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The impact of body weight on ovarian cancer outcomes

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Abstract

Background—Obesity is a known risk factor and poor prognostic factor for much co-morbidity including cancer. However, the influence of body mass index (BMI) on ovarian cancer outcomes is inconclusive. Therefore, the objective of this study was to evaluate the impact of BMI and weight changes on survival in patients with advanced ovarian cancer after primary treatment.

Methods and Materials—All patients diagnosed with advanced epithelial ovarian cancer from 1/00–12/07 undergoing primary cytoreductive surgery and adjuvant chemotherapy were identified. Patients were divided into three categories: under/normal weight (BMI<25), overweight (BMI 25–30), and obese (BMI>30). Adjusted hazard ratios for progression free (PFS) and overall survival (OS) were calculated via Cox proportional hazard models.

Results—One hundred ninety-eight patients met inclusion criteria. For all patients, the mean BMI was 26 (range 16.4–49.1) with 43% of patients being classified as normal weight, 29% overweight, and 28% as obese. Median 5-yr OS was 48.2 months (95% CI 16.4–49.1 months), and no differences in OS were noted between BMI groups. Unadjusted median PFS for patients with normal weight was 13.7 months, compared to 15.5 and 17.9 months for the overweight and obese group. Adjusted analysis of BMI over time indicates a trend of increased risk for patients who gain weight in the 6 months after primary therapy on disease progression (HR: 1.68, 95% CI 0.87–3.26).

Conclusions—After adjustment for confounders, such as stage, grade, histology, age and debulking status, data suggest a trend towards a shorter PFS in patients with a normal BMI. However, OS was not significantly related to BMI and weight change in the 6 months after completion of treatment had no effect on PFS or OS. Further research should be directed at elucidating relationships between weight and cancer biology.

Keywords

ovarian cancer; body mass index; obesity

INTRODUCTION

The World Health Organization defines a body mass index (BMI) of 25 to 30 as being overweight and a BMI greater than 30 as obese. Currently, in the United States, 65% of adults are overweight, with 30% considered obese [1]. In addition to health concerns such as heart disease and diabetes, obesity is associated with increased cancer-related mortality [2, 3].

Though a well established link has been demonstrated between obesity and cancers of the endometrium, breast and colon; the association with ovarian cancer and treatment outcomes has been contentious [4–7]. A retrospective study in women with advanced ovarian cancer found that obese women had an adverse outcome when compared to their normal weight counterparts [8]. In contrast, an ancillary study of the Scottish Randomised Trial in Ovarian Cancer I (SCOTROC I) showed no difference in survival outcomes based on BMI at the time of diagnosis [9]. Furthermore, the effect of weight changes following the completion of therapy on ovarian cancer outcomes is unknown. Therefore, the purpose of this study was to examine if weight and weight changes have an effect on ovarian cancer recurrence and survival.

MATERIALS AND METHODS

Approval to conduct this study was obtained from the Institutional Review Board at The Ohio State University Medical Center (OSUMC). All patients with pathologically confirmed FIGO stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (hereinafter referred to as ovarian cancer) who underwent primary cytoreductive surgery at the OSUMC between January 2000 and December 2007 were identified through tumor registries. Patients were included if they received adjuvant therapy with a platinum containing regimen and follow-up at the OSUMC. Patients were excluded if they had low grade disease, non-epithelial histology, or received neoadjuvant chemotherapy.

Individual subject data was retrospectively collected from inpatient and ambulatory medical records. Clinical data was abstracted: patient age at diagnosis, race, height and weight at initial presentation. In addition to pre-operative data, weight was collected at the post-operative visit, after completion of chemotherapy, at follow-up visits every 3 months for the first two years, and every 6 months for the next three years. While we acknowledge that postoperative weight can be subject to acute weight changes in the perioperative period, we used postoperative weight (as measured at the postoperative visit three weeks after surgery) because many advanced ovarian cancer patients have large volume ascites that is removed at the time of surgery. At the postoperative visit most patients will have equilibrated perioperative fluid shifts, have regained strength and nutritional status, and are at a stable baseline weight.

BMI at each of these time points was calculated using the standard formula and patients were classified into one of three categories: 1) under and normal weight (BMI < 25); 2) overweight (BMI 25–30); and 3) obese (BMI > 30). Peri-operative data collected included the following: tumor histology and grade, FIGO stage, debulking status—optimal (defined

as ≥ 1 cm of residual disease at the completion of surgery) or suboptimal (>1 cm residual disease), chemotherapy regimen, platinum sensitivity, date of progression, begin and end dates of chemotherapy and date of death.

The gynecologic oncology group (GOG) carboplatin calculator was used to calculate the carboplatin dose. This calculator used the Jelliffe formula to estimate the glomerular filtration rate based on age and creatinine, and the Calvert formula ($AUC \times (GFR + 25)$) to calculate the carboplatin dose. To calculate the body surface area (BSA) we used actual body weight. The BSA was capped at 2.0.

Time to progression was defined as the time from surgery until the date of noted progression. Patients with no recorded progression were censored at date of their last known follow up. Time to chemotherapy initiation was defined as the date of surgery to the time chemotherapy started. Crude estimates of survival times were calculated using the method of Kaplan and Meier and Cox proportional hazards models were used to estimate hazard ratios and to adjust for confounders [10, 11].

To investigate how weight change in the first six months following chemotherapy would impact survival, we modeled BMI status as a time varying covariate, where we assessed the change in BMI group measured at the time of a patient's last chemotherapy visit until six months following the end of chemotherapy. When modeling the change in BMI from chemotherapy to 6 months post chemotherapy, time to progression was calculated as the time from the end of chemotherapy until the date of noted progression. These models, therefore, pertain to patients who survived and who were not censored before the end of chemotherapy. Model assumptions, including proportional hazards and covariate functional form were reviewed for all final models. All p-values presented are two-sided. Analyses were carried out in Stata (version 10.1, StataCorp, College Station, TX).

RESULTS

One hundred ninety-eight patients met inclusion criteria, and of these, postoperative and subsequent weights were available for 187 patients. The mean BMI at the postoperative visit was 26.9 (range 16.4–49.1). Forty-three percent of patients were classified as under or normal weight, 29% were overweight and 28% were classified as obese at the time of surgery. Patients in each BMI group were similar with respect to age, race, tumor grade, debulking status, platinum sensitivity, as demonstrated in Table 1.

The majority of patients (78%) began adjuvant chemotherapy within 3 weeks of surgery. Several different regimens were used, however, all regimens were included a platinum drug (Table 2). One hundred and seventy-one patients received intravenous chemotherapy and 27 patients received a combination of intravenous (IV) and intraperitoneal (IP) chemotherapy. One patient received one cycle of paclitaxel as consolidation therapy on GOG protocol 212, which was discontinued due to neuropathy. None of the other patients received consolidation or maintenance treatment.

Recurrence was documented in 164 patients (83%), with a crude estimate of median time to progression of 1.26 years (95% CI 1.12–1.42). These data suggest that the risk of

progression was increased in patients who were normal or underweight post surgery compared to those who were considered obese, even after adjustment for stage, grade, histology, age and debulking status (Figure 1) (Underweight/Normal vs. Obese: HR=1.44, 95% CI: 0.94–2.21, p-value=0.09). This relationship remains for the subset of patients who were not suboptimal (>1 cm residual disease) (HR=1.51, 95% CI: 0.95–2.38, p-value=0.08).

Crude estimates of PFS were: 1.14 years (95% CI: 1.05–1.42) for patients in the under/normal weight group; 1.29 (95% CI: 1.05–1.53) for the overweight group; and 1.49 (95% CI: 1.06–2.04) for the obese group. The unadjusted median overall survival estimate was 3.9 years (95% CI: 3.1–4.7). BMI post surgery was not strongly associated with overall survival in either unadjusted or adjusted analyses. Adjusted overall survival estimates are illustrated in Figure 2.

Further analysis of BMI over time indicated that there was a suggestion of increased risk of progression in patients who gain weight from the time they finish chemotherapy to 6 months after this time (HR: 1.68, 95% CI: 0.87–3.26 after adjustment for potential confounders listed above).

DISCUSSION

As obesity rates have reached epidemic proportions, its effect on ovarian cancer outcomes, though inconsistent, warrants investigation. Epidemiologic studies have demonstrated that a high BMI is associated with a slight-moderate increase in the development of ovarian cancer [12, 13]. This link was also demonstrated in an analysis of the Women's Health Initiative study, which showed that a reduction in dietary fat was associated with a 40% reduction in ovarian cancer risk [14]. Though these studies have shown that obesity may be linked to an increased risk of ovarian cancer, its effect on outcomes have been less clear [12]. One study did note that an increased total and saturated fat intake adversely affected ovarian cancer outcome [15]. Whether obesity contributes to the hormonal milieu which may affect cancer biology of ovarian cancer or is a surrogate for nutritional status is unknown.

There are several studies that have evaluated the impact of BMI on ovarian cancer outcomes. In a prospective cohort study, an inverse relationship was noted between survival time and BMI in women with ovarian cancer [6]. Pavelka and colleagues reported that for patients with advanced ovarian cancer, obesity was independently associated with both shorter time to recurrence and overall survival [8]. The authors attributed under-dosing of chemotherapy as a possible contributing factor. In the SCOTROC I trial, where chemotherapy dosages were not capped based on body weight, the investigators noted no difference between BMI subgroups and progression free or overall survival [9]. Similar findings were also demonstrated in several other studies when patients were stratified by debulking status [15–17].

These latter findings are consistent with our results, in which post-operative body weight did not influence overall survival. There is some data to suggest that obese patients may be underdosed for carboplatin. Wright et al compared the hematologic side effects in normal weight, overweight, and obese patients who were treated with carboplatin (AUC 7.5) and

paclitaxel for ovarian cancer [18]. They found that obese patients experienced significantly less toxicity and required fewer dose reductions than the normal weight patients. They concluded that obese patients may not receive the correct dose of carboplatin based on the Jelliffe formula. On the other hand, the PFS and OS in their study were not different between body weight groups. Furthermore, carboplatin is hydrophilic in nature and does not distribute easily through adipose tissues. Therefore, the changes in side effects without a corresponding survival difference may not reflect a difference in cytotoxic activity of carboplatin. Patients in our study were dosed based on the older version of the GOG carboplatin calculator, and again no differences in survival were found and carboplatin dosing may still be appropriate for overweight and obese patients.

Of note, the GOG has recently changed the carboplatin calculator from using the Jelliffe formula now to using the Cockcroft-Gault formula, which includes (adjusted) body weight, age and creatinine. A recent pharmacokinetic study showed that for obese and overweight patients using the adjusted body weight in the Cockcroft-Gault formula resulted in the most accurate carboplatin dose [19].

Our results also demonstrated that obesity did not affect the ability to achieve optimal cytoreduction, which is consistent with the literature as well [20]. Interestingly, our results found a trend toward a shorter progression free survival in patients with a low or normal BMI compared to those in the obese subgroup. One possible explanation for this finding may be related to the ability to tolerate chemotherapy in the normal/low body weight group. These findings are consistent with a study that demonstrated a trend toward improved survival in obese patients [7]. Furthermore, in a Gynecologic Oncology Group ancillary data study, it was noted that patients who lost weight during chemotherapy treatment experienced a shorter overall survival than patients who maintained or even gained weight [21]. Based on these results, as well as our observation of a trend towards a shorter PFS in the under/normal weight patients, we speculate that low weight may reflect a poor nutritional status, which may influence tolerance to adjuvant therapy. In our study population, there was a trend where a greater proportion of under or normal weight patients had chemotherapy dose reductions or delays compared with overweight or obese patients; however this result was not statistically significant.

Furthermore, to our knowledge, this is the first study in ovarian cancer to show that the changes in body weight after completion of adjuvant treatment did not have a significant effect on overall survival. In a study of patients with stage III colon cancer, Meyerhardt and colleagues showed that BMI was not independently associated with recurrence or overall survival outcomes [22]. Regardless of BMI, these patients showed a favorable impact in patients who engaged in physical activity, resulting in a decrease in cancer recurrence and mortality. Thus, it is reasonable to encourage all patients to engage in physical activity and maintain a healthy body weight [23].

Though our findings are consistent with the literature, there are several limitations of the current study that must be considered. As a retrospective study, potential for selection bias and missing data may affect data analysis. Furthermore, post-operative weight was considered a baseline weight and may not have been accurate due to factors such as short-

term nutritional changes and post-operative fluid retention. A prospective study of patients with ovarian cancer demonstrated that despite weight loss following surgery, women regained weight during the following year, suggesting that weight changes may be a return to a baseline [24]. Lastly, BMI was used as the sole measure and other factors which affect nutritional status may not have been accounted for.

Despite these limitations, these data are similar to the results of a majority of studies in ovarian and colorectal, as we did not find a significant difference in survival with weight change after completion of adjuvant therapy for ovarian cancer. Though not statistically significant, our results suggest an increased risk of progression in patients who gained weight from the time they finished chemotherapy; and this may be of interest in light of the ongoing studies of nutrition, body weight, and ovarian cancer. Additional studies, prospective in nature, will be required to understand the true impact of baseline weight and weight changes on ovarian cancer outcomes.

In conclusion, we were unable to demonstrate a difference in survival between BMI subgroups or weight changes following adjuvant chemotherapy in patients with advanced ovarian cancer. However, as obesity has become an epidemic, additional research needs to be conducted to further elucidate the role of weight change on ovarian cancer development, progression, and survival.

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Figure 1.

Figure 2.

Table 1

Patient Characteristics

	Underweight or Normal Weight (n=81)	Overweight (n=54)	Obese (n=52)	p-value
Age (mean, SD)	57.2 (12.5)	59.3 (9.7)	58.6 (8.8)	0.52
Race/Ethnicity				0.18
Caucasian	78 (97.5)	49 (90.7)	49 (94.2)	
Other	2 (2.5)	65 (9.3)	3 (5.8)	
Grade				0.92
1 or 2	10 (13.3)	6 (11.3)	7 (14.3)	
3	65 (86.7)	47 (88.7)	42 (85.7)	
Stage				0.06
III	67 (82.7)	48 (88.9)	50 (96.2)	
IV	14 (17.3)	6 (11.1)	2 (3.9)	
Debulking				0.40
Optimal	70 (86.4)	45 (83.3)	48 (92.3)	
Suboptimal	11 (13.6)	9 (16.7)	4 (7.7)	
Platinum Sensitive				0.94
Yes	56 (69.1)	36 (66.7)	35 (67.3)	
No	25 (30.9)	18 (33.3)	17 (32.7)	
Dose reduction/Delay				0.11
No	33 (41.3)	24 (45.3)	30 (60.0)	
Yes	47 (58.8)	29 (54.7)	20 (40.0)	

Table 2

Overview of the different chemotherapy regimens used in this study.

Chemotherapy regimen	Number of patients
carboplatin/paclitaxel	132
GOG 182: Arm 1 carboplatin/paclitaxel	2
Arm 2 carboplatin/paclitaxel/gemcitabine	4
Arm 3 carboplatin/paclitaxel/PEG doxorubicin	8
Arm 4 carboplatin/topotecan×4, carboplatin/paclitaxel×4	6
Arm 5 carboplatin/paclitaxel/gemcitabine × 4, carboplatin/paclitaxel × 4	9
IV/IP paclitaxel/cisplatin/docetaxel or paclitaxel	27
GOG 218 carboplatin/paclitaxel/bevacizumab; maintenance placebo	3
cisplatin/paclitaxel	5
carboplatin/cyclophosphamide	1
cisplatin/gemcitabine	1