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Pre- and post-diagnosis body mass index, weight change and ovarian cancer mortality

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Abstract

Purpose—The purpose of this study was (1) to investigate the association between BMI self-reported at three time points (during their 20s, 5 years before diagnosis and, post-diagnosis) and mortality among 388 women with newly diagnosed epithelial ovarian cancer and (2) weight change between these 3 time points and mortality.

Methods—Women completed interview-administered questionnaires on average 9 months post-diagnosis. Women were followed 5 years after diagnosis or until death, whichever came first. Cox proportional hazard regression was used to estimate associations between BMI during the 20s, BMI 5 years prior to diagnosis, BMI post-diagnosis (i.e., at the time of interview) and weight changes between these time points and mortality.

Results—The five-year survival rate was 54% (178 deaths, 146 from ovarian cancer). BMI measured continuously at all three time points was associated with a higher risk of ovarian cancer mortality ($P \leq 0.05$). The strongest association was observed with BMI in 20s and all cause mortality comparing women with BMI ≥ 25 kg/m^2 to BMI < 25 kg/m^2 (HR = 1.82; 95% CI, 1.02–3.27; P for trend = 0.045). For weight change from 20s to 5 years prior to diagnosis and ovarian cancer specific mortality, we observed a 68% higher risk of ovarian cancer mortality (HR = 1.68; 95% CI, 1.11–2.55; P for trend = 0.015, comparing women with <10 lbs weight gain to women with ≥10 lbs weight gain).

Conclusion—BMI prior to and after diagnosis and weight gain throughout adulthood is associated with ovarian cancer mortality.

Keywords

ovarian cancer; BMI; weight; prognosis; mortality

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Conflict of Interest Statement
The authors declare that there are no conflicts of interest.

Introduction

Ovarian cancer is the number one cause of cancer death from all gynecological cancers worldwide [1]. The typical insidious onset of ovarian cancer and lack of an effective screening method leads to late diagnosis and more advanced disease stages. Over 60% of ovarian cancer cases are diagnosed as distant metastases [1]. The one-year survival rate of ovarian cancer is 75%, while only 45% survive to five years [2]. Epithelial ovarian cancer represents about 90% of all ovarian malignancies [3].

Rates of obesity are on the rise in the developed world. Over 30% of adults in the US are considered obese, with over 65% of the population being overweight or obese [4]. While there is some evidence that obesity is associated with higher risk of ovarian cancer [5–7] and poor prognosis with hormone mediated cancers such as breast and endometrium [8–16], few studies have examined the association between obesity and ovarian cancer survival. To our knowledge, seven studies have been published that examined the association between obesity and risk of ovarian cancer mortality. Three of the studies found inverse associations between BMI and ovarian cancer survival [17–19]; however, three studies found no association [20–22], and one recent study found a suggestion of improved survival with higher BMI [23]. Methods for data collection varied among these studies from measured, self-reported, to medical chart-review, with BMI measured primarily at only one time point, which may have lead to the inconsistency in findings. Thus, the purpose of our study was to further elucidate the association between self-reported BMI measured at two time points prior to diagnosis and one time point after diagnosis, weight change, and ovarian cancer mortality. Based on the known research, we hypothesized that higher BMI and weight gain throughout adulthood would be associated with higher risk of ovarian cancer mortality.

Material and Methods

Subjects

The study cohort consisted of 494 patients with ovarian cancer, who had originally participated in a population-based case-control study in Connecticut (CT) [24]. The case-control study enrolled English-speaking residents of Connecticut between the ages of 35 and 79, who were diagnosed with new histologically confirmed primary borderline or invasive epithelial ovarian cancer from September 1, 1998 to February 28, 2003. Among the 720 women diagnosed with ovarian cancer during this time point, 497 (69%) were enrolled into the case-control study. The reasons for nonparticipation among the 223 cases were: death before contact (n=86, 12%), subject refusal (n=108, 15%), too ill (n=7, 1%) and lost to follow up (n=22, 3%).

The present study was based on follow-up of the cases by record linkage with the Connecticut Tumor Registry (CTR). Of the 497 cases enrolled in the case-control study, 388 cases with invasive disease were followed for 5 years post-diagnosis or death, whichever came first, with 109 borderline cases not included in the analysis. The study was approved by the Connecticut Department of Public Health, the Yale Human Investigation Committee, and all 31 Connecticut hospital institution review boards.

Weight Measurements

Exposure data was collected through an interview-administered in-person questionnaire, completed when the participants were recruited into the case-control study on average 9 months after diagnosis. Subjects were prompted to report their adult height and weight at three time points: during the 20s, 5 years before diagnosis, and post-diagnosis at the time the questionnaire was completed. Height was recorded to the nearest tenth of an inch and weights were recorded in pounds.

BMI was calculated as the weight in kilograms divided by the square of height in meters using the self-reported height and weight measures. BMI was dichotomized per World Health Organization (WHO) recommended categories using BMI < 25 kg/m^2 as the referent category compared to BMI ≥ 25 kg/m^2 as the exposure (overweight) category. Additional analysis were conducted using three categories BMI < 25 kg/m^2, 25 < BMI < 30 and BMI ≥ 30 kg/m^2 with BMI < 25 kg/m^2 as the reference category. Weight change variables were determined by calculating the difference between self-reported weights (in lbs) from each time point: typical weight during the 20s, 5 years before ovarian cancer diagnosis, and post-diagnosis. Weight change was dichotomized into ≥ 10 lbs weight gain compared to < 10 lbs weight gain as the reference category. The selection of 10 lbs was based on results of nationally representative surveys that indicate on average the US female population experiences about 2 kg weight gain over 10 years. Thus, it could be assumed that up to 10 lbs of weight gain during midlife would be expected in a typical American woman [25,26].

Covariates

Data on clinical variables such as date of diagnosis and disease stage were extracted from the Connecticut Tumor Registry. Surveillance, Epidemiology, and End Results (SEER) summary staging was collected and reported by the CTR and used as disease stage. Histological classification of tumor type was performed based on information in pathology reports that had been used to confirm study eligibility. Information on other covariates or potential prognostic factors was obtained through interview-administered questionnaires completed at the time of participant recruitment to the case-control study.

The following self-reported characteristics were examined in relation to ovarian cancer prognosis: reproductive factors: parity (nulliparious, ≥1 children); age at first birth (nulliparious, <25 years old, ≥25 years old); use of oral contraceptives (never, ever); age at menarche; menopausal status (premenopausal, postmenopausal); hormone replacement therapy use (premenopausal, postmenopausal with no hormone therapy use, postmenopausal with hormone therapy use); history of smoking (never, past, current); and education (<12 years of education, ≥12 years of education).

Other ovarian cancer prognostic and lifestyle factors considered were histology (invasive serous, invasive non-serous, all borderline); disease stage; chemotherapy; and family history of ovarian cancer (history of disease in mother or sister(s)).

Outcome Assessment

Two survival outcomes were considered for this study: all cause mortality and ovarian cancer mortality. Follow-up information and vital status of the cases were ascertained from the CTR records. For all cause mortality, survival time in years was calculated from study entry to death. Censoring occurred at 5 years from study entry. For the ovarian cancer mortality, causes of death reported as C56 per ICD-10 codes were defined as death due to ovarian cancer. Censoring occurred with death from all other causes or at 5 years from study entry.

Statistical Analysis

Cox proportional hazard models were used to compute hazard ratios (HR) and their 95% confidence intervals (CI) and to adjust for potential confounders. For the multivariate models we adjusted for age at diagnosis, stage of disease, disease histology, education, oral contraceptive use, menopausal status, hormone replacement therapy use, parity, age at first live birth, family history of ovarian cancer and time from ovarian cancer diagnosis to study enrollment. Smoking history and chemotherapy were also examined as a potential confounder. However, we did not adjust for them in the final model because inclusion of the

smoking and chemotherapy variables did not change the parameter estimates of interest more than 10% and thus no appreciable confounding was observed. Analyses of BMI or weight change and mortality were performed on both all-cause mortality and ovarian specific mortality. We also examined whether the associations between BMI or weight change and ovarian cancer mortality varied by stage of disease, by calculating stratum-specific estimates, keeping other covariates in the Cox model. Additional stratified analyses were conducted to examine whether the association between BMI or weight change and ovarian cancer mortality varied by status of chemotherapy or disease histology. CIs not overlapping unity or p-values < 0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Within 5 years of follow-up, 178 (46%) of the 388 women with ovarian cancer were deceased, 146 (82%) as a result of the ovarian cancer itself. This is equivalent to a 5-year survival rate of 54%. Table 1 presents the distribution of select participant characteristics at study entry. The mean age at diagnosis was 59 years with a mean time from diagnosis of ovarian cancer to enrollment into the case-control study of 9 months (9.3 months ± 8.68, mean time post-diagnosis; range 1–52 months). A total of 203 (52.3%) women had BMI < 25 kg/m^2 at study entry, and these women did not differ significantly in the reported characteristics from women with BMI ≥ 25 kg/m^2. In addition, comparing the characteristics of study participants to non-participants, the women not enrolled in the study were on average older at diagnosis (mean age of 60) and were contacted regarding the study an average of 11 months post-diagnosis.

Table 2 lists the multivariate-adjusted HRs for ovarian cancer mortality by BMI at three time points. After adjustment, the continuous model of BMI in 20s showed that for each 1 kg/m^2 increase in BMI during the 20s there was a significant 6% higher risk of ovarian cancer mortality. The dichotomized model of BMI in 20s on all-cause mortality demonstrated an 82% higher risk of mortality comparing women with BMI ≥ 25 kg/m^2 to BMI < 25 kg/m^2 (HR = 1.82; 95% CI 1.02–3.27). BMI 5 years prior to diagnosis measured continuously was associated with a significant 3% higher risk of ovarian cancer mortality for each 1kg/m^2 increase in BMI. The estimated association between dichotomized BMI 5 years before diagnosis and risk of ovarian cancer mortality was not significant (HR = 1.30; 95% CI, 0.92–1.83). The continuous variable for post-diagnosis BMI and ovarian cancer mortality was the only analysis using BMI at this time point to show a significant association (HR = 1.03; 95% CI, 1.00–1.06).

Stratified analyses that examined stratum-specific estimates for stage of disease, chemotherapy or disease histology showed that the HRs for BMI assessed at each time point and all cause and ovarian cancer mortality did not vary significantly by the strata (data not shown).

Results for the analyses of weight change between the three time points and ovarian cancer mortality are presented in Table 3. The multivariate adjusted association between weight change from the 20s to 5 years prior to disease diagnosis and ovarian cancer specific mortality was the only significant finding. The result showed an approximate 70% higher risk of ovarian cancer mortality in women with ≥ 10 lbs weight gain from their 20s to 5 years prior to diagnosis compared to the women who gained < 10 lbs (HR = 1.68; 95% CI, 1.11–2.55).

Discussion

Body weight has previously been examined as a potential prognostic factor for ovarian cancer with inconsistent findings. To our knowledge, seven studies have been published that examined the association between BMI and ovarian cancer mortality with mixed results. We observed significant associations between pre- and post-diagnosis BMI and ovarian cancer mortality. The strongest findings showed that women overweight during their 20s had a great then 80% higher risk of mortality compared to their non-overweight counterparts. Similarly, the prospective follow-up cohort study of 635 Swedish ovarian cancer patients using self-reported BMI measures found overweight/obesity at age 18 was also negatively associated with ovarian cancer survival [19]. In addition, the prospective cohort study following 214 Chinese women with ovarian cancer examined the association between BMI at age 21 and ovarian cancer mortality. While the hazard ratio comparing survival of women with BMI ≥ 25 kg/m^2 to BMI < 20 kg/m^2 showed a potential relationship, the dose-response trend was not significant [18].

In our study, continuous post-diagnosis BMI was found to be associated with higher risk of ovarian cancer mortality. This result corroborates the finding from a retrospective medical chart review of 216 ovarian cancer patients that found continuous post-operative BMI to be a significant negative prognostic factor on both disease free and overall survival in women with advance disease [17]. However, the other studies that examined the relationship between post-diagnosis BMI and survival using self-reported measures or chart-review did not find significant associations [18,19,21–23]. On the other hand, a retrospective review of clinical records of 824 ovarian cancer patients was the only study to find a positive association between BMI at diagnosis (pre-operation) and ovarian cancer survival [23].

Women who experienced weight gain of 10 lbs or greater from 20s to 5 years prior to diagnosis was shown to have poorer ovarian cancer mortality compared to those who gained less than 10 lbs in our study. To our knowledge, our study is the only study that has examined BMI at multiple time points in adulthood, in addition to weight change from early adulthood to diagnosis on ovarian cancer mortality.

In our study, we hypothesized that obesity at the time of ovarian cancer diagnosis would not be as strong a predictor of disease survival, compared to obesity earlier in life, due to varying lengths of time the women were overweight or obese. Women who were overweight during the 20s were more likely to be overweight or obese for a significantly longer time than women who had healthy BMI (BMI < 25 kg/m^2) during their 20s even if weight was gained later on [25]. In our study, 90% of the women who were overweight in the 20s were also overweight post-diagnosis. Consistent with this hypothesis of overweight and obesity duration, results from our study showed a stronger association between BMI during the 20s and ovarian cancer mortality but much weaker associations were found with BMI assessed after diagnosis or 5 years prior to diagnosis. In addition, women who gained at least 10 lbs between their 20s and 5 years prior to diagnosis were seen to have poorer survival compared to women who gained less than 10 lbs. These findings are consistent with studies that observed stronger associations for BMI in adolescence or early adulthood on ovarian cancer risk compared to current BMI [27–29]. Several mechanisms have been proposed to explain the potential prognostic effect of obesity on ovarian cancer mortality. These include increased levels of circulating or tissue sex and metabolic hormones [30], increased levels of inflammatory and other cytokines [31,32] and possible under-dosing of chemotherapy treatment in obese patients [33].

Currently, there are no effective screening tests for ovarian cancer. Coupled with the typically insidious onset of the disease, diagnosis can be difficult and is often not made until

later stages in women with advanced disease. Such women may have been living with latent, undiagnosed disease for some time. BMI 5 years prior to diagnosis could represent BMI at diagnosis if a screening test for ovarian cancer existed. Thus, to demonstrate that there is an association between weight gain between the 20s and 5 years prior to diagnosis may be representative of the potential predictive value of weight change if an effective screening method could be found to diagnose ovarian cancer in earlier stages.

Continuous post-diagnosis BMI as self-reported on average 9 months after ovarian cancer diagnosis was found to be predictive of ovarian cancer mortality, however, the dichotomized post-diagnosis BMI variable was not shown to be associated with ovarian cancer mortality. Since weight loss and cachexia can occur in ovarian cancer patients with later stage disease [34], potential weight loss in the participants because of latent disease may have contributed to misclassification and null findings with dichotomized BMI and weight change post-diagnosis on survival.

Some of the limitations of our study include a higher 5-year survival rate of 54%, than the 46% overall 5-year survival rate reported by the American Cancer Society [2]. The mean time from diagnosis to study entry for our study participants was 9 months, thus women who died shortly after diagnosis were not included in our study, contributing to the higher survival rate. Self-reported weight and height were used in our study, potentially subject to bias and error. Height of study participants was measured at the post-diagnosis study interview. When comparing measured and reported height a correlation of $r = 0.968$, $p < 0.0001$ was observed and indicates a strong correlation between reported and measured height. However, since the study included only ovarian cancer patients, any bias or errors that may have occurred from the use of self-reported measures are most likely nondifferential. Lastly, although we followed ovarian cancer patients prospectively from recruitment (~9 months post-diagnosis) for five years or until death, the weight history data (for the 20s and 5 years prior to diagnosis) was collected retrospectively, which introduces potential limitations due to problems with inaccurate recall.

The main strengths of our study are the population-based recruitment strategy used to obtain our cohort of ovarian cancer patients and the examination of the association between BMI and weight change from multiple time points and survival. While our sample size is comparable with earlier studies, we were able to follow our cohort for five years after diagnosis.

In summary, the results of our study suggest that BMI in early adulthood and weight gain throughout adulthood are associated with ovarian cancer mortality. A large-scale study designed to specifically examine weight, measured at multiple time points at and after diagnosis, and its interactions with genetic and molecular markers, on ovarian cancer prognosis is needed to confirm these findings.

Research Highlights

- BMI in adulthood is associated with higher risk of ovarian cancer death.
- Post-diagnosis BMI is associated with higher risk of ovarian cancer death.
- Weight gain in adulthood is associated with higher risk of ovarian cancer death.

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Table 1

Description of the study participants, by post-diagnosis BMI (N = 388)[1]

Characteristic	All (n = 388)	BMI < 25 (n = 203)	BMI ≥ 25 (n = 185)	p†
Age at diagnosis (years), mean ± SD	58.55 ± 10.81	59.20 ± 11.46	57.84 ± 10.03	0.218
Time since diagnosis (months), mean ± SD	9.28 ± 8.68	8.67 ± 7.96	9.95 ± 9.38	0.145
Weight (lbs), mean ± SD	153.08 ± 35.73	129.17 ± 14.65	179.32 ± 34.71	<0.0001
BMI, mean ± SD	26.17 ± 5.82	22.02 ± 1.90	30.73 ± 5.23	<0.0001
SEER[2] Stage, n (%)				0.279
1	64 (16.80)	35 (20.96)	29 (15.76)	
2	79 (20.73)	38 (22.75)	41 (22.28)	
3+	238 (62.47)	124 (74.25)	114 (61.96)	
Known Chemotherapy Treatment, n (%)	300 (77.32)	157 (77.34)	143 (77.30)	0.575
Tumor Histology, n (%)				0.799
Invasive Serous	250 (64.43)	132 (65.02)	118 (63.78)	
Invasive Non-serous	138 (35.57)	71 (34.98)	67 (36.22)	
Race, n (%)				0.771
White	368 (96.08)	194 (96.52)	174 (95.60)	
Other	15 (3.92)	7 (3.48)	8 (4.40)	
Education ≥ 12 yrs, n (%)	349 (89.95)	186 (91.63)	163 (88.11)	0.250
Age at Menarche, mean ± SD	12.68 ± 1.50	12.79 ± 1.38	2.55 ± 1.62	0.122
Parity, n (%)	308 (79.38)	159 (78.33)	149 (80.54)	0.450
Age at First Birth, n (%)				0.213
Nulliparious	81 (20.88)	45 (22.17)	36 (19.84)	
< 25 years	163 (42.01)	77 (37.93)	86 (45.24)	
≥ 25 years	143 (36.86)	81 (39.90)	62 (34.92)	
Oral Contraceptive use, n (%)	214 (55.15)	111 (54.68)	103 (55.68)	0.844
Menopausal and HRT[3] status, n (%)				0.515
Premenopausal	88 (22.86)	43 (21.29)	45 (24.59)	
Postmenopausal and no HRT use	164 (42.60)	83 (41.09)	81 (44.26)	
Postmenopausal and with HRT use	133 (34.55)	76 (37.62)	57 (31.15)	
Family History of Ovarian Cancer, n (%)	28 (7.22)	15 (7.39)	13 (7.03)	0.891
Smoking history, n (%)				0.664
Never	178 (45.88)	90 (44.33)	88 (47.57)	
Former	181 (46.65)	99 (48.77)	82 (4432)	
Current	29 (7.47)	14 (6.90)	15 (8.11)	

[1] Post-diagnosis BMI self-reported on average within the first year post-diagnosis.

[2] Surveillance Epidemiology and End Results (SEER)

[3] Hormone Replacement Therapy (HRT)

Table 2

BMI at three time points and risk of ovarian cancer mortality in women diagnosed with ovarian cancer (N=388).

		Multivariable-Adjusted Model[1]		
	Events / Cases	**HR**	**95% CI**	**P-value/ P for trend**
BMI during 20s				
Continuous	144/382	1.06	(1.01, 1.12)	0.013
BMI Dichotomized				
BMI < 25	131/351	1.00		
BMI ≥ 25	13/31	1.82	(1.02, 3.27)	0.045
BMI 5 yrs prior[2]				
Continuous	145/381	1.03	(1.01, 1.06)	0.020
BMI Dichotomized				
BMI < 25	72/205	1.00		
BMI ≥ 25	73/176	1.30	(0.92, 1.83)	0.135
Post-diagnosis BMI[3]				
Continuous	146/388	1.03	(1.00, 1.06)	0.054
BMI Dichotomized				
BMI < 25	76/203	1.00		
BMI ≥ 25	70/185	1.05	(0.75, 1.48)	0.782

[1] Adjusted for age, stage, histology, education, oral contraceptive use, menopausal status and HRT use, parity, age at first birth, family history of ovarian cancer and time from ovarian cancer diagnosis to study enrollment

[2] Self reported BMI of 5 years prior to diagnosis

[3] Denotes the post-diagnosis self-reported BMI by the study participants when the study questionnaire was completed (approximately 9 months after diagnosis)

Table 3

Weight changes at three time points and risk of ovarian cancer mortality in women diagnosed with ovarian cancer (N=388).

		Multivariable-Adjusted Model[1]		
	Events / Cases	**HR**	**95% CI**	**P-value/ P for trend**
Age 20s to 5 yrs prior[2]				
Change < 10 lbs	38/106	1.00		
Change ≥ 10 lbs	106/271	1.68	(1.11, 2.55)	0.015
Age 20s to Post-diagnosis[3]				
Change < 10 lbs	48/123	1.00		
Change ≥ 10 lbs	97/260	1.19	(0.79, 1.78)	0.362
5 yrs prior[2] to Post-diagnosis				
Change < 10 lbs	110/287	1.00		
Change ≥ 10 lbs	35/93	1.07	(0.71, 1.60)	0.758

[1] Adjusted for age, stage, histology, education, oral contraceptive use, menopausal status and HRT use, parity, age at first birth, family history of ovarian cancer and time from ovarian cancer diagnosis to study enrollment

[2] Self reported weight 5 years prior to diagnosis

[3] Denotes the post-diagnosis self-reported weight by the study participants when the study questionnaire was completed (approximately 9 months after diagnosis)