0 (0.7–1.4) 0.9 (0.7–1.3) 1.1 (0.7–1.6) 1.0 1.2 (1.0–1.5) 1.2 (1.0–1.6) 1.2 (0.9–1.6)	Age, race, religion, cigarette smoking, age at menarche, age at first pregnancy, parity, type of menopause, age at menopause, history of fibrocystic breast disease, family history of BC (in the mother or sister(s)), BMI, years of education, tea, alcohol consumption, location of the hospital, year of interview, number of previous non-obstetric hospitalizations	Strengths: selection of two control groups, the exhaustive adjustment for potential confounders, additional examination of decaffeinated coffee Limitations: selection of hospital-based controls in both groups (which may have introduced selection bias), possibility of recall bias regarding coffee consumption

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Katsouyanni et al. (1986) Greece (Athens), 1983–1984	Cases: 120 patients admitted in two teaching hospitals in the greater Athens area Controls: 120 admitted for accidents and orthopaedic disorders in a third teaching hospital, chosen sequentially on the basis of sex and age Exposure assessment method: questionnaire; dietary histories concerning the consumption frequency of 120 foods and drinks obtained by interview regarding the period prior to onset of disease	Breast	*Coffee: frequency of use (tertiles)* 1st tertile 2nd tertile 3rd tertile	 29 65 24	 1.00 [0.97] [0.89]	Adjusted for age, interviewer, length of schooling, other significant food groups	Crude ORs were estimated by the numbers given in table 2 of the respective publication Strengths: detailed assessment of diet by face-to-face interviews Limitations: potential selection bias for cases and controls (not selected from the same hospitals as cases), lack of detailed information and investigation of coffee (no OR reported)
Schairer et al. (1987) USA, 1977–1980 (diagnosis)	Cases: 1510 participants in the BC Detection Demonstration Project Controls: 1882 participants of the same project Exposure assessment method: questionnaire, home interviews for both seasonal and year-round consumption of methylxanthine-containing beverages, including regular and decaffeinated coffee	Breast	*Brewed coffee consumption (cups/day)* 0 < 1 2 3 4 ≥ 5 Trend test *P* value, 0.27 *Instant coffee consumption (cups/day)* 0 < 1 2 3 4 ≥ 5 Trend test *P* value, 0.04	 171 502 311 205 127 194 766 555 106 48 19 16	 1.0 1.0 (0.8–1.3) 1.0 (0.7–1.2) 0.9 (0.7–1.2) 0.9 (0.7–1.3) 1.0 (0.8–1.3) 1.0 0.9 (0.8–1.1) 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.9 (0.5–1.7) 0.7 (0.3–1.3)	Unclear which factors were adjusted for	Crude, unmatched ORs are probably reported Strengths: detailed assessment of coffee in multiple levels of consumption Limitations: possibility of recall bias, lack of information on adjustment for potential confounders

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ewertz & Gill (1990) Denmark, 1983–1984	Cases: 1474 from Danish Cancer Registry Controls: 1322 age-stratified random samples from the general population Exposure assessment method: self-administered semi-quantitative FFQs	Breast	*Coffee consumption (cups/day)* < 3 3–5 6–9 ≥ 10	 358 643 348 82	 1.00 0.83 (0.68–1.00) 0.86 (0.69–1.07) 0.81 (0.57–1.15)	Age at diagnosis, place of residence	Strengths: use of cancer registry for identifying cases, population-based controls, FFQ, large number of cases Limitations: FFQ validated for fat and β-carotene intakes (main exposures) but not for coffee, possibility of recall bias, lack of adjustment for several important confounders
McLaughlin et al. (1992) USA (18 contiguous counties in eastern New York State), 1982 and 1984 (enrolment)	Cases: 1617 identified through hospital diagnostic index, tumour registry, pathology files, and the New York State Cancer Registry Controls: 1617 frequency-matched to cases on year of birth and county of residence from New York State Department of Motor Vehicles' files Exposure assessment method: questionnaire; telephone interviews	Breast	*All coffee: drinker vs non-drinker* Non-drinker Drinker	 154 1463	 1.00 0.98 (0.76–1.26)	Age, county of residence, race, menstrual status, age at first live birth, history of benign breast disease, family history of breast cancer, alcohol intake	Strengths: large numbers, thorough identification of BC cases, 70–80% participation rate, population-based controls Limitations: crude assessment of coffee intake (ever vs never consumed), apparent lack of adjustment for smoking, possibility of recall bias

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Levi et al. (1993a) Switzerland, 1992	Cases: 107 admitted to the University Hospital of Lausanne and linked to incidence data from Vaud Cancer Registry Controls: 318 admitted to hospital for acute, non-hormone-related, gynaecological, metabolic, or neoplastic disorders Exposure assessment method: questionnaire; interviewer assessment of weekly frequencies of coffee intake before the occurrence of symptoms	Breast	*Tertiles of coffee consumption* 1st tertile 2nd tertile 3rd tertile [Trend test *P* value, 0.93]	 32 42 33	 1.0 0.8 0.9	Age	Strengths: identification of cases confirmed with linkage to incidence data from Vaud Cancer Registry Limitations: no CI are reported, information for adjusting the reported ORs is not clear, limited adjustment is mentioned in the text
Tavani et al. (1998) Italy, 1983–1991 and 1991–1994	Cases: 5984 histologically confirmed BC, aged 22–74 yr Controls: 5504 admitted to hospital for non-traumatic orthopaedic disorders (32%), acute surgical conditions (17%), and miscellaneous other illnesses, aged 15–74 yr Exposure assessment method: questionnaire; frequency of consumption of regular coffee, cappuccino, decaffeinated coffee	Breast	*Coffee consumption (cups/day)* Non-drinkers < 2 2 > 2 to < 4 ≥ 4	 812 1430 1596 1346 784	 1.00 1.17 (1.03–1.33) 1.17 (1.04–1.33) 1.21 (1.06–1.37) 0.96 (0.83–1.11)	Study/centre, age, education, BMI, smoking status, total alcohol intake, age at menarche and menopause, parity and age at first birth, use of oral contraceptives, use of HRT, history of benign breast disease, family history of BC	Reports no trend but gives no *P* value Strengths: substantial numbers, participants from many areas, adjusted for important risk factors Limitations: hospital-based cases and controls, possibility of recall bias

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2003) USA (Los Angeles City), 1995–1998	Cases: 501 Chinese, Japanese and Filipino women participants of Los Angeles County Cancer Surveillance Program, and California Cancer Registry Controls: 594 selected from the same neighbourhoods as cases Exposure assessment method: FFQ, in-person interviews recording dietary intake during the year before cancer diagnosis (for cases) or during the previous year (for controls)	Breast	*Regular coffee consumption (mL/day)* None > 0–120 > 120 to ≤ 240 > 240 Trend test *P* value, 0.14 *Regular and decaffeinated coffee consumption (mL/day)* None > 0–120 > 120 to ≤ 240 > 240 Trend test *P* value, 0.14	 193 96 107 105 135 94 120 152 	 1.00 1.16 (0.78–1.72) 0.90 (0.63–1.29) 0.77 (0.53–1.12) 1.00 0.91 (0.60–1.38) 0.80 (0.55–1.19) 0.77 (0.52–1.13) 	Education, age at menarche, pregnancy, current BMI, total caloric intake, menopausal status, use of menopausal hormones, intake of soy, dark green vegetables, smoking history, alcohol intake, physical activity, family history of BC	Decaffeinated coffee examined also. Main exposure was green tea consumption. Strengths: population-based cases, adjustment for many risk factors, detailed assessment of exposure Limitations: potential of recall bias, modest sample size, low participation rate, results confined to Chinese, Japanese, and Filipino women who live in the USA
Baker et al. (2006) USA, 1982–1988	Cases: 1932 identified from the RPCI tumour registry Controls: 1895 randomly selected from a pool of 5700 eligible subjects, who received medical services at RPCI for non-neoplastic conditions Exposure assessment method: questionnaire; coffee consumption recorded collected using the PEDS questionnaire	Breast	*Regular coffee consumption (cups/day): premenopausal women* None < 1 1 2–3 ≥ 4 Trend test *P* value, 0.03 *Regular coffee consumption (cups/day): postmenopausal women* None < 1 1 2–3 ≥ 4 Trend test *P* value, 0.57	 136 45 34 126 57 462 159 180 472 261 	 1.00 1.23 (0.73–2.07) 0.95 (0.52–1.71) 0.94 (0.65–1.39) 0.62 (0.39–0.98) 1.00 0.89 (0.69–1.15) 0.93 (0.73–1.19) 1.11 (0.92–1.34) 0.99 (0.79–1.23) 	Age, residence, and age at birth of first child Adjusted for age and residence	Strengths: substantial numbers, examination of decaffeinated coffee, examination of the associations by menopausal status and histologic subtype of BC Limitations: limited adjustment for risk factors, no measures of relative risk for BC overall, potential selection bias due to selection of hospital-based controls with a suspicion of neoplastic disease

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gronwald et al. (2006) Poland, unknown	Cases: 348 Polish women with a diagnosed mutation in *BRCA1* who were seen at the International Hereditary Cancer Centre or affiliated outpatient clinics Controls: 348; details not given Exposure assessment method: questionnaire, mailed questionnaire	Breast	*Regular coffee consumption among* BRCA1 *mutation carriers* No Yes	 NR NR	 1.0 0.8 (0.5–1.1)	Year of birth, age at diagnosis, age at menarche, parity, smoking, breast-feeding, oral contraceptive use	Strengths: matched design, first study to concentrate on high-risk women with *BRCA1* mutation Limitations: unclear validation of the questionnaire, no response rate provided, no information on when the study was conducted, no detailed classification of coffee
Nkondjock et al. (2006) USA, Canada, Poland and Israel, 1970–2002 (diagnosis), 1977–2000 (questionnaire)	Cases: 845 *BRCA1* or *BRCA2* women with invasive BC Controls: 845 *BRCA1* or *BRCA2* women, matched by mutation in the same gene, year of birth and country Exposure assessment method: questionnaire administered by each of the individual centres at the time of a clinic appointment or at their home at a later date	Breast	*Average lifetime total coffee intake (cups/day)* 0 1–3 4–5 ≥ 6 Trend test *P* value, 0.03 *Average lifetime caffeinated coffee intake (cups/day)* 0 1–3 4–5 ≥ 6 Trend test *P* value, 0.02	 264 498 65 18 298 486 51 10	 1.00 0.89 (0.70–1.13) 0.73 (0.48–1.10) 0.51 (0.26–0.98) 1.00 0.90 (0.72–1.12) 0.75 (0.47–1.19) 0.31 (0.13–0.71)	Parity, smoking, oral contraceptive use, alcohol consumption, BMI at age 30	Strengths: substantial numbers, use of coffee as the main exposure, assessment of average lifetime coffee consumption as well as of decaffeinated coffee, adjustment for important risk factors Limitations: possibility of recall bias since the questionnaire assessing coffee consumption was distributed after BC diagnosis

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hirose et al. (2007) Japan, 1990–2000	Cases: 2122 Japanese women who visited the Aichi Cancer Center, whose data were obtained from the hospital-based epidemiological research programme Controls: 12 425 confirmed as free of cancer Exposure assessment method: questionnaire designed for the study, completed before diagnosis of BC for the cases	Breast	*Coffee intake (cups/day)* None Occasional 1–2 ≥ 3 Trend test *P* value, 0.85	 448 430 974 254	 1.00 1.00 (0.85–1.17) 1.00 (0.86–1.15) 1.04 (0.85–1.28)	Age, year, motivation for consultation, parity, age at first delivery, smoking, drinking, exercise, BMI, several dietary variables	Hormone-related cancer risk (breast, endometrial, and ovarian cancer) was the end-point examined. No modification with menopausal status was evident. Strengths: information on coffee intake and potential confounders was collected before diagnoses, substantial numbers of cases/controls were used Limitations: potential for selection bias due to use of non-cancer patients as controls, no apparent information with respect to the actual conditions of control subjects
Kotsopoulos et al. (2007) USA, Canada, 1970–2002	Cases: 170 cases from a registry of *BRCA1* and *BRCA2* mutation carriers at the Centre for Research in Women's Health in Toronto, Ontario Controls: 241, sourced as above Exposure assessment method: questionnaire completed at the time blood was drawn for genetic testing, or within a year of receiving the test result	Breast	*Coffee consumption (caffeinated or decaffeinated, before age 35 yr) of women with* BRCA1 *mutation* Never Ever Trend test *P* value, 0.04	 66 104	 1.00 0.61 (0.38–0.97)	Year of birth, parity, and smoking status	Shares data with Nkondjock et al. (2006). Strengths: detailed assessment of average lifetime coffee consumption and the assessment of past exposure to coffee Limitations: low power to investigate effect modifications, limited adjustment, assessment of exposure before the age of 35 yr makes comparison with other studies difficult, discrepancy in reporting ORs for coffee between table 2 and in results section

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bissonauth et al. (2009) Canada, 2004–2006	Cases: 280 early-onset BC patients who attended the breast centre of CHUM Hotel Dieu Controls: 280 women free from cancer, from the same families as cases or other families with BC Exposure assessment method: interviewer-administered validated FFQ covering the 2-year period before diagnosis (cases) or interview (controls)	Breast	*Coffee consumption (cups/day)* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.03 *Coffee consumption (cups/day): premenopausal women* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.1 *Coffee consumption (cups/day): postmenopausal women* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.13	 102 90 88 56 64 48 30 40 42 	 1.00 1.79 (1.17–2.57) 1.40 (1.09–2.24) 1.00 1.12 (0.63–1.56) 1.09 (0.45–1.99) 1.00 1.23 (0.70–1.82) 1.30 (0.66–1.88) 	Age, education, physical activity, smoking, coffee consumption, total energy intake	Strengths: high quality of the FFQ which was interviewer administered Limitations: this study is described as nested case–control, but such a description is not justified by the information given in the manuscript
Rabstein et al. (2010) Germany, 2000–2004	Cases: 1020 women with histopathologically confirmed BC from the major hospitals of the region Controls: 1047 random sample from population registries, frequency-matched to cases by year of birth in 5-year classes Exposure assessment method: questionnaire, in-person interviews	Breast	*Coffee consumption (cups/day)* None 1–3 ≥ 4	 145 496 379	 1.00 1.02 (0.79–1.32) 1.19 (0.91–1.55)	Unclear	Strengths: population-based controls, high response rates Limitations: modest-to-large sample size, several different exposures, only age-adjusted ORs for coffee in relation to breast cancer risk, concerns about multiple testing

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2011) Sweden and Germany, 1993–1995 (Sweden), 2002–2005 (Germany)	Cases: 2818 (Swedish) and 2651 (German) postmenopausal women from registries Controls: 3111 (Sweden); 5395 (Germany) from population registries matched by age (Sweden) or age and region (Germany) Exposure assessment method: Swedish study: coffee consumption 1 year before interview recorded by mailed questionnaire; Germany: face-to-face interview through an FFQ recording consumption in the past year from diagnosis (cases) and FFQ completion (controls)	Breast	*Main study in Sweden: coffee consumption (cups/day) of postmenopausal women* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 5 > 5 Trend test *P* value, 0.127 *Validation study in Germany: coffee consumption (cups/day) of postmenopausal women* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 5 > 5 Trend test *P* value, 0.173	 298 1277 904 328 1086 1050 358 157 	 1.00 1.01 (0.84–1.23) 1.00 (0.82–1.22) 0.84 (0.66–1.06) 1.00 0.97 (0.87–1.07) 0.95 (0.82–1.10) 0.87 (0.71–1.07) 	Age at enrolment, HRT, smoking, education, daily alcohol consumption	Strengths: so-called validation of results obtained from the Swedish study by means of the German MARIE study (but no formal investigation of validation), large sample size, comprehensive design and analysis Limitations: recall bias, multiple testing concerns
Lowcock et al. (2013) Canada (Ontario), 2002 and 2003	Cases: 3062 from the Ontario Cancer Registry Controls: 3427 selected through RDD of Ontario households, frequency-matched on 5-year age groups Exposure assessment method: 178-item modified Block FFQ recording consumption within the previous 2 yr	Breast	*Caffeinated coffee (cups/day)* Never < 1 1 to < 2 2 to < 3 3 to < 5 ≥ 5	 540 581 594 772 429 71	 1.00 0.91 (0.77–1.07) 0.97 (0.82–1.15) 1.00 (0.85–1.17) 1.07 (0.89–1.29) 0.71 (0.51–0.98)	Age, smoking status, ethnicity, level of strenuous physical activity as a teenager (after model selection)	Strengths: substantial numbers of cases/controls; population-based selection of cases/controls Limitations: possibility of recall bias, lack of adjustment for reproductive factors

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mizoo et al. (2013) Japan, 2010–2011	Cases: 472 consecutive patients with non-invasive or invasive BC aged > 20 yr at four hospitals Controls: 464 women who underwent BC screening at medical centres Exposure assessment method: self-administered questionnaires recording coffee consumption in the pre-diagnostic period (cases) or at recruitment (controls)	Breast	*Coffee consumption (times/wk):* ≤ 1 1 2–3 ≥ 4	 132 154 135 45	 1.00 0.77 (0.55–1.09) 0.68 (0.48–0.96) 0.91 (0.55–1.51)	Age	Limitations: modest size, lack of adjustment for factors other than age, possibility of selection bias due to controls being women who underwent BC screening (and may therefore have a family history of cancer), unclear reporting of study design

BC, breast cancer; BMI, body mass index; CHUM, Centre hospitalier de l'Université de Montréal; CI, confidence interval; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; MARIE, Mamma Carcinoma Risk Factor Investigation; NR, not recorded; OR, odds ratio; PEDS, Patient Epidemiology Data System; RDD, random-digit dialling; RPCI, Roswell Park Cancer Institute; wk, week(s); yr, year(s)

year before diagnosis and to the controls using a similar approach. Response rates for cases and controls were 88% and 79%, respectively. Results suggested a non-significant inverse association between coffee and breast cancer risk, but no test for trend was reported. [The strengths of this study included the use of a cancer registry for identifying cases, hence the inclusion of practically all breast cancer cases identified during the indicated period as well as an adequate numbers of cases. The study was however limited by the fact that the FFQ was validated for fat and β-carotene intakes (main exposures) but not coffee; there was also no adjustment for several confounders.]

McLaughlin et al. (1992) investigated breast cancer risk with methylxanthine consumption in a case–control study of 3234 women conducted in New York State, USA. A total of 1617 primary breast cancer cases (aged 20–79 years) were identified during 1982–1984 through the diagnostic index, tumour registry, and pathology files maintained by each hospital, as well as the New York State Cancer Registry. An equal number of controls were frequency-matched to the cases on year of birth and county of residence via random selection from the files of New York State Department of Motor Vehicles. Data on reproductive, contraceptive, and lifestyle histories, including frequency and quantity of consumption of coffee and decaffeinated coffee, were obtained through telephone interviews using structured questionnaires. Odds ratios adjusted for matching factors and other variables [but apparently not for smoking] revealed null association of coffee intake (assessed as ever vs never consumed) with breast cancer risk. [The advantages of this study were the large number and thorough identification of breast cancer cases. Disadvantages included the crude assessment of coffee intake (ever vs never consumed) and limited adjustment for confounders.]

Wu et al. (2003) investigated the association between consumption of green tea and the risk of breast cancer in a population-based, case–control study among Chinese, Japanese, and Filipino women (aged 25–74 years) in Los Angeles County during 1995–1998. A total of 501 out of 841 incident breast cancer cases, identified by the Los Angeles County Cancer Surveillance Program and the California Cancer Registry, were included in the study (non-participation rate was 42.5%). Control subjects (n = 594) were selected from the same neighbourhoods as cases, with replacement of controls who declined participation (68% participated at first attempt). Controls were frequency-matched to cases on specific Asian ethnicity and 5-year age group. Coffee intake during the year before cancer diagnosis for cases or during the previous year for controls was determined through a validated FFQ by in-person interviews. Odds ratios from conditional logistic regression, adjusting for several potential confounders including family history of breast cancer, revealed an inverse but non-statistically significant association between breast cancer risk and regular coffee (or regular plus decaffeinated coffee) intake, with no indication for trend. [The strengths of this study included the population-based cases, adjustment for many risk factors, and detailed assessment of beverage intake through an established FFQ. Limitations included the neighbourhood controls, low participation rate, and the fact that the results related only to Chinese, Japanese, and Filipino women living in the USA.]

Rabstein et al. (2010) explored the associations between potential sources of exposure to aromatic and heterocyclic amines (AHA) (including coffee consumption), as well as *N*-acetyltransferase 2 (NAT2) acetylation status, and the incidence of receptor-defined breast cancer. The population-based case–control study (GENICA; Gene Environmental Interaction and breast Cancer in Germany) was conducted within the greater region of Bonn, Germany during 2000–2004. Cases (1020) were recruited from the major hospitals of the region (response rate, 88%). Controls

(1047) were a random sample from the population registries, frequency-matched to cases by year of birth (response rate, 67%). Data on breast cancer risk factors (including coffee intake) were obtained from in-person interviews. Odds ratios adjusted for several potential confounders indicated that coffee intake was not associated with breast cancer overall, but a positive association with ER– (OR, 1.78; 95% CI, 1.05–3.02) and PR– (OR, 1.63; 95% CI, 1.00–2.67) breast cancer for those drinking ≥ 4 cups/day of coffee, compared with non-consumers, was apparent. Moreover, there was an indication of an interaction between both acetylation status and coffee intake with respect to breast cancer overall and by receptor status. [This was a complicated study dealing with several different exposures, creating the problem of multiple testing. The Working Group noted that the presentation and interpretation of the interaction between coffee and NAT2 acetylation status was unclear.]

Li et al. (2011) assessed coffee consumption in relation to postmenopausal breast cancer risk overall and by ER tumour subtypes in data from two studies. The main study was a population-based case–control study (2818 cases and 3111 controls) of postmenopausal women aged 50–74 years, resident in Sweden during 1993–1995 and identified through six Swedish regional cancer registries. Participation rate was 84%. Control subjects were randomly selected from a Swedish register and were frequency-matched to cases by age (participation rate, 82%). Analyses undertaken in this main study were validated using subjects drawn from the population-based case–control Mamma Carcinoma Risk Factor Investigation (MARIE) study undertaken during 2002–2005 in two study regions in Germany. MARIE subjects consisted of 2651 cases of postmenopausal breast cancer (women aged 50–74 years at diagnosis) and 5395 controls, randomly selected from the population registries and frequency-matched by year of birth and study region. In the Swedish study, data on coffee consumption 1 year before the interview were recorded in a section of an extensive mailed questionnaire. In the MARIE study, in-person FFQs recording consumption in the year before the date of diagnosis for cases and the date of questionnaire completion for controls were administered. In the Swedish study, odds ratios adjusted for covariates retained after model selection indicated a modest decrease in overall breast cancer risk in the fully adjusted model; the odds ratio for a coffee intake of > 5 cups/day versus ≤ 1 cup/day was 0.84 (95% CI, 0.66–1.06; *P* for trend, 0.127). For ER– and PR– breast cancer tumours, a statistically significant risk reduction was estimated from fully adjusted models for heavy coffee drinkers (coffee intake > 5 cups/day vs ≤ 1 cup/day) with odds ratios of 0.43 (95% CI, 0.25–0.72; *P* for trend, 0.0003) and 0.67 (95% CI, 0.44–1.01; *P* for trend, 0.034), respectively. For ER+ and PR+ cancers, the respective associations were inverse but not statistically significant. Similar findings in magnitude and direction were observed in the validation study, but did not reach statistical significance. [This study had the advantages of the validation of results by the German MARIE study, a large sample size, and a comprehensive design and analysis. The Working Group noted the multiple testing concerns in subgroups due to the estimation of the association in two studies, however.]

Lowcock et al. (2013) studied 3062 breast cancer cases (aged 25–74 years) diagnosed in 2002 or 2003, identified from the Ontario Cancer Registry, and 3427 controls (aged 25–74 years) selected through RDD and frequency-matched to cases by 5-year age groups. Cases and controls completed a 178-item modified Block FFQ, which included coffee and other caffeine-containing items as well as decaffeinated coffee, within the 2 years preceding the questionnaire completion. Odds ratios adjusted for covariates retained after model selection showed a significant reduction in breast cancer risk with the highest category of coffee consumption (OR, 0.71; 95% CI, 0.51–0.98)

for ≥ 5 cups/day versus non-consumers, but there was no evidence of a dose–response relationship. In analysis stratified for smoking, results similar to the overall data were observed for ever and never smokers. High coffee intake was also associated with reduced risk of ER– breast cancer (OR, 0.41; 95% CI, 0.19–0.92) and postmenopausal breast cancer (OR, 0.63; 95% CI, 0.43–0.94) for ≥ 5 cups/day versus non-consumers. Coffee intake was associated with a reduced, albeit not statistically significant, ER+ or premenopausal breast cancer risk. CYP1A2 genotype (variant rs762551) did not modify the indicated associations. [The Working Group noted the substantial numbers of cases/controls and the population-based design.]

Mizoo et al. (2013) reported results from a multicentre, case–control study of 472 breast cancer patients and 464 control subjects conducted in Japan during 2010–2011, examining associations between lifestyle as well as single nucleotide polymorphisms (SNPs) and breast cancer risk. [The Working Group noted that this is described as a population-based case–control study, but based on its description it was not possible to confirm this specific design.] Cases were consecutive patients with non-invasive or invasive breast cancer from four hospitals. Controls underwent breast cancer screening at certain medical centres. Questionnaires extracting details of lifestyle and dietary factors, including coffee consumption in the pre-diagnostic period (cases) or at recruitment (controls), were self-administered. Of the women who originally agreed to participate, 92.4% cases and 88% controls returned the questionnaires. [The Working Group noted the lack of information regarding the original number of identified cases and pool of controls.] Coffee intake of 2–3 cups/day (but not of ≥ 4 cups per day) versus < 1 cup/day was associated with a significantly decreased risk for breast cancer; the age-adjusted odds ratio was 0.68 (95% CI, 0.48–0.96). No modifications by SNPs were observed for the association between coffee intake and risk of breast cancer. [The Working Group noted that in table 1 of Mizoo et al. (2013), 'times/week' is used instead of 'cups/day' for coffee consumption, although 'cups/day' was used in the methods section. Further limitations of this study included: its modest size; insufficient adjustment; selection of cases/controls among consecutive patients; the possibility of selection bias due to controls being women who underwent breast cancer screening (and may therefore have had a family history of cancer); and no clear description of study design.]

(b) Hospital-based case–control studies

Lubin et al. (1985) conducted a hospital-based case–control study in Israel. Breast cancer cases were diagnosed between 1975 and 1979 [the Working Group noted that in the abstract this year is reported as 1978, but in the methods section as 1979] in the greater Tel Aviv metropolitan area. Two control series – surgical controls (SC) hospitalized primarily due to orthopaedic problems (34%) or hernia (22%), and neighbourhood controls (NC) drawn from voting lists – were used. All controls were matched individually to a case by age, country of origin, and length of residence in Israel. The analysis included 738 case-control pairs using surgical controls and 807 case-control pairs using neighbourhood controls. Information regarding the frequency of consumption of 250 food and beverage items 1 year before interview and during the 10 preceding years was sought through face-to-face interviews. Response rates among the eligible subjects were 96% for cases and surgical controls, and 72% for neighbourhood controls. Odds ratios for breast cancer risk adjusted for the matching factors indicated an inverse association with past coffee intake, an association which was similar in magnitude in breast cancer/SC and breast cancer/NC pairs. For women consuming ≥ 4 cups/day of coffee, the odds ratio was 0.7 (95% CI, 0.4–1.1) for SC and 0.6 (95% CI, 0.2–0.9) for NC. Similar results

were evident for current coffee consumption. [The strengths of this study were the inclusion of two control sets, the face-to-face interviews, and detailed information on exposure which considered both present and past exposure. Limitations were the lack of adjusting for confounders and possibility of selection bias due to the medical conditions of the selected surgical controls.]

Rosenberg et al. (1985) analysed data obtained in a case–control programme for the surveillance of drug effects in hospitals located in eastern USA. A total of 2651 cases [the Working Group noted that 2651 cases are reported most often, but 2650 are reported in the materials and methods section] of primary breast cancer inpatients were included. There were two control groups: 1501 women admitted for acute non-malignant conditions (trauma or infections); and 385 women with malignant melanoma, lymphoma, and leukaemia. About 5% of cases and controls (or their doctors) refused to participate. Information on several factors was obtained from nurse-interviewers including the usual consumption per day of caffeinated and decaffeinated coffee in the several months before admission. Odds ratios for breast cancer risk associated with coffee intake were adjusted for a large number of potential confounders including reproductive and family history, somatometry, and smoking. With either control group, odds ratios were close to 1.0 with no apparent trend and no indication of differential associations by age, reproductive history, history of fibrocystic breast disease, family history of breast cancer, or BMI. [The selection of two control groups was considered a strength of this study, as well as the exhaustive adjustment for potential confounders. The study also benefited from the additional examination of caffeinated and decaffeinated coffee in relation to breast cancer. It was limited by possible selection bias due to the recruitment of hospital-based controls with malignancies.]

La Vecchia et al. (1986) conducted a hospital-based, case–control study of breast cancer in two regions of northern Italy with 616 pairs of cases and controls selected from patients admitted to hospitals of the Greater Milan area and Porderone. Subjects were interviewed by trained personnel for the amount (cups/day) and duration (years) of coffee consumption. Eligible controls were women aged < 75 years admitted to hospitals covering the same areas for diseases unrelated to coffee or breast cancer risk factors. The 616 controls selected at random had mostly musculoskeletal conditions (65%). Refusal rate to be interviewed was about 2% for cases and controls. Adjusted odds ratios for coffee drinking were 1.1 (95% CI, 0.7–1.7) for ≥ 4 cups/day. There was no tendency for increasing breast cancer risk with increasing quantity or duration of coffee drinking. The results did not change after adjustment for several potential confounding factors, including the major risk factors for breast cancer. [The Working Group noted that this study was apparently included in the larger study by Tavani et al. (1998), which is described below. A strength of this study was the adjustment for potential confounders, but it was limited by possible selection bias due to hospital-based controls.]

Katsouyanni et al. (1986) conducted a hospital-based case–control study in Athens, Greece, to evaluate the role of diet in breast cancer risk. The study included 120 cases admitted to two teaching hospitals in the Greater Athens area. A total of 120 controls admitted for accidents and orthopaedic disorders in a third teaching hospital were chosen sequentially on the basis of sex and age. Dietary histories for the period preceding the onset of disease were obtained by interview. For coffee intakes (tertiles of frequency of consumption were low, moderate, and high) the study only reported a test for a linear trend for breast cancer risk (adjusting for age, interviewer, and years of schooling) that was not significant. [The Working Group computed crude odds ratios based on the numbers shown in table 2 of Katsouyanni et al. (1986). The strengths of this study were the detailed assessment of diet by

face-to-face interviews and inclusion of subjects from teaching hospitals. Limitations included the probability of selection bias for cases and controls, as well as minimal information on coffee consumption since vegetable intake was the main interest in this study.]

Levi et al. (1993a) examined the association between dietary factors including coffee intake and the risk of breast cancer in a case–control study in Switzerland which served as pilot for the SEARCH Programme of the International Agency for Research on Cancer. A total of 107 breast cancer cases (aged 32–75 years) admitted to the University Hospital of Lausanne, linked with the incidence data from Vaud Cancer Registry, and 318 controls admitted for traumas and other conditions were interviewed. No association between coffee intakes and breast cancer risk was evident; the odds ratio (apparently crude) for the 3rd versus 1st tertile of consumption was 0.9. [Although Levi et al. reported that the estimated association and trend were not significant, no confidence intervals or *P* value were provided. It was also not clear whether these are crude odds ratios or odds ratios adjusted for age, education, and total energy (as mentioned in the text).]

Tavani et al. (1998) examined the association between coffee (mostly espresso and mocha) as well as decaffeinated coffee and risk of breast cancer by combining data from two Italian case–control studies: during 1983–1991 in the Milan area (described previously La Vecchia et al., 1986); and during 1991–1994 in Milan, Pordenone, Genoa, and Forli in northern Italy, Latina in central Italy, and Naples in southern Italy. Less than 4% of cases/controls approached refused to participate. A total of 5984 cases (aged 11–74 years) and 5504 controls (aged 15–74 years) were included. Controls were admitted to the same hospitals as cases for non-neoplastic, non-hormone-related diseases; patients with gynaecological, hormonal, or neoplastic diseases were excluded. Odds ratios for coffee intake in relation to breast cancer risk, adjusted for several factors including family history of breast cancer, showed no overall association. No evidence for effect modification by several factors including BMI, smoking, menopausal status, or family history of breast cancer was apparent. [The strengths of this study were the substantial numbers (as a result of combining two case–control studies) and adjustment for various important risk factors; limitations were the hospital-based cases (due to the absence of a registry for the selection of cases) and controls (probability of selection bias).]

Baker et al. (2006) conducted a case–control study of patients treated at Roswell Park Cancer Institute (RPCI) who agreed to complete the Patient Epidemiology Data System (PEDS) questionnaire, which also enquired about daily regular and decaffeinated coffee consumption. About 50% of women initially contacted returned the PEDS questionnaire. Cases were 1932 women with incident breast cancer (aged 23–97 years) identified from the RPCI tumour registry. Control subjects were 1895 women (aged 21–97 years) randomly selected from a pool of 5700 eligible subjects admitted to RPCI for suspected neoplastic disease, but not subsequently diagnosed with any benign/neoplastic disease. Controls were frequency-matched to cases on 5-year age intervals and residence either inside or outside western New York. Among premenopausal women, increased consumption of regular coffee was associated with decreased breast cancer risk; the odds ratio for coffee consumption of ≥ 4 cups/day compared with non-consumers was 0.62 (95% CI, 0.39–0.98; *P* for trend, 0.03). In postmenopausal women, breast cancer risk was not associated with consumption of coffee. Results did not differ by histologic subtype of breast cancer. [The strengths of this study included the substantial number of subjects and examination of the associations by menopausal status and histologic subtype of breast cancer. Limitations included: limited adjustment; no measures of relative risk for breast cancer overall provided; and potential

for selection bias due to recruitment of hospital-based controls with a suspicion of neoplastic disease.]

Hirose et al. (2007) examined the associations between coffee intake and hormone-related cancer risk (cancer of the breast, endometrium, and ovary) among Japanese women (aged 40–79 years) attending as first-visit outpatients at the Aichi Cancer Center. A total of 2122 breast cancer cases were identified, while the control group comprised 12 425 women free from cancer. Coffee consumption was collected via a questionnaire designed for the study which was completed at the participants' first visit (i.e. before diagnosis for the cases). Odds ratios adjusted for a large number of covariates indicated null associations between coffee intake and breast cancer risk, with no apparent trend. [This study was strengthened by several factors, including: the information on exposures (including coffee intake) and potential confounders being collected before diagnoses, eliminating the possibility of recall bias; the substantial numbers of cases/controls; and the comprehensive design. Limitations included the possibility of selection bias due to the use of hospital-based, non-cancer patients as controls. No information was given with respect to the actual conditions of control subjects, although the characteristics of control subjects were not found to differ from those of the general population.]

(c) *Studies considering* BRCA1/BRCA2 *mutations*

Gronwald et al. (2006) examined the role of reproductive and lifestyle factors on risk of breast cancer among Polish women with a diagnosed mutation in *BRCA1* who had completed a baseline risk-factor mailed questionnaire which also recorded coffee consumption. A total of 348 breast cancer patients and 348 control subjects, matched by year of birth and age at diagnosis of the case, were identified. Odds ratios for coffee consumption (regular user: yes versus no) with respect to breast cancer risk, adjusting for year of birth, age at diagnosis, age at menarche, parity, smoking, breast-feeding, and oral contraceptive use, indicated no association (OR, 0.8; 95% CI, 0.5–1.1). [The study had several limitations: no information on the data or validation of the questionnaire was given; corresponding response rates were not provided; no information on when the study was conducted was reported; and no detailed classification of coffee was made. The main advantage was the investigation of high-risk *BRCA1* mutation carriers.]

Nkondjock et al. (2006) studied carriers of the *BRCA1* or *BRCA2* gene mutation identified from 40 clinical cancer genetics centres in Canada, Israel, Poland, and the USA. In the 845 case–control pairs matched by mutation, birth year, and country, lifetime coffee consumption was assessed through a detailed standardized questionnaire administered by each participating centre. Regarding cases, the average time between date of diagnosis and date of questionnaire completion was an average of 7.8 years. The date of interview of the controls was after the breast cancer diagnosis of the matching case. Odds ratios (95% CI) for breast cancer risk for drinkers of 1–3, 4–5, and ≥ 6 cups/day of caffeinated coffee compared with non-drinkers, adjusted for parity, smoking, oral contraceptive use, alcohol consumption, and BMI at age 30, were 0.90 (0.72–1.12), 0.75 (0.47–1.19), and 0.31 (0.13–0.71), respectively (*P* for trend, 0.02). These associations were also evident in country-specific analyses. The corresponding odds ratios for total coffee intake (caffeinated plus decaffeinated) were similar in magnitude and direction to the results obtained for caffeinated coffee, whereas the association was null for decaffeinated coffee consumption. When stratifying by type of mutation, inverse associations were more evident within the *BRCA1* mutation carriers than the *BRCA2* carriers (but this group was small). [The Working Group noted that part of these data were included in the study of Kotsopoulos

et al. (2007), described below. The strengths of this study were the substantial subject numbers (given that it was conducted among *BRCA1* and *BRCA2* mutation carriers) due to its multicentre design; the assessment of average lifetime coffee consumption, as well as of decaffeinated coffee; and adjustment for important risk factors.]

Kotsopoulos et al. (2007) analysed some of the data used by Nkondjock et al. (2006) (Canada and the USA) to examine whether the CYP1A2 genotype modifies the association between coffee consumption and risk of breast cancer among *BRCA1* mutation carriers. Coffee consumption (caffeinated or decaffeinated) before the age of 35 years was classified as ever or never. Breast cancer cases were 170 women with a history of invasive breast cancer; control subjects included 241 women with no history of breast cancer. Both cases and controls were carriers of a mutation in *BRCA1*. The adjusted odds ratio for breast cancer risk was 0.61 (95% CI, 0.38–0.97) for the ever versus never consumers, with a *P* for trend of 0.04. [The Working Group noted a discrepancy between odds ratios shown in table 2 of Kotsopoulos et al. (2007) and those reported in the results section of the manuscript; odds ratios listed in table 2 are reported here.] In a separate analysis by CYP1A2 genotype, an inverse association was evident among the AC or CC alleles (OR, 0.36; 95% CI, 0.18–0.73; *P* for trend, 0.005) but not among women with the AA allele (OR, 0.93; 95% CI, 0.49–1.77; *P* for trend, 0.82) with the interaction between the CYP1A2 genotype and coffee consumption in relation to breast cancer risk being significant (*P* interaction, 0.04) [The Working Group noted that this study mainly investigates whether the inverse association of coffee with breast cancer risk among *BRCA1* carriers can be further explained through a potential interaction of coffee intake with the CYP1A genotype. The study strengths included the detailed assessment of average lifetime coffee consumption and the assessment of past exposure to coffee, as well as adjustment for important risk factors. Assessing exposure before the age of 35 years makes comparison with other studies difficult, however, and the classification of coffee as ever versus never is rather crude.]

Bissonauth et al. (2009) conducted a case–control study of the association between coffee (and other dietary variables) and risk of breast cancer for non-carriers of *BRCA1/2* mutations among French-Canadian women. Cases were 280 early-onset breast cancer patients who attended the breast centre of CHUM (Centre hospitalier de l'Université de Montréal) Hotel Dieu during 2004–2006, and who were found from DNA testing not to be carriers of six specific mutations in *BRCA1* or *BRCA2*. Controls (n = 280) free from cancer, from the same families as cases or other families with breast cancer and not carriers of any of the six mutations, were matched for age and language. Dietary information was obtained by an interviewer-administered, validated, detailed FFQ covering the 2-year period before diagnosis (cases) or date of interview (controls). Adjustment was performed only for statistically significantly potential confounders associated with breast cancer risk in univariate analyses. A positive association was noted between coffee consumption and breast cancer risk: for drinkers of ≤ 2, > 2 to ≤ 8, and > 8 cups/day compared with non-drinkers, odds ratios (95% CI) were 1.00, 1.79 (1.17–2.57), and 1.40 (1.09–2.24), respectively (*P* for trend, 0.03). When analyses were repeated by menopausal status the associations were effectively null, especially among premenopausal women. [This study benefited from the high-quality FFQ which was interviewer administered, but was limited by the retrospective measures of exposure which may have resulted in recall bias.]

2.4.3 Meta-analyses

Tang et al. (2009), Yu et al. (2011), and Li et al. (2013a) (updating the 2009 meta-analysis conducted by Tang et al.) reported results for the

association of coffee intake with breast cancer incidence, based on meta-analyses of published studies.

The most recent meta-analysis was conducted by Jiang et al. (2013) who analysed 37 cohort and case–control studies identified by a search of PubMed, and by reviewing the reference lists of retrieved articles, with a total of 59 018 breast cancer cases among 966 263 participants. Pooled relative risks with 95% confidence intervals were calculated using fixed- and random-effects models, and the dose–response association was assessed by restricted cubic spline models and multivariate random-effect meta-regression. The overall meta-relative risk of breast cancer (fixed-effects model) was 0.97 (95% CI, 0.93–1.00) for the highest compared with lowest coffee consumption, whereas the meta-relative risk for an increment of 2 cups/day was 0.98 (95% CI, 0.96–1.00). The corresponding meta-relative risks for caffeine intakes were 0.99 (95% CI, 0.94–1.04) and 0.99 (95% CI, 0.98–1.01) for an increase in caffeine of 200 mg/day. No significant association was found between risk of breast cancer and consumption of decaffeinated coffee. A statistically significant inverse association between coffee/caffeine and risk of breast cancer was observed for postmenopausal women (meta-RR, 0.94; 95% CI, 0.8–0.99) and *BRCA1* mutation carriers (meta-RR, 0.69; 95% CI, 0.53–0.89). Sensitivity analysis showed that no individual study had excessive influence on the pooled association between breast cancer risk and intakes of coffee and caffeine. The Egger test showed no evidence of significant publication bias for the analysis of breast cancer risk and coffee (*P* for trend, 0.23) and caffeine (*P* for trend, 0.35). Statistical heterogeneity was moderate to low in all analyses. [The Working Group noted this was the largest meta-analysis estimating the association between coffee consumption with risk of breast cancer. A major strength was the large number of participants included, allowing for finer conclusions and exhaustive subgroup analysis. A dose–response analysis was also performed with advanced statistical methodology to better describe the association between risk of breast cancer and coffee and caffeine intake. However, it should be noted that the pooled relative risk among the *BRCA1* mutation carriers should be interpreted with caution since only three studies were included.]

2.5 Cancer of the endometrium

Fourteen cohort and eleven case–control studies investigated the association between coffee intake and risk of cancer of the endometrium. As BMI and smoking are important confounders, studies not adjusting for these factors (Jacobsen et al. 1986; Levi et al., 1993b; Stensvold & Jacobsen 1994; Goodman et al., 1997; Bravi et al., 2009b) were considered uninformative and were excluded from further review. A case–control study (Petridou et al., 2002a) considering all risk factors for endometrial cancer was also excluded because it was updated by Petridou et al. (2002b).

Among cohort studies, eight were focused on the relation between coffee consumption and endometrial cancer. One study considered the relation between coffee and endometrial cancer type I and type II separately (Uccella et al., 2013), and two studies focused on the association between coffee consumption and selected cancers (both considering mortality as the end-point) (Nilsson et al., 2010; Hashibe et al., 2015). Among the published case–control studies, four focused on the association between coffee consumption and endometrial cancer, and four on the relation to diet or various risk factors. The Working Group also reviewed five meta-analyses of the above-indicated studies, published from 2009 to 2015.

2.5.1 Cohort studies

See Table 2.9.

Shimazu et al. (2008) investigated the association between coffee intake and risk of cancer of the endometrium in the JPHC Prospective Study. Among 53 724 women, enrolled in 1990 for Cohort I (aged 40–59 years) and during 1993–1994 for Cohort II (aged 40–69 years), 117 incident endometrial cancer cases were identified by the major hospitals of the areas and population-based cancer registries. Coffee intake was assessed at baseline using a self-administered FFQ tested for reproducibility. There was a statistically significant inverse association between risk of endometrial cancer and daily coffee intake, with an adjusted hazard ratio of 0.38 (95% CI, 0.16–0.91) for an intake of ≥ 3 cups/day and an inverse trend in risk (*P* for trend, 0.007). The relation was not heterogeneous in strata of exogenous hormone use, BMI, menopausal status, and parity. [The strengths of this study included: linkage with registries; FFQ tested for reproducibility (correlation coefficient, 0.38); high response rate (83%); low loss to follow-up; exclusion of women with previous malignancy; and full adjustment for confounding. It was however limited by the lack of information on hysterectomy and number of cups/day for occasional consumption.]

Friberg et al. (2009) studied the association between coffee consumption and endometrial cancer incidence using a cohort of 60 634 Swedish women who participated in a health mammography screening (the Swedish Mammograpy Cohort) during 1987–1990. After a mean follow-up of 17.6 years, 677 incident cases of endometrial cancer were identified through linkage to the National Swedish Cancer Register and the National Cancer Register. Information on coffee consumption (cups/day) was obtained from two validated FFQs self-administered at an interval of approximately 8 years. Incidence relative risks adjusted for age, BMI, and smoking indicated an overall statistically significant inverse association between daily intake of coffee and risk of endometrial cancer for an intake of ≥ 4 cups/day (RR, 0.75; 95% CI, 0.58–0.97) and for an increment of 1 cup/day (RR, 0.90; 95% CI, 0.83–0.97) (*P* for trend, 0.02). Analysis of long-term coffee consumption revealed a significant inverse association only in the 2–3 cups/day category compared with the reference group (RR, 0.82; 95% CI, 0.68–0.98). The inverse association was found only in obese women; a relative risk of 0.80 (95% CI, 0.69–0.93) for an increment of 1 cup/day for BMI > 30 versus a relative risk of 1.00 (95% CI, 0.88–1.15) for a BMI of of 20–25 was reported, and was not significantly stronger in more inactive or diabetic women. No differences were found in strata of postmenopausal hormone use and smoking. [The strengths of this study were: linkage with Cancer Registries; FFQ tested for validity (correlation coefficient, 0.6); and high response rate (74%). Limitations included the lack of information on previous malignancy and on eventual hysterectomy.]

Nilsson et al. (2010) investigated whether consumption of filtered or boiled coffee is associated with a risk of developing cancer overall. Data on diet were collected through a semiquantitative FFQ for 30 639 women ≥ 30 years of age, recruited within the population-based health survey VIP with a participation rate of 57–67%. Subjects were followed up for a median of 6 years (range 0–15 years) and 108 cases of endometrial cancer were identified by linking the VIP database with the regional cancer registry. Cox regression was used to estimate hazard ratios for cancer risk overall and by site with respect to total, brewed, or boiled coffee consumption, adjusting for age, BMI, smoking, education, and recreational physical activity. For endometrial cancer, no association with coffee consumption was found with a relative risk of 0.88 (95% CI, 0.44–1.78) for an intake of ≥ 4 cups/day. [The main strength of this study was its linkage with the cancer registry. Limitations included: no mention of FFQ testing;

Table 2.9 Cohort studies on cancer of the endometrium and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shimazu et al. (2008) Japan, 1990–1994	53 724; two cohorts of JPHC Study Exposure assessment method: FFQ	Endometrium	*Coffee consumption* ≤ 2 cups/wk 3–4 cups/wk 1–2 cups/day ≥ 3 cups/day Trend test *P* value, 0.007	 66 16 29 6	 1.00 0.97 (0.56–1.68) 0.61 (0.39–0.97) 0.38 (0.16–0.91)	Age, BMI, menopausal status, age at menopause, parity, exogenous hormone use, smoking, green vegetables, beef, pork, green tea, geographic area	Strengths: FFQ tested for reproducibility, high response rate, low loss to follow-up, fully adjusted for confounding Limitations: no information on eventual hysterectomy
Friberg et al. (2009) Sweden, 1987–1990, follow-up until 1997	60 634 participants of SMC aged 40–76 yr Exposure assessment method: FFQ, average consumption from two questionnaires (about 8 yr apart)	Endometrium	*Coffee consumption at baseline (cups/day)* ≤ 1 2–3 ≥ 4 Increment of 1 cup/day Trend test *P* value, 0.02 *Coffee consumption over long term (cups/day)* ≤ 1 2–3 ≥ 4 Increment of 1 cup/day Trend test *P* value, 0.03	 271 312 94 677 224 304 149 677	 1.00 0.78 (0.64–0.95) 0.75 (0.58–0.97) 0.90 (0.83–0.97) 1.00 0.82 (0.68–0.98) 0.85 (0.69–1.05) 0.93 (0.86–1.00)	Age, BMI, smoking	Strengths: linkage with cancer registries, FFQ tested for validity, high response rate, the assessment of long-term coffee consumption effect by using updated information Limitations: no information on eventual hysterectomy, no adjustment for menstrual and reproductive factors
Nilsson et al. (2010) Sweden, 1992–2007	30 639 women (aged > 30 yr) Exposure assessment method: FFQ	Endometrium	*Coffee consumption (occasions/day)* < 1 1–3 ≥ 4	 11 67 30	 1.00 0.92 (0.48–1.76) 0.88 (0.44–1.78)	Age, BMI, education, physical activity, smoking	Strengths: linkage with cancer registry Limitations: no mention of FFQ testing, no adjustment for menstrual and reproductive factors, exposure reported as occasions/day rather than cups/day, very short follow-up for some subjects, small number of cases in some of the categories

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Giri et al. (2011) USA, 1993–1998	45 696 post-menopausal women (aged 50–79 yr) recruited at 40 clinical centres Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/day)*			Age, ethnicity, BMI, smoking, estrogen use, estrogen plus progestin use	Strengths: women with previous cancer and hysterectomy were excluded Limitations: no detailed information on validation/reproducibility, no information on loss to follow-up and on participation rate, no adjustment for menstrual and reproductive factors
			< 1	126	1.00		
			1	71	1.12 (0.84–1.50)		
			2–3	168	0.91 (0.72–1.16)		
			≥ 4	62	0.86 (0.63–1.18)		
			Trend test *P* value, 0.23				
Je et al. (2011) USA, 1980	67 470 women aged 34–59 yr Exposure assessment method: FFQ, average intake from information collected every 4 yr	Endometrium	*Coffee consumption (cups/day)*			Age, BMI, age at menarche, age at menopause, parity, age last birth, HRT, smoking pack-years, total energy intake, calendar year of the current FFQ, alcohol intake, duration of OC use	Strengths: women with previous cancer and hysterectomy excluded, repeated measures of coffee intake, fully adjusted
			< 1	168	1.00		
			1	140	0.94 (0.73–1.19)		
			2–3	275	0.94 (0.77–1.16)		
			≥ 4	89	0.68 (0.52–0.90)		
			Trend test *P* value, 0.01				
Gunter et al. (2012) USA, 1995–1996	111 429 women aged 50–71 yr Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/day)*			Age, BMI, smoking, age at menarche, age at first birth, parity, age at menopause, HRT use, OC use, diabetes, physical activity, ethnicity	Strengths: women with previous cancer and hysterectomy were excluded, linkage with cancer registries, fully adjusted, information on validation/reproducibility of FFQ available Limitations: no information on participation rate
			0	231	1.00		
			< 1	276	0.87 (0.73–1.05)		
			1	273	0.82 (0.68–0.98)		
			2–3	573	0.83 (0.71–0.97)		
			> 3	133	0.64 (0.51–0.80)		
			Increment of 1 cup/day	1486	0.94 (0.90–0.97)		
			Trend test *P* value, 0.004				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Uccella et al. (2013) USA, 1986	23 356 post-menopausal women (aged 55–69 yr) Exposure assessment method: FFQ	Endometrium	*Coffee consumption: type I endometrial cancer*			Age, diabetes, hypertension, age at menarche, age at menopause, BMI, waist to hip ratio, smoking pack-years, total energy intake, alcohol consumption, smoking status, duration of HRT use	Strengths: exclusion of women with previous cancer and hysterectomy , information on validity/ reproducibility, linkage with cancer registries, fully adjusted Limitations: no information on participation rate
			≤ 1 cup/mo	64	1.00		
			< 1 cup/wk	64	0.95 (0.66–1.36)		
			1 cup/day	55	0.75 (0.52–1.09)		
			2–3 cups/ day	188	0.95 (0.71–1.28)		
			≥ 4 cups/day	100	0.71 (0.51–0.99)		
			Trend test *P* value, 0.11				
			Coffee consumption: type II endometrial cancer				
			≤ 1 cup/mo	7	1.00		
			< 1 cup/wk	8	0.98 (0.36–2.72)		
			1 cup/day	13	1.31 (0.51–3.35)		
			2–3 cups/ day	26	1.01 (0.43–2.36)		
			≥ 4 cups/day	17	0.84 (0.33–2.12)		
			Trend test *P* value, 0.64				
Gavrilyuk et al. (2014) Norway, 1991–1997, 2003–2007	97 926 women aged 30–70 yr, only post-menopausal included Exposure assessment method: FFQ	Endometrium	*Coffee (cups/day)*			Age, parity, smoking, BMI, duration of OC use, HRT	Strengths: population-based cohort; women with previous cancer, previous hysterectomy, and incident uterine sarcoma during follow-up excluded; linkage with cancer registries; fully adjusted; FFQ tested for validity and reproducibility Limitations: Lack of information on decaffeinated coffee
			≤ 1	82	1.00		
			2–3	171	0.91 (0.70–1.19)		
			4–7	177	0.84 (0.65–1.10)		
			≥ 8	32	0.52 (0.34–0.79)		
			Trend test *P* value, 0.003				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Weiderpass et al. (2014) Sweden, 1991–1992	42 270 women aged 30–49 yr Exposure assessment method: FFQ, coffee intake only at baseline; second FFQ in 2002–2003 in a subgroup	Endometrium	*Coffee (cups/day)*			Age, education, parity, BMI, diabetes, smoking status, number of cigarettes/ day, menopausal status, duration of OC use, duration of breastfeeding	Similar results in the analyses stratified according to BMI and smoking status Strengths: women with previous breast cancer and hysterectomy excluded, FFQ tested for reproducibility (correlation coefficient, 0.61), linkage with cancer registries, full adjustment, information on response rate (51.3%) Limitations: no information on validity, caffeine assessed only through caffeinated coffee, no separate information for coffee/ decaffeinated coffee
			< 2	23	1.00		
			2–3	47	0.65 (0.39–1.10)		
			> 3	74	0.64 (0.39–1.06)		
			Trend test *P* value, 0.1743				
Hashibe et al. (2015) USA, 1992–2001	32 392 postmenopausal women (age 55–74 yr) Exposure assessment method: FFQ	Endometrium	*All coffee (cups/day)*			Age, BMI, race, education, alcohol consumption, years on birth control, parity, OC, HRT, age at menopause, smoking status, smoking frequency, smoking duration, time since smoking cessation	Strengths: women with previous cancers excluded, linkage with registries, fully adjusted Limitations: no information on reproducibility/validity of FFQ, no information on hysterectomy, no information on participation rates, no clear information on follow-up length
			< 1	106	1.00		
			1–1.9	36	0.67 (0.45–0.99)		
			≥ 2	112	0.72 (0.55–0.95)		
			Increment of 1 cup/day	254	0.92 (0.85–1.00)		
			Trend test *P* value, 0.0205				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Merritt et al. (2015) USA, 1976–1980 (NHS), 1989–1991 (NHS-II)	155 406 women in NHS (age 30–55 yr) and in NHS-II (age 25–42 yr) Exposure assessment method: FFQ, average intake from information collected every 4 yr	Endometrium	*Coffee consumption (g/day)*			Age, cohort, time period, BMI, total energy intake, smoking, age at menarche, OC, menopause, HRT, parity	Strengths: women with previous cancer and hysterectomy excluded, FFQ tested for reproducibility/ validity, repeated measures of coffee intake (every 4 yr), fully adjusted
			0	365	1.00		
			16.6–270.2	286	0.88 (0.76–1.03)		
			289.1–592.5	439	0.92 (0.80–1.06)		
			≥ 609.1	314	0.82 (0.70–0.96)		
			Trend test *P* value, 0.04				
			Quartiles (cumulative average intake)				
			1	263	1.00		
			2	378	1.08 (0.92–1.27)		
			3	363	0.98 (0.83–1.16)		
			4	370	0.89 (0.75–1.05)		
			Trend test *P* value, 0.03				
Merritt et al. (2015) European countries, EPIC, 1992–2000	301 107 women aged 25–70 years Exposure assessment method: FFQ	Endometrium	*Quartiles (baseline intake, g/day)*			BMI, total energy intake, smoking, age at menarche, OC, HRT, parity, age, study centre, menopausal status	Strengths: women with previous cancer and hysterectomy excluded, FFQ tested for validity, fully adjusted, very low loss at follow-up (0.8%) Limitations: no information on reproducibility, no information on participation rate
			1	329	1.00		
			2	275	0.77 (0.66–0.91)		
			3	369	0.88 (0.74–1.04)		
			4	330	0.81 (0.68–0.97)		
			Trend test *P* value, 0.09				
Yang et al. (2015) UK, 1996–2001	560 356 middle-aged women Exposure assessment method: FFQ, average consumption (information at baseline and 4 yr later)	Endometrium	*Coffee (cups/day)*			Age, region, socioeconomic level, age at menarche, OC, BMI, smoking, alcohol consumption, physical activity, tea, non-alcoholic fluid intake, height, duration of OC use, duration of HRT use, menopausal status	Strengths: large number of cases; women with previous breast cancer and hysterectomy excluded, linkage with registries, fully adjusted, FFQ tested for reproducibility Limitations: no information on validation of FFQ
			< 1	1009	0.99 (0.92–1.06)		
			1–2	1839	1.00 (0.95–1.05)		
			3–4	842	0.94 (0.88–1.01)		
			≥ 5	377	0.92 (0.82–1.03)		
			Increment of 1 cup/day	4067	0.98 (0.96–1.01)		
			Daily consumers	3058	0.97 (0.94–1.01)		

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NHS, Nurses' Health Study; OC, oral contraceptive; SMC, Swedish Mammography Cohort; wk, week(s); yr, year(s)

no adjustment for main confounders, except for female hormones (menstrual/reproductive factors and exogenous hormone use); very short follow-up for some subjects; no information on loss to eventual hysterectomy; exposure mentioned as occasions/day rather than cups/day (occasion may be different from cup); and the small number of cases in some of the categories.]

Giri et al. (2011) studied the association between coffee consumption and incidence of endometrial cancer among 45 696 postmenopausal women recruited in 40 clinical centres in the USA using the WHI Observational Study research material obtained from a National Heart, Lung, and Blood Institute biological specimen repository. During the mean follow-up period of 7.5 years, there were 427 incident cases of endometrial cancer. Information on consumption of coffee (caffeinated and decaffeinated) was obtained through a self-administered FFQ. Coffee, both caffeinated and decaffeinated, was not associated with endometrial cancer incidence with an adjusted hazard ratio of 0.86 (95% CI, 0.63–1.18) for an intake of ≥ 4 cups/day (*P* for trend, 0.23), although a tendency for a lower risk for such consumption emerged mainly for decaffeinated coffee (HR, 0.51; 95% CI, 0.25–1.03). A significant inverse association was found for caffeinated coffee in obese women (HR, 0.66; 95% CI, 0.45–0.97) for an intake of ≥ 2 cups/day (*P* for trend, 0.05). [A strength of this study was that women with previous cancer and hysterectomy were excluded from the cohort. Limitations included: no information on loss to follow-up (defined as low) and on participation rate; no information on FFQ validation/reproducibility, although the same questionnaire was administered 3 years after baseline; and no adjustment for main confounders, except for menstrual and reproductive factors.]

Je et al. (2011) assessed total coffee consumption (either caffeinated or decaffeinated) in relation to risk of endometrial cancer in the Nurses' Health Study (NHS) using 67 470 women. The first validated FFQ (Pearson correlation coefficient, 0.78) was self-administered in 1980 and repeated in 1984, 1986, 1990, 1994, 1998, and 2002, and coffee intake considered in the analyses was the cumulative average intake from all previous FFQs. During 26 years of follow-up, a total of 672 cases of endometrial cancer were ascertained. Coffee intake was inversely related to endometrial cancer incidence, with a relative risk of 0.68 (95% CI, 0.52–0.90) for an intake of ≥ 4 cups/day and a linear trend in risk (*P* for trend, 0.01). The inverse association was weaker and not significant for decaffeinated coffee (RR, 0.72; 95% CI, 0.52–1.01). Stratification for selected covariates showed that the inverse association was: statistically significant in ever smokers (RR, 0.65; 95% CI, 0.44–0.95) and in postmenopausal women with a BMI of ≥ 25 (RR, 0.67; 95% CI, 0.46–0.98); stronger but not significant in women with a BMI of ≥ 30 (RR, 0.62; 95% CI, 0.38–1.01); and similar in strata of HRT use. [This study had several strengths, including repeated measures of coffee intake, validation of FFQ, exclusion of women with previous cancer and hysterectomy, and full adjustment. No information on participation rate was provided, however.]

Gunter et al. (2012) analysed data from the US-based cohort NIH-AARP Diet and Health Study, including 111 429 women followed up for a mean of 9.3 years; 1486 cases of endometrial cancer were ascertained during this period. Intake of coffee (caffeinated and decaffeinated) was assessed in cups/day at baseline through a FFQ. A significant inverse association with incidence of endometrial cancer was found for total coffee and either regular or decaffeinated, with a significant trend. The hazard ratios for an increment of 1 cup/day were 0.94 (95% CI, 0.90–0.97), 0.90 (95% CI, 0.86–0.95), and 0.93 (95% CI, 0.87–0.99) for total, decaffeinated, and regular coffee, respectively. Stratified analyses by smoking status yielded similar hazard ratios, while there was no significant association in HRT users or in women with a BMI < 25. [The main

strengths of this study included the substantial number of cases, exclusion of women with previous cancer and hysterectomy, linkage with cancer registries, validation/reproducibility of FFQ, and full adjustment. However, no information on participation rate was included.]

Uccella et al. (2013) investigated the association between coffee/tea consumption and the risk of endometrial cancer among 23 356 women in the IWHS. During the 20-year period of follow-up, 542 cases of endometrial cancer (471 type I and 71 type II) were identified. Coffee consumption was measured by a FFQ tested for reproducibility and validity, and was classified as ≤ 1 cup/month (reference group), < 1 cup/week, and 1, 2–3, and ≥ 4 cups/day [the Working Group noted a mistake in the reported classification]. Compared with never intake or intake of ≤ 1 cup/month, a significant inverse association for endometrial cancer type I was found for consumption of ≥ 4 cups/day of total coffee with a relative risk of 0.71 (95% CI, 0.51–0.99) with no trend in risk. For caffeinated coffee the corresponding relative risk was 0.65 (95% CI, 0.47–0.89; *P* for trend, 0.033); no significant association was found for decaffeinated coffee with a relative risk of 0.76 (95% CI, 0.50–1.15). There was no relation between coffee intake and endometrial cancer type II. The relative risks for ≥ 4 cups/day were 0.84 (95% CI, 0.33–2.12) for total, 0.85 (95% CI, 0.37–1.93) for caffeinated, and 1.08 (95% CI, 0.41–2.80) for decaffeinated coffee. The inverse association with total and caffeinated coffee was statistically significant for type I endometrial cancer in obese women, with a relative risk of 0.53 (95% CI, 0.34–0.84) for an intake of ≥ 4 cups/day and inverse trend in risk. No consistent heterogeneity was found in data stratified for smoking and HRT use. [This study had several strengths: exclusion of women with previous cancer and hysterectomy; FFQ tested for validity/reproducibility; linkage with cancer registries; and full adjustment. However, no information was provided on participation rate.]

Gavrilyuk et al. (2014) examined the association between coffee consumption and risk of endometrial cancer among 97 926 Norwegian women; the subjects, selected from the Central Population Registry of Norway, accepted an invitation to participate in the Norwegian Women and Cancer (NOWAC) Study (response rate was 54.2%). By the end of follow-up (mean 10.9 years), 462 cases of endometrial cancer were identified by linkage of cancer registries. A FFQ tested for validity (Spearman correlation coefficient, 0.82) and reproducibility was self-administered at baseline. For women enrolled during 2003–2007 it also included information on the most common methods of coffee preparation in Norway (filtered, boiled, and instant coffee). Intake of coffee (either filtered or boiled) was inversely associated with incidence of endometrial cancer with a relative risk of 0.52 (95% CI, 0.34–0.79) for an intake of ≥ 8 cups/day and a significant trend in risk (*P* for trend, 0.003). The relative risks were 0.45 (95% CI, 0.21–1.01) for only boiled coffee and 0.55 (95% CI, 0.32–0.94) for only filtered coffee. For an intake of ≥ 8 cups/day, stratified analyses showed that the inverse association was statistically significant only in overweight women with a BMI ≥ 25 kg/m^2 (RR, 0.39; 95% CI, 0.21–0.73) and in current smokers (RR, 0.37; 95% CI, 0.17–0.81). [The strengths of this study included: population-based cohort; exclusion of women with previous cancer and hysterectomy; linkage with cancer registries; full adjustment; and a FFQ tested for validity and reproducibility.]

Weiderpass et al. (2014) evaluated the effect of coffee intake on incidence of endometrial cancer in 42 270 women residing in Sweden as part of the Swedish Women's Lifestyle and Health cohort study (response rate 51.3%). After a follow-up of about 18 years, 144 cases of type I endometrial cancer were ascertained. The information on coffee intake was obtained using an open-ended questionnaire that asked how many cups/day or cups/week women

consumed, while also considering portion sizes (small, 0.75 g; medium, 150 g; large, 225 g). To test reproducibility, similar questions were used in a comparable population giving a Spearman correlation coefficient (r_S) of 0.61. Coffee intake of > 3 cups/day tended to have a favourable effect on risk of endometrial cancer, but this effect did not reach statistical significance (RR, 0.64; 95% CI, 0.39–1.06). There was no heterogeneity in strata of BMI or smoking status. [The strengths of this study included: population-based cohort; exclusion of women with previous breast cancer and hysterectomy; linkage with cancer registries; full adjustment; and information on reproducibility. No information was provided on questionnaire validity, however.]

Hashibe et al. (2015) investigated the association between cancer and consumption of coffee and tea in the PLCO prospective study. At entry, participants were randomized to receive routine health care or screening for prostate, lung, colorectal, and ovarian cancer. A self-administered FFQ was compiled in 1998–2001 at baseline; follow-up started at FFQ administration and stopped in May 2011. Among 32 392 at baseline, 254 incident cases of endometrial cancer were reported. Coffee intake was inversely associated with endometrial cancer incidence, with an adjusted relative risk of 0.72 (95% CI, 0.55–0.95) for ≥ 2 cups/day (*P* for trend, 0.0205). The inverse relation for a consumption increment of 1 cup/day was not statistically significant (RR, 0.92; 95% CI, 0.85–1.00). There was a non-significant inverse relation in never smokers. [The strengths of this study included a linkage with cancer registry, an adjustment for main confounders, and the exclusion of women with previous cancer. Limitations included a lack of information on FFQ testing, participation rate, eventual hysterectomy, or follow-up length. Although this study included never smokers, there was no analysis of coffee intake and cancer risk within this group.]

Merritt et al. (2015) evaluated the effect of diet, including coffee, on risk of cancer of the endometrium using data from three cohort studies: NHS, NHS-II, and EPIC. The analysis included 68 063 women from NHS, which was established in 1976–1980 among female nurses aged 30–55 years, and 87 343 women from the NHS-II, comprising female nurses aged 25–42 years during 1989–1991 and 301 107 women from the EPIC cohort who were aged 25–70 years in 1992–2000 with no previous cancer or hysterectomy. In the NHS, the first validated FFQ (Pearson correlation coefficient, 0.78) was self-administered in 1980 and repeated in 1984, 1986, 1990, 1994, 1998, and 2002, and coffee intake considered in the analyses was the cumulative average intake from all previous FFQs. The EPIC FFQ was validated and self-administered or interviewer-administered (depending on the study centre) only at baseline. During follow-up, 1531 and 1303 cases of endometrial cancer were identified in the NHS cohorts and the EPIC cohort, respectively. For all cohorts combined, a significant inverse association was found: the pooled HR for the highest compared to the lowest level of consumption was 0.82 (95% CI 0.73-0.92). For the NHS cohorts the corresponding HR was 0.82; 95% CI, 0.70–0.96, *P* for trend, 0.04) and for the EPIC cohort, the HR was 0.81 (95% CI, 0.68–0.97, *P* for trend, 0.09). [The strengths of this study included: the linkage to registries; the exclusion of women with previous cancer and hysterectomy; the repeated measures of coffee intake for the NHS cohorts; the validation of FFQs; and full adjustment. No information on reproducibility was provided in the EPIC study, and no information on participation rate was included for any of the cohorts. The Working Group noted an overlap with the populations studied by Je et al. (2011).]

Yang et al. (2015) considered the effect of coffee intake on the incidence of endometrial cancer in the Million Women Study, a population-based cohort of 560 356 women residing in England and Scotland, selected from those invited to attend routine screening for breast cancer (response rate

65%). After a mean follow-up period of 9.3 years, 4067 cases of endometrial cancer were identified. Women were asked to report consumption of coffee in cups/day at baseline and, on average, 4 years after baseline. A total of 57% of women provided the same information, giving a Spearman correlation coefficient ranging over 0.67–0.78 depending on the time between the two reports; the mean consumption from repeated responses was used when available. No association between coffee intake and incidence of endometrial cancer was found, with relative risks of 0.92 (95% CI, 0.82–1.03) for an intake of ≥ 5 cups/day and 0.98 (95% CI, 0.96–1.01) for an increment of 1 cup/day. There was no heterogeneity in strata of BMI, smoking status, or the addition of milk to coffee. [This study benefited from being a population-based cohort, the high number of cases of endometrial cancer, the exclusion of women with previous cancer and hysterectomy, the linkage with cancer registries, full adjustment, and including information on reproducibility. No information on validity was provided, however.]

2.5.2 Case–control studies

See Table 2.10.

Kalandidi et al. (1996) analysed various risk factors for cancer of the endometrium using data obtained in a study which considered women admitted to two Athens hospitals during 1992–1994. Cases were 145 women with incident, invasive cancer of the endometrium. Controls were 298 women admitted to Athens hospitals for orthopaedic disorders. Information was obtained from physician-administered interviews and odds ratios were adjusted for multiple risk factors. There was no significant association between coffee consumption and risk of endometrial cancer, with an odds ratio of 1.04 (95% CI, 0.86–1.27) for an increment of consumption of 1 cup/day. [The physician-administered FFQs, full adjustment, and high participation rate among cases (83%) and controls (88%) were the strengths of this study. A limitation was the use of hospital controls including only orthopaedic disorders. Further, no information was provided on mean or range of age of subjects, previous cancer incidence among cases and controls, hysterectomy among controls, FFQ validity/reproducibility, or intake of caffeinated/decaffeinated coffee.]

Jain et al. (2000) analysed the relation between nutritional factors and cancer of the endometrium in a study conducted in Canada. A total of 552 cases were included, and controls were 562 women with an intact uterus, matched to cases for age and geographic area. Information was obtained from an interviewer-administered validated FFQ. There was no observed association between coffee drinking and risk of endometrial cancer, with an adjusted odds ratio of 0.68 (95% CI, 0.45–1.04) for > 500 g/day of coffee with no trend in risk (*P* for trend, 0.3). [The strengths of this study included: the identification of cases through the cancer registry, population controls, exclusion of women with hysterectomies among controls, validated interviewer-administered FFQ, and full adjustment. No information was provided on the intake of caffeinated/decaffeinated coffee, however.]

Petridou et al. (2002b) analysed various risk factors for cancer of the endometrium in a study conducted in an Athens hospital in 1999. Cases were 84 women with a diagnosis of endometrial cancer identified through medical records, and controls were 84 women with an intact uterus who had been admitted to the same hospital for minor gynaecological conditions. Full participation rate was reported for cases and controls, and subjects with previous cancer were eliminated. Information was obtained from an interviewer-administered FFQ, tested for validity. There was a favourable effect of coffee drinking on the risk of endometrial cancer with an odds ratio of 0.39 (95% CI, 0.17–0.93) for ≥ 4 cups/week. [The strengths of this study were: the exclusion of

Table 2.10 Case–control studies on cancer of the endometrium and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kalandidi et al. (1996) Greece, 1992–1994	Cases: 145 hospital-based Controls: 298 hospital-based (orthopaedic) Exposure assessment method: FFQ	Endometrium	*All types of coffee consumption (cups/day)* Increment of 1 cup/day	145	1.04 (0.86–1.27)	Age, education, occupation, age at menarche, age at menopause, parity, OC, HRT, smoking, alcohol consumption, height, BMI, total energy intake, induced abortions, miscarriages	Strengths: high participation rate among cases and controls, FFQ tested for validity, physician-administered FFQ, fully adjusted Limitations: hospital controls (only orthopaedic diseases), no information on hysterectomy, no information on age
Jain et al. (2000) Canada, 1994–1998	Cases: 552 identified through Ontario Cancer Registry Controls: 562 population controls with intact uterus from Ontario Ministry of Finance, matched by age and geographic areas Exposure assessment method: FFQ, home interviews	Endometrium	*Coffee consumption (g/day), quartiles* 0 ≤ 250 > 250–500 > 500 Trend test *P* value, 0.3	87 197 140 128	1.00 0.80 (0.54–1.18) 1.18 (0.78–1.79) 0.68 (0.45–1.04)	Age, total energy intake, smoking, diabetes, OC, HRT, education, parity, age at menarche, body weight, geographic region	Response rate among cases (70%) and controls (41%) Strengths: population-based study, validated and interviewer-administered FFQ, excluded women who have undergone hysterectomy, fully adjusted
Petridou et al. (2002b) Greece, 1999	Cases: 84 hospital-based Controls: 84 hospital-based (small gynaecological operations) Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/wk)* No ≥ 4	29 55	1.00 0.39 (0.17–0.93)	Age, education, height, BMI, age at menarche, menopause, parity, alcohol consumption, smoking, cholecystectomy, pregnancies, abortions	Strengths: exclusion of controls with previous cancer or hysterectomy, interviewer-administered FFQ, high participation rate, fully adjusted Limitations: small numbers, hospital controls with mild gynaecological conditions

Table 2.10 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Terry et al. (2002) Sweden, 1994–1995	Cases: 709 cases identified through six regional cancer registries Controls: 2870 population-based Exposure assessment method: FFQ	Endometrium	*Coffee consumption (quartiles, median cups/wk)* 1 (4) 2 (11) 3 (22) 4 (30) Trend test *P* value, 0.19	 250 167 137 155	 1.00 0.9 (0.6–1.3) 0.8 (0.6–1.1) 0.7 (0.5–1.0)	Age, BMI, smoking, physical activity, diabetes, fatty fish, quintiles of total food, various dietary items	Postmenopausal women aged 50–74 years Strengths: identification of cases through cancer registries, population controls, exclusion of previous endometrial/breast cancer, exclusion of controls having undergone hysterectomy, FFQ tested for validity and reproducibility Limitations: self-administered FFQ, no adjustment for menstrual and reproductive factors, no adjustment for hormone use
Hirose et al. (2007) Japan, 1990–2000	Cases: 229 cases identified through medical records and cancer registries Controls: 12 425 first-visit outpatients Exposure assessment method: self-administered FFQ, which was then checked by an interviewer	Endometrium	*All coffee (cups/day)* 0 < 1 1–2 ≥ 3 Trend test *P* value, < 0.01	 72 50 90 13	 1.00 0.70 (0.45–1.08) 0.64 (0.43–0.94) 0.41 (0.19–0.87)	Age, year of interview, motivation for consultation, parity, age at first delivery, smoking, alcohol consumption, type of breakfast, physical activity, BMI, various dietary items	Strengths: cases identified through medical records and cancer registries, checking of FFQ, exclusion of previous cancer among controls Limitations: hospital controls, no exclusion of controls having undergone hysterectomy, no information on FFQ validity/ reproducibility and other characteristics, no adjustment for menstrual factors and exogenous hormones

Table 2.10 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Koizumi et al. (2008) Japan, 2002–2005	Cases: 107 hospital-based Controls: 214 women attending cancer screening programme Exposure assessment method: FFQ	Endometrium	*All coffee consumption* < 4 times/wk 5 times/wk – 1 cup/day ≥ 2 cups/day Trend test *P* value, 0.014	 48 25 34	 1.0 0.6 (0.3–1.2) 0.4 (0.2–0.9)	Age, geographic area, education, BMI, smoking, age at menarche, OC, diabetes, energy intake, number of pregnancies, menopausal status	Inverse association only in postmenopausal women, similar inverse association in strata of BMI and education Strengths: population controls, previous cancer excluded, exclusion of controls having undergone hysterectomy, high participation rate, FFQ tested for validity/reproducibility, fully adjusted Limitations: self-administered FFQ
McCann et al. (2009) USA, 1982–1998	Cases: 513 hospital-based (tumour registry and diagnostic index) Controls: 512 hospital-based Exposure assessment method: FFQ, referred to few years before the administration	Endometrium	*All coffee consumption (cups/day)* 0 0.5 1–2 > 2 Trend test *P* value, 0.5	 170 68 165 110	 1.00 0.77 (0.50–1.18) 0.89 (0.63–1.24) 0.71 (0.49–1.03)	Age, HRT, OC, education, smoking, BMI, decaffeinated coffee, tea	Strengths: cases identified by cancer registries, information for caffeinated/decaffeinated coffee, exclusion of controls with previous hysterectomy and cancer, fully adjusted Limitations: hospital controls, self-administered FFQ, no clear information on participation rate among controls, no information on validity/ reproducibility of FFQ
Bandera et al. (2010) USA, 2001–2005	Cases: 417 population-based Controls: 395 population-based Exposure assessment method: FFQ	Endometrium	*All coffee consumption (cups/day)* 0 ≤ 1 1–2 > 2 Trend test *P* value, 0.11	 70 181 110 52	 1.00 1.05 (0.58–1.89) 1.02 (0.56–1.88) 0.69 (0.36–1.33)	Age, education, race, age at menarche, parity, OC, HRT, BMI, menopause, smoking (pack-years), smoking status, age at menopause, addition of sugar/honey/milk/cream/ non-dairy cream	Strengths: cases identified through cancer registries, population controls, exclusion of controls having undergone hysterectomy, FFQ tested for validity and reproducibility, fully adjusted Limitations: low participation rate, self-administered FFQ

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; OC, oral contraceptive; wk, week(s)

women with previous cancer among cases and controls, and of women with hysterectomies among controls; the validated interviewer-administered FFQ; the high participation rate; and full adjustment. The study was however limited by: the low number of participants; hospital controls with mild gynaecological conditions; and a lack of information on age of participants and intake of caffeinated/decaffeinated coffee.]

Terry et al. (2002) analysed the relation of dietary factors to cancer of the endometrium in a study conducted in Sweden. The 709 cases of endometrial cancer were identified through six regional cancer registries. Controls were 2870 women with an intact uterus selected from a national population registry. Cases and controls with previous endometrial or breast cancer were excluded, and information was obtained from a self-administered questionnaire. A non-significant inverse association between coffee drinking and risk of endometrial cancer was observed, with an adjusted odds ratio of 0.7 (95% CI, 0.5–1.0) for the highest quartile of coffee intake (corresponding to a median intake of 30 cups/week), with no trend in risk (*P* for trend, 0.19). [This study benefited from the identification of cases through cancer registries, population-based controls, the exclusion of cases with previous endometrial/breast cancer and of controls with hysterectomies, the high participation rate, and that fact that FFQs were tested for validity/reproducibility (correlation coefficient, 0.3–0.6). It was however limited by the self-administered FFQ (except for a few telephone interviews), the lack of information on intake of caffeinated/decaffeinated coffee, and the lack of adjustment for menstrual/reproductive factors and HRT use.]

Hirose et al. (2007) examined the associations between coffee intake and the risk of cancer of the breast, endometrium, and ovary among Japanese women (described in Section 2.4.2 (b) on breast cancer). A total of 229 cases of endometrial cancer were reported. Coffee intake decreased the risk of endometrial cancer with an odds ratio of 0.41 (95% CI, 0.19–0.87) for consumption of ≥ 3 cups/day compared with non–drinkers, with a significant trend in risk (*P* for trend, < 0.01). The inverse association was statistically significant in women aged < 55 years but not in older women, with odds ratios for ≥ 3 cups/day versus non-drinkers of 0.40 (95% CI, 0.16–0.99; *P* for trend, 0.03) and 0.33 (95% CI, 0.08–1.45), respectively. The inverse association was also statistically significant in women with a BMI ≤ 22 kg/m^2 but not for women with a BMI of > 22, with odds ratios for ≥ 3 cups/day versus non-drinkers of 0.08 (95% CI, 0.01–0.60; *P* for trend, 0.001) and 0.78 (95% CI, 0.34–1.81), respectively. The inverse association was consistent in data stratified for smoking, alcohol drinking, and fruit consumption. [This study had several strengths, including the facts that cases were identified through medical records and cancer registries, the self-administered FFQs were checked by an interviewer, and controls with previous cancer were excluded. It was however limited by: the hospital-based controls; the lack of information on exclusion of hysterectomized women from controls, FFQ validity/reproducibility, and other characteristics; the lack of adjustment for menstrual factors and exogenous hormones; and no separate information for coffee/decaffeinated coffee.]

Koizumi et al. (2008) analysed the association between coffee consumption and risk of cancer of the endometrium in a study conducted at two centres in Japan. Cases were 107 women aged < 80 years with endometrial endometrioid adenocarcinoma (endometrial cancer type I) identified from the histopathological records. Controls were 214 women matched with cases for age and geographical region, identified among women attending a cancer screening programme. Cases and controls were excluded if they had had any cancer, and controls were excluded if they had hysterectomies. Coffee consumption was collected through a self-administered questionnaire before surgery for cases and by mail

for controls. Coffee was inversely related to the risk of endometrial cancer type I, with an intake of ≥ 2 cups/day compared with < 4 times/week [not specified whether 'time' is equal to 'cup'] yielding an adjusted odds ratio of 0.4 (95% CI, 0.2–0.9) with a trend in risk (*P* for trend, 0.014). No heterogeneity was found in strata of BMI and education, but the inverse association was found only in postmenopausal women with an intake of ≥ 2 cups/day compared with ≤ 4 times/week yielding an odds ratio of 0.3 (95% CI, 0.1–0.8) with a trend in risk (*P* for trend, 0.016); the corresponding odds ratio in premenopausal women was 1.2 (95% CI, 0.3–4.3). [The strengths of this study included: the use of population-based controls; the exclusion of previous cancer among cases and controls, and of hysterectomies among controls; the high participation rate; the fact that the FFQ was tested for validity/reproducibility; and full adjustment of data. It was however limited by the self-administered FFQ and lack of separate information for caffeinated and decaffeinated coffee intake.]

McCann et al. (2009) analysed the association between consumption of coffee and tea and risk of cancer of the endometrium in a study conducted at the RPCI in USA during 1982–1998. Cases were 513 women newly diagnosed with endometrial cancer, identified from the tumor registry. Controls were 512 subjects matched to cases by age, identified among women who had received medical services at the same institute with a suspicion of neoplastic disease but were not diagnosed with malignant conditions. There was no information provided on participation rate, but about 50% of patients returned the mailed questionnaire. Coffee consumption was collected through a self-administered FFQ questionnaire. Regular coffee consumption was associated with a decreased risk of endometrial cancer, with an odds ratio of 0.71 (95% CI, 0.49–1.03; *P* for trend, 0.50) for > 2 cups/day versus non-drinkers. The results were similar in data stratified for BMI. Decaffeinated coffee was not related to overall risk of endometrial cancer (OR, 1.17; 95% CI, 0.74–1.84) for an intake of > 2 cups/day or in strata of BMI. [The strengths of this study were identification of cases by cancer registries, exclusion of controls with cancer diagnosis or hysterectomy, consideration of caffeinated and decaffeinated coffee intake, and full adjustment. It was however limited by the use of hospital-based controls, the self-administered FFQ, and lack of information about FFQ validity/reproducibility.]

Bandera et al. (2010) considered the association between the consumption of coffee and tea and the risk of cancer of the endometrium using data from the Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE) study conducted in six New Jersey counties (USA). The 417 cases (aged > 21 years) were identified through the New Jersey State Cancer Registry (participation rate 42%). The 395 controls were identified from various sources: RDD for women aged < 65 years (participation rate 49%); lists for Medicare/Medicaid services for those aged ≥ 65 years (participation rate 22%); and households in randomly selected neighbourhoods for those aged ≥ 55 years (participation rate 43%). Women with hysterectomies were excluded from controls. Coffee consumption was collected through a self-administered FFQ tested for validity (Block version 98.2). Coffee consumption was not related to incidence of endometrial cancer, with an odds ratio of 0.69 (95% CI, 0.36–1.33) for > 2 cups/day compared with non-drinkers (*P* for trend, 0.11). [The study benefited from identification of cases through cancer registries, the use of population-based controls, the exclusion of hysterectomized women from controls, the testing of the FFQ for validity/reproducibility, and full adjustment. Limitations noted included a low participation rate, no information on previous cancer among cases and controls, the self-administered FFQ, and a lack of information regarding consumption of caffeinated and decaffeinated coffee separately.]

2.5.3 Meta-analyses

Bravi et al. (2009a) conducted the first meta-analysis of the association of endometrial cancer and coffee consumption by performing a MEDLINE search of the literature spanning 1966 to July 2008; the nine observational studies identified (two cohort and seven case–control) included a total of 2610 cases. A meta-relative risk for an increment of 1 cup/day of 0.93 (95% CI, 0.89–0.97) was estimated, with substantial heterogeneity between the studies. Yu et al. (2011) studied coffee intake in association with cancer incidence based on cohort studies, but the Working Group found the meta-analysis had important methodological limitations. Je & Giovannucci (2012) searched the electronic databases MEDLINE and Embase for epidemiologic studies published between 1966 and October 2011, and reviewed the reference lists of retrieved articles. The analyses were based on 16 observational studies for a total of 6628 cases, including 6 cohort (3144 cases) and 10 case–control studies (3484 cases). There was no indication of publication bias based on funnel plots and the Egger test. The summary relative risks with 95% confidence interval were calculated using random-effects models because of the heterogeneity among studies. The pooled relative risks (95% CI) for the study-specific highest versus the study-specific lowest consumption were: 0.71 (0.62–0.81) based on all studies; 0.70 (0.61–0.80) for the 6 cohort studies; and 0.69 (0.55–0.87) for the 10 case–control studies. Sensitivity analysis showed that excluding the study of Levi et al. (1993b) (which did not adjust for BMI) increased the strength of the inverse association. The inverse association was similar in the 12 studies after adjusting for smoking and BMI, and apparently stronger in the 3 studies conducted in Japan (RR, 0.40; 95% CI, 0.25–0.63) than in the 8 studies conducted in Europe (RR, 0.79; 95% CI, 0.63–0.99) or 5 in North America (RR, 0.69; 95% CI, 0.60–0.79). The pooled relative risks for an increment of 1 cup/day were 0.92 (95% CI, 0.90–0.95) based on 14 studies, 0.94 (95% CI, 0.90–0.97) for the cohort studies, and 0.90 (95% CI, 0.86–0.95) for the case–control studies. The inverse association was again apparently stronger in studies conducted in Japan (RR, 0.76; 95% CI, 0.68–0.86) than in Europe (RR, 0.93; 95% CI, 0.90–0.97) or North America (RR, 0.94; 95% CI, 0.91–0.97). Coffee intake therefore appeared consistently inversely associated with risk of endometrial cancer. [This meta-analysis benefited from searching also within the Embase database; the inclusion of 'dietary factors' among keywords, resulting in the inclusion of all published studies; checking for publication bias; deep analysis that allowed information on dose–response relationship, and in strata of study design and geographical area; appropriate statistical analysis; clear information on number of studies included in subgroup analyses; analyses for a subgroup of papers adjusting for smoking and BMI; and a sensitivity analysis with the exclusion of each paper in turn. No subgroup analyses based on BMI and menopausal status was performed, however.]

In a report of the association between intake of coffee and tea and risk of cancer of the endometrium, part of the UK-based Million Women Study, Yang et al. (2015) included a meta-analysis from searching in PubMed and Embase [there was no indication of the date of the reference search, which appears to have been around the end of 2012] and looking at the reference lists of retrieved articles. Analyses were based on eight cohort and eight case–control studies. Compared with the previous meta-analysis of Je & Giovannucci (2012), this meta-analysis included two further cohorts but excluded two case–control studies. [The strengths of this analysis were the stratification by study design and geographical region, and investigation of dose–response relationship. It was however limited by: the unspecificied date of the literature search; no inclusion of the keyword 'diet', which led to the exclusion of two papers; no check for

publication bias; and no sensitivity analysis with the exclusion of each paper in turn.]

Zhou et al. (2015) reported the results of a meta-analysis of prospective cohort studies updated to May 2015, based on 13 studies. The relative risks (95% CI) were 0.80 (0.74–0.86) for the highest versus the lowest coffee intake and 0.95 (0.93–0.97) for an increment of 1 cup/day. The inverse association for the highest versus the lowest coffee intake was similar for regular (RR, 0.66; 95% CI, 0.52–0.85) and decaffeinated coffee (RR, 0.77; 95% CI, 0.63–0.94), and was apparently stronger in women with a BMI > 25 kg/m^2 and in those who never used HRT. [The Working Group noted that the analyses in strata of BMI excluded several relevant studies.] The only cohort study published after this meta-analysis had similar results (Hashibe et al., 2015). [The strengths of this analysis were the investigation of a dose–response relationship, stratification by many covariates, and sensitivity analysis with the exclusion of each paper in turn. It was however limited by the fact that the stratified analyses did not include all papers.]

2.6 Cancer of the prostate

More than for any other cancer, the incidence of cancer of the prostate must be interpreted in the context of diagnostic intensity and screening behaviour. Latent prostate cancer is quite common, and screening by prostate-specific antigen (PSA) has allowed for the detection of many of these lesions. Consequently, incidence rates in some countries, the USA being a prime example, reflect the sum of clinical disease and latent disease. There is therefore a focus on identifying risk factors for clinically important prostate cancer, or disease that is most likely to progress, both for biological relevance and to deal with confounding by screening. As a result, the Working Group considered associations for risk of total prostate cancer, but also for risk of fatal, advanced (based on stage), and high-grade (based on Gleason grade, a histological assessment of differentiation) disease. In studies that combined stage and grade-based definitions, we refer to this as 'aggressive' disease.

Studies that did not control for smoking behaviour were judged to be non-informative. Smoking is not associated with total prostate cancer incidence, but is associated with prostate cancer mortality (US Department of Health and Human Services, 2014). Because smoking is also strongly associated with coffee intake in many populations, and because many high-quality studies of coffee and prostate cancer with adjustment for smoking are available, those without adjustment for smoking were excluded.

2.6.1 Cohort studies

See Table 2.11.

Four cohort studies, three of prostate cancer incidence (Severson et al., 1989; Le Marchand et al., 1994, an updated report from the cohort in Nomura et al., 1986; Ellison, 2000) and one of fatal prostate cancer (Hsing et al., 1990), that did not control for smoking were reviewed but excluded from evaluation due to the potential for confounding.

Jacobsen et al. (1986) studied the association between coffee drinking and risk of multiple cancers in a cohort of Norwegian men. Smoking information was only provided for part of the study population, so only those results were considered here. Among those 10 517 men, there were 205 cases of cancer of the prostate. Coffee consumption in the population was very high, so the comparison group was ≤ 2 cups/day. Men consuming ≥ 7 cups/day had an odds ratio of 0.89 (*P* for trend, 0.14). Results were adjusted only for age in 10-year groups, area of residence, and cigarette smoking, and confidence intervals were not provided. [Strengths included the prospective design and high-quality cancer registry. There was no consideration of stage or grade; however, the study was conducted before the introduction

Table 2.11 Cohort studies on cancer of the prostate and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jacobsen et al. (1986) Norway, 1964–1967/1978	10 517 Norwegian men who completed a questionnaire in 1964 followed by one in 1967 on coffee habits Exposure assessment method: FFQ	Prostate	*Baseline coffee intake (cups/day)*			Age (10-year groups), residence, smoking	Only included analyses from the subgroup of men who also provided information on smoking habits for adjustment Strengths: prospective design, high-quality cancer registry, conducted before introduction of PSA screening Limitations: high coffee intake in the target population made a wide reference group (non-drinkers up to 2 cups/day), analysis adjusted for age in 10-yr groups
			≤ 2	62	1.17		
			3–4	79	0.97		
			5–6	43	0.91		
			≥ 7	21	0.89		
			Trend test *P* value, 0.14				
Stensvold & Jacobsen (1994) Norway, 1977/1982–1990	21 735 men aged 35–54 yr from three counties in Norway identified via cardiovascular screening programme Exposure assessment method: FFQ	Prostate: all combined	*All coffee (cups/day)*			Age, residence, smoking	Strengths: prospective design, high-quality cancer registry, before PSA screening Limitations: see Jacobsen et al. (1986)
			≤ 2	8	1.0		
			3–4	6	0.3		
			5–6	13	0.6		
			≥ 7	11	0.4		
			Trend test *P* value, > 0.05				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nilsson et al. (2010) Sweden, 1992–2007	32 425 residents in Västerbotten county, Sweden Exposure assessment method: FFQ, nine frequency options for both filtered and boiled coffee	Prostate: ICD7:177 malignant neoplasm of prostate Prostate	*Total coffee (boiled + filtered) from baseline questionnaire (occasions/day)*			Age, BMI, smoking, education, physical activity	Strengths: long follow-up, high-quality cancer registry Limitations: no information on cancer grade, stage, or PSA testing
			< 1	60	1.00		
			1–3	384	0.92 (0.70–1.21)		
			≥ 4	209	1.03 (0.77–1.38)		
			Filtered coffee from baseline questionnaire (occasions/day)				
			< 1	196	1.00		
			1–3	343	0.98 (0.82–1.16)		
			≥ 4	114	1.07 (0.85–1.36)		
			Boiled coffee from baseline questionnaire (occasions/day)				
			< 1	452	1.00		
			1–3	161	0.99 (0.82–1.18)		
			≥ 4	40	1.13 (0.81–1.56)		
Wilson et al. (2011) USA, 1986–2006	47 911 men, health professionals in the USA aged 40–75 in 1986 Exposure assessment method: validated FFQ in 1986 and every 4 yr thereafter	Prostate: all combined	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*			Age and calendar period, race, BMI at age 21, current BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer, multivitamin use, processed meat intake, tomato sauce intake, calcium intake, α-linolenic acid, supplemental vitamin E, alcohol consumption, energy intake, history of PSA testing, height	Strengths: validated FFQ with repeated diet measurements, long follow-up (20 yr), prostate cancer risk analysed by grade/ stage/lethality, adjusted for PSA screening Limitations: sample size for very high intakes of coffee (> 5 cups/day) was small
			None	587	1.00		
			< 1	1139	0.94 (0.85–1.05)		
			1–3	2438	0.94 (0.86–1.04)		
			4–5	719	0.93 (0.83–1.04)		
			≥ 6	152	0.82 (0.68–0.98)		
			Trend test *P* value, 0.1				
		Prostate: lethal	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	89	1.00		
			< 1	150	0.76 (0.58–1.00)		
			1–3	298	0.71 (0.55–0.92)		
			4–5	93	0.76 (0.56–1.04)		
			≥ 6	12	0.40 (0.22–0.75)		
			Trend test *P* value, 0.03				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2011) (cont.)		Prostate: advanced stage	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	122	1.00		
			< 1	211	0.81 (0.64–1.02)		
			1–3	422	0.75 (0.60–0.93)		
			4–5	122	0.73 (0.56–0.95)		
			≥ 6	19	0.47 (0.28–0.77)		
			Trend test *P* value, 0.004				
		Prostate: non-advanced stage	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	353	1.00		
			< 1	729	1.01 (0.88–1.15)		
			1–3	1554	0.99 (0.87–1.12)		
			4–5	483	1.02 (0.88–1.18)		
			≥ 6	102	0.93 (0.74–1.16)		
			Trend test *P* value, 0.77				
		Prostate: grade 8–10	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	61	1.00		
			< 1	111	0.84 (0.61–1.16)		
			1–3	255	0.87 (0.65–1.18)		
			4–5	78	0.88 (0.61–1.26)		
			≥ 6	11	0.53 (0.27–1.02)		
			Trend test *P* value, 0.29				
		Prostate: grade 7	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	174	1.00		
			< 1	295	0.85 (0.70–1.04)		
			1–3	641	0.85 (0.71–1.02)		
			4–5	226	0.94 (0.76–1.16)		
			≥ 6	41	0.69 (0.49–0.99)		
			Trend test *P* value, 0.50				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2011) (cont.)		Prostate: grade 2–6	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	232	1.00		
			< 1	489	1.02 (0.87–1.20)		
			1–3	1045	1.01 (0.87–1.18)		
			4–5	298	0.96 (0.80–1.15)		
			≥ 6	70	1.00 (0.75–1.31)		
			Trend test *P* value, 0.53				
Shafique et al. (2012) Scotland, 1970/1973–2007	6017 men aged 21–75 yr Exposure assessment method: questionnaire; details of how coffee assessed were not provided; full diet unknown, appears that only coffee and alcohol were assessed	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, cholesterol levels, systolic blood pressure, BMI, alcohol intake, tea intake, smoking status, social class	Strengths: long-term follow-up (28 yr median), analysis by cancer grade as well as by total prostate cancer, clean reference group of never drinkers Limitations: smaller cohort, baseline coffee intake with very long follow-up, lack of information on PSA screening
			0	139	1.00		
			1–2	114	0.95 (0.72–1.24)		
			≥ 3	65	0.93 (0.66–1.31)		
			Trend test *P* value, 0.64				
		Prostate	*Cups of coffee continuous*				
			Per 1 cup/ day	318	0.96 (0.81–1.13)		
		Prostate: all combined	*Baseline coffee intake (survivor) (cups/day)*				
			0	81	1.00		
			1–2	67	0.84 (0.60–1.21)		
			≥ 3	38	0.74 (0.47–1.16)		
			Trend test *P* value, 0.23				
		Prostate: aggressive/ advanced (Gleason 8–10)	*Baseline coffee intake (survivor) (cups/day)*				
			0	39	1.00		
			1–2	20	0.51 (0.28–0.92)		
			≥ 3	11	0.47 (0.22–1.01)		
			Trend test *P* value, 0.03				
		Prostate: aggressive/ advanced (Gleason 7)	*Baseline coffee intake (survivor) (cups/day)*				
			0	12	1.00		
			1–2	14	1.23 (0.53–2.84)		
			≥ 3	12	1.79 (0.69–4.62)		
			Trend test *P* value, 0.17				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shafique et al. (2012) (cont.)		Prostate: aggressive/ advanced (Gleason < 7)	*Baseline coffee intake (survivor) (cups/day)*				
			0	17	1.00		
			1–2	17	1.04 (0.51–2.17)		
			≥ 3	7	0.54 (0.19–1.57)		
			Trend test *P* value, 0.48				
		Prostate: aggressive/ advanced (unknown Gleason)	*Baseline coffee intake (survivor) (cups/day)*				
			0	13	1.00		
			1–2	16	1.17 (0.52–2.64)		
			≥ 3	8	0.88 (0.31–2.48)		
			Trend test *P* value, 0.89				
Discacciati et al. (2013) Sweden, 1997–2010	44 613 men aged 45–79 yr residing in two central Sweden counties during 1997–1998 Exposure assessment method: FFQ	Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day)*			Age, tea, alcohol consumption, BMI, diabetes, family history of prostate cancer, smoking status, physical activity, education, energy intake	Strengths: analysis of risk performed by stage, grade, and fatal disease; validated FFQ Limitations: subhazard ratios are not comparable to other studies, lack of information on PSA screening, use of 1–3 cups/ day as reference group, coffee consumption was self-reported
			None	28	1.24 (0.83–1.97)		
			< 1	63	1.19 (0.90–1.56)		
			1–3	316	1.00		
			4–5	82	1.01 (0.79–1.30)		
			≥ 6	26	0.88 (0.58–1.31)		
			Trend test *P* value, 0.18				
		Prostate: aggressive/ advanced (advanced–stage)	*Baseline coffee intake (cups/day)*				
			None	37	0.96 (0.68–1.35)		
			< 1	93	0.97 (0.78–1.21)		
			1–3	582	1.00		
			4–5	153	0.95 (0.79–1.14)		
			≥ 6	53	0.87 (0.66–1.16)		
			Trend test *P* value, 0.49				
		Prostate: localized	*Baseline coffee intake (cups/day)*				
			None	129	1.13 (0.93–1.37)		
			< 1	212	1.00 (0.86–1.16)		
			1–3	1397	1.00		
			4–5	457	0.93 (0.83–1.03)		
			≥ 6	173	0.81 (0.69–0.96)		
			Trend test *P* value, 0.005				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2013b) Japan (Ohsaki), 1994–2005	18 853 National Health Insurance beneficiaries aged 40–79 resident in the Ohsaki Public Health Center administrative region Exposure assessment method: validated FFQ with five response categories for coffee	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, education, BMI, physical activity, marital status, walking, smoking status, family history of cancer, tea intake, job status, energy intake, passive smoking, alcohol consumption, miso soup consumption	Strengths: validated FFQ, reference group of non-drinkers of coffee, population with relatively stable dietary habits Limitations: small number of cases, low coffee consumption in this study population, lack of PSA testing information (PSA testing is not as common in Japan as it is in Europe/ USA), coffee intake assessed once at baseline
			Never	84	1.00		
			Occasionally	124	0.81 (0.61–1.07)		
			1–2	86	0.73 (0.53–1.00)		
			≥ 3	24	0.63 (0.39–1.00)		
			Trend test *P* value, 0.02				
		Prostate: aggressive/ advanced (advanced-stage or high-grade)	*Baseline coffee intake (cups/day)*			Age, education, BMI, physical activity, marital status, walking, smoking status, family history of cancer, tea intake, job status, energy intake, passive smoking, alcohol consumption, miso soup consumption, time period of diagnosis	
			Never	24	1.00		
			Occasionally	50	1.26 (0.73–2.16)		
			1–2	27	0.73 (0.38–1.39)		
			≥ 3	8	0.90 (0.38–2.12)		
			Trend test *P* value, 0.33				
		Prostate: localized	*Baseline coffee intake (cups/day)*				
			Never	18	1.00		
			Occasionally	29	0.89 (0.48–1.65)		
			1–2	27	1.16 (0.61–2.20)		
			≥ 3	4	0.54 (0.18–1.66)		
			Trend test *P* value, 0.77				
		Prostate: missing stage (cases)	*Baseline coffee intake (cups/day)*				
			Never	42	1.00		
			Occasionally	45	0.55 (0.35–0.85)		
			1–2	32	0.50 (0.30–0.81)		
			≥ 3	12	0.61 (0.31–1.20)		
			Trend test *P* value, 0.03				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) USA, 1995–2006	288 391 members of the AARP from six US states and two US cities, aged 50–71 yr during 1995–96 Exposure assessment method: FFQ	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, race, height, BMI, physical activity, smoking status, diabetes, family history of prostate cancer, history of PSA testing, tomato sauce, α-linolenic acid, energy intake	Strengths: very large cohort, PSA screening information for 69% of cohort, clean reference group of non-drinkers of coffee, long follow-up period Limitations: US state cancer registries are of varying quality, coffee intake only assessed at baseline
			None	2136	1.00		
			< 1	3894	1.03 (0.98–1.08)		
			1	3781	1.00 (0.95–1.06)		
			2–3	9835	1.00 (0.96–1.05)		
			4–5	2902	1.00 (0.94–1.06)		
			≥ 6	787	0.94 (0.87–1.02)		
			Trend test *P* value, 0.08				
		Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day)*				
			None	87	1.00		
			< 1	144	0.89 (0.68–1.16)		
			1	139	0.81 (0.62–1.06)		
			2–3	400	0.87 (0.69–1.11)		
			4–5	110	0.77 (0.58–1.03)		
			≥ 6	37	0.80 (0.53–1.18)		
			Trend test *P* value, 0.2				
		Prostate: aggressive/ advanced (advanced-stage)	*Baseline coffee intake (cups/day)*				
			None	264	1.00		
			< 1	510	1.10 (0.95–1.28)		
			1	440	0.97 (0.83–1.14)		
			2–3	1185	0.98 (0.86–1.12)		
			4–5	401	1.08 (0.92–1.27)		
			≥ 6	127	1.15 (0.92–1.43)		
			Trend test *P* value, 0.62				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) (cont.)		Prostate: aggressive/ advanced (non-advanced-stage)	*Baseline coffee intake (cups/day)*				
			None	1744	1.00		
			< 1	3168	1.03 (0.97–1.09)		
			1	3097	1.01 (0.95–1.07)		
			2–3	8048	1.01 (0.96–1.07)		
			4–5	2325	0.99 (0.93–1.06)		
			≥ 6	611	0.92 (0.84–1.01)		
			Trend test *P* value, 0.07				
		Prostate: aggressive/ advanced (all combined)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	1901	1.00		
			< 1	3272	1.01 (0.95–1.07)		
			1	3084	0.98 (0.92–1.04)		
			2–3	7459	0.97 (0.92–1.02)		
			≥ 4	2366	0.98 (0.92–1.04)		
			Trend test *P* value, 0.16				
		Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	68	1.00		
			< 1	112	0.94 (0.70–1.27)		
			1	107	0.87 (0.64–1.19)		
			2–3	252	0.86 (0.66–1.13)		
			≥ 4	72	0.81 (0.58–1.14)		
			Trend test *P* value, 0.19				
		Prostate: aggressive/ advanced (advanced-stage)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	230	1.00		
			< 1	419	1.09 (0.93–1.28)		
			1	352	0.97 (0.82–1.14)		
			2–3	875	0.96 (0.83–1.11)		
			≥ 4	311	1.07 (0.90–1.27)		
			Trend test *P* value, 0.82				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) (cont.)		Prostate: aggressive/ advanced (non-advanced-stage)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	1557	1.00		
			< 1	2674	1.00 (0.94–1.07)		
			1	2553	0.99 (0.93–1.05)		
			2–3	6171	0.98 (0.93–1.03)		
			≥ 4	1933	0.98 (0.92–1.05)		
			Trend test *P* value, 0.28				
Tverdal (2015) Norway, 1985/1999 – 2010	224 234 men aged 40–42 yr and samples of men of age 20–39 and 43–69 yr invited to participate in Norwegian cardiovascular screening programme during 1985–1999 Exposure assessment method: questionnaire, recording coffee (boiled, filtered, instant, decaffeinated) consumption during 1985–1994 and coffee (boiled, other) consumption from 1994 onwards	Prostate: all combined	*Baseline intake, type of coffee*			Age, smoking status, BMI, height, physical activity, total cholesterol, triglycerides, systolic blood pressure, diabetes, cups/day, year of examination	Strengths: large study with long follow-up period (up to 25 yr), wide range of coffee intakes all cases verified by histological examination Limitations: no analysis shown for fatal prostate cancer, inadequate breakdown by cancer type and severity as seen in other studies, lack of information on PSA screening, coffee consumption habits only assessed once
			None	389	1.00		
			Not boiled	3503	0.94 (0.83–1.06)		
			Boiled and not boiled	500	0.94 (0.81–1.09)		
			Boiled only	1348	0.82 (0.72–0.94)		
			Baseline intake, all types of coffee (cups/day)				
			None	389	1.00		
			< 1 to 4	2404	0.88 (0.79–0.98)		
			5–8	2305	0.88 (0.79–0.98)		
			≥ 9	642	0.78 (0.69–0.89)		
			Trend test *P* value, < 0.01				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tverdal (2015) (cont.)			*Baseline intake, non-boiled coffee (cups/day)*				
			None	389	1.00		
			< 1 to 4	1669	0.89 (0.80–0.99)		
			5–8	1467	0.91 (0.81–1.02)		
			≥ 9	367	0.86 (0.74–1.00)		
			Trend test *P* value, 0.22				
			Baseline intake, boiled and non-boiled coffee (cups/day)				
			None	389	1.00		
			< 1 to 4	176	0.83 (0.69–0.99)		
			5–8	248	0.88 (0.75–1.04)		
			≥ 9	76	0.74 (0.57–0.96)		
			Trend test *P* value, 0.02				
			Baseline intake, boiled coffee only (cups/day)				
			None	389	1.00		
			< 1 to 4	559	0.84 (0.73–0.96)		
			5–8	590	0.80 (0.70–0.92)		
			≥ 9	199	0.66 (0.55–0.80)		
			Trend test *P* value, 0.00				
Hashibe et al. (2015) USA, 1992–2001 (enrolment), 2011	46 667 men in PLCO cancer screening trial enrolled from 10 centres across USA, FFQ began in 1998 and screening ended in late 2006 Exposure assessment method: FFQ	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, race, education	Strengths: validated FFQ, long follow-up time, prospective design, large sample size Limitations: unclear whether smoking was adjusted for in the prostate cancer models, no analysis by stage or grade, no in-depth analysis of low or high coffee intakes, coffee intake measured once at baseline
			< 1	889	1.00		
			1–1.9	417	1.02 (0.91–1.15)		
			≥ 2	1731	1.02 (0.94–1.10)		
			Trend test *P* value, 0.7				

AARP, American Association of Retired Persons; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; yr, year(s)

of PSA testing, so cases will represent fairly advanced cancers relative to those diagnosed in more recent studies. The limitations of the study were the crude adjustment for confounders and a very wide and somewhat high coffee intake (up to 2 cups/day) in the reference group.]

In another Norwegian cohort, Stensvold & Jacobsen (1994) studied the risk of various cancers among 21 735 younger men (aged 35–54 years at baseline) followed for an average of 10 years. With 38 cases of cancer of the prostate, there was no association between coffee intake and risk. Coffee consumption was again high so those consuming ≥ 7 cups/day were compared with those consuming ≤ 2 cups/day; an adjusted hazard ratio of 0.4 was observed, with a non-significant trend. Confidence intervals were not provided. [Strengths include the prospective study design and high-quality cancer registry. There was no consideration of stage or grade; however, the study was conducted before the introduction of PSA testing, so cases will represent fairly advanced cancers relative to those diagnosed in more recent studies. Limitations were the same as for the previous study with the addition of the small number (n = 38) of cases, likely due to the younger age of the cohort.]

In the VIP cohort (Nilsson et al., 2010) described in Sections 2.2.1, 2.4.1, and 2.5.1, 653 prostate cancer cases were ascertained. There was no suggestion of an association between total, filtered, or boiled coffee intake and risk of prostate cancer after adjustment for age, BMI, smoking, education, and recreational physical activity. Rates of coffee consumption in the population were high so the lowest/reference category was < 1 occasion/day, which is somewhat high compared with other studies. The analysis of filtered coffee intake was not adjusted for boiled coffee intake, making interpretation difficult. [Strengths included the prospective design, long follow-up period, and high-quality cancer registry. Limitations included a lack of information on stage or grade of disease. In addition, there was no information provided on PSA testing although the study took place well into the PSA era.]

The HPFS (Wilson et al., 2011) enrolled US male health professionals aged 40–75 years in 1986 and followed them through until 2006; questionnaires were issued every 2 years and FFQs every 4 years. With 5035 cases of prostate cancer, there was an inverse association between higher total coffee intake and overall risk of prostate cancer risk (HR, 0.82; 95% CI, 0.68–0.98) for ≥ 6 cups/day compared with non-drinkers of coffee (P for trend, 0.10). The association was significantly inverse for lethal (n = 642, defined as distant metastasis or fatal prostate cancer) and advanced (n = 896, defined as lethal or stage T3b or above at diagnosis) disease; hazard ratios (95% CI) were 0.40 (0.22–0.75; P for trend, 0.03) and 0.47 (0.28–0.77; P for trend, 0.004), respectively, for ≥ 6 cups/day compared with non-drinkers. There was an inverse association for high-grade (n = 516, Gleason 8–10) disease, but no association for non-advanced or low-grade (Gleason 2–6) disease. Similar inverse associations were seen for lethal and advanced disease for both regular and decaffeinated coffee. In all analyses, coffee intake was updated over time and PSA testing was adjusted for as a time-varying covariate. Two other analyses from this cohort, one of antioxidant intake (Russnes et al., 2014) and one of acrylamide intake (Wilson et al., 2012), also reported similar associations between total coffee intake and total prostate cancer risk, but with less detailed analysis. [Strengths included: the prospective design; long follow-up; repeated measures of diet to update coffee intake every 4 years; and analysis by stage, grade, and lethality. In addition, PSA testing was included in multivariable models. Coffee intake in the population allowed for a clean reference group of never drinkers. Limitations included a lower sample size for very high intakes of coffee compared with some of the European study populations.]

Shafique et al. (2012) used data from a Scottish cohort of 6017 men enrolled between 1970 and 1973, median follow-up 28 years, to investigate the association between coffee consumption and risk of prostate cancer. Coffee intake was assessed via self-administered questionnaire, although a full dietary questionnaire was not administered. With 318 cases of prostate cancer, there was no association between coffee intake and risk; a hazard ratio of 0.93 (95% CI, 0.66–1.31) was observed for ≥ 3 cups/day versus no coffee. There was a suggestion of an inverse association between coffee intake and risk of high-grade disease (Gleason score 8–10), with a hazard ratio of 0.47 (95% CI, 0.22–1.01; *P* for trend, 0.03) for ≥ 3 cups/day versus none. [Strengths included the prospective design, long-term follow-up, analysis by grade of disease, and the clean reference group of non-drinkers. Limitations included the smaller cohort size, lack of food intake data for adjustment for other dietary factors, and lack of information on PSA screening (although the follow-up period extended well into the PSA era). Although the follow-up period was long, there was a concern about misclassification of coffee intake over such a long time period with a single baseline measure.]

In the cohort of Swedish men, Discacciati et al. (2013) examined coffee intake and risk of fatal, aggressive, and non-aggressive disease among 44 613 men. There were 3601 cases, including 515 cases of fatal cancer. Fine and Gray competing risks models were used to calculate subhazard ratios. Coffee intake was inversely associated with non-aggressive disease (defined by stage, grade, and PSA at diagnosis), but not with aggressive or fatal disease. The subhazard ratio (SHR) for fatal prostate cancer was 0.88 (95% CI, 0.58–1.31) for ≥ 6 cups/day compared with 1–3 cups/day, while the subhazard ratio was 1.24 (95% CI, 0.83–1.97) for no coffee compared with 1–3 cups/day. The *P* value for linear trend was 0.18, and the subhazard ratio per 1 cup/day increment was 0.98 (95% CI, 0.93–1.03). For the analysis of fatal prostate cancer, deaths from causes other than prostate cancer were treated as competing events. The possibility of reverse causation, that is, lower urinary tract symptoms (LUTS) from preclinical disease causing men to reduce coffee intake before diagnosis, was also assessed. LUTS symptoms at baseline, assessed from a standard battery of questions, were not significantly associated with coffee intake after adjusting for age. [Strengths included the prospective design and analysis by stage, grade, and fatal disease. There was also a validated FFQ and high coffee intake in the population, allowing for robust analysis of ≥ 6 cups/day. Limitations included the use of only Fine and Gray competing risk models, resulting in subhazard ratio estimates rather than hazard ratios; these results are difficult to compare with those from other cohorts. The study was also limited by a lack of information on PSA testing, although the follow-up extended well into the PSA era, as well as a high-intake reference group (1–3 cups/day).]

Li et al. (2013b) studied the association between coffee consumption and risk of prostate cancer in the Ohsaki cohort, which included 18 853 men aged 40–79 years at enrolment in 1994; follow-up continued until 2005. A validated FFQ assessed coffee intake with five response options. With 318 total cases, coffee intake was inversely associated with risk of prostate cancer with a hazard ratio of 0.63 (95% CI, 0.39–1.00; *P* for trend, 0.02) for ≥ 3 cups/day compared with non-drinkers. Coffee intake was not associated with aggressive disease (n = 109), although stage and grade information was only available for 59% of cases. In addition, aggressive disease was defined as extra-prostatic, regional, or distant spread, or by a Gleason grade of 8–10 only among cases missing stage information. Information on PSA testing was not available. [Strengths included the prospective design, validated FFQ, and clean reference group of non-drinkers. Limitations included the low number of cases and low coffee consumption in the population,

limiting the upper intake categories that could be assessed. There was a lack of PSA testing information; however, rates in Japan are lower than in the USA and Europe, so this is possibly less of a concern.]

In the very large NIH-AARP cohort, Bosire et al. (2013) examined coffee intake among 288 391 men who completed a validated FFQ in 1995–1996, with follow-up until 2006. A total of 23 335 cases of cancer of the prostate were diagnosed, 917 of which were fatal. Coffee intake was not significantly associated with risk of total, fatal, or advanced prostate cancer. The hazard ratio (95% CI) for ≥ 6 cups/day compared with no coffee was 0.94 (0.87–1.02; *P* for trend, 0.08) for total, 0.80 (0.53–1.18; *P* for trend, 0.20) for fatal, and 1.15 (0.92–1.43; *P* for trend, 0.62) for advanced prostate cancer (n = 2927; defined as stage T3 and above or fatal prostate cancer). Analyses among never smokers only and among men who reported a PSA test yielded similar results. [Strengths included the prospective design and very large cohort size, with almost 3000 advanced cases of prostate cancer. PSA testing information was available from 69% of cohort members from a second questionnaire 1–2 years after baseline, and there was also a clean reference group of non-drinkers. Limitations included possible misclassification of prostate cancer, particularly by stage and grade, as US state cancer registries are of varying quality.]

Another large study in Norway (Tverdal, 2015) used data from 224 234 men aged 20–69 years who participated in a cardiovascular screening programme. Men were asked about consumption of boiled, filtered, instant, and decaffeinated coffee, or about boiled and non-boiled coffee depending on the time period. Total coffee intake was associated with a significantly lower risk of total prostate cancer, with a hazard ratio of 0.78 (95% CI, 0.69–0.89; *P* for trend, < 0.01) for those consuming ≥ 9 cups/day versus non-drinkers. Consumption of boiled coffee only or of boiled and non-boiled coffee was associated with a lower risk. Consumption of only non-boiled coffee was only suggestively associated with lower risk. Among a subset of cases with stage information available, there were no significant associations with regionally advanced or distantly spread disease; however, results were not shown. There were 622 cases of fatal prostate cancer, but risk of fatal disease was not analysed. [Strengths included its prospective design, very large size, and long follow-up period. There was a wide range of coffee intakes, allowing for a clean reference group and a high consumption category of ≥ 9 cups/day. Limitations included the lack of analysis for fatal prostate cancer and a lack of results for regionally or distantly advanced cases. There was also a lack of PSA screening information, although the follow-up period extended well into the PSA era.]

The PLCO Cancer Screening Trial (Hashibe et al., 2015) assessed the association between coffee consumption and risk of multiple cancers among men and women in either the screening or control groups who completed a baseline validated FFQ. There were 46 667 men and 3037 incident cases of prostate cancer. Coffee intake was not associated with prostate cancer risk, with a hazard ratio of 1.02 (95% CI, 0.94–1.10; *P* for trend, 0.70) for ≥ 2 cups/day compared with < 1 cup/day. No analysis was conducted by stage or grade. Due to the high rates of PSA screening in both the intervention and control arms of the study, there were very few advanced cancers diagnosed. [The Working Group noted that it was not clear from the paper whether smoking was adjusted for in the prostate cancer analysis. Strengths included the large study population, long follow-up time, and validated FFQ. Limitations included the lack of analysis by stage and grade, lack of adjustment for PSA testing, and unclear reporting of adjustment for smoking status. In addition, because many cancer sites were included in the analysis, the coffee categories are fairly large to accommodate less-common cancers. As a result, there was little

analysis of very high or low intakes despite the large number of cases.]

2.6.2 Case–control studies

See Table 2.12.

Case–control studies that did not control for smoking were reviewed but excluded from evaluation due to the potential for confounding (Slattery & West, 1993; Grönberg et al., 1996; Jain et al., 1998; Hsieh et al., 1999; Chen et al., 2005; Gallus et al., 2007; Ganesh et al., 2011b; Deneo-Pellegrini et al., 2012). Of these, three population-based case–control studies found no association between coffee consumption and risk of cancer of the prostate (Slattery & West, 1993; Grönberg et al., 1996; Jain et al., 1998). Three of the five hospital-based studies (Hsieh et al., 1999; Ganesh et al., 2011b; Deneo-Pellegrini et al., 2012) found no association, while two found positive associations (Chen et al., 2005; Gallus et al., 2007). One case-only study of prostate cancer aggressiveness (defined by stage, grade, and PSA at diagnosis) was not considered for evaluation as there was no comparison to cancer-free controls (Arab et al., 2012).

This left only four case–control studies under consideration (Villeneuve et al., 1999; Sharpe & Siemiatycki, 2002; Geybels et al., 2013; Wilson et al., 2013). All four were population-based studies, and two (Geybels et al., 2013; Wilson et al., 2013) assessed the association between coffee consumption and advanced-stage and high-grade disease in addition to total prostate cancer risk. Wilson et al. (2013) also assessed the association for fatal prostate cancer.

Villeneuve et al. (1999) conducted a population-based case–control study in Canada, with 1623 cases aged 50–74 years and 1623 controls selected through several methods depending on the province. Coffee intake was not associated with prostate cancer risk in multivariable models. [Strengths included the population-based design, large sample size, and use of a clean reference group of non-drinkers. Limitations included a lack of information on PSA testing, although the study period was at the very beginning of the PSA testing era. In addition, the time between diagnosis and questionnaire for cases was 6 months to 1 year on average, raising concerns about accuracy of diet recall. Finally, participants with missing data for any covariates were excluded from multivariable models, so the age-adjusted and fully adjusted models were not comparable.]

Sharpe & Siemiatycki (2002) conducted a population-based case–control study in Montreal, Canada, that included cases with 15 different types of cancer. The analysis included 399 histologically confirmed cases of cancer of the prostate who completed in-person interviews, 476 prostate cancer controls, and 621 other cancers as controls. Compared with never drinking coffee at least weekly, weekly or daily coffee drinking was not associated with prostate cancer risk. A more detailed categorization of daily coffee drinking, including age when daily drinking began, duration of daily drinking, cups/day, or cumulative daily consumption (based on drink-years), were also not associated with risk. However, confidence intervals were wide as the number of cases and controls in the reference group of 'never drank coffee at least weekly' was low. [Strengths included the population-based design. Limitations included a lack of information on the dietary assessment instrument and its validity. Further, there was no analysis by stage or grade, and no information on PSA screening although the study was conducted within the PSA screening era.]

Wilson et al. (2013) conducted a population-based case–control study in Sweden including incident cases of cancer of the prostate from regional cancer registries. Coffee was assessed as an open-ended question, asking men to provide the number of cups they drank per week or day. Stage and grade were available for 95% of cases. There was no association between coffee intake and risk of total prostate cancer

Table 2.12 Case–control studies on cancer of the prostate and coffee consumption

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (1999) Canada, 1994–1997	1623 cases and 1623 controls aged 50–74 yr identified from province cancer registries; population-based controls sampled from health insurance plan lists, other government lists or RDD Exposure assessment method: FFQ		*Coffee intake 2 yr previous (cups/day)*			Age, province of residence, race, years since quitting smoking, smoking pack-years, BMI, rice and pasta intake, grains and cereals intake, alcohol, fruit and juice intake, tofu intake, meat intake, income, family history of cancer	Strengths: population-based study, large number of cases, clean reference group of non-drinkers Limitations: lack of information on PSA testing, long time between diagnosis and interview (concerns about accuracy of recall), participants with missing data excluded from multivariable models
			None	134	1.0		
			< 1	358	0.8 (0.6–1.1)		
			1 to < 4	551	1.0 (0.7–1.3)		
			≥ 4	367	1.1 (0.8–1.5)		
			Trend test *P* value, 0.06				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sharpe & Siemiatycki (2002) Canada (Montreal), 1979–1985	Cases: 399 aged 47–70 yr diagnosed at any hospital in Montreal Controls: 476 selected from electoral lists or RDD, 621 other cancer controls Exposure assessment method: questionnaire recording weekly and daily coffee drinking and age started, allowing calculation of cumulative intake	Prostate	*Duration of daily drinking (yr)*			Age, ethnicity, respondent (direct/proxy), family income, BMI, cumulative cigarette smoking, cumulative alcohol consumption	Strengths: population-based study Limitations: diet assessment instrument and its validity not specified, only participants who did face-to-face interviews are included (response rate for this subset is not given), no information on stage or grade available, no analysis of advanced or aggressive prostate cancer
			Never drank weekly	29	1.0		
			< 20	28	1.0 (0.5–2.1)		
			20–39	89	0.8 (0.4–1.4)		
			> 39	209	1.2 (0.7–2.1)		
			Age at start of daily drinking (yr)				
			Never drank weekly	29	1.0		
			< 15	50	1.4 (0.7–2.7)		
			15–19	124	1.3 (0.7–2.3)		
			20–24	69	1.0 (0.5–1.8)		
			≥ 25	83	0.7 (0.4–1.4)		
			Never drank weekly	29	1		
			Drank weekly, never daily	23	0.9 (0.4–2.0)		
			Drank daily	347	1.1 (0.6–1.8)		
			Cumulative consumption (drink-years)				
			Never drank weekly	29	1.0		
			< 57	108	1.0 (0.6–1.9)		
			57–119	93	1.0 (0.6–1.8)		
			> 119	125	1.1 (0.6–2.0)		

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2013) Sweden, 2001–2002	Cases: 1489 incident pathologically confirmed prostate cancer identified from four of six regional cancer registries in Sweden Controls: 1112 randomly selected from Swedish population register, frequency matched to cases by 5-yr age group and region of residence Exposure assessment method: 261-item FFQ recording intake over previous 12 mo, open-ended question on cups of coffee per week or day	All prostate	*Coffee intake in year before questionnaire (cups/day)*			Age, region, smoking (never/ former/current), BMI, education, calcium intake, zinc intake, total energy intake	Strengths: population-based study, assessed risk of fatal and non-fatal and by stage and grade in addition to total prostate cancer, validated FFQ Limitations: response rate lower in controls than cases, lowest (reference) group is < 1 cup/day, no information on PSA screening
			< 1	139	1.0		
			1 to < 2	150	0.97 (0.62–1.52)		
			2 to < 4	644	0.98 (0.65–1.49)		
			4–5	413	1.06 (0.69–1.62)		
			> 5	143	0.97 (0.60–1.57)		
			Trend test *P* value, 0.84				
		Fatal prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	31	1.0		
			1 to < 2	24	0.59 (0.32–1.09)		
			2 to < 4	133	0.79 (0.49–1.26)		
			4–5	94	0.93 (0.57–1.51)		
			> 5	25	0.64 (0.34–1.19)		
			Trend test *P* value, 0.81				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2013) (cont.)		Advanced-stage prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	35	1.0		
			1 to < 2	32	0.70 (0.40–1.23)		
			2 to < 4	159	0.83 (0.53–1.29)		
			4–5	119	1.02 (0.64–1.62)		
			> 5	32	0.73 (0.41–1.30)		
			Trend test *P* value, 0.98				
		High-grade prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	30	1.0		
			1 – < 2	22	0.54 (0.29–1.01)		
			2 to < 4	98	0.59 (0.36–1.95)		
			4–5	62	0.61 (0.36–1.03)		
			> 5	19	0.50 (0.26–0.98)		
			Trend test *P* value, 0.13				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Geybels et al. (2013) USA (Washington State), 2002–2005	Cases: 894 men aged 35–74 yr identified through Seattle–Puget Sound SEER Program cancer registry Controls: 860 identified by RDD, frequency matched in 5-yr age groups and recruited evenly through study period Exposure assessment method: FFQ recording intake in 2 yr before diagnosis for cases or reference date for controls	All prostate	*Coffee intake 2 yr prior*			Age, race, family history of prostate cancer, smoking (never/former/current), PSA screening	Strengths: population-based study, information on stage/ grade/PSA at diagnosis available from cancer registry, information on PSA testing in the prior 5 yr was assessed and included as potential confounder Limitations: response rate lower in controls than in cases
			≤ 1 cup/wk	246	1.0		
			2–6 cups/wk	113	1.22 (0.88–1.69)		
			1 cup/day	154	1.13 (0.84–1.51)		
			2–3 cups/day	273	1.16 (0.90–1.50)		
			≥ 4 cups/day	108	1.16 (0.82–1.63)		
			Trend test *P* value, 0.32				
		High-grade prostate cancer	*Coffee intake 2 yr prior*				
			≤ 1 cup/wk	39	1.00		
			2–6 cups/wk	28	1.72 (1.00–2.97)		
			1 cup/day	30	1.30 (0.77–2.19)		
			2–3 cups/day	51	1.25 (0.78–1.99)		
			≥ 4 cups/day	18	1.04 (0.55–1.96)		
			Trend test *P* value, 0.81				
		Advanced-stage prostate cancer	*Coffee intake 2 yr prior*				
			≤ 1 cup/wk	46	1.00		
			2–6 cups/wk	18	1.01 (0.55–1.83)		
			1 cup/day	31	1.27 (0.77–2.11)		
			2–3 cups/day	51	1.23 (0.78–1.93)		
			≥ 4 cups/day	23	1.33 (0.74–2.38)		
			Trend test *P* value, 0.24				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (1999) Canada, 1994–1997	Cases: 1623 aged 50–74 yr identified from 8 of 10 province cancer registries in Canada Controls: 1623 population-based sampled from health insurance plan lists, other government lists, or RDD Exposure assessment method: FFQ, recording diet 2 yr previously	Prostate	*Coffee intake 2 yr prior (cups/day)*			Age, province of residence, race, yrs since quitting smoking, smoking pack-years, BMI, rice and pasta intake, grains and cereals intake, alcohol, fruit and juice intake, tofu intake, meat intake, income, family history of cancer	69% response rate in both cases and controls Strengths: population-based study, large number of cases, clean reference group of non-drinkers Limitations: lack of information on PSA testing, time between diagnosis and questionnaire 1 yr on average in Ontario and 6 mo in other provinces, concerns about accuracy of recall, participants with missing data were excluded from multivariable models
			None	134	1.0		
			< 1	358	0.8 (0.6–1.1)		
			1 to < 4	551	1.0 (0.7–1.3)		
			≥ 4	367	1.1 (0.8–1.5)		
			Trend test *P* value, 0.06				

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; mo, month(s); PSA, prostate-specific antigen; RDD, random-digit dialling; SEER, Surveillance, Epidemiology and End Results; wk, week(s); yr, year(s)

(OR, 0.97; 95% CI, 0.6–1.57) for > 5 cups/day. There was a suggestion of an inverse association for fatal disease and for advanced disease (stage T4, N1, or M1 at diagnosis, or fatal disease); odds ratios of 0.64 (95% CI, 0.34–1.19) and 0.73 (95% CI, 0.41–1.30), respectively, were reported for those consuming > 5 cups/day compared with < 1 cup/day. For high-grade disease, defined as Gleason grade 8–10, there was a statistically significant lower risk in the highest category with an odds ratio of 0.50 (95% CI, 0.26–0.98), although the *P* value for a linear trend across intakes was not significant (*P* for trend, 0.13). As coffee consumption in this population was high, the lowest and reference intake category was < 1 cup/day rather than non-drinkers of coffee. [The strengths of this study included: the population-based design; use of a validated FFQ; and the analysis of stage, grade, and fatal disease. Limitations included the lower response rate in controls compared with cases, raising concern about selection bias. In addition, the high coffee intake in the population did not allow for a clean reference group of non-drinkers. Finally, there was no information on PSA screening, despite being conducted during the PSA screening era.]

Geybels et al. (2013) conducted a population-based case–control study in Washington State, USA, with 894 cases and 860 controls. Diet was assessed through a validated 120-item FFQ, and stage and grade information were available from the cancer registry through which cases were identified. Coffee intake was not significantly associated with risk of total prostate cancer, with an odds ratio of 1.16 (95% CI, 0.82–1.63) for men consuming ≥ 4 cups/day compared with those consuming ≤ 1 cups/week. Coffee intake was not associated with high-grade disease, defined as Gleason grade 4+3 or above (OR, 1.04; 95% CI, 0.55–1.96), or advanced-stage disease, defined as having regional or distant spread (OR, 1.33; 95% CI, 0.74–2.38). Results were adjusted for PSA testing within the 5-year period before date of diagnosis for cases, or before some reference date assigned to controls to match the distribution of diagnosis dates, helping to eliminate concern about confounding due to differences in screening practices associated with coffee intake. [The strengths of this study included the population-based design, and the analysis by stage and grade. In addition, PSA testing in the 5 years prior was assessed and included as a potential confounder. The limitations of this study included the lower response rate in controls than cases, raising a concern about selection bias.]

2.6.3 Meta-analyses

Seven meta-analyses of coffee consumption and risk of prostate cancer have been conducted recently, six of which focus on prostate cancer and one of which assesses multiple cancer sites. Of these, two (Discacciati et al., 2014; Lu et al., 2014) are recent enough to include the recent cohort studies reviewed above, provide a detailed analysis of results for fatal disease as well as disease by stage and grade, and do not include studies without an adjustment for smoking. To be included in the meta-analysis by Discacciati et al. (2014), studies had to report results by prostate cancer aggressiveness, report the number of cases and person-years by coffee category, and adjust for smoking. There were five cohort studies, two population-based case–control studies, and one hospital-based case–control study of benign prostatic hypertrophy (BPH). Six studies assessed high-grade prostate cancer (*n* = 1965, Gleason 8–10 in four studies, Gleason 4+3 and up in one study, and Gleason 7–10 in one study) and estimated a meta-relative risk for a 3 cups/day increase of 0.89 (95% CI, 0.78–1.00). For six studies of advanced prostate cancer (*n* = 5724, T3 or above in two studies, T3b or above in one study, T4 or above in one study, and unspecified TNM stage 'extraprostatic extension' or above in two studies), the relative risk was 0.95 (95% CI, 0.85–1.06). For four studies of fatal prostate cancer (*n* = 2381), the relative risk was

0.89 (95% CI, 0.82–0.97). All studies but one in the meta-analysis were reviewed above.

The meta-analysis of high-grade disease included data from a non-peer-reviewed letter to the editor of the *Journal of the National Cancer Institute* (Polesel et al., 2012), which used data from a hospital-based Italian case–control study. This analysis included Gleason 7 tumours in its definition of high-grade disease. The pooled relative risk for high-grade prostate cancer would be more inverse with elimination of this study. There was no indication of between-study heterogeneity or publication bias. Cohort studies found stronger inverse associations for all three outcomes than case–control studies; however, there were only two case–control studies of advanced prostate cancer and one case–control study of fatal prostate cancer.

The Lu et al. (2014) meta-analysis of fatal and advanced disease included the same four fatal and six advanced prostate cancer studies as Discacciati et al. (2014), but calculated a meta-relative risk for the highest versus lowest categories as reported in the original reports. Using a random-effects model, the meta-relative risk was 0.66 (95% CI, 0.43–0.90) for fatal disease and 0.85 (95% CI, 0.58–1.12) for advanced disease.

Another recent meta-analysis of only cohort studies included studies that did not adjust for smoking and considered only total prostate cancer risk (Cao et al., 2014). The meta-analysis of Yu et al. (2011), which covered multiple cancer sites, preceded the most recent cohort studies of coffee and prostate cancer. Similarly, the Park et al. (2010) meta-analysis preceded the most recent cohort studies and included studies that did not adjust for smoking. The Zhong et al. (2014) meta-analysis included studies that did not adjust for smoking, and the risk of prostate cancer was not examined by stage or grade in detail. The Liu et al. (2015a) meta-analysis also included studies that did not adjust for smoking, and mixed stage- and grade-based outcomes in defining advanced and non-advanced disease.

2.7 Cancer of the lung

2.7.1 Cohort studies

Table 2.13 (web only; available at: http://publications.iarc.fr/566)

Of the eight cohort studies that examined the association between coffee consumption and risk of lung cancer, seven focused on incidence (Jacobsen et al., 1986; Nomura et al., 1986; Stensvold & Jacobsen, 1994; Bae et al., 2013; Hashibe et al., 2015; Guertin et al., 2016; Lukic et al., 2016) and one study focused on mortality (Khan et al., 2004).

One cohort study from the Republic of Korea (Bae et al., 2013) was excluded from this review due to a lack of adjustment for any lung cancer risk factors, including tobacco smoking.

Among the cohort studies that observed a positive association between coffee consumption and lung cancer risk, results were attenuated after adjusting for tobacco smoking. The Working Group concluded that this could be an indication that increases in lung cancer risk could be due to residual confounding by tobacco smoking.

Nomura et al. (1986) observed a non-significant positive association for consumption of ≥ 5 cups/day coffee (OR, 1.44) after adjusting for smoking status, duration, and number of cigarettes consumed, but there was no evidence of an exposure–response trend (*P* for trend, 0.19) among 7355 Japanese men in Hawaii (born during 1900–1919). There was no evidence of an exposure–response trend among non-smokers, although this analysis was based on only 9 cases. [The main strength of this study was its prospective design. It was however limited by being based on only a single-day history of coffee intake. The lung cancer results may be due to residual confounding by smoking, as supported by the negative findings among non-smokers. Confidence intervals were not provided.]

Jacobsen et al. (1986) reported significant positive associations in a Norwegian study of

13 664 men and 2891 women; compared with drinking ≤ 2 cups/day, consuming ≥ 7 cups/day of coffee significantly increased the risk of lung cancer (OR, 1.82; *P* for trend, 0.02). [The strengths of this study included the prospective design and the relatively short follow-up. Limitations included the single measurement of coffee intake, and lack of confidence intervals which could not be calculated.]

Stensvold & Jacobsen (1994) found a positive association between coffee drinking and risk of lung cancer after adjustment for cigarettes smoked per day in the highest exposure group of > 7 cups/day (RR, 2.4; $P < 0.01$; 95% CI, not reported), and a significant trend among 42 973 men and women participating in a cardiovascular screening in three counties of Norway. [Strengths included the complete follow-up by linkage of national data by national personal identification number. Residual confounding by smoking was however possible, as this study did not control for duration of smoking or smoking status.]

In a cohort of 1524 men and 1634 women aged over 40 years from 45 health-centre areas of Hokkaido, Japan, Khan et al. (2004) observed no association between coffee intake and lung cancer mortality in both men and women after adjusting for smoking. [Strengths included the population-based and prospective design. The study was limited by the small number of cases, however.]

In the NIH-AARP Diet and Health Study of 457 366 subjects, Guertin et al. (2016) observed a strong positive association between coffee intake and lung cancer (HR, 4.56; 95% CI, 4.08–5.10) for consumption of ≥ 6 cups/day adjusted for age and sex; the association was substantially attenuated after adjusting for smoking, however (HR, 1.27; 95% CI, 1.14–1.42). Similar findings were observed for each different histological type and for participants drinking predominantly caffeinated or decaffeinated coffee. There was little evidence for an association either for never smokers or within most categories of tobacco use. [The Working Group noted that the association observed could be due to residual confounding by tobacco smoking, imperfect adjustment by lifetime tobacco use, or other risk factors. Strengths included the large scale, prospective design, large numbers of outcomes, and ability to categorize decaffeinated or caffeinated. Limitations included the self-reporting of coffee consumption, the recording of typical coffee consumption over the past year, the lack of data on cumulative exposure (coffee consumption is considered relatively stable over time), and the fact that one third of the cancer cases were histologically unknown.]

Hashibe et al. (2015) reported that coffee intake was not associated with lung cancer after adjusting for smoking status, frequency, duration, and time since cessation in the PLCO cohort, which included nearly 100 000 persons. Compared with drinking < 1 cup/day, hazard ratios (95% CI) for 1–1.9 cups/day and ≥ 2 cups/day were 1.03 (0.83–1.27) and 1.10 (0.94–1.28), respectively (*P* for trend, 0.196). [Strengths included the prospective design and large sample size. Limitations included the lack of data on age when coffee consumption began, duration of coffee drinking, and any change in coffee drinking habits.]

Lukic et al. (2016) observed positive associations between coffee consumption and risk of lung cancer among 91 767 Norwegian women in the Norwegian Women and Cancer (NOWAC) Study. Compared with consumers of low quantities of coffee (≤ 1 cup/day), large-quantity consumers (> 7 cups/day) had a significantly higher risk of lung cancer in age-adjusted analysis (HR, 5.65; 95% CI, 4.20–7.60). This association was substantially attenuated after further adjusting for smoking status, age at smoking initiation, number of pack-years smoked, and exposure to smoking during childhood, as well as education, BMI, and physical activity level; an increase in risk was still observed in the

highest coffee consumption group (> 7 cups/day) however, with a hazard ratio of 2.01 (95% CI, 1.47–2.75). No statistically significant association was observed in never smokers (HR, 1.42; 95% CI, 0.44–4.57) for consumption of > 5 cups/day (*P* for trend, 0.30). [Strengths included the population-based design, the large scale, validation of questionnaire, repeated measurements of coffee consumption and smoking exposure, use of updated information, and high validity of coffee consumption. Limitations included possible residual confounding from smoking.]

2.7.2 Case–control studies

See Tables 2.14 and 2.15 (web only; available at: http://publications.iarc.fr/566).

Among the 17 case–control studies that examined the association between coffee consumption and the risk of lung cancer; 12 studies (Mettlin, 1989; Restrepo et al., 1989; Chen et al., 1990; Mendilaharsu et al., 1998; Kubík et al., 2001, 2004a,b, 2008; Takezaki et al., 2001; Baker et al., 2005; Ganesh et al., 2011a; Luqman et al., 2014) were hospital-based and five were population-based (Axelsson et al., 1996; Nyberg et al., 1998; Hu et al., 2002; Chiu et al., 2010; Sanikini et al., 2015a).

There were four reports (Kubík et al., 2001, 2004a, b, 2008) and two case–control studies (Mettlin, 1989; Baker et al., 2005) from the same study population. Five case–control studies analysed the risk by histological subtypes (Takezaki et al., 2001; Kubík et al., 2001, 2008; Baker et al., 2005; Sanikini et al., 2015a). Two USA-based case–control studies (Mettlin, 1989; Baker et al., 2005) also analysed the risk for caffeinated and decaffeinated coffee separately.

The Working Group considered studies to be informative only if they controlled for smoking. Consequently, one case–control study from Pakistan (Luqman et al., 2014) was excluded from this review due to a lack of adjustment for any lung cancer risk factors, including tobacco smoking.

(a) Population-based case–control studies

Axelsson et al. (1996) reported that coffee drinking was not associated with lung cancer in a population-based case–control study (308 male cases, 504 controls) in west Sweden, after adjusting for number of cigarettes/day, number of years smoked, and other covariates. [Strengths included the population-based controls, and in-person direct interviews of cases and controls.]

In Stockholm, Sweden, Nyberg et al. (1998) reported that coffee drinking was non-significantly associated with a decreased risk of lung cancer (OR, 0.5; 95% CI, 0.24–1.06) for consumption of ≥ 3 cups/day, after adjusting for passive smoking status (ever-exposure status, years since last exposure, and hour-years of exposure to environmental tobacco smoke) and other covariates. A total of 124 cases of lung cancer (35 men and 89 women) of age > 30 years from major county hospitals were frequency-matched with 235 controls (72 men and 163 women) derived from a population register. [Strengths included the fact that 96% of cases had a histological or cytological confirmation for diagnosis, and the use of only never smokers.]

Hu et al. (2002) reported no association between coffee intake and risk of lung cancer in never-smoking women in Canada after controlling for 10-year age groups, province, education, and social class. [Strengths included the population-based design and restriction to never-smoking women. Limitations included the misclassification of exposure variables and covariates, the low response rate (61.6%) of cases, and the small sample size.]

In Hong Kong Special Administrative Region, China, Chiu et al. (2010) observed a significantly decreased risk in the middle category of coffee consumption (OR, 0.41; 95% CI, 0.21–0.78) for 1–10 coffee–years, compared with never drinkers, after adjusting

for smoking and other potential confounders. [Strengths included the population-based design. Limitations included use of data from a single centre, and the fact that coffee consumption is low in this population.]

In the ICARE (Investigation of occupational and environmental causes of respiratory cancers) study, Sanikini et al. (2015a) reported that coffee consumption was positively associated with lung cancer (OR, 1.65; 95% CI, 1.28–2.12) without adjustment for smoking by cumulative smoking index (CSI). After adjustment for CSI, however, coffee consumption was not associated with lung cancer (OR, 1.09; 95% CI, 0.80–1.49). No association was detected in analyses stratified by sex, histological subtype, and smoking status. [Strengths included: the large-scale, multicentre, and population-based design; the large sample size; provision of comprehensive information on coffee consumption and potential confounders; careful adjustment for smoking; and analysis by histological type, sex, and smoking status. Limitations included the potential for recall bias and the non-differential misclassification of exposure.]

(b) Hospital-based case–control studies

In a hospital-based case–control study among patients admitted to Roswell Park Memorial Institute (RPMI) in Buffalo, New York, Mettlin (1989) reported odds ratios (95% CI) for < 1 cup/day, 2–3 cups/day, and ≥ 4 cups/day compared with never drinkers of coffee of 1.01 (0.67–1.51), 0.94 (0.65–1.37), and 1.26 (0.86–1.84), respectively, in multivariable models adjusted for smoking and other potential confounders. An association was not evident for either total or decaffeinated coffee intake. [Strengths included the relatively accurate matching and use of control variables. Limitations included the hospital-based, single-centre design and the possibility of residual confounding.]

Baker et al. (2005) reported findings regarding the association between coffee consumption and lung cancer among current and former smokers using the same case–control study in Buffalo, New York, as for Mettlin (1989), but with a more restricted set of cases and controls. While the previous report by Mettlin (1989) included subjects with all types of smoking status, never smokers were excluded from the analysis by Baker et al. (2005). Compared with non-drinkers of coffee, elevated lung cancer risk was observed for those who consumed 2–3 cups/day (OR, 1.34; 95% CI, 0.99–1.82) or ≥ 4 cups/day (OR, 1.51; 95% CI, 1.11–2.05) of regular coffee, although a reduced risk was observed for decaffeinated coffee. Compared with non-drinkers, odds ratios (95% CI) for consumption of ≤ 1 cup/day and ≥ 2 cups/day were 0.67 (0.54–0.84) and 0.64 (0.51–0.80) of decaffeinated coffee, respectively. Similar results were observed by histological subtype. [Strengths included matching of smoking status; the use of current and former smokers only; analysis by histology; and a separate analysis for regular and decaffeinated coffee. Limitations included the single-centre, hospital-based design.]

In Colombia, Restrepo et al. (1989) observed no association between coffee consumption and risk of lung cancer; an odds ratio of 1.1 (95% CI not reported) was observed for drinking > 7 cups/day (*P* for trend, 0.67) after adjusting for number of cigarettes smoked per day and alcohol consumption. [Strengths included coverage of a well-defined population and adjustment by socioeconomic level. Limitations included the hospital-based study design.]

In Taiwan, China, Chen et al. (1990) reported that coffee drinking was found to be significantly associated with epidermoid carcinoma (OR, 2.10) after adjusting only for sex and age, but coffee drinking was not significantly associated with any pathological type of lung cancer after cigarette smoking was adjusted for. [Strengths included analysis by pathological subtype. Limitations

included the hospital-based study design and lack of provision of confidence intervals.]

In Uruguay, Mendilaharsu et al. (1998) observed coffee intake had no effect on the risk of all lung cancer, or for squamous and small-cell lung cancer. [Limitations included the hospital-based design and the possibility of differential misclassification of exposure due to preclinical disease.]

In Nagoya, Japan, Takezaki et al. (2001) reported that an association between coffee consumption and lung adenocarcinoma in both men and women and lung squamous cell carcinoma in women was not evident, while in men a positive association of coffee intake was observed with lung squamous cell carcinoma (OR, 1.61; 95% CI, 1.09–2.39) was seen for consumption of ≥ 3 cups/day of coffee. [The main strength of this study was its large scale. Limitations included the potential for selection bias since controls were recruited from non-cancer hospital outpatients. The duration of smoking was not controlled for in the analysis and the amount smoked was only crudely controlled for (< or > 20 cigarettes/day); residual confounding by smoking was therefore possible in this study.]

Kubík et al. reported the findings from a hospital-based case–control study in the Czech Republic that examined the association between coffee consumption and the risk of lung cancer (Kubík et al., 2001, 2004a, b, 2008). In the most recent report, recruitment of cases and controls was extended to 2006 (Kubík et al., 2008). Stratified analysis by smoking status showed no association for both non-smokers and smokers, and in both men and women; for daily or several times per week versus less, odds ratios (95% CI) were 0.86 (0.59–1.26) and 0.76 (0.48–1.20) for female non-smokers and smokers, respectively, and 0.91 (0.43–1.92) and 1.07 (0.61–1.86) for male non-smokers and smokers, respectively. Null associations were consistently observed in any histological subtype of cancer. Similar associations were reported in earlier publications fom this study (Kubík et al., 2001, 2004a, b). [Strengths included the large number of subjectss, and stratified analysis by histology and smoking status. Limitations included the hospital-based case–control design and the self-reporting of coffee consumption.]

In Mumbai, India, Ganesh et al. (2011a) reported that coffee drinkers had a significantly increased risk of lung cancer (OR, 1.9; 95% CI, 1.3–2.7) after adjusting for age, literacy status, cigarette smoking, bidi smoking, tobacco chewing, and alcohol drinking, as well as consumption of milk, chicken, red meat, fish, and chilli, and exposure to pesticide. The definition of coffee drinker was unclear, however. Cigarette smoking (yes/no) was only crudely controlled for, and there was a strong possibility that the increased risk observed for coffee drinking was due to residual confounding by smoking. [Limitations included the hospital-based design; the poor-quality, inadequate adjustment for confounding, and the unclear definition of exposure.]

2.7.3 Meta-analyses

Four meta-analyses of the association between coffee drinking and risk of lung cancer have been published (Tang et al., 2010; Wang et al., 2012; Galarraga & Boffetta, 2016; Xie et al., 2016). The most recent meta-analysis (Galarraga & Boffetta, 2016), assessing the effect of coffee consumption on risk of lung cancer independently of tobacco use, addressed the potential role of tobacco as a confounder. Using PubMed and Embase databases, and the references from the retrieved articles up to 2015, 8 cohort and 13 case–control studies involving 19 892 cases and 623 645 non-cases were included in the meta-analysis. The summary relative risk (95% CI) of lung cancer for coffee drinking compared with never drinkers, without controlling for tobacco smoking, was 1.09 (95% CI, 1.00–1.19). Coffee drinking was not associated with lung

cancer risk among non-smokers (summary RR 0.92; 95% CI, 0.75–1.10). The summary relative risk for 1 cup/day increase, unadjusted for smoking, was 1.04 (95% CI, 1.03–1.05); the corresponding relative risk for non-smokers was 0.95 (95% CI, 0.83–1.09). The results stratified by different geographic regions (Asia, Europe, North and South America) were not heterogeneous. The study indicated that when the potential confounding effect from smoking is controlled for, coffee drinking does not appear to be a risk factor for lung cancer.

2.8 Cancer of the larynx

The association between coffee consumption and cancer of the larynx has been examined in seven case–control studies and one large prospective cohort study (Ren et al., 2010); the latter reported no association. A significantly increased risk was observed in four (Restrepo et al., 1989; Pintos et al., 1994; Zvrko et al., 2008; Vassileiou et al., 2012) of the seven case–control studies. However, all of the studies that reported evidence of an association had inadequately controlled for smoking and alcohol use; no association was observed in the three other studies that tightly controlled for smoking and alcohol drinking (La Vecchia et al., 1990; Bosetti et al., 2002; Galeone et al., 2010a). Two meta-analyses of the association of cancer of the larynx and coffee drinking have also been conducted. These studies are discussed in Sections 2.8.1–2.8.3 below.

2.8.1 Cohort studies

See Table 2.16 (web only; available at: http://publications.iarc.fr/566).

One cohort study with 481 563 subjects, members of the NIH-AARP Diet and Health Study, assessed the association between cancer of the larynx and coffee consumption (Ren et al., 2010); no association was found. The hazard ratio for the highest category of exposure was 1.01 (95% CI, 0.71–1.44) and the *P* value for the test of the exposure–response trend was 0.95. [The Working Group regarded this study as the most informative because of its prospective design, large size, and extensive control for smoking, alcohol, diet, and other risk factors.]

2.8.2 Case–control studies

See Table 2.17 (web only; available at: http://publications.iarc.fr/566).

The earliest case–control study to report findings on the association between coffee consumption and cancer of the larynx was that by Restrepo et al. (1989) in Medellin, Columbia. An association between laryngeal cancer and the highest category of exposure (OR, 2.87 for > 7 cups/day) and a statistically significant (*P* for trend, 0.01) exposure–response relationship was observed in a logistic regression analysis. The logistic model included variables that controlled for current smoking (packs/day), but did not include information on former smoking or duration of smoking. [The Working Group believed there was potential for residual confounding by tobacco smoking in this study.]

La Vecchia et al. (1990) did not find evidence of an exposure–response relationship (*P* for trend, 0.65) between coffee consumption and the risk of laryngeal cancer in the Greater Milan area. Although the study provided detailed information on smoking and alcohol consumption, the results from analyses controlling for these risk factors was not presented; however, La Vecchia et al. (1990) reported that none of the results were materially changed when smoking and alcohol consumption were controlled for.

Pintos et al. (1994) reported a statistically significant ($P < 0.009$) exposure–response relationship between coffee consumption and laryngeal cancer in southern Brazil. A significant increased risk was observed among those who drank 2 cups/day and ≥ 3 cups/day with odds

ratios of 4.29 (95% CI, 1.40–12.90) and 2.87 (95% CI, 1.00–1.83), respectively. This study controlled for cigarette smoking (pack-years) and lifetime alcohol consumption. It did not control for smoking status, however (i.e. former versus current). [The study may have been biased by the use of other diseases as controls if these other sites were associated with coffee consumption (e.g. gastritis or prostatic diseases).]

Bosetti et al. (2002) reported that consumption of coffee was not associated with an increased risk of laryngeal cancer in a study in northern Italy and the Swiss canton of Vaud, which tightly controlled for smoking (smoking status and cigarettes/day) and alcohol consumption (drinks/week).

Zvrko et al. (2008) reported that drinking > 5 cups/day of coffee was found to be associated with a significant increased risk of laryngeal cancer (OR, 4.52; 95% CI, 1.01–20.12) in Montenegro. Cigarette smoking and alcohol consumption were only crudely controlled for with yes/no responses to smoking duration of > 40 years, > 30 cigarettes per day, hard liquor consumption, and > 2 alcoholic drinks/day. [The Working Group judged that there was a strong possibility of residual confounding by tobacco and alcohol consumption in this study.]

Galeone et al. (2010a) conducted a pooled analysis of seven case–control studies of cancer of the larynx from France, Italy, Switzerland, and the USA. Data from the Bosetti et al. (2002) and the La Vecchia et al. (1990) studies (described earlier in this section) were a part of this study. The study included 1224 incident cases of laryngeal cancer and 7239 controls. Five of the included studies were hospital-based and two used population-based controls. The analysis controlled for tobacco smoking as cigarette pack years and duration of cigar and pipe smoking, alcohol consumption, age, study centre, education, intake of fruit or vegetables, race/ethnicity, sex, and body weight. Exposures to caffeinated and decaffeinated coffee were considered separately. For caffeinated coffee, the odds ratio in the highest exposure group (> 4 cups/day) was 0.96 (95% CI, 0.64–1.45) and there was no evidence of an exposure–response relationship (*P* for trend, 0.82). The data were sparse for decaffeinated coffee, and there was no indication of an increased risk in the highest exposure group of ≥ 1 cup/day (OR, 0.84; 95% CI, 0.34–2.06) or evidence of an exposure–response relationship (*P* for trend, 0.75).

Vassileiou et al. (2012) reported that coffee consumption (yes/no) was significantly associated with an increased risk of cancer of the larynx in Greece. The association was primarily attributable to consumption of "Turkish" coffee (OR, 1.77; 95% CI, 1.24–2.52), and a significant exposure–response relationship between consumption of Turkish coffee and laryngeal cancer was observed (*P* for trend, 0.002) in a logistic model. [It is unclear from the paper which other covariates were controlled for in the logistic analysis but it appears that smoking and alcohol drinking were represented by yes/no variables. The Working Group judged that there was a strong possibility of residual confounding by tobacco and alcohol consumption in this study.]

2.8.3 Meta-analyses

A recent meta-analysis (Chen & Long, 2014) reported a summary risk estimate of 1.47 (95% CI, 1.03–2.11) and evidence of an exposure–response relationship between coffee consumption and cancer of the larynx (*P* for trend, 0.001). The results were unchanged when the meta-analysis was restricted to studies considered to be of high quality (i.e. > 6 on a scale of 1–9) based on the Newcastle–Ottawa scale. However, there was significant evidence of heterogeneity in the analysis (I^2, 72.8%; *P* for trend, 0.002). Several of the studies that were considered to be of high quality (i.e. Pintos et al., 1994; Zvrko et al., 2008; Vassileiou et al., 2012) did not (as discussed in Section 2.8.2 above) adequately control for

confounding by tobacco smoking and alcohol drinking. It is also noteworthy that the two studies with the highest scores for quality (8) (Ren et al., 2010; Galeone et al., 2010a) both had null findings. [The Working Group did not agree with the conclusions of the analysis by Chen & Long that "The results from this meta-analysis of observational studies demonstrate that coffee consumption would increase the laryngeal cancer risk" because of the lack of adequate control for confounding by smoking and alcohol in several of the included case–control studies, the lack of an association in the single cohort study which the group considered the most informative study, and the very large heterogeneity.]

An earlier meta-analysis by Turati et al. (2011b) did not demonstrate a significant association between coffee consumption and cancer of the larynx (RR, 1.56; 95% CI, 0.60–4.02). However, it was based on fewer studies then the analysis by Chen & Long (2014) and only included three of the eight published case-control studies (Pintos et al., 1994; Bosetti et al., 2002; Zvrko et al., 2008). There was also significant evidence of heterogeneity of the findings across the three studies (P for heterogeneity, 0.036; I^2, 70.0%).

2.9 Cancer of the ovary

See Table 2.18 and Table 2.19 (web only; available at: http://publications.iarc.fr/566).

The evidence for the association between coffee consumption and incidence and mortality of cancer of the ovary is based on 13 reports from cohort studies (including a nested case–control study, and a pooled analysis of that nested case–control study with another case–control study) and 21 case–control studies. The lack of adjustment for female endogenous and exogenous hormones has been considered a limitation, but not an exclusion criterion. Tobacco smoking is an important potential confounder.

2.9.1 Cohort studies

Table 2.18 (web only; available at: http://publications.iarc.fr/566).

The Working Group reviewed 11 cohort studies that reported on the association between coffee consumption and risk of cancer of the ovary. All studies presented multivariable analyses adjusted for important potential confounders including age; all but two studies adjusted for smoking (Tavani et al., 2001; Larsson & Wolk, 2005).

Three cohort studies were not reviewed further due to methodological limitations. Snowdon & Phillips (1984) assessed cancer mortality for selected sites among Seventh-day Adventists; however, there is no information on the cohort size for women separately, it is based on 51 cases of ovarian cancer, and it is adjusted only for age. Jacobsen et al. (1986) considered cancer mortality at selected sites, included 12 cases of ovarian cancer, and adjusted the relative risk only for age. Both studies found no association between coffee consumption and ovarian cancer. The study by Stensvold & Jacobsen (1994) considered cancer incidence at selected sites (93 cases of ovarian cancer) but adjusted only for age, area of residence, and smoking; this study found an increased risk of ovarian cancer with coffee drinking, but no trend in risk.

Larsson & Wolk (2005) reported no association between coffee intake either at baseline (RR, 0.99; 95% CI, 0.88–1.11 for an increment of 1 cup/day) or long-term (RR, 0.98; 95% CI, 0.88–1.01 for an increment of 1 cup/day) with risk of cancer of the ovary in the Swedish Mammography Cohort. Further, no association was found for risk of serous carcinoma of the ovary. [The strengths of this study included: population-based cohort; linkage with population registers; exclusion of previous malignancies and oophorectomy; FFQ tested for validity; and full adjustment for confounding. No information on type of coffee (regular/decaffeinated) was provided, however.]

Silvera et al. (2007) reported a hazard ratio of 1.62 (95% CI, 0.95–2.75; *P* for trend, 0.06) for the association between risk of ovarian cancer and coffee intake in the Canadian National Breast Screening Study (NBSS), adjusted for several potential confounders including smoking and endogenous and exogenous hormones. [The strengths of this study included linkage with registries; FFQ tested for validity/reliability; exclusion of women with previous ovarian cancer and oophorectomy; and full adjustment for confounding. No information on type of coffee (regular/decaffeinated) was provided, however.]

Steevens et al. (2007) reported that coffee was not associated with incidence of cancer of the ovary, with a relative risk of 1.04 (95% CI, 0.97–1.12; *P* for trend, 0.35) for an increment in consumption of 1 cup/day in the Netherlands Cohort Study on Diet and Cancer; data were adjusted for age, smoking, oral contraceptives, parity, and tea. [The strengths of this study included linkage to cancer registry; no loss to follow-up; exclusion of women with previous cancer and oophorectomy from the cohort; and FFQ tested for validity/reproducibility. However, the results were not adjusted for menstrual factors.]

In the IWHS, Lueth et al. (2008) found no association for total coffee (*P* for trend, 0.51), decaffeinated coffee (*P* for trend, 0.36), or total caffeine (*P* for trend, 0.53). A significant increased risk was found for ≥ 5 cups/day of caffeinated coffee compared with non-drinkers (HR, 1.81; 95% CI, 1.11–2.95), with no trend in risk (*P* for trend, 0.15), after adjusting for multiple risk factors. [The strengths of this study included: linkage with cancer registries; exclusion of women with previous cancer and oophorectomy; FFQ tested for validity/reproducibility; and fully adjusted results (further adjustment did not modify the hazard ratio).]

In the NHS cohort Tworoger et al. (2008) reported that caffeinated coffee intake was not statistically related to incidence of cancer of the ovary, although a weak inverse relation emerged (RR, 0.75; 95% CI, 0.55–1.02) for ≥ 3 cups/day versus non-drinkers (*P* for trend, 0.03) after adjusting for risk factors. Decaffeinated coffee (follow-up starting in 1984) was not associated with risk of ovarian cancer (*P* for trend, 0.97). Coffee consumption was inversely associated with risk of ovarian cancer in oral contraceptive users (RR, 0.64; 95% CI, 0.44–0.93). [The strengths of this study included minimal loss to follow-up; repeated measures of coffee intake; validation of FFQ; exclusion of women with previous cancer and oophorectomy; and full adjustment.]

Kotsopoulos et al. (2009) pooled the results of the New England Case–Control Study (NECC) with a case–control study nested within the NHS and NHS-II cohorts. Kuper et al. (2000b) previously assessed the association between coffee consumption and risk of ovarian cancer in this study population. There was no association between coffee consumption and risk of ovarian cancer for all women or postmenopausal women in the NECC and NHS/NHS-II studies, with pooled estimates adjusted for multiple risk factors of 0.99 (95% CI, 0.77–1.28; *P* for trend, 0.34) and 0.83 (95% CI, 0.66–1.04; *P* for trend, 0.51), respectively. For premenopausal women, the odds ratio was 1.35 (95% CI, 1.03–1.78; *P* for trend, 0.003) for the NECC study and 0.60 (95% CI, 0.26–1.41; *P* for trend, 0.20) for the NHS/NHS-II study, with a pooled odds ratio of 1.00. There were no clear gene–environment interactions between caffeine-metabolizing genes and ovarian cancer. [The strengths of this study included: the population-based controls; interviewer-administered FFQ for most participants; fully adjusted; and strata of selected covariates. However, no clear information on the general methods for the participants of the nested case–control study from the NHS-II cohort was provided.]

Within the VIP, Nilsson et al. (2010) reported an adjusted hazard ratio of 1.41 (95% CI, 0.53–3.74) for ≥ 4 occasions/day total coffee consumption (*P* for trend, 0.490) for the risk of ovarian cancer;

similar hazard ratios were reported for filtered coffee. [The strengths of this study included the linkage with cancer registry and a high participation rate. Limitations included: no mention of validity/reproducibility of FFQ; no adjustment for menstrual/reproductive factors and exogenous hormone use; very short follow-up for some subjects; and no information on eventual oophorectomy.]

In the EPIC cohort study, Braem et al. (2012) reported an adjusted hazard ratio of 1.05 (95% CI, 0.75–1.46) for the highest quintile of intake compared with the lowest with no trend in risk (*P* for trend, 0.43); results were adjusted for several potential confounders, including smoking and endogenous and exogenous hormones. [The strengths of this study included: its large size; linkage to registries; exclusion of women with previous cancer and oophorectomy; very low loss to follow-up (although not clearly reported); validation of FFQ; and full adjustment. Limitations included: self-administered or interviewer-administered FFQ, depending on the study centre; categorization into country-specific quintiles in millilitres, rather than in absolute amount of coffee intake in cups/day.]

In the PLCO prospective study, Hashibe et al. (2015) reported an adjusted relative risk of 1.17 (95% CI, 0.82–1.67) for the highest compared with the lowest coffee intake (*P* for trend, 0.3982), and of 1.04 (95% CI, 0.95–1.14) for an increment of 1 cup/day. [This study benefited from linkage with the cancer registry and adjustment for main confounders. Limitations included no mention of FFQ testing, no information provided on eventual oophorectomy, and no clear information provided on follow-up length.]

Within the NOWAC study, Lukic et al. (2016) reported an adjusted hazard ratio of 0.87 (95% CI, 0.50–1.51) for > 7 cups/day total coffee consumption (*P* for trend, 0.89). The hazard ratios were similar for non-smokers. [Strengths included: linkage with cancer registry, exclusion of women with previous cancer, adjustment for main confounders, and FFQ tested for validity/reproducibility. Limitations included a lack of information on eventual oophorectomy; further, no information was provided on coffee drinking and smoking status for approximately 27% of subjects at follow-up.]

2.9.2 Case–control studies

In the USA, Hartge et al. (1982) reported an odds ratio of 1.4 (95% CI, 0.6–3.0) for risk of ovarian cancer in coffee drinkers. The results were similar when the analyses were restricted to non-smokers. [Strengths included an interviewer-administered FFQ and the elimination of controls admitted for diet-modifying diseases. Limitations included: the use of hospital controls; the lack of information on the length of the study (years), age of subjects, participation rate, oophorectomy among controls, FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormone use.]

In a case–control study conducted in the USA in the RPMI, Byers et al. (1983) reported no association between coffee intake and risk of cancer of the ovary in any of the three strata of age considered (OR, 0.97, non-significant for ≥ 3 cups/day). [Strengths included: the interviewer-administered FFQ; elimination of controls admitted for diet-modifying diseases; and a 100% participation rate of cases and controls. Limitations included: the use of hospital controls; no information on oophorectomy among controls, FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormone use.]

In Boston, USA, Cramer et al. (1984) reported an odds ratio of 2.0 ($P > 0.05$) in drinkers of ≥ 5 cups/day coffee who also smoked ≥ 50 pack-years of cigarettes. For coffee drinkers who also smoked and drank alcohol, the relative risk was 1.79 (95% CI, 0.69–4.62 for coffee consumption at least once a week). [The strengths of this study included: population controls; exclusion of bilateral oophorectomized women from

controls; interviewer-administered FFQ; and a high participation rate of cases and controls. Limitations included: a lack of information on FFQ validity/reproducibility and no adjustment for smoking, menstrual factors, and exogenous hormone use.]

In a hospital-based case–control study in Italy, La Vecchia et al. (1984) reported an adjusted odds ratio of 2.2 (95% CI, 1.2–3.9) for ≥ 4 cups/day of coffee, with a significant trend in risk of ovarian cancer (*P* for trend, < 0.003). The risk of ovarian cancer increased with the duration of coffee drinking (*P* for trend, 0.02). [The strengths of this study included: high participation rates; exclusion of previous cancer and gastrointestinal diseases among cases and controls and of oophorectomized controls; interviewer-administered FFQ; and fully adjusted results. Limitations included the use of hospital controls, and a lack of information about FFQ validity/reproducibility.]

In a study from 10 Athens hospitals (Greece), Tzonou et al. (1984) observed no significant association between coffee consumption and risk of ovarian cancer, and no trend in risk with the amount consumed (adjusted non-significant RR, 1.5; *P* for trend, 0.14). [This study includes the same cases as for that of Trichopoulos et al. (1981). Strengths included: the interviewer-administered FFQ; no refusal to participate (percent not reported); and adjustment for major covariates. Limitations included: the use of hospital controls including only orthopaedic disorders; very little information on methods; no information on oophorectomy among controls, FFQ validity/reproducibility, no adjustment for potential confounders; and no confidence interval reported.]

In a US hospital-based study, Miller et al. (1987) reported no association between coffee consumption of ≥ 5 cups/day and risk of ovarian cancer using either cancer (RR, 1.0; 95% CI, 0.5–1.8) or non-cancer (RR, 1.1; 95% CI, 0.6–2.0) controls. No association was also reported for decaffeinated coffee after adjusting for many covariates. [The strengths of this study included: high participation rates, exclusion of previous cancer among cases and controls, nurse-administered FFQ, and fully adjusted results. Limitations included: the use of hospital controls, no exclusion of oophorectomized women from controls, and a lack of information about FFQ validity/reproducibility.]

From a study based in Hokkaido, Japan, Mori et al. (1988) reported no significant association between daily coffee consumption and risk of ovarian cancer (RR, 1.4; 95% CI, 0.8–2.5), although the amount consumed in cups/day was not specified. [The strengths of this study included the interviewer-administered FFQ and no refusal to participate. Limitations included: the use of hospital controls including gynaecological disorders; no information on oophorectomy among controls, FFQ validity/reproducibility, or cups/day of coffee; and no specification of variables used for adjustment for potential confounders.]

In California, USA, Whittemore et al. (1988) reported odds ratios for ovarian cancer risk adjusted for smoking that were consistently above unity for any amount of coffee consumption, but with no trend in risk. The odds ratio was 2.07 (95% CI, 0.97–4.38) for ≥ 4 cups/day and 1.01 (95% CI, 0.93–1.08) for an increment in consumption of 1 cup/day. The direct relation increased with the duration of coffee drinking, with an odds ratio of 3.41 (95% CI, 1.46–7.96) in drinkers of at least 40 years compared with non-drinkers; the odds ratio for an increase of 10 years in duration of coffee drinking was 1.11 (95% CI, 0.89–1.38), however. Lifelong consumption of coffee (cup-years) was also directly associated, but the odds ratio for the overall trend per 10 cup-years among coffee drinkers was 1.01 (95% CI, 0.99–1.03). The association was consistently stronger for hospital-based compared with population-based controls. [The strengths of this study included: interviewer-administered FFQ;

a high response rate; exclusion of oophorectomized women from controls; and the provision of information on duration of and lifetime coffee drinking. Limitations included: no information on ascertainment of cases, FFQ validity/reproducibility, and no adjustment for many potential confounders.]

In a study conducted in two major cancer hospitals in Athens, Polychronopoulou et al. (1993) reported no association between coffee drinking and risk of ovarian cancer after a multivariate analysis. The odds ratio for an increment of 1 cup/day was 1.04 (95% CI, 0.82–1.30). [The strengths of this study included: population-based controls, exclusion of women with previous cancer or oophorectomy from controls, interviewer-administered FFQ, a high participation rate, and fully adjusted results. Limitations included a lack of information on FFQ validity/reproducibility]

In a population-based case–control study conducted in the USA, Kuper et al. (2000b) reported a relative risk of 1.88 (95% CI, 1.14–3.09) for ≥ 4 cups/day coffee, with no trend in risk with dose (*P* for trend, 0.17) after adjusting for risk factors. Stratified analyses showed that the increased risk was evident in premenopausal women; an odds ratio of 2.78 (95% CI, 1.44–5.37) for drinkers of ≥ 4 cups/day, with a significant trend in risk (*P* for trend, 0.0004), was reported. No relation was found in postmenopausal women (OR, 1.26; 95% CI, 0.57–2.81) for ≥ 4 cups/day. There were no differences in strata of histological subtypes of ovarian cancer. [The strengths of this study included: population-based design; cases identified by medical records and cancer registries; FFQ tested for validity/reproducibility, although the validity was not specific for coffee intake; interviewer-administered FFQ; and adjustment for major confounders. Limitations included the failure to exclude oophorectomized women from controls.]

In Italy, Tavani et al. (2001) reported no association between coffee or cappuccino consumption and risk of ovarian cancer (OR, 0.93; 95% CI, 0.69–1.27) for ≥ 4 cups/day, adjusting for covariates. Decaffeinated coffee had an inverse association, with an odds ratio of 0.64 (95% CI, 0.42–0.96) for drinkers compared with non-drinkers. Stratified analyses showed no heterogeneity in strata of age, education, parity, oral contraceptive use, BMI, total energy intake, and family history of ovarian/breast cancer. [Strengths of this study included: very large size; exclusion of previous cancer from cases and controls and oophorectomized women from controls; FFQ tested for validity/reproducibility; interviewer-administered FFQ; fully adjusted; and separate information for caffeinated/decaffeinated coffee and cappuccino. The study was however limited by the use of hospital-based controls.]

In a population-based study in Hawaii, USA, Goodman et al. (2003) reported an odds ratio of 1.5 (95% CI, 0.8–2.7) for ≥ 7 cups/day total coffee, with a non-significant trend in risk with dose (*P* for trend, 0.27) on adjusting for age, race, use of oral contraceptives, and tubal ligation. Regular coffee or caffeine were positively related to risk of ovarian cancer, with an odds ratio of 1.7 (95% CI, 1.0–3.1) for ≥ 7 cups/week of caffeinated coffee compared with non-drinkers (*P* for trend, 0.07) and 2.3 (95% CI, 1.3–4.0) for > 1.24 g/week of caffeine; a significant trend in risk was only observed for caffeinated coffee (*P* for trend, 0.02). Decaffeinated coffee drinking was not associated with an increased risk of ovarian cancer. For consumption of regular coffee, the odds ratios were consistent across strata of menopausal status and for mucinous histological type. Similar results were found in a larger group of women for which blood samples were not available. [The strengths of this study included use of population-based controls, interviewer-administered FFQ for most participants, fully adjusted results, separate information for coffee/decaffeinated coffee/caffeine, and in strata of selected covariates. Limitations included

failure to exclude oophorectomized women from controls, and a lack of information about FFQ validity/reproducibility.]

In an Australian study, Jordan et al. (2004) observed that coffee was inversely associated with risk of ovarian cancer (OR, 0.62; 95% CI, 0.41–0.95) for ≥ 4 cups/day, with a significant trend in risk (*P* for trend, 0.05) after adjustingfor multiple risk factors. The inverse association was found for invasive serous tumours (*P* for trend, 0.01), invasive endometrioid/clear-cell tumours (*P* for trend, 0.01), and overall for invasive tumours (*P* for trend, 0.009), while there was no association for invasive mucinous and all borderline tumours. The inverse association was evident only in postmenopausal women (*P* for trend, 0.005). No heterogeneity was found in strata of smoking, alcohol, BMI, parity, and in women with invasive stage I or advanced disease. [The strengths of this study included the use of population-based controls, the exclusion of oophorectomized women from controls, FFQ tested for validity/reproducibility (not for the coffee question), and fully adjusted results. Limitations included the fact that FFQs were interviewer-administered among cases and self-administered among controls.]

In Sweden, Riman et al. (2004) reported a non-significant inverse association between coffee drinking and risk of ovarian cancer, with an odds ratio of 0.68 (95% CI, 0.42–1.10) for ≥ 6 cups/day of coffee with no trend in risk (*P* for trend, 0.18). The results were similar for all histological subtypes (serous, mucinous, and clear-cell tumours) while there was no association for endometrioid subtype. [The strengths of this study included the use of population-based controls, its large size, the exclusion of oophorectomized women among controls, high participation rate, and fully adjusted data. Limitations included the self-administered FFQ or telephone interview for more controls than cases, and a lack of information regarding FFQ validity/reproducibility and intake of caffeinated/decaffeinated coffee.]

In a study conducted within the RPCI, USA, Baker et al. (2007) reported that regular coffee was not related to risk of ovarian cancer (OR, 1.05; 95% CI, 0.73–1.52) for ≥ 4 cups/day, and no heterogeneity was found in strata of borderline tumours or serous, mucinous, endometrioid, and clear-cell histological subtypes. Decaffeinated coffee was inversely associated with overall risk of ovarian cancer; an odds ratio of 0.71 (95% CI, 0.51–0.99) for ≥ 2 cups/day compared with non–drinkers, with an inverse statistically significant trend in risk (*P* for trend, 0.002), was reported. Stratified analyses showed that the decreased risk did not reach statistical significance for serous, mucinous, and borderline tumours, and that there was no association for endometrioid and clear-cell tumours. [The strengths of this study were the identifiication of cases through cancer registries and the provision of information on caffeinated/decaffeinated coffee. Limitations included: the use of hospital-based controls, self-administered FFQ, no exclusion of oophorectomized women from controls, no information on FFQ validity/reproducibility, and no adjustment for confounders.]

Using data from the Hospital-based Epidemiological Research Program at Aichi Cancer Centre (HERPACC) in Japan, Hirose et al. (2007) observed a non-significant positive association between coffee intake and risk of ovarian cancer (OR, 1.33; 95% CI, 0.68–2.60) for ≥ 3 cups/day versus non-drinkers (*P* for trend, 0.88). [This study benefited from cases being identified through medical records and cancer registries, and the checking of the self-administered FFQ by an interviewer. Limitations included the hospital-based controls, no exclusion of oophorectomized women from controls, no information on FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormones.]

In a study conducted in a 13-county area of Washington State, USA, Song et al. (2008) reported an odds ratio for regular coffee of 0.87 (95% CI, 0.64–1.19) for ≥ 3 cups/day. The intake of decaffeinated coffee or caffeine equivalent to the content of ≥ 3 cups/day of regular coffee were not related to the risk of ovarian cancer (*P* for trend, 0.54 and 0.38, respectively). [The strengths of this study were its large size, identification of cases through cancer registries as part of the SEER Program; population-based controls, exclusion of oophorectomized women from controls, and the provision of information on caffeinated/decaffeinated coffee and caffeine consumption. Limitations included the self-administered FFQ, no information on FFQ validity/reproducibility, and no adjustment for menstrual factors.]

In the Danish MALignant OVArian cancer (MALOVA) study, Gosvig et al. (2015) reported that coffee was inversely related to invasive ovarian cancer (although not always statistically significant); odds ratios (95% CI) for an increment of 1 cup/day of coffee were 0.90 (0.84–0.97) for overall, 0.89 (0.83–0.97) for serous, 0.90 (0.77–1.06) for endometrioid, and 0.88 (0.74–1.05) for other types of ovarian cancer. No association was evident for mucinous ovarian cancer (OR, 1.07; 95% CI, 0.90–1.28). Coffee consumption was not related to overall, serous, or mucinous borderline risk of ovarian cancer. [The strengths of this study included cases identified by cancer registries, use of population-based controls, exclusion of oophorectomized women from controls, and fully adjusted results. Limitations included the self-administered FFQ as part of a larger questionnaire on other variables, and no information was provided on on FFQ validity/reproducibility.]

2.9.3 Meta-analyses

Braem et al. (2012) added a meta-analysis to their analysis within the EPIC cohort study. The literature was searched up to April 2011 using PubMed and Embase, and manually in reference lists of retrieved articles. Studies were included if they met the following criteria: cohort studies; frequency of coffee consumption was reported; the exposure was total and/or caffeinated and/or decaffeinated coffee; the number of cases and person-years were provided; the outcome was ovarian cancer. Seven articles were included in the meta-analyses (three studies were not included as they did not report 95% CI), with a total of 3236 cases of ovarian cancer. There was some heterogeneity across studies, and no evidence of publication bias. The summary hazard ratio for the study-specific highest versus the lowest coffee intake was 1.13 (95% CI, 0.89–1.43); the results did not change on exclusion of the study of Nilsson et al. (2010), which did not adjust for parity and oral contraceptive use. The hazard ratio for an increment of 1 cup/day was 1.02 (95% CI, 0.99–1.05), showing no association between coffee intake and risk of ovarian cancer. [The strengths of this meta-analysis were the comprehensive selection of studies and the detailed extraction information, allowing the computation of a dose–response association between coffee intake and risk of ovarian cancer.]

2.10 Childhood cancer

2.10.1 Childhood leukaemia

See Table 2.20 (web only; available at: http://publications.iarc.fr/566).

In general, childhood leukaemia refers to diagnoses in children less than 15 years of age. Almost all are acute leukaemias (AL), including acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), and a few other rare or unspecified types. Together, AML and other

non-ALL leukaemias are sometimes referred to as acute non-lymphoblastic leukaemia (ANLL).

Seven case–control studies reporting results of the association between maternal coffee consumption during pregnancy and risk of childhood leukaemia in the offspring are described below. Six of the seven studies included all acute leukaemias, and four of these studies presented results separately for ALL and AML (or ANLL). One study (Milne et al., 2011) included ALL cases only. Unless otherwise stated, the studies included children younger than 15 years. There were no cohort studies.

The child's sex and age were used as matching variables in all studies. The following variables were also identified as confounders, and considered in the analysis of the association between maternal coffee consumption and risk of childhood leukaemia in one or more studies: socioeconomic status (e.g. maternal education, socioprofessional category, and income); mother's ethnicity/country of birth; mother's age at the child's birth; birth order; and breastfeeding. There is little or no evidence that maternal smoking is associated with risk of childhood leukaemia. Maternal alcohol consumption is not considered a confounder of this association, and studies that did examine it as a potential confounder reported that it did not alter the findings. Maternal recall of coffee consumption during pregnancy up to 15 years in the past may have led to error in exposure assessment, although most childhood leukaemias are diagnosed within the first 6 years of life. Further, there is evidence that diet during a past pregnancy (3–7 years previously) is generally recalled with similar accuracy as adult diet; this may partly reflect the influence of current diet on recall of past diet (Bunin et al., 2001). However, it cannot be excluded that mothers of children with leukaemia overestimate exposure.

(a) Case–control studies

An early case–control study of childhood leukaemia reported that "there was no apparent risk associated with coffee consumption" but did not present data (Peters et al., 1994).

Ross et al. (1996) analysed data on infant leukaemia (diagnosed at ≤ 1 year of age) from three North American case–control studies of childhood leukaemia. In total, there were 303 cases in the original studies. Ross et al. recontacted women up to 10 years after the original studies, and 84 matched sets of infant cases and controls were available for analysis. Controls (n = 97) had been recruited through RDD and matched to cases on year of birth, geographical area, and, in two of the three studies, race. Maternal intake of coffee was assessed as part of a dietary questionnaire completed by telephone interview. Regular coffee intake was associated with an increased risk of infant leukaemia, with an adjusted odds ratio of 2.5 (95% CI, 1.0–6.2) for ≥ 4 cups/week (P for trend, 0.04). Odds ratios for ALL and AML individually were similarly elevated, but estimates were imprecise. [Strengths included presentation of results for infant AL, ALL, and AML separately, and inclusion of exposure–response analysis. Limitations included the small sample size and potential for selection bias, given the low participation rate.]

Petridou et al. (1997) conducted a hospital-based case–control study of childhood leukaemia in Greece. The investigators recruited 153 cases confirmed by bone marrow analysis and 300 hospital-based controls admitted with "acute conditions", matched on age, sex, and town or region. Maternal coffee intake was assessed by interview and categorized as < 3 and ≥ 3 cups/week. No association was observed, with an adjusted odds ratio of 0.89 (95% CI, 0.55–1.46). [Strengths included control for confounding by multiple factors. Limitations included: a lack of detail about control diagnosis/reason for hospitalization; analysis of all

types of childhood leukaemia together; exposure was categorized as only binary, so an exposure–response analysis was not possible; and the modest sample size.]

Milne et al. (2011) conducted a population-based case–control study in Australia that included 337 incident cases of childhood ALL and 697 controls recruited by nationwide RDD. Controls were frequency-matched to the cases on age, sex, and state of residence. Maternal coffee intake during the last 6 months of the index pregnancy was assessed by FFQ, and reported in cups/day. No overall association between maternal coffee consumption and risk of ALL was observed; the adjusted odds ratio for any coffee consumption was 0.89 (95% CI, 0.61–1.30), and there was no evidence of an exposure–response association (*P* for trend, 0.50). [Strengths included the use of population-based cases and controls, standardized questionnaires, adjustment for a range of confounders, and assessment of exposure–response relationship. The study was however limited by the low participation rate.]

Several independent case–control studies of childhood leukaemia were conducted in France, described in the following paragraphs.

Menegaux et al. (2005) conducted a study including 280 incident cases of childhood acute leukaemia from hospitals in Paris, Lille, Lyon, and Nancy. Controls comprised 288 children admitted to the same hospitals as the cases, mainly with orthopaedic conditions. Recruitment was stratified by age, sex, hospital, and ethnic origin. Maternal coffee intake during pregnancy was assessed by face-to-face interview using a standardized questionnaire. The adjusted odds ratios (95% CI) for AL were 1.0 (0.7–1.5), 2.1 (1.2–3.8), and 2.8 (0.9–8.1) for ≤ 3 cups/day, 4–8 cups/day, and > 8 cups/day, respectively, compared with non-drinkers (*P* value for trend, < 0.05). Positive associations were also seen for both ALL and ANLL, although results for the latter were imprecise. For ALL, the corresponding odds ratios (95% CI) were 1.1 (0.7–1.8), 2.4 (1.3–4.7), and 3.1 (1.0–9.5), respectively, while for ANLL they were 1.6 (0.6–4.3), 2.8 (0.7–10.4), and 3.0 (0.3–35.1). [Strengths included standardized interviews, adjustment for a range of confounders, presentation of results for ALL and ANLL separately, and assessment of exposure–response relationship. The study was however limited by the use of hospital-based controls and the modest sample size for ANLL.]

Menegaux et al. (2007) conducted a second study including 470 incident cases of childhood acute leukaemia (407 ALL and 62 AML) and 567 controls. Cases were diagnosed between 1995 and 1998 in 14 regions of France, and identified through the National Registry of Childhood Blood Malignancies (NRCL). The four regions that provided cases in Menegaux et al. (2005) were excluded from this study. Controls were recruited by RDD and frequency-matched to cases on age, sex, and region. Mothers completed a standardized self-administered questionnaire that asked about a range of exposures, including coffee consumption, during pregnancy. Overall, maternal coffee intake was not significantly associated with risk of AL, ALL, or AML; odds ratios (95% CI) for > 3 cups/day versus none were 1.5 (0.9–2.4), 1.4 (0.9–2.4), and 1.4 (0.5–4.4), respectively. [Strengths included use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. The modest sample size for AML was a limitation.]

Bonaventure et al. (2013) reported results from the Etude Sur les Cancers et les Leucémies de l'Enfant (ESCALE) study, a population-based case–control study conducted in France. The cases comprised 764 children diagnosed with AL (including 648 ALL and 101 AML), identified through the National Registry of Childhood Haematopoietic Malignancies (NRCH) during 2003–2004. Controls were selected contemporaneously from French households with landline telephones using RDD, with quotas applied

to ensure their age and sex distributions were comparable to the case group and the French population. Data were collected by telephone interview. The adjusted odds ratios (95% CI) for > 2 cups/day for AL, ALL, and AML were 1.6 (1.2–2.1), 1.5 (1.1–2.0), and 2.4 (1.3–4.3), respectively, with *P* values for trend of < 0.001, 0.0027, and 0.002, respectively. [Strengths included the use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of an exposure–response relationship.]

Orsi et al. (2015) reported results from the ESTELLE study, a nation-wide French population-based case–control study of childhood malignancies. In this study, 747 children newly diagnosed with leukaemia in 2010 and 2011 (including 636 ALL, 100 AML, and 11 unspecified) were identified by the investigators of the NRCH. Controls (n = 1421) were children free from cancer selected using RDD and a quota sampling method; the latter was applied to ensure their age and sex distributions were comparable to the case group and the French population. Data on maternal coffee intake during the index pregnancy were collected during a standardized telephone interview. Maternal coffee consumption was not found to be associated with AL overall (adjusted OR for > 2 cups/day 1.1, 95% CI: 0.9–1.5) or with AML (OR for > 2 cups/day 0.5, 95% CI: 0.2–1.1), while for ALL, the OR for > 2 cups/day was 1.3 (95% CI: 1.0–1.7). [Strengths included the use of population-based controls, a standardized CATI interview, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. *P* values for trend were not provided, however.]

(b) Meta-analyses

Three meta-analyses of the association between maternal coffee consumption and childhood leukaemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake (Milne et al., 2011; Cheng et al., 2014; Thomopoulos et al., 2015). The results are presented only for the most recent meta-analysis of Thomopoulos et al. (2015), which included all studies published to date. High maternal coffee intake during pregnancy was positively associated with AL overall, ALL, and AML with summary odds ratios (95% CI) of 1.57 (1.16–2.11), 1.43 (1.22–1.68), and 1.81 (0.93–3.53), respectively. [A limitation of this meta-analysis was that "high level" coffee intake was not defined consistently in the included studies, varying from ≥ 4 times/week (Ross et al., 1996) to ≥ 8 cups/day (Menegaux et al., 2007).]

Another meta-analysis (Yan et al., 2015) lacked methodological detail and excluded some relevant studies. Ross et al. (1996) was a study of only infants (of age ≤ 1 year). The authors also included unpublished data from one of their own studies.

2.10.2 Wilms tumour

Bunin et al. (1987) reported that there was no association with maternal coffee drinking in a case-control study of risk factors for Wilms tumour, but did not present an effect estimate. Three other case–control studies (e.g., Schüz et al., 2001) reported findings for the association of Wilms tumour and maternal coffee or tea consumption combined; these studies were excluded from further consideration because of the ambiguous exposure definition.

2.10.3 Childhood cancer of the brain

Three population-based case–control studies have reported findings for prenatal exposure to coffee and risk of childhood brain tumours. All reported non-significant positive associations, with odds ratios (95% CI) of 1.9 (0.9–3.9) for any coffee (Cordier et al., 1994), 1.4 (0.8–2.4) for > 3 cups/day (Plichart et al., 2008), and

1.35 (0.90–2.04) for ≥ 2 cups/day (Greenop et al., 2014). None of the studies reported a significant exposure–response trend overall. However, in a subgroup analysis of cases of age < 5 years at diagnosis, Greenop et al. observed significantly elevated odds ratios (95% CI) of 1.76 (1.09–2.84) for any maternal coffee intake, 1.55 (0.92–2.63) for > 0–2 cups/day, and 2.52 (1.26–5.04) for ≥ 2 cups/day (Greenop et al., 2014). A significant trend (P = 0.007) was also observed in this age group. Two earlier population-based case–control studies reported no significant association between maternal consumption of caffeinated beverages (including coffee, tea, and cola drinks) and risk of astrocytoma (Bunin et al., 1994) or primitive neuroectodermal tumours (Bunin et al., 1993) in children aged < 6 years.

[The strengths of these studies included their population-based controls, appropriate assessment of and adjustment for confounders, and examination of the exposure–response trend in the three most recent studies. The main limitation was suboptimal response rates, leading to the potential for selection bias.]

2.11 Cancer of the oral cavity and pharynx

Twenty-six studies that evaluated associations between coffee consumption and cancers of the oral cavity and pharynx were reviewed by the Working Group: seven were prospective cohort studies, eighteen were case–control studies, and one (Galeone et al., 2010a) was a pooled analysis of nine case–control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. However, several were not considered for evaluation; two studies did not present risk estimates for the association between coffee consumption and oral or pharyngeal cancer (McLaughlin et al. 1988; Lagiou et al. 2009); two did not specifically analyse coffee consumption as an exposure (Franceschi et al., 1999; Escribano Uzcudun et al., 2002); and one (Hashibe et al. 2015) did not have oral or pharyngeal cancers as outcomes. Four meta-analyses of the indicated studies were also identified and reviewed (Turati et al., 2011b; Yu et al., 2011; Zhang et al., 2015; Li et al., 2016).

2.11.1 Cohort studies

Table 2.21 (web only; available at: http://publications.iarc.fr/566)

The six informative cohort studies were conducted in Japan (Naganuma et al., 2008), Norway (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Tverdal et al., 2011), and the USA (Ren et al., 2010; Hildebrand et al., 2013). Four studies provided data for incident (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Naganuma et al., 2008; Tverdal et al., 2011) or fatal (Hildebrand et al., 2013) oral and pharyngeal cancers combined, and one study reported separate associations for each cancer site (Ren et al., 2010). All studies controlled for tobacco smoking and alcohol drinking. All of the studies that treated oropharyngeal cancer as a single entity reported null or inverse associations with coffee consumption (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Naganuma et al., 2008; Tverdal et al., 2011; Hildebrand et al., 2013). Ren et al. (2010) reported no association with oral cancer and a positive, non-significant association with pharyngeal cancer.

2.11.2 Case–control studies

The 14 informative case–control studies were undertaken in Brazil (Franco et al., 1989; Pintos et al., 1994; Biazevic et al., 2011), Colombia (Restrepo et al., 1989), Denmark (Bundgaard et al., 1995), France (Radoï et al., 2013), India (Heck et al., 2008), Italy (La Vecchia et al., 1989b; Franceschi et al., 1992), Italy and Switzerland (Tavani et al., 2003; Rodriguez et al., 2004), Japan (Takezaki et al., 1996a; Oze et al., 2014), and the

USA (Mashberg et al., 1993). [The Working Group noted that the studies by Tavani et al. (2003) and Rodriguez et al. (2004) may partly overlap.] All but two of these studies (Bundgaard et al., 1995; Radoï et al., 2013) were hospital-based.

Most studies investigated cancers of the oral cavity and pharynx combined. Aggregated data were also reported for oral, pharyngeal, and laryngeal cancer (Oze et al. 2014) and for cancers of the mouth and hypopharynx (Restrepo et al., 1989). Data for cancer of the oral cavity alone were reported in five studies (Franco et al., 1989; Franceschi et al. 1992; Pintos et al., 1994; Bundgaard et al. 1995; Radoï et al. 2013); data for cancer of the pharynx and hypopharynx alone were reported by Pintos et al. (1994) and Heck et al. (2008), respectively. Adjustment for at least age, sex, smoking status, and alcohol intake was performed in all studies.

The estimated association between coffee consumption and oral and/or pharyngeal cancer incidence was null or inverse in all but three studies: Franco et al. (1989) reported a non-statistically significant increased risk of cancer of the oral cavity for coffee consumption of ≥ 6 cups/day versus < 1 cup/day (OR, 1.5; 95% CI, 0.9–2.6; *P* for trend, 0.14), and Bundgaard et al. (1995) estimated a similarly increased odds ratio of 1.4 (95% CI, 0.4–4.5) for oral squamous cell cancer among drinkers versus non-drinkers of coffee. Restrepo et al. (1989) reported a statistically significant sex- and age-adjusted odds ratio for the association between coffee (≥ 7 cups/day vs 0 cups/day) and cancers of the oral cavity and hypopharynx, reduced after additional adjustment for socioeconomic level, smoking, and alcohol intake, of 5.12 (*P* for trend, 0.002) [95% CI not reported].

Heck et al. (2008) reported odds ratios (95% CI) for hypopharyngeal cancer for highest versus lowest coffee consumption of 1.07 (0.41–2.81; *P* for trend, 0.7) for never smokers and 0.81 (0.39–1.66; *P* for trend, 0.4) for ever smokers. In the remaining studies, the estimated odds ratios for the highest versus lowest coffee consumption ranged over 0.25–0.90 and were statistically significant in six studies (Franceschi et al., 1992; Tavani et al., 2003; Rodriguez et al., 2004; Biazevic et al., 2011; Radoï et al. 2013; Oze et al., 2014). In the pooled analyses of data from the INHANCE consortium, Galeone et al. (2010a) used individual-level data from five hospital-based case–control studies and four population-based case–control studies of head and neck cancers conducted in Europe and North and Central America. Caffeinated coffee intake was inversely related to the risk of cancer of the oral cavity and pharynx combined; odds ratios (95% CI) of 0.96 (0.94–0.98) for an increment of 1 cup/day and 0.61 (0.47–0.80) in drinkers of > 4 cups/day versus non-drinkers were reported (*P* for trend, < 0.01). In a separate analysis by anatomical site, the respective estimates were 0.46 (0.30–0.71; *P* for trend, < 0.01) for oral cavity and 0.58 (0.41–0.82; *P* for trend, 0.02) for oropharynx/hypopharynx. [The Working Group noted that this paper reported that results on coffee drinking had been published by four out of nine of the studies before the pooled analysis undertaken in their paper, but it is not clear from the indicated references which studies are meant. There may therefore be some overlap between this pooled analysis and some of the case–control studies reviewed individually.]

2.11.3 Meta-analyses

Meta-analyses of the association between coffee intake and risk of cancer of the upper aerodigestive tract (Turati et al., 2011b) and cancer risk overall (Yu et al., 2011) were published in 2011. Summary relative risks (95% CI) for oral cavity/pharyngeal cancer were 0.64 (0.51–0.80) and 0.40 (0.12–0.68) for the highest versus lowest level of coffee drinking in the two studies, respectively. [The Working Group noted that the meta-relative risk for highest versus lowest consumption in Yu et al. (2011) was taken from Supplementary Table S2 of the publication.]

Zhang et al. (2015) undertook a meta-analysis of 12 studies focusing on the association between oral cancer and coffee intake, comprising 4037 cases and 1 872 231 participants. The summary relative risk of oral cancer for the highest versus lowest level of coffee consumption was 0.69 (95% CI, 0.54–0.89).

The most recent meta-analysis of 11 case–control and 4 cohort studies through 2015 that reported on cancer of the oral cavity alone or in combination with cancer of the pharynx was undertaken by Li et al. (2016). The summary relative risk of oral cancer for the highest versus the lowest consumption of coffee was 0.63 (95% CI, 0.52–0.75; I^2, 53.1%). Results were consistent in subgroup analysis by study design, with 0.60 (95% CI, 0.49–0.74) for case–control and 0.66 (95% CI, 0.45–0.98) for cohort studies), by country (Americas, Asia, and Europe), by number of cases and study quality score, as well as in analysis by trim and fill undertaken to examine potential publication bias. Heterogeneity, however, remained medium–high even in subgroup analyses. The pooled analysis by Galeone et al. (2010a) is not included in this meta-analysis.

2.12 Cancer of the oesophagus

In reviewing data on the association between coffee consumption and cancer of the oesophagus, the Working Group considered only studies that adjusted for the important potential confounders of tobacco smoking and alcohol drinking. One cohort study that presented results for oral and oesophageal cancers combined was excluded from the Working Group evaluation (Tverdal et al., 2011).

2.12.1 Cohort studies

Four pertinent cohort studies (Jacobsen et al., 1986; Naganuma et al., 2008; Ren et al., 2010; Zamora-Ros et al., 2014) were identified; three of these studies observed no association. A study based in Japan (Naganuma et al., 2008) observed an inverse association. The earliest cohort study from Norway (Jacobsen et al., 1986) analysed a very small number of cases (n = 15). The other cohort studies were sufficiently large and adequately designed. Two studies conducted stratified analyses by histological type (Ren et al., 2010; Zamora-Ros et al., 2014), but did not observe notable differences in the association by histological type.

2.12.2 Case–control studies

Eight case–control studies in the Americas, Asia, and Europe (La Vecchia et al., 1989b; Brown et al., 1995; Garidou et al., 1996; Inoue et al., 1998; Castellsagué et al., 2000; Terry et al., 2000; Tavani et al., 2003; Chen et al., 2009) were identified. All studies were hospital-based with the exception of one study from Sweden that applied population-based controls from a National Register. (Terry et al., 2000). Six studies (La Vecchia et al., 1989b; Brown et al., 1995; Garidou et al., 1996; Inoue et al., 1998; Castellsagué et al., 2000; Terry et al., 2000) among the eight found no notable association between coffee intake and risk of cancer of the oesophagus. Among the two more recent studies, one observed significantly decreased risk (Tavani et al., 2003) and one observed a decreased risk of cancer, particularly in the middle third part of the oesophagus (Chen et al., 2009).

2.12.3 Meta-analyses

Two meta-analyses of coffee consumption and the risk of cancer of the oesophagus have been published (Turati et al., 2011b; Zheng et al., 2013). The summary relative risk reported by the most recent meta-analysis (Zheng et al., 2013) was 0.88 (95% CI, 0.76–1.01) for highest versus lowest coffee consumption. The other meta-analysis (Turati et al., 2011b) reported summary relative risks for the same comparison category of 0.87

(95% CI, 0.65–1.17) for squamous cell carcinoma and 1.18 (95% CI, 0.81–1.71) for adenocarcinoma of the oesophagus.

2.13 Cancer of the stomach, small intestine, gall bladder, and biliary tract

2.13.1 Cancer of the stomach

(a) Cohort studies

Twelve cohort studies that reported on the association between coffee consumption and cancer of the stomach were identified (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Galanis et al., 1998; Tsubono et al., 2001; Khan et al., 2004; Larsson et al., 2006a; Nilsson et al., 2010; Ren et al., 2010; Bidel et al., 2013; Ainslie-Waldman et al., 2014; Hashibe et al., 2015; Sanikini et al., 2015b).

Nine studies observed no association (Jacobsen et al., 1986; Galanis et al., 1998; Tsubono et al., 2001; Khan et al., 2004; Nilsson et al., 2010; Bidel et al., 2013; Ainslie-Waldman et al., 2014; Hashibe et al., 2015; Sanikini et al., 2015b). One early study from Norway reported risk estimates of < 1 that were not statistically significant (Stensvold & Jacobsen, 1994). One study from Sweden (Larsson et al., 2006a) showed positive associations for both baseline and cumulative consumption of coffee. One study from the USA showed an increased risk for gastric cardia cancer but not for non-cardia cancer (Ren et al., 2010). A nested case–control study within a cohort from Singapore observed a significant inverse association in analyses adjusted for *Helicobacter pylori* (Ainslie-Waldman et al., 2014). In general, the data were inconclusive on the association between coffee intake and cancer of the stomach.

(b) Case–control studies

Fourteen case–control studies that reported on the association between coffee consumption and cancer of the stomach were identified (Correa et al., 1985; La Vecchia et al., 1989b; Agudo et al., 1992; Hoshiyama & Sasaba, 1992; Hansson et al., 1993; Inoue et al., 1998; Komoto et al., 1998; Chow et al., 1999; Terry et al., 2000; Muñoz et al., 2001; Rao et al., 2002; De Stefani et al., 2004; Gallus et al., 2009; Icli et al., 2011). The majority of the studies were hospital-based (Correa et al., 1985; La Vecchia et al., 1989b; Agudo et al., 1992; Inoue et al., 1998; Komoto et al., 1998; Muñoz et al., 2001; Rao et al., 2002; De Stefani et al., 2004; Gallus et al., 2009; Icli et al., 2011) and the remainder were population-based (Hoshiyama & Sasaba, 1992; Hansson et al., 1993; Chow et al., 1999; Terry et al., 2000). All studies but two, conducted in Uruguay (De Stefani et al., 2004) and Turkey (Icli et al., 2011), found no association between coffee intake and risk of cancer of the stomach. The remaining studies (De Stefani et al., 2004; Icli et al., 2011) observed significant inverse associations. However, results from the study by Icli et al. (2011) were only adjusted for age, so potential confounding could not be ruled out.

(c) Meta-analyses

Eight meta-analyses of the association of cancer of the stomach and coffee consumption were available for review (Botelho et al., 2006; Xie et al., 2014; Fang et al., 2015; Li et al., 2015; Liu et al., 2015b; Shen et al., 2015; Zeng et al., 2015; Deng et al., 2016). The latter seven meta-analyses focused on prospective studies only. These were published around the same time and employed slightly different methods, but yielded similar results. Summary relative risks (95% CI) for highest versus lowest consumption of the most recent meta-analysis (Deng et al., 2016) was 1.36 (1.06–1.74) for the USA, 0.96 (0.72–1.27) for Asia, and 1.12 (0.86–1.46) for Europe.

2.13.2 Cancer of the small intestine, gall bladder, and biliary tract

One case–control study of adenocarcinoma of the small intestine cancer (Negri et al., 1999), one case–control study for extrahepatic bile duct cancer (Yen et al., 1987), and one case–control study for cancer of the gallbladder (Poland) (Zatonski et al., 1992) have been published, all of which reported null associations with coffee intake. One case–control study in Canada found a decreased risk of cancer of the bile duct with coffee intake (Ghadirian et al., 1993).

In one cohort study from Japan (Makiuchi et al., 2016), there was no clear association between coffee consumption and cancer of the biliary tract, gallbladder, or extrahepatic bile duct.

2.14 Cancer of the colorectum

Several cohort and case–control studies, pooled analyses, and meta-analyses have been conducted to evaluate the association between coffee drinking and cancer of the colorectum. The Working Group's review gave the greatest weight to data from well-conducted prospective cohort studies. Case–control studies were seen as less informative because they necessarily assess diet after the onset of disease; reported dietary intakes of people with colorectal cancers can therefore be influenced by the disease.

2.14.1 Cohort studies

Table 2.22 (web only; available at: http://publications.iarc.fr/566)

The Working Group evaluated 18 cohort studies of coffee drinking and colorectal cancers (Phillips & Snowdon, 1985; Hartman et al., 1998; Terry et al., 2001; Mucci et al., 2003; Michels et al., 2005; Larsson et al., 2006b; Oba et al., 2006; Lee et al., 2007a; Naganuma et al., 2007; Bidel et al., 2010; Nilsson et al., 2010; Peterson et al., 2010; Simons et al., 2010; Sinha et al., 2012; Dominianni et al., 2013; Dik et al., 2014; Yamada et al., 2014; Lukic et al., 2016) and a large pooled analysis (Zhang et al., 2010).

Phillips & Snowdon (1985) investigated the association of coffee intake with colorectal cancer mortality in a large cohort of California Seventh-day Adventists. After 21 years of follow-up, the relative risk of colorectal cancer mortality in men and women combined was 1.5 (95% CI, 1.0–2.2) for an intake of ≥ 2 cups/day with a trend in risk (*P* for trend, 0.02).

Among participants of the ATBC Cancer Prevention trial of 29 133 male smokers in Finland (Hartman et al., 1998), the relative risks (95% CI) of drinking 4–5 cups/day or > 6 cups/day compared with ≤ 4 cups/day were 0.73 (0.47–1.16) and 0.69 (0.42–1.13), respectively. The corresponding odds ratios (95% CIs) for rectal cancer were 1.05 (0.63–1.75) and 0.77 (0.43–1.40).

Among 61 463 Swedish women followed for an average of 9.6 years (Terry et al., 2001), the adjusted relative risks (95% CI) for consumption of 1, 2–3, and ≥ 4 cups/day compared with drinking < 1 cup/day were 0.96 (0.66–1.40), 0.93 (0.67–1.29), and 1.04 (0.70–1.54), with a *P* for trend of 0.95. Results were similar for colon and rectal cancers separately, and for subsites within the colon.

In the follow-up period of the NHS and HPFS cohorts until 1998 (Michels et al., 2005), there was no association between higher caffeinated coffee intake and risk of colorectal cancer (HR, 0.98; 95% CI, 0.69–1.38) for > 5 cups/day compared with non-drinkers of coffee (*P* for trend, 0.60). For colon cancer alone, the association was similar. For rectal cancer, the hazard ratio was 1.55 (95% CI, 0.97–2.45) for ≥ 4 cups/day (the highest category) compared with non-drinkers (*P* for trend, 0.31). There was an inverse association between decaffeinated coffee and colorectal cancer risk (HR, 0.82; 95% CI, 0.67–0.99) for ≥ 2 cups/day compared with non-drinkers (*P* for trend, 0.08). Results among non-smokers were

similar to those in the full study population for both caffeinated and decaffeinated coffee.

A large Japanese cohort study of more than 50 000 men and women (Oba et al., 2006) found that coffee consumption was inversely associated with colon cancer risk in women, but not in men. The relative risks (95% CI) for ≥ 1 cup/day versus never and < 1 cup/day were 0.43 (0.22–0.85) and 0.81 (0.46–1.42), respectively, with an inverse trend observed for women (*P* for trend, < 0.01).

Larsson et al. (2006b) studied the association between coffee drinking and risk of colorectal cancer among participants from two population-based cohort studies of women and men in Sweden. Coffee consumption was not associated with risk of colorectal cancer, colon cancer, or rectal cancer in women or men. The multivariate rate ratio for colorectal cancer in both cohorts combined was 1.00 (95% CI, 0.97–1.04) for an increment of 1 cup/day of coffee.

Naganuma et al. (2007) examined coffee consumption and colorectal cancer risk in the Miyagi Cohort Study of approximately 48 000 men and women in Japan. For a consumption frequency of ≥ 3 cups/day versus none, there was no association between coffee intake and risk of colorectal cancer (HR, 0.95; 95% CI, 0.65–1.39; *P* for trend, 0.55) for women or men; results were similar for both colon and rectal cancer.

Bidel et al. (2010) examined the association between coffee consumption and risk of colorectal cancer in a randomly selected cohort of Finnish men and women making up 6.6% of the population. After a mean follow-up period of 18 years, the multivariate-adjusted hazard ratio of colorectal cancer incidence for ≥ 10 cups/day of coffee compared with non-drinkers was 0.98 (95% CI, 0.47–2.03) for men (*P* for trend, 0.86), 1.24 (95% CI, 0.49–3.14) for women (*P* for trend, 0.83), and 1.03 (95% CI, 0.58–1.83) for men and women combined (*P* for trend, 0.61).

In the JPHC Study of > 96 000 men and women (Lee et al., 2007a), the multivariate hazard ratio for ≥ 3 cups/day of coffee compared with never drinkers was 0.44 (95% CI, 0.19–1.04; *P* for trend, 0.04). No significant association was found for rectal cancer in women or for colorectal cancer in men.

Simons et al. (2010) evaluated coffee intake in the context of total fluid intake with colorectal cancer within the Netherlands Cohort Study. After 13.3 years of observation, no association was observed between coffee consumption and colorectal cancer, colon cancer overall, or cancer in the proximal or distal colon in women or men. However, a significant positive trend with coffee intake was observed for rectal cancer in men (HR, 1.60; 95% CI, 0.96–2.66) for > 6 cups/day versus ≤ 2 cups/day (*P* for trend, 0.05).

Nilsson et al. (2010) evaluated filtered and boiled coffee consumption and colorectal cancer in a 15-year follow-up of over 60 000 participants in the VIP in Sweden. For subjects consuming ≥ 4 cups/day compared with < 1 cup/per day of coffee, a hazard ratio of 1.43 (95% CI, 0.86–2.38; *P* for trend, 0.168) was reported. The risk was similar for boiled coffee, while for ≥ 4 cups/day of filtered coffee compared with < 1 cup/day the hazard ratio was 0.73 (95% CI, 0.50–1.08; *P* for trend, 0.116).

After 12 years of observation during the Singapore Chinese Health Study (Peterson et al., 2010) of over 60 000 men and women, there was no association or exposure–response relationship between coffee consumption and the risk of colorectal cancer for the entire cohort; multivariate hazard ratio for ≥ 2 cups/day versus < 1 cup/day was reported as 0.90 (95% CI, 0.73–1.11; *P* for trend, 0.31). There was also no association between coffee consumption and cancer of the rectum. However, there was a statistically significant decreased risk for consumption of ≥ 2 cups/day versus < 1 cup/day (HR, 0.56; 95% CI, 0.35–0.90; *P* for trend, 0.01) for ever smokers with advanced colon cancer, and no association among never smokers (*P* for interaction, 0.009).

Sinha et al. (2012) evaluated coffee intakes in relation to colon and rectal cancer in the NIH-AARP Diet and Health Study of 489 706 men and women. Participants who reported drinking ≥ 6 cups/day of coffee (HR, 0.74; 95% CI, 0.61–0.89; *P* for trend, < 0.001) had a lower risk of colon cancer than non-coffee drinkers, particularly of proximal tumours (HR, 0.62; 95% CI, 0.49–0.81; *P* for trend, < 0.0001). Results were similar for drinkers of predominantly caffeinated coffee. There were significant trends for both colon and rectal cancers for decaffeinated coffee drinking, but individual hazard ratios were not significant.

Dominianni et al. (2013) investigated the association between coffee intake and colorectal cancer risk among women and men participating in the PLCO Cancer Screening Trial in the USA. Increasing coffee intake was not associated with a higher risk of colorectal cancer; for consumption of ≥ 4 cups/day versus none, a hazard ratio of 1.08 (95% CI, 0.79–1.48) was reported (*P* for trend, 0.229). Associations were similar for caffeinated and decaffeinated coffee, and were consistently null by cancer site and stage.

In the JACC Study with 58 221 participants (Yamada et al. 2014), drinking > 4 cups/day of coffee versus < 1 cup/day yielded a hazard ratio of 1.79 (95% CI, 1.01–3.18) for men (*P* for trend, 0.03). However, coffee consumption was not associated with an increased risk of colon cancer among women, or with an increased risk of rectal cancer in women or men.

In the EPIC study of more than 500 000 participants in 10 European countries (Dik et al., 2014), median follow-up 11.6 years, the hazard ratio for the association between high coffee consumption (> 625 mL/day) versus none or low consumption and colorectal cancer risk was 1.06 (95% CI, 0.95–1.18; *P* for trend, 0.58) after adjustment for multiple risk factors. Associations were similar for caffeinated and decaffeinated coffee, for colon and rectal cancer, and for subsites within the colon.

Lukic et al. (2016) investigated whether consumption of boiled, filtered, or instant coffee is associated with the risk of developing cancer overall or at four specific sites within the population-based Norwegian Women and Cancer Study. No association between coffee consumption and the risk of colorectal cancer was found, with a hazard ratio of 0.98 (95% CI, 0.72–1.32) for > 7 cups/day (*P* for trend, 0.10).

A pooled analysis (Zhang et al., 2010) of primary data from 13 cohort studies evaluated the relationships between consumption of coffee, tea, and sugar-sweetened carbonated soft drinks and risk of colon cancer. Among 731 441 participants, 5604 incident cases of colon cancer were identified. Compared with non-drinkers of coffee, the pooled multivariable relative risk was 1.07 (95% CI, 0.89–1.30) for coffee consumption of > 1400 g/day (*P* for trend, 0.68). No statistically significant between-studies heterogeneity was observed for the highest category of coffee consumed (*P* for trend, > 0.20), and the associations were not modified by risk factors including sex, BMI, or physical activity (*P* for trend, > 0.05).

2.14.2 Case–control studies

Twenty-eight hospital- and population-based case–control studies in the Americas, Asia, Australia, and Europe were identified. The number of cases varied substantially from < 100 cases to > 3500 cases. Fifteen of these studies found inverse associations between coffee consumption and colorectal cancer (La Vecchia et al., 1988; Lee et al., 1989; Rosenberg et al., 1989; Benito et al., 1990; Kato et al., 1990; Baron et al., 1994; Centonze et al., 1994; Franceschi et al., 1997; Tavani et al., 1997a; Favero et al., 1998; Inoue et al., 1998; Levi et al., 1999; Woolcott et al., 2002; Wang et al., 2013b; Theodoratou et al., 2014). Three studies found null associations between coffee consumption and colorectal cancer overall (Hunter et al., 1980; Fredrikson et al., 1995; Muñoz et al., 1998). Other studies reported null associations only for

colon cancer (Kotake et al., 1995; Slattery et al., 2000) or rectal cancer (Jarebinski et al., 1989). Six studies found evidence of increased risk (Vlajinac et al., 1987; Slattery et al., 1990; Boutron-Ruault et al., 1999; Yeh et al., 2003; Kontou et al., 2013; Green et al., 2014), but in one study this was seen primarily in men (Boutron-Ruault et al., 1999). In two other studies, an increase in odds of coffee consumption was observed for for overall cancer of the large bowel (Jarebinski et al., 1988) and for rectal cancer only (Kotake et al., 1995). However, these positive studies were small in terms of the number of subjects.

2.14.3 Meta-analyses

Seven meta-analyses were available for review (Giovannucci, 1998; Je et al., 2009; Galeone et al., 2010b; Yu et al., 2011; Li et al., 2013c; Tian et al., 2013; Gan et al., 2017). In the most recent meta-analysis including both case–control studies (n = 25) and cohort studies (n = 16) published up until 2012 (Li et al., 2013c), inverse associations with coffee consumption were estimated for colorectal and colon cancer but not rectal cancer. The inverse associations were stronger in case–control studies (e.g. meta-OR, 0.85; 95% CI, 0.75–0.97 for colorectal cancer for the highest levels of consumption versus the lowest) than in cohort studies (e.g. meta-OR, 0.94; 95% CI, 0.88–1.01). Testing and graphical analysis gave no indication of publication bias. A subsequent analysis of the same studies using flexible dose–response models suggested inverse relationships for consumption of > 2 cups/day for both types of study design, although more pronounced for case–control studies (Tian et al., 2013). A later meta-analysis of only cohort studies (n = 19) reported similar results (e.g. meta-RR, 0.98; 95% CI, 0.90–1.06) for highest versus lowest consumption (Gan et al., 2017).

2.15 Cancer of the kidney

Cancer of the kidney comprises different histologic subtypes, with renal cell carcinoma accounting for 90% of cases and transitional cell carcinoma of the renal pelvis accounting for the remainder. The two subtypes likely have different etiologies; renal pelvis cancer has features in common with bladder cancer. Despite this, some studies (particularly older studies) have grouped renal cell carcinoma and renal pelvis cancer together in examining risk factors. Smoking is an established risk factor for both types of kidney cancer, which is significant as a potential confounder given the positive association between smoking and coffee consumption in many populations. Type 2 diabetes, obesity, and hypertension are also risk factors for renal cell carcinoma; this risk is significant given coffee's consistent inverse association with type 2 diabetes risk, and its positive effects on insulin levels and glucose metabolism. Ideally, studies assessing the association between coffee consumption and renal cell carcinoma should adjust for smoking and all of these metabolic factors.

2.15.1 Combined cancer of the kidney

Three cohort studies of total kidney cancer (renal cell carcinoma and renal pelvis combined) have reported data for coffee intake. A Norwegian cohort study (Jacobsen et al., 1986) of 10 517 men (which also recorded information on smoking) found a fairly strong inverse association between coffee intake and total kidney cancer; a relative risk of 0.15 for ≥ 7 cups/day versus ≤ 2 cups/day (P for trend, 0.008) was reported, but was only based on 31 cases. [Results were adjusted only for age in 10-year groups, residence, and smoking status.] Another Norwegian cohort (Stensvold & Jacobsen, 1994) of 43 000 men and women found a suggestive inverse association for total kidney cancer among men; for consumption of ≥ 7 cups/day versus ≤ 2 cups/day, a relative risk

of 0.7 [confidence intervals and *P* values were not presented] and a non-significant trend were reported, based on 30 cases. Only 13 cases were diagnosed in women in this study, and the relative risk for ≥ 5 cups/day versus < 5 cups/day was 1.2 with a non-significant trend. [These results for men and women were adjusted only for age, county of residence, and cigarettes smoked per day.] Finally, the more recent study by Hashibe et al. (2015) in the PLCO Cancer Screening Trial cohort found a non-significant hazard ratio of 0.84 (95% CI, 0.65–1.09) comparing high levels (≥ 2 cups/day) versus low levels (< 1 cup/day) of consumption. For consumption levels of ≥ 4 cups/day, the hazard ratio was 0.43 (95% CI, 0.20–0.93; *P* for trend, 0.10). This analysis included 318 cases and adjusted for sex, race, and smoking. Smoking was adjusted for in considerable detail, but BMI, type 2 diabetes, and hypertension were not considered. [The Hashibe et al. (2015) study was notable for adequate case numbers and adjusting for confounders; however, some key confounders (BMI and hypertension) were not considered. The Norway-based studies of Jacobsen et al. (1986) and Stensvold & Jacobsen (1994) were very limited by low case numbers and a lack of adjustment for risk factors other than age or smoking. All studies were limited by the study of total kidney cancer rather than separating renal cell carcinoma and renal pelvis cancer.]

A meta-analysis of coffee and urologic cancer risk (Huang et al., 2014) included results from Jacobsen et al. (1986), Stensvold & Jacobsen (1994), Washio et al. (2005) [a cohort study of fatal renal cell carcinoma, considered non-informative by the Working Group due to lack of control for smoking], and Lee et al. (2006), a study of renal cell carcinoma risk (discussed in Section 2.15.3 below). Coffee consumption was not associated with risk of cancer of the kidney in this meta-analysis, with a meta-relative risk of 0.95 (95% CI, 0.56–1.59) per increment of 2 cups/day. [The strengths of this meta-analysis included the dose–response meta-analysis. It was however limited by combining studies of total kidney cancer and renal cell carcinoma only, and combining studies of incidence and mortality.]

2.15.2 Renal pelvis cancer

Five case–control studies of coffee drinking and renal pelvis cancer (or renal pelvis plus ureter cancer) were identified. Two were considered non-informative due to a lack of control for smoking (Schmauz & Cole, 1974; Armstrong et al., 1976). Another study by Wakai et al. (2004) was considered non-informative for renal pelvis cancer as it included mainly bladder cancer cases and only 5 cases of renal pelvis cancer.

The remaining two studies were US population-based case–control studies; one was based in Minneapolis–St Paul (McLaughlin et al., 1983) and the other in Los Angeles County (Ross et al., 1989). With 74 cases, McLaughlin et al. found no association between coffee intake and renal pelvis cancer risk in either men or women, adjusting for smoking, with an odds ratio for ≥ 7 cups/day versus none of 1.1 for men (95% CI, 0.2–8.7) and 0.4 for women (95% CI, 0.03–4.0). With 187 cases, Ross et al. found a suggestion of a positive association between coffee intake and renal pelvis cancer risk when smoking and several other risk factors were adjusted for, with an odds ratio of 1.8 for ≥ 7 cups/day compared with none and a *P* value for trend of 0.11 [confidence intervals for the relative risk were not presented]. [Both studies benefited from the use of population-based controls. They were however disadvantaged by limited precision and limited adjustment for confounders.]

2.15.3 Renal cell carcinoma

Twelve case–control studies of the association between coffee consumption and renal cell carcinoma were identified. Four were considered non-informative due to a lack of control

for smoking (Armstrong et al., 1976; Goodman et al., 1986; Yu et al., 1986; Talamini et al., 1990), and one (Bravi et al., 2007b) was not considered as a more detailed report (Montella et al., 2009) from the same case–control study was available. An additional study (McCredie et al., 1988) was considered non-informative as no analytical results were presented for coffee, only a statement that there was no association.

Of the remaining case–control studies, two were hospital-based and three were population-based. The hospital-based case-control studies (Benhamou et al., 1993; Montella et al., 2009) found no associations between coffee intake and risk of renal cell carcinoma. Of the population-based case–control studies, one in Denmark (Mellemgaard et al., 1994) found a significant inverse association with renal cell carcinoma risk in men, but not in women; for > 8 cups/day versus < 2 cups/day, the odds ratio was 0.4 (95% CI, 0.2–1.0; *P* for trend, 0.02) for men and 1.5 (95% CI, 0.5–4.8; *P* for trend, 0.07) for women. A study in Sweden (Mucci et al., 2004) found association for the highest versus lowest quartile with an odds ratio of 0.7 (95% CI, 0.4–1.1). A large study in Canada (Hu et al., 2009) with 1138 cases and 5039 controls found a significant positive association with an odds ratio of 1.33 (95% CI, 1.07–1.66) for those consuming > 2.5 cups/day compared with < 0.5 cups/day, and a significant trend across categories; for an increment of 1 cup/day, an odds ratio of 1.06 (95% CI, 1.02–1.10; *P* for trend, 0.006) was reported. All three studies adjusted for smoking and BMI along with other covariates. [These studies benefited from adjustment for both smoking and BMI; however, all except for Hu et al. had low case numbers and wide confidence intervals.]

There were four cohort studies of the association between coffee drinking and risk of renal cell carcinoma. One cohort study on the risk of fatal renal cell carcinoma was considered non-informative due to a lack of control for smoking (Washio et al., 2005). Another of these was a pooled analysis of individual-level data from 13 prospective studies (Lee et al., 2007b). This analysis included 1478 incident renal cell cancer cases, and yielded a hazard ratio of 0.84 (95% CI, 0.67–1.05; *P* for trend, 0.22) among individuals consuming ≥ 3 cups/day of coffee compared with < 1 cup/day (Lee et al., 2007b). The inverse association for coffee was statistically significant among women (HR, 0.71; 95% CI, 0.53–0.97; *P* for trend, 0.07) but was not observed among men (RR, 1.00; 95% CI, 0.73–1.37; *P* for trend, 0.83), although the test for interaction was not significant. Smoking, BMI, hypertension, and alcohol intake, among other possible confounders, were adjusted for across studies. In an analysis stratified by smoking status, there was a significant inverse association among never smokers for an increment of 1 cup/day (RR, 0.91; 95% CI, 0.84–0.98) and no association among former (RR, 0.98; 95% CI, 0.90–1.06) and current (RR, 0.98; 95% CI, 0.90–1.08) smokers. [The strengths of this study were the large number of cases and adequate adjustment for covariates including smoking, BMI, and hypertension.]

A separate publication (Lee et al., 2006) from the NHS and HPFS studies, both of which were included in the pooled analysis, was also considered informative as it was based on updated coffee intake information collected every 4 years rather than simply baseline information. Follow-up was 20 years for NHS and 14 years for HPFS. The pooled hazard ratio across the two cohorts, based on 248 cases, was 0.84 (95% CI, 0.54–1.30; *P* for trend, 0.41) for ≥ 3 cups/day compared with < 1 cup/month. [This study benefited from its prospective design, multiple assessments of coffee intake over time, and complete adjustment for confounders. The number of cases was only 248 however, even with two large cohorts combined.]

Two other cohort studies were not included in the pooled analysis (Nilsson et al., 2010; Allen et al., 2011). A Norwegian cohort (Nilsson et al., 2010) of 64 604 men and women with median

follow-up of 6 years and 56 cases of renal cell carcinoma found a strong inverse association between total coffee consumption (filtered and boiled coffee combined); a hazard ratio for drinking coffee ≥ 4 occasions/day compared with < 1 occasion/per day of 0.30 (95% CI, 0.11–0.79; *P* for trend, 0.009) was reported. Results were adjusted for age, sex, BMI, smoking, education, and physical activity. [The strengths of this study included its prospective design. It was however limited by the low number of cases and lack of clarity regarding occasions/day versus cups/day.]

A cohort of 779 369 women in the UK (Allen et al., 2011) including 588 cases of renal cell carcinoma (average follow-up 5.2 years) found no association between coffee intake and risk, adjusting for region, socioeconomic status, BMI, and smoking. The relative risk per drink per day was 0.98 (95% CI, 0.94–1.02; *P* for trend, 0.4). [This study benefited from being a very large prospective cohort with a large number of cases. The results were not adjusted for hypertension, however. The Working Group also noted that results as presented were difficult to interpret.]

2.16 Malignant melanoma

Thirteen pertinent studies – seven cohort studies and six case–control studies – reporting results for an association between coffee consumption and risk of cutaneous malignant melanoma were available for review. Most of the studies presented relative risks for consumption of coffee overall, others for caffeinated and decaffeinated coffee separately, and a few presented results for caffeinated coffee only. Where available, the results for total coffee are provided in the following.

Of the cohort studies, one early small study (19 cases) reported a non-significantly elevated relative risk (2.63) [95% CI not given] for ≥ 7 cups/day versus ≤ 2 cups/day after adjustment for age, sex, and residence (*P* for trend, 0.16) (Jacobsen et al., 1986). Three others presented largely null associations (Paffenbarger et al., 1978; Nilsson et al., 2010; Wu et al., 2015a). Another three cohort studies reported inverse associations in part or overall with coffee intake. In a 12-year follow-up of over 50 000 Norwegians enrolled in a cardiovascular screening programme (Veierød et al., 1997), the adjusted incidence rate ratio (IRR) among women was 0.4 (95% CI, 0.2–0.9) for ≥ 7 cups/day versus ≤ 2 cups/day (*P* for trend, < 0.01), while the corresponding incidence rate ratio for men was 1.5 (95% CI, 0.5–4.6). Another cohort study included women from the NHS and NHS-II and men from the HPFS after 20–32 years of follow-up (Wu et al., 2015b). The adjusted pooled hazard ratio for women and men in all three studies for > 2 cups/day caffeinated coffee vs never was 0.85 (95% CI, 0.66–1.11; *P* for trend, 0.18). The corresponding hazard ratio in the two women's cohorts combined was 0.76 (95% CI, 0.64–0.89; *P* for trend, 0.001), and a hazard ratio of 1.1 (95% CI, 0.86–1.3) was reported for men (*P* for trend, 0.55). The other cohort study reported a hazard ratio of 0.80 (95% CI, 0.68–0.93) for ≥ 4 cups/day versus no coffee (*P* for trend, 0.01) in a large cohort of non-Hispanic white men and women in the US (Loftfield et al., 2015). Wu et al. (2015a, b) and Loftfield et al. (2015) examined associations between risk of cutaneous malignant melanoma and caffeinated and decaffeinated coffee separately, and reported null associations.

Of the six case–control studies, four reported no association (Gallagher et al., 1986; Green et al., 1986; Holman et al., 1986; Naldi et al., 2004). Two reported reduced risks of cutaneous malignant melanoma with increased coffee consumption. In the first of these, the adjusted odds ratio for high coffee intake (not defined) was 0.7 (95% CI, 0.5–1.0; *P* for trend, 0.02) (Osterlind et al., 1988), while the second reported an odds ratio of 0.46 (95% CI, 0.31–0.68) for ≥ 7 cups/week versus < 7 cups/week (Fortes et al., 2013).

Three meta-analyses of this association were available (Wang et al., 2016; Liu et al., 2016;

Yew et al., 2016). The most comprehensive meta-analysis, judged to be highest in quality by the Working Group, included 12 studies with a total of 832 956 participants and 7140 cases of cutaneous malignant melanoma (Wang et al., 2016). The summary relative risk for the highest versus lowest category of total coffee consumption was 0.80 (95% CI, 0.69–0.93); a linear inverse dose–response relationship was evident, where the meta-relative risk decreased by 3% with each additional 1 cup/day. Sex-specific summary relative risks for the highest versus lowest category of total coffee consumption were 0.75 (95% CI, 0.63–0.89) for women and 1.11 (95% CI, 0.91–1.36) for men.

[The strengths of the studies on cutaneous malignant melanoma included large size, long follow-up periods, pathological confirmation of cases, adjustment for relevant confounders (including sun-related variables in the three most recent cohort studies and all case–control studies), updated data on coffee intake in most cohort studies, sex-specific analyses, and investigation of exposure–response associations. However, the metric of coffee intake varied among studies, and the reference category in some studies included people who drank 2 cups/day of coffee, which could lead to an underestimation of an association. The four earliest cohort studies did not adjust for sun-related variables.]

One case–control study of the association between coffee consumption and incidence of uveal melanoma was identified (Holly et al., 1990). After adjustment for host factors and sun exposure, an increased risk of this cancer was observed among coffee drinkers: the odds ratio for ≥ 6 cups/day was 2.32 (95% CI, 1.53–3.53; *P* for trend, < 0.001). However, while increased odds ratios were seen for both sexes separately, a significant increase was seen only in women. There was a higher than usual proportion of non-coffee drinkers among women in the control group.

2.17 Non-melanoma cancer of the skin

Three cohort studies and three case–control studies have reported on the association between coffee consumption and risk of non-melanoma skin cancer.

Two cohort studies found evidence of inverse associations. The first reported a relative risk for non-melanoma skin cancer overall of 0.56 [95% CI not given] for ≥ 7 cups/day versus ≤ 2 cups/day (*P* for trend, 0.01) (Jacobsen et al., 1986). The second reported a reduction in risk of basal cell carcinoma only, with adjusted relative risks of 0.79 (95% CI, 0.74–0.85; *P* for trend, < 0.0001) in women and 0.90 (95% CI, 0.80–1.01; *P* for trend, 0.003) in men for > 3 cups/day caffeinated coffee versus < 1 cup/month (Song et al., 2012). A third cohort study found no association between intake of caffeinated or decaffeinated coffee and the incidence of basal or squamous cell carcinoma (Miura et al., 2014).

The three case–control studies (Corona et al., 2001; Milán et al., 2003; Ferrucci et al., 2014) investigated basal cell carcinoma only, and did not report any significant positive or inverse association with coffee drinking.

[The strengths of the studies of non-melanoma skin cancer included large sample size, long cohort follow-up, pathological confirmation of cases, adjustment for relevant confounders (including sun-related variables in cohort studies published since 2010 and all case–control studies), and investigation of exposure–response associations. However, the methods of exposure assessment differed among studies and two hospital-based case–control studies used patients with other dermatological conditions as controls.]

2.18 Adult cancer of the brain

Four prospective cohort studies and two hospital-based case–control studies reported findings for adult brain or central nervous system

tumours in relation to coffee consumption. One cohort study (Efird et al., 2004) reported a positive association of glioma with consumption of ≥ 7 cups/day of coffee (OR, 1.7; 95% CI, 0.8–3.6; *P* for trend, 0.17). A second study (Holick et al., 2010) reported a reduced odds ratio for glioma among consumers of ≥ 4 cups/day, (OR 0.80, 95% CI, 0.54–1.17; *P* for trend, 0.51) with no evidence of a dose–response relationship. The two other cohort studies reported no association of glioma or meningioma with coffee intake (Michaud et al., 2010; Dubrow et al., 2012). Neither of the case–control studies found any association (Burch et al., 1987; Hochberg et al., 1990). A meta-analysis of these six studies concluded there was no association between coffee intake and brain tumour (glioma) risk, with a summary odds ratio of 1.01 (95% CI, 0.83–1.22) for the highest versus lowest levels of intake (Malerba et al., 2013b).

2.19 Adult haematopoietic cancers

The association between coffee consumption and several adult haematopoietic cancers has been assessed in a single cohort study (Ma et al., 2010) and eight reports from five case–control studies (Oleske et al., 1985; Franceschi et al., 1989; Tavani et al., 1994, 1997b; Chiu et al., 2008; Balasubramaniam et al., 2013a, b; Parodi et al., 2016).

Ma et al. (2010) assessed the etiological role of coffee drinking in acute myeloid leukaemia in the US-based NIH-AARP Diet and Health Study during 1995–2003. Significant inverse associations were observed between AML and and tertile of coffee intake, with risk estimates of approximately 0.6 in in each tertile and no evidence of dose-response (*P* for trend, 0.24).

Of the five case–control studies that assessed adult leukaemia or non-Hodgkin lymphoma (NHL), including hairy cell leukaemia (HCL), multiple myeloma (MM), and chronic lymphocytic leukaemia (CLL), odds ratios were < 1 in a hospital-based study of leukaemia and NHL in India (Balasubramaniam et al., 2013a, b), in population-based studies of NHL and HCL in the USA (Oleske et al., 1985; Chiu et al., 2008), and in an investigation of lymphoid and myeloid cancers in Italy (Parodi et al., 2016). A hospital-based case–control study in a different region of Italy reported non-significantly increased risk of multiple myeloma, but not other NHL or Hodgkin lymphoma, among higher coffee consumers (Franceschi et al., 1989; Tavani et al., 1994, 1997b). [In general, the assessment of coffee consumption in these studies was crude, that is, via an unvalidated questionnaire.]

2.20 Other cancers

Systematic searches for epidemiological studies that reported associations between coffee drinking and cancer outcomes identified studies of several other cancer sites. Most were case–control studies that reported associations for a wide range of exposures and risk factors, and were not specifically focused on coffee consumption. The number of studies available for each of these cancers was small.

2.20.1 Cancer of the thyroid

For thyroid cancer, case–control studies on potential risk factors in Germany, Greece, and Japan reported inverse associations with coffee drinking (Linos et al., 1989; Takezaki et al., 1996b; Frentzel-Beyme & Helmert, 2000), while a similar study in the USA reported no association (Mack et al., 2002). A pooled analysis of nine thyroid cancer case–control studies from several countries (Mack et al., 2003), most of which did not report data for coffee consumption in the original publications, found no association with coffee drinking (RR, 0.9; 95% CI, 0.8–1.1). A cohort study of the relationship between thyroid cancer and coffee consumption in Japan reported no association in women and a non-statistically

significant positive association (RR, 1.18) among men drinking ≥ 1 cup/day (Michikawa et al., 2011).

2.20.2 Cancer of the vulva

Three hospital-based case–control studies on risk factors for cancer of the vulva reported on associations with coffee consumption. Two studies in the USA reported statistically significant increased risks (OR, 1.72–2.42) for women drinking > 4–5 cups/day of coffee (Mabuchi et al.,1985a; Sturgeon et al., 1991), while a study in Italy reported no association with regular coffee drinking (Parazzini et al., 1995).

2.20.3 Cancer of the breast in men

The association between coffee drinking and breast cancer in men was examined in three studies of dietary and lifestyle risk factors in the USA and Canada. Two studies reported inverse associations between the amount of coffee consumed and the risk of breast cancer in men; these associations were statistically significant for coffee consumption overall in a Canadian study (Johnson et al., 2002) and for total caffeinated coffee consumption in a study in the USA (Rosenblatt et al., 1999). In another study in the USA, Mabuchi et al. (1985b) reported no difference in the proportions of coffee drinkers among cases and controls, but measures of relative risk were not reported.

2.20.4 Soft tissue sarcoma

A hospital-based case–control study of risk factors for soft tissue sarcoma in Italy reported no association with frequency of coffee consumption (Tavani et al., 1997b).

2.20.5 Cancer of the testes

A prospective study of pregnant women in the USA found an inverse, non-statistically significant association between mothers' coffee drinking during pregnancy and development of testicular cancer in their sons (Mongraw-Chaffin et al., 2009).

2.21 All cancers combined

The association between coffee consumption and the occurrence of all cancers combined has been investigated in a number of prospective cohort studies from Europe, Japan, and North America. Most studies found no association between coffee consumption and incidence (e.g. Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Nilsson et al., 2010; Floegel et al., 2012; von Ruesten et al., 2013; Hashibe et al., 2015) or mortality (e.g. Andersen et al., 2006; Happonen et al., 2008; Sugiyama et al., 2010; Tamakoshi et al., 2011; Gardener at al., 2013; Löf et al., 2015; Saito et al., 2015) of all cancers combined, with no exposure–response trends and no statistically significant overall increase or decrease in risk among the heaviest consumers. One study reported non-significantly increased mortality from all cancers among men who drank ≥ 6 cups/day of coffee with a significant trend (HR, 1.08; 95% CI, 0.98–1.19; *P* for trend, 0.02), but no association among women (Freedman et al., 2012). Another study that found no association with cancer mortality in the full cohort reported increased mortality in a subgroup of women aged > 50 years consuming > 5 cups/day of coffee (RR, 1.40; 95% CI, 1.05–1.89) (Löf et al., 2015). A statistically significant inverse exposure–response trend (*P* for trend, 0.01) was reported for cancer mortality among women, but not men, in a study by Tamakoshi et al. (2011).

Two meta-analyses of prospective studies estimated null associations between coffee consumption and mortality from all cancers combined (Malerba et al., 2013a; Crippa et al., 2014).

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