2.6   Breast cancer

Overall, more than 100 epidemiological studies—two thirds case–control and one third cohort—have evaluated the association between the consumption of alcoholic beverages and the risk for breast cancer. In addition, two pooled analyses, the largest of which included data from more than 50 studies, have been conducted. For ease of presentation, the data from the individual studies that were included in this pooled analysis are not presented in Tables 2.28 or 2.29, except for studies that examined detailed exposure effects, such as duration of alcoholic beverage consumption, that were not considered in the pooled analysis.

2.6.1   *Pooled and meta-analyses*

The pooling of data from many epidemiological studies permits the use of uniform definitions across studies and reduces the inevitable statistical variability in the findings from one study to another. This is particularly important when the associated risks are relatively small and individual studies lack statistical power. Hamajima *et al.*

(2002) (The Collaborative Group on Hormonal Factors on Breast Cancer) collated and re-analysed individual data from 53 studies on 58 515 women who had breast cancer, which constituted most of the evidence available worldwide at that time. Results from this pooled analysis showed a linear increase in risk for breast cancer with increasing levels of alcoholic beverage consumption, with a relative risk of 1.46 (95% CI, 1.34–1.60) for women who drank ≥ 45 g alcohol per day (median, 58 g per day) compared with non-drinkers. This corresponds to an increase of 7.1% (95% CI, 5.5–8.7%) per 10 g per day (Table 2.28; see Figure 2.1). The results were consistent across studies and between cohort and case–control studies included in the analysis (Figure 2.2).

A previous meta-analysis of 38 case–control and cohort studies (Longnecker, 1994), most of which were included in the Collaborative Group analysis, and a pooled analysis of six cohort studies, based on 4330 incident cases of breast cancer (Smith-Warner *et al.*, 1998), reported results consistent with the findings of the Collaborative Group (Hamajima *et al.*, 2002). The latter study showed a 9% increase in risk per 10 g intake of alcohol per day (8% after correction for measurement error), which was adjusted for a wide range of potential confounding factors (Smith-Warner *et al.*, 1998).

2.6.2   *Additional cohort studies*

Two cohort studies were conducted among women who had a high intake of alcoholic beverages; both were conducted in Sweden and reported a significant increase in incidence rates for breast cancer among alcoholics compared with national incidence rates (Sigvardsson *et al.*, 1996; Kuper *et al.*, 2000b) (Table 2.29). However, neither of these studies provided information on individual exposures, or adjusted for potential confounders.

The majority of the 21 additional cohort studies conducted in the general population also showed an increase in risk for breast cancer with increased alcoholic beverage consumption (Table 2.30). The largest of these studies, conducted by the European Prospective Investigation into Cancer and Nutrition (EPIC) and based on 4300 cases, reported a significant 13% increase in risk for breast cancer for intakes of ≥ 20 g alcohol per day, which corresponds to an increase in risk of 3% per 10 g intake of alcohol per day (95% CI, 1–5%) (Tjønneland *et al.*, 2007).

2.6.3   *Additional case–control studies*

The majority of the 35 case–control studies that were not included in the pooled analyses have reported positive associations with increasing alcoholic beverage intake, which were statistically significant in 14 studies (Table 2.31).

2.6.4   *Measurements of alcoholic beverage intake*

Taken together, all of the results from these studies suggest that low to moderate alcoholic beverage intake (i.e. in the order of one drink per day) is associated with
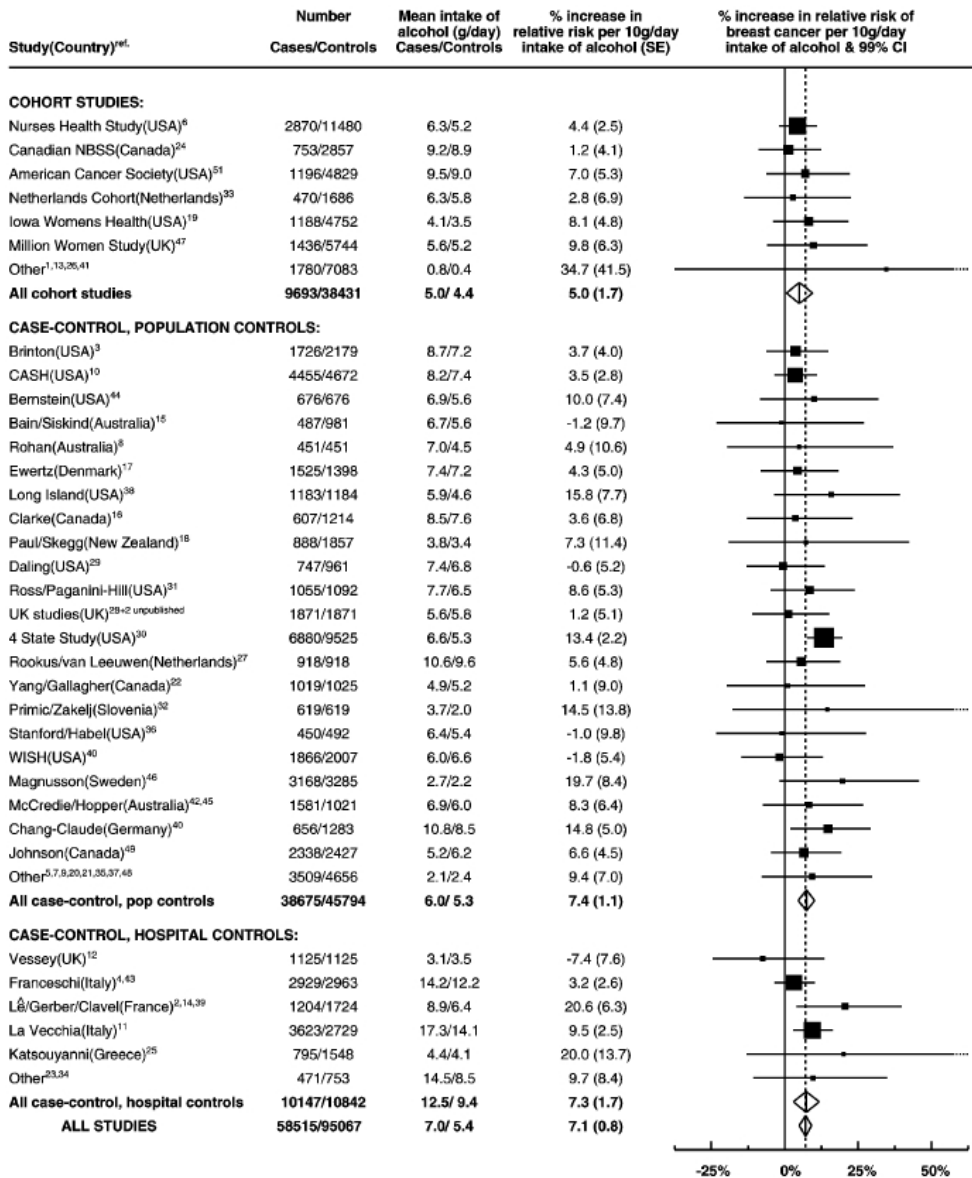
Figure 2.1. Relative risk for breast cancer in relation to reported alcoholic beverage consumption (adjusted by study, age, parity, age at first birth and tobacco smoking).
Pooled analysis of data from 53 studies that included 58 515 women with breast cancer

Alcohol consumption, g/day (~ number of drinks daily)
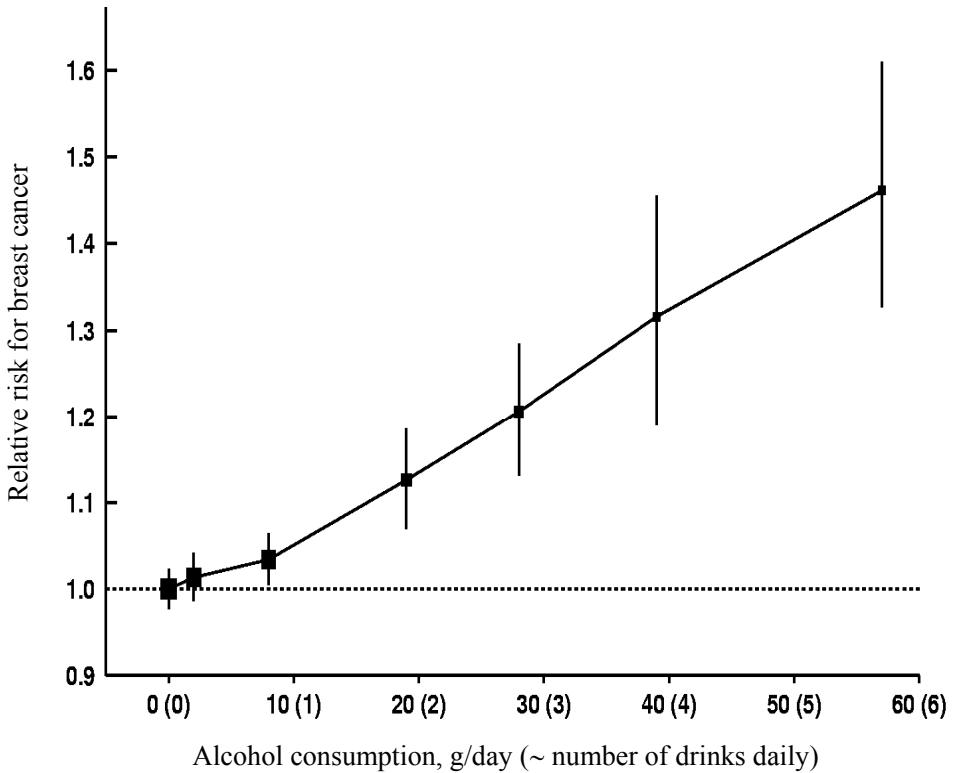
From Hamajima *et al.* (2002)

Figure 2.2. Details of and results from studies on the relation between alcohol consumption and breast cancer. Relative risks are stratified by age, parity, age at first birth and smoking history.

Study(Country)[ref.]	Number Cases/Controls	Mean intake of alcohol (g/day) Cases/Controls	% increase in relative risk per 10g/day intake of alcohol (SE)	% increase in relative risk of breast cancer per 10g/day intake of alcohol & 99% CI
COHORT STUDIES:				
Nurses Health Study(USA)[6]	2870/11480	6.3/5.2	4.4 (2.5)	
Canadian NBSS(Canada)[24]	753/2857	9.2/8.9	1.2 (4.1)	
American Cancer Society(USA)[51]	1196/4829	9.5/9.0	7.0 (5.3)	
Netherlands Cohort(Netherlands)[33]	470/1686	6.3/5.8	2.8 (6.9)	
Iowa Womens Health(USA)[19]	1188/4752	4.1/3.5	8.1 (4.8)	
Million Women Study(UK)[47]	1436/5744	5.6/5.2	9.8 (6.3)	
Other[1,13,26,41]	1780/7083	0.8/0.4	34.7 (41.5)	
All cohort studies	**9693/38431**	**5.0/ 4.4**	**5.0 (1.7)**	
CASE-CONTROL, POPULATION CONTROLS:				
Brinton(USA)[3]	1726/2179	8.7/7.2	3.7 (4.0)	
CASH(USA)[10]	4455/4672	8.2/7.4	3.5 (2.8)	
Bernstein(USA)[44]	676/676	6.9/5.6	10.0 (7.4)	
Bain/Siskind(Australia)[15]	487/981	6.7/5.6	-1.2 (9.7)	
Rohan(Australia)[8]	451/451	7.0/4.5	4.9 (10.6)	
Ewertz(Denmark)[17]	1525/1398	7.4/7.2	4.3 (5.0)	
Long Island(USA)[38]	1183/1184	5.9/4.6	15.8 (7.7)	
Clarke(Canada)[16]	607/1214	8.5/7.6	3.6 (6.8)	
Paul/Skegg(New Zealand)[18]	888/1857	3.8/3.4	7.3 (11.4)	
Daling(USA)[29]	747/961	7.4/6.8	-0.6 (5.2)	
Ross/Paganini-Hill(USA)[31]	1055/1092	7.7/6.5	8.6 (5.3)	
UK studies(UK)[28+2 unpublished]	1871/1871	5.6/5.8	1.2 (5.1)	
4 State Study(USA)[30]	6880/9525	6.6/5.3	13.4 (2.2)	
Rookus/van Leeuwen(Netherlands)[27]	918/918	10.6/9.6	5.6 (4.8)	
Yang/Gallagher(Canada)[22]	1019/1025	4.9/5.2	1.1 (9.0)	
Primic/Zakelj(Slovenia)[32]	619/619	3.7/2.0	14.5 (13.8)	
Stanford/Habel(USA)[36]	450/492	6.4/5.4	-1.0 (9.8)	
WISH(USA)[40]	1866/2007	6.0/6.6	-1.8 (5.4)	
Magnusson(Sweden)[46]	3168/3285	2.7/2.2	19.7 (8.4)	
McCredie/Hopper(Australia)[42,45]	1581/1021	6.9/6.0	8.3 (6.4)	
Chang-Claude(Germany)[49]	656/1283	10.8/8.5	14.8 (5.0)	
Johnson(Canada)[48]	2338/2427	5.2/6.2	6.6 (4.5)	
Other[5,7,9,20,21,35,37,48]	3509/4656	2.1/2.4	9.4 (7.0)	
All case-control, pop controls	**38675/45794**	**6.0/ 5.3**	**7.4 (1.1)**	
CASE-CONTROL, HOSPITAL CONTROLS:				
Vessey(UK)[12]	1125/1125	3.1/3.5	-7.4 (7.6)	
Franceschi(Italy)[4,43]	2929/2963	14.2/12.2	3.2 (2.6)	
Lê/Gerber/Clavel(France)[2,14,39]	1204/1724	8.9/6.4	20.6 (6.3)	
La Vecchia(Italy)[11]	3623/2729	17.3/14.1	9.5 (2.5)	
Katsouyanni(Greece)[25]	795/1548	4.4/4.1	20.0 (13.7)	
Other[23,34]	471/753	14.5/8.5	9.7 (8.4)	
All case-control, hospital controls	**10147/10842**	**12.5/ 9.4**	**7.3 (1.7)**	
ALL STUDIES	**58515/95067**	**7.0/ 5.4**	**7.1 (0.8)**	

-25% 0% 25% 50%

Table 2.28 Pooled and meta-analyses of female breast cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Longnecker (1994)	Meta-analysis of 38 case–control and cohort studies	Varied	*Alcohol intake (drinks/day)* Non-drinker 1 2 3	Not stated	 1.0 1.11 (1.07–1.16) 1.24 (1.15–1.34) 1.38 (1.23–1.55)	As defined per study	Variation across studies found
Smith-Warner *et al.* (1998), pooling project	Pooled analysis of six cohort studies; 322 647 women followed up for up to 11 years; 4335 cases of invasive breast cancer identified	Self-administered questionnaire	*Average intake (g/day)* Non-drinker >0–<1.5 1.5–4.9 5.0–14.9 15–29.9 30–59.9 ≥60 *p* for trend *Per 10 g/day* Uncorrected Corrected Beer Wine Spirits	 1462 680 882 727 360 194 30	 1.0 1.07 (0.96–1.19) 0.99 (0.90–1.10) 1.06 (0.96–1.17) 1.16 (0.98–1.38) 1.41 (1.18–1.69) 1.31 (0.86–1.98) <0.001 1.09 (1.04–1.13) 1.08 (1.0–1.16) 1.11 (1.04–1.19) 1.05 (0.98–1.12) 1.05 (1.01–1.10)	Age at menarche, parity, age at first birth, menopausal status, history of benign breast disease, hormone replacement therapy use, oral contraceptive use, family history, smoking, education, body mass index, height, fat intake, fibre intake, energy intake	Correction for measurement error made little difference to the estimate; similar associations found for beer, wine and spirits; no difference by subgroup of menopausal status, family history, hormone-replacement therapy use or body mass index

Table 2.28 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Bagnardi *et al.* (2001)	Meta-analysis of 49 studies (12 cohort, 37 case–control, with a total of 44 033 cases)	Varied	*Alcohol intake (g/day)* 25 50 100	244 033	 1.31 (1.27–1.36) 1.67 (1.56–1.78) 2.71 (2.33–3.08)	As per study	Significant heterogeneity between the studies
Hamajima *et al.* (2002), Collaborative Group on Hormonal Factors in Breast Cancer	Pooled analysis of 53 case–control and cohort studies; 58 515 invasive breast cancers; 95 067 controls	Varied	*Alcohol intake (g/day)* 0 <5 5–14 15–24 25–34 34–44 ≥45 Increase per 10 g/day	58 515	Relative risk (floated SE) 1.0 (0.012) 1.01 (0.014) 1.03 (0.015) 1.13 (0.028) 1.21 (0.036) 1.32 (0.059) 1.46 (0.060) 7.1% (SE, 0.8%)	Study, age, parity, age at first birth, smoking	No differences by subgroup of age at diagnosis, race, family history, menopausal status, parity, age at first birth, breastfeeding, education, age at menarche, height, weight, hormone replacement therapy use, oral contraceptive use, smoking
	Pooled analysis of 42 case–control studies		*Increase per 10 g/day* Population controls Hospital controls	 38 675 10 147	 7.4% (SE, 1.1%) 7.3% (SE, 1.7%)		
	Pooled analysis of 11 cohort studies		Increase per 10 g/day	9 693	5.0% (SE, 1.7%)		

CI, confidence interval; SE, standard error

Table 2.29 Cohort studies of breast cancer and alcoholic beverage consumption among special populations

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Standardized incidence ratio (95% CI)	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden, Alcoholics	Analytical cohort of 15 508 alcoholics (identified via Temperence Board records) in 1944–77; comparison group of 15 500 women, matched by age and region (identified via population register); follow-up not stated; 268 cases identified through cancer registry	Alcoholics	Comparison group (expected) Alcoholics (observed)	191 268	1.0 1.4 (1.2–1.7)	Age, region	Excluded ~6000 older women with no identification number; large changes in alcohol availability and attitudes during follow-up; not adjusted for potential confounders; no individual exposure data
Kuper *et al.* (2000b), Sweden, Hospital Discharge Records for Alcoholism	Analytical cohort of 36 856 women diagnosed with alcoholism from hospital discharge data, 1965–95; compared with national incidence rates; matched by age, sex, calendar time; excluding first year of follow-up; 514 cases identified through cancer registry	Hospital discharge related to alcoholism	National rates (expected) Alcoholics (observed)	Not stated 514	1.0 1.15 (1.05–1.25)	Age, sex, calendar time	No individual exposure information; no adjustment for potential confounders; no association found with age at diagnosis or menopausal status

CI, confidence interval

Table 2.30 Cohort and nested case–control studies of breast cancer and alcoholic beverage consumption in the general population

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Schatzkin *et al.* (1987), USA, NHANES I Epidemiologic Follow-up Study	Analytical cohort of 7188 women, aged 25–74 years; recruited 1971–75; median follow-up, 10 years; 121 cases identified through hospital records or death certificates	Interviewer-administered questionnaire	*Intake (g/day)* Non-drinker Any >0–1.2 1.3–4.9 ≥5	57 64 25 19 20	1.0 1.5 (1.1–2.2) 1.4 (0.9–2.3) 1.5 (0.9–2.6) 1.6 (1.0–2.7)	Age	Results presented for age-adjusted relative risks only; multivariate adjustment gave similar results, but based on fewer numbers (complete-case analysis); risk for any drinking versus none higher among younger versus older women, pre- versus post-menopausal women and lean versus overweight women; no differences in risk by subgroup of age at first birth, parity, age at menarche, family history, fat intake, smoking

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dupont & Page (1985), USA, Nashville hospitals (retrospective cohort study)	Analytical cohort study of 3303 women with benign breast disease (100% histological confirmation); aged >20 years; recruited 1958-68 (response rate 84%); follow-up for a median of 17 years; 135 cases identified from death certificates and verified by pathology records	Self-administered questionnaire to patients or their next-of-kin; or via telephone interview.	*Alcohol* No Yes	76 37	1.3 (1.1–1.7) 1.7 (1.2–2.3)	Age, length of follow-up	Risk compared to women in the Third National Cancer Survey (Atlanta); mortality only; cohort of women with benign breast disease
Garfinkel *et al.* (1988), USA, American Cancer Society	Analytical cohort of 581 321 women across the USA, 1959–60, aged ≥30 years; mortality follow-up until 1972; 2933 deaths identified from death certificates	Self-administered questionnaire	*Intake (drinks/ day)* None Occasional 1 2 3 4 5 ≥6	2334 153 236 110 45 23 12 20	1.00 1.00 (0.82–1.13) 1.18 (1.03–1.36) 1.06 (0.86–1.30) 1.28 (0.95–1.74) 1.36 (0.90–2.07) 2.10 (1.18–3.72) 1.60 (1.00–2.56)	Age, education, age at first birth, family history, meat intake, smoking	Based on mortality only

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Simon *et al.* (1991), USA, Tecumseh Community Health Study	Analytical cohort of 1954 women recruited in 1959–60, aged ≥21 years years; follow-up for 28 years; 87 self-reported cases verified by pathology and medical records	Interviewer-administered questionnaire	Overall *No. of drinks/ day* Never Former 0–<1 1–1.9 ≥2	87	1.0 0.93 (0.40–2.18) 1.08 (0.64–1.82) 1.23 (0.49–3.10) 1.12 (0.25–5.01)	Age, body mass index, subscapular and triceps skinfold measurements, education, smoking, family history, age at menarche, parity, age at first birth	No difference in risk by menopausal status (but low numbers)
Høyer & Engholm (1992), Denmark, Glostrup Population Study	Analytical cohort of 5207 women recruited 1964–86, aged 30–80 years; follow-up until 1989; 51 cases identified through registry	Self-administered questionnaire	*Intake (drinks/ week)* 0 1–3 4–8 ≥9 *p* for trend	51	1.0 0.7 (0.3–1.6) 1.3 (0.7–2.5) 0.8 (0.3–2.0) 0.2	None stated	

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Boice *et al.* (1995), USA, American Registry of Radiologic Technologists	Nested case–control study of 79 016 women recruited 1926–82, aged 23–90 years; follow-up for mean of 29 years; 528 cases matched with 2628 controls on age, year of diagnosis, follow-up time	Self-administered questionnaire	*Intake (drinks/ week)* None <1 1–6 7–13 ≥14 Unknown	133 183 135 57 13 7	1.0 0.86 (0.67–1.10) 0.91 (0.69–1.20) 0.86 (0.61–1.22) 2.12 (1.06–4.27) 1.91 (0.74–4.92)	Age at menarche, age at menopause, age at first birth, family history, breast biopsy	

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Holmberg *et al.* (1995); Suzuki *et al.* (2005), Sweden, Swedish Mammography Cohort	Holmberg *et al.* (1995): nested case–control study of screening cohort, recruited 1987–90, aged 40–70 years; 380 cases ascertained through pathology departments and screening programme (response rate, 73%); 525 controls matched by age, date of diagnosis, region (response rate, 86%)	Self-administered questionnaire	Never Ever *Intake (g/day)* Never <0.76 0.76–2 ≥2	71 205 71 54 79 72	1.0 1.7 (0.2–2.4) 1.0 1.2 (0.8–1.8) 1.9 (1.2–2.9) 1.6 (1.0–2.4)	Family history, parity, age at first birth, education, body mass index	Stronger association for ever versus never drinking in women >50 versus <50 years; risk increased with increasing duration of drinking; no significant association with age at first started drinking

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Holmberg *et al.* (1995); Suzuki *et al.* (2005) (contd)	Suzuki *et al.* (2005): analytical cohort of 51 847 women, recruited 1987–90, aged 55–70 years;; follow-up until 2004 through cancer registry, verified by pathology and medical records; 1284 cases		*Intake in last 6 months (based on intake in 1987 and 1997; g/day)* None <3.4 3.4–9.9 ≥10 *p* for trend	314 476 343 151	1.0 1.08 (0.94–1.25) 1.10 (0.94–1.29) 1.43 (1.16–1.76) 0.012	Age, body mass index, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, oral contraceptive use, hormone replacement use, family history, benign breast disease, energy intake, fibre and fat intake	Results also by receptor status (see accompanying table)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Goodman *et al.* (1997a), Japan, Life Span Study	Analytical cohort of 22 000 residents of Hiroshima and Nagasaki in 1945, recruited 1979–1981, age range not stated; follow-up until 1989; 161 cases identified through cancer registry; 98% histologically confirmed	Self-administered questionnaire	*Alcohol use* Never Drinker	106 40	1.0 0.91 (0.61–1.31)	City, age, age at the time of the bombings, radiation dose to the breast	No association in women who drank beer, sake or other alcoholic beverages
Lucas *et al.* (1998), USA, Study of Osteoporotic Fractures	Analytical cohort of 7250 women recruited 1986–88, aged ≥65 years; follow-up 3 years after interview; 104 self-reported cases confirmed by medical records or through cancer registry	Self-administered questionnaire administered 1 year after recruitment; alcoholic beverage intake adjusted for atypical drinking (i.e. heavy drinking in past 30 days)	*Average no. of drinks per week* None <2 2–7 ≥8	 21 38 17 8	*No family history of breast cancer* 1.0 1.13 (0.66–1.93) 1.41 (0.74–2.67) 1.70 (0.75–3.84)	No adjustment	Includes 4 cases with in-situ cancer; no association in women with a positive family history, but few cases (*n*=20)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Zhang *et al.* (1999), USA, Framingham Study	Analytical cohort of 2764 women recruited in 1948, aged 28–62 years; plus 2284 recruited in 1971 in offspring cohort; follow-up until 1993; 287 cases (221 in original cohort, 66 in offspring cohort) identified through hospital admissions data and death certificates; verified from pathology and medical records (98% in original cohort and 100% in offspring cohort)	Self-administered questionnaire; intake assessed at several time points	*Average intake (g/day)* None 0.1–4.9 5–14.9 ≥15	69 110 55 53	1.0 0.8 (0.6–1.1) 0.7 (0.5–1.1) 0.7 (0.5–1.1)	Age, education, height, body mass index, physical activity, age at first birth, parity, age menarche, age at menopause, smoking, hormone replacement therapy use	Similar risks for each cohort separately; no association with type of drink

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Vachon *et al.* (2001), USA, Minnesota Breast Cancer Family Study	Cohort of 426 families with breast cancer (probands, family members and their spouses; *n*=9032), recruited 1944–52, aged ≥18 years; follow-up until 1990; 558 cases identified from self-report and through death certificates	Telephone interviews (surrogate and self-reported)	Overall *Lifetime intake* Never < Weekly Weekly Daily	558	1.0 1.23 (1.00–1.51) 1.14 (0.86–1.51) 1.28 (0.85–1.91)	Age, birth cohort, familial clustering, type of respondent, smoking	Higher risk in first-degree relatives for daily versus never drinkers; validation study verified 136 of 138 breast cancers through medical and pathology records
Tjønneland *et al.* (2003, 2004), Denmark, Diet, Cancer and Health Study	Analytical cohort of 23 778 women, recruited 1993–97, aged 50–64 years; follow-up until 2000; 425 cases identified through registry	Self-administered questionnaire	*Intake (g/day)* None <6 6–12 13–24 25–60 ≥61 Occasional	10 122 9 93 93 9 9	1.21 (0.64–2.31) 1.0 0.97 (0.74–1.28) 1.18 (0.90–1.56) 1.45 (1.10–1.92) 1.35 (0.68–2.66) 1.32 (0.67–2.60)	Parity, age at first birth, benign breast disease, education, hormone replacement therapy use and duration, body mass index.	No significant difference by beverage type or frequency of intake (days per week) for a given alcohol intake; association for 10 g/day intake similar by hormone replacement therapy use, although only significant in past users.
			Recent intake (per 10 g/day)	423	1.09 (1.00–1.18)	As above plus intake earlier in life	No association with intake earlier in life or cumulative intake

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dumeaux *et al.* (2004), Norway, Norwegian Women and Cancer Study	Analytical cohort of 86 948 women recruited 1991–97, aged 30–70 years; follow-up until 2001; 1130 cases identified through registries and death certificates	Self-administered questionnaire	*Intake in last year (g/day)* None 0.1–4.9 5–9.9 ≥10 *p* for trend	244 554 188 96	1.0 1.24 (1.06–1.44) 1.35 (1.11–1.64) 1.69 (0.32–2.15) <0.0001	Age, breast screening, age at menarche, parity, age at first birth, family history, menopausal status, hormone replacement therapy use, body mass index	Interaction with oral contraceptive use; increased risk among long-term users who consumed >10 g/day alcohol versus non-drinkers who had never used oral contraceptives; stronger association for high alcohol intake (≥10 g/day) in post- versus pre-menopausal women

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Horn-Ross *et al.* (2004), USA, California Teachers Study	Analytical cohort of 103 460 women recruited 1995–96, aged 21–84 years; follow-up until 2001; 1742 invasive cases, ascertained through cancer registry and death certificates	Self-administered questionnaire	*Intake in past year (g/day)* Non-drinkers <5 5–9 10–14 15–19 ≥20 *Postmenopausal* Non-drinkers <5 5–9 10–14 15–19 ≥20	95 53 55 42 27 23 311 181 150 126 82 123	*Pre-/ perimenopausal* 1.0 0.93 (0.66–1.30) 1.05 (0.75–1.47) 1.09 (0.75–1.57) 1.28 (0.83–1.97) 1.21 (0.76–1.92) 1.0 1.03 (0.86–1.24) 1.04 (0.86–1.27) 1.08 (0.88–1.33) 0.91 (0.71–1.16) 1.32 (1.06–1.63)	Age, race, energy intake, family history, age at menarche, parity, age at first birth, physical activity, body mass index, hormone replacement use and duration	Overall risk ≥20 g/ day versus none, 1.28 (1.06–1.54); differences by menopausal status not significant; no clear pattern for age at started drinking; increased risk for ≥20 g/day among ever users of hormone replacement therapy versus non-drinkers who were never users; increased risk for ≥20 g/day among postmenopausal women who had a history of benign breast disease versus non-drinkers with no benign breast disease; no differences by subgroups of family history, body mass index, parity, physical activity

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Mattisson *et al.* (2004), Sweden, Malmö Diet and Cancer Cohort	Analytical cohort of 11 726 women, recruited 1991–96, aged ≥50 years; follow-up until 2001; 342 cases (312 invasive; 30 *in situ*) identified through cancer registry	Interviewer-administered diet history (7-day diary)	*Intake (g/day)* None <15 15–29 ≥30	22 257 39 11	0.89 (0.57–1.39) 1.0 0.88 (0.62–1.24) 1.68 (0.91–3.12)	Interviewer, method version, season, age, energy, change in dietary habits, height, waist, hormone use, age at first birth, age at menarche, physical activity, smoking, education	Adjustment for energy from fat made little difference; association with high intake of wine (>20.8 cl/day versus <2.9 cl/day, relative risk for 2.1; 95% CI, 1.24–3.60)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Petri *et al.* (2004), Denmark, Copenhagen City Heart Study and Glostrup Population Study (data for Glostrup Study also presented in Høyer & Engholm, 1992)	Analytical cohort of 13 074 women, aged 20–97 years; dates of recruitment not stated; followed-up until 1996; 473 cases identified through cancer registry	Self-administered questionnaire	*Average intake (drinks/week)* <1 1–6 7–13 14–27 ≥28 *Premenopausal* <1 1–6 7–13 14–27 ≥28 *Postmenopausal* <1 1–6 7–13 14–27 ≥28	 148 207 72 36 10 17 36 12 5 6 131 171 60 31 4	 0.91 (0.73–1.13) 1.0 1.11 (0.85–1.45) 1.10 (0.77–1.57) 1.19 (0.58–2.41) 1.17 (0.66–2.07) 1.0 1.22 (0.66–2.25) 0.86 (0.33–2.21) 3.49 (1.36–8.99) 0.87 (0.69–1.10) 1.0 1.09 (0.81–1.47) 1.15 (0.78–1.69) 0.57 (0.18–1.78)	Age, cohort, parity, hormone replacement therapy use	No difference by beverage type overall; stronger association for high intakes among premenopausal women, but based on very small numbers; positive association for spirits in postmenopausal women, but not for wine or beer (but again based on small numbers)

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Baglietto *et al.* (2005), Australia, Melbourne Collaborative Cohort Study	Analytical cohort of 17 447 women recruited 1990–94, aged 40–69 years; follow-up until 2003; 537 cases identified through registries and histologically verified	Structured interview	*Intake in last year (g/day)* Never Former 1–19 20–39 ≥40	171 16 286 43 21	1.0 1.03 (0.62–1.73) 1.12 (0.93–1.36) 0.87 (0.62–1.22) 1.41 (0.90–2.33)	Age, energy and folate intake	Adjustment for education, body mass index, age at menarche, parity, hormone replacement therapy, multivitamins had little effect; stronger association for high alcohol intake (≥40 g/day) among women with low folate intake; no association with alcoholic beverages at higher folate intake
Lin *et al.* (2005), Japan, Japanese Collaborative Cohort	35 844 women recruited 1988–90, aged 40–79 years; follow-up until 1997; 151 cases ascertained through registries	Self-administered questionnaire	*Current intake (g/day)* Non-drinker Former drinker Current 0.1–4.9 5–14.9 ≥15 *p* for trend	151 103 3 45 13 5 11	1.0 0.82 (0.20–3.33) 1.27 (0.87–1.84) 1.07 (0.57–2.00) 0.83 (0.34–2.04) 2.93 (1.55–5.54) 0.01	Age, body mass index, study area, family history, walking, hormone replacement therapy, age at menarche, parity, age at first birth, age at menopause	Significant association for binge drinking (>23 g/day on one occasion); no association for age at started drinking or frequency of consumption

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hirvonen *et al.* (2006), France, Supplementation and Vitamins and Minerals Antioxidant Study	Analytical cohort of 4396 women recruited in 1994, aged 35–60 years; followed-up until 2002; 95 cases identified through clinical examination every 2 years and via self-report; validated through medical and pathology records	3 or more telephone-administered 24-hour recalls completed during the first year following recruitment	*Red wine (mL/day)* 0 1–149 ≥150 *p* for trend *White wine or rose (mL/day)* 0 1–149 ≥150 *p* for trend	 39 25 31 62 14 19	 1.0 1.06 (0.64–1.76) 1.24 (0.76–2.03) 0.39 1.0 0.87 (0.49–1.56) 1.09 (0.64–1.84) 0.88	Age, smoking, parity, oral contraceptive use, family history, menopausal status	
Stolzenberg-Solomon *et al.* (2006), USA, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	Analytical cohort of 25 400 women, recruited 1993–2001 into screening arm, aged 55–74 years; follow-up until 2003; 691 self-reported cases (including 96 *in situ*), 72% verified by pathology and medical records, and through cancer registry	Self-administered questionnaire	*Intake (g/day)* <0.01 >0.01–0.43 >0.43–1.39 >1.39–7.62 >7.62 *p* for trend	 104 138 158 118 173	 1.0 1.23 (0.95–1.58) 1.20 (0.94–1.54) 0.97 (0.75–1.26) 1.37 (1.08–1.76) 0.02	Age, education (best fit model)	Stronger association for high alcohol intake (>7.62 g/day) among women with low folate intake; no association with alcoholic beverages at higher folate intake

Table 2.30 (continued)

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Tjønneland *et al.* (2007), European Prospective Investigation into Cancer and Nutrition	Analytical cohort of 274 688 women, recruited 1993–2000, aged 35–70 years; follow-up for 6.4 years; 4285 incident cases (all invasive) identified through registries and active follow-up	Self-administered questionnaire	*Recent intake (g/day)*			Height, weight, age at menarche, parity, oral contraceptive use, hormone replacement use, menopausal status, smoking, education	No differences by subgroups of body mass index or hormonal replacement therapy use; no association for age started drinking; similar association for wine, beer and spirits
			None	612	1.01 (0.91–1.13)		
			>0–1.5	701	1.0		
			1.6–4.7	723	0.98 (0.89–1.09)		
			4.8–10	731	0.97 (0.88–1.08)		
			10.1–19	759	1.07 (0.96–1.19)		
			≥20	765	1.13 (1.01–1.25)		
			20–23.6	211	1.08 (0.92–1.26)		
			23.7–29.9	154	1.03 (0.86–1.23)		
			30–37.1	194	1.36 (1.15–1.60)		
			≥37.2	206	1.09 (0.93–1.28)		
			Increase per 10 g/day		1.03 (1.01–1.05)		
			Lifetime alcohol				
			Increase per 10 g/day		1.02 (0.99–1.06)		

CI, confidence interval

Table 2.31 Case–control studies of breast cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Williams & Horm (1977), USA, Third National Cancer Survey, 1969–71	7518 (all sites, men and women), aged ≥35 years; histological confirmation not stated; 57% randomly selected	Randomly selected patients with cancer of other non-related sites	Interviewer-administered questionnaire	*Total alcohol (oz/year)* None 1 2	 1.0 1.28 (significant) 1.55 (significant)	Age, race, smoking	Increased risk for wine (low intake only) and hard liquor (low and high intake); no association with beer
Byers & Funch (1982), New York, USA, 1957–65	1314, aged 30–69 years; all admitted to hospital; response rate not stated	770 hospital-based (non-malignant); not matched; response rate not stated	Interviewer-administered questionnaire	*Drinks/month* Never Former <3 3–8 9–25 ≥26	 1.0 0.59 1.11 1.02 1.09 1.13 all non-significant	Age	No differences by type of drink; no association for lifetime alcoholic beverage intake; few heavy drinkers
Rosenberg *et al.* (1982), Canada, Israel, USA, 1976–80	1152, aged 30–69 years; verification by hospital discharge records or pathology records; response rate, 94% overall (cases and controls)	2702 hospital-based (519 endometrial/ ovarian cancer; 2702 non-malignant); matching criteria not stated	Interviewer-administered questionnaire	*Intake in previous year (days/week)* Never Former <4 ≥4	 1.0 1.6 (1.1–2.4) 1.9 (1.5–2.4) 2.5 (1.9–3.4)	Age, region	Results presented using non-malignant controls; similar association using cancer controls; increased risk seen for beer, wine and spirits among regular drinkers

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Begg *et al.* (1983), Canada, USA, 1982, survey of cancer patients	997 overall (cases and controls); response rate not stated	730 hospital-based (other cancers excluding head and neck and uncertain origin); matching criteria not stated	Interviewer-administered questionnaire	*Drinks/week* None 1–7 >7	1.0 0.9 (0.8–1.1) 1.4 (0.9–2.0)	Age, smoking	
O'Connell *et al.* (1987), North Carolina, USA, 1977–78	276, aged ≥30 years; 100% histologically confirmed; response rate, 93%	1519 population-based (selected from a stratified sample of households); response rate, 85%	Interviewer-administered questionnaire	*Usual intake (drinks/week)* None or <1 ≥1	1.0 1.45 (0.99–2.12)	Age, race, smoking, hormone replacement therapy use, oral contraceptive use	Higher risk in white versus black women, and in pre- versus postmenopausal women
Harris & Wynder (1988) 20 sites, USA, 1969–84	1467, ages not stated; verified by medical records and pathology reports; response rate not stated	10 178 hospital-based (non-malignant and not related to alcohol or tobacco); matched by age; response rate not stated	Interviewer-administered questionnaire	*Usual intake (g/day)* Never <5 5–15 >15	1.0 1.03 0.97 0.96	Education, occupation, marital status, smoking, age at diagnosis, year of interview	No association by subgroup of body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Cusimano *et al.* (1989a), Sicily, 1983–85	143, aged ≥30 years; 100% histologically confirmed; response rate, 68%	260 hospital-based (non-malignant); matched by age, health service; response rate, 91%	Interviewer-administered questionnaire	No Yes	1.0 1.68 (1.10–2.56)	Socioeconomic status	Stronger association in women with a family history of breast cancer
Kato *et al.* (1989), Japan, 1980–86	1740, aged ≥20 years; ascertained through registry; response rate not stated	8920 hospital-based (other cancers not related to alcohol); not matched; response rate not stated	Not stated; exposure information obtained at the hospital	<Daily Daily *p* for trend	1.0 1.35 (1.01–1.80) <0.01	Age, smoking, marital status, residence, occupation, family history	Higher risk for post- versus premenopausal women, and for beer versus sake or whisky
Iscovich *et al.* (1989), Argentina, 1984–88	150, all ages; 100% histologically confirmed; response rate, 99%	150 population-based (same neighbourhood, not on a special diet) and hospital-based (in- and out patients); matched by age; response rate not stated	Interviewer-administered questionnaire	*Quartile of intake* 1 2 3 4	 1.0 0.37 1.10 0.60		Results presented for population controls; similar results when using hospital-based controls

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Toniolo *et al.* (1989), Italy, 1983–86	250, aged 25–75 years; 100% histologically confirmed; response rate, 91%	499 population-based (electoral roll); matched by age; response rate, 79%	Interviewer-administered questionnaire	*Usual intake (g/ day)* None >0–10 >10–20 >20–30 >30–40 >40 *p* for trend	 1.0 0.9 (0.5–1.5) 1.2 (0.7–1.9) 1.0 (0.7–1.6) 1.2 (0.6–2.4) 1.6 (0.9–2.9) 0.17	Age, body mass index, menopausal status, non-alcohol energy intake	Increased risk also for wine-only drinkers; few women with high intakes (>30 g/day)
Van't Veer *et al.* (1989), Netherlands, 1985–87	120, aged 25–44 years (*n*=47) and 55–64 years (*n*=73); 96% histologically confirmed; response rate, 80%	164 population-based (population registry surrounding hospitals); matched by age; response rate, 55%	Interviewer-administered questionnaire	*Usual intake (g/ day)* *Premenopausal* None 1–4 5–14 15–29 ≥30 ≥30 vs 1–4 *p* for trend *Postmenopausal* None 1–4 5–14 15–29 ≥30 30 vs 1–4 *p* for trend	 1.0 0.3 (0.0–1.7) 0.5 (0.1–2.9) 0.8 (0.1–4.9) 2.3 (0.3–19.1) 8.5 (1.1–65.1) 0.04 1.0 0.8 (0.3–2.3) 1.0 (0.3–3.6) 1.1 (0.3–4.3) 0.9 (0.2–4.5) 1.1 (0.5–2.4) 0.37	Age, region, season, reproductive factors, education, family history, smoking, body mass index, fat intake	Increased risk if started drinking aged <25 years versus older ages, and in post- versus premenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Young (1989), Wisconsin, USA, 1981–82	277, aged 35–89 years; identified through hospital registry; response rate, 64%.	372 population-based (drivers' licence records); response rate, 57%; 433 hospital-based; (no alcohol-related disease); matched by age; response rate, 61%	Self-administered questionnaire	*Drinks/week aged 18–35 years* None 1–5 ≥6 *Drinks/week aged >35 years* None 1–5 ≥6	 1.0 1.74 (1.37-2.21) 3.17 (2.20-4.57) 1.0 1.13 (0.87–1.46) 2.67 (1.91–3.71)	None; adjustments made little difference	Results presented using population controls; weaker, but still significant association when cancer controls used; slightly stronger association if started drinking <35 years
Nasca *et al.* (1990) NY State, USA, 1982–84	1617, aged 20–79 years; verified by pathology reports; response rate, 79%	1617 population-based (drivers' licence files); matched by age, region; response rate, 72%	Interviewer-administered questionnaire (telephone)	*Usual intake (g/day)* None <1.5 1.5–4.9 5.0–14.9 ≥15	 1.0 1.07 (0.83–1.36) 1.04 (0.78–1.39) 1.10 (0.87–1.39) 1.26 (0.98–1.64)	Age, race, age at first birth, menopausal status, benign breast disease, family history	Increased risk for later age at starting (i.e. ≥31 years); no association for duration of use

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zaridze *et al.* (1991), Moscow, 1987–89	139, aged <41–≥71 years; verification not stated; response rate, 99%	139 hospital-based (outpatients); matched by age, region; response rate, 94%	Interviewer-administered questionnaire	*Alcohol intake (g/week)* *Premenopausal* 0 <0.93 0.93–2.12 2.13–6.46 ≥6.46 *p* for trend	1.0 4.60 (0.46–46.14) 4.58 (0.38–55.89) 6.37 (0.72–56.34) 7.98 (0.79–80.47) 0.08	Age at menarche, age at first birth	
				Postmenopausal 0 <0.93 0.93–2.12 2.13–6.46 ≥6.46 *p* for trend	1.0 2.26 (0.66–7.76) 7.06 (1.70–29.40) 3.10 (0.83–11.55) 0.78 (0.06–8.89) 0.003	Age at menarche, education	
Harris *et al.* (1992), New York, USA, 1987–89	604, all ages; verified by pathology and medical records; response rate not stated	520 hospital-based (unrelated to risk factors); matched by age, date of diagnosis, hospital; response rate not stated	Interviewer-administered questionnaire	*Premenopausal (n=192)* 0 g/day 1–15 g/day ≥16 g/day *Postmenopausal (n=412)* 0 g/day 1–15 g/day ≥16 g/day	1.0 1.2 (0.7–1.9) 0.7 (0.3–1.5) 1.0 1.1 (0.8–1.6) 0.8 (0.5–1.3)	Age, family history, age at menarche, parity, age at first birth, breastfeeding, smoking, oral contraceptive use	

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al.* (1992d), Japan, 1990–91	908, aged ≥20 years; 100% histologically confirmed; response rate not stated	908 (244 breast cancer screening and 664 hospital-based [including benign breast disease and excluding hormone-related cancers]); matched by age; response rate not stated	Self-administered questionnaire	None Occasional Daily *p* for trend	1.0 0.99 (0.80–1.22) 0.97 (0.71–1.33) 0.64	None stated	~20% of controls had benign breast disease or gynaecological diseases
Pawlega (1992), Poland, 1987	127, aged ≥35 years; 100% histologically confirmed; response rate, 75%	250 population-based (electoral roll); matched by age, place of residence	Mailed self-administered questionnaire	**Intake 20 years ago** *<50 years* Never vodka Ever vodka *≥50 years* Never vodka Ever vodka	 1.0 4.4 (1.6–12.4) 1.0 1.2 (0.8–2.6)	Age, education, social class, marital status, no. of people in household, body mass index, smoking	

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Martin-Moreno *et al.* (1993), Spain, 1990–91	762, aged 18–75 years; 100% histologically confirmed; response rate, 89%	988 population-based (municipal rolls); matched by age; response rate, 82%	Interviewer-administered questionnaire	*Intake (g/day)* None <2.41 2.41–7.60 7.61–20.40 ≥20.41 *p* for trend	 1.0 1.2 (0.9–1.6) 1.5 (1.1–2.1) 1.7 (1.2–2.3) 1.7 (1.3–2.3) 0.001	Age, region, socioeconomic status, body mass index, family history, age at menarche, menopausal status, age at menopause, age at first birth, energy intake	Increased risk for wine, sherry and spirits; no association with beer or liqueurs; slightly higher risk in post- versus premenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wakai *et al.* (1994), Japan, 1990-91	314, aged >25 years; 100% histologically confirmed; response rate not stated	900 hospital-based (outpatients at department of breast surgery; included women with benign breast disease); matched by age; response rate not stated	Self-administered questionnaire	*Current alcohol drinking* No Yes	 1.0 1.04 (0.77–1.39)	Age, menopausal status, family history, history of benign breast disease, age at menarche, age at menopause, regularity of menstrual cycles, duration of menstrual cycles, age at first birth, parity, breastfeeding, smoking, height, weight	No significant association in pre- or postmenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Freudenheim *et al.* (1995, 1999), New York, USA, 1986–91	740, aged 40–85 years; 100% histologically confirmed; response rate, 58%	810 population-based (drivers' licence and HCFA records); matched by age; response rate, 50%	Interviewer-administered questionnaire	*Total drink intake over 20 years* 0–479 480–1300 1301–4560 4561–6719 ≥6720 *p* for trend	 1.0 1.13 (0.84–1.53) 0.99 (0.73–1.35) 0.95 (0.59–1.52) 0.86 (0.61–1.21) 0.76	Age, education, menopausal status, age at menarche, age at first birth, family history, benign breast disease, body mass index, energy intake, fat, carotenoids, vitamin C, α-tocopherol, folic acid, fibre	No association for cumulative intake by beverage type; no association for drinking 2, 10 or 20 years or at 16 years old; weak association with beer; Freudenheim *et al.* (1999) reported slight increased risk in premenopausal (*n*=134) versus postmenopausal (*n*=181), but not significant; results for alcohol intake 2, 10 and 20 years ago very similar

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gomes *et al.* (1995), Brazil, 1978–87	300, aged 25–75 years; 100% histologically confirmed	600 hospital-based (300 outpatients, 300 gynaecology patients); matched by age, date of diagnosis	Information from patient records	*Current intake* No Yes	 1.0 1.16 (0.68–1.97)	No adjustment	
Longnecker *et al.* (1995), USA, 1988–91 [included in Collaborative Project, but incorporated here for details on lifetime exposure]	6662, aged <75 years; ascertained through cancer registry; response rate, 80%	9163 population-based (drivers' licence records and HCFA records); matched by age; response rate, 84%	Interviewer-administered questionnaire (via telephone) Lifetime intake (age 16 years to baseline [recent past])	*Most recent intake (g/day)* 0 >0–5 6–11 12–18 19–32 33–45 ≥46 per 13 g/day *p* for trend *Lifetime intake (g/day)* 0 >0–5 6–11 12–18 19–32 33–45 ≥ 46 per 13 g/day *p* for trend	 1.0 1.08 (0.98–1.19) 1.09 (0.96–1.23) 1.17 (1.01–1.37) 1.49 (1.24–1.79) 1.95 (1.42–2.66) 1.96 (1.43–2.67) 1.24 (1.15–1.33) <0.0001 1.0 1.13 (1.01–1.26) 1.24 (1.08–1.42) 1.39 (1.16–1.67) 1.69 (1.36–2.10) 2.30 (1.51–3.51) 1.75 (1.16-2.64) 1.31 (1.20–1.43) <0.001	Age, state, age at first birth, parity, body mass index, age at menarche, education, benign breast cancer, family history	Slightly stronger association in post- versus premenopausal women (but both statistically significant); no association for intake when aged <30 years, especially among older women; similar association found for beer, wine and spirits

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Haile *et al.* (1996), Canada, USA, 1935–89 (Connecticut), 1970–89 (Los Angeles), 1975–89 (Canada)	144 premenopausal bilateral cases, aged <50 years; 100% histologically confirmed; response rate, 55%	232 sister controls; response rate, 55%	Mailed self-administered questionnaire	*Drinks/week* None 1–3 ≥3	1.0 1.2 (0.6–2.3) 1.8 (1.0–3.4)	Age, body mass index	Premenopausal bilateral breast cancer only; no difference according to family history of breast cancer
Royo-Bordonada *et al.* (1997), EURAMIC study, Europe (5 countries), 1991–92	315, aged 50–74 years; 100% histologically confirmed; response rate, 86%	364 population-based (population registries, GP records); matched by age, centre; response rate, 41%	Interviewer-administered questionnaire	*Alcohol intake (tertiles)* Never Former 1 2 3 *p* for trend	 1.0 1.73 (1.07–2.79) 1.00 (0.60–1.67) 1.01 (0.60–1.73) 1.18 (0.69–2.03) 0.81	Age, centre, body mass index, smoking, parity, age at first birth, age at menopause, age at menarche, hormone replacement therapy, family history, benign breast disease	Higher risk for age started drinking <40 years versus ≥ 40 years; no difference by subgroup of body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Viel *et al.* (1997), France, 1986–89	154, aged 30–50 years; 100% histologically confirmed; response rate, 90%	154 population-based (women who attended a preventative health clinic); matched by age, socioeconomic status; response rate, 100%	Self-administered questionnaire; verified by interviewer	*Alcohol intake (kcal/day)* None 1–60 ≥60 *p* for trend	1.0 0.77 (0.41–1.47) 2.69 (1.40–5.17) 0.007	Parity, total energy intake	Premenopausal only; increased risk for amount of red wine and duration of red wine intake; no association with white wine, beer or fortified wine (but very low intake)
Tung *et al.* (1999), Japan, 1990-95	376, aged ≥29 years; histological confirmation not stated; response rate, 47%	430 hospital-based (non-malignant, non-endocrine, not related to nutritional or metabolic disease); matching criteria not stated; response rate, 77%	Self-administered questionnaire	*Drinking* None Former Current	1.0 0.42 (0.19–0.95) 0.86 (0.61–1.22)	Age at menarche, age at first birth, weight, height, smoking, education	No association in pre- or postmenopausal women

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Huang et al. (2000); Kinney et al. (2000); Marcus et al. (2000), North Carolina Breast Cancer Study, 1993–96	Huang et al. (2000): 862, aged 20–74 years; 100% histologically confirmed; response rate, 77%	790 population-based (drivers' licence and HCFA records); matched by age, race; response rate, 68%	Interviewer-administered questionnaire	*Drank alcohol recently* No Yes	 1.0 1.0 (0.8–1.2)	Age, race, sampling design	Results also by receptor status (see accompanying table)
	Marcus et al. (2000): 864; recent intake	790		*Recent intake (drinks/week)* None 0.1–6.9 7–13.9 ≥14	 1.0 0.9 (0.8–1.2) 1.2 (0.8–1.8) 1.2 (0.8–1.8)		No association with age at started drinking
	Kinney et al. (2000): 890; lifetime intake	841		*Lifetime intake (<25, 25–49, ≥50 years, g/week)* Never <13 13–90.0 91–181.0 ≥182 *p* for trend	 1.0 0.9 (0.7–1.2) 1.0 (0.7–1.3) 1.2 (0.8–1.9) 0.8 (0.5–1.3) 0.96	Age, race, family history, age at menarche, parity, previous breast biopsy, body mass index, education, smoking	No association for type of beverage; no significant association with binge drinking; no differences by race, age, menopausal status, use of hormone replacement therapy or body mass index

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Männistö *et al.* (2000), Finland, 1990–95	301 (113 pre-, 188 postmenopausal), aged 25–75 years; 100% histologicaly confirmed; response rate not stated	443 population-based (national register); matched by urban/rural residence, age; response rate, 72%	Interviewer-administered and self-administered questionnaire	*Intake (g/week)* *Premenopausal* Never 1–12 13–36 ≥37 Former *Postmenopausal* Never 1–12 13–29 ≥30 Former	1.0 0.8 (0.4–1.9) 0.9 (0.4–1.9) 1.0 (0.4–2.2) 1.4 (0.3–6.2) 1.0 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.8 (0.4–1.6) 0.6 (0.2–1.7)	Age, area, age at menarche, age at first birth, oral contraceptive use, hormone replacement therapy use, family history, benign breast disease, education, smoking, physical activity, body mass index, waist-hip ratio	Results are presented for alcohol as measured from interviewer-administered questionnaire; no association from self-reported questionnaire either; no association with age at first use, or cumulative intake < age 30 years or over lifetime

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Baumgartner *et al.* (2002), New Mexico, 1992–94	712 (332 Hispanic, 380 white), aged 30–74 years; ascertained through registry; response rate, 68% (Hispanics) and 77% (white)	844 population-based (random-digit dialling); matched by age, race, area; response rate, 76% (Hispanic) and 86% (white)	Interviewer-administered questionnaire	*Recent intake (g/week or drinks/week)*		Age, area, education, age at menarche, menopausal status, parity, age at first birth, breastfeeding, oral contraceptive use, benign breast disease, family history, smoking, body mass index, physical activity, energy intake, fat intake	Increased risks in postmenopausal women at high intakes (≥42 drinks) for both races (but not significant); no association for age at first use or duration of drinking; results also by receptor status (see accompanying table)
					Hispanic		
				Non-drinker	1.0		
				<8	1.21 (0.68–2.15)		
				8–20 (1 drink)	1.00 (0.54–1.85)		
				21–41 (2 drinks)	0.75 (0.37–1.53)		
				42–84 (2–4 drinks)	1.24 (0.52–2.93)		
				85–147 (5–7 drinks)	1.35 (0.63–2.93)		
					White		
				Non-drinker	1.0		
				<8	0.49 (0.28–0.85)		
				8–20 (1 drink)	0.46 (0.27–0.79)		
				21–41 (2 drinks)	0.44 (0.25–0.77)		
				42–84 (2–4 drinks)	0.60 (0.35–1.05)		
				85–147 (5–7 drinks)	0.49 (0.24–1.00)		
				≥148 (≥8 drinks)	1.56 (0.85–2.86)		

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gammon *et al.* (2002); Terry *et al.* (2006), Long Island Breast Cancer Study Project, 1996–97	Gammon *et al.* (2002): 1508 (*in situ* and invasive), aged 20–98 years; verified by medical records; response rate, 82% Terry *et al.* (2006) current alcohol (g/day)	1556 population-based (random-digit dialling and HCFA records); matched by age; response rate, 63%	Interviewer-administered questionnaire	*Intake* Never Ever *Current intake (g/day)* None <0.5 0.5–5 5–15 ≥15 *p* for trend *Lifetime intake (g/day)* None <15 15–30 ≥30 *p* for trend	1.0 1.00 (0.86–1.15) 1.0 0.67 (0.50–0.91) 0.83 (0.63–1.11) 0.99 (0.75–1.31) 1.04 (0.74–1.45) 0.2 1.0 1.12 (0.88–1.42) 1.35 (0.96–1.91) 0.81 (0.55–1.19) 0.5	Age Age, race, education, body mass index, lifetime intake Age, race, education, body mass index, current intake	No association when stratified by body mass index, menopausal status or hormone replacement therapy use; no association with drinking at specific ages; results also for receptor status (see accompanying table); no difference by subgroups of body mass index, menopausal status or hormone-replacement therapy use

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Lenz *et al.* (2002), Canada, 1996–97	556, aged 50–75; identified through pathology departments and cancer registry; 100% histologically confirmed; response rate, 81%	577 hospital-based (other cancers not related to alcohol); response rate, 76%	Interviewer-administered questionnaire	*Use* Never Ever Infrequent Regular Current regular (i.e. weekly or daily)	1.0 1.2 (0.9–1.7) 1.2 (0.8–1.8) 1.3 (0.9–1.8) 1.5 (1.0–2.2)	Age, family history, age at oophorectomy, education, marital status, race, age at menarche, oral contraceptive use, hormone replacement therapy use, breast feeding, smoking, body mass index, age at first birth, proxy respondent status	Similar association for type of drink (slightly higher for wine drinkers with long duration of intake); no association with age at first started drinking, duration of intake or lifetime alcoholic beverage intake

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Althuis *et al.* (2003), USA (Atlanta, Seattle and New Jersey), 1990–92	1750 premenopausal women, aged 20–54 years; includes in-situ and invasive cancers identified through hospital records; response rate, 86%	1557 population-based (random-digit dialling); all premenopausal women; no matching criteria; response rate, 78%	Interviewer-administered questionnaire	**Alcohol intake (drinks/week)** *Aged <35 years (n=265)* None <3 3–6.9 7–13.9 ≥14 *Aged 35–44 years (n=1214)* None <3 3–6.9 7–13.9 ≥14 *Aged 45–54 years (n=271)* None <3 3–6.9 7–13.9 ≥14	1.0 1.33 (0.8–2.2) 0.99 (0.6–1.7) 1.29 (0.6–2.7) 1.71 (0.7–4.0) 1.0 1.04 (0.3–1.3) 1.00 (0.8–1.3) 1.04 (0.7–1.5) 1.95 (1.2–3.3) 1.0 1.98 (1.2–3.2) 1.95 (1.1–3.4) 1.84 (1.0–3.5) 4.24 (1.2–14.6)	Study site, screening history, age, race, oral contraceptive use, parity, age at first birth, family history, age at menarche, body mass index	No significant difference by age group; overall relative risk for ≥14 drinks/week versus none, 2.06 (95% CI, 1.4–3.1)

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Choi *et al.* (2003), Republic of Korea, 1995–2001	346, all ages; verification not stated; response rate not stated	332 hospital-based (non-malignant and no hormone-related or benign breast disease); response rate not stated	Interviewer-administered questionnaire	*Use* <1 month ≥1 month	1.0 1.4 (0.99–2.11)	Age, family history	Association stronger in post- versus premenopausal (no results stated)
Wrensch *et al.* (2003), Marin County, CA, USA, 1997–99	285, all ages; identified through cancer registry; verification not stated; response rate, 71%	286 population-based (random-digit dialling); matched by race, age; response rate, 87%	Interviewer-administered questionnaire	*Intake (aged ≥ 21, drinks/week)* <1 1–1.9 2 ≥3 *p* for trend	1.0 1.1 (0.7–1.8) 2.3 (1.2–4.4) 3.6 (1.2–11.5) 0.004	Smoking, socioeconomic status, religion, parity, breastfeeding, oral contraceptive use, hormone replacement therapy use, body mass index, screening history, family history, benign breast disease, radiation treatment, age at menarche, menopausal status	Stronger association for age started drinking >21 years versus <21 years; slightly stronger association in women aged <50 versus ≥50 years

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
McDonald *et al.* (2004), CARE Study, 5 centres in the USA, 1994–98	4575, aged 35–64 years; response rate, 77%	4682 population-based (random-digit dialling), matched by site, race, age; response rate, 65%	Interviewer-administered questionnaire	*Drinks/week 2 years ago* None <7 >7 7–<14 >14 Odds ratio for trend	1.0 1.0 (0.9–1.1) 1.2 (1.0–1.3) 1.2 (1.0-1.4) 1.2 (1.0-1.5) 1.1 (1.0–1.1)	Site, race, age, menopausal status, age at menarche, age at menopause, parity, age at first birth, body mass index, family history, oral contraceptive use, hormone replacement therapy use	Similar association for intake 1–10 years before recruitment; no significant difference by menopausal status; slightly stronger association for wine than for beer or spirits; stronger association for older women drinking >14 drinks/ week

Table 2.31 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Ma *et al.* (2006), Los Angeles, USA, 2000–03	1725, aged 20–49 years; 100% histologically confirmed; response rate, 62%	440 population-based (neighbourhood walk algorithm); matched by age, race; response rate, 74%	Interviewer-administered questionnaire	*Drinks/week in last 5 years* Never <3 3–5 6–11 >12 *p* for trend	1.0 1.01 (0.76–1.35) 0.93 (0.63–1.37) 1.16 (0.75–1.81) 1.77 (1.01–3.08) 0.12	Age, race, education, family history, age at menarche, parity, body mass index, oral contraceptive use, menopausal status, hormone replacement use	Results also by receptor status (see accompanying table)

CI, confidence interval; HCFA, Health Care Finance and Administration

an increased risk for breast cancer, and that the risk increases with increasing intake (Figure 2.1). Hamajima *et al.* (2002) (The Collaborative Group on Hormonal Factors in Breast Cancer) found a significantly increased risk (relative risk, 1.13; 95% CI, 1.07–1.20) for an intake of 18 g alcohol per day. No single study was large enough to estimate reliably the risk for breast cancer at such low levels of intake.

Several studies have examined the effect of lifetime alcoholic beverage intake by total amount (Freudenheim *et al.*, 1995; Longnecker *et al.*, 1995; Kinney *et al.*, 2000; Gammon *et al.*, 2002) or by 10 g intake of alcohol per day (Longnecker *et al.*, 1995; Smith-Warner *et al.*, 1998; Hamajima *et al.* 2002; Tjønneland *et al.*, 2003) on the risk for breast cancer. One large case–control study, based on more than 6000 cases, reported an increase in risk of 31% per 13 g intake of alcohol per day (Longnecker *et al.*, 1995). In contrast, the EPIC cohort found no association with lifetime alcoholic beverage intake after adjustment was made for current alcoholic beverage intake (Tjønneland *et al.*, 2007).

Most studies that examined the age at which a woman started to drink in relation to risk for breast cancer reported no association (Freudenheim *et al.*, 1995; Holmberg *et al.*, 1995; Lenz *et al.*, 2002; Horn-Ross *et al.*, 2004; Tjønneland *et al.*, 2004; Lin *et al.*, 2005; Terry *et al.*, 2006; Tjønneland *et al.*, 2007).

One large case–control study found that, among women who had not recently consumed alcoholic beverages, consumption before the age of 30 years was positively associated with risk for breast cancer, which suggests a continuing increased risk with past consumption (Longnecker *et al.*, 1995). Overall, however, there is limited information on the association between cessation of drinking and subsequent risk for breast cancer, and therefore no firm conclusions can be drawn.

2.6.5   *Tumour type*

Three cohort (Table 2.32) and 12 case–control studies (Table 2.33) examined whether the association between alcoholic beverage intake and risk for breast cancer differed by estrogen receptor (ER) or progesterone receptor (PR) status.

Three cohort studies (Potter *et al.*, 1995; Colditz *et al.*, 2004; Suzuki *et al.*, 2005) (see Table 2.32) evaluated the association of alcoholic beverage intake according to receptor status. All three studies reported a significant association between alcoholic beverage consumption and risk for breast cancer for the most common subgroup of ER+ tumours; the small number of cases in the other subgroups may limit the power to detect significant differences between different subgroups of tumours. The Iowa Women's Health Study (Gapstur *et al.*, 1995; Potter *et al.*, 1995; Sellers *et al.*, 2002) reported a higher risk with increasing alcoholic beverage intake for ER–/PR– tumours and the Swedish Mammography Cohort Study found a higher risk for ER+/PR+ and ER+/PR– tumours (Suzuki *et al.*, 2005); both studies found stronger associations for users of hormone replacement therapy compared with non-users, although these were based on small numbers of cases and should be interpreted with caution.

Table 2.32 Cohort studies of alcoholic beverage intake and breast cancer by hormone-receptor status

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gapstur *et al.* (1995); Potter *et al.* (1995); Sellers *et al.* (2002), Iowa Women's Health Study	37 105 women, aged 55–69 years; recruited in 1986; follow-up until 1992 through registry; 939 cases identified through cancer registry (610 had receptor status)	*Intake in last year* None Any *ER–/PR+ (99)* None Any *ER–/PR– (80)* None Any	*ER+/PR+ (414)* 1.0 1.17 (0.95-1.44) 1.0 1.23 (0.81–1.87) 1.0 1.37 (0.86–2.18)	Age at menopause, hormone replacement therapy use, current body mass index and at age 18 years, waist:hip ratio, age at menarche, type of menopause, family history, parity, age at first birth, oral contraceptive use	Gapstur *et al.* (1995) found higher risk for women who consumed ≥ 4 g/day and had ever used hormone replacement therapy versus non-drinkers who had never used hormone replacement therapy for ER+/PR+ and ER–/PR– tumours; no association with other tumour subtypes; also interaction by family history and body mass index. Sellers *et al.* (2002) reported higher risk for women who consumed ≥ 4 g/day and had a low folate intake for ER– tumours; no association with other tumour subtypes

Table 2.32 (continued)

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Colditz *et al.* (2004), Nurses Health Study	66 145 women; aged 30–55 years; recruited in 1976; follow-up from 1980 until 2000; 2096 self-reported invasive cancers verified through medical and pathology records with ER/PR status	*Cumulative intake before menopause* β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend β coefficient (SE) *p* for trend	*ER+/PR+ (1281)* 0.0003 (0.00009) 0.001 *ER+/PR– (318)* 0.0002 (0.0002) 0.20 *ER–/PR– (417)* −0.00003 (0.0002) 0.86 *ER–/PR+ (80)* 0.0002 (0.0004) 0.68	Not clearly stated	No strong association with alcoholic beverage intake after menopause for any tumour subgroup; no difference by hormone replacement therapy use for any tumour subgroup

Table 2.32 (continued)

Reference, name of study	Cohort description	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Suzuki *et al.* (2005), Swedish Mammography Cohort	51 847 women, aged 55–70 years; recruited 1987–90; follow-up until 2004 through cancer registry; verified by pathology and medical records; 1188 invasive cases with ER/PR status	*Intake in last 6 months (1987 and 1997; g/day)* None <3.4 3.4–9.9 ≥10 *p* for trend	*ER+/PR+ (716)* 1.0 1.07 (0.89–1.30) 1.09 (0.88–1.35) 1.35 (1.02–1.80) 0.05	Age, body mass index, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, oral contraceptive use, hormone replacement therapy use, family history, benign breast disease, energy intake, fibre and fat intake	Stronger association with increasing alcohol intake in hormone replacement therapy users versus never users for ER+/PR+ tumours; no difference for other tumour subtypes
		None <3.4 3.4–9.9 ≥10 *p* for trend	*ER+/PR– (279)* 1.0 1.10 (0.78–1.55) 1.30 (0.91–1.87) 2.36 (1.56–3.56 <0.01		
		None <3.4 3.4–9.9 ≥10 *p* for trend	*ER–/PR– (143)* 1.0 1.11 (0.72–1.71) 1.09 (0.68–1.75) 0.80 (0.38–1.67) 0.45		
		None <3.4 3.4–9.9 ≥10 *p* for trend	*ER–/PR+ (50)* 1.0 1.27 (0.63–2.57) 1.30 (0.58–2.89) 0.62 (0.13–2.90) 0.57		

CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; SE, standard error; +, positive; –, negative

Table 2.33 Case–control studies of alcoholic beverage intake and breast cancer by hormone-receptor status

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
McTiernan *et al.* (1986), Cancer and Steroid Hormone Study, Washington, USA, 1981–82	329 (240 with receptor status) identified through cancer registry, aged 25–54 years; 100% histologically confirmed; response rate, 79%	332 population-based (random-digit dialling); matched by age, all in same region; response rate, 87%	Interviewer-administered questionnaire	*No. of drinks/week* Never/rarely 1–6 ≥7 Never/rarely 1–6 ≥7	*ER+ (143)* 1.0 1.2 (0.7–1.9) 1.7 (1.1–2.8) *ER– (97)* 1.0 1.1 (0.6–2.0) 2.1 (1.1–3.6)	Adjusted for age, age at menarche, benign breast disease, age at first birth, parity
Nasca *et al.* (1994) NY State, USA, 1982–84	1152, aged 20–79 years; verified by pathology reports; response rate, 79%	1617 population-based (drivers' licence records); matched by age, region; response rate, 72%	Interviewer-administered questionnaire (telephone)	*Intake (g/day)* None <1.5 1.5–4.9 5.0–14.9 ≥15 *p* for trend None <1.5 1.5–4.9 5.0–14.9 ≥15 *p* for trend	*ER+ (794)* 1.0 1.18 (0.88–1.57) 1.28 (0.91–1.80) 1.28 (0.96–1.70) 1.35 (0.99–1.85) 0.07 *ER– (358)* 1.0 0.92 (0.62–1.36) 1.19 (0.77–1.83) 0.94 (0.64–1.35) 1.05 (0.70–1.59) 0.73	Unadjusted results shown; adjustment for age, menopausal status, smoking, race, age at menopause, age at first birth, history of benign breast disease and family history made no difference to the risk estimates.

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Yoo *et al.* (1997), Japan, 1988–92	1154 (455 had receptor status), aged ≥25 years; 100% histologically confirmed; response rate not stated	21 714 hospital-based (non-malignant); response rate not stated	Self-administered questionnaire	*Intake* Never Ever Never Ever Never Ever Never Ever	*ER+/PR+ (176)* 1.0 1.0 (0.71–1.41) *ER+/PR– (114)* 1.0 0.96 (0.60–1.52) *ER–/PR– (141)* 1.0 0.68 (0.44–1.05) *ER–/PR+ (24)* 1.0 0.80 (0.32–2.02)	Adjusted for age, occupation, family history, age at menarche, menstrual regularity, age at menopause, parity, age at first birth, breastfeeding, smoking

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Enger *et al.* (1999), 2 studies in Los Angeles, USA, 1983–89	424 premenopausal, aged <41 years; response rate, 77%; 760 postmenopausal, aged 55–64 years; response rate, 67%; 100% histologically confirmed; included invasive and in-situ cancers	760 premenopausal population-based; matched by region, parity, age; response rate, 79%; 1506 postmenopausal; response rate, 80%; all controls identified through a neighbourhood walk algorithm	Interviewer-administered questionnaire	**Intake (g/day)** *Premenopausal* 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day 0 1–5 6–13 ≥14 *p* for trend Increase per 13 g/day	*ER+/PR+ (205)* 1.0 0.73 (0.46–1.15) 1.07 (0.69–1.65) 1.10 (0.67–1.80) 0.56 1.10 (0.91–1.32) *ER+/PR- (52)* 1.0 0.45 (0.18–1.10) 0.16 (0.04–0.69) 0.71 (0.30–1.68) 0.21 0.88 (0.59–1.30) *ER–/PR– (149)* 1.0 0.68 (0.40–1.16) 0.90 (0.53–1.51) 1.04 (0.60–1.81) 0.84 1.08 (0.89–1.31)	Adjusted for age, socioeconomic status, education, age at menarche, age at first birth, parity, breastfeeding, physical activity, family history (premenopausal, also oral contraceptive use); insufficient data for ER–/PR+; no differences by subgroup of body mass index or hormone replacement therapy use among ER+/PR+ cases

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Enger *et al.* (1999) (contd)				*Postmenopausal*	*ER+/PR+ (450)*	
				0	1.0	
				1–13	0.97 (0.74–1.27)	
				14–26	1.18 (0.80–1.75)	
				≥27	1.76 (1.14–2.71)	
				p for trend	0.03	
					ER+/PR- (159)	
				0	1.0	
				1–13	0.75 (0.49–1.14)	
				14–26	1.36 (0.80–2.33)	
				≥27	1.10 (0.53–2.26)	
				p for trend	0.65	
				Increase per 13 g/day	1.05 (0.90–1.24)	
					ER–/PR– (127)	
				0	1.0	
				1–13	0.81 (0.52–1.26)	
				14–26	0.91 (0.47–1.75)	
				≥27	1.37 (0.68–2.76)	
				p for trend	0.77	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Gammon *et al,* (1999), USA, New Jersey, 1990–92 [data also reported in Althuis *et al.* (2003)]	509 in-situ and invasive cancers, aged 20–44 years; identified through hospital records; 401 had tissue blood material for assessment of HER-2 amplification; response rate, 83%	462 population-based (random-digit dialling); matched by age; response rate, 77%	Interviewer-administered questionnaire	*Alcohol intake (drinks/week)* None <7 ≥7 None <7 ≥7	*HER2+ (159)* 1.0 0.95 (0.65–1.40) 1.24 (0.65–2.36) *HER2- (212)* 1.0 1.43 (1.00–2.04) 1.54 (0.84–2.80)	Adjusted for age; premenopausal women only
Huang *et al.* (2000), North Carolina Breast Cancer Study, 1993–96	862, aged 20–74 years; 100% histologically confirmed; response rate, 77%	790 population-based (drivers' licence and HCFA records), matched by age, race; response rate, 68%	Interviewer-administered questionnaire	*Most recent intake* No Yes No Yes No Yes No Yes	*ER+/PR+ (381)* 1.0 0.8 (0.6–1.1) *ER+/PR– (78)* 1.0 1.5 (0.9–2.8) *ER–/PR– (262)* 1.0 0.9 (0.6–1.2) *ER–/PR+ (64)* 1.0 1.5 (0.8–2.8)	Adjusted for age, race, age at menarche, parity/age at first birth, breastfeeding, abortion/miscarriage, body mass index, waist:hip ratio, oral contraceptive use, hormone replacement therapy use, family history, chest X-ray, smoking, education; no significant difference by menopausal status

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Baumgartner *et al.* (2002), New Mexico, 1992–94	281 (128 Hispanic, 153 white), aged 30–74 years; response rate, 68% (Hispanics) and 77% (white); ascertained through registry	532 population-based (random digit dialling); matched by age, race, area; response rate, 76% (Hispanic) and 86% (white)	Interviewer-administered questionnaire	*Recent intake (g/week)* Non-drinker <8 8–41 (1–2 drinks) ≥42 (≥3 drinks) Non-drinker <148 (<8 drinks) ≥148 (≥8 drinks) Non-drinker <8 8–41 (1–2 drinks) ≥42 (≥3 drinks) Non-drinker <148 (<8 drinks) ≥148 (≥8 drinks)	ER+/PR+ *Hispanic* 1.0 0.83 (0.35–1.98) 0.97 (0.49–1.91) 1.78 (0.86–3.68) *White* 1.0 0.46 (0.28–0.74) 2.13 (1.03–4.43) ER–/PR– *Hispanic* 1.0 1.04 (0.39–2.79) 0.39 (0.17–1.08) 1.43 (0.55–3.74) *White* 1.0 0.37 (0.19–0.73) 1.62 (0.51–5.18)	Adjusted for age, area, education, age at menarche, menopausal status, parity, age at first birth, breastfeeding, oral contraceptive use, benign breast disease, family history, smoking, body mass index, physical activity, energy intake, fat intake; too few cases for ER+/PR– and ER–/PR+

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Britton *et al.* (2002), Women's Interview Study of Health, multi-site USA, 1990–92	1556 (1212 had receptor status); aged 20–44 years; identified through registry and medical records; response rate, 86%	1397 population-based (random-digit dialling); matched by age, region; response rate, 79%	Interviewer-administered questionnaire	*Usual intake (drinks/week)* None <7 ≥7 *ER+/PR– (117)* None <7 ≥7 *ER–/PR– (360)* None <7 ≥7 *ER-/PR+ (118)* None <7 ≥7	*ER+/PR+ (615)* 1.0 1.11 (0.88–1.41) 1.33 (0.94–1.87) 1.0 0.86 (0.55–1.35) 0.94 (0.47–1.86) 1.0 1.08 (0.81–1.43) 1.38 (0.93–2.06) 1.0 0.87 (0.55–1.39) 1.64 (0.90–2.98)	Adjusted for site, age, race, education, body mass index, waist:hip ratio, parity, age at first birth, breastfeeding, oral contraceptive use, smoking, physical activity, age at menarche, family history, menopausal status

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Cotterchio *et al.* (2003), 2 studies in Canada (ECSS, WHS), 1995–98	3748 (2638 had receptor status), aged 25–74 years; confirmed by pathology reports; response rate, 86% for ECSS, 73% for WHS	373 population (Ministry of Finance rolls); matched by age, all in same region; response rate, 80% for ECSS, 61% for WHS	Self-administered questionnaire	Drinks/week *Premenopausal* 0 ≤1 1.5–3 ≥3.5 *Postmenopausal* 0 ≤1 1.5–3 ≥3.5 *Premenopausal* 0 ≤1 1.5–3 ≥3.5 *Postmenopausal* 0 ≤1 1.5–3 ≥3.5	*ER+/PR+ (479)* 1.0 1.08 (0.72–1.60) 0.84 (0.55–1.28) 1.38 (0.91–2.10) *(1332)* 1.0 1.03 (0.23–1.30) 0.90 (0.69–1.15) 1.27 (1.00–1.64) *ER–/PR– (256)* 1.0 1.31 (0.78–2.19) 1.36 (0.81–2.28) 0.92 (0.51–1.68) *(442)* 1.0 1.06 (0.75–1.50) 0.90 (0.62–1.32) 1.13 (0.79–1.64)	Adjusted for age at menarche, parity, age at first birth, oral contraceptive use, age at menopause, hormone replacement therapy use, body mass index, smoking, breastfeeding, benign breast disease, family history, age, oopherectomy; significant difference for ER+/PR+ versus ER–/PR– in premenopausal women; no significant differences for postmenopausal women

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Li *et al.* (2003), 3 sites in Seattle, USA, 1997–99	975; aged 65–79 years; cases identified through cancer registry and verified by medical and pathology records; response rate, 81%	998 population-based (HCFA records); matched by date; response rate, 74%	Interviewer-administered questionnaire	*Intake in last 20 years (g/day)*		Adjusted for age, family history, body mass index; no significant association with alcohol intake overall
				Never	*ER+ (789)* 1.0	
				Ever	1.3 (1.0–1.6)	
				<1.5	1.2 (0.8–1.8)	
				1.5–4.9	1.6 (1.0–1.8)	
				5–14.0	1.2 (0.9–1.6)	
				15–29.9	1.2 (0.9–1.8)	
				≥30	1.7 (1.1–2.7)	
				p for trend	0.71	
				Never	*PR+ (648)* 1.0	
				Ever	1.3 (1.1–1.7)	
				<1.5	1.2 (0.8–1.9)	
				1.5–4.9	1.4 (1.0–2.0)	
				5–14.0	1.2 (0.9–1.6)	
				15–29.9	1.3 (0.9–1.9)	
				≥30	1.8 (1.1–2.8)	
				p for trend	1.0	
				Never	*ER− (106)* 1.0	
				Ever	1.1 (0.7–1.7)	
				<1.5	1.1 (0.4–2.7)	
				1.5–4.9	1.1 (0.5–2.1)	
				5–14.0	1.0 (0.6–1.9)	
				15–29.9	1.4 (0.7–2.7)	
				≥30	1.2 (0.5–3.2)	
				p for trend	0.54	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Li *et al.* (2003) (contd)					*PR– (244)*	
				Never	1.0	
				Ever	1.1 (0.8–1.4)	
				<1.5	1.0 (0.5–1.9)	
				1.5–4.9	1.0.(0.6–1.6)	
				5–14.0	1.1 (0.7–1.6)	
				15–29.9	1.1 (0.6–1.8)	
				≥30	1.4 (0.7–*2.7)*	
				p for trend	0.71	
McDonald *et al.* (2004), CARE Study, multisite, USA, 1994–98	4575, aged 35–64 years; response rate, 77%	4685 population-based (random-digit dialling); matched by site, race, age; response rate, 65%	Interviewer-administered questionnaire	*Drinks/week*	*ER+/PR+ (2155)*	Adjusted for site, race, age, menopausal status, age at menarche, age at menopause, parity, age at first birth, body mass index, family history, hormone replacement therapy use, oral contraceptive use; slightly stronger association in postmenopausal women across all subtypes, except for ER–/PR–
				None	1.0	
				<7	1.0 (0.9–1.1)	
				≥7	1.2 (1.0–1.4)	
					ER+/PR– (370)	
				None	1.0	
				<7	1.3 (1.04–1.70)	
				≥7	1.6 (1.2–2.3)	
					ER–/PR– (1071)	
				None	1.0	
				<7	0.9 (0.8–1.1)	
				≥7	1.0 (0.8–1.2)	
					ER–/PR+ (202)	
				None	1.0	
				<7	0.8 (0.5–1.1)	
				≥7	1.4 (0.98–2.1)	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Ma *et al.* (2006), Los Angeles, USA, 2000–03	1725 (1419 had receptor status), aged 20–49 years; 100% histologically confirmed; response rate, 62%	440 population-based (neighbourhood walk algorithm); matched by age, race; response rate, 74%	Interviewer-administered questionnaire	*Intake in last 5 years (drinks/week)*	*ER+/PR+ (739)*	Adjusted for age, race, education, family history, age at menarche, parity, body mass index, oral contraceptive use, menopausal status, hormone replacement therapy use; differences not statistically significant between ER–/PR– and ER+/PR+; data not shown for ER–/PR+ or ER+/PR–
				Never	1.0	
				<3	1.11 (0.81–1.53)	
				3–5	1.01 (0.66–1.54)	
				6–11	1.26 (0.78–2.03)	
				>12	2.10 (1.17–3.79)	
				p for trend	0.03	
					ER–/PR– (334)	
				Never	1.0	
				<3	0.89 (0.61–1.30)	
				3–5	0.76 (0.45–1.28)	
				6–11	1.06 (0.60–1.86)	
				>12	1.71 (0.87–3.38)	
				p for trend	0.42	

Table 2.33 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors and comments
Terry *et al.* (2006), Long Island Breast Cancer Study Project, 1996–97	1508 (ER status for 66%), aged 20–98 years; verified by pathology reports; response rate, 82%; included in-situ and invasive cancers	1556 population-based (HCFA records and random-digit dialling); matched by age; response rate, 63%	Interviewer-administered questionnaire	*Lifetime intake (g/day)* *ER+ (730)* None <15 ≥15 *PR+ (636)* None <15 ≥15 *ER+/PR+ (583)* None <15 ≥15 *ER– (265)* None <15 ≥15 *PR– (355)* None <15 ≥15 *ER–/PR– (212)* None <15 ≥15	 1.0 1.04 (0.85–1.27) 1.14 (0.86–1.51) 1.0 1.08 (0.89–1.33) 0.97 (0.71–1.32) 1.0 1.06 (0.86–1.32) 0.98 (0.72–1.35) 1.0 1.03 (0.77–1.39) 1.27 (0.85–1.90) 1.0 0.97 (0.75–1.27) 1.52 (1.08–2.14) 1.0 0.99 (0.71–1.37) 1.41 (0.92–2.16)	Adjusted for age, race, education, body mass index; alcohol not associated with risk overall; stronger association for ≥15 g/day intake for ER+ cases among lean women (body mass index <25); no association among overweight women

CI, confidence interval; ECSS, Enhanced Cancer Surveillance Study; ER, estrogen receptor; HCFA, Health Care Finance and Administration records; PR, progesterone receptor; WHS, Women Health Study ;+, positive; –, negative

Of the case–control studies, only one reported a stronger association for ER+/PR+ tumours than for ER–/PR– tumours in premenopausal women (relative risks, 1.4 and 0.9, respectively, for ≥3.5 drinks per week versus non-drinkers), although no significant difference was found in postmenopausal women (Cotterchio *et al*., 2003).

2.6.6   *Types of alcoholic beverage*

Results from studies that have looked at the type of alcoholic beverage consumed and risk for breast cancer have suggested an increased risk with increasing alcoholic beverage consumption regardless of the beverage type. Estimates from a pooled analysis of six cohort studies showed risks of 11%, 5% and 5% per 10 g intake of beer, wine and spirits per day, respectively (Smith-Warner *et al*., 1998), which suggests that the effect is principally due to the presence of alcohol.

2.6.7   *Subgroups of women*

Evidence of whether the association of alcoholic beverage intake and risk for breast cancer varied by lifestyle and other factors was available in the study of Hamajima *et al*. (2002) (Collaborative Group on Hormonal Factors in Breast Cancer). This pooled analysis indicated that the association of alcoholic beverages with the risk for breast cancer was not modified by tobacco smoking, age at diagnosis, reproductive factors, having a mother or sister with a history of breast cancer, use of oral contraceptives or use of hormone replacement therapy (see Fig. 2.3).

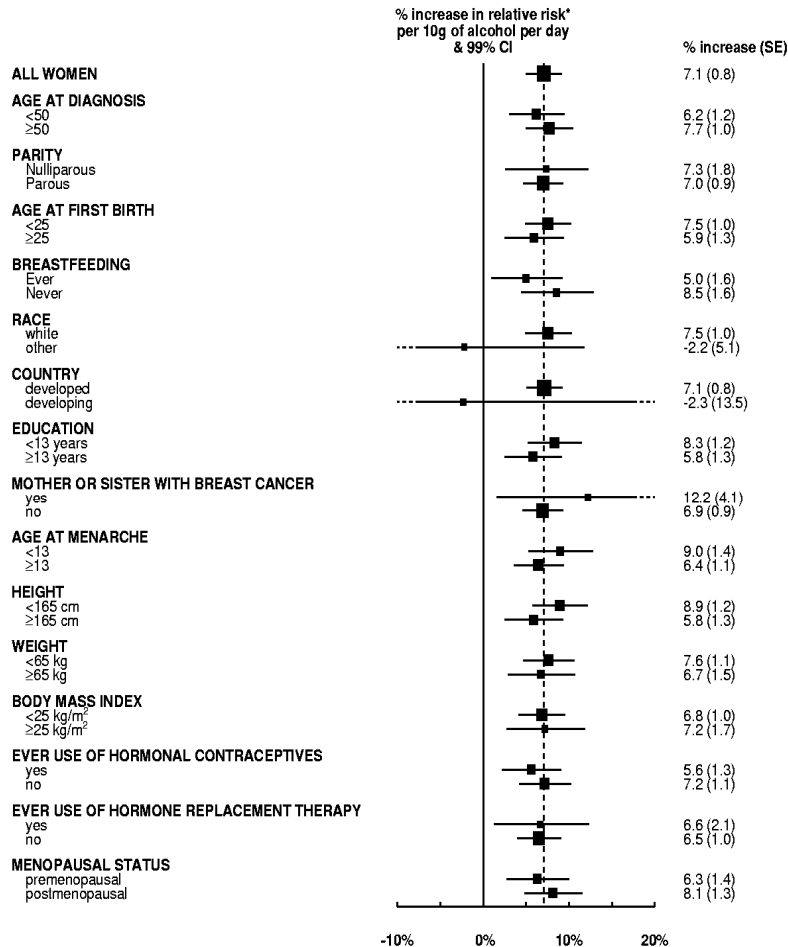### 2.6.8   *Male breast cancer*

Overall, one cohort study (Table 2.34) and eight case–control studies (Table 2.35) have evaluated the association between consumption of alcoholic beverages and the risk for male breast cancer.

One cohort study of male alcoholics in Sweden has reported on the relationship with male breast cancer; this study found no difference in the rates of male breast cancer between alcoholics and the general population, based on 13 cases (Weiderpass *et al*., 2001c; Table 2.34).

Two case–control studies were based on a population of alcoholics as reported from hospital records. One study reported a significant twofold increased risk for alcoholics (Olsson & Ranstam, 1988) and the other found no association (Keller, 1967). [Both studies included small numbers of exposed cases, had a high proportion of cases for whom data were missing and, in Olsson and Ranstam (1988), different risk estimates were produced when different groups of controls were used.] A European case–control study, based on 74 cases, found a sixfold increase in risk in the highest category of alcoholic beverage consumption (>90 g alcohol per day) compared with light drinkers and non-drinkers, corresponding to an increase in risk per 10 g intake of alcohol per day of 17% for beer and wine, but not spirits (Guénel *et al*., 2004). All other studies

Figure 2.3. Percentage increase in the relative risk for breast cancer per 10 g of alcoholic beverage consumption per day in various subgroups of women (adjusted by study, age, parity, age at first birth and tobacco smoking).
Pooled analysis of data from 53 studies that included 58 515 women with breast cancer

From Hamajima et al. (2002)

Table 2.34 Cohort study of male breast cancer and alcoholic beverage consumption

Reference, location, name of study	Cohort description (no. in analysis)	Exposure assessment	Exposure categories	No. of cases	Standardized incidence ratio (95% CI)	Adjustment factors	Comments
Weiderpass *et al.* (2001c), Cohort of Alcoholics (hospital discharge records)	145 811 men diagnosed as alcoholics in hospital records; recruited 1965–95; follow-up through linkage with cancer registry; comparison with national incidence rates; matched by age, sex, calendar time	Incidence rates in alcoholics compared with national rates	Comparison group Alcoholics	13	1.0 1.1 (0.6–2.0)	Age, calendar time	No individual exposure information; no adjustment factor

CI, confidence interval

Table 2.35 Case–control studies of male breast cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Keller (1967), Veterans Administration hospitals, USA, 1958–63	181 (adenocarcinoma), aged 26–88 years	Group 1: 181 hospital-based (discharge lists of medical procedures); matched by age, place of residence; Group 2: 181 hospital-based (bladder or kidney cancer); matched by age, place of residence, hospital characteristics	Indication of alcoholism abstracted from medical records	*Chronic alcoholism* No Yes	No data, but similar proportions of cases and controls were alcoholics.		14 cases, 10 group 1 controls and 9 group 2 controls were alcoholics; information on alcoholic beverage intake was missing for >50%.
Mabuchi *et al.* (1985a), New York, USA, 1972–75	52 identified through hospital medical and pathology records; 100% histologically confirmed; response rate, 81%	52 hospital-based; matched by age, sex, race, marital status (selected from hospital lists); response rate not stated	Interviewer-administered questionnaire	Usual intake of ≥1 glass/day	No relative risk reported (no association with wine, beer, mixed drink, whisky)		

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Casagrande *et al.* (1988), Los Angeles, USA, 1978–85	75, aged 20–74 years; 100% histologically confirmed; response rate, 61%	75 population-based (neighbourhood survey); matched by age, race; response rate not stated	Interviewer-administered questionnaire	Alcohol drinks intake (oz/ week)	No relative risk reported; 12.2 oz/wk in cases and 12.8 oz/wk in controls; *p*=0.81		No significant difference by wine, beer and spirits
Olsson & Ranstam (1988), Sweden, 1970–86	95 identified through registry, aged 21–99 years; verified through medical records	383 hospital-based (lung cancer and non-Hodgkin lymphoma); matched on hospital	Indication of alcoholism abstracted from medical records	*Chronic alcoholism* No Yes	1.0 2.3 (not significant; using lung cancer controls) 13.5 (significant; using non-Hodgkin lymphoma controls)		Only 8 cases were alcoholics

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Thomas *et al.* (1992); Rosenblatt *et al.* (1999), 10 states, USA, 1983–86	227 identified through registry, all ages; 100% histologically confirmed; response rate, 75%	300 population-based (random-digit dialling and HCFA records); matched by age, cancer registry area; response rate, 45%	Interviewer-administered questionnaire	*Lifetime intake (no. of drinks)* None 1–2314 2315–7774 7775– 20 878 ≥20 879	1.0 0.6 (0.3–1.3) 1.2 (0.6–2.2) 1.0 (0.6–1.9) 0.9 (0.5–1.7)	Matching factors	Thomas *et al.* (1992): No association with current intake or intake during period of life when one drank the most, or with age at which one started drinking
Hsing *et al.* (1998b), USA, 1985–86. National (US) Mortality Followback Survey	178 identified from death certificates, aged 25–74 years; response rate, 88%	512 decedants of other causes, excluding smoking- or alcohol-related causes; matched by age, race; response rate not stated	Questionnaire completed by next of kin	*Intake (drinks/ day)* None Ever 1 2 3–4 ≥5	1.0 0.9 (0.6–1.6) 0.8 (0.5–1.6) 1.1 (0.6–2.0) 0.9 (0.5–1.8) 0.9 (0.5–1.8)	Age at death, socioeconomic status	Exposure information taken from next of kin; drinking could be overascertained in the controls.
Petridou et al. (2000), Greece, 1996–97	23 identified in 2 hospitals; 100% histologically confirmed; response rate not stated	76 hospital-based, matched by age, sex (visitors and patients of trauma unit); response rate not stated	Interviewer-administered questionnaire	*Drinks/ week* None <7 ≥7 *p* for trend	1.0 1.15 (0.26-6.07) 0.44 (0.09-2.48) 0.12	None	

Table 2.35 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Johnson *et al.* (2002), Canada, National Cancer Surveillance System 1994–98	81 identified through cancer registry, aged 42–74 years; 100% histologically confirmed; response rate, 68%	1905 population-based (health insurance records and random-digit dialling); matched by age, sex; response rate, 65%	Self-administered questionnaire	*Intake (servings/ week)* None < 3 3–9 ≥10 *p* for trend	 1.0 0.66 (0.35–1.26) 0.91 (0.50–1.65) 0.63 (0.33–1.23) 0.3	Age, marital status, coffee, physical activity, body mass index, area	
Guénel *et al.* (2004), multisite, Europe, 1995–97	74 identified through pathology and clinical departments; aged 35–70 years; 100% histologically verified; response rate, 87%	1432 population (population registers and electoral roll); matched by age, sex, region; response rate, 52%–78% by region	Interviewer-administered questionnaire	*Intake 5 years ago (g/ day)* 0–15 16–30 31–45 46–60 61–75 76–90 >90 Per 10 g/ day	 1.0 0.87 (0.30–2.47) 1.37 (0.46–4.08) 2.28 (0.73–7.11) 4.45 (1.12–17.7) 4.68 (1.07–20.6) 5.62 (1.54–20.6) 1.17 (1.05–1.30)	Age, region, smoking, gynaecomastia, diabetes, fertility problems, head injury, body mass index	Increased risk for wine and beer, but not spirits; similar results found when using hospital-based controls (rare cancers); adjustment for confounders made little difference to the estimates.

CI, confidence interval; HCFA, Health Care Finance and Administration

have found no association (Mabuchi *et al*., 1985a; Casagrande *et al*., 1988; Hsing *et al*., 1998b; Rosenblatt *et al*., 1999; Petridou *et al*., 2000; Johnson *et al*., 2002).