2.2.13 Cancer of the ovary

Cancer of the ovary accounts for about 4% of all cancer diagnoses in women. Risk of ovarian cancer is known to be reduced with use of oral contraceptives, and increased with *BRCA* gene mutations and use of estrogen (unopposed) HRT. There are histologically distinct subtypes of ovarian cancer, including serous, mucinous, clear cell, endometrioid, and other/mixed types (Jayson et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and ovarian cancer was *inadequate*. The 2007 WCRF review did not draw any conclusions regarding body fatness and ovarian cancer risk (WCRF/AICR, 2007). On the basis of many more studies, including pooled analyses, the WCRF Continuous Update Project in 2014 concluded that there was a small but convincing positive association between BMI and ovarian cancer risk, but limited and inconsistent evidence regarding waist circumference (WCRF/AICR, 2014).

Table 2.2.13a, Table 2.2.13b, and Table 2.2.13c present the findings from cohort studies, case–control studies, and meta-analyses, respectively, published since 2000. Findings are presented by BMI at baseline, with comments on findings according to weight change over the life-course and waist circumference.

(a) Cohort studies

The evidence published since 2000 includes 15 cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) (Table 2.2.13a) and several meta-analyses of cohort studies (Table 2.2.13c). In general, findings were consistent across studies, suggesting a modest positive association between baseline BMI and ovarian cancer risk. A meta-analysis including 13 cohort studies found significant increases in risk of 7% in overweight women and of 23% in obese women compared with women of normal BMI (Liu et al., 2015). Aune et al. (2015), in a meta-analysis including 25 prospective studies, found a summary relative risk per 5 kg/m^2 increase in BMI of 1.07 (95% CI, 1.03–1.11) [moderate heterogeneity (54%) across studies was reported] (Aune et al., 2015).

The association is stronger in never-users of HRT (Leitzmann et al., 2009). The Collaborative Group on Epidemiological Studies of Ovarian Cancer found the relative risk per 5 kg/m^2 increase in BMI to be 1.10 (95% CI, 1.07–1.13; P_{trend} = 0.02) in never-users of HRT, but 0.95 (95% CI, 0.92–0.99; P_{trend} = 0.02) in ever-users of HRT (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

The Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) also examined the relationship between BMI and ovarian cancer risk separately by histological type. The association was broadly similar across the common histological subtypes of ovarian cancer, except for serous tumours of borderline malignancy, for which the association was considerably greater than for the other tumour subtypes.

There was no consistency in the evidence for whether BMI earlier in life is more or less predictive of ovarian cancer than is BMI at a later age. The systematic review by Aune et al. (2015) and a twin cohort study by Lundqvist and collaborators (Lundqvist et al., 2007) found marginally stronger associations with BMI in early adulthood than with BMI later in life. However, a pooled analysis including 13 548 cases found the opposite (Olsen et al., 2013). Two cohort studies examining weight gain from age 18–20 years reported positive associations (Ma et al., 2013 based on 152 cases; P_{trend} = 0.05; Canchola et al., 2010), whereas the meta-analyses by Aune et al. (2015) based on 6 cohort studies and 1338 cases did not find evidence of this association [significant heterogeneity was reported in this study; $P_{heterogeneity}$ = 0.01].

In three of the four cohorts that included measurements of waist circumference, this was found to be less associated with ovarian cancer risk than was BMI (Chionh et al., 2010; Lahmann et al., 2010; Ma et al., 2013); one study showed significant positive associations stronger than those reported with BMI (Canchola et al., 2010).

(b) *Case–control studies*

A total of 35 case–control studies (including 7 hospital-based studies) from Asia, Australia, Canada, Europe, and the USA and several meta-analyses including case–control studies have been published since 2000 on the association between BMI at diagnosis and ovarian cancer risk (Table 2.2.13b and Table 2.2.13c). An increase in risk was generally observed, although estimates were not statistically significant in most individual studies. However, a meta-analysis including 13 case–control studies and presenting low heterogeneity (I^2 = 11.3%) found significant increased risk of ovarian cancer in overweight women (RR, 1.09; 95% CI, 1.00–1.19) and in obese women (RR, 1.31; 95% CI, 1.12–1.54) compared with women of normal BMI (Liu et al., 2015). Another meta-analysis of 47 epidemiological studies, which included 30 case–control studies, showed a significant 5% increase in risk in those studies with population-based controls (n = 17) and a significant 8% decrease in risk in those studies with hospital-based controls (n = 13) [the decreased risk in hospital-based studies is probably due to selection bias related to BMI] (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

When stratifying by menopausal status or HRT use, the Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) reported a significant interaction with HRT use, with evidence of a 10% increased risk only among never-users of HRT (n = 11 456 cases). A pooled analysis from 15 case–control studies (Olsen et al., 2013) also reported that the associations were stronger among premenopausal women who had never used HRT.

In the few studies that examined the relationship between BMI and ovarian cancer risk separately by histological type, the associations seemed to be confined to non-serous and low-grade serous tumours (Olsen et al., 2013). An earlier pooled analysis of 10 case–control studies found no association for serous cancers, but there was an association for all other ovarian cancer types (Kurian et al., 2005). The risk was significantly increased in both invasive and borderline ovarian cancer subtypes, with a somewhat stronger association with borderline tumours (Olsen et al., 2013).

Among the 10 studies that reported on the association between BMI in young adulthood and ovarian cancer risk, 7 observed a non-significant increase in risk, two observed a significant increase in risk (Lubin et al., 2003; Olsen et al., 2013), and one observed a significant decrease in risk (Kuper et al., 2002). Four studies evaluated BMI change between early adulthood and diagnosis and showed no significant association with ovarian cancer risk (Lubin et al., 2003; Zhang et al., 2005; Greer et al., 2006; Peterson et al., 2006).

(c) *Mendelian randomization studies*

One large-scale Mendelian randomization study has been conducted to assess the association of childhood and adult BMI with ovarian cancer risk, separated into histological subtypes including clear cell, endometrioid, and serous cancer (Gao et al., 2016; Table 2.2.13d). With each 1 kg/m^2 increase in adult BMI (assuming that a standard deviation was equivalent to 4.5 kg/m^2), there was evidence for an increased risk of all ovarian cancer (OR, 1.07; 95% CI, 1.01–1.13; P = 0.02) and weak, not statistically significant, evidence for an increased risk of clear cell ovarian cancer (OR, 1.12; 95% CI, 0.96–1.31; P = 0.14) and serous ovarian cancer (OR, 1.06; 95% CI, 0.99–1.13; P = 0.09). There was no evidence for

statistically significant associations between childhood BMI and risk of any ovarian cancer types.

In sensitivity analyses exploring the validity of the genetic variants used, there was evidence for negative pleiotropy in the association between adult BMI and endometrioid ovarian cancer [thus suggesting that the positive association may have been underestimated in the main analyses].

Table 2.2.13a Cohort studies of measures of body fatness and cancer of the ovary

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	495 477 Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 873 437 126 49	 1.00 1.15 (1.02–1.29) 1.16 (0.96–1.40) 1.51 (1.12–2.02) [0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat intake, vegetable intake, HRT use	Women who had either a hysterectomy or ovarian surgery were excluded
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 61 39 21	 1.0 1.03 (0.68–1.56) 1.25 (0.75–2.08) [0.44]	Age, smoking, occupation	
Lacey et al. (2006) Breast Cancer Detection Demonstration Project Follow-Up Study USA 1973–1997	46 026 Incidence	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2	 7 219 83 20 11	 0.95 (0.45–2.01) 1.00 1.00 (0.78–1.29) 0.94 (0.59–1.48) 1.55 (0.84–2.84) 1.01 (0.98–1.03)	Age, race, menopausal status, parity, OC use, HRT use	
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 058 twins (mean age, 56 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1 86 57 7	 0.4 (0.1–2.6) 1.0 1.2 (0.8–1.6) 0.7 (0.3–1.5) [0.95]	Age, country, smoking, physical activity, education level, diabetes, parity	
	22 432 twins (mean age, 30 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 120 31 3	 0.7 (0.3–1.4) 1.0 1.5 (1.0–2.3) 0.8 (0.2–2.6) [0.01]	Age, smoking, physical activity, education level, diabetes, parity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1996–2001	1.2 million Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 478 631 510 349 438	 0.98 (0.89–1.07) 1.00 0.99 (0.91–1.08) 1.13 (1.02–1.25) 1.12 (1.02–1.23) 1.14 (1.03–1.27)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	
Schouten et al. (2008) Pooling Project of Prospective Studies of Diet and Cancer (12 cohorts pooled) North America and western Europe Follow-up varied by cohort	531 583 Incidence	BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}] BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}]	Postmenopausal: 426 291 222 206 191 Premenopausal: 64 34 14 14 22	 1.0 0.91 (0.78–1.06) 0.95 (0.80–1.13) 0.96 (0.80–1.14) 1.07 (0.87–1.33) [0.53] 1.0 1.29 (0.83–2.00) 0.95 (0.50–1.81) 1.28 (0.59–2.79) 1.72 (1.02–2.29) [0.13]		
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481, postmenopausal Incidence	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m²	 3 13 30 53 42 30 5	 0.98 (0.29–3.24) 0.85 (0.43–1.68) 1.00 1.63 (1.01–2.63) 1.62 (0.98–2.67) 1.57 (0.91–2.73) 0.93 (0.32–2.67) 1.04 (0.99–1.09)	Age, smoking, alcohol consumption, physical exercise, income level at study entry	Ovary and other unspecified female genital organs
Leitzmann et al. (2009) NIH-AARP cohort USA 1996–2003	94 525 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	Never-users of HRT: 39 43 43	 1.00 1.39 (0.89–2.14) 1.83 (1.18–2.84) [0.007]	Age, race/ethnicity, family history, OC use, physical activity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Leitzmann et al. (2009) (cont.)		BMI	Ever-users of HRT:			
		< 25	102	1.00		
		25–29.9	43	0.68 (0.48–0.98)		
		≥ 30	33	0.96 (0.65–1.43)		
		[P_{trend}]		[0.53]		
Canchola et al. (2010) California Teachers Study Cohort USA 1995–2007	56 091 Never-users of HRT Incidence	BMI			Race, OC use, parity, wine intake, physical activity, smoking, tubal ligation	Weight gain from age 18 yr to baseline positively associated
		< 25	57	1.0		
		25–29.9	29	1.1 (0.71–1.8)		
		≥ 30	21	1.2 (0.72–2.0)		
		WC (in)				
		< 35	32	1.0		
		≥ 35	29	1.8 (1.1–3.0)		
Chionh et al. (2010) Melbourne Collaborative Cohort Study Australia 1990–2008	18 700 Incidence	BMI			Country of birth, education level, age at menarche, parity, OC use, hysterectomy, tobacco use, physical activity, energy intake from diet	
		< 25	39	1.00		
		25–29.9	40	1.05 (0.66–1.65)		
		≥ 30	34	1.58 (0.96–2.62)		
		per 5 kg/m^2		1.22 (1.00–1.48)		
		[P_{trend}]		[0.06]		
		WC, quartiles				
		Q1	24	1.00		
		Q2	27	0.97 (0.56–1.69)		
		Q3	30	1.03 (0.59–1.78)		
		Q4	32	0.96 (0.54–1.69)		
		[P_{trend}]		[0.71]		
Kotsopoulos et al. (2010) Nurses' Health Study 1 and 2 USA 1976–2006	182 700 Incidence	BMI			Age, age at menarche, parity, OC use, tubal ligation, height, family history of breast or ovarian cancer, caffeine intake, hysterectomy; for WC, additionally adjusted for BMI	
		< 21	125	1.00		
		21–22.9	155	0.97 (0.77–1.23)		
		23–24.9	168	1.02 (0.81–1.29)		
		25.0–29.9	242	0.96 (0.77–1.19)		
		≥ 30	177	1.12 (0.89–1.42)		
		[P_{trend}]		[0.29]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kotsopoulos et al. (2010) (cont.)		WC (in)				
		< 28	67	1.0		
		28–29.9	65	0.91 (0.64–1.29)		
		30–31.9	56	0.89 (0.61–1.30)		
		32–34.9	68	0.90 (0.61–1.33)		
		≥ 35	79	1.00 (0.62–1.88)		
		[P_{trend}]		[0.65]		
Lahmann et al. (2010) EPIC cohort Europe 1992–2007	226 798 Incidence	BMI			Age, parity, age at menarche, smoking, OC use	Stronger association in postmenopausal women than in premenopausal women
		< 25	287	1.00		
		25–29.9	211	1.14 (0.94–1.37)		
		≥ 30	113	1.33 (1.05–1.68)		
		[P_{trend}]		[0.02]		
		WC, quartiles				Similar association in premenopausal and postmenopausal women
		Q1	122	1.00		
		Q2	155	1.03 (0.81–1.31)		
		Q3	175	1.10 (0.87–1.41)		
		Q4	159	1.12 (0.86–1.45)		
		[P_{trend}]		[0.32]		
Yang et al. (2012) NIH-AARP cohort USA 1995–2006	169 391 Incidence	BMI			Age, OC use, HRT use, parity	Stronger association with endometrioid histological subtype
		< 30	617	1.00		
		≥ 30	197	1.15 (0.98–1.35)		
Ma et al. (2013) Shanghai Women's Health Study (SWHS) (population-based cohort) Shanghai, China 1996–2009	70 258 Incidence	BMI			Age, education level	Weight gain from age 20 yr also positively associated with risk
		< 18.5	7	1.73 (0.80–3.75)		
		18.5–24.9	75	1.00		
		25.0–29.9	55	1.49 (1.05–2.13)		
		≥ 30	15	2.42 (1.37–4.28)		
		[P_{trend}]		[0.008]		
		WC, quartiles			Age, education level	
		Q1	27	1.00		
		Q2	34	1.36 (0.82–2.26)		
		Q3	41	1.50 (0.92–2.46)		
		Q4	50	1.61 (0.98–2.64)		
		[P_{trend}]		[0.06]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	2 864 658 Incidence	BMI per 5 kg/m^2	3684	1.09 (1.04–1.14)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers
Gay et al. (2015) Singapore Breast Cancer Screening Project (SBCSP) Singapore 1994–2012	28 234 Incidence	BMI < 18.5 18.5–22.9 23–27.4 ≥ 27.5 [P_{trend}]	 6 28 56 17	 1.96 (0.64–5.97) 1.00 1.34 (0.69–2.58) 0.55 (0.19–1.55) [0.22]	Age, housing, family history of breast cancer	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.13b Case–control studies of measures of body fatness and cancer of the ovary

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Greggi et al. (2000) Italy 1998	440 Hospital	BMI < 22.5 22.5–26 > 26	 118 129 140	 1.0 (0.8–1.5) (0.8–1.6)	Age, education level, parity, OC use, family history of ovarian cancer	
Purdie et al. (2001) Australia 1990–1993	775 Population	BMI, percentiles < 15th 15th–35th 35th–65th 65th–85th ≥ 85th [P_{trend}]	518 total	 1.0 (0.7–1.6) 1.5 (1.0–2.2) 1.0 1.3 (0.9–1.9) 1.7 (1.1–2.6) [0.12]	Age, age squared, geographical location, education level, parity, duration of OC use, smoking history, ever-use of talc in the perineal region, tubal sterilization, hysterectomy, history of breast or ovarian cancer in a first-degree relative	Stronger risks were observed in premenopausal women above the 65th percentile
Dal Maso et al. (2002) Italy 1992–1999	1031 Hospital	BMI < 21 21– < 25 25– < 30 ≥ 30 [P_{trend}]	 143 406 299 173	 1.00 0.99 (0.77–1.27) 0.76 (0.58–0.99) 1.07 (0.79–1.44) [0.53]	Age, education level, parity, OC use	A significant association was observed with waist-to-hip ratio. No association was observed with increased body weight
Kuper et al. (2002) USA 1992–1997	563 Population	BMI < 20 ≥ 20– < 25 ≥ 25– < 30 ≥ 30	 67 255 138 104	 1.00 0.97 (0.64–1.45) 1.02 (0.65–1.60) 1.24 (0.77–2.01)	Age, site, parity, OC use, family history of breast, ovarian, or prostate cancer in a first-degree relative, tubal ligation, education level, marital status	In stratified analyses, a higher risk with BMI and weight was observed in premenopausal women
Lubin et al. (2003) Israel 1994–1999	1269 Population	BMI at age 18 yr < 19.1 19.1–20.9 21.0–22.8 22.9–35.2 [P_{trend}]		 1.00 1.16 (0.89–1.51) 1.13 (0.87–1.48) 1.42 (1.08–1.85) [0.009]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lubin et al. (2003) (cont.)		BMI change from age 18 yr				
		< 0.73		1.00		
		0.73–2.70		0.82 (0.63–1.06)		
		2.71–5.71		0.79 (0.60–1.03)		
		≥ 5.72		0.91 (0.69–1.20)		
		[P_{trend}]		[0.50]		
Yen et al. (2003) Taiwan, China 1993–1998	86 Hospital	BMI			Age, income during marriage, education level	
		< 25	63	1.00		
		≥ 25	23	0.77 (0.45–1.33)		
Pan et al. (2004) Canada 1994–1997	442 Population	BMI	442 total		5-year age group, province of residence, education level, pack-years of smoking, alcohol consumption, total energy intake, vegetable intake, dietary fibre intake, recreational physical activity, menopausal status, number of live births, age at menarche, age at end of first pregnancy	
		< 25		1.00		
		25– < 30		1.16 (0.90–1.50)		
		≥ 30		1.95 (1.44–2.64)		
Pike et al. (2004) USA 1992–1998	477 Population	BMI			Ethnicity, age, education level, SES, family history of ovarian cancer, tubal legation, use of talc in the genital area, nulliparity, age at last birth, number of births, number of incomplete pregnancies, OC use, menopausal status, age at natural menopause, age at surgical menopause, HRT use	
		< 25	261	1.00		
		25–29	120	0.97 (0.71–1.33)		
		30–34	56	1.29 (0.83–1.99)		
		≥ 35	40	1.46 (0.87–2.44)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Riman et al. (2004) Sweden 1993–1995	655 Population	BMI 1 yr ago < 22 22– < 25 25– < 27 27– < 30 ≥ 30	 122 197 127 115 93	 1.00 0.99 (0.77–1.28) 1.06 (0.80–1.40) 1.10 (0.83–1.46) 1.37 (1.01–1.85)	Age, parity, and age at menopause as categorized variables, duration of OC use, ever-use of HRT	Stronger associations were observed for the mucinous histological subgroup, and no associations for the serous and endometrioid types
Hoyo et al. (2005) USA 1999–2003	593 Population	BMI < 25 25–29.99 ≥ 30	 230 158 192	 1.0 1.0 (0.7–1.3) 1.4 (1.0–1.8)	Race, age, parity, history of ovarian cancer, history of breast cancer, hysterectomy, OC use, menstrual status	Positive non-significant associations with weight gain from age 18 yr (3rd tertile, 204 cases) and with WC (3rd tertile, 213 cases). In stratified analyses, associations with recent BMI were only significant among Whites (vs African Americans)
Kurian et al. (2005) Pooled analysis of 10 case–control studies of ovarian cancer in the USA	1834 cases with invasive epithelial ovarian cancer Serous: 1067 Mucinous: 254 Endometrioid: 373 Clear cell: 140 Controls: 7 population, 3 hospital	BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24	Serous: 241 Mucinous: 57 Endometrioid: 82 Clear cell: 28 	 1.00 0.72 (0.59–0.88) 1.0 1.3 (0.88–2.0) 1.0 1.3 (0.95–1.9) 1.0 0.9 (0.55–1.6)	Parity, OC use	
Zhang et al. (2005) China 1999–2000	254 Hospital	BMI at diagnosis < 18.5 18.5–21.9 22.0–24.9 ≥ 25.0 [P_{trend}]	 93 28 86 47	 1.60 (0.91–2.83) 1.00 0.98 (0.69–1.41) 0.88 (0.57–1.34) [0.19]	Age at diagnosis, locality, tobacco smoking, alcohol consumption, parity, menopausal status, HRT, OC use, ovarian cancer in first-degree relatives, total energy intake	No significant associations were observed with body weight at diagnosis or with BMI/weight change. Statistically significant associations with BMI and weight were observed 5 yr before diagnosis

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Zhang et al. (2005) (cont.)		BMI at age 21 yr				
		< 18.5	134	0.94 (0.62–1.45)		
		18.5–21.9	41	1.00		
		22.0–24.9	66	1.04 (0.73–1.50)		
		≥ 25.0	11	1.20 (0.56–2.56)		
		[P_{trend}]		[0.37]		
Beehler et al. (2006) USA 1982–1998	427 Hospital	BMI			Age, geographical area, year of study participation	
		≤ 24.9	229	1.00		
		25.0–29.9	116	1.02 (0.77–1.36)		
		≥ 30.0	82	1.17 (0.84–1.65)		
Greer et al. (2006) USA 1994–1998	762 Population	BMI, quartiles			Age, race, number of live births, family history of ovarian cancer, tubal ligation, OC use	Highest BMI (4th quartile, 69 cases) and adult weight gain were associated with increased ovarian cancer risk among nulliparous women only
		Q1	173	1.00		
		Q2	196	1.10 (0.85–1.44)		
		Q3	192	1.14 (0.87–1.49)		
		Q4	201	1.24 (0.95–1.63)		
		[P_{trend}]		[0.12]		
Huusom et al. (2006) Denmark 1995–1999	202 Population	BMI			Age, childbirth, number of additional births, age at first birth, breastfeeding, duration of OC use, smoking, intake of milk	Significant associations with BMI among the serous histological subgroup only
		< 22	67	1.00		
		22–24	52	0.76 (0.51–1.14)		
		25–26	29	1.06 (0.64–1.74)		
		27–29	29	1.33 (0.80–2.19)		
		≥ 30	24	1.09 (0.64–1.84)		
Peterson et al. (2006) USA 1993–2001	700 Population	Recent BMI			Age, state, enrolment period, education level, family history of breast or ovarian cancer, OC use, parity, history of bilateral tubal ligation	Positive, non-significant association with recent weight was reported
		< 18.5	13	1.12 (0.62–2.03)		
		18.5–24.9	304	1.00		
		25.0–29.9	232	1.23 (0.67–2.23)		
		30.0	151	1.29 (0.70–2.37)		
		[P_{trend}]		[0.15]		
		Weight change (kg)				
		Loss	45	1.00 (0.68–1.48)		
		0–9.06 gain	93	1.00		
		9.07–15.87 gain	121	0.89 (0.66–1.20)		
		15.88–23.58 gain	90	0.90 (0.65–1.24)		
		23.59 gain	85	0.77 (0.56–1.06)		
		[P_{trend}]		[0.14]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Rossing et al. (2006) USA 1994–1998	355 Population	BMI 5 yr before diagnosis or reference date < 25 25– < 30 ≥ 30	 130 96 127	 1.0 1.2 (0.9–1.7) 1.5 (0.9–2.4)	Age, race, study site, number of full-term births, duration of OC use, weight/BMI	Similar associations were observed for BMI and for weight at ages 18 yr and 30 yr
Máchová et al. (2007) Czech Republic 1987–2002	174 Population	BMI 18.5– < 25 ≥ 25– < 30 ≥ 30	174 total	 1.00 1.05 (0.68–1.61) 1.38 (0.87–2.20)	Age, smoking, hypertension, height	
Olsen et al. (2007) Meta-analysis (Australia, North America, western Europe)	Meta-analysis Population	BMI at age 17–20 yr ≥ 25 vs < 25 ≥ 25 vs < 25		Overall: 1.22 (1.02–1.45) Case–control: 1.21 (0.97–1.52)		
Soegaard et al. (2007) Denmark 1995–1999	554 Population	BMI at age 30–39 yr, quartiles Q1 Q2 Q3 Q4	 124 153 114 138	 1.00 1.31 (0.98–1.73) 1.00 (0.74–1.36) 1.23 (0.92–1.65)	Age, pregnancy, additional pregnancies, duration of OC use	Associations seemed somewhat stronger in mucinous and endometrioid tumours; no association with BMI ≥ 25 in adulthood
Lurie et al. (2008) USA 1993–2006	274 Population	BMI ≤ 18.5 18.5– < 25 25– < 30 ≥ 30	 6 141 64 64	 1.00 1.72 (0.64–4.75) 1.44 (0.50–4.09) 1.63 (0.57–4.71)		
Nagle et al. (2008) Australia NR	Endometrioid: 142 Clear cell: 90 Controls: 1508 Population	BMI 1 yr before diagnosis < 18 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	Endometrioid: 2 52 46 30	 0.9 (0.2–4.0) 1.0 1.3 (0.8–2.0) 1.2 (0.7–1.9) [0.41]	Age, education level, parity, OC use	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Nagle et al. (2008) (cont.)			Clear cell:			
		< 18	3	2.9 (0.8–11.1)		
		18.5–24.9	23	1.0		
		25–29.9	27	1.7 (0.9–3.0)		
		≥ 30	25	2.2 (1.2–4.1)		
		[P_{trend}]		[0.01]		
Boyce et al. (2009) USA 1988–2008	72 Population	BMI			Age, race	This study investigated granulosa cell tumours
		20–24.9	14	1.00		
		25–29.9	15	1.72 (0.82–3.59)		
		30–39.9	22	5.02 (2.52–10.0)		
		> 40	5	6.60 (2.19–19.8)		
Delort et al. (2009) Auvergne, France 1996–1999, 2005–2006	55 (with no *BRCA* mutation) Mammographic screening centre	BMI			Age	BMI at age 20 yr not significantly associated with increased risk. WC significantly associated with increased risk
		< 20	10	1.00		
		20–25	29	0.88 (0.62–1.26)		
		25.1–30	9	0.78 (0.38–1.60)		
		> 30	6	0.69 (0.24–2.02)		
Moorman et al. (2009) USA 1999–2008	African American: 143/189 White: 943/868 Population	BMI	White:		Age	
		< 25	312	1.00		
		25– < 30	212	0.96 (0.76–1.22)		
		30– < 35	114	1.08 (0.80–1.45)		
		≥ 35	83	1.04 (0.75–1.45)		
		BMI	African American:			
		< 25	17	1.00		
		25– < 30	26	0.84 (0.39–1.78)		
		30– < 35	22	0.94 (0.43–2.07)		
		≥ 35	42	1.62 (0.79–3.35)		
Reis & Kizilkayabeji (2010) Turkey 2002–2003	217 Hospital	BMI			Not specified	
		18.5–24.99	86	1.00		
		≥ 25	131	1.96 (1.41–2.72)		
		[P_{trend}]		[< 0.001]		
Bandera et al. (2011) USA 2004–2008	205 Population	BMI			Age	
		18.5–25	90	1.00		
		25–29.9	54	1.07 (0.69–1.65)		
		30–34.9	36	1.39 (0.83–2.32)		
		≥ 35	24	1.54 (0.81–2.89)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Bodmer et al. (2011) United Kingdom 1995–2009	1611 Hospital	BMI < 25 25–29.9 ≥ 30	 562 453 293	 1.00 1.08 (0.94–1.23) 1.11 (0.95–1.29)		
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23	All: 36 348 116 Serous: 15 175 60 Mucinous: 8 58 14	 1.00 1.15 (0.72–1.85) 1.77 (1.04–3.02) 1.00 1.43 (0.77–2.69) 2.26 (1.13–4.52) 1.00 0.87 (0.38–1.98) 1.00 (0.38–2.61)	Age, OC use, parity, menopausal status, ovarian and/or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption; for weight, additional adjustment for height	Asian population cut-offs used for BMI Significant associations were observed for weight (kg), especially in the serous ovarian cancer subtype
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago, tertiles vs T1: ≤ 20.00 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 Weight (kg), tertiles vs T1: ≤ 50 T3: ≥ 55.1 T3: ≥ 55.1 T3: ≥ 55.1	All: 158 221 Serous: 83 112 Mucinous: 26 35 All: 187 Serous: 100 Mucinous: 27	 1.24 (0.89–1.72) 1.75 (1.28–2.40) 1.47 (0.97–2.22) 1.98 (1.33–2.95) 1.31 (0.69–2.49) 1.84 (1.00–3.38) 1.84 (1.34–2.54) 2.23 (1.50–3.33) 1.67 (0.91–3.06)	Age, OC use, parity, menopausal status, ovarian or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
King et al. (2013) USA 2001–2008	205 Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 91 54 36 24	 1.00 1.07 (0.69–1.65) 1.39 (0.83–2.32) 1.54 (0.82–2.89)	Age	
Olsen et al. (2013) Pooled analyses of 15 case–control studies	13 548 cases Invasive: 8763 Borderline: 2465 1 study hospital -based, 14 studies population-based	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m² BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m²	Invasive: 183 4020 2500 1166 511 383 Borderline: 57 1080 662 379 150 137	 1.08 (0.84–1.39) 1.00 1.00 (0.92–1.09) 1.06 (0.97–1.16) 1.21 (1.07–1.38) 1.22 (1.05–1.41) 1.04 (1.00–1.08) 1.13 (0.82–1.55) 1.00 1.23 (1.09–1.39) 1.61 (1.40–1.85) 1.68 (1.37–2.06) 1.96 (1.57–2.46) 1.18 (1.14–1.23)	Age, parity, OC use, family history of breast or ovarian cancer in a first-degree relative, race/ethnicity where appropriate	BMI in early adulthood was significantly associated with 8% and 15% increased risk of invasive and borderline ovarian cancer subtypes, respectively
Le et al. (2014) Canada 2001–2007	608 Population	BMI < 25 25–30 30–35 ≥ 35	 330 180 57 41	 1.00 0.80 (0.59–1.09) 0.87 (0.54–1.41) 0.91 (0.53–1.58)	Age	
Schildkraut et al. (2014) USA 2010–2014	403 Population	BMI < 24.9 25–29.9 30–34.9 ≥ 35	 54 95 107 113	 1.00 1.31 (0.86–1.99) 1.50 (0.99–2.27) 1.27 (0.85–1.91)	Age, months of OC use, parity	Study in African American women

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Burghaus et al. (2015) Germany 2002–2013	289 Hospital	BMI, tertiles (median) Low (21.7) Medium (25.0) High (30.1)	NR	Low vs medium: 0.99 (0.83–1.17) High vs medium: 1.26 (1.09–1.46) High vs low: 1.28 (0.95–1.72)	Age, OC use, pregnancies, self-reported endometriosis	

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; WC, waist circumference; yr, year or years

Table 2.2.13c Meta-analyses of measures of body fatness and cancer of the ovary

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Olsen et al. (2007)	16 studies for adult BMI (8 case–control and 8 cohort) and 9 for BMI in early adulthood (5 case–control and 4 cohort) NR	Adult BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI at age 17–20 yr 18.5–24.9 ≥ 25	 1.00 1.16 (1.01–1.32) 1.30 (1.12–1.50) 1.00 1.22 (1.02–1.45)		In adult BMI, no difference was observed when stratifying by study design type
Guh et al. (2009)	9 cohort studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30	 1.00 1.18 (1.12–1.23) 1.28 (1.20–1.36)	Unadjusted RRs	
Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012)	47 studies (17 prospective and 30 case–control) 25 157 cases	BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 1.00 (0.95–1.05) 1.05 (1.00–1.11) 1.08 (1.02–1.13) 1.07 (0.99–1.17) 1.13 (1.06–1.20) [0.01]	Study, age at diagnosis, parity, menopausal status/hysterectomy, OC use, HRT use, height	In stratified analyses, associations were only significant among never-users of HRT (RR, ~1.1 for overweight; ~1.2 for obesity)
Poorolajal et al. (2014)	10 cohort studies and 9 case–control studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.08 (0.90–1.31) 1.27 (1.19–1.35) Cohort: 1.00 1.26 (0.97–1.63) 1.26 (1.06–1.50)	NR	In stratified analysis by menopausal status, stronger associations were found in all cases in the premenopausal period
Aune et al. (2015)	25 studies 19 825 cases	BMI per 5 kg/m^2 increase	1.07 (1.03–1.11)	Maximally adjusted HR, RR, or OR were used (covariates NR)	Non-linearity, with risk increasing significantly from BMI above 28 kg/m^2; relatively stronger risk with BMI increase in early adulthood, based on 6 studies (RR, 1.12); no association with weight gain

Table 2.2.13c (continued)

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Liu et al. (2015)	26 studies (13 case–control and 13 cohort) 12 963 cases	BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.09 (1.00–1.18) 1.31 (1.21–1.54)		No associations with BMI were found in postmenopausal women
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Cohort: 1.00 1.07 (1.01–1.13) 1.23 (1.10–1.39)		
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Overall: 1.00 1.07 (1.02–1.12) 1.28 (1.16–1.41)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HR, hazard ratio; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; OR, odds ratio; RR, relative risk; yr, year or years

Table 2.2.13d Mendelian randomization studies of measures of body fatness and cancer of the ovary

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI) P_{trend}	Comments
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	Women from 3 studies of individuals of European ancestry	13 492 (4369 cases and 9123 controls)	Increase of 1 SD in genetically predicted childhood BMI or adult BMI	Childhood BMI: 1.07 (0.82–1.39) P_{trend} = 0.62 Adult BMI: 1.07 (1.01–1.13) P_{trend} = 0.02	Similar associations were found for adult BMI with serous ovarian cancer, and moderate but not statistically significant with clear cell and endometrioid histological subtypes. No associations were observed between childhood BMI and subtypes of ovarian cancer

BMI, body mass index (in kg/m^2); CI, confidence interval; SD, standard deviation

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