RESEARCH ARTICLE

Body Mass Index Effects on Risk of Ovarian Cancer: A Meta-Analysis

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Abstract

Objectives: The association between body mass index (BMI) and ovarian cancer risk is unclear and requires further investigation. The present meta-analysis was conducted to assess the effect of overweight and obesity on ovarian cancer risk in the premenopausal and postmenopausal periods. Data sources: Major electronic databases were searched until February 2014 including Medline and Scopus. Reference lists and relevant conference databases were searched and the authors were contacted for additional unpublished references. Review Methods: All cohort and case-control studies addressing the effect of BMI on ovarian cancer were included, irrespective of publication date and language. The effect measure of choice was risk ratio (RR) for cohort studies and odds ratio (OR) for case-control studies. The results were reported using a random effects model with 95% confidence intervals (CIs). Results: Of 3,776 retrieved studies, 19 were ultimately analyzed including 10 cohort studies involving 29,237,219 person-years and 9 case-control studies involving 96,965 people. The results of both cohort and case-control studies showed being overweight and obesity increased the risk of ovarian cancer compared to women with normal weight during both premenopausal and postmenopausal periods: RR=1.08 (95%CI: 0.97, 1.19) and OR=1.26 (95%CI: 0.97, 1.63) for overweight and RR=1.27 (95%CI: 1.16, 1.38) and OR=1.26 (95%CI: 1.06, 1.50) for obesity. Conclusions: There is sufficient evidence that an increase in BMI can increase the risk of ovarian cancer regardless of the menopausal status, mimicking a dose-response relationship although the association is not very strong.

Keywords: Ovarian neoplasms - body mass index - risk factor - meta-analysis - menopause

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Introduction

Ovarian cancer is the sixth cancer among women worldwide (Permuth-Wey and Sellers, 2009) and the most fatal neoplasm among gynecological cancers (Organization, 2000; Delort et al., 2009). Ovarian cancer accounts for about 4% of all female cancers (Anderson et al., 2004). Its five-year survival rate is 37% (Beehler et al., 2006; Leitzmann et al., 2009).

The etiology of ovarian cancer is not well known. At present, only a small number of risk factors have been identified, including age, nulliparity, and family history of ovarian cancer. In contrast, parity and oral contraceptive pill can reduce the risk of ovarian cancer (Brinton et al., 2004; Beehler et al., 2006; Peterson et al., 2006; Bandera, 2007; Leitzmann et al., 2009).

The prevalence of overweight and obesity is increasing dramatically in most parts of the world and is generally higher in women than in men (Organization, 2000). As living standard improve, obesity is becoming epidemic conditions not only in developed countries, but also in less developed countries (Sangrajrang et al., 2013). Obesity is an important risk factor for some cancers (Gulcelik et al., 2012; Minatoya et al., 2013; Acmaz et al., 2014; Kaneko et al., 2014). The results a review study in 2013 showed that obesity is one factor which has strong correlation with increased breast cancer risk (Alegre et al., 2013) and the results a meta-analysis in 2012 showed that overweight and obesity may increase the risk of breast cancer during the postmenopausal period (Cheraghi et al., 2012). Another meta-analysis study in 2014 did not showed any significant between obesity and colorectal cancer (Joshi and Lee, 2014).

Several epidemiologic studies have investigated the relation between body mass index (BMI) and ovarian cancer but the results are inconsistent. Several epidemiological studies demonstrated significant relation between BMI and ovarian cancer in the premenopausal (Kuper et al., 2002; Niwa et al., 2005; Beehler et al., 2006; Delort et al., 2009) and postmenopausal (Schouten et al., 2003; Niwa et al., 2005; Olsen et al., 2008; Delort et al., 2009) periods while other studies did not support

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such results (Lukanova et al., 2006; Delort et al., 2009; Kotsopoulos et al., 2010).

A meta-analysis was conducted in Australia in 2001. Significant relation was reported between BMI and ovarian cancer risk. But, it was limited to case-control studies (Purdie et al., 2001). Another meta-analysis with the same topic was conducted by Schouten et al in 2008. They included 12 cohort studies and searched Medline database alone. The results showed significant relation between BMI and ovarian cancer risk in the premenopausal period but not in the postmenopausal period (Schouten et al., 2008). The present meta-analysis is an update of the previous meta-analyses that were conducted to assess the results of both cohort and case-control studies in order to estimate the overall effect of overweight and obesity on ovarian cancer risk in the premenopausal and postmenopausal periods.

Materials and Methods

Definitions

Natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause has occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause" (World Health Organisation, 1996). Ovarian cancer is the cancer of the ovaries, the egg-releasing and hormone-producing organs of the female reproductive tract. Ovarian tumors are divided into epithelial and non-epithelial, the former being classified as clear cell, endometrioid, mucinous, serous, and mixed (World Health Organization, 2000).

BMI is weight in kilograms divided by the square of the height in meters. Based on the World Health Organization classification, BMI is divided into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 k/m^2). and obese (≥30 kg/m^2) (World Health Organization, 1995).

Criteria for including studies

Prospective cohort and case-control studies addressing the relation between BMI and ovarian cancer were included, irrespective of publication date and language. The exposure of interest was obesity and overweight. The outcome of interest was ovarian cancer of any type that was approved pathologically irrespective of the tumor stage.

Search methods

We found and combined the following keywords: "(Cancer OR Carcinoma OR Malignancy OR Tumor OR Tumour) AND (Ovary OR Ovarian) AND (Body Mass Index OR BMI OR Body Size OR Overweight OR Obese OR Obesity)". We searched international electronic databases including Medline and Scopus until February 2014. Furthermore, the following conference databases were searched for unpublished data:

Advances in Ovarian Cancer Research: From Concept to Clinic September 18-21, 2013; available from: www.aacr.org

American Cancer Society; available from: www.cancer.org

International Agency for Research on Cancer; available from: www.iarc.fr

American Society of Clinical Oncology; available from: www.asco.org

9th Annual International Symposium on Ovarian Cancer and Gynecologic Malignancies October 5, 2013; available from: www.gotoper.com

In addition, the reference lists of all retrieved studies were screened and the authors of studies were contacted for additional unpublished studies.

Data collection and analysis

Two authors (EJ and SZM) separately screened the title and abstract of the retrieved studies and then reviewed the full texts to extract studies that met the inclusion criteria of this meta-analysis (Figure 1). The authors were not blinded to the author's names, journals and study results. Any disagreements were resolved by discussion among authors. The inter authors reliability based on Kappa statistics was 65%. Two authors (EJ and SZM) extracted the data from the studies. The extracted variables included study design, year and country of study conduction, number of exposures and outcomes, body mass index, and the status of menopause. The extracted data were entered in the electronic data sheet.

We assessed the risk of bias of the included studies using Newcastle Ottawa Statement Manual (Wells et al., 2009). The scales allocate stars, a maximum of nine, for quality of selection, comparability, exposure and outcome of study participants. Two authors (EJ and SZM) assessed the studies independently. The studies with 6 star-items or more were considered as low risk and those with 5 star-items or less as high risk.

The effect measure of choice for cohort studies was risk ratio (RR) and that of case-control studies was odds ratio (OR). RR was defined as the proportion of the ovarian cancer in exposed people to a specified person-year (a statistical measure representing one person at risk of development of the disease during a period of 1 year). OR was defined as the proportion of the exposed population in whom the ovarian cancer has developed over the proportion of the unexposed population in whom the disease has developed. The effect measure was estimated for the premenopausal and postmenopausal periods separately as well as the whole period.

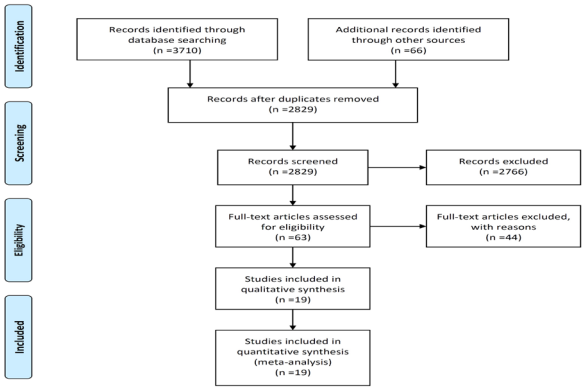

Figure 1. Flow Chart of the Trial Selection Process Through the Phases of Meta-Analysis

Heterogeneity and publication bias

The statistical heterogeneity was explored using chi-square test (Chi2) with 5% significance level (P<0.05). The I^2 statistic was used to assess inconsistency across the study results (Higgins et al., 2003). The Begg (Begg and Mazumdar, 1994) and Egger (Egger et al., 1997) tests were employed to assess publication bias quantitatively. Both Review manager 5 (Review Manager (RevMan) [Computer program] (2008) RevMan. Version 5.20 for Windows. Copenhagen: The Nordic Cochrane Centre, 2008) and statistical software Stata 12 were used for data analysis. Data were analyzed and the results were reported by a random effect model (DerSimonian and Laird, 1986) with 95%CI.

Results

Description of studies

We retrieved 3776 studies to February 2014, including 3710 references through electronic database, 64 references through checking references lists and two references through personal contact with authors of the studies. No

Table 1. Characteristics of the Included Studies as Well as Quality of the Studies Based on Newcastle Ottawa Statement Manual

1st author (yr)	Design	Type	BMI	Country	Pyr/SS	RR/ OR	95% CI	Quality		
								Sel	Com	Exp/Out
Anderson (2004)	Pcohort	Post	Over	USA	153453	1.13	0.83, 1.53	***	*	***
Anderson (2004)	Pcohort	Post	Obese	USA	94783	1.17	0.83, 1.65	***	*	***
Beehler (2006)	Case-control	Pre	Over	USA	88	1.16	0.69, 1.93	***	*	**
Beehler (2006)	Case-control	Post	Over	USA	272	0.95	0.69, 1.31	***	*	**
Beehler (2006)	Case-control	Pre	Obese	USA	58	2.23	1.25, 3.98	***	*	**
Beehler (2006)	Case-control	Post	Obese	USA	150	1.12	0.76, 1.65	***	*	**
Chionh (2010)	Pcohort	Total	Over	Australia	85119	0.78	0.50, 1.21	****	*	***
Chionh (2010)	Pcohort	Total	Obese	Australia	36769	1.57	1.00, 2.48	****	*	***
Delort (2009)	Case-control	Pre	Over	France	35	0.57	0.07, 4.61	****	*	*
Delort (2009)	Case-control	Post	Over	France	163	0.53	0.22, 1.30	****	*	*
Delort (2009)	Case-control	Pre	Obese	France	20	3.39	0.84, 13.73	****	*	*
Delort (2009)	Case-control	Post	Obese	France	61	0.72	0.21, 2.44	****	*	*
England (2003)	Pcohort	Total	Over	Norway	6989110	1.19	1.13, 1.25	****	*	***
England (2003)	Pcohort	Total	Obese	Norway	2777300	1.27	1.19, 1.36	****	*	***
Kotsopoulos (2010)	Pcohort	Pre	Over	USA	499993	1.34	1.00, 1.80	**	*	***
Kotsopoulos (2010)	Pcohort	Post	Over	USA	509654	0.88	0.73, 1.06	**	*	***
Kotsopoulos (2010)	Pcohort	Pre	Obese	USA	338193	1.02	0.82, 1.26	**	*	***
Kotsopoulos (2010)	Pcohort	Post	Obese	USA	302032	1.02	0.82, 1.26	**	*	***
Kuper (2002)	Case-control	Pre	Over	USA	121	1.27	0.83, 1.95	****	*	**
Kuper (2002)	Case-control	Post	Over	USA	141	0.99	0.65, 1.51	****	*	**
Kuper (2002)	Case-control	Pre	Obese	USA	88	1.69	1.04, 2.74	****	*	**
Kuper (2002)	Case-control	Post	Obese	USA	94	1.08	0.67, 1.75	****	*	**
Lacey (2006)	Pcohort	Total	Over	USA	155690	1.03	0.80, 1.32	***	*	***
Lacey (2006)	Pcohort	Total	Obese	USA	58755	1.02	0.70, 1.48	***	*	***
Lahman (2010)	Pcohort	Pre	Over	Europe	22669	1.03	0.69, 1.55	****	*	***
Lahman (2010)	Pcohort	Post	Over	Europe	38571	1.27	1.02,1.58	****	*	***
Lahman (2010)	Pcohort	Pre	Obese	Europe	6501	1.7	0.99, 2.91	****	*	***
Lahman (2010)	Pcohort	Post	Obese	Europe	17747	1.59	1.22, 2.06	****	*	***
Leitzmann (2009)	Pcohort	Pre	Over	USA	9625	0.86	0.25, 2.94	***	*	***
Leitzmann (2009)	Pcohort	Post	Over	USA	192498	0.86	0.65, 1.14	***	*	***
Leitzmann (2009)	Pcohort	Pre	Obese	USA	5517	1.13	0.29, 4.35	***	*	***
Leitzmann (2009)	Pcohort	Post	Obese	USA	130577	1.13	0.84, 1.50	***	*	***
Moorman (2009)	Case-control	Total	Over	USA	552	0.92	0.74, 1.15	****	*	**
Moorman (2009)	Case-control	Total	Obese	USA	572	1.02	0.82, 1.27	****	*	**
Nagle (2008)	Case-control	Total	Over	Australia	526	1.42	1.01, 2.01	****	*	***
Nagle (2008)	Case-control	Total	Obese	Australia	396	1.42	0.98, 2.06	****	*	***
Niwa (2005)	Pcohort	Total	Over	Japan	57032	1.95	0.99, 3.86	***	*	***
Niwa (2005)	Pcohort	Total	Obese	Japan	5588	1.53	0.21, 11.36	***	*	***
Olsen (2008)	Case-control	Pre	Over	Australia	118	1.69	1.01, 2.83	****	*	***
Olsen (2008)	Case-control	Post	Over	Australia	488	1	0.78, 1.28	****	*	***
Olsen (2008)	Case-control	Pre	Obese	Australia	97	1.13	0.63, 2.03	****	*	***
Olsen (2008)	Case-control	Post	Obese	Australia	320	0.67	0.50, 0.90	****	*	***
Peterson (2006)	Case-covntrol	Pre	Over	USA	446	8.76	5.74, 13.35	****	*	***
Peterson (2006)	Case-control	Post	Over	USA	1625	1.03	0.83, 1.28	****	*	***
Peterson (2006)	Case-control	Pre	Obese	USA	317	1.56	1.07, 2.28	****	*	***
Peterson (2006)	Case-control	Post	Obese	USA	884	1.14	0.88, 1.47	****	*	***
Riman (2001)	Case-control	Total	Over	Sweden	1503	1.25	0.91, 1.74	****	*	***
Riman (2001)	Case-control	Total	Obese	Sweden	492	2.12	1.42, 3.14	****	*	***
Schouten (2003)	Pcohort	Post	Over	Netherland	4306	1.09	0.79, 1.51	***	*	***
Schouten (2003)	Pcohort	Post	Obese	Netherland	1056	1.44	0. 90, 2.31	***	*	***
Weiderpass (2012)	Pcohort	Total	Over	Japan	11282	0.89	0.55, 1.43	***	*	***
Weiderpass (2012)	Pcohort	Total	Obese	Japan	1430	0.7	0.17, 2.84	***	*	***
Wernli (2008)	Case-control	Total	Over	USA	2120	1.08	0.91, 1.29	****	*	***
Wernli (2008)	Case-control	Total	Obese	USA	1250	1.22	1.00, 1.50	****	*	***

BMI: Body Mass Index; Pyr: Person-year; SS: Sample size; Sel: Selection; Com: Comparability; Exp: Exposure; Out: Outcome; Pre: Premenopausal period; Post: Postmenopausal period

new reference was found through searching conference databases. A number of 884 references were excluded because of duplication, 2766 references were excluded after screening the title and abstract and 44 after reviewing full texts. Eventually, 19 studies remained for meta-analysis (Figure 1) including 10 cohort studies (Engeland et al., 2003; Schouten et al., 2003; Anderson et al., 2004; Niwa et al., 2005; Lacey Jr et al., 2006; Leitzmann et al., 2009; Chionh et al., 2010; Kotsopoulos et al., 2010; Lahmann et al., 2010; Weiderpass et al., 2012) involving 29,237,219 person-years and 9 case-control studies (Riman et al., 2001; Kuper et al., 2002; Beehler et al., 2006; Peterson et al., 2006; Nagle et al., 2008; Olsen et al., 2008; Wernli et al., 2008; Delort et al., 2009; Moorman et al., 2009) involving 96,965 people (Table 1).

Effect of exposure

The effect of overweight and obesity on ovarian cancer during the premenopausal and postmenopausal periods was assessed using risk ratio (RR) in cohort studies (Figure 2 and 3) and odd ratio (OR) in case-control studies (Figure 4 and 5). The results of both cohort and case-control studies showed an increased risk of ovarian cancer in the overweight and obese women compared to those with normal weight: RR=1.08 (95%CI: 0.97, 1.19) and OR=1.26 (95%CI: 0.97, 1.63) for overweight and RR=1.27 (95%CI: 1.16, 1.38) and OR=1.26 (95%CI: 1.06, 1.50) for obesity.

Based on Newcastle Ottawa Statement Manual (Wells GA), the quality of the cohort and case-control studies was six and more, which was nearly the same. Therefore,

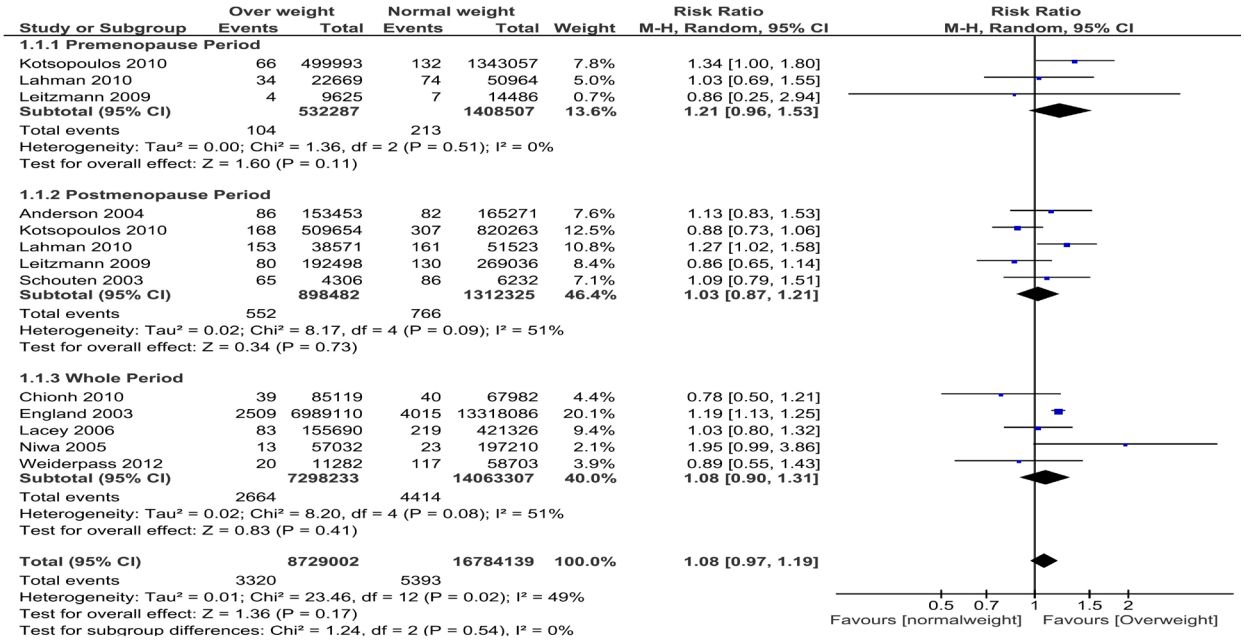

Figure 2. Forest Plot of the Risk Ratio Estimates of Ovarian Cancer and Overweight in the Premenopausal and Postmenopausal Periods

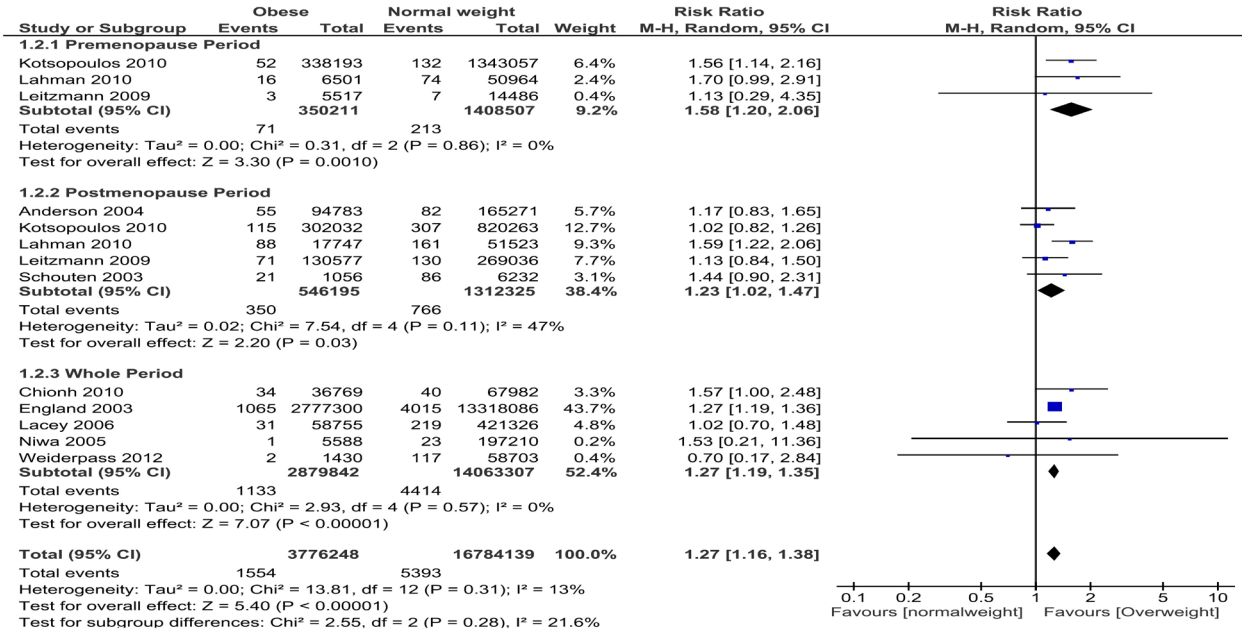

Figure 3. Forest Plot of the Risk Ratio Estimates of Ovarian Cancer and Obesity in the Premenopausal and Postmenopausal Periods

subgroups analysis is not run based on the quality of the studies.

Heterogeneity and publication bias

The between studies heterogeneity was assessed using the Chi2 test and the I^2 statistics. There was no significant heterogeneity between the results of cohort studies (Figure 2 and 3). However, there was a significant heterogeneity between the results of case-control studies addressing the effect of overweight on ovarian cancer in the premenopausal period and those addressing the effect of obesity on ovarian cancer in the whole period (Figure 3 and 4).

Publication bias was assessed using Begg and Egger tests by overweight and obesity in cohort and case-control studies. The results of Begg and Egger tests showed publication bias neither in the cohort studies addressing the effect of overweight (p=0.493 and p=0.842, respectively) and obesity (p=0.583 and p=0.802, respectively) on ovarian cancer nor in the case-control studies addressing the effect of overweight (p=0.882 and p=0.480, respectively) and obesity (p=0.586 and p=0.578, respectively) on the risk of development of ovarian cancer, independent of menopausal status.

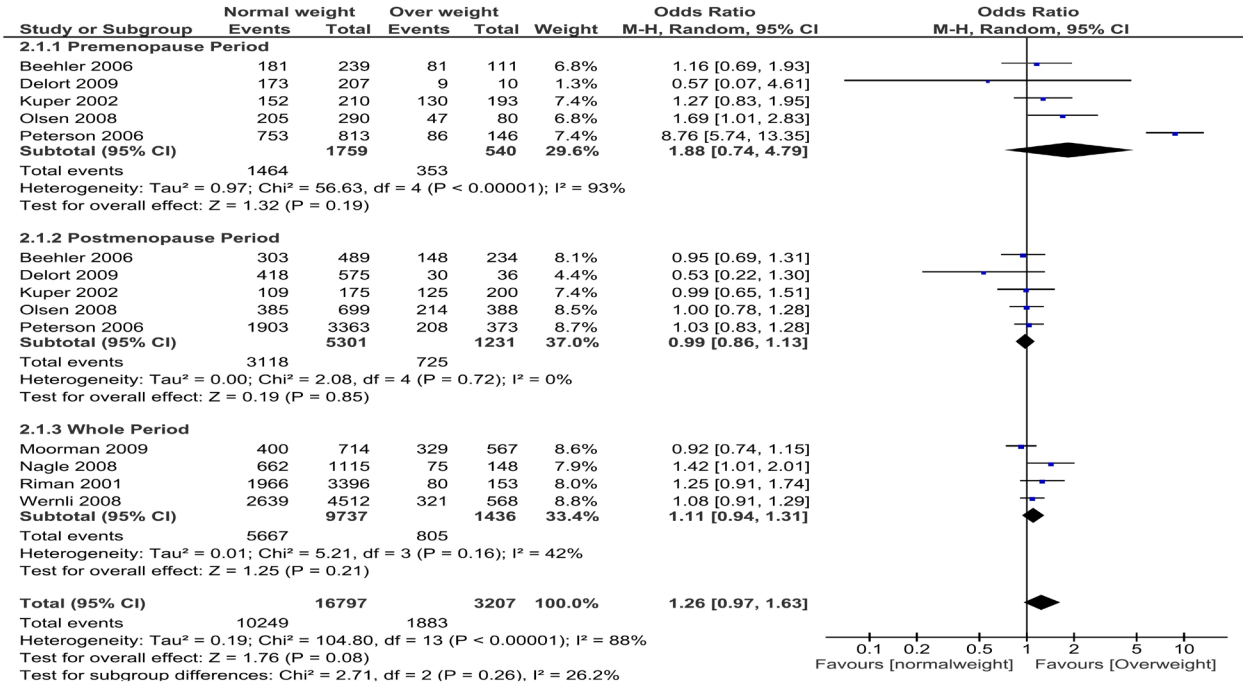

Figure 4. Forest Plot of the Odds Ratio Estimates of Ovarian Cancer and Overweight in the Premenopausal and Postmenopausal Periods

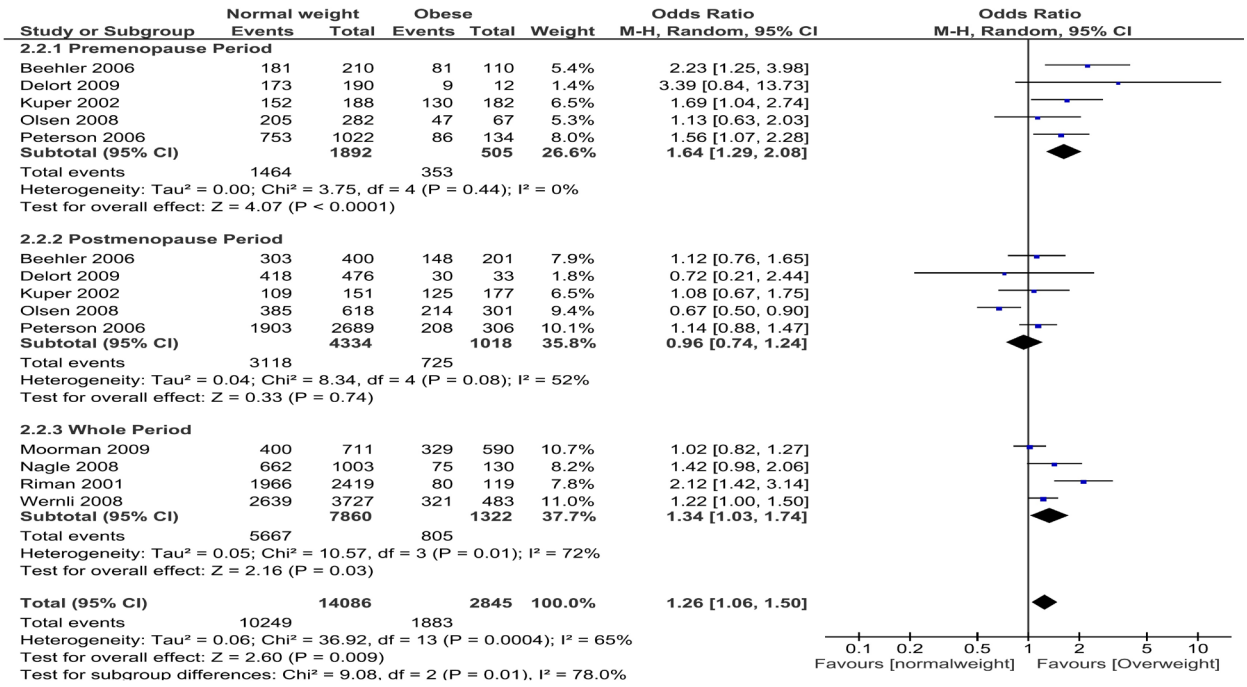

Figure 5. Forest Plot of the Odds Ratio Estimates of Ovarian Cancer and Obesity in the Premenopausal and Postmenopausal Periods

Discussion

The results of this meta-analysis showed that overweight may increase the risk of ovarian cancer 8% and 26% based on the cohort and case-control studies respectively. In addition, obesity can increase the risk of ovarian cancer 27% and 26% based on cohort and case-control studies respectively. These results show a dose-response relationship between BMI and ovarian cancer risk in the premenopausal and postmenopausal periods.

The Collaboration Group on Epidemiological Studies of Ovarian Cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012) conducted a meta-analysis in order to assess the effect of body size on the ovarian cancer risk. 47 epidemiologic studies indexed in PubMed until 2011 were retrieved. They reported that ovarian cancer risk increased significantly with BMI so that the relative risk of ovarian cancer was 1.03 and 1.10 per 5 kg/m^2 increase in BMI based cohort and case-control studies respectively. However, this meta-analysis was limited to studies indexed in PubMed.

A meta-analysis with similar topic was conducted by Schouten et al in 2008 (Schouten et al., 2008). Data from 12 prospective cohort studies conducted in North America and Western Europe were analyzed. They showed no association between BMI and ovarian cancer risk in the postmenopausal period, RR=1.02 (95%CI: 0.95, 1.08) but a mild association in the premenopausal period, RR=1.12 (95%CI: 0.96, 1.31). As meta-analysis was limited to the 12 prospective cohort studies that were conducted in North America and Western Europe, this limitation may reduce the generalizability of the results.

Another meta-analysis was conducted by Olsen et al in 2007 (Olsen et al., 2007). They searched Medline database until April 2006 and retrieved 28 case-control and cohort studies. It was shown that the risk of ovarian cancer increased with BMI. The overall effect of obesity on ovarian cancer was 1.30 (95%CI: 1.12, 1.50) and that of overweight was 1.16 (95%CI: 1.01, 1.32). This meta-analysis searched Medline database alone and did not run subgroup analysis to assess the potential interaction between BMI and the menopausal status.

The results of the cohort studies were homogenous but those of case-control studies were heterogeneous. The source of this heterogeneity was due to the results of the Peterson et al (Peterson et al., 2006) study which addressed the effect of overweight on ovarian cancer in the premenopausal period and Riman et al (Riman et al., 2001) who addressed the effect of obesity on ovarian cancer in the whole period. After removing these two outliers from the meta-analysis, the results became homogenous. In these studies, the data on women's weight and height were collected through a self-reporting data collection tool rather than through physical measurement. This might be the reason for the difference between the results of these studies from other included studies.

The Begg and Egger tests for publication bias were statistically significant neither for cohort nor for case-control studies. This indicates that the sensitivity of the search strategy was good enough to find the eligible studies.

There were a few limitations in our study as follows: (a) Three studies seemed potentially eligible to be included in our meta-analysis, but their full texts were not accessible. We contacted the authors to send us the full texts, but received no reply. This issue might raise the possibility of selection bias; (b) We planned to search ISI Web of Science to find further relevant studies but access to this database was not possible. This might introduce selection bias; (c) We could not assess the effect of confounding variables such as hormone therapy, nulliparity and family history of ovarian cancer. This issue may raise the possibility of the information bias; (d) In some studies included in the meta-analysis, the participants self-reported their weight and height. Literature showed that overweight and obese women are more likely to underreport their weight and those who are underweight are more likely to overreport their weight (Lawlor et al., 2002; Taylor et al., 2006). This might introduce information bias into the results. Despite these limitations, this meta-analysis could efficiently assess the association between BMI and ovarian cancer in the premenopausal and postmenopausal periods as well as the whole period based on cohort and case-control studies separately.

There is sufficient evidence that an increase in BMI can increase the risk of ovarian cancer regardless of the menopausal status mimicking a dose-response relationship, although the association is not very strong.

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