

Obesity and Ovarian Cancer Survival: A Systematic Review and Meta-analysis

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Abstract

Studies that have examined the association between obesity and ovarian cancer survival have provided conflicting results. We reviewed and quantitatively summarized existing evidence, exploring potentially important sources of variability, such as the timing of body mass index (BMI) assessment and different cutpoints used to categorize BMI. A systematic search of MEDLINE and EMBASE was conducted to identify original data evaluating the association between obesity and survival in women with ovarian cancer. Adjusted hazard ratios (HR) from studies were pooled using a random-effects model. The meta-analysis of 14 studies showed slightly poorer survival among obese than in non-obese women [pooled HR, 1.17; 95% confidence interval (CI), 1.03–1.34]. This estimate did not vary appreciably when BMI was measured before diagnosis (1.13; 0.95–1.35), at the time of diagnosis (1.13; 0.81–1.57) or at the commencement of chemotherapy (1.12; 0.96–1.31). We found a slightly stronger association in studies that only included women with a BMI ≥ 30 in their "obese" group (1.20) than in studies that also included overweight women (BMI ≥ 25 ; 1.14). Women with ovarian cancer who are obese appear to have slightly worse survival than non-obese women. However, there is a large amount of inter-study variation, which means that no solid conclusions can be drawn. *Cancer Prev Res*; 5(7); 901–10. ©2012 AACR.

Introduction

Ovarian cancer is a highly fatal disease, with only about 40% of women with ovarian cancer still alive more than 5 years postdiagnosis (1). This poor survival is largely attributable to the fact that approximately 75% of all cases of ovarian cancer in developed countries are diagnosed with metastatic spread beyond the pelvis (1, 2). While stage of disease at diagnosis remains the most important predictor of survival time, other known prognostic factors include age at diagnosis, tumor grade, and the amount of residual disease following surgery (3, 4). However, at the time of diagnosis, none of these factors are amenable to intervention to improve survival.

Potentially modifiable factors such as obesity, commonly measured by body mass index (BMI), have been found to be associated with poorer survival in a number of cancers including breast (5), prostate (6), and colorectal cancer (7). Few studies have examined the association between obesity and ovarian cancer survival and those that have provided conflicting results. Furthermore,

it is unclear whether sources of heterogeneity between studies, such as the timing of BMI assessment or the cutoff points used to classify BMI, may be contributing to these discrepancies.

A recent meta-analysis (8) of studies published up to December 2010 found that women with ovarian cancer who were obese during early adulthood (3 studies) or before diagnosis had worse survival (5 studies); however, no association with obesity measured around diagnosis (5 studies). Currently, it is unclear whether BMI in early adulthood or before diagnosis, the focus of the previous meta-analysis, is the relevant biologic window. For example, the practice of chemotherapy dose capping in obese patients (to prevent toxicity) may have negative implications on survival outcomes (9), so body size at the commencement of chemotherapy may be more relevant. Since this previous meta-analysis, there have been a number of additional epidemiologic studies published on the association between BMI and ovarian cancer survival, and we have also identified additional studies that were not included in the previous meta-analysis (10–15).

Given the growing number of studies in the literature and increasing interest in the role of lifestyle factors in cancer survival, our aim was to systematically re-evaluate the literature examining the association between obesity and survival in women with ovarian cancer and to conduct an updated, more comprehensive meta-analysis to quantify the magnitude of risk. A second specific objective was to explore potentially important sources of variability, such as the timing of BMI assessment and the different cutoff points used to categorize BMI.

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Materials and Methods

Search strategy

This systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (16). A systematic search of MEDLINE and EMBASE, from inception to September 2011, was conducted to identify studies examining the association between obesity and survival in women with ovarian cancer. The search included terms for ovarian cancer (*ovarian neoplasms OR ovarian cancer OR ovarian tumor OR ovarian tumour OR ovarian carcinoma*) AND obesity (*body size OR body weight OR overweight OR obesity OR body mass index*) AND survival (*survival analysis OR survival rate OR proportional hazards model OR survival OR prognosis*). The reference lists of all eligible articles and reviews were also scanned to identify additional studies for inclusion.

Study selection and data extraction

Studies were eligible for inclusion in the systematic review if they contained original data examining the association between obesity (assessed by any measure) and survival (ovarian cancer-specific survival or overall survival) in a cohort of women newly diagnosed with ovarian cancer. To be eligible for inclusion in the meta-analysis, studies had to additionally provide hazard ratio (HR) estimates. For all eligible studies, information was extracted on study design, country, years of diagnosis, years of follow-up, age, stage, definitions and categories of BMI, the timing of when BMI was measured, median survival, effect estimates, and variables adjusted for in analyses. Where more than one HR was reported, the most fully adjusted HR was extracted for the meta-analysis.

Statistical analysis

HR estimates were pooled using random-effects meta-analysis (17), and the heterogeneity across studies was

assessed using the I^2 statistic (18). Studies examining overall survival were pooled with studies examining ovarian cancer-specific survival as previous research has shown that there are very few competing causes of death in this population of women due to the highly fatal nature of ovarian cancer (1). Where multiple measurements of obesity were taken throughout the course of the cancer (e.g., from prediagnosis through to the commencement of chemotherapy), the estimate closest to body weight before diagnosis was used for primary analyses as most studies examined prediagnosis body weight. The majority of studies ($n = 9$) reported estimates for categories of BMI, similar to that of the World Health Organization guidelines (19). For the 2 studies that reported the effect of BMI as a continuous variable (14, 20), we used the reported effect sizes and 95% confidence intervals (CI) per 1-unit increase in BMI to estimate the HR and corresponding 95% CIs for a 5-unit change in BMI for comparability with the estimates reported in other studies.

Prespecified sensitivity analyses were conducted to assess whether there was a differential effect on survival according to when obesity was measured (before diagnosis, at diagnosis, or at chemotherapy) as well as the definition of obesity used for analysis ($BMI \geq 30$, $BMI \geq 25$ or per 5-unit increase in BMI). Publication bias was assessed by examining funnel plot asymmetry (21, 22). All analyses were conducted using Stata 11.0 (23).

Results

Systematic review

The primary search identified 57 eligible titles. After review of the abstracts, we identified 20 studies that were eligible for inclusion in the systematic review (Fig. 1 and Table 1). The 20 studies included women diagnosed with ovarian cancer between 1977 and 2007 with cohorts from the United States ($n = 11$), Sweden ($n = 2$), Germany

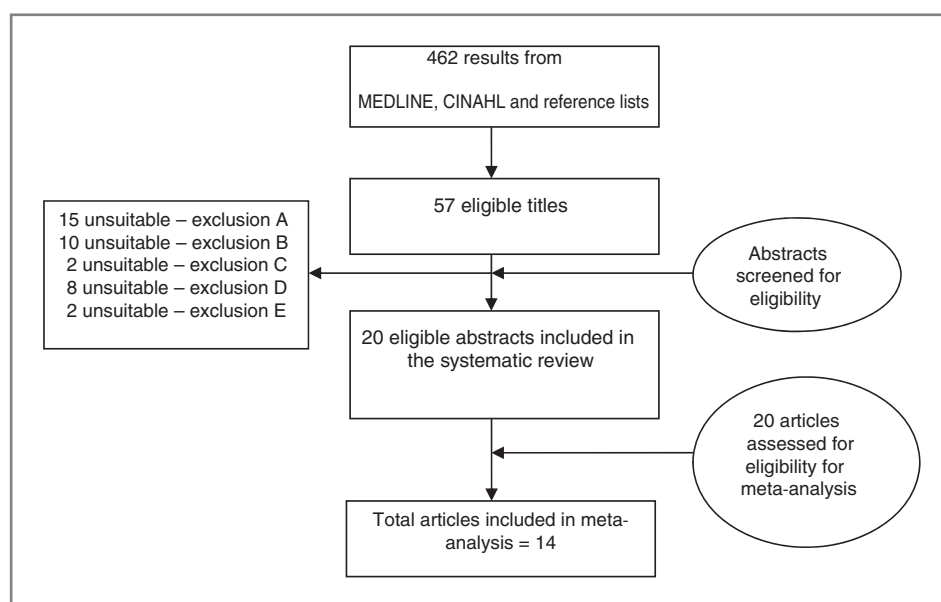


Figure 1. Study selection: exclusion criteria for the systematic review. Studies which did not evaluate a prognostic outcome (recurrence, disease-free survival, progression-free survival, all-cause mortality, or ovarian cancer-specific survival/mortality) in ovarian cancer patients (A); did not report original data (B); examined possible molecular pathways for obesity-related cancer survival (C); did not assess obesity status or did not analyze the effect of obesity on ovarian cancer prognosis (D); and contained overlapping populations (E).

Table 1. Characteristics of studies examining the association between obesity and long-term outcomes in patients with ovarian cancer

Source (country)	N	Years of diagnosis	Follow-up, y	Age, y	Stage	Exposure (BMI category)	Median survival time, mo	HR (95% CI)	Adjustment variables
Observational cohorts									
Dolecek and colleagues (USA; ref. 13)	341	1994–1998	Maximum, 11	Range, 18–74	All	18.5–24.9 ^b ≥30		1.0 1.20 (0.72–1.98)	Age, stage, grade, race, residual lesions, smoking, OC use, parity
Fotopoulou and colleagues (Germany; ref. 10)	306	2000–2010	Median, 0.97 Range, 0.01–5.2	Range, 18–92	All	<25 ^b ≥25		1.0 0.73 (0.39–1.37)	Age, stage, grade, lymph node status, residual tumour, ascites, IMO level involvement, nonserous histology, distant metastases
Kjaerbye-Thygesen and colleagues (Denmark; ref. 27)	295	1994–1999	Median, 7.3 Range, 5.4–9.5	Range, 35–79	III	18.5–24.9 ^a ≥25	33.6 25.2	1.0 1.83 (1.38–2.42)	Age, radicality of surgery, histology, platinum-based chemotherapy, smoking
Lamkin and colleagues (USA; ref. 14)	74	2001–2005	Mean, 2.01 Range, 0.02–6.08	Median, 62 Range, 33–87	All	Per 1-unit ^b increase in BMI		1.01 (0.97–1.04)	Nil
Matthews and colleagues (USA; ref. 34)	304	1996–2005	Maximum, 10	BMI < 30 (mean, 62.2) BMI ≥ 30 (mean, 58.3)	II–IV	18.5–24.9 ^e ≥35	40 48	—	—
Moysich and colleagues (USA; ref. 28)	359	1982–1998	Minimum, 9	Mean alive, 47.5 Mean dead, 58.3	All	<25 ^a ≥30	57 59	1.0 0.99 (0.71–1.38)	Age, stage
Munstedt and colleagues (Germany; ref. 31)	824	1986–2005	Median, 5.13	Median, 60.5	All	20–25 ^b 30–40	20.28 23.04	—	—
Nagle and colleagues (Australia; ref. 29)	609	1990–1993	Mean, 7.3 Range, 5–8.3	Range, 18–79	All	<22.2 ^a ≥25.8	<i>P</i> _{trend} = 0.053	1.0 0.96 (0.74–1.23)	Age, stage, grade, total energy intake, residual, ascites, smoking, parity, OC use

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Table 1. Characteristics of studies examining the association between obesity and long-term outcomes in patients with ovarian cancer (Cont'd)

Source (country)	N	Years of diagnosis	Follow-up, y	Age, y	Stage	Exposure (BMI category)	Median survival time, mo	HR (95% CI)	Adjustment variables
Pavelka and colleagues (USA; ref. 20)	149	1996–2003	Not stated	Range, 18–79	III–IV	Per 1-unit ^c increase in BMI	18.5–24.9 ≥30 80 62 P = 0.28	1.05 (1.005–1.097)	Nil
Schlumbrecht and colleagues (USA; ref. 15)	127	2002–2007	Mean, 3.1 Range, 0.3–7.2	Not stated	All	Not stated ^c		1.0 0.95 (0.68–2.43)	Not stated
Schlumbrecht and colleagues (USA; ref. 11)	194	1977–2009	Median, 5.1 Range, 0.1–31.9	Mean, 44.9 Range, 14–79	All	<25 ^c ≥30–<35 ≥35		1.0 1.02 (0.43–2.38) 2.53 (1.19–5.38)	Nil
Schildkraut and colleagues (USA; ref. 30)	257	1980–1982	Median, 8.3 Range, 0.1–14.2	Mean, 43.7 Range, 20–64	All	<27.9 ^a ≥27.9	52 64 P = 0.51	1.0 1.1 (0.7–1.7)	Age, stage, p53 status
Skirnisdottir and colleagues (Sweden; ref. 32)	446	1994–2003	Mean, 3.9 Range, 0–12.3	Mean, 62.5	All	<25 ^c >25		1.0 0.94 (0.74–1.21)	Age, stage, histology
Suh and colleagues (Korea; ref. 33)	486	2000–2010	Median, 2.83 Range, 0–13.2	BMI ≥ 23 (mean, 53.2) BMI <23 (mean, 48.6)	All	<23 ^c ≥23	P = 0.67	—	—
Yang and colleagues (Sweden; ref. 26)	635	1993–1995	Not stated	Range, 50–74	All	18.5–24.9 ^a ≥30		1.0 1.22 (0.86–1.71)	Age, stage, grade
Zhang and colleagues (China; ref. 35)	207	1999–2000	Minimum, 3	Mean alive, 46.7 Mean dead, 51.6	All	<20 ≥25 ^a ≤20 ^b ≥25		1.0 2.33 (1.12–4.87) 1.0 0.76 (0.38–1.52)	Age, stage, grade, ascites, residual lesions, chemotherapy, total energy intake, menopausal status
Zhou and colleagues (USA; ref. 12)	388	1998–2003	Maximum, 5	Mean, 58.6	All	<25 ^a ≥25 <25 ^d ≥25		1.0 1.30 (0.92–1.83) 1.0 1.05 (0.75–1.48)	Age, stage, histology, education, OC use, menopausal status, HRT use, parity, age at first birth, family history of ovarian cancer, time from diagnosis to study

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Table 1. Characteristics of studies examining the association between obesity and long-term outcomes in patients with ovarian cancer (Cont'd)

Source (country)	N	Years of diagnosis	Follow-up, y	Age, y	Stage	Exposure (BMI category)	Median survival time, mo	HR (95% CI)	Adjustment variables
Treatment cohorts									
Barrett and colleagues (multiple countries; ref. 24)	1,067	1998–2000	Not stated	Median, 59 Range, 19–85	IC–IV	18.5–24.9 ^c ≥30	Not attained 34.3 P = 0.10	—	—
Hess and colleagues, (USA; ref. 25)	790	1995–1998	Median, 4	Range, 21–90	III	<25 ^c ≥30	54.3 48.4	—	—
Wright and colleagues (USA; ref. 9)	387	Not stated	Median, 4.4	Median, 56.8 Range, 21–85	Not stated	"Across BMI strata" ^{h,c}	P = 0.62 P = 0.41	—	—

Abbreviations: HRT, hormone replacement therapy; OC, oral contraceptive.
^aBMI measured before diagnosis.
^bBMI measured at/around time of diagnosis.
^cBMI measured at the commencement of chemotherapy.
^dBMI measured 9 months post-chemotherapy.
^eTime of BMI measurement not stated.

($n = 2$), Denmark ($n = 1$), Australia ($n = 1$), China ($n = 1$), Korea ($n = 1$), and 1 cohort involving multiple countries. Sample size ranged from 74 to 1,067, with a median of 350. The majority of the studies were observational cohorts; however, 3 were cohorts of women with ovarian cancer participating in randomized trials (9, 24, 25).

All studies used BMI as a measure of obesity; however, the time point when BMI was measured, as well as the cutoff points used to categorize BMI for analysis varied between studies. Five studies used data on height and weight obtained 1 year before diagnosis (26) or from reports of women's usual adult weight (27–30), 4 studies measured BMI at the time of diagnosis (10, 13, 14, 31), 8 at the commencement of chemotherapy (9, 11, 15, 20, 24, 25, 32, 33), 1 study did not state when BMI was measured (34), and 2 studies assessed BMI at multiple time points (12, 35) including 5 years before diagnosis (12, 35). The cutoff points used to categorize the obese group were in accord with the World Health Organization's International Classification of Obesity in approximately half of the studies (BMI ≥ 30 kg/m² being obese; $n = 9$; ref. 19). However, 8 studies used a combined overweight/obese group (BMI ≥ 25 kg/m²), 2 studies analyzed their data per 1-unit increase in BMI, 2 studies analyzed data as semicontinuous variables across BMI strata, and 1 study did not state how BMI was categorized for analysis. Five studies used the World Health Organization's classification of normal BMI (18.5–24.9 kg/m²) as the reference group (13, 24, 26, 27, 34) whereas others used variations including all women with a BMI < 20 or BMI < 25 . Median follow-up time varied considerably between studies ranging from less than 1 year to greater than 10 years. Thirteen studies used all-cause mortality as the

endpoint, whereas 7 studies used ovarian cancer-specific deaths as the endpoint. Nine of the studies adjusted for the key prognostic factors of stage at diagnosis and age, other prognostic factors were adjusted for less consistently.

Three observational cohorts (31, 33, 34) and the 3 treatment cohorts (9, 24, 25) did not report HRs and so were not included in our initial meta-analysis. All of these studies reported that survival time did not differ significantly between BMI strata, with the exception of the study by Munstedt and colleagues, which found a trend toward improved survival in women who were obese (31). Estimates for 2 of these studies (25, 31) were, however, included in the previous meta-analysis (8), thus we conducted a sensitivity analysis including this additional information.

Meta-analysis

Our meta-analysis of the 14 studies showed slightly poorer survival among the obese group compared with non-obese women with ovarian cancer [pooled HR (pHR), 1.17; 95% CI, 1.03–1.34; Fig. 2]. This estimate did not vary appreciably when we restricted it to studies where BMI was measured before diagnosis (pHR, 1.13; 0.95–1.35), at the time of diagnosis (pHR, 1.13; 0.81–1.57), or at the time of chemotherapy (pHR, 1.13; 0.92–1.39; Fig. 3). There was a large amount of inter-study heterogeneity among the BMI cutoff points used to define both the "obese" group and the "reference" group for analysis. The survival differential varied only slightly depending on whether the "obese" group included only women with a BMI ≥ 30 (pHR, 1.20; 95% CI, 0.94–1.53), obese and overweight women (BMI ≥ 25 ; pHR, 1.14; 95% CI, 0.92–1.41), or whether results were analyzed per 5-unit increase in BMI (pHR, 1.15;

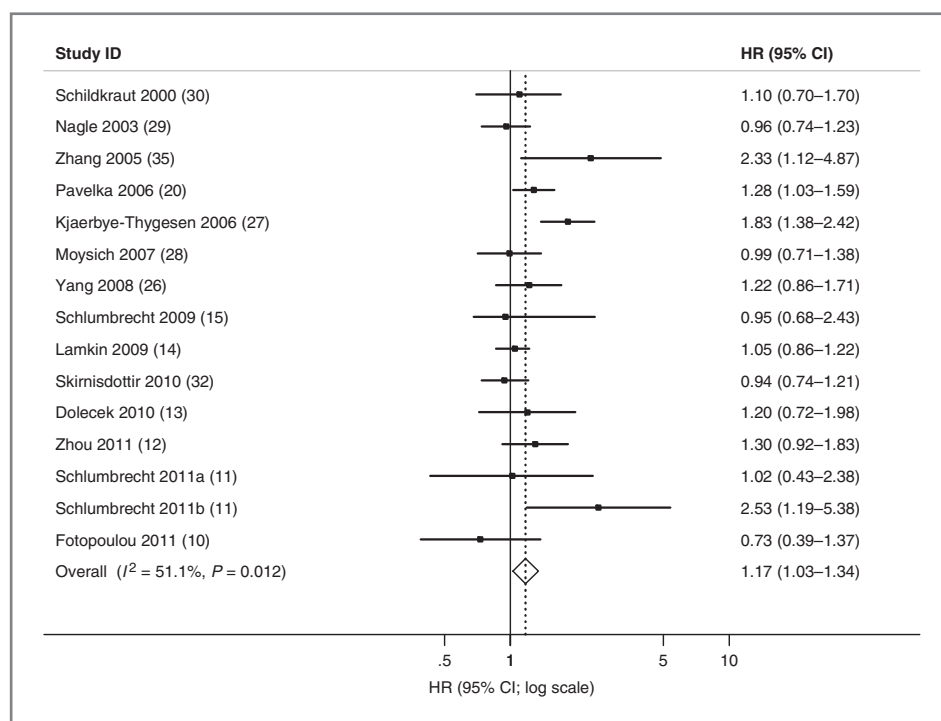
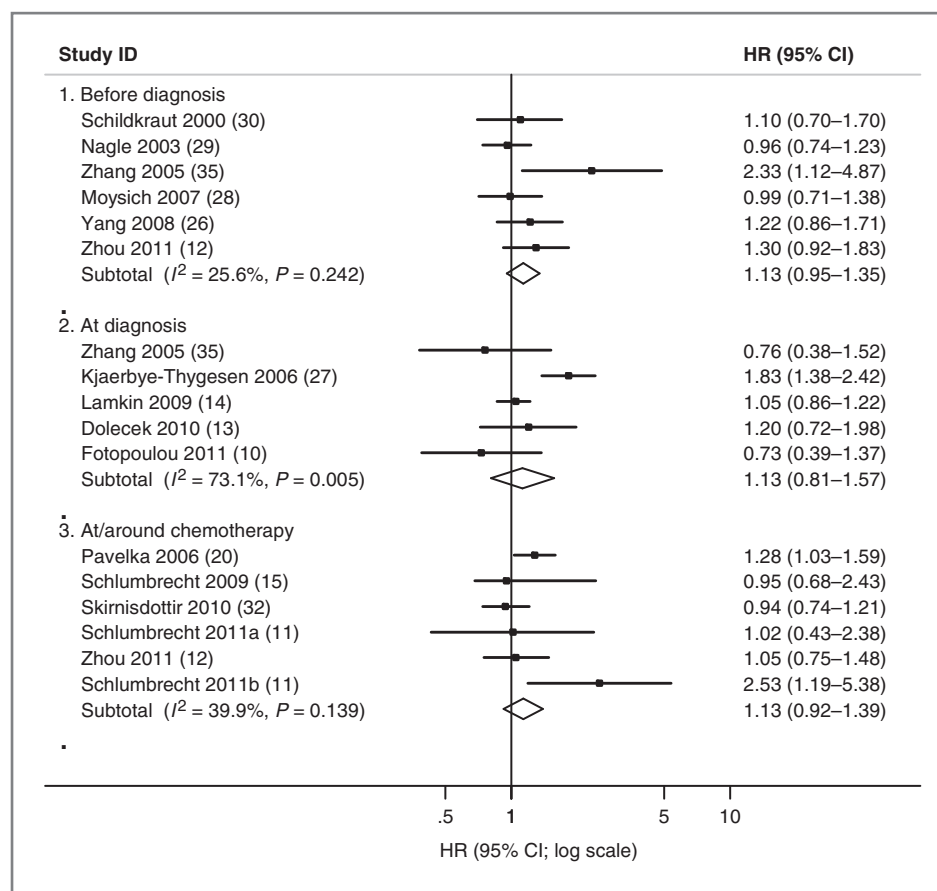


Figure 2. Meta-analysis and pHR of the effect of obesity on survival in patients with ovarian cancer. Note: Schlumbrecht 2011a: BMI = 30–35; Schlumbrecht 2011b: BMI ≥ 35 .

Figure 3. Sensitivity analyses of pHRs of the effect of obesity on survival in patients with ovarian cancer, stratified by the timing of when obesity was measured. Note: Schlumbrecht 2011a: BMI = 30–35; Schlumbrecht 2011b: BMI \geq 35.



95% CI, 0.95–1.39; Fig. 4). Because studies used different methods to account for confounding, we conducted a *post hoc* sensitivity analysis excluding all studies that did not adjust for at least age and stage ($n = 5$) and obtained a pHR of 1.17 (95% CI, 0.97–1.40). Inclusion of the estimates for the 2 additional studies (as reported by Yang and colleagues; ref. 8) reduced the estimate slightly to 1.13 (95% CI, 1.01–1.28).

Publication bias

The funnel plot of the effect estimates of obesity and ovarian cancer survival was close to symmetrical, and there was no evidence of publication bias using the Egger weighted regression method ($P_{\text{bias}} = 0.44$) or the Begg rank correlation method ($P_{\text{bias}} = 0.32$).

Discussion

In this meta-analysis, we have found consistent evidence that survival among obese women with ovarian cancer is slightly worse than survival among non-obese women. On the basis of our analysis of the published literature, we estimate that the risk of survival among obese women with ovarian cancer is 15% to 20% worse than women with a BMI in the "healthy" range. Our results were consistent regardless of whether BMI was measured before diagnosis,

at diagnosis, or at/around the commencement of chemotherapy. Compared with the previous meta-analysis, our summary estimate is larger for obesity measured at or around the time of diagnosis (pHR, 1.13 vs. 0.94; ref. 8). This is, in part, due to the different criteria used to define obesity at or around the time of diagnosis and hence the inclusion of different studies in the 2 pooled calculations. The other major difference between our meta-analysis and the previous meta-analysis was the HR from one of the studies. The study by Pavelka and colleagues reported an HR of 1.05 per 1-unit increase in BMI (20), so for consistency with the other studies in our meta-analysis, we converted this estimate to give an expected HR of 1.28, for a 5-unit increase in BMI. These estimates contrast markedly, however, with the HR of 0.53 that Yang and colleagues included in their meta-analysis (8).

Our meta-analysis also adds to the previous analysis in that it explored several potentially important sources of inter-study variability. One such source of variation is the BMI cutoff points used to classify the obese and reference groups for analysis. Inclusion of underweight women (who are likely to have worse outcomes) in the reference group and/or overweight women in the obese group may underestimate the true association between obesity and ovarian cancer survival. Our sensitivity analysis, which stratified studies by how they defined obesity, suggested that there

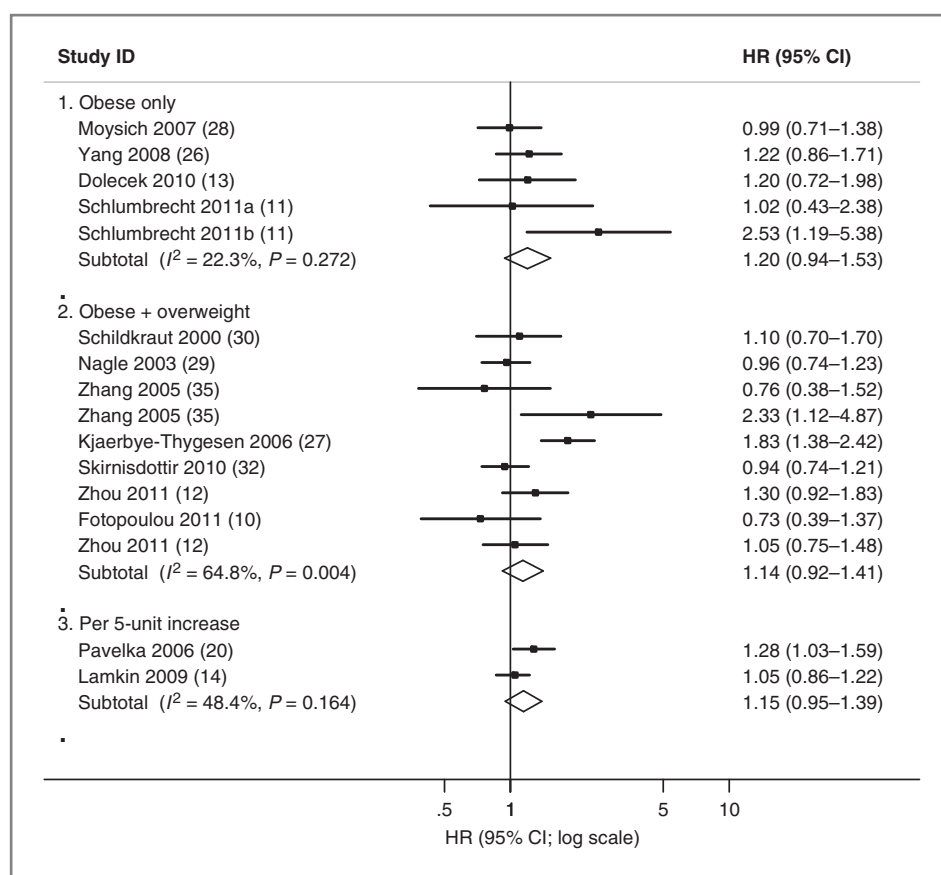


Figure 4. Meta-analysis and pHRs of the effect of obesity on survival in patients with ovarian cancer stratified by the cutoff points used to define obesity in analyses: Obese-only (BMI ≥ 30) versus obese and overweight (BMI ≥ 25). Note: Schlumbrecht 2011a: BMI = 30–35; Schlumbrecht 2011b: BMI ≥ 35 .

was a slightly stronger effect in studies that only included women with a BMI ≥ 30 in their "obese" group (pHR, 1.20) than in studies that also included overweight women (BMI ≥ 25 ; pHR, 1.14). We also identified a large amount of variability about the time point when BMI was measured. Changes in weight and body composition commonly occur throughout the course of ovarian cancer. Both weight loss, generally due to cachexia, and weight gain, typically due to ascites, can be presenting symptoms for ovarian cancer, particularly in women with advanced disease (36). Weight change can also occur during treatment and is likely to be associated with outcome (weight gain being an indicator of improved survival and weight loss an indicator for poor survival; ref. 25). The timing of BMI measurement is therefore particularly important as it determines the specific research questions being asked.

First, women who are obese before, or at diagnosis, may have more biologically aggressive tumors as excess adiposity is associated with the upregulation of a number of cellular proliferation pathways which may lead to increased tumor growth and metastasis (37). For example, leptin, an adipocytokine produced by white adipose tissue, is known to act as a growth factor in a number of cancer cell lines including breast, endometrial, and prostate cancers (38, 39) and is also involved in promoting angiogenesis (40).

Second, chemotherapy dosage is calculated on the basis of body surface area. Because of concerns of relative

overdosing in obese patients with a large body surface area, it is well documented that empiric dose capping of chemotherapeutic drugs (usually at a body surface area of either 1.8 or 2 m²) occurs in some centers (41). Furthermore some, but not all, observational studies have shown that dose intensity (42) and the cumulative dose (20) of chemotherapy may be lower in obese women (compared with normal weight). Evidence also suggests that obese women with ovarian cancer who have their doses capped at 2.0 m² experience similar or lower rates of chemotherapy-induced toxicities compared with those who were dosed according to their actual body weight, a further indication that obese women may be receiving suboptimal treatment, and therefore be at an increased risk of disease progression and reduced survival (9,43). Obesity is also associated with other comorbidities such as diabetes and cardiovascular disease, which may also lead to women being treated with reduced doses of chemotherapy (44), as well as being independently associated with overall survival. The potential role of reverse causation (where deteriorating health status may influence body size) also needs to be considered.

Interestingly, in our sensitivity analysis, the association between obesity and survival did not appear to vary appreciably by whether a woman's obesity status was measured before diagnosis, at diagnosis, or at the time of chemotherapy. However, the paucity of published data in relation to

differences in the timing of BMI measurement and associations with ovarian cancer survival limit conclusions that can be drawn. Therefore, future studies should include careful planning of the timing of obesity measurement to elucidate the causal mechanisms surrounding adverse survival in obese women with ovarian cancer.

Implications for further research

Differences in dosing protocols for obese women may explain some of the disparities seen in the results of different studies in this meta-analysis; however, few studies provided information on dosing protocols. Future studies should ideally specify dosing protocols, such as the percentage of women receiving chemotherapy dose reductions, to help in interpreting their results.

To date, no studies have examined other measures of obesity, such as waist-hip ratio (WHR), which has been shown to be associated with reduced survival in women with breast cancer (45, 46). WHR considers the anatomic distribution of adipose tissue, which is a more accurate indicator of metabolic stress associated with increased adiposity, particularly when compared with BMI, which is unable to distinguish lean muscle mass from fat mass (47–49). In addition, as obesity appears to be differentially associated with the incidence of ovarian cancer in pre- and postmenopausal women and with different histologic subtypes of cancer (50, 51), future large-scale studies and pooled cohorts should aim to assess whether there is a differential effect of obesity on survival according to these factors as well as other prognostic factors.

Strengths of our review are the broad search strategy and that references from all included studies and relevant narrative reviews were cross-checked for additional publications. However, as with any meta-analysis, any biases and confounding inherent in the original studies will also be present in our analyses (52). We have attempted to minimize the effect of confounding by using the most adjusted estimates provided by studies. Our sensitivity analysis,

which excluded studies that did not adjust (or restrict) for at least stage and age, suggested that the association between obesity and ovarian cancer survival was robust to potential confounding.

Conclusion

The results of our meta-analysis, based on more studies than previous reviews, suggest that obesity is associated with a weak adverse effect on the survival of women with ovarian cancer. However, the large amount of inter-study heterogeneity means that no firm conclusions can be drawn. Further studies need to be conducted with a particular focus on selecting the timing of the measurement of obesity based on specific mechanistic hypotheses such as the role of relative underdosing of chemotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.M. Protani, C.M. Nagle, P.M. Webb

Development of methodology: M.M. Protani, C.M. Nagle

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.M. Protani

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.M. Protani, P.M. Webb

Writing, review, and/or revision of the manuscript: M.M. Protani, C.M. Nagle, P.M. Webb

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.M. Protani

Study supervision: C.M. Nagle, P.M. Webb

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