EUROPEAN JOURNAL OF CANCER 43 (2007) 690–709

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Obesity and the risk of epithelial ovarian cancer: A systematic review and meta-analysis

Catherine M. Olsen[a,b,*], *Adèle C. Green*[a], *David C. Whiteman*[a], *Shahram Sadeghi*[a,b], *Fariba Kolahdooz*[a,b], *Penelope M. Webb*[a]

[a]*Cancer and Population Studies Group, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Herston, Brisbane, Qld 4029, Australia*

[b]*School of Population Health, University of Queensland, Brisbane, Australia*

ARTICLE INFO

Article history:
Received 9 September 2006
Received in revised form 2 November 2006
Accepted 27 November 2006
Available online 12 January 2007

Keywords:
Epidemiology
Ovarian neoplasms
Obesity
Body mass index
Body weight

ABSTRACT

Obesity is a risk factor for several hormone-related cancers but evidence for an effect on risk of epithelial ovarian cancer remains inconclusive. Many studies evaluating this association have had insufficient statistical power to detect modest effects, particularly for histological subtypes of ovarian cancer. We have therefore assembled the published evidence on obesity and ovarian cancer in a systematic literature review and meta-analysis. We identified eligible studies using Medline and manual review of retrieved references, and included all population-based studies that assessed the association between overweight, body mass index (BMI 25–29.9) and obesity (BMI $\geqslant$ 30) and histologically confirmed ovarian cancer. Meta-analysis was restricted to those studies that expressed effect as an odds ratio (OR), risk ratio, or standardised incidence ratio and 95% confidence interval (CI). We identified 28 eligible studies, of which 16 on adult obesity and 9 on obesity in early adulthood were suitable for meta-analysis. Overall, 24 of 28 studies reported a positive association between obesity and ovarian cancer, and in 10 this reached statistical significance. The pooled effect estimate for adult obesity was 1.3 (95%CI 1.1–1.5) with a smaller increased risk for overweight (OR 1.2; 95%CI 1.0–1.3). The pooled OR was stronger among case–control studies (OR = 1.5) than cohort studies (OR = 1.1). Overweight/obesity in early adulthood was also associated with an increased risk of ovarian cancer. There was no evidence that the association varied for the different histological subtypes of ovarian cancer. Ovarian cancer should be added to the list of cancers likely to be related to obesity.

1. Introduction

Ovarian cancer remains the leading cause of death from gynaecological malignancy.[1] Due to a lack of effective screening approaches, most women present at an advanced stage associated with poor survival, and thus preventive strategies are urgently needed to reduce mortality. A number of studies have found an association between obesity and hormone-dependent cancers including endometrial cancer and postmenopausal breast cancer[2–4] but the relation with ovarian

* *Corresponding author:* Address: Cancer and Population Studies Group, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Herston, Brisbane, Qld 4029, Australia. Tel.: +61 7 3362 0265; fax: +61 7 3845 3502.
E-mail address: Catherine.Olsen@qimr.edu.au (C.M. Olsen).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.11.010

cancer is unclear.[5] The prevalence of overweight and obesity is increasing dramatically in most parts of the world, and is generally higher in women than in men.[6] This is predicted to have major consequences for the incidence of obesity-related diseases. Quantitative assessment of the association between obesity and ovarian cancer is thus important and may also provide further insight into the aetiology of this complex disease.

The interpretation of the results of epidemiologic studies evaluating the relation between obesity and ovarian cancer has been hampered by differences in methodology and inconsistent approaches in defining obesity. A systematic review and meta-analysis conducted by Purdie and colleagues[7] in 2001 concluded that there was a small-to-moderate positive relation between high body mass index (BMI) and ovarian cancer risk,[7] with significant pooled relative risks (RR) for the effect of the highest relative weight or BMI relative to the lowest category of 1.4 for 11 population-based case–control studies and 1.2 for five cohort studies. The definition of obesity was not consistent across these studies, and the meta-analysis compared only the highest category of weight or BMI to the lowest category presented for each study. Furthermore, there have been a significant number of other relevant epidemiological studies published on the association between obesity and ovarian cancer since this analysis was conducted. In addition, the previous review focused on BMI in the period of time of diagnosis, which may not be the relevant etiologic window. Since obesity early in life has been associated with an increased risk of other hormone-dependent cancers, and a reduced risk of premenopausal breast cancer[8,9], it is also relevant to evaluate the association between BMI in early adulthood and risk of ovarian cancer.

The aim of this review was to systematically evaluate the published evidence about the relationship between obesity and ovarian cancer. We also conducted a meta-analysis of population-based studies to estimate the magnitude of the associations between BMI at different ages and ovarian cancer risk.

2. Methods

2.1. Selection of studies

Eligible studies were identified using PubMed® software to search Medline (US National Library of Medicine, Bethesda, MD) for relevant articles published up to April 2006, and by manually searching the reference list of the retrieved articles. For computer searches, we used the following MeSH terms or text words: 'obesity', 'weight', 'body weight', 'body mass', 'body mass index', 'anthropometric', 'anthropometry', combined with 'ovarian cancer', 'ovarian malignancy' or 'ovarian neoplasm'. The search was not limited to studies published in English.

We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria. Where multiple reports from one study were found, the most recent or the most complete publication was used.

Studies were included in the systematic review if they were a population-based case–control or cohort study that permitted assessment of an association between overweight or obesity and histologically confirmed ovarian cancer. Studies were included in the meta-analysis if the following criteria were fulfilled: (1) clear definition of obesity as defined by a body mass index (BMI) in kg/m^2; (2) results expressed as an odds ratio (OR), a risk ratio (RR), or standardised incidence ratio (SIR) together with 95% confidence intervals (CI). We included studies reporting the different measures of relative risk since ovarian cancer is a rare disease, and in such instances ORs and SIRs provide a valid estimate of the relative risk. We did not include case–control studies that used hospitalised controls since the prevalence of obesity is known to be higher in hospitalised patients[10], thus selection of such controls might result in biased estimates of effect.

The following information was recorded for each study: study type, years of data collection (case–control studies), duration of follow-up (cohort studies), age-range of participants, country, variables for which statistical adjustment was performed, number of cases and controls or person years, timing and categories of BMI measurement, point estimates (RR, OR, or SIR) and 95% CIs. When several risk estimates were presented, we used those adjusted for the greatest number of potential confounders.

2.2. Statistical methods

We conducted pooling using random-effects models. For adult BMI, we calculated weighted pooled risk estimates for two categories of BMI as defined by the World Health Organisation (WHO)[11] for adults (age 24+): overweight (BMI 25–29.9) and obesity (BMI of 30 or more) compared to 'normal' weight (BMI 18.5–24.9) as the reference category. Where non-standard categories of BMI were used, we selected the category most similar to those defined by the WHO. We included studies that used a reference BMI category that was less than the WHO defined 'normal BMI', if the RR estimate for the 'normal BMI' category was 1.0 compared to the reference category. We assessed heterogeneity for each pooled estimate with a Cochran's Q test for heterogeneity. We also stratified the meta-analyses by study type. Finally, we conducted sensitivity analyses omitting each study in turn to determine whether the results could have been influenced excessively by a single study.

For BMI in young adulthood, we included studies reporting on BMI from 17 to 20 years. This therefore includes individuals considered by WHO as 'adolescents' (10–19 years),[12] and those defined as 'youth' by the United Nations (15–24 years). In this meta-analysis, we pooled the studies to present the effect of the highest category of BMI presented for each study relative to the given reference category. The highest categories ranged from $\geqslant 21.7$ to $\geqslant 30\ kg/m^2$.

We evaluated publication bias by qualitatively assessing a funnel plot on the natural logarithms of the effect estimates for the risk of ovarian cancer related to obesity *versus* their variance.[13]

3. Results

The primary computerised literature search identified 121 potentially relevant studies. On screening the titles and abstracts, 76 were excluded because they were not relevant, or

were hospital-based case–control studies. We retrieved 45 manuscripts for further review, of which seventeen population-based case–control studies,[7,14–29] 11 cohort studies,[2,30–39] one previous meta-analysis[7] and two pooled analyses[40,41] met the criteria for inclusion in the systematic review. We did not include the pooled estimates by Kurian and colleagues[40] or Harris and colleagues[41] in the meta-analysis of adult BMI because four of the studies included in each pooled analysis did not meet our inclusion criteria. In addition, the analysis conducted by Harris and colleagues[41] was restricted to low-malignant potential tumours, and that by Kurian and colleagues[40] did not provide an effect estimate for women overall, but only by histological subtype. Similarly we did not include the pooled estimates from the study by Purdie and colleagues[7] because all eligible studies included in this pooled analysis had already been included in the cur-

Table 1 – Characteristics of case–control studies investigating the association between body mass index in adulthood and epithelial ovarian cancer

Author, publication date, country	Study date	Age range[a]	Cases/Controls	Exposure measure
Peterson, 2006 USA	1993–1995 1998–2001	20–79	700 5943	Self-reported One-year prior to diagnosis/interview; age 20
Greer, 2006 USA	1994–1998	20–68	762 1348	Self-reported BMI calculated from 'recent weight'; age 18
Hoyo, 2005 USA	1999–2003	20–74	593 628	Self-reported One-year prior to diagnosis/interview; age 18
Riman, 2004 Sweden	1993–1995	50–74	655 3899	Self-reported One-year prior to interview
Pike, 2004 USA	1992–1998	18–74	467 660	One-year prior to diagnosis/interview
Pan, 2004 Canada	1994–1997	21–76	442 2492	Self-reported Two years prior to interview
Mills, 2004 USA	2000–2001	18+	256 1122	Self-reported
Lubin, 2003 Israel	1994–1999	Not given	1269 2111	Self-reported Weight 'most adult life'; age 18
Kuper, 2002 USA	1992–1997	Not given	563 523	Self-reported; age 18 One-year prior to diagnosis/interview
Lukanova, 2002 USA, Sweden, Italy	1985–2002	30–70	122 233	Three cohorts – weight/height self-reported or measured at baseline
Purdie, 2001 Australia	1990–1993	18–79	775 846	Self-reported 'Usual weight before your illness'
Ness, 2002 USA	1994–1998	20–69	767 1367	Self-reported 6 months prior to diagnosis/interview
Farrow, 1989 USA	1975–1979	35–74	277 665	Self-reported Weight at age 30, current height
Slattery, 1989 USA	1984–1987	20–79	85 492	Self-reported 'Adult height and weight'
Shu, 1989 China	1984–1986	18–70	172 172	Self-reported 'Average adult weight'
Cramer, 1987 USA	1978–1981	Not given	215 215	Self-reported
Casagrande, 1979 USA	1973–1976	25–49	150 150	Self-reported Weight and height at date of diagnosis; for controls, at date of diagnosis of matched case

a Age at diagnosis (age at interview for controls)

Table 2 – Characteristics of cohort studies investigating the association between body mass index in adulthood and epithelial ovarian cancer

Author, publication date, country	Study date	Age range[a]	Cases/Cohort size	Exposure measure
Lukanova, 2006 Sweden	1985–1996	29–61	90 35,362	Measured at baseline
Rapp, 2005 Austria	1985–2001	19–93	121 78,484	Measured at baseline
Niwa, 2005 Japan	1988–1999	40–79	38 36,456	Self-reported at baseline
Anderson, 2004 USA	1986–2000	55–69	223 41,836	Measured at baseline; Self-reported at age 18
Engeland, 2003 Norway	1963–1999	20–74	7882 1,100,000	Measured at baseline (adult BMI) Measured at mean age 17 years (range 14–19)
Schouten, 2003 The Netherlands	1986–1993	55–69	172 62,573	Self-reported at baseline Self-reported at age 20
Jonsson, 2003 Sweden	1969–1997	44–83	118 11,598	Self-reported at baseline
Fairfield, 2006 USA	1976–1996	30–55	402 109,445	Self-reported; Height at baseline Current (recent) weight used to calculate BMI Self-reported at age 18
Wolk, 2001 Sweden	1964–1993	Not given	77 19,964	Obese cohort: Height and weight recorded from hospital records
Mink, 1996 USA	1986–1992	55–69	97 31,396	Self-reported at baseline
Törnberg, 1994 Sweden	1963–1987	25–75	330 47,003	Measured at baseline

a Age at baseline.

rent meta-analysis. The individual studies are summarised in Tables 1 and 2 for case–control and cohort studies, respectively. Study results are presented in Appendices 1 and 2.

3.1. *Adult BMI*

Of the 17 case–control studies, seven reported a significant positive relationship for the highest category of BMI and risk of ovarian cancer,[7,15,18,20,21,24,27] and a further nine reported a positive but non-significant association.[14,17,19,22,23,25,26,28,29] Only one case–control study[16] reported a significant inverse relationship and this was only in comparison to a non-standard reference group of <23 kg/m^2 (Appendix 1). Three of the 11 cohort studies reported a significantly increased risk for the highest category of BMI,[33,36,39] and a further five reported a non-significantly increased risk.[2,30,31,35,37] Two cohort

Table 3 – Meta–analysis results: BMI and epithelial ovarian cancer

	BMI category	Pooled effect estimate (95%CI)	*P* heterogeneity	Number of studies
BMI in adulthood				
Overall	Obese	1.30 (1.12–1.50)	0.001	16
Case–control studies	Obese	1.49 (1.29–1.72)	0.24	8
Cohort studies	Obese	1.12 (0.95–1.32)	0.04	8
Overall	Overweight	1.16 (1.01–1.32)	0.001	14
Case–control studies	Overweight	1.19 (0.99–1.44)	0.02	8
Cohort studies	Overweight	1.07 (0.92–1.25)	0.14	6
BMI 17–20 years				
Overall	Overweight/obese	1.22 (1.02–1.45)	0.09	9
Case–control studies	Overweight/obese	1.21 (0.97–1.52)	0.10	5
Cohort studies	Overweight/obese	1.22 (0.88–1.70)	0.13	4

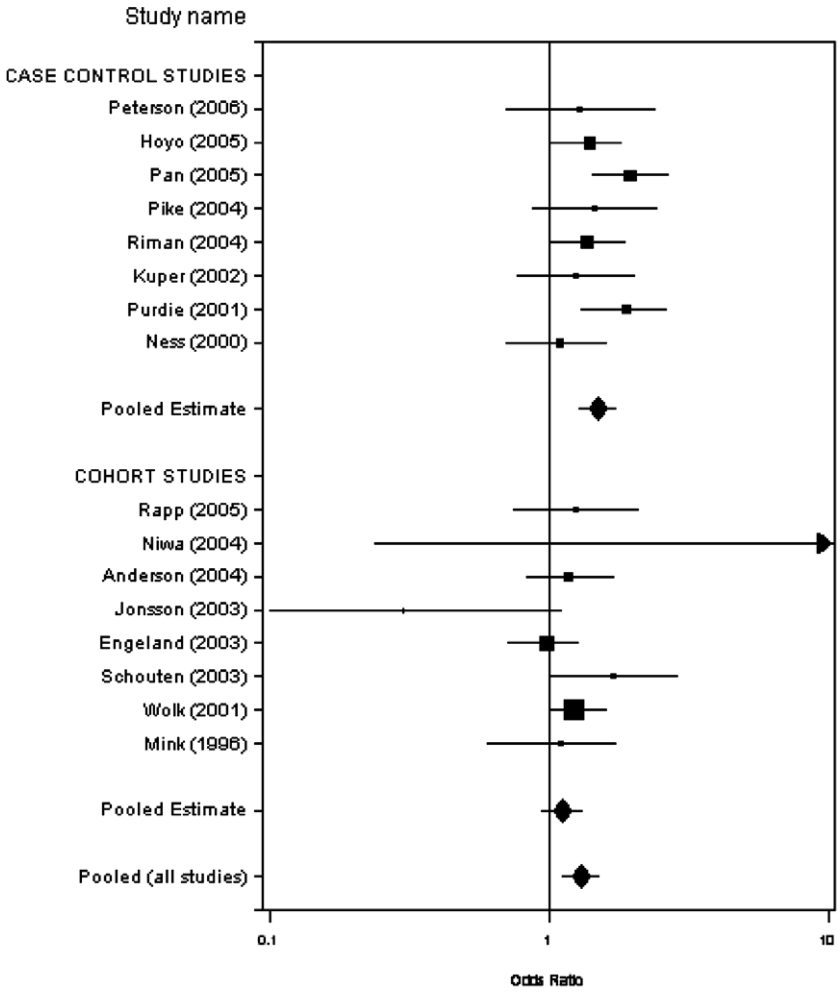

Fig. 1 – Forest plot of the association between adult obesity and ovarian cancer using a random-effects model. Each line represents an individual study result with the width of the horizontal line, indicating 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of the study.

studies reported no relationship,[32,38] and only one reported a non-significant inverse association.[34]

Sixteen of the 28 studies identified in this review presented risk estimates for measures of 'obesity' compared to BMI in the 'normal' range (eight case–control studies[7,15,17,19–21,23,28] and eight cohort studies,[2,30–34,36,37]) and 14 studies presented risk estimates for 'overweight' women compared to 'normal' women (eight case–control studies[7,15,17,19–21,23,28] and six cohort studies.[2,30–34]) These studies were thus sufficiently comparable to permit meta-analysis.

For all studies, the pooled RR of ovarian cancer for obese women compared with those in the 'normal' range was 1.30 (95%CI 1.12–1.50) with significant heterogeneity ($p = 0.001$) (Table 3, Fig. 1). Sensitivity analysis revealed that the effect estimate from one cohort study[32] significantly affected the summary statistics: omitting this study, the pooled RR for all studies was 1.35 (95% CI 1.19–1.54) with no significant heterogeneity ($p = 0.1$). For the eight case–control studies, the pooled RR was 1.49 (95% CI 1.29–1.72) with no evidence of heterogeneity ($p = 0.24$). The summary statistics were not altered by sensitivity analyses, with the pooled RR ranging from 1.44 to 1.55. For the eight cohort studies, the pooled RR was 1.12 (95% CI 0.95–1.32) with evidence of statistical heterogeneity ($p = 0.04$). Omitting the cohort studies that did not control for potential confounders including age and parity and/or oral contraceptive use[2,32,36,37] made no material change to the summary statistics (pooled RR 1.12; 95% CI 0.64–1.96), but did reduce the heterogeneity somewhat ($p = 0.08$). Sensitivity analysis again showed that one cohort study[32] was significantly affecting the summary statistics: omitting this, the pooled RR for cohort studies was higher (1.20; 95% CI 1.01–1.42), with no evidence of heterogeneity ($p = 0.31$). The summary statistics were not significantly influenced by any other cohort study. Omitting the three cohort studies in which BMI was measured up to 25 years or more before diagnosis[32,34,36] resulted in a pooled RR of 1.26 (95% CI 1.01–1.57; $p = 0.78$).

For all studies, the pooled RR of ovarian cancer in women in the overweight BMI category compared to those in the 'normal' category was 1.16 (95% CI 1.01–1.32) with significant heterogeneity ($p = 0.001$) (Fig. 2). After stratifying by study-type, the pooled RR estimates were 1.19 (95% CI 0.99–1.44) for case–control studies and 1.07 (95% CI 0.92–1.25) for cohort studies. Heterogeneity was evident among the case–control studies ($p = 0.02$); this was removed when the study by Pan

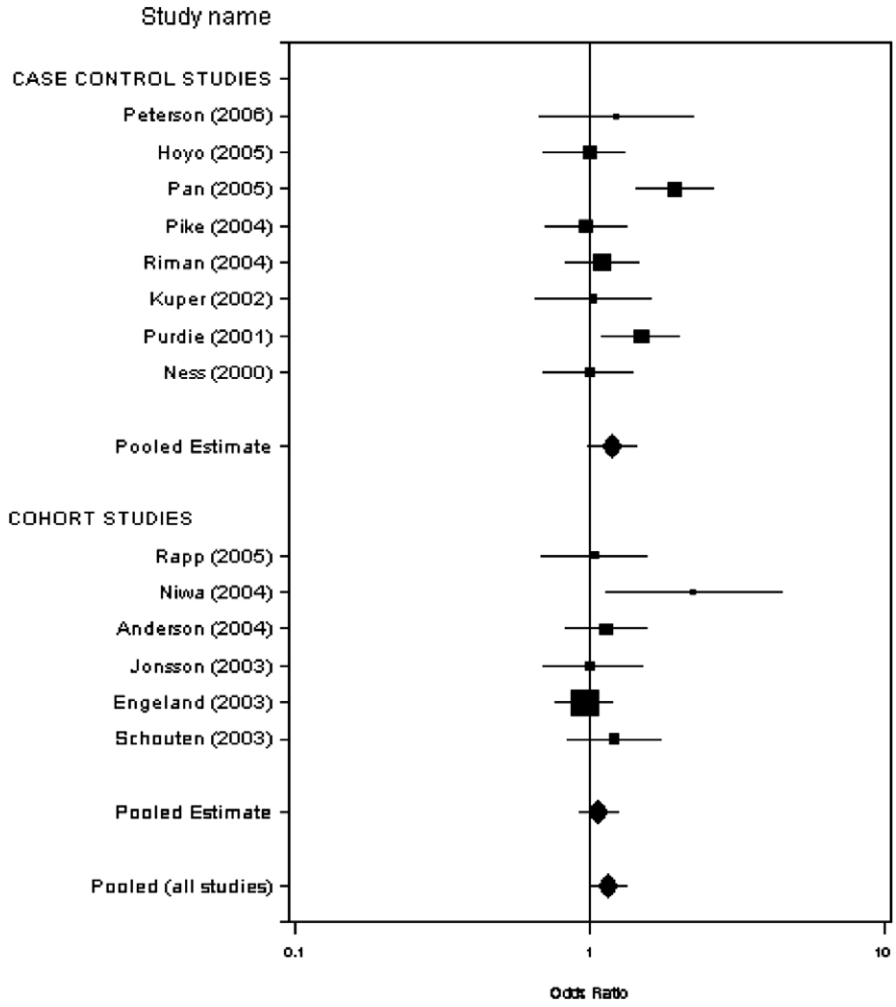

Fig. 2 – Forest plot of the association between adult overweight and ovarian cancer using a random-effects model. Each line represents an individual study result with the width of the horizontal line, indicating 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of the study.

and colleagues[20] was excluded (pooled RR 1.11; 95% CI 0.98–1.25; $p = 0.47$). The study by Pan and colleagues showed a stronger association between BMI in the 'overweight' range and risk of ovarian cancer (OR 1.16; 95% CI 0.90–1.50) than was found in the other studies (Fig. 2). We cannot explain why this study showed a stronger association as it did not differ significantly from the other case–control studies included in the meta-analysis in terms of the population profile, study design or implementation. No other case–control study significantly influenced the study statistics which ranged from 1.11 to 1.23 omitting individual studies. We observed no heterogeneity for effect estimates among cohort studies ($p = 0.14$), with pooled RRs ranging from 1.06 to 1.16 after omitting individual studies.

3.2. *Menopausal status*

Three case–control studies[7,17,28] and one cohort study[35] stratified their analyses by menopausal status. Menopause was clearly defined in all studies, and women with uncertain menopausal status were excluded from the analyses. Three of the four studies[7,17,35] reported higher risk estimates associated with high BMI among premenopausal women, and a smaller increased risk[7] or no increased risk associated with high BMI[17,35] for postmenopausal women. Only the case–control study by Peterson and colleagues[28] reported lower risk estimates for overweight or obesity in premenopausal women than postmenopausal women.

3.3. *Histological subtypes*

Six case–control studies,[7,14,17,21,24,29] two cohort studies[32,35] and one pooled analysis[40] provided information on adult BMI and risk of the major histological subtypes of epithelial ovarian cancer (Table 4). Only one study,[24] and the pooled analysis by Kurian and colleagues[40] found a significant increasing risk with increasing BMI for the endometrioid subtype. Farrow and colleagues[24] reported an increased risk for the highest category of BMI in premenopausal women only (OR 8.9; 95%CI 1.8–44.3). Greer and colleagues[14] reported a non-significantly increased risk for nulliparous women only (OR2.7; 95% CI 1.0–7.6). Three other studies[7,17,21] found no association between high BMI and risk of the endometrioid subtype.

Table 4 – Adult BMI and risk of epithelial ovarian cancer by histological subtype

		Serous OR (95%CI)	Mucinous OR (95%CI)	Endometrioid OR (95%CI)	Clear-cell OR (95%CI)
Greer *et al.* (2006)	<21.8	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Nulliparous	>28.7	3.4 (1.5–7.8)	2.3 (0.8–6.4)	2.7 (1.0–7.6)	1.2 (0.4–3.7)
Parous	>28.7	1.2 (0.8–1.8)	1.2 (0.4–1.5)	1.2 (0.6–2.3)	0.5 (0.1–1.5)
Riman *et al.* (2004)	<22	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	22–24.9	1.0 (0.7–1.4)	0.9 (0.4–2.1)	1.1 (0.7–1.7)	0.8 (0.3–2.2)
	25–26.9	0.9 (0.6–1.3)	0.9 (0.8–4.4)	1.2 (0.7–1.9)	1.2 (0.4–3.4)
	27–29.9	0.9 (0.6–1.3)	1.1 (0.4–2.9)	1.3 (0.8–2.1)	2.2 (0.8–5.7)
	⩾30	0.9 (0.6–1.4)	1.8 (1.2–6.6)	1.3 (0.8–2.4)	2.7 (1.0–7.5)
Mills *et al.* (2004)	<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)[a]	
	25–29	1.1 (0.7–1.8)	1.9 (0.5–6.8)	1.7 (0.8–3.5)	
	⩾30	0.8 (0.4–1.5)	2.8 (0.8–10.3)	1.7 (0.8–3.8)	
Engeland *et al.* (2003)		No significant relationship with any subtype[b]			
Fairfield *et al.* (2002)		No relationship[b]			
Kuper *et al.* (2002)	<20	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
	20–24.9	1.2 (0.7–2.1)	0.8 (0.4–1.7)	0.9 (0.5–1.8)	
	25–29.9	1.0 (0.5–1.8)	1.3 (0.6–2.9)	0.9 (0.4–1.8)	
	⩾30	1.3 (0.7–2.5)	1.3 (0.5–3.1)	1.0 (0.4–2.1)	
Purdie *et al.* (2001)	Normal BMI (35^{th}–65^{th})	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	High BMI⩾85^{th}	2.1 (1.5–3.1)	1.6 (0.8–3.3)	0.9 (0.4–2.1)	1.9 (0.8–4.7)
Farrow *et al.* (1989)	<19.8	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
	19.8–20.99	1.5 (0.7–3.0)	0.5 (0.2–1.6)	1.7 (0.3–10.2)	
	21–22.29	1.2 (0.6–2.4)	1.0 (0.4–2.5)	2.0 (0.4–11.4)	
	22.3–24.09	1.1 (0.5–2.3)	1.4 (0.6–3.3)	4.1 (0.8–19.8)	
	⩾24.1	2.2 (1.1–4.2)	0.7 (0.3–2.1)	4.7 (1.0–22.7)	
Kurian *et al.* (2005) (pooled analysis)	<24	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
	⩾24	0.7 (0.6–0.9)	1.3 (0.9–2.0)	1.3 (1.0–1.9)	0.9 (0.6–1.6)

a Endometrioid and clear-cell subtypes combined.
b Data were not presented.

Three studies reported significantly increased risks associated with the highest category of BMI for the serous subtype[7,14,24]: Purdie and colleagues[7] reported an OR of 2.1 (95% CI 1.5–3.1), Farrow and colleagues[24] reported an overall OR of 2.2 (95% CI 1.1–4.2) with a stronger effect among premenopausal women, while Greer and colleagues[14] observed a significantly increased risk in nulliparous women only (OR 3.4; 95% CI 1.5–7.8). Five other studies,[17,21,29,32,35] and the pooled analysis[40] found no association between overweight or obesity and the serous subtype. Only one of eight studies[21] observed a significantly increased risk associated with overweight or obesity for the mucinous subtype (OR 1.8; 95% CI 1.2–6.6), although a further three studies[7,17,29] and the pooled analysis[42] reported non-significant increased risks associated with the highest category of BMI. Only one study observed a significantly increased risk associated with overweight or obesity for the clear-cell subtype[21] (OR 2.7; 95% CI 1.0–7.5); two other studies[7,14] and the pooled analysis[40] found no association.

3.4. *BMI in young adulthood*

Five case–control studies[14,15,17,18,28] and four cohort studies[31–33,35] presented data on BMI in early adulthood and risk of ovarian cancer. Of these, only one case–control study[18] and one cohort study[32] found a significantly increased risk for the highest category of BMI compared to the lowest. Three other case–control studies[14,15,28] and two cohort studies[31,35] reported a non-significantly increased risk, whilst one case–control study[17] reported a non-significantly decreased risk, and one cohort study reported no relationship.[33]

Pooling the data from five case control studies[14,15,17,18,28] and four cohort studies[31–33,35] that reported on BMI in young adulthood gave a summary risk estimate of 1.22 (95% CI 1.02–1.45) with no significant heterogeneity (Fig. 3). We found no difference between those from summary risk estimates from case control studies and cohort studies (pooled RRs 1.21 and 1.22, respectively).

Two case–control studies[17,28] and one cohort study[35] stratified their analysis of BMI in early adulthood by menopausal status. The two case–control studies[17,28] found very little variation in the association by menopausal status, whilst the cohort study[35] reported a significantly increased risk for BMI ⩾ 25 in premenopausal women only.

Fairfield and colleagues[35] found that higher BMI at age 18 was more strongly associated with the serous subtype of ovarian cancer among premenopausal women though this result was based on only 45 cases (RR 2.90; 95% CI 1.04–8.08). There

was insufficient power to estimate the risk of BMI at age 18 associated with the risk of endometrioid or mucinous subtypes in either menopausal women or amongst all women. Greer and colleagues[14] found for the subgroup of nulliparous women only that higher BMI at age 18 was weakly associated with serous (OR 1.46; 95% CI 0.7–3.04) and mucinous (OR 1.39; 95% CI 0.42–4.63) subtypes, more strongly but not significantly with endometrioid (OR 2.28; 95% CI 0.85–6.15) and not with clear-cell tumours.

3.5. *Publication bias*

The funnel plot of the effect estimates for the risk of ovarian cancer related to obesity was close to symmetrical, suggesting that there was no appreciable publication bias.

4. Discussion

We have found consistent epidemiological evidence that the risk of ovarian cancer increases with increasing BMI. Based on our survey of the published literature, we estimate that the risk of epithelial ovarian cancer among obese women may be 30% higher than women with a body mass index in the 'healthy' range. The risk for being overweight was less than that seen for obesity, and was of marginal statistical significance; overweight women had a 16% increased risk of ovarian cancer compared to women with a 'normal' body mass index. It is important to note that although there was significant heterogeneity across different study types, this was due to the inclusion of three cohort studies that based their risk estimates on a single, baseline measure of BMI and had follow-up of >25 years.[32,34,36] It is highly likely that women will have gained weight during the long follow-up period, thus there may have been significant misclassification. In addition, two of these studies were only adjusted for age,[32,34] and not for other potentially important confounders, whilst there was no assessment for confounding in the analysis for the third cohort study.[36] Our findings, which are based on an updated group of studies, are similar to those obtained by Purdie and colleagues[7] in their meta-analysis of 11 case–control studies and 5 cohort studies published between 1979 and 2001 (OR 1.4 for population-based case–control studies; 1.2 for cohort studies).

The risk conferred by being overweight or obese in early adulthood was 22%; however, it is important to note that

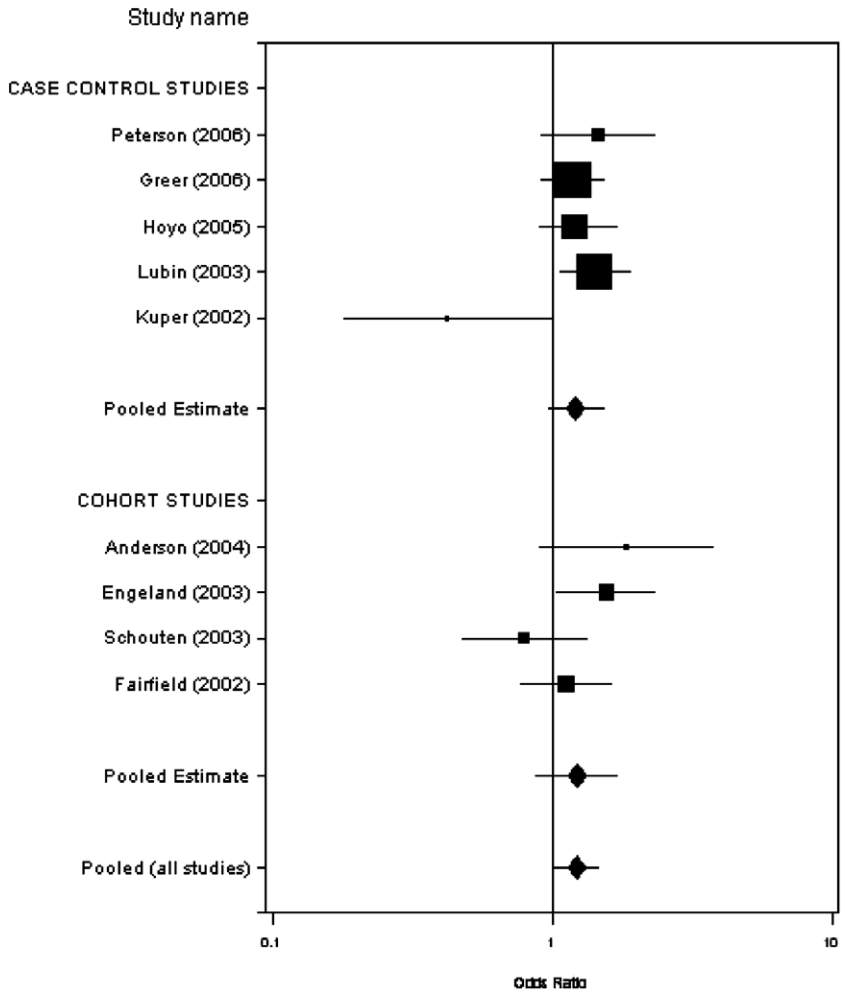

Fig. 3 – Forest plot of the association between overweight/obesity in early adulthood and ovarian cancer using a random-effects model. Each line represents an individual study result with the width of the horizontal line, indicating 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of the study.

the studies included in this meta-analysis did not adjust their analyses for adult BMI. The WHO currently recommend that the BMI-for-age data from the National Center for Health Statistics be used as reference data in choosing BMI cutoffs for obesity in children and adolescents,[6] although a number of problems associated with this have been identified. Given the current debate on appropriate BMI cut points for this age-group,[43] together with the non-uniform presentation of results, we could not differentiate with certainty between the effects of overweight and obesity in this meta-analysis.

A previous study by Szamborski and colleagues[44] observed an increased prevalence of overweight amongst women with the endometrioid subtype. The pathology of endometrioid ovarian tumours is similar to adenocarcinomas of the endometrium,[45] for which obesity is a well-established risk factor,[3,46] thus it might also be expected to be a strong risk factor for endometrioid ovarian cancer. Only two of seven studies reported an increased risk for the endometrioid subtype of ovarian cancer,[14,24] and in the case of the latter study, this increased risk was seen for nulliparous women only. We did not find sufficient evidence to conclude with confidence that obesity is a significant risk factor for the endometrioid subtype.

Several limitations should be considered in interpreting the results of this meta-analysis. Firstly, these findings may simply reflect the confounding effects of other factors. For example, obese women may have different reproductive, hormonal or lifestyle characteristics from non-obese women and this may explain the findings. However, given that there was no material difference in the summary estimate when the studies that did not control for these characteristics were excluded, we are confident that the observed relationship between obesity and risk was not confounded by these factors. Secondly, we cannot exclude the possibility of publication bias since our search was restricted to studies published in indexed journals, and we did not search for unpublished studies. The funnel plot of the effect estimates for the risk of ovarian cancer related to obesity, however, was close to symmetrical suggesting that there was no appreciable publication biases. The studies contributing to the summary estimates are vulnerable to various types of bias. The majority of the studies in the meta-analysis used 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.[47–50] This might lead to non-differential misclassification bias which may attenuate the true association between obesity and ovarian cancer. Weight change during cohort follow-up could also lead to non-differential misclassification of BMI, especially if the aetiologically relevant period is after baseline measurement which was sometimes more than 20 years before diagnosis. We cannot exclude the possibility of differential misclassification in the retrospective case–control studies. Under-reporting of weight may occur unequally among cases and controls. Weight loss several years before the time of cancer diagnosis would bias the risk towards the null in case–control studies. There is also 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. Such selection bias might explain the stronger relationships we observed between obesity and ovarian cancer risk in the retrospective case–control studies compared to the cohort studies.

Assuming that our findings reflect true increases in ovarian cancer risk for obese women, the question arises as to how this effect might be mediated. Adiposity influences the synthesis and bioavailability of endogenous sex steroids (oestrogens, androgens and progesterone). Endogenous hormones are believed to be involved in the aetiology of ovarian cancer,[51] and obesity is a well-established risk factor for two other hormone-related cancers in women, postmenopausal breast cancer[4,52–55] and endometrial cancer.[46,56,57] The relationship between obesity and postmenopausal breast cancer is thought to be mediated by the synthesis of oestrogen in body fat,[4] since postmenopausal obesity (but not premenopausal obesity) is associated with higher levels of endogenous oestrogen.[58] It is therefore unlikely that endogenous oestrogen levels are responsible for the increased risk of ovarian cancer observed in obese premenopausal women, and other hormonal factors should be considered.

Other plausible hormonal candidates include insulin and androgen.[59] High BMI has been associated with increased serum testosterone concentrations among women, especially postmenopausal women.[60] High androgen and high insulin levels characterise the condition of polycystic ovary syndrome (PCOS), which has been found to be a risk factor for ovarian cancer in one study.[61] Obesity is associated with increased insulin levels, which lead to increases in the insulin-like growth factor-1 (IGF-I),[59] and high levels of IGF-I have been associated with other hormone-dependent cancers: breast and prostate.[58,62] Some research has shown that IGF-1 levels rise with increasing BMI in a non-linear relationship peaking at BMI 24–27 kg/m^2.[63,64] Lukanova and colleagues[65] found a strong direct relationship between circulating IGF-1 levels and risk of developing ovarian cancer before age 55 and they suggest that IGF-1 may increase ovarian cancer risk by increasing cell proliferation and inhibiting apoptosis,[66] and/or by modulating the synthesis and bioavailability of sex steroid hormones.[51,67]

Another important hormone that may mediate the relationship between obesity and risk of ovarian cancer is progesterone. Compared to women of 'normal' weight, premenopausal obese women have reduced serum progesterone levels[68] and there is a significant body of evidence suggesting that progesterone plays a protective role in ovarian carcinogenesis.[51] Circulating progesterone levels are higher during pregnancy,[69] and this may explain the increased risk associated with obesity observed for nulliparous women. Obesity is also associated with increased serum leptin levels,[70]; however, at present the role of leptin in ovarian carcinogenesis has not been elucidated.[71]

In conclusion, the findings of our meta-analysis and systematic review suggest that obesity in adulthood is a modest but statistically significant risk factor for ovarian cancer. This finding is of public health significance since obesity is a potentially modifiable risk factor, in contrast to almost all other known risk factors for ovarian cancer. With a prevalence of

Appendix 1. Summary of published study results on adult BMI and risk of epithelial ovarian cancer

Study	Design	Age range ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
Peterson (2006)	Case–control	20–79 1993–1995; 1998–2001	Massachusetts, WI, USA	700/5943	Age, state, enrolment period, education, family history of breast or ovarian cancer, oral contraceptive use, parity, history of tubal ligation	<18.5	13	126	1.1	(0.6–2.0)	
						18.5–24.9	304	2770	1.0	(Ref)	
						25.0–29.9	232	1939	1.2	(0.7–2.2)	
						⩾30.0	151	1108	1.3	(0.7–2.4)	
						<18.5	6	27	0.5	(0.2–1.5)	Premeno-pausal
						18.5–24.9	86	753	1.0	(Ref)	
						25.0–29.9	60	386	0.8	(0.3–2.1)	
						⩾30.0	48	269	1.3	(0.3–2.3)	
						<18.5	7	93	1.5	(0.7–3.3)	Postmeno-pausal
						18.5–24.9	208	1903	1.0	(Ref)	
						25.0–29.9	165	1460	1.5	(0.7–3.2)	
						⩾30.0	98	786	1.5	(0.7–2.3)	
Greer (2006)	Case–control	20–68, 05/1994–07/1998	Delaware valley, USA	762/1348	Age, race, number of live births, family history of ovarian cancer, tubal ligation, oral contraceptive use	<21.8	173	330	1.0	(Ref)	
						21.8–24.6	196	341	1.1	(0.9–1.4)	
						24.6–28.7	192	339	1.1	(0.9–1.5)	
						>28.7	201	338	1.2	(1.0–1.6)	
Hoyo (2005)	Case–control	20–74, 01/1999–03/2003	North Carolina, USA	593/628	Age, race, parity, ovarian cancer history, breast cancer history, hysterectomy, oral contraceptive use, Menstrual status	<25	230	254	1.0	(Ref)	
						25–29.99	158	190	1.0	(0.7–1.3)	
						⩾30	192	166	1.4	(1.0–1.8)	
Riman (2004)	Case–control	50–74, 93–95	Sweden	655/3899	Age, parity, age at menopause, oral contraceptive use, use of HRT	< 22	122	725	1.0	(Ref)	
						22–24.9	197	1241	1.0	(0.8–1.3)	
						24.9–26.9	127	755	1.1	(0.8–1.4)	
						27–29.9	115	675	1.1	(0.8–1.5)	
						⩾30	93	453	1.4	(1.0–1.9)	

(*continued on next page*)

Appendix 1 – *continued*

Study	Design	Age range ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
Pike (2004)	Case–control	18–74, 10/1992–10/1998	Los Angeles County, USA	467/660	Age, ethnicity, SES, of education, family history ovarian cancer, tubal ligation, use of genital area talc, parity, oral contraceptive use, menopausal status, age at menopause, age at last birth, HRT use	<25 25–29 30–34 ⩾35	261 120 56 40	397 165 60 38	1.0 1.0 1.3 1.5	(Ref) (0.7–1.3) (0.8–2.0) (0.9–2.4)	
Pan (2004)	Case–control	21–76, 1994–1997	Canada, 8 states	442/2492	Age, location, education, smoking, alcohol intake, total caloric intake, vegetable intake, dietary fiber intake, recreational physical activity, menopausal status, number of live births, age at menarche, age at end of 1st pregnancy	<25 25–29.9 ⩾30			1.0 1.2 2.0	(Ref) (0.9–1.5) (1.4–2.6)	
Mills (2004)	Case–control	18+ 2000–2001	California, USA	256/1122	Age, race/ethnicity, oral contraceptive use, breastfeeding	<20 20–24 25–29 ⩾30	4 66 70 39	43 435 364 249	1.0 1.66 2.00 1.75	(Ref) (0.6–4.9) (0.7–5.9) (0.6–5.3)	
Lubin (2003)	Case–control	Not given 1994–1999	Israel	1269/2111	Age, menopausal status, parity, oral contraceptive use, infertility, and family history of breast or ovarian cancer in a 1st degree relative	<21.6 21.6–24.2 24.3–27.5 27.6–49.3			1.0 1.3 1.4 1.5	(Ref) (1.1–1.7) (1.1–1.7) (1.2–1.9)	

Kuper (2002)	Case–control	Age range not given 05/1992–03/1997	Massachusetts/New Hampshire USA	563/523	Age, site, parity, oral or contraceptive use, family history of breast, ovarian, prostate cancer in a 1st degree relative, tubal ligation, education, marital status	<20	67	62	1.0	(Ref)	
						20–24.9	255	261	1.0	(0.6–1.5)	
						25–29.9	138	124	1.0	(0.7–1.6)	
						⩾30	104	78	1.2	(0.8–2.0)	
						<20	43	47	1.0	(Ref)	Premeno-
						20–24.9	130	152	1.0	(0.6–1.6)	pausal
						25–29.9	63	58	1.2	(0.7–2.2)	
						⩾30	52	36	1.6	(0.8–2.9)	
						<20	24	15	1.0	(Ref)	Postmeno-
						20–24.9	125	109	1.0	(0.6–1.5)	pausal
						25–29.9	75	66	0.8	(0.7–1.6)	
						⩾30	52	42	1.0	(0.8–2.0)	
Lukanova (2002)	Nested case–control (three cohorts)	32–70 1985–1991 30–70 1980–present 35–70 1987–1992	New York, USA	122/233	Age, study cohort, age at time of recruitment into study, menopausal status, parity, oral contraceptive use, smoking	<23.1	43	58	1.0	(Ref)	
						23.1–25.4	29	58	0.6	(0.3–1.2)	
						25.5–28.4	26	58	0.6	(0.3–1.2)	
						⩾28.4	24	59	0.5	(0.2–0.9)	
			Milan, Italy								
						Percentile:					
Purdie (2001)	Case–control	18–79, 08/90–12/93	Australia	775/846	Age, age squared, geographic location, education, parity, duration of oral contraceptive use, talc use, tubal ligation, hysterectomy, history of breast or ovarian cancer in 1st degree relative	<15th	109	134	1.1	(0.8–1.5)	
						15th–35th	155	169	1.4	(1.0–1.8)	
						35th–65th	204	278	1.0	(Ref)	
						65th–85th	164	164	1.5	(1.1–2.0)	
						⩾85th	143	101	1.9	(1.3–2.6)	
						<15th	48	59	1.4	(0.8–2.4)	Premeno-
						15th–35th	47	68	1.3	(0.8–2.3)	pausal
						35th–65th	61	95	1.0	(Ref)	
						65th–85th	54	48	1.9	(1.1–3.2)	
						⩾85th	47	34	2.3	(1.3–4.2)	
						<15th	59	74	1.0	(0.7–1.6)	Postmeno-
						15th–35th	103	100	1.5	(1.0–2.2)	pausal
						35th–65th	155	185	1.0	(Ref)	
						65th–85th	110	116	1.3	(0.9–1.9)	
						⩾85th	96	67	1.7	(1.1–2.6)	

(*continued on next page*)

Appendix 1 – *continued*

Study	Design	Age range ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
Ness (2000)	Case–control	20–69, 05/1994–07/1998	Delaware Valley, USA	767/1367	Age, number of pregnancies, family history of ovarian cancer, race	<20	73	125	1.0	(Ref)	
						20–24	326	586	1.0	(0.7–1.4)	
						25–29	214	376	1.0	(0.7–1.4)	
						⩾30	154	271	1.1	(0.7–1.6)	
Farrow (1989)	Case–control	35–74, 1975–1979	Washington/ Utah, USA	277/665	Age, parity, oral contraceptive use	<19.8	44	140	1.0	(Ref)	
						19.8–20.99	55	132	1.3	(0.8–2.1)	
						21–22.29	54	142	1.2	(0.7–1.9)	
						22.3–24.09	57	132	1.3	(0.8–2.1)	
						⩾24.1	63	113	1.7	(1.1–2.7)	
Slattery (1989)	Case–control	20–79, 08/1984–05/1987	USA	85/492	Age	<20.6	18	161	1.0	(Ref)	
						20.6–23.0	31	165	1.3	(0.7–2.6)	
						>23.0	36	165	1.2	(0.6–2.3)	
Shu (1989)	Case–control	18–70, 09/84–06/86	Shanghai, China	172/172	Education, animal fat intake	<18.9	35	43	1.0	(Ref)	
						18.9–20.8	56	43	2.1	(1.0–4.2)	
						20.8–22.3	35	42	1.2	(0.6–2.6)	
						>22.3	46	44	1.6	(0.8–3.3)	
Cramer (1984)	Case–control	Not given 11/78–09/81	Boston, USA	215/215	Age, parity	<22	35	42	1.0	(Ref)	
						22–25	64	67	1.2	(0.7–2.2)	
						25–29	60	58	1.2	(0.6–2.3)	
						⩾29	56	48	1.5	(0.8–2.9)	
Casagrande (1979)	Case–control	25–49, 1973–1976	Los Angeles, USA	150/150	Ovulatory age	Normal	34	20	1.0	(Ref)	
									2.1		
Lukanova (2006)	Cohort	29–61, 1985–1996	Northern Sweden	90	Age, calendar year, smoking	18.5–22.1	13		1.0	(Ref)	
						22.2–24.2	17		1.1	(0.6–2.4)	
						24.3–26.9	23		1.4	(0.7–2.8)	
						⩾27	37		2.1	(1.1–4.1)	
								P/years			
Rapp (2005)	Cohort	19–93, 1985–2001	Austria	121	Age, smoking status, occupational group	18.5–24.9	61	490	1.0	(Ref)	
						25–29.9	39	245	1.0	(0.7–1.6)	
						30–34.9	21	141	1.3	(0.8–2.1)	

Niwa (2005)	Cohort	40–79, 1988–1999	Japan	38	Age, study area, family history of breast/ovarian cancer, smoking, alcohol consumption, age at menarche, age at menopause, parity, education	<18.5 18.5–24.9 25–29.9 ⩾30	1 23 13 1	17,268 197,210 57,032 5588	0.4 1.0 2.2 1.8	(0.1–3.2) (Ref) (1.1–4.5) (0.2–13.3)	
Anderson (2004)	Cohort	55–69, 01/86–12/00	Iowa, USA	223	Age, family history, hysterectomy status, oophorectomy status, parity, smoking, oestrogen replacement therapy	<25 25–30 ⩾30	82 86 55	165,271 153,453 94,783	1.0 1.1 1.2	(Ref) (0.8–1.6) (0.8–1.7)	
Engeland (2003)	Cohort	20–74, 1963–1999	Norway	7882	Age at measurement, birth cohort	<18.5 18.5–24.9 25.0–29.9 ⩾30		P/years	1.1 1.0 1.0 1.0	(0.9–1.3) (Ref) (0.9–1.0) (0.9–1.1)	
Schouten (2003)	Cohort	55–69, 09/86–12/93	The Netherlands	172	Age at baseline, oral contraceptive use, parity, HRT use, height	⩽24.9 25–29.9 ⩾30	86 65 21	6,232 4306 1056	1.0 1.2 1.7	(Ref) (0.8–1.7) (1.0–2.9)	
Jonsson (2003)	Cohort	44–83, 1969–1997	Sweden	118	Age at baseline	<18.5 18.5–24.9 25–29.9 ⩾30	1 69 39 2	P/years	0.4 1.0 1.0 0.3	(0.1–3.1) (Ref) (0.7–1.5) (0.1–1.1)	
Fairfield (2002)	Cohort	30–55, 1976–05/96	11 states, USA	402 Cohort 109,445	Age, oral contraceptive use, parity, age at menarche, smoking, tubal ligation history	<21.0 21.0–22.9 23.0–24.9 25.0–29.9 ⩾30 <21.0 21.0–22.9 23.0–24.9	67 89 97 95 54 25 27 28	334,400 388,893 342,893 427,003 210,651 192,848 200,806 151,941	1.0 1.1 1.3 0.9 1.1 1.0 1.0 1.2	(Ref) (0.8–1.5) (0.9–1.7) (0.7–1.3) (0.7–1.5) (Ref) (0.6–1.7) (0.7–2.1)	Premeno-pausal

(*continued on next page*)

Appendix 1 – *continued*

Study	Design	Age range ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
					25.0–29.9	22	163,592	0.8	(0.5–1.5)		
					⩾30	19	82,084	1.4	(0.8–2.5)		
					<21.0	38	117,476	1.0	(Ref)	Postmeno-	
					21.0–22.9	56	157,418	1.1	(0.7–1.7)	pausal	
					23.0–24.9	64	162,940	1.2	(0.8–1.8)		
					25.0–29.9	66	225,285	0.9	(0.6–1.3)		
					⩾30	33	108,954	0.9	(0.6–1.4)		
Wolk (2001)	Cohort	Not given, 1964–1993	Sweden	77 Cohort 19,964	No adjustment	Normal			1.0 1.2	(Ref) (1.1–1.5)	
Mink (1996)	Cohort	55–69, 1985–1992	Iowa, USA	97 Cohort 31,396	Age	<23.45	24	51,701	1.0	(Ref)	
						23.45–26.02	20	51,920	0.8	(0.5–1.5	
						26.03–29.51	26	52,420	1.1	(0.6–1.9)	
						>29.51	27	52,052 P/years	1.1	(0.6–1.9)	
Tornberg (1994)	Cohort	25–75, 1963–1987	Sweden	330 Cohort 47,003	Age	<22	65	228,144	1.0	(Ref)	
						22–23.9	81	210,996	1.2		
						24–25.9	59	198,651	0.8		
						26–27.9	49	140,827	0.9		
						⩾28	76	177,567	1.1		
						<22	24	149,603	1.0	(Ref)	Women
						22–23.9	28	105,243	1.4		<55 years
						24–25.9	16	75,604	1.1		
						26–27.9	12	42,750	1.4		
						⩾28	16	44,377	1.7		
						<22	41	78,541	1.0	(Ref)	Women
						22–23.9	53	105,753	1.0		>55yrs
						24–25.9	43	123,046	0.7		
						26–27.9	37	98,077	0.7		
						⩾28	60	133,190	0.9		

Appendix 2. Summary of published study results on BMI at age 17–20 and risk of epithelial ovarian cancer

Study	Design	Age range, ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
Peterson (2006)	Case–control	20–79, 93–95; 98–01	Massachusetts, Wisconsin, USA	700/5943	Age, state, enrolment period, education, family History of breast or Ovarian cancer, oral Contraceptive use, parity, history of tubal ligation	<18.9	52	559	1.0	(Ref)	
						18.9–20.1	68	601	1.2	(0.8–1.8)	
						20.1–21.3	74	596	1.4	(0.9–2.0)	
						21.3–22.9	71	546	1.3	(0.9–2.0)	
						22.9–24.9	84	605	1.4	(0.9–2.0)	
						⩾25.0	43	263	1.5	(0.9–2.3)	
						<18.9	15	203	1.0	(Ref)	Premeno-pausal
						18.9–20.1	26	262	1.3	(0.7–2.6)	
						20.1–21.3	23	249	1.3	(0.6–2.5)	
						21.3–22.9	28	230	1.5	(0.8–3.0)	
						⩾22.9	30	273	1.2	(0.6–2.4)	
						⩾25.0	18	112	1.4	(0.6–3.2)	
						<18.9	36	324	1.0	(Ref)	Postmeno-pausal
						18.9–20.1	40	298	1.2	(0.7–2.0)	
						20.1–21.3	49	304	1.4	(0.9–2.3)	
						21.3–22.9	43	279	1.3	(0.8–2.1)	
						⩾22.9	54	294	1.5	(0.9–2.3)	
						⩾25.0	25	137	1.5	(0.8–2.6)	
Greer (2006)	Case–control	20–68, 05/94–07/98	Delaware valley, USA	762/1348	Age, race, number of live births, family history of ovarian cancer, tubal ligation, oral contraceptive use	<18.7	189	350	1.0	(Ref)	
						18.7–20.2	165	348	0.9	(0.9–1.2)	
						20.3–21.9	197	310	1.2	(0.7–1.6)	
						>22.0	208	338	1.2	(0.9–1.5)	
Hoyo (2005)	Case–control	20–74, 01/99–03/03	North Carolina, USA	593/628	Age, race, parity, ovarian cancer history, breast cancer history, hysterectomy, oral contraceptive use, menstrual status	<18.5	141	150	1.0	(Ref)	
						18.5–19.9	130	149	1.0	(0.7–1.4)	
						20.0–21.6	134	157	1.0	(0.7–1.4)	
						⩾21.7	170	150	1.2	(0.9–1.7)	

(*continued on next page*)

Appendix 2 – *continued*

Study	Design	Age range, ref. years	Geographic location	No. cases/ controls	Adjusted variables		Study results				Notes
							Cases	Controls	OR/RR	CI	
Lubin (2003)	Case–control	Not given, 1994–1999	Israel	1269/2111	age, menopausal status, parity, oral contraceptive use, infertility, and family history of breast or ovarian cancer in a 1st degree relative	<19.1			1.0	(Ref)	
						19.1–20.9			1.2	(0.9–1.5)	
						21.0–22.8			1.1	(0.9–1.5)	
						22.9–35.2			1.4	(1.1–1.9)	
Kuper (2002)	Case–control	Age range not given 05/92–03/97	Massachusetts/ New Hampshire USA	563/523	Age, site, parity, oral or contraceptive use, family history of breast, ovarian, prostate cancer in a 1st degree relative, tubal ligation, education, marital status	<20	238	226	1.0	(Ref)	
						20–24.9	278	247	1.1	(0.8–1.4)	
						25–29.9	39	35	1.1	(0.6–1.8)	
						⩾30	9	17	0.4	(0.2–1.0)	
						<20	116	121	1.0	(Ref)	Premenopausal
						20–24.9	141	140	1.0	(0.7–1.5)	
						25–29.9	24	20	1.1	(0.6–2.2)	
						⩾30	7	12	0.5	(0.2–1.5)	
						<20	122	105	1.0	(Ref)	Postmenopausal
						20–24.9	137	107	1.1	(0.7–1.6)	
						25–29.9	15	15	1.0	(0.4–2.2)	
						⩾30	2	5	0.3	(0.1–1.5)	
								P/years			
Anderson (2004)	Cohort	55–69, 01/86–12/00	Iowa, USA	223	Age, family history, hysterectomy status, oophorectomy status, parity, smoking, oestrogen replacement therapy	<25	195	365,934	1.0	(Ref)	
						25–29.9	19	36,786	1.0	(0.6–1.7)	
						⩾30	8	8885	1.8	(0.9–3.7)	

Engeland (2003)	Cohort	20–74, 1963–1999	Norway	7882	Age at measurement, birth cohort	<25th			1.2	(0.9–1.7)	
						25th–74th			1.0	(Ref)	
						75th–84th			1.4	(1.0–2.0)	
						⩾85th			1.6	(1.0–2.3)	
								P/years			
Schouten (2003)	Cohort	55–69, 09/86–12/93	The Netherlands	172	Age at baseline, oral contraceptive use, parity, HRT use, height	<20	40	2,941	1.0	(Ref)	
						20–20.9	28	1,389	1.5	(0.9–2.5)	
						21–22.9	44	3,098	1.1	(0.7–1.7)	
						⩾23	28	2,610	0.8	(0.5–1.3)	
Fairfield (2002)	Cohort	30–55, 1976–05/96	11 states, USA	402	Age, oral contraceptive use, parity, age at menarche, smoking, tubal ligation history	<20.0	112	416,498	1.0	(Ref)	
						20.0–20.9	46	226,544	0.8	(0.5–1.1)	
						21.0–22.9	90	307,099	1.1	(0.8–1.4)	
						23.0–24.9	46	144,513	1.1	(0.8–1.6)	
						⩾25	37	116,191	1.1	(0.8–1.6)	
						<20.0	25	173,855	1.0	(Ref)	Premenopausal
						20.0–20.9	13	97,404	0.9	(0.5–1.8)	
						21.0–22.9	24	129,005	1.3	(0.7–2.2)	
						23.0–24.9	14	57,897	1.6	(0.8–3.1)	
						⩾25	15	47,932	2.1	(1.1–3.9)	
						<20.0	79	207,890	1.0	(Ref)	Postmenopausal
						20.0–20.9	29	110,938	0.7	(0.5–1.1)	
						21.0–22.9	62	153,418	1.1	(0.8–1.5)	
						23.0–24.9	30	75,262	1.0	(0.7–1.6)	
						⩾25	22	58,769	0.9	(0.6–1.5)	

Conflict of interest statement

None declared.

Acknowledgements

C.O. is supported by a University of Queensland Postdoctoral Research Fellowship. D.W. and P.W. are supported by Senior Research Fellowships from the National Health and Medical Research Council of Australia and Queensland Cancer Fund, respectively.

REFERENCES

1. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975–2002, featuring population-based trends in cancer treatment. *J Natl Cancer Inst* 2005;**97**:1407–27.
2. Rapp K, Schroeder J, Klenk J, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. *Br J Cancer* 2005;**93**:1062–7.
3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;**348**:1625–38.
4. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst* 2003;**95**:1218–26.
5. Weight control and physical activity: Vainio H, Bianchini F, editors. *IARC handbooks of cancer prevention*. Lyon: IARC Press; 2002. p. 83–199.
6. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; **894**: (i–xii), 1–253.
7. Purdie DM, Bain CJ, Webb PM, et al. Body size and ovarian cancer: case–control study and systematic review (Australia). *Cancer Causes Control* 2001;**12**:855–63.
8. Verla-Tebit E, Chang-Claude J. Anthropometric factors and the risk of premenopausal breast cancer in Germany. *Eur J Cancer Prev* 2005;**14**:419–26.
9. Magnusson CM, Roddam AW, Pike MC, et al. Body fatness and physical activity at young ages and the risk of breast cancer in premenopausal women. *Br J Cancer* 2005;**93**:817–24.
10. Quesenberry Jr CP, Caan B, Jacobson A. Obesity, health services use, and health care costs among members of a health maintenance organization. *Arch Intern Med* 1998;**158**:466–72.
11. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;**854**:1–452.
12. Young people's health–a challenge for society. Report of a WHO Study Group on young people and health for all by the year 2000. *World Health Organ Tech Rep Ser* 1986;**731**:1–117.
13. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001;**20**:641–54.
14. Greer JB, Modugno F, Ness RB, Allen GO. Anthropometry and the risk of epithelial ovarian cancer. *Cancer* 2006;**106**: 2247–57.
15. Hoyo C, Berchuck A, Halabi S, et al. Anthropometric measurements and epithelial ovarian cancer risk in African-American and White women. *Cancer Causes Control* 2005;**16**:955–63.
16. Lukanova A, Toniolo P, Lundin E, et al. Body mass index in relation to ovarian cancer: a multi-centre nested case–control study. *Int J Cancer* 2002;**99**:603–8.
17. Kuper H, Cramer DW, Titus-Ernstoff L. Risk of ovarian cancer in the United States in relation to anthropometric measures: does the association depend on menopausal status? *Cancer Causes Control* 2002;**13**:455–63.
18. Lubin F, Chetrit A, Freedman LS, et al. Body mass index at age 18 years and during adult life and ovarian cancer risk. *Am J Epidemiol* 2003;**157**:113–20.
19. Pike MC, Pearce CL, Peters R, et al. Hormonal factors and the risk of invasive ovarian cancer: a population-based case–control study. *Fertil Steril* 2004;**82**:186–95.
20. Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y. Association of obesity and cancer risk in Canada. *Am J Epidemiol* 2004;**159**:259–68.
21. Riman T, Dickman PW, Nilsson S, et al. Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol* 2004;**19**:1011–9.
22. Cramer DW, Welch WR, Hutchison GB, Willett W, Scully RE. Dietary animal fat in relation to ovarian cancer risk. *Obstet Gynecol* 1984;**63**:833–8.
23. Ness RB, Grisso JA, Klapper J, et al. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. Steroid Hormones and Reproductions. *Am J Epidemiol* 2000;**152**:233–41.
24. Farrow DC, Weiss NS, Lyon JL, Daling JR. Association of obesity and ovarian cancer in a case–control study. *Am J Epidemiol* 1989;**129**:1300–4.
25. Slattery ML, Schuman KL, West DW, French TK, Robison LM. Nutrient intake and ovarian cancer. *Am J Epidemiol* 1989;**130**:497–502.
26. Shu XO, Gao YT, Yuan JM, Ziegler RG, Brinton LA. Dietary factors and epithelial ovarian cancer. *Br J Cancer* 1989;**59**:92–6.
27. Casagrande JT, Louie EW, Pike MC, et al. Incessant ovulation and ovarian cancer. *Lancet* 1979;**2**:170–3.
28. Peterson NB, Trentham-Dietz A, Newcomb PA, et al. Relation of anthropometric measurements to ovarian cancer risk in a population-based case–control study (United States). *Cancer Causes Control* 2006;**17**:459–67.
29. Mills PK, Riordan DG, Cress RD. Epithelial ovarian cancer risk by invasiveness and cell type in the Central Valley of California. *Gynecol Oncol* 2004;**95**:215–25.
30. Niwa Y, Yatsuya H, Tamakoshi K, et al. Relationship between body mass index and the risk of ovarian cancer in the Japanese population: findings from the Japanese Collaborate Cohort (JACC) study. *J Obstet Gynaecol Res* 2005;**31**:452–8.
31. Anderson JP, Ross JA, Folsom AR. Anthropometric variables, physical activity, and incidence of ovarian cancer: The Iowa Women's Health Study. *Cancer* 2004;**100**:1515–21.
32. Engeland A, Tretli S, Bjorge T. Height, body mass index, and ovarian cancer: a follow-up of 1.1 million Norwegian women. *J Natl Cancer Inst* 2003;**95**:1244–8.
33. Schouten LJ, Goldbohm RA, van den Brandt PA. Height, weight, weight change, and ovarian cancer risk in the Netherlands cohort study on diet and cancer. *Am J Epidemiol* 2003;**157**:424–33.
34. Jonsson F, Wolk A, Pedersen NL, et al. Obesity and hormone-dependent tumors: cohort and co-twin control studies based on the Swedish Twin Registry. *Int J Cancer* 2003;**106**:594–9.
35. Fairfield KM, Willett WC, Rosner BA, et al. Obesity, weight gain, and ovarian cancer. *Obstet Gynecol* 2002;**100**:288–96.
36. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001;**12**:13–21.

37. Mink PJ, Folsom AR, Sellers TA, Kushi LH. Physical activity, waist-to-hip ratio, and other risk factors for ovarian cancer: a follow-up study of older women. *Epidemiology* 1996;**7**:38–45.
38. Tornberg SA, Carstensen JM. Relationship between Quetelet's index and cancer of breast and female genital tract in 47,000 women followed for 25 years. *Br J Cancer* 1994;**69**:358–61.
39. Lukanova A, Bjor O, Kaaks R, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer* 2006;**118**:458–66.
40. Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? *Gynecol Oncol* 2005;**96**:520–30.
41. Harris R, Whittemore AS, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. III. Epithelial tumors of low malignant potential in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;**136**:1204–11.
42. Jordan SJ, Purdie DM, Green AC, Webb PM. Coffee, tea and caffeine and risk of epithelial ovarian cancer. *Cancer Causes Control* 2004;**15**:359–65.
43. Bellizzi MC, Dietz WH. Workshop on childhood obesity: summary of the discussion. *Am J Clin Nutr* 1999;**70**:173S–5S.
44. Szamborski J, Czerwinski W, Gadomska H, Kowalski M, Wacker-Pujdak B. Case control study of high-risk factors in ovarian carcinomas. *Gynecol Oncol* 1981;**11**:8–16.
45. Russell P. Surface epithelial-stromal tumors of the ovary. In: Kurman RJ, editor. *Blaustein's Pathology of the Female Genital Tract*. 4th ed. New York: Springer-Verlag; 1994. p. 705–82.
46. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:1531–43.
47. Kuskowska-Wolk A, Karlsson P, Stolt M, Rossner S. The predictive validity of body mass index based on self-reported weight and height. *Int J Obes* 1989;**13**:441–53.
48. Troy LM, Hunter DJ, Manson JE, et al. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord* 1995;**19**:570–2.
49. Lawlor DA, Bedford C, Taylor M, Ebrahim S. Agreement between measured and self-reported weight in older women. Results from the British Women's Heart and Health Study. *Age Ageing* 2002;**31**:169–74.
50. Taylor AW, Dal Grande E, Gill TK, et al. How valid are self-reported height and weight? A comparison between CATI self-report and clinic measurements using a large cohort study. *Aust N Z J Public Health* 2006;**30**:238–46.
51. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *J Natl Cancer Inst* 1998;**90**:1774–86.
52. Friedenreich CM. Review of anthropometric factors and breast cancer risk. *Eur J Cancer Prev* 2001;**10**:15–32.
53. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 2002;**13**:741–51.
54. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 2000;**152**:514–27.
55. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. *Am J Epidemiol* 1997;**145**:1011–9.
56. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). *Cancer Causes Control* 2000;**11**:185–92.
57. Trentham-Dietz A, Nichols H, Hampton J, Newcomb P. Weight change and risk of endometrial cancer. *Int J Epidemiol* 2006;**35**:151–8.
58. Hankinson SE, Willett WC, Manson JE, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 1998;**90**:1292–9.
59. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;**4**:579–91.
60. Kha KT, Barrett-Connor E. Fasting plasma glucose levels and endogenous androgens in non-diabetic postmenopausal women. *Clin Sci (Lond)* 1991;**80**:199–203.
61. Schildkraut JM, Schwingl PJ, Bastos E, Evanoff A, Hughes C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. *Obstet Gynecol* 1996;**88**:554–9.
62. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998;**279**:563–6.
63. Allen NE, Appleby PN, Kaaks R, et al. Lifestyle determinants of serum insulin-like growth-factor-I (IGF-I), C-peptide and hormone binding protein levels in British women. *Cancer Causes Control* 2003;**14**:65–74.
64. Holmes MD, Pollak MN, Hankinson SE. Lifestyle correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:862–7.
65. Lukanova A, Lundin E, Toniolo P, et al. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. *Int J Cancer* 2002;**101**:549–54.
66. Coppola D, Saunders B, Fu L, Mao W, Nicosia SV. The insulin-like growth factor 1 receptor induces transformation and tumorigenicity of ovarian mesothelial cells and down-regulates their Fas-receptor expression. *Cancer Res* 1999;**59**:3264–70.
67. Helzlsouer KJ, Alberg AJ, Gordon GB, et al. Serum gonadotropins and steroid hormones and the development of ovarian cancer. *Jama* 1995;**274**:1926–30.
68. Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. *Proc Nutr Soc* 2001;**60**:81–9.
69. Yen S. Endocrinology of pregnancy. In: Creasy R, Resnik R, editors. *Maternal-fetal medicine: principles and practice*. 3rd ed. Philadelphia: Saunders; 1994. p. 382–412.
70. Fortuny Mdel C, Diaz BB, Cabrera de Leon A. Leptin, estrogens and cancer. *Mini Rev Med Chem* 2006;**6**:897–907.
71. Choi JH, Park SH, Leung PC, Choi KC. Expression of leptin receptors and potential effects of leptin on the cell growth and activation of mitogen-activated protein kinases in ovarian cancer cells. *J Clin Endocrinol Metab* 2005;**90**:207–10.
72. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *Jama* 2006;**295**:1549–55.