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Obesity and survival among women with ovarian cancer: results from the Ovarian Cancer Association Consortium

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Background: Observational studies have reported a modest association between obesity and risk of ovarian cancer; however, whether it is also associated with survival and whether this association varies for the different histologic subtypes are not clear. We undertook an international collaborative analysis to assess the association between body mass index (BMI), assessed shortly before diagnosis, progression-free survival (PFS), ovarian cancer-specific survival and overall survival (OS) among women with invasive ovarian cancer.

Methods: We used original data from 21 studies, which included 12 390 women with ovarian carcinoma. We combined study-specific adjusted hazard ratios (HRs) using random-effects models to estimate pooled HRs (pHR). We further explored associations by histologic subtype.

Results: Overall, 6715 (54%) deaths occurred during follow-up. A significant OS disadvantage was observed for women who were obese (BMI: 30–34.9, pHR: 1.10 (95% confidence intervals (CIs): 0.99–1.23); BMI: $\geqslant$35, pHR: 1.12 (95% CI: 1.01–1.25)). Results were similar for PFS and ovarian cancer-specific survival. In analyses stratified by histologic subtype, associations were strongest for women with low-grade serous (pHR: 1.12 per 5 kg m^{-2}) and endometrioid subtypes (pHR: 1.08 per 5 kg m^{-2}), and more modest for the high-grade serous (pHR: 1.04 per 5 kg m^{-2}) subtype, but only the association with high-grade serous cancers was significant.

Conclusions: Higher BMI is associated with adverse survival among the majority of women with ovarian cancer.

Ovarian cancer survival is poor, with only ~30–50% of women alive 5 years after diagnosis and over 140 000 deaths globally per year (Jemal *et al*, 2011). The key prognostic factors – age, stage and grade of tumour – are not modifiable at diagnosis. Understanding how potentially modifiable factors such as obesity influence survival following a diagnosis of ovarian cancer could potentially be harnessed as a means of reducing a woman's risk of cancer progression or recurrence.

Women who are overweight or obese have increased risks of developing many types of cancer, including ovarian, when compared with women of normal weight (Reeves *et al*, 2007). Two large pooled analyses recently confirmed that this increased risk for ovarian cancer is modest (odds ratios ~10% increase in risk per 5 kg m^{-2} increase in body mass index (BMI) (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012; Olsen *et al*, 2013) and may be restricted to non-high-grade serous subtypes (Olsen *et al*, 2013). Evidence that obesity is a poor prognostic factor for several malignancies including the breast, prostate and colon is increasing (Calle *et al*, 2003; Parekh *et al*, 2012) and several lines of evidence suggest that obesity may also be associated with poor survival among women with ovarian cancer (Ptak *et al*, 2013; Diaz *et al*, 2013; Makowski *et al*, 2014). A recent meta-analysis of 14 studies concluded that women with ovarian cancer, who were obese, had 17% worse survival compared with those of normal weight (Protani *et al*, 2012). However, the studies in this meta-analysis varied greatly in the timing of obesity measurement: from usual adult weight to weight at the time of diagnosis, or at the commencement of chemotherapy. Most of the studies included had a relatively small sample size (median = 301) and, as a consequence, variation by histologic subtype could not be investigated. Furthermore, few studies had examined progression-free survival (PFS) or ovarian cancer-specific survival.

Using data from 21 case–control studies from the Ovarian Cancer Association Consortium (OCAC), we sought to evaluate the association between BMI and survival (PFS, ovarian cancer-specific and overall survival (OS)), overall and by histologic subtype, in over 12 000 women with invasive epithelial ovarian cancer.

MATERIALS AND METHODS

The OCAC consortium was founded in 2005 to combine data from individual case–control studies, to provide increased accuracy of estimates of genetic associations with ovarian cancer (Ramus *et al*, 2008). Twenty-one studies summarized in Table 1 provided BMI data and clinical follow-up information, allowing calculation of 5-year survival estimates for invasive ovarian, fallopian tube or peritoneal cancer cases (full study name and acronym are listed in Supplementary Table 1). All of the studies were approved by their institutional review board and all study participants provided informed consent.

Analysis variables. In all but two studies (HSK and PVD), both height and weight were self-reported. For 10 studies, women recalled their weight ~1 year before diagnosis (AUS (Merritt *et al*, 2008), BEL (Song *et al*, 2009), HOP (Lo-Ciganic *et al*, 2012), JPN

Table 1. Characteristics of 21 OCAC studies included in analysis

Site	Country	Source of cases	Diagnosis years	Age range	Number of cases	Reference period for BMI measurement (before diagnosis)	Median (range) BMI (kg m^{-2})	Median (range) follow-up time among living (years)	Number (%) dead	5-Year survival (%)
AUS (Merritt *et al*, 2008)	Australia	Population	2002–2006	20–80	1404	1 Year	26.1 (46.7)	7.3 (8.0)	875 (62.3)	48.5
BAV (Song *et al*, 2009)	Germany	Hospital/Clinic	2002–2006	22–84	431	5 Years	25.9 (34.2)	5.6 (25.1)	236 (54.8)	47.4
BEL (Song *et al*, 2009)	Belgium	Hospital/Clinic	2007–2012	18–85	477	1 Year	24.7 (34.5)	3.5 (28.8)	133 (27.9)	70.0
CON (Risch *et al*, 2006)	USA	Population	1998–2003	36–81	388	5 Years	24.6 (43.6)	8.3 (10.1)	224 (57.7)	57.6
DOV (Rossing *et al*, 2007; Bodelon *et al*, 2012)	USA	Population	2002–2005	35–74	1146	5 Years	25.1 (44.8)	4.4 (8.8)	486 (42.4)	55.0
GER (Royar *et al*, 2001)	Germany	Population	1993–1996	21–75	240	At diagnosis	24.4 (40.6)	14.5 (3.9)	167 (69.6)	47.1
HAW (Goodman *et al*, 2008; Lurie *et al*, 2008)	USA	Population	1993–2008	24–85	429	5 Years	25.1 (36.9)	7.3 (16.5)	217 (50.6)	62.2
HOP (Lo-Ciganic *et al*, 2012)	USA	Population	2003–2009	25–85	652	1 Year	27.4 (51.1)	5.1 (9.1)	335 (51.4)	51.3
HSK (du Bois *et al*, 2003; Harter *et al*, 2011)	Germany	Hospital/clinic	2000–2007	29–80	111	At diagnosis	24.2 (21.3)	5.0 (10.7)	65 (58.6)	48.2
JPN (Hamajima *et al*, 2001)	Japan	Hospital/clinic	2001–2005	23–75	65	1 Year	22.4 (12.5)	3.6 (9.2)	29 (44.6)	44.1
MAC + MAY (Kelemen *et al*, 2008; Goode *et al*, 2010, 2011)	USA	Hospital/clinic	1999–2012	21–85	944	1 Year	26.6 (41.3)	3.3 (22.0)	503 (53.3)	44.0
MAL (Glud *et al*, 2004; Soegaard *et al*, 2007)	Denmark	Population	1994–1999	32–80	573	5 Years	23.6 (42.2)	13.8 (4.5)	438 (76.4)	43.5
NCO (Schildkraut *et al*, 2008, 2010)	USA	Population	1999–2008	22–74	916	1 Year	26.6 (47.4)	7.2 (8.6)	551 (60.2)	50.2
NEC (Terry *et al*, 2005; Merritt *et al*, 2013)	USA	Population	1992–2003	21–77	847	1 Year	24.6 (50.3)	13.3 (10.6)	490 (57.9)	58.7
NJO (Bandera *et al*, 2011; Chandran *et al*, 2011; Gifkins *et al*, 2012)	USA	Population	2002–2008	25–81	240	1 Year	25.8 (51.4)	6.2 (7.4)	113 (47.1)	61.0
POL (Garcia-Closas *et al*, 2007)	Poland	Population	2000–2003	24–74	268	5 Years	23.9 (21.9)	5.3 (7.1)	142 (53.0)	49.0
PVD (Hogdall *et al*, 2010; Risum *et al*, 2011)	Denmark	Hospital/clinic	2004–2012	30–84	191	At diagnosis	24.2 (32.1)	4.8 (4.9)	102 (53.4)	46.6
STA (McGuire *et al*, 2004)	USA	Population	1997–2001	21–64	499	At diagnosis	24.4 (44.7)	11.0 (13.3)	284 (56.9)	54.6
TBO (Pal *et al*, 2005, 2007; Lacour *et al*, 2011)	USA	Population	2000–2012	26–85	245	At diagnosis	24.8 (32.9)	5.9 (7.9)	131 (53.5)	49.9
UCI (Ziogas *et al*, 2000)	USA	Population	1993–2005	21–84	394	1 Year	24.1 (41.2)	8.7 (17.6)	179 (45.4)	73.5
USC (Pike *et al*, 2004; Wu *et al*, 2009)	USA	Population	1992–2009	20–84	1930	1 Year	24.6 (42.4)	8.0 (17.7)	1015 (52.6)	57.4
TOTAL				18–85	12 390		25.1 (54.6)	6.9 (28.8)	6715 (54.2)	53.6

(Hamajima *et al*, 2001), MAC (Goode *et al*, 2011) and MAY (Kelemen *et al*, 2008; Goode *et al*, 2010), NCO (Schildkraut *et al*, 2008, 2010), NEC (Terry *et al*, 2005; Merritt *et al*, 2013), NJO (Bandera *et al*, 2011; Chandran *et al*, 2011; Gifkins *et al*, 2012), UCI (Ziogas *et al*, 2000) and USC (Pike *et al*, 2004; Wu *et al*, 2009)); for six studies, they were asked to recall their weight ~5 years before diagnosis (BAV (Song *et al*, 2009), CON (Risch *et al*, 2006), DOV (Rossing *et al*, 2007; Bodelon *et al*, 2012), HAW (Goodman *et al*, 2008; Lurie *et al*, 2008), MAL (Glud *et al*, 2004; Soegaard *et al*, 2007) and POL (Garcia-Closas *et al*, 2007)); for three studies, it was recalled weight around the time of diagnosis (GER (Royar *et al*, 2001), STA (McGuire *et al*, 2004) and TBO (Lacour *et al*, 2011; Pal *et al*, 2005, 2007)); and for two studies, it was reported in the medical records around the time of diagnosis (PVD (Hogdall *et al*, 2010; Risum *et al*, 2011) and HSK (du Bois *et al*, 2003; Harter *et al*, 2011). This information was used to calculate BMI as weight in kilograms divided by the square of height in metres (kg m^{-2}), which was classified using the World Health Organization (WHO) definitions of obesity (<18.5 'underweight'; 18.5–24.9 'normal weight'; 25–29.9 'overweight'; 30–34.9 'class I obesity'; 35–39.9 'class II obesity'; and ⩾40 'class III obesity') (World Health Organisation, 1995). Among the 21 OCAC studies, 756 (5.3%) women were with missing BMI information. Of the 12 390 women included in the analyses, BMI ranged from 13.7 to 68.3 kg m^{-2}. Three hundred and seven women were underweight (BMI <18.5) and 71 (0.6%) had BMI values >50 kg m^{-2}.

Covariate information. Each OCAC study submitted their data to Duke University using a standard format. Here the variables were reviewed, discrepancies were checked with individual studies and data merged where necessary. The data included information about variables potentially associated with BMI and/or survival: age (at diagnosis), tumour stage summarized from International Federation of Gynecology and Obstetrics or the Surveillance, Epidemiology, and End Results (SEER) stage (localized, regional,

distant and unknown) and tumour grade (well, moderately, poorly undifferentiated and unknown). Residual disease remaining after primary cytoreductive surgery (no macroscopic disease, macroscopic disease ⩽2 cm, macroscopic disease, macroscopic disease, size unknown and tumour not resected) was reported in 9 of the studies and cigarette smoking status (never, current and former smoker) was reported in 17 studies.

Clinical data, definitions and analysis. Vital status and survival time were determined by each study and OS time was calculated from date of diagnosis to date of death, or last follow-up. Cause of death information was available for 1511 of the 6715 women who had died (23%) and, of these, most (94%) had died from ovarian cancer; thus, all-cause mortality was used as the primary outcome. Where time from diagnosis to study recruitment was provided (19 of the 21 studies, not available for HSK and PVD), the left truncation was used to account for time elapsed between date of diagnosis and date of study recruitment, in order to reduce potential survivorship biases arising from the exclusion of eligible women who had died before recruitment. Additional analyses were conducted using death from ovarian cancer as the end point and PFS (defined by each study as time from date of diagnosis to the first confirmed sign of disease progression (clinical, biochemical (i.e., CA125) or radiological progression), death or last follow-up date) where such data were available.

Statistical analysis. We used a two-stage method of analysis. In the first stage, each study was analysed separately. For each study, we used Cox proportional hazards regression models to compute adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between BMI (standard WHO categories and per 5 kg m^{-2} increase) and survival. The HR for ovarian cancer per 5 kg m^{-2} increase in BMI was estimated by fitting a log linear trend across intervals of BMI (2.5 units) using the overall median value for each interval, except for the top interval where we used site-specific median values rounded to the nearest integer, to account for the greater variability of BMI in the upper category across study sites. We repeated this analysis using the continuous value of BMI for each woman. We expected that the relationship between BMI and survival might not be linear at very low BMI levels; hence, we excluded women in the 'underweight' range (BMI $<$18.5 kg m^{-2}) from these analyses. All study-specific models were adjusted for age (continuous), tumour stage (classified as localized, regional and distant) and tumour grade (well differentiated, moderately differentiated and poorly/undifferentiated). We also adjusted study-specific models for race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian and others) where more than 5% of the study population was not classified as the predominant race. Data on residual disease and cigarette smoking status were not available for all studies; however, we did include these variables in models restricted to studies where they were available. For each study-specific model, we examined possible violation of the proportional hazards assumption by evaluating whether covariate associations with BMI varied over time and allowing them to vary if needed. In the second stage, the pooled BMI effect (pooled HR (pHR)) was calculated using random-effects meta-analysis according to the method of DerSimonian and Laird (1986).

We computed pHRs for BMI for all invasive ovarian cases. Where between-study heterogeneity was evident, we examined the data for potential sources of this heterogeneity considering sample size, study design, study site/region, diagnosis years and median follow-up times (calculated using the reverse Kaplan–Meier method (Clark *et al*, 2003; Schemper and Smith, 1996)), median BMI, 5-year survival per cent, race/ethnicity and timing of BMI measurement. We also conducted subgroup analyses to examine whether associations between BMI and survival were modified by histologic subtype (low- (well differentiated) and high-grade tumours (moderate/poorly/undifferentiated), serous, mucinous, endometrioid and clear cell cancers), where these data were available. The statistical significance of any observed stratum differences was assessed by including a cross-product term in survival models. All *P*-values are two-sided. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and Stata 11 (College Station, TX, USA).

RESULTS

Table 1 shows the characteristics of the 21 studies that contributed data from a total of 12 390 women with invasive epithelial ovarian cancer to this analysis. Twelve studies were conducted in the United States, seven in Europe and one each in Australia and Japan. The number of women with invasive epithelial ovarian cancer participating in the studies ranged from 65 (JAP) to 1930 (USC). Women were 18–85 years of age at diagnosis between 1992 and 2012 (most of the OCAC studies capped recruitment at 80 or 85 years and also excluded women younger than 18 years; thus, our cases are slightly younger than those reported in the SEER programme); 15 studies were population based and 6 were hospital/clinic based (two studies from the same population, MAC and MAY, were combined). During the follow-up period, half (54%) of the women had died. The median follow-up time among living women was 6.9 years (maximum 14.5 years). The median BMI was 25.1 kg m^{-2} (interquartile range: 22.3–29.3 kg m^{-2}).

The clinical characteristics of all the women included in this analysis are shown in Table 2. Women had a mean age of 58 years at diagnosis and the majority had serous (62%), poorly

Table 2. Clinical characteristics of 12 390 participants included in analysis

Characteristic[a]	N[b]	%
Age		
Age, years (median)	58.0	
<40	741	6.0
40– <50	2286	18.5
50– <60	3847	31.1
60– <70	3515	28.4
70– <85	2001	16.2
Histology		
Serous	7530	62.4
Serous low-grade	500	4.1
Serous high-grade	6443	53.4
Mucinous	733	6.1
Endometrioid	1683	14.0
Clear cell	896	7.4
Other histology	1222	10.1
Stage		
Localized	2066	17.0
Regional	2285	18.8
Distant	7809	64.2
Grade		
Well-differentiated	1336	12.1
Moderately differentiated	2597	23.5
Poorly differentiated	6158	55.7
Undifferentiated	975	8.8
Residual disease after surgery		
No macroscopic disease	1804	46.8
Macroscopic disease ⩽2 cm	974	25.3
Macroscopic disease >2 cm	250	6.5
Macroscopic disease, size unknown	713	18.5
Tumour not resected	115	3.0

[a]Participants with unknown histology (n = 326), unknown serous high- or low-grade status (n = 587), stage (n = 230), grade (n = 1324) and residual disease (n = 8534) were not included in percentages.
[b]Numbers may not add to 12 390 due to missing data.

differentiated (56%) and/or distant stage (64%) cancers. Among those with residual disease data available ($n=3856$), 47% had no macroscopic disease after cytoreductive surgery.

In multivariate analyses (all histologies combined), we found that women who were overweight (BMI: 25–29.9), obese (BMI: 30–34.9) and morbidly obese (BMI: $\geqslant 35$) experienced worse survival compared with women within the normal weight range (pHRs: 1.05 (95% CIs: 0.96–1.15), 1.10 (95% CIs: 0.99–1.22) and 1.15 (95% CIs: 0.98–1.37), respectively). However, in the overweight and morbidly obese groups there was significant heterogeneity between the studies (all $P<0.05$). Using BMI as a continuous variable, risk of death increased by 3% for each 5-unit increase in BMI over 18.5 kg m^{-2} (HR: 1.03, (95% CIs: 1.00–1.07)); however, again significant heterogeneity was present between the studies (I^2 40%, $P=0.03$) (Figure 1). Exploration of the heterogeneity showed that the largest difference in pHR was seen for study size with no apparent heterogeneity among the 18 studies, with $\geqslant 200$ participants but significant heterogeneity among those with fewer women (Figure 2). The pHR per 5-unit increase in BMI kg m^{-2} was 1.03 (95% CIs: 1.01–1.06) for studies with $\geqslant 200$ women *vs* 1.21 for studies with <200 women (95% CIs: 0.75–1.96). We also saw significant heterogeneity in other strata, in all except one instance (diagnosis years); the group with significant heterogeneity included at least two, if not all three of the small studies. When we repeated these analyses excluding the three small studies (HSK, JPN and PVD), we found that women who were obese still experienced worse survival (pHR: 1.10 (95% CIs: 0.99–1.23)) than women within the normal weight range (Table 3). This association was similar for those who were morbidly obese (pHR 1.12 (95% CIs: 1.01–1.25)) and the pHR per 5-unit increase in BMI kg m^{-2} was 1.03 (95% CIs: 1.00–1.06); I^2 9%, $P=0.35$) (Table 3). The evidence of heterogeneity disappeared in the obese and morbidly obese groups; however, there remained significant heterogeneity between the studies in the overweight group (I^2 46%, $P=0.02$). When we further excluded the study site where the confidence interval did not include the pooled estimate (MAL), there was no remaining heterogeneity in the overweight group (I^2: 10.4%, $P=0.3$).

Data on residual disease were not available for all studies; however, including this variable in models restricted to studies where the data were available did not result in appreciable changes to the pooled estimates (Supplementary Table 2). Similarly, data on cigarette smoking status were not available for all studies and including this variable in models did not result in appreciable changes (Supplementary Table 3).

The results stratified by histologic subtype are shown in Figure 3. This analysis included only the 12 studies with adequate numbers of cases and events to generate estimates for each histologic subtype. The strongest associations were seen for the low-grade serous and endometrioid subtypes, but neither result was significant (pHR: 1.12 (95% CIs: 0.96–1.31) and 1.08 (95% CIs: 0.95–1.23), respectively, per 5-unit increase in BMI). A more modest but significant association was observed for the high-grade serous subtype (pHR per 5-unit increase in BMI: 1.04 (95% CIs: 1.00–1.09)). No association was noted between BMI and survival among women with mucinous or clear cell tumours. Tests for heterogeneity (between the four main subtypes and for low- *vs* high-grade serous subtypes) did not reach statistical significance (both $P=1.0$).

We also assessed PFS (in 11 studies, $n=4133$ cases) and ovarian cancer-specific survival (in 9 studies, $n=3091$) and similar results were noted to those for OS. For the 11 studies where we had both PFS and OS data, the pHR for obese women (BMI: $\geqslant 30$) compared with women within the normal weight range was 1.10 (95% CIs: 0.99–1.23) for PFS and 1.12 (955 CIs: 1.01–1.26) for OS. In the nine studies with the cause of death data, the pHR for obese

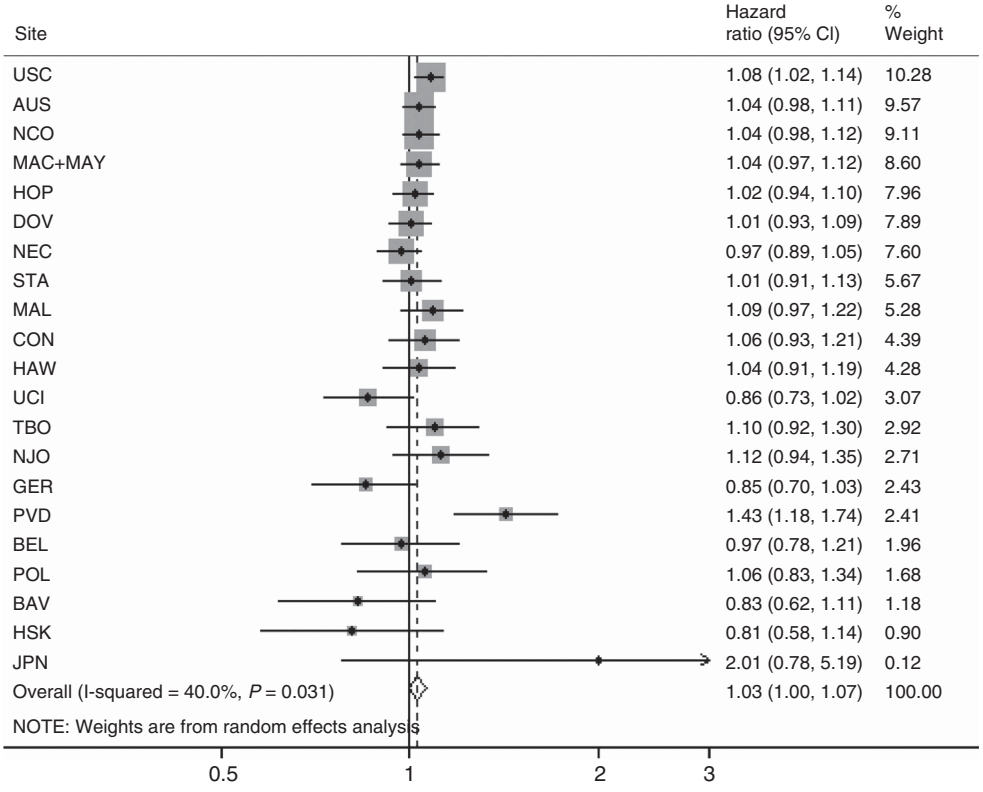

Figure 1. The association between BMI (per 5 kg m^{-2}) and OS following a diagnosis of invasive ovarian cancer, all subtypes, overall and by study site. Estimates are adjusted for age at diagnosis (continuous), stage (local/regional/distant/unknown), grade (well-/moderately-/poorly plus undifferentiated/unknown) and ethnicity (if $<95\%$ of participants at a site shared a common ethnicity) estimates are further adjusted for the interaction of age, stage, grade and/or race with time as appropriate at each site.

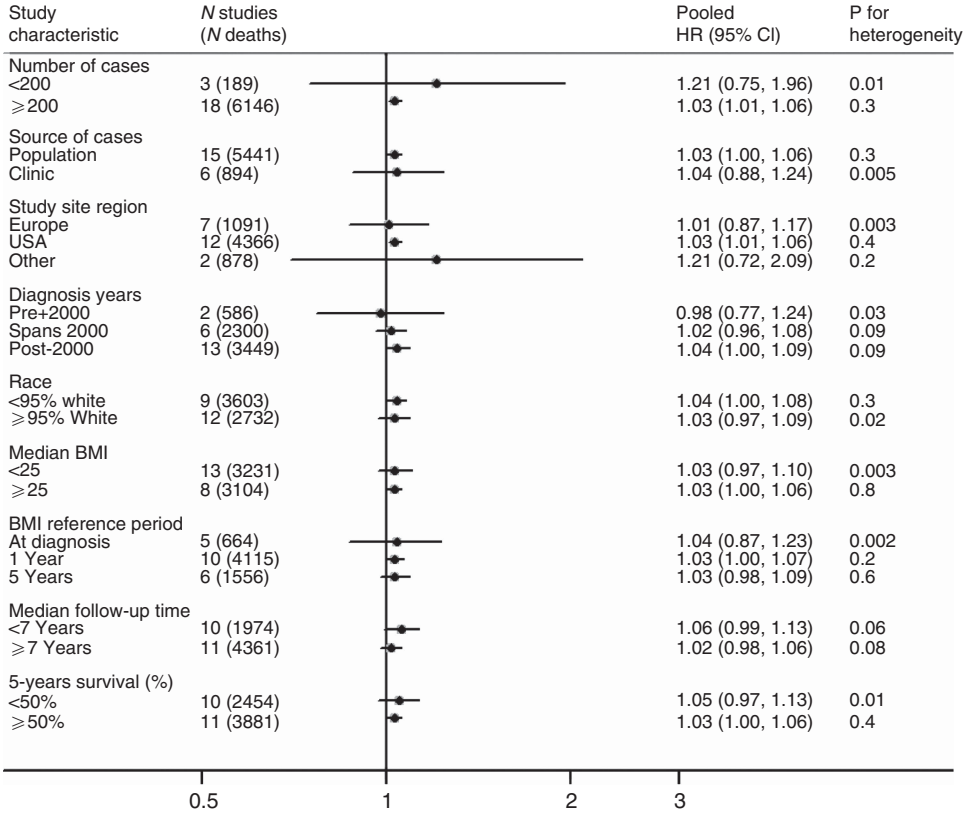

Figure 2. The association between BMI (per 5 kg m^{-2}) and OS following a diagnosis of invasive ovarian cancer, all subtypes in 21 studies, stratified by study characteristics. Estimates are adjusted for age at diagnosis (continuous), stage (local/regional/distant/unknown), grade (well-/moderately-/poorly plus undifferentiated/unknown) and ethnicity (if <95% of participants at a site shared a common ethnicity) estimates are further adjusted for the interaction of age, stage, grade and/or race with time as appropriate at each site. Study site region 'Other' = AUS and JPN.

Table 3. The association between BMI and OS following a diagnosis of invasive ovarian cancer, all subtypes, two-stage pooled analysis, studies where $N \geqslant 200$ (18 studies)

BMI (kg m^{-2})	Study sites (n)[a]	Cases (n)	I^2 (%)	pHR[b]	95% CI
<18.5	18	284	29.7	1.18	0.94–1.48
18.5–24.9 (Ref)	18	5385	–	REF	
25–29.9	18	3374	46.0	1.03[c]	0.95–1.13
30–34.9	18	1547	34.9	1.10	0.99–1.23
⩾35	17	1097	9.5	1.12	1.01–1.25
Per 5 kg m^{-2} [d]	18	11 403	9.1	1.03	1.00–1.06

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; pHR = pooled HR; OS = overall survival.
[a]Excludes study sites HSK, JPN, PVD.
[b]Pooled HR combined study site-specific estimates adjusting for age at diagnosis (continuous), stage (local/regional/distant/unknown), grade (well-/moderately-/poorly plus undifferentiated/unknown) and ethnicity (if <95% of participants at a site shared a common ethnicity) estimates are further adjusted for the interaction of age, stage, grade and/or race with time as appropriate at each site.
[c]Significant heterogeneity noted (P-value for heterogeneity 0.017).
[d]Excludes participants with BMI <18.5 kg m^{-2}.

women (BMI: ⩾30) compared with women within the normal weight range was 1.17 (95% CIs: 1.00–1.37) for ovarian-cancer specific survival and 1.16 (95% CIs: 1.03–1.31) for OS.

DISCUSSION

This study is, to our knowledge, the largest evaluation to date, of BMI and survival following a diagnosis of ovarian cancer. We found that obesity was associated with a 10–12% OS disadvantage among women with ovarian cancer and results were similar for PFS and ovarian cancer-specific mortality. In subtype analyses, associations were strongest for women with low-grade serous and endometrioid cancers, and more modest for high-grade serous cancers (12%, 8% and 4% increases in mortality per 5-unit increase in BMI, respectively), but only the association with high-grade serous cancers, by far the largest subgroup, reached statistical significance. No increase in risk was noted for the less common clear-cell or mucinous subtypes, which are estimated to account for ~8% of all epithelial ovarian cancers.

Several mechanisms have been proposed to underlie the effects of obesity on ovarian cancer outcomes. Makowski *et al* (2014) recently showed that the obese state promotes tumour progression in animal models of serous ovarian cancer and concluded that metabolic consequences of obesity may be involved in the pathogenesis of ovarian cancer. Aberrant adipokine production, specifically upregulation of leptin and downregulation of adiponectin in the obese state, may explain an association between obesity and ovarian cancer outcomes. Leptin has both mitogenic and anti-apoptotic properties in cancer cell lines and is involved in promoting angiogenesis (Khandekar *et al*, 2011; Chen *et al*, 2013; Ptak *et al*, 2013). Conversely, adiponectin has anti-proliferative effects through the induction of apoptosis (Kelesidis *et al*, 2006; Barb *et al*, 2007). In a recent cohort study of 161 women with advanced-stage ovarian cancer, Diaz *et al* (2013) found that women with increased leptin to adiponectin (L:A) ratios experienced significantly shorter disease-free survival time than those with low L:A ratio. Obesity may also affect ovarian cancer survival through its effect on inflammatory cytokines, markers of insulin resistance and obesity-related hormones such as oestrogen, through the

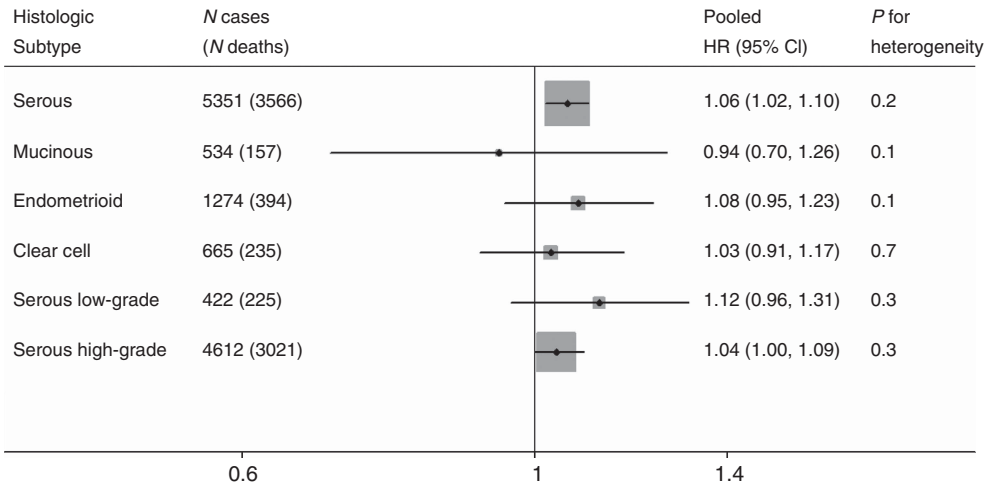

Figure 3. The association between BMI (per 5 kg m^{-2}) and OS following a diagnosis of invasive ovarian cancer, by histologic subtype, two-stage pooled analysis. Pooled HR combined study site-specific estimates adjusting for age at diagnosis (continuous), stage (local/regional/distant/unknown), grade (well-/moderately-/poorly plus undifferentiated/unknown) (except for low- and high-grade serous estimates) and ethnicity (if <95% of participants at a site shared a common ethnicity) estimates are further adjusted for the interaction of age, stage, grade and/or race with time as appropriate at each site. Excludes participants with BMI <18.5 kg m^{-2}. Includes study sites with adequate numbers of cases and events to generate an estimate for each histologic group. Pooled HR for serous, mucinous, endometrioid and clear-cell includes study sites: AUS, BAV, CON, DOV, HAW, HOP, MAL, NCO, NEC, STA, TBO and USC. Pooled HR for serous low-grade and serous high-grade includes study sites: AUS, BAV, BEL, DOV, HOP, MAL, NCO, NEC, NJO, STA, UCI and USC.

conversion of androgens to oestrogen in adipose tissue. *In-vitro* studies have shown that oestrogens have pro-proliferative actions on ovarian cancer cells (Galtier-Dereure *et al*, 1992; Langdon *et al*, 1994; Karlan *et al*, 1995). The oestrogen receptor is expressed in up to 80% of epithelial ovarian cancers with the highest expression in serous and endometrioid tumours (Modugno *et al*, 2012; Sieh *et al*, 2013), the two subtypes in this study with the strongest associations. Finally, oestrogen may also have a role in the motility and invasion of ovarian cancer cells (Hua *et al*, 2008; Zhu *et al*, 2012).

From a treatment perspective, obese women may have worse survival because of the practice of dose capping when prescribing chemotherapy (Modesitt and van Nagell, 2005; Pavelka *et al*, 2006; Poniewierski *et al*, 2008; Au-Yeung *et al*, 2014). Dose capping involves the use of ideal rather than the actual body weight when calculating the dose to be given or dose capping at a body surface area of 2.0 m^2 (equivalent to a BMI of $\sim$30 kg m^{-2}) and occurs largely, it is thought, due to concerns regarding the potential for chemotherapy-related toxicities if the full dose is given (Field *et al*, 2008). Evidence from an Australian study of 330 women with late-stage ovarian cancer has shown that underdosing of carboplatin was common among the obese women (Au-Yeung *et al*, 2014). They also reported that reduced dose intensity of carboplatin was associated with worse PFS. Recently, published guidelines from the American Society of Clinical Oncology recommend that full weight-based doses of chemotherapy be used to treat obese patients with cancer, in particular where the goal of treatment is cure (Griggs *et al*, 2012).

The strengths of our study include the large sample size, which allowed us to examine associations both overall and separately for the different histologic subtypes of ovarian cancer. We included age, ethnicity, clinical factors and study site in our models, and sensitivity analysis suggested that any residual confounding by cigarette smoking would have been minimal. We also assessed PFS and ovarian cancer-specific survival, where such data were available, and the results were essentially unchanged, suggesting that obesity is not just increasing non-ovarian cancer deaths, but progression and cause-specific survival. However, most studies relied on retrospective self-reports of weight and height; hence, there is some potential for recall error; however, it is unlikely to have differed by outcome and thus our results may underestimate the true magnitude of the association. It is possible that our measure of usual weight (before diagnosis) may be influenced by weight loss due to cachexia or weight gain due to the presence of ascites, both of which may be presenting symptoms for ovarian cancer, in particular in women with advanced disease. However, the adverse association between obesity and ovarian cancer survival appeared consistent regardless of when BMI was measured, suggesting this is not a major problem. One potential limitation of our analysis is that the data were not originally collected to look at survival and, as a result, clinical data were not always available and/or complete. However, the major advantage of using the data in this way is cost effectiveness; the time, effort and cost associated with collecting similar data from an equal number of women with ovarian cancer for a new study specifically looking at survival would be prohibitive.

In conclusion, this analysis of data from OCAC has shown that obesity before or at ovarian cancer diagnosis is associated with worse survival, when compared with women within the normal-weight range. As ovarian cancer remains a highly fatal disease and the prevalence of obesity continues to increase, studies focusing on causal mechanisms involved in adverse survival are needed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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