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Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium

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Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Abstract

Whilst previous studies have reported that higher body-mass index (BMI) increases a woman's risk of developing ovarian cancer, associations for the different histological subtypes have not been well defined. As the prevalence of obesity has increased dramatically, and classification of ovarian histology has improved in the last decade, we sought to examine the association in a pooled analysis of recent studies participating in the Ovarian Cancer Association Consortium. We evaluated the association between BMI (recent, maximum, and in young adulthood) and ovarian cancer risk using original data from 15 case-control studies (13,548 cases, 17,913 controls). We combined study-specific adjusted odds ratios (ORs) using a random–effects model. We further examined the associations by histological subtype, menopausal status and post-menopausal hormone use. High BMI (all time-points) was associated with increased risk. This was most pronounced for borderline serous (recent BMI: pooled OR=1.24 per 5kg/m^2; 95%CI 1.18–1.30), invasive endometrioid (1.17; 1.11–1.23) and invasive mucinous (1.19; 1.06–1.32) tumours. There was no association with serous invasive cancer overall (0.98; 0.94–1.02), but increased risks for low grade serous invasive tumours (1.13, 1.03–1.25) and in pre-menopausal women (1.11; 1.04–1.18). Among post–menopausal women, the associations did not differ between HRT users and non–users. Whilst obesity appears to increase risk of the less common histological subtypes of ovarian cancer, it does not increase risk of high grade invasive serous cancers, and reducing BMI is therefore unlikely to prevent the majority of ovarian cancer deaths. Other modifiable factors must be identified to control this disease.

Keywords

ovarian cancer; obesity; body mass index

INTRODUCTION

It is widely accepted that being overweight or obese increases a woman's risk of developing endometrial and post–menopausal breast cancer (Calle and Kaaks 2004). The association with ovarian cancer is less clear, largely because individual studies have had insufficient power to reliably detect moderate effects or to consider the different histological subtypes of ovarian cancer. In 2008, a pooled analysis of cohort studies concluded that BMI was associated with ovarian cancer in pre-menopausal women only, however this analysis only included 2000 cases and thus also had limited power to evaluate the different histological subtypes separately (Schouten, et al. 2008). A recent pooled analysis conducted to overcome these limitations concluded that among women who have not used hormone replacement therapy (HRT), the risk of ovarian cancer increases by 10% for every 5kg/m^2 increase in body–mass index (BMI) (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). This association did not vary significantly for the different histological subtypes of ovarian cancer, with the exception of borderline serous cancers where the excess relative risk was substantially greater than for the other tumour types. There was no increase in risk with increasing BMI among women who had used HRT.

However, the mean year of diagnosis of the cases in the studies included in the previous report was 1992 (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012) and over the last few decades, most countries have seen dramatic increases in the prevalence of overweight and obesity (Finucane, et al. 2011). Classification of the different histological subtypes of ovarian cancer has also improved in recent years (Gilks and Prat 2009) and it is possible that misclassification in earlier studies might have masked differences between the histological subtypes. In particular, it is now recognized that low and high grade invasive serous cancers are distinct entities and that many cancers previously described as high grade endometrioid tumours should really be classified as high grade serous cancers (Gilks and Prat 2009). We therefore sought to confirm the results of the previous analysis in a second, independent pooled analysis using data from more recent studies that met the inclusion criteria for the Ovarian Cancer Association Consortium (OCAC) collaboration (Ramus, et al. 2008). We examined the associations by histological subtype and tumour grade and by menopausal status and HRT use because, if the effects of obesity on ovarian cancer risk are mediated through oestrogenic pathways, then any association between BMI and risk may be more evident among women who have not used exogenous oestrogens. We also evaluated the relation between body–size at different ages and ovarian cancer risk.

METHODS

OCAC was founded in 2005 to foster collaborative efforts in discovering and validating associations between genetic polymorphisms and ovarian cancer risk. A detailed description has been provided elsewhere (Ramus et al. 2008) but, briefly, studies were eligible for inclusion if they included at least 200 cases of ovarian cancer and 200 controls, with controls from broadly the same population as cases, and provided DNA for genetic analyses. Table 1 summarizes the characteristics of the fifteen case–control studies (fourteen population–based and one clinic–based) that provided data for these analyses (Ziogas, et al. 2000; Royar, et al. 2001; Glud, et al. 2004; Pike, et al. 2004; Terry, et al. 2005; Hoyo, et al. 2005; Risch, et al. 2006; Garcia-Closas, et al. 2007; Rossing, et al. 2007; Kelemen, et al. 2008; Lurie, et al. 2008; Merritt, et al. 2008; Moorman, et al. 2008; Wu, et al. 2009; Balogun, et al. 2011; Bandera, et al. 2011; Ness, et al. 2011). Race/ethnicity was categorized as non–Hispanic White (88%), Hispanic White (3%), Black (4%), Asian (3%), or other (2%). All studies had ethics approval, and all study participants provided informed consent.

Analysis Variables

There was some variation in the way weight information was collected by the individual studies (Supplementary Table A). Weight in early adulthood was reported by 14 studies (all except MAY); this was reported as weight at age 18 for nine studies and at age 20 for two studies (AUS, GER), while three studies reported weight ‘in your 20s’ (CON, MAL, USC). Recent weight was reported by 11 studies (AUS, CON, DOV, HOP, MAL, MAY, NCO, NJO, NEC, UCI, USC); for most studies this was reported as weight one year prior to diagnosis/reference date, but five years prior to diagnosis/reference date was used for four studies (CON, DOV, MAL, USC). To minimize overlap between our analyses of recent weight and the previous pooled analysis,[3] we excluded two studies (GER, HAW) that were included in the previous analysis, but included two (NEC, USC) that had contributed only part of their data to the previous analysis (total overlap ~1200 cases). Maximum weight was reported by 8 studies (AUS, DOV, GER, HAW, HOP, NCO, NJO, POL). Body mass index (BMI), calculated as weight in kilograms divided by the square of height in metres (kg/m^2), was classified using the World Health Organization (WHO) definitions of obesity (<18.5 ‘underweight’; 18.5–24.9 ‘normal weight’; 25–29.9 ‘overweight’; 30–34.9 ‘class I obesity’; 35–39.9 ‘class II obesity’; and ≥40 ‘class III obesity’) (W.H.O., 1995). For subgroup

analyses there were small numbers in the upper classes of obesity for BMI in early adulthood so these groups were combined.

Covariate Information

Each case–control study provided information on potential confounding variables including age, cancer grade, race/ethnicity, parity, breastfeeding, oral contraceptive (OC) and hormone replacement therapy (HRT) use, family history of breast or ovarian cancer in a first degree relative, menopausal status, and history of hysterectomy or tubal ligation. All data were cleaned and checked for internal consistency and clarification was provided by the original investigators when needed.

Statistical Analysis

We used Stukel's two–stage method of analysis to obtain study–specific odds ratios (ORs) and pooled odds ratios (pORs) and 95% confidence intervals (CIs) (Stukel, et al. 2001). In the first stage, each study was analyzed separately, controlling for study–specific confounders. The pooled exposure effect was estimated in a second–stage using a meta–analytic approach. A weighted average of the log relative risk (RR) was estimated, taking into account the random effects using the method of DerSimonian and Laird (DerSimonian and Laird 1986). Statistical heterogeneity among studies was evaluated using the Cochran Q test and I^2 statistics (Higgins and Thompson 2002). All models were stratified by age in 5–year groups and adjusted for parity (0, 1, 2, 3, 4+ full–term births), oral contraceptive use (0, ≤60, >60 months), and family history of breast or ovarian cancer in a first degree relative. We also adjusted study–specific results for race/ethnicity (non–Hispanic white, Hispanic white, black, Asian, other) where more than 10% of the study population was not classified as non–Hispanic white and inclusion of a term for race/ethnicity altered the odds ratio by 10% or more. Other potential confounders considered but not included in final models since they did not make any material change to the BMI associations were: breastfeeding, history of hysterectomy, tubal ligation, menopausal status and HRT. Adjusting for history of endometriosis made no material change to the pooled estimates for the endometrioid or clear cell subtypes and thus it was not included in final models. Data on smoking status were not available for all studies, however including smoking status in models where it was available did not result in significant changes to the pooled estimates and thus it was not included in final models. Covariate data were mostly complete and uniformly coded for all studies with a few exceptions. The parity variable included all full–term births (live and still births) for all studies except MAY which recorded only live births. Secondly, tubal ligation and breastfeeding data were unavailable for the MAY study. These missing covariates were therefore not included in the first stage models for this study.

We initially computed odds ratios for each of the primary exposure variables for invasive and borderline cancers separately and then further classified tumours by their histological subtype (serous, mucinous, endometrioid, clear cell). In the subtype–specific models, adjacent levels of confounders were collapsed where necessary to avoid zero cells in the two–stage models. Where heterogeneity was evident, we examined the data for potential sources of this heterogeneity including type of control group (population versus hospital–based) and style of questionnaire (self–completed versus in–person interview). The relative risk of ovarian cancer per 5 kg/m^2 increase in body mass index was estimated by fitting a log–linear trend across categories of body mass index (18.5–<20,20–,22.5–,25–,27.5–,30–,32.5–,35–,37.5–,40+ kg/m^2) using the overall median value within each category, except for the top category where we used the site–specific median as this varied between sites. Since we were interested in the effects of being overweight and speculated that the relation between BMI and cancer risk might not be linear at very low BMI levels, these analyses excluded women in the 'underweight' range (BMI<18.5 kg/m^2).

We also conducted subgroup analyses to assess the interaction between recent BMI, menopausal status and use of any hormone replacement therapy (pre/peri–menopausal, postmenopausal and never used HRT, postmenopausal and had used HRT). There was some heterogeneity in how menopausal status was defined across studies, so we also conducted analyses stratified by age at diagnosis (<50, ≥50 years). To avoid problems with zero cells in some studies in these and other sub–group analyses, we pooled all data and computed ORs using logistic regression stratified by study site and age in 5–year groups in order to maximize the statistical power. The statistical significance of any observed stratum–specific differences was then assessed by including a cross–product term (using the continuous BMI variables defined above) in regression models.

Analyses were conducted using SAS (SAS Institute, Cary, North Carolina, USA) and Stata 10 (College Station, TX, USA).

RESULTS

Eleven studies contributed to analyses of recent BMI, eight studies for maximum BMI and 14 studies for BMI in early adulthood (Table 1). Using the two–stage method of analysis, we observed significantly increased risks of both invasive and borderline ovarian cancers associated with higher BMI at all three time–points. The association was modest for invasive tumours with an increase in risk of 4% per 5 kg/m^2 for recent BMI and 8% for BMI in early adulthood, but was stronger for borderline tumours with increases of 15–18% per 5 kg/m^2 for the different time–points (Table 2).

Results of the pooled analyses stratified by histological subtype are presented in Tables 3 and 4 for invasive and borderline tumours respectively. Overall, risk of invasive serous cancer was not associated with any measure of BMI (Table 3). However, stratification by tumour grade (data available for 91% of cases) revealed positive associations between all measures of BMI and risk of low grade (G1) invasive serous tumours (OR=1.13, 1.18 and 1.24 per $5kg/m^2$ for recent, maximum and young adult BMI respectively, all $p<0.01$) but not high grade (G2–G4) tumours (OR=0.96, 0.96 and 0.98, respectively). Higher BMI (all BMI variables) was significantly associated with an increased risk of invasive endometrioid ovarian cancer. This association was restricted to low and intermediate grade (G1–G2) tumours (OR per $5kg/m^2$ 1.25, 1.22 and 1.20 for recent, maximum and young adulthood BMI respectively, all $p\leq0.001$) and was not seen for high grade (G3–G4) endometrioid cancers (OR=0.97, 1.02 and 0.90, respectively) (data on grade available for 93% of cases). The associations between BMI and invasive mucinous and clear cell cancers were less clear, with increased risks of both tumour types associated with high recent BMI and, for mucinous cancers, BMI in young adulthood, but not maximum BMI. The results for recent BMI were essentially unaltered when we restricted the analysis to include only studies that assessed weight around 5 years prior to diagnosis to reduce potential bias due to recent weight loss in cases. Considering all non–serous invasive cancers together, the association with recent BMI remained significant after adjusting for maximum BMI or BMI in young adulthood, however after adjusting for recent BMI there was no association with either maximum BMI (OR=1.02, 95%CI 0.95–1.11 per $5kg/m^2$) or BMI in young adulthood (OR=0.96, 95%CI 0.86–1.08 per $5kg/m^2$).

Increasing BMI (all BMI variables) was associated with increased risks of both borderline serous and mucinous ovarian cancers, with significant trends with increasing BMI that were stronger for borderline serous cancers (20–25% increase per 5 kg/m^2) than borderline mucinous cancers (9–11% per 5 kg/m^2; Table 4).

Although there was some heterogeneity among studies for some of the pooled estimates, heterogeneity for the estimates per 5kg/m^2 only reached statistical significance for recent BMI and risk of clear cell tumours and the combined group of all invasive tumours; sensitivity analyses by study design features suggested that no single factor could explain this observed heterogeneity.

When we combined all tumour types and stratified by ever use of HRT, we observed a significant association between BMI and cancer risk among women who had not used HRT (OR per 5 kg/m^2 = 1.10; 95%CI 1.07–1.14) but no association among women who had used HRT (1.02; 0.97–1.07). However, we saw markedly different patterns of association when we considered pre– and post–menopausal women and the different histological subtypes of cancer separately (Table 5). When we stratified by menopausal status and use of HRT, we saw significant interaction for recent BMI and risk of invasive serous cancers ($p \leq 0.001$). A significant trend of increasing risk with increasing BMI was observed in premenopausal women, with no association among postmenopausal women who had never used HRT, and a significant inverse association among those who had used HRT. Further stratification of the pre-menopausal group suggested the positive association was stronger for G1 (OR 1.34, 95%CI 1.14–1.59) but still statistically significant for G2–4 tumors (OR 1.07, 95% CI 1.00–1.15; $p<0.05$). A similar pattern was seen in analyses of maximum BMI and BMI in young adulthood (data not shown), suggesting the lack of a positive association among post–menopausal women was not simply an artefact due to recent weight loss among women with serous cancer. For all other invasive subtypes combined, the association was somewhat stronger among pre–menopausal women than post–menopausal women but did not differ by HRT use among post–menopausal women. The association with borderline tumours did not vary by menopausal status or HRT use. When we stratified by age at diagnosis (<50, ≥50 years) instead of menopausal status the results did not differ materially (data not shown).

DISCUSSION

The results of our pooled analysis confirm that being overweight or obese is associated with an overall increased risk of both invasive and borderline ovarian cancer, however for invasive cancers this association appears to be restricted to the non–serous and low–grade serous subtypes. Furthermore, most of our risk estimates were very consistent with those from a previous pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012) with a strong increase in risk of borderline serous cancer (pooled OR/RR=1.24 per 5kg/m^2 in our analysis vs. 1.29 in the previous report) and intermediate risks for clear cell (1.06 vs. 1.05) and invasive (1.19 vs. 1.15) and borderline (1.09 vs. 1.06) mucinous cancers. Like the previous report, we saw no increase in risk of invasive serous cancer overall (0.98 vs. 1.00), however we did see an increased risk of low–grade invasive serous cancers (OR=1.13) which are now thought to arise via a different aetiological pathway from their high–grade counterparts. The only subtype for which our results differed appreciably was invasive endometrioid cancers where we saw a 17% increase in risk per 5 kg/m^2 overall, and a 25% increase after excluding high–grade endometrioid cancers which are likely to be misclassified serous tumours (Gilks and Prat 2009), compared to only an 8% increase in the previous study (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

Since endometrioid ovarian tumours are histologically similar to endometrial cancer (Russell 1994), which is strongly associated with obesity (Crosbie, et al. 2010), it seems plausible that obesity might also be a relatively strong risk factor for this subtype of ovarian cancer. The roughly 70–80% risk increases we observed even among the groups of women with highest BMI were, however, considerably lower than the nine–fold risk previously reported for endometrial cancer (Crosbie et al. 2010). Historically, the histopathologic

classification of ovarian cancer cell types has only been modestly reproducible (Hernandez, et al. 1984; Cramer, et al. 1987; Sakamoto, et al. 1994), and particularly problematic was the specific diagnosis of serous versus endometrioid carcinomas (Stalsberg, et al. 1988). A recent development is the recognition that many carcinomas formally considered high grade endometrioid are better classified as high grade serous (Gilks and Prat 2009; Kobel, et al. 2010; Madore, et al. 2010). When we excluded high–grade endometrioid tumours from our analysis the associations with BMI were considerably strengthened while, as for invasive serous cancers, we saw no association with high grade endometrioid tumours. It is thus possible that misclassification of serous and endometrioid tumours may explain, in part, why a significant association between obesity and endometrioid ovarian cancers has not previously been consistently reported and why it was not observed in the previous large pooled analysis which included mostly older studies and did not consider tumour grade (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Time trends in the use of various regimens of HRT, as well as the increasing prevalence of obesity over calendar time, may also play a role.

As in the previous pooled analysis, we observed an association between increasing BMI and risk of borderline ovarian tumours, with the strength of the association somewhat stronger for serous than mucinous tumours. High BMI has been associated with benign ovarian tumours (Jordan, et al. 2007), and there is evidence from epidemiological, histopathological and molecular studies that these borderline tumours may develop from benign tumours in a neoplastic progression (Jordan, et al. 2006). Our finding that low grade but not high grade invasive serous tumours were also associated with BMI supports this theory of progression for low grade serous cancers.

We can only speculate as to why we observed heterogeneity in the association between BMI and risk of invasive serous tumours between pre– and post–menopausal women, however this could not be explained by a higher proportion of G1 tumors in the pre-menopausal group. The endocrine consequences of obesity may have differential effects on the pathogenesis of serous ovarian cancer in pre– and postmenopausal women. Whilst postmenopausal obesity is associated with higher levels of endogenous oestrogen due to the synthesis of oestrogen in body fat (Key, et al. 2001), in premenopausal women, obesity lowers sex–hormone binding globulin (Key et al. 2001; Tworoger, et al. 2006) but does not significantly influence the levels of oestrogens and androgens as the ovaries produce more steroids than the peripheral fat tissue. Other hormonal factors that may mediate the relationship between obesity and risk of ovarian cancer include progesterone (Risch 1998) and insulin (Calle and Kaaks 2004). Compared to women of ‘normal’ weight, premenopausal obese women have reduced serum progesterone levels due to an increase in anovulatory cycles (Key et al. 2001), and there is a significant body of evidence suggesting that progesterone plays a protective role in ovarian carcinogenesis (Risch 1998). Obesity is associated with increased insulin levels, which lead to increases in the insulin–like growth factor–1 (IGF–I) (Calle and Kaaks 2004). There is no clear relation between adiposity and IGF-1 however high levels of IGF-1 have been associated with ovarian cancer in women younger than 55 years of age (Lukanova, et al. 2002).

Our observation that the positive association with BMI was stronger among pre-menopausal women is consistent with the earlier analysis of cohort studies (Schouten et al. 2008). However, in contrast to the recent pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012), we found no suggestion of effect modification by use of HRT in postmenopausal women. Although the overall association did appear to be restricted to women who had never used HRT, this was driven by the stronger associations seen among pre–menopausal women who rarely use HRT. Similarly, the apparent lack of association among HRT users was driven by the strong inverse association with invasive

serous cancers, the most common histological subtype, in this group. For the cancers that showed an overall association with BMI, non–serous invasive cancers and borderline cancers, the risk estimates among post–menopausal women did not differ by use of HRT. Whilst data on recent or current use of menopausal hormonal therapy was not available for the current analyses, the possibility that recent use may modify the relationship between body mass index and ovarian cancer risk deserves further exploration.

Strengths of our study include the large number of cases and controls made possible by pooling data from 15 individual case–control studies. Individual level data were combined into a single dataset following a rigorous data cleaning and harmonization protocol, giving enhanced ability to control for confounding in individual studies (Stukel et al. 2001). Pooling these data increased our statistical power to examine BMI in relation to the different histological subtypes of ovarian cancer, and allowed sub–group analyses to examine the effects by tumour grade, age, menopausal status, and for postmenopausal women, by use of HRT. Additionally, all studies contributing to the pooled analyses were conducted in the past two decades and, aside from early cases from the NEC and USC studies, a total of approximately 1200 cases (10%), there was no overlap with the previous pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Histological misclassification is likely to be considerably less of a concern for these recent studies than in studies conducted in the more distant past, although some degree of misclassification remains likely.

However, as with any pooled–analysis, some limitations must be acknowledged. First the majority of the studies included in the pooled analyses relied upon retrospective self–reports of weight and height. Research has shown that women with higher BMI are more likely to underestimate weight, whereas underweight women are more likely to overestimate body weight (Kuskowska-Wolk, et al. 1989; Troy, et al. 1995; Lawlor, et al. 2002; Taylor, et al. 2006); this may have attenuated the true associations. We cannot exclude the possibility of selection bias due to self–selection of more health conscious women, who are less likely to be overweight or obese, into control groups; this would have lead to overstated risk estimates. Such misclassification, however, is likely to be non–differential with respect to the different histological subtypes. Finally, weight loss several years before the time of cancer diagnosis would, if present, bias risk estimates towards the null although the similar patterns of risk seen for all three measures of BMI, and for analyses of recent BMI restricted to studies that asked women to report their usual weight approximately five years prior to diagnosis, suggest this has not occurred to any great extent.

In summary, obesity appears to moderately increase the risk of developing the less common histological subtypes of ovarian cancer, particularly borderline and low grade invasive serous cancers and endometrioid cancers. With the possible exception of pre–menopausal women, it does not, however, appear to increase risk of the more common high grade invasive serous cancers that account for the majority of ovarian cancer deaths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the fifteen studies included in the pooled analyses of BMI and ovarian cancer.

Study	Diagnosis Years	Age range	Geographic location	Number of: Cases [a]	Number of: Controls [a]	Case Sources (Response Rate)	Histology [b] Invasive cases (%)		Borderline cases (%)		Control Sources (Response Rate)	BMI Measurement: Recent	BMI Measurement: Early adulthood	BMI Measurement: Maximum
Clinic–based														
Mayo Clinic Ovarian Cancer Case Control Study (MAY)	2000–2008	20–91	Upper Midwest, USA	715	945	Mayo Clinic (84%)	Ser Muc End CC Other	405 (57%) 19 (3%) 100 (14%) 44 (6%) 47 (7%)	Ser Muc Other	59 (8%) 27 (4%) 14 (2%)	Women seeking general examinations (65%)	Y		
Population–based														
Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer) (AUS)	2002–2006	18–80	Australia	1579	1485	Cancer registries, treatment centres (84%)	Ser Muc End CC Other	756 (48%) 49 (3%) 150 (9%) 98 (6%) 192 (12%)	Ser Muc Other	150 (9%) 169 (11%) 15 (1%)	Electoral roll (47%)	Y	Y	Y
Connecticut Ovary Study (CON)	1998–2003	34–81	Connecticut, USA	483	551	Cancer registries, pathology departments (69%)	Ser Muc End CC Other	221 (46%) 19 (4%) 74 (15%) 35 (7%) 25 (5%)	Ser Muc Other	69 (14%) 36 (7%) 4 (1%)	Random digit dialling (61%)	Y	Y	
Diseases of the Ovary and their Evaluation Study (DOV)	2002–2005	35–74	Washington, USA	1569	1848	Cancer Surveillance System, SEER (77%)	Ser Muc End CC Other	672 (43%) 33 (2%) 187 (12%) 87 (6%) 176 (11%)	Ser Muc Other	234 (15%) 156 (10%) 24 (2%)	Random digit dialling (69%)	Y	Y	Y
German Ovarian Cancer Study (GER)	1993–1998	21–75	Germany	254	519	Hospital admissions (58%)	Ser Muc End CC Other	106 (42%) 26 (10%) 26 (10%) 6 (2%) 63 (25%)	Ser Muc Other	15 (6%) 9 (4%) 3 (1%)	Population registries (51%)		Y	Y
Hawaii Ovarian Cancer Study (HAW)	1993–2008	18–93	Hawaii, US	883	1089	Cancer registry (78%)	Ser Muc End CC Other	312 (35%) 70 (8%) 116 (13%) 81 (9%) 122 (14%)	Ser Muc Other	88 (10%) 87 (10%) 7 (1%)	Department of Health annual survey (80%)		Y	Y
Hormones and Ovarian Cancer Prediction (HOP)	2003–	25–80	NY, OH and PA, US	771	1803	Cancer registries, pathology databases, physician offices (69%)	Ser Muc End CC Other	364 (47%) 36 (5%) 97 (13%) 52 (7%) 125 (16%)	Ser Muc Other	58 (8%) 29 (4%) 10 (1%)	Random digit dialling (81%)	Y	Y	Y
The Danish Malignant Ovarian Tumour Study (MAL)	1994–1999	35–79	Denmark	744	1552	Danish Cancer Registry, 16 gynecologic departments 79%)	Ser Muc End CC Other	337 (45%) 50 (7%) 75 (10%) 43 (6%) 39 (5%)	Ser Muc Other	103 (14%) 87 (12%) 10 (1%)	Danish Central Population Register (67%)	Y	Y	
North Carolina Ovarian Cancer Study (NCO)	1999–2007	20–75	North Carolina, US	1087	1083	North Carolina Central Cancer Registry (70%)	Ser Muc End CC Other	470 (43%) 43 (4%) 138 (13%) 88 (8%) 122 (11%)	Ser Muc Other	155 (14%) 64 (6%) 5 (0%)	Random digit dialling (63%)	Y	Y	Y

Study	Diagnosis Years	Age range	Geographic location	Number of: Cases [a]	Number of: Controls [a]	Case Sources (Response Rate)	Histology [b]	Invasive cases (%)		Borderline cases (%)		Control Sources (Response Rate)	BMI Measurement: Recent	BMI Measurement: Early adulthood	BMI Measurement: Maximum
New England–based Case–Control Study of Ovarian Cancer (NEC)	1992 – 2008	18–78	New England, US	1960	2097	Hospital tumour boards, State cancer registries (72%)	Ser Muc End CC Other	819 (43%) 89 (5%) 296 (16%) 192 (10%) 70 (4%)	Ser Muc Other	242 (13%) 145 (8%) 35 (2%)	Random digit dialling and townbook selection (69%)	Y	Y	
New Jersey Ovarian Cancer Study (NJO)	2004–2008	23–96	New Jersey, US	224	448	NJ State Cancer Registry (47%)	Ser Muc End CC Other	129 (58%) 11 (5%) 31 (14%) 30 (13%) 23 (10%)			Random digit dialling, Medicare and Medicaid lists, area sampling (40%)	Y	Y	Y
Polish Ovarian Cancer Study (POL)	2001–2003	24–74	Poland	283	1071	Hospitals in Warsaw and Lodz (71%)	Ser Muc End CC Other	116 (41%) 19 (7%) 39 (14%) 10 (4%) 78 (28%)	Ser Muc Other	17 (6%) 3 (1%) 1 (0%)	Electoral roll (67%)		Y	Y
UC Irvine Ovarian Cancer Study (UCI)	1994–2004	18–86	Orange and San Diego counties, US	588	565	Orange County Cancer Surveillance Program, Tumour registry (70%)	Ser Muc End CC Other	211 (36%) 28 (5%) 72 (12%) 37 (6%) 43 (7%)	Ser Muc Other	122 (21%) 74 (13%) 1 (0%)	Random digit dialling (80%)	Y	Y	
UK Ovarian Cancer Population Study (UKO)	2006–	50–76	United Kingdom	687	1026	Gynecologic oncology NHS centres (86%)	Ser Muc End CC Other	348 (51%) 69 (10%) 106 (15%) 65 (9%) 99 (14%)			Postmenopausal women participating in UKCTOPCS* (97%)		Y	
Los Angeles County Case–Control Studies of Ovarian Cancer (USC)	1993–	19–86	Los Angeles, US	1721	1831	Cancer Surveillance Program of Los Angeles (73%)	Ser Muc End CC Other	826 (48%) 112 (7%) 183 (11%) 87 (5%) 110 (6%)	Ser Muc Other	240 (14%) 158 (9%) 5 (0%)	Neighbourhood controls (73%)	Y	Y	

*United Kingdom Collaborative Trial of Ovarian Cancer Screening;

[a]Numbers of participants with body–size information;

[b]S=serous; M=mucinous; E=endometrioid; CC=clear cell; Other includes both ‘other’ histologies and subjects with unknown histology

Table 2

Adjusted[a] pooled odds ratios (95% confidence intervals) for ovarian cancer in relation to BMI, by tumour behaviour[b]

	Invasive					Borderline				
BMI (kg/m^2)	**Studies**	**I^2 (%)**	**Cases**	**Controls**	**pOR (95%CI)**	**Studies**	**I^2 (%)**	**Cases**	**Controls**	**pOR (95%CI)**
Recent BMI										
<18.5	11	26.6	183	282	1.08 (0.84–1.39)	10	0·0	57	281	1.13 (0.82–1.55)
18.5–24.9 (Ref)	11		4020	6796	1.0	10		1080	6599	1.0
25–29.9	11	31.2	2500	4077	1.00 (0.92–1.09)	10	13.8	662	3930	1.23 (1.09–1.39)
30–34.9	11	0.0	1166	1808	1.06 (0.97–1.16)	10	1.1	379	1741	1.61 (1.40–1.85)
35–39.9	11	1.7	511	692	1.21 (1.07–1.38)	10	0.0	150	672	1.68 (1.37–2.06)
≥ 40	11	0.0	383	503	1.22 (1.05–1.41)	9	0.0	137	486	1.96 (1.57–2.46)
Per 5 kg/m^2 [c]	11	47.7			1.04 (1.00–1.08)*	9	0.0			1.18 (1.14–1.23)
Maximum BMI										
<18.5	6	0.0	24	33	1.22 (0.69–2.14)	3	0.0	5	19	1.00 (0.33–3.03)
18.5–24.9 (Ref)	8		1393	2683	1.0	7		296	2548	1.0
25–29.9	8	6.2	1427	2566	1.02 (0.92–1.13)	7	19.7	275	2409	1.13 (0.91–1.41)
30–34.9	8	0.0	823	1335	1.17 (1.04–1.31)	7	17.0	199	1236	1.58 (1.24–2.03)
35–39.9	8	60.2	388	592	1.29 (0.99–1.68)*	6	0.0	105	544	1.70 (1.30–2.22)
≥ 40	8	15.9	310	490	1.16 (0.96–1.41)	5	30.5	108	455	1.90 (1.35–2.68)
Per 5 kg/m^2 [c]	8	45.3			1.06 (1.01–1.11)	7	35.8			1.17 (1.08–1.26)
BMI early adulthood										
<18.5	14	0.0	1646	2931	0.94 (0.88–1.01)	12	13.0	416	2718	0.97 (0.85–1.11)
18.5–24.9 (Ref)	14		7278	12364	1.0	12		1819	11245	1.0
25–29.9	14	0.0	788	1151	1.12 (1.01–1.24)	11	0.0	248	983	1.27 (1.09–1.49)
30–34.9	14	0.0	176	233	1.21 (0.98–1.49)	10	0.0	66	210	1.32 (0.98–1.78)
≥35	12	0.0	76	108	1.08 (0.78–1.49)	10	0.0	43	100	1.86 (1.25–2.78)
Per 5 kg/m^2 [c]	14				1.08 (1.03–1.14)	12				1.15 (1.08–1.24)

[a] Stratified by age in 5–year groups and adjusted for parity (0,1,2,3,4+ full–term births), hormonal contraceptive use (0, ≤ 60, >60 months), family history of breast or ovarian cancer in a first degree relative and, where appropriate, race/ethnicity.

[b] Numbers may not sum to total because of missing data

[c] Excludes women in the underweight range (BMI < 18.5 kg/m^2)

* Significant heterogeneity noted (p–value for heterogeneity <0·05)

Table 3

Adjusted[a] pooled odds ratios (95% confidence intervals) for invasive ovarian cancer in relation to BMI, by histological subtype[b]

			Serous		Mucinous		Endometrioid		Clear Cell	
	Studies (n)	Controls (n)	Cases (n)	pOR (95% CI)	Cases (n)	pOR (95% CI)	Cases (n)	pOR (95% CI)	Cases (n)	pOR (95% CI)
Recent BMI	11									
<18.5		282	91	0.93 (0.72–1.20)	19	2.48 (1.03–4.51)	33	1.47 (0.98–2.21)	18	2.69 (1.34–5.41)
18.5–24.9 (Ref)		6796	2475	1.0	207	1.0	592	1.0	353	1.0
25–29.9		4077	1477	0.93 (0.86–1.02)	134	1.19 (0.95–1.50)	380	1.12 (0.96–1.30)	227	1.05 (0.79–1.40)*
30–34.9		1808	665	0.94 (0.84–1.05)	68	1.48 (0.92–2.37)*	205	1.37 (1.14–1.64)	98	1.14 (0.79–1.63)*
35–39.9		692	275	1.06 (0.90–1.23)	29	2.03 (1.10–3.77)	97	1.74 (1.36–2.23)	48	1.59 (1.14–2.24)
≥ 40		503	170	0.89 (0.74–1.08)	29	2.70 (1.76–4.16)	82	1.86 (1.42–2.24)	37	1.58 (1.04–2.40)
Per 5 kg/m^2 [c]				0.98 (0.94–1.02)		1.19 (1.06–1.32)		1.17 (1.11–1.23)		1.06 (0.96–1.17)*
Maximum BMI	8									
18.5–24.9 (Ref)		2683	793	1.0	86	1.0	177	1.0	120	1.0
25–29.9		2566	787	0.93 (0.73–1.17)*	84	1.22 (0.88–1.69)	194	1.20 (0.96–1.45)	112	0.95 (0.72–1.26)
30–34.9		1335	445	1.03 (0.89–1.18)	34	1.08 (0.70–1.67)	129	1.63 (1.26–2.10)	69	1.22 (0.88–1.70)
35–39.9		592	199	1.18 (0.81–1.72)*	20	1.30 (0.74–2.27)	67	1.78 (1.29–2.46)	33	1.30 (0.84–2.00)
≥ 40		490	147	0.98 (0.68–1.41)*	17	1.37 (0.76–2.46)	60	1.82 (1.29–2.56)	27	1.12 (0.70–1.82)
Per 5 kg/m^2 [c]				1.00 (0.93–1.07)		1.05 (0.94–1.17)		1.18 (1.09–1.28)		1.04 (0.95–1.13)
Early adult	14									
<18.5		2931	918	0.94 (0.86–1.03)	102	0.94 (0.74–1.19)	243	0.93 (0.80–1.09)	164	1.08 (0.83–1.39)
18.5–24.9 (Ref)		12364	4161	1.0	465	1.0	1121	1.0	648	1.0
25–29.9		1151	401	1.04 (0.92–1.18)	54	1.20 (0.88–1.64)	150	1.33 (1.10–1.62)	64	1.05 (0.75–1.45)
30–34.9		231	73	1.03 (0.78–1.37)	19	1.90 (1.12–3.21)	39	1.51 (1.03–2.21)	14	1.10 (0.61–1.99)
≥ 35		110	36	1.15 (0.75–1.76)	7	2.18 (0.96–4.95)	18	1.85 (1.05–3.24)	6	2.73 (1.08–6.88)
Per 5 kg/m^2 [c]				1.02 (0.95–1.10)		1.22 (1.07–1.40)		1.14 (1.04–1.25)		1.02 (0.89–1.16)

[a] Stratified by age in 5–year groups and adjusted for parity (0,1,2,3,4+ full–term births), hormonal contraceptive use (0, ≤ 60, >60 months), family history of breast or ovarian cancer in a first degree relative and, where appropriate, race/ethnicity; pooled across study sites using random effects models.

[b] Numbers may not sum to total because of missing data

[c] Excludes women in the underweight range (BMI < 18.5 kg/m^2)

* Significant heterogeneity noted (p–value for heterogeneity <0·05)

Table 4

Adjusted[a] pooled odds ratios (95% confidence intervals) for borderline ovarian cancer in relation to BMI, by histological subtype.

			Serous [b]		Mucinous [b]	
	Studies (n)	**Controls (n)**	**Cases (n)**	**pOR (95% CI)**	**Cases (n)**	**pOR (95% CI)**
Recent BMI	10					
<18.5		281	23	1.12 (0.70–1.79)	33	1.61 (1.08–2.39)
18.5–24.9 (Ref)		6599	568	1.0	454	1.0
25–29.9		3930	403	1.40 (1.22–1.62)	234	1.08 (0.91–1.28)
30–34.9		1741	236	1.86 (1.55–2.24)	122	1.32 (1.05–1.67)
35–39.9		672	101	2.11 (1.66–2.70)	41	1.29 (0.91–1.84)
≥ 40		486	85	2.23 (1.69–2.94)	41	1.68 (1.16–2.43)
Per 5 kg/m^2 [c]				1.24 (1.18–1.30)		1.09 (1.02–1.16)
Maximum BMI	7					
18.5–24.9 (Ref)		2548	135	1.0	138	1.0
25–29.9		2409	153	1.39 (1.00–1.93)	113	0.99 (0.75–1.30)
30–34.9		1236	115	2.00 (1.51–2.65)	78	1.39 (0.99–1.96)
35–39.9		544	66	2.40 (1.71–3.38)	35	1.26 (0.68–2.32)
≥ 40		455	71	2.73 (1.92–3.88)	30	1.29 (0.79–2.11)
Per 5 kg/m^2 [c]				1.25 (1.17–1.34)		1.09 (0.98–1.21)
BMI early adulthood	12					
<18.5		2718	222	0.90 (0.77–1.06)	171	1.07 (0.88–1.31)
18.5–24.9 (Ref)		11245	1034	1.0	699	1.0
25–29.9		983	152	1.40 (1.12–1.74)	86	1.22 (0.95–1.55)
30–34.9		210	40	1.48 (1.03–2.14)	26	1.57 (1.00–2.47)
≥ 35		100	29	2.34 (1.47–3.74)	12	2.00 (1.00–4.01)
Per 5 kg/m^2 [c]				1.22 (1.12–1.33)		1.11 (0.99–1.24)

[a] Stratified by age in 5–year groups and adjusted for parity (0,1,2,3,4+ full–term births), hormonal contraceptive use (0, ≤ 60, >60 months), family history of breast or ovarian cancer in a first degree relative and, where appropriate, race/ethnicity; pooled across study sites using random effects models.

[b] Numbers may not sum to total because of missing data

[c] Excludes women in the underweight range (BMI < 18.5 kg/m^2)

Table 5

Adjusted[a] odds ratios (95% confidence intervals) for ovarian cancer in relation to recent BMI, by menopausal status and use of hormone replacement therapy.

	Controls (n)	Invasive Serous[b]		All other Invasive Cancers[b]		All Borderline [b]	
		Cases (n)	OR (95% CI)	Cases (n)	OR (95% CI)	Cases (n)	OR (95% CI)
Premenopausal women							
18.5–24.9 (Ref)	2049	484	1.0	514	1.0	529	1.0
25–29.9	919	272	1.23 (1.03–1.47)	275	1.26 (1.06–1.51)	254	1.22 (1.02–1.46)
30–34.9	417	121	1.21 (0.96–1.54)	139	1.40 (1.11–1.76)	147	1.63 (1.30–2.05)
35–39.9	152	55	1.50 (1.07–2.10)	76	1.78 (1.30–2.45)	65	2.00 (1.44–2.78)
≥ 40	136	47	1.43 (0.99–2.06)	72	1.81 (1.30–2.52)	52	1.76 (1.22–2.53)
Per 5 kg/m^2 [c]			1.11 (1.04–1.18)		1.17 (1.11–1.24)		1.19 (1.12–1.27)
Postmenopausal women, no HRT							
18.5–24.9 (Ref)	1343	652	1.0	347	1.0	157	1.0
25–29.9	1054	425	0.87 (0.74–1.01)	312	1.20 (1.00–1.43)	124	1.17 (0.90–1.51)
30–34.9	522	216	0.93 (0.77–1.12)	153	1.24 (0.99–1.55)	82	1.60 (1.19–2.16)
35–39.9	226	87	0.89 (0.67–1.16)	67	1.24 (0.91–1.69)	30	1.36 (0.88–2.09)
≥ 40	157	61	0.87 (0.63–1.21)	65	1.64 (1.18–2.29)	33	2.12 (1.37–3.29)
Per 5 kg/m^2 [c]			0.97 (0.92–1.03)		1.10 (1.03–1.17)		1.17 (1.08–1.27)
Postmenopausal women who used HRT							
18.5–24.9 (Ref)	1650	778	1.0	313	1.0	138	1.0
25–29.9	1123	440	0.86 (0.75–1.00)	221	1.08 (0.89–1.31)	112	1.35 (1.03–1.76)
30–34.9	480	183	0.86 (0.71–1.05)	101	1.19 (0.92–1.54)	60	1.64 (1.18–2.28)
35–39.9	167	75	1.08 (0.78–1.45)	31	1.15 (0.76–1.74)	20	1.67 (1.00–2.78)
≥ 40	111	23	0.49 (0.30–0.77)	31	1.64 (1.06–2.52)	13	1.48 (0.80–2.76)
Per 5 kg/m^2 [c]			0.92 (0.87–0.98)		1.09 (1.01–1.18)		1.16 (1.05–1.28)

[a] Stratified by study site (AUS, DOV, HOP, MAY, NEC, NJO, UCI, USC) and age in 5–year groups, and adjusted for parity (0,1,2,3,4+ full–term births), hormonal contraceptive use (0, ≤ 60, >60 months), family history of breast or ovarian cancer in a first degree relative.

[b] Numbers may not sum to total because of missing data

[c] Excludes women in the underweight range (BMI < 18.5 kg/m^2)