Null Results in Brief

Usual Adult Body Mass Index Is Not Predictive of Ovarian Cancer Survival

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Introduction

Although obesity has been proposed as both a risk factor and prognostic factor for hormonally mediated cancers such as endometrial and breast, it is less clear whether this also applies to ovarian cancer (1). In addition, some authors have suggested that obese patients may receive potentially subtherapeutic doses of chemotherapy, when the calculated chemotherapy dose (based on body weight) exceeds the maximum dose patients (1). Large cohort studies have shown higher ovarian cancer mortality with increasing body mass index (BMI); however, these studies could not differentiate obesity's effect on cancer incidence from the effect on prognosis (1-3). Three recent studies have suggested that obesity may be associated with worse prognosis among ovarian cancer patients (4-6), whereas one study did not identify an association (7). To address this issue, the current study investigated whether survival differed by premorbid BMI among women with ovarian cancer treated at Roswell Park Cancer Institute (RPCI) in Buffalo, NY.

Materials and Methods

The study population included 409 patients diagnosed at RPCI between 1982 and 1998 who also completed a comprehensive epidemiologic questionnaire. Details about the data collection and study population have been described elsewhere (8-11). Briefly, as part of this 16-page questionnaire, patients were prompted to report their current height, current weight, and usual weight before diagnosis. Information on the survival, staging, and treatment was obtained from the RPCI tumor registry and was matched to questionnaire information. Medical records were also reviewed to collect additional clinical data, including information on past medical history [notably hypertension, diabetes, thyroid problems, and gastroesophageal reflux disease (GERD)]. These conditions have the potential to confound the association between BMI and survival because they are known to be associated with BMI and are also associated with increased toxicity and decreased tolerance of chemotherapy, potentially worsening ovarian cancer prognosis. Because complete information on the adequacy of cytoreduction was not identified in the majority of patients' medical records, this prognostic characteristic was not included in the current analysis. Usual BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Patients were categorized as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), and obese (BMI $\geq$30.0). As few individuals were underweight (n = 8), these individuals were combined with normal weight patients and were used as the reference group for all analyses. Patients with incomplete information on either usual BMI or survival were excluded (n = 14), resulting in the analysis of 395 ovarian cancer patients.

Survival time was calculated in months from date of diagnosis to date of death, loss to follow-up, or March 2006. Eighty-nine percent of all deaths were due to ovarian cancer. Kaplan-Meier curves were used to compare survival by BMI category, and differences were tested with the log-rank test. Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed using Cox regression, and the proportional hazard assumption was confirmed for all covariates. Characteristics that were associated with prognosis were considered candidates for inclusion in adjusted models using a forward selection technique. Because 36 individuals lacked information on at least one covariate, 359 individuals were included in adjusted models.

Results

After a minimum of 9 years of follow-up, 300 of the 395 women with ovarian cancer were deceased. Table 1 displays potential prognostic characteristics by vital status, confirming the role of established factors such as age at diagnosis, Federation Internationale des Gynaecologistes et Obstetristes (FIGO) stage, tumor grade, and histologic subtype. Consistent with previous studies, platinum-based chemotherapy was associated with worse survival, likely as a marker of more severe disease. Evaluation of past medical history revealed a worse prognosis for individuals with a history of diabetes or GERD. No association was noted between survival and other medical conditions.

As displayed in Table 2, ovarian cancer survival was not associated with being overweight (adjusted HR, 1.01; 95% CI, 0.76-1.34) or obese (adjusted HR, 0.94; 95% CI, 0.68-1.30). When BMI was examined in a continuous manner, no linear association was noted with unit increases in BMI (adjusted HR, 1.00; 95% CI, 0.98-1.02). Results did not differ when analyses were stratified by stage, grade, histologic subtype, or age at diagnosis, nor did they differ when analyses were repeated using disease-specific death as the outcome of interest (data not shown).

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Table 1. Characteristics of 395 ovarian cancer patients, by survival status, RPCI

Characteristic	Alive (n = 95) n (%)	Dead (n = 300) n (%)	Crude HR (95% CI)*
Age at diagnosis (y)			
Mean (SD)	47.5 (14.1)	58.3 (12.3)	1.04 (1.03-1.04)
<40	27 (28.4)	22 (7.3)	Reference
40-49	28 (29.5)	52 (17.3)	1.75 (1.06-2.87)
50-59	23 (24.2)	85 (28.3)	2.92 (1.82-4.68)
≥60	17 (17.9)	141 (47.0)	3.93 (2.49-6.18)
FIGO stage			
I	44 (46.3)	39 (13.2)	Reference
II	17 (17.9)	22 (7.4)	1.19 (0.71-2.02)
III	30 (31.6)	180 (60.8)	3.38 (2.38-4.79)
IV	4 (4.2)	55 (18.6)	4.36 (2.88-6.61)
Tumor grade			
1: Well differentiated	33 (36.3)	32 (11.1)	Reference
2: Moderately differentiated	21 (23.1)	79 (27.5)	2.45 (1.62-3.70)
3: Poorly differentiated	36 (39.6)	166 (57.8)	2.93 (2.00-4.30)
4: Undifferentiated	1 (1.1)	10 (3.5)	3.72 (1.83-7.58)
Tumor histology			
Serous	45 (47.4)	225 (75.0)	Reference
Mucinous	17 (17.9)	17 (5.7)	0.39 (0.27-0.64)
Endometrioid	24 (25.3)	30 (10.0)	0.45 (0.31-0.67)
Clear cell	8 (8.4)	20 (6.7)	0.73 (0.46-1.16)
Unknown	1 (1.1)	8 (2.7)	1.01 (0.50-20.5)
Received platinum-based chemotherapy	70 (73.7)	268 (89.3)	1.97 (1.36-2.86)
History of diabetes	3 (3.3)	25 (8.6)	1.61 (1.07-2.44)
History of hypertension	19 (20.9)	64 (22.0)	1.00 (0.76-1.32)
History of thyroid disorder	3 (3.3)	17 (5.8)	1.10 (0.67-1.79)
History of arthritis	10 (11.0)	42 (14.4)	0.96 (0.69-1.33)
History of GERD	1 (1.1)	7 (2.4)	2.30 (1.08-4.88)

*Computed using Cox proportional hazard model.

Discussion

In this follow-up study of 395 women with ovarian cancer, survival was not associated with usual adult BMI. To our knowledge, only four studies have been published, which examined BMI specifically as a potential prognostic factor for women with ovarian cancer (4-7). The first, in 2000, found no association between obesity (defined as BMI >27.9 kg/m^2) and crude survival in a cohort of 257 U.S. women with invasive or borderline ovarian tumors (7). In contrast, a cohort of 207 Chinese ovarian cancer patients found an association between self-reported BMI 5 years before diagnosis and mortality; compared with individuals with a BMI <20, increased mortality was suggested for women whose BMI was 20.0 to 22.4 (HR, 1.79; 95% CI, 0.90-3.55), 22.5 to 24.9 (HR, 1.71; 95% CI, 0.84-3.46), or ≥25.0 (HR, 2.33; 95% CI, 1.12-4.87; ref. 5). However, mortality was not associated with either BMI at age 21 or BMI at diagnosis, and the study included few individuals who were either overweight or obese. A medical record review of 216 U.S. ovarian cancer patients reported by Pavelka et al. identified a statistically significant linear association between BMI and either cancer recurrence (HR, 1.04) or death (HR, 1.05), although interpretations were complicated by the use of postoperative BMI, which may not be representative of premorbid BMI (6). Lastly, a follow-up of 295 Danish women with stage III ovarian cancer who participated in the Malignant Ovarian Cancer (MALOVA) study found increased mortality for individuals who were obese 5 years before diagnosis (HR, 1.83; 95% CI, 1.38-2.42; HR per unit increase in BMI, 1.05; 95% CI, 1.02-1.08) but no association with BMI at age 20 to 29 (4).

It is unclear whether results differ between studies due to varying degrees of obesity in the study population, changing biological effects based on the time period under investigation, or due to confounding by other important prognostic factors. For example, obesity has the potential to affect prognosis through other mechanisms. Some authors have speculated that obese patients may receive inadequate surgery, although two studies have shown that obese patients were equally likely to have optimal surgical cytoreduction (6, 13). In addition, difficulty determining the optimal chemotherapy dose may result in suboptimal treatment for obese patients (1). However, lower dosing also has the ability to minimize toxicity, improving tolerability of chemotherapy.

The current study has several limitations. Most notably, analyses were based on self-reported usual adult BMI. As such, we were unable to assess whether BMI at particular time periods would be more relevant. In addition, although participants were instructed to report their premorbid weight, it is possible that estimates were influenced by subtle weight changes before diagnosis. The current study also lacked information on adequacy of cytoreduction, an important prognostic factor. However, other prognostic factors were well documented, and previous studies have suggested that adequacy of cytoreduction does not differ as a function of BMI (6, 12, 13). In addition, a small proportion of people were excluded from the study for missing information on BMI or

Table 2. Ovarian cancer survival by usual BMI, RPCI

	Survival in months median (range)	Alive (n = 95) n (%)	Dead (n = 300) n (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Usual BMI (kg/m^2)					
Normal (BMI <25)	57 (1-283)	49 (51.6)	161 (53.7)	Reference	Reference
Overweight (BMI 25.0-29.9)	58 (5-273)	23 (24.2)	85 (28.3)	1.05 (0.81-1.37)	1.10 (0.82-1.47)
Obese (BMI ≥30)	59 (2-244)	23 (24.2)	54 (18.0)	0.90 (0.66-1.23)	0.99 (0.71-1.38)

*Adjusted for age at diagnosis and Federation Internationale des Gynaecologistes et Obstetristes stage.

were excluded from adjusted analyses due to missing information on covariates. However, these numbers are small and unlikely to be responsible for the null finding observed.

However, the current study also has several strengths, including the long length of follow-up (between 9 and 23 years) and a larger cohort than other studies of this nature. Power estimates were calculated using software developed by Dupont and Plummer (14) based upon the following conditions: $\alpha = 0.05$, 77 obese patients, median survival time of 57 months for normal weight patients, 192 months of study accrual, 87 months of additional follow-up time, and a ratio of 210:77 normal weight/obese patients. Under these conditions, the study had 80% power to detect an HR of 1.52 for obese patients, and 99% power to detect a HR of 2.0. As such, the study was adequately powered to detect differences of the magnitude noted in previous studies.

In summary, the current study did not identify an association between ovarian cancer survival and being overweight or obese. Further research is warranted to investigate the potential role of obesity in ovarian cancer prognosis.

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