Assessment of the Effects of Severe Obesity and Lifestyle Risk Factors On Stage of Endometrial Cancer

Marisa A. Bittoni¹², James L. Fisher², Jeffrey M. Fowler³, George L. Maxwell⁵, and Electra D. Paskett¹²⁴

Abstract

**Background:** Lifestyle risk factors, including obesity, have been associated with increased risk of endometrial cancer (EC). Women with higher obesity levels tend to have less aggressive EC disease stage and histology. This study further investigated associations between nonmodifiable risk factors, such as age, race, and grade, and modifiable lifestyle factors, such as diet and physical activity expenditure, in relation to severe obesity and late versus early EC stage at diagnosis.

**Methods:** Demographic, anthropometric, and lifestyle surveys were administered to 177 women with histologically confirmed EC. Logistic regression analyses assessed the relationship between obesity and other risk factors on EC stage at diagnosis.

**Results:** In multivariate models, body mass index (BMI) < 35 was not significantly associated with late EC stage at diagnosis (OR = 1.67, P = 0.219) when adjusting for grade and age. Grade was significantly associated with EC stage when controlling for BMI and age (OR = 8.48, P = .000). Women more than the age of 60 had a fourfold increased risk of diagnosis at late versus early EC stage when adjusting for other risk factors. Age had a confounding effect on the obesity-EC stage association.

**Conclusions:** Our results corroborate those of past studies showing that BMI is not an independent risk factor for EC stage and that age may have confounded the obesity-EC stage association. Because of mixed results and implications for treatment outcomes, however, further research examining these variables is warranted.

**Impact:** Our results provide further insight into the obesity-EC-stage association, especially the confounding effect of age. Future studies should examine modifiable lifestyle factors in larger and more diverse populations.

Cancer Epidemiol Biomarkers Prev; 22(1); 1–6. ©2012 AACR.

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the United States, with more than 46,470 new cases expected in 2012 (1). Risk factors for EC include early age at menarche, nulliparity, menopause and obesity. Obese women have up to 9 times the risk of developing EC as their normal-weight counterparts (2, 3), and obesity is also the most potentially modifiable risk factor for EC (4). The mechanism by which obesity may increase cancer risk is by increasing circulating levels of estrone, which leads to excess estrogen, increases the mitotic activity of endometrial cells, and promotes cellular replication that leads to hyperplasia and carcinoma (5).

Past studies have shown that women with higher levels of obesity tend to have less aggressive disease stage and histology of EC (3, 6–8), which is because of a higher incidence of better-differentiated, less invasive adenocarcinomas with less frequent lymph node metastases (8). A survival advantage because of obesity, however, has not always been shown, as a significant percentage of obese women may exhibit lymph node metastasis at diagnosis (7). Cohn and colleagues found that morbidly obese patients [body mass index (BMI) > 40 kg/m²] with Stage 2 EC had significantly worse 5-year survival rates than obese patients (BMI = 30–40 kg/m²) or those with ideal body weights (defined by Cohn and colleagues as BMI < 30 kg/m²; ref. 9).

Others have observed that the relationship between obesity and EC may be confounded by other factors, such as tumor grade, age, and race. Temkin and colleagues found that BMI was not an independent risk factor for EC survival, and that the apparent protective effect of obesity on survival was because of obese subjects being younger, and having lower grade and earlier stage tumors (3). While most studies have examined the effect of obesity on EC survival, associations between obesity and EC stage, as well as the effect of other risk factors, have not been well documented (6, 10).
Diet and physical activity, especially diets consisting of high fat, high glycemic load, and low fruit/vegetable consumption, as well as low levels of physical activity, have also shown associations with increased EC risk, but no documented associations have been found with EC stage (11–14). As earlier stage EC normally has better prognosis, it is especially important to identify modifiable risk factors that are associated with late versus early stage disease. Fader and colleagues confirmed the importance of examining modifiable risk factors, especially the effect of healthier lifestyles, with regard to EC outcomes (15).

The purpose of this study was to further investigate the association between obesity and other risk factors on EC stage at diagnosis. The effect of both nonmodifiable risk factors, such as age, race, and grade, and modifiable lifestyle factors, such as diet (fat, fruit/vegetable consumption, and glycemic load) and physical activity expenditure, were examined in relation to severe obesity and late versus early stage at EC diagnosis.

Materials and Methods

Study design/participants

Women from 3 hospitals [The Ohio State University (OSU), Walter Reed Army Medical Center, and Duke University Medical Center] who were diagnosed with EC were asked to consent to this study during their preoperative visit with a gynecologic oncologist. Criteria for inclusion in this study were: age 18 years or more, historically confirmed EC diagnosis, and literacy in English. Women were asked to complete the questionnaires before surgery. Of 208 women who were eligible to participate in this study, 177 women agreed to provide consent, resulting in a response rate of 85%. This study was approved by the Institutional Review Boards of all participating institutions.

Data collection/measures

Demographic and anthropometric data were obtained from perioperative clinic data during presurgical visits with the gynecologic oncologist. Trained oncology nurses recorded the information in the patient’s medical chart.

Dietary intake data (past 30 days) were obtained using the validated General Population Food Frequency Questionnaire (FFQ), developed by the Fred Hutchinson Cancer Research Center (FHCRC; ref. 16). Completed questionnaires were scanned and assessed at the FHCRC to obtain dietary nutrient data, which were subsequently sent to our group for statistical analyses.

Physical activity data were obtained from the validated Women’s Health Initiative (WHI) survey that assessed recreational physical activity, including mild, moderate and strenuous physical activity (17).

Statistical analysis

Descriptive statistics (frequencies, means, and standard deviations) were calculated using demographic, anthropometric, pathology, and lifestyle measures from participants. Odds ratios obtained from logistic regression analyses were used to assess the relationship between obesity and other risk factors on EC stage at diagnosis. The outcome variable was EC stage, as defined by the International Federation of Gynecology and Obstetrics (FIGO; ref. 18). EC stage was dichotomized as early stage (1/2) versus late stage (3/4) because of the small sample size. Obesity was defined by the formula for BMI = weight (kg)/height(m)^2. Because of small strata, BMI was dichotomized using the median (BMI < 35 = 0 vs. ≥35 = 1), which is defined as Class II/severe obesity (19). Age was also dichotomized in this analysis using the median (age ≤ 60 = 0 vs. >60 = 1). Race was assessed as white = 1 versus non-white = 0. Grade was dichotomized using the FIGO classifications (well or moderately differentiated = 0 vs. poorly differentiated = 1), with the categories combined because of small strata. Lifestyle variables included total calories, fruits, and vegetables consumed per day, total grams of carbohydrate, fat and fiber consumed per day, glycemic load, and total energy expenditure (metabolic equivalents, or METs), which were also dichotomized based on their median values. Log transformations were conducted on highly skewed variables. Women whose cancer stage and grade were missing or could not be assessed were excluded from the analyses (n = 3 and 5, respectively), resulting in data from 169 women available for this analysis.

Univariate logistic regression analyses were first conducted between obesity and risk factors related to EC stage at diagnosis. Using forward selection, the variables were added to a multivariable model by selecting the variables with the lowest variables were added to a multivariable model by selecting the variables with the lowest P value until the P value was no longer significant (alpha = 0.05). Analyses were conducted using Stata 10 (20).

Results

Table 1 displays the descriptive characteristics of women by EC stage. Overall, 68% of women had a BMI ≥ 30, which is considered obese, and half the women were severely obese (median BMI = 35). Women diagnosed at late versus early EC stage were older (median = 63 and 58 years, respectively), were less likely to be severely obese (BMI ≥ 35; 40% and 55% kg/m^2, respectively), and were more likely to have poorly differentiated tumors (39% vs. 9%, respectively; P < 0.0001). The mean calorie intake and METs were 1,561 and 8, respectively, with no significant differences in diet and physical activity variables by EC stage at diagnosis.

Table 2 displays the lifestyle variables by level of obesity and shows that the mean calories and fat intake were significantly higher for severely obese women compared with those who were not severely obese (P < 0.05). Both of the physical activity variables were significantly lower for severely obese versus women who were not severely obese (P < 0.05). The results of univariate and multivariate logistic regression models are shown in Table 3. In the univariate
analysis, BMI < 35 was marginally associated with late EC stage (OR = 2.18, P = 0.051). Age > 60 was significantly associated with late EC stage (OR = 3.39, P = 0.004). Grade showed a 7-fold increased risk of being in late versus early EC stage for women with poorly differentiated cancer (P = 0.000). Grade and age were assessed for possible interactions with BMI, but neither was significant.

The multivariate model (Table 3) shows that BMI < 35 was not significantly associated with late EC stage at diagnosis (OR = 1.67, P = 0.219) when adjusting for grade and age. Grade was significantly associated with EC stage at diagnosis when controlling for BMI and age (OR = 3.98, P = 0.004). There was almost a 4-fold increased risk of being diagnosed in late versus early EC stage for women more than the age of 60 when adjusting for other factors. Age was also shown to be a confounder for obesity and grade, as the ORs decreased by 18% and 10%, respectively, when it was added to the model. In addition, age was associated with obesity (χ² = 4.42; P = 0.03) and was also associated with stage in each strata of severely obese and not severely obese women (χ² = 3.86, P = 0.05; χ² = 4.28, P = 0.04, respectively), thereby rendering it a confounder.

Discussion

This study examined the associations of severe obesity and other modifiable and nonmodifiable risk factors on EC stage at diagnosis. The results showed that BMI was not an independent predictor of EC stage in this study, which confirms the results of several studies, including a recent study using WHI data (3, 21), but the authors indicated that because of the close monitoring in the WHI trial and other study characteristics, participants may not have been representative of the general population or the general population.
population. In contrast to our results, several studies have shown independent associations of obesity with EC stage (6–8, 22).

Grade and age were associated with EC stage at diagnosis in this study, as expected, with an 8- and 4-fold increase, respectively, in the odds of being in late versus early EC stage for women with poorer grade and older age (C21, 60). Age was also a confounder. Our results corroborate those of Temkin and colleagues, which also showed factors such as age and grade to be confounders in the obesity-EC stage association (3).

Diet and physical activity variables showed no significant associations with EC stage at diagnosis in this study, although the groups differed significantly with respect to several dietary and physical activity factors, such as increased caloric and fat intake, along with decreased physical activity levels among severely obese women, which was expected. The diets of women in this study were also relatively high in glycemic load, which has shown associations with increased EC risk in past studies (12). Many participants also reported low overall levels of energy expenditure from recreational physical activity in this study, which has also shown increased EC risk (13). Others have suggested that the efficacy of dietary factors in preventing cancer may be stage dependent (23). Therefore, future studies on this issue are warranted, as the identification of modifiable risk factors can affect treatment outcomes, as previously discussed.

### Table 2. Lifestyle variables of study participants by obesity level

<table>
<thead>
<tr>
<th>Diet</th>
<th>Severe obesity (BMI &gt; 35)</th>
<th>Not severe obesity (BMI &lt; 35)</th>
<th>Total (N = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal/d)a</td>
<td>1716.7(820.5) 1495.0</td>
<td>1406.0(412.3) 1332.3</td>
<td>1561.4(693.4) 1439.2</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>202.2(108.0) 169.3</td>
<td>179.8(67.7) 168.9</td>
<td>194.3(89.1) 178.1</td>
</tr>
<tr>
<td>Fat (g/d)a</td>
<td>66.7(37.0) 64.2</td>
<td>49.9(20.0) 45.7</td>
<td>58.9(34.7) 51.7</td>
</tr>
<tr>
<td>Fiber (g/d)</td>
<td>15.8(8.0) 14.7</td>
<td>16.6(6.5) 15.4</td>
<td>16.2(7.5) 15.9</td>
</tr>
<tr>
<td>Glycemic load</td>
<td>101.6(58.9) 82.3</td>
<td>89.3(35.1) 86.5</td>
<td>90.8(45.4) 80.5</td>
</tr>
<tr>
<td>Fruit (number/d)</td>
<td>0.7(0.4) 0.9</td>
<td>0.7(0.4) 1.0</td>
<td>0.7(0.4) 0.9</td>
</tr>
<tr>
<td>Vegetables (number/d)</td>
<td>0.5(0.6) 0.5</td>
<td>0.6(0.5) 1.0</td>
<td>0.5(0.4) 0.7</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Mean(SD) Median</td>
<td>Mean(SD) Median</td>
<td>Mean(SD) Median</td>
</tr>
<tr>
<td>Total minutes per weeka</td>
<td>89.6(88.1) 62.5</td>
<td>208.9(153.5) 167.5</td>
<td>144.8(138.8) 100.1</td>
</tr>
<tr>
<td>Metabolic equivalents a (kg/cal/wk)</td>
<td>4.4(4.6) 3.5</td>
<td>13.1(11.6) 9.0</td>
<td>8.3(8.1) 4.6</td>
</tr>
</tbody>
</table>

NOTE: Median BMI = 35 was the cutoff point used to define severely obese and not severely obese.

aP < 0.05 based on t tests; there were no other significant differences by obesity level.

### Table 3. Results of univariate and multivariate logistic regression analyses on late versus early stage EC (N = 169)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 35</td>
<td>2.18</td>
<td>(1.00–4.77)</td>
<td>0.051</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>3.39</td>
<td>(1.47–7.81)</td>
<td>0.004</td>
</tr>
<tr>
<td>Race (non-white)</td>
<td>1.82</td>
<td>(0.58–5.67)</td>
<td>0.304</td>
</tr>
<tr>
<td>Grade (poor vs. well/moderate differentiation)</td>
<td>7.02</td>
<td>(2.71–13.20)</td>
<td>0.000</td>
</tr>
<tr>
<td>Dietary fat (g)</td>
<td>1.32</td>
<td>(0.49–3.57)</td>
<td>0.580</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>1.08</td>
<td>(0.40–2.89)</td>
<td>0.877</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>1.54</td>
<td>(0.57–4.16)</td>
<td>0.388</td>
</tr>
<tr>
<td>Fruits consumed (per day)</td>
<td>0.97</td>
<td>(0.62–1.60)</td>
<td>0.923</td>
</tr>
<tr>
<td>Vegetables consumed (per day)</td>
<td>1.04</td>
<td>(0.69–1.65)</td>
<td>0.819</td>
</tr>
<tr>
<td>Glycemic load</td>
<td>1.08</td>
<td>(0.40–2.89)</td>
<td>0.877</td>
</tr>
<tr>
<td>Physical activity expenditure (METs)</td>
<td>0.98</td>
<td>(0.92–1.04)</td>
<td>0.546</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 35</td>
<td>1.67</td>
<td>(0.37–4.20)</td>
<td>0.219</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>3.81</td>
<td>(1.44–10.08)</td>
<td>0.007</td>
</tr>
<tr>
<td>Grade (poor vs. well/moderate differentiation)</td>
<td>8.48</td>
<td>(2.90–14.40)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Because of inconsistent results in the obesity-EC association among researchers, as previously indicated, further studies are warranted, as this information can be useful in the management and treatment of EC in obese women (3, 7, 9). For example, obese patients have been shown to be less likely to undergo lymph node evaluation than ideal body weight women because of a less aggressive disease stage and histology in obese women, as well as increased difficulty reported in conducting lymph node dissection (7). However, it was concluded that conducting adequate lymphadenectomy is important for obese women who are in earlier EC stage, as their risk of extrauterine disease, including lymph node metastases, can be similar to that of ideal weight women (7, 8).

Strengths of this study include that it examined a population of women with severe versus nonsevere BMI, who had histologically confirmed EC from 3 diverse sites in the United States. Demographic and anthropometric data were obtained from perioperative clinic data versus self-report; only diet and physical activity data were self-reported. Trained study staff ensured uniformity of data collection and consistent reporting procedures across sites.

Limitations of this study include its cross-sectional design, which limited the ability to make causal inferences, and the fact that we were not able to assess survival. Misclassification of diet and physical activity variables could have occurred, as those surveys were based on participant recall. The low reported mean caloric intake (1,561 calories) may have been underestimated, which is a common problem with FFQs (24). In addition, the limited sample size may have resulted in reduced power. The BMI cutoff point of 35, which defines severe obesity, is justified, as women with EC are typically overweight or obese (10).

Selection bias could also have occurred, as the women who agreed to participate in this study may have been different from those who did not participate. Therefore, these results may not be generalizable to all women with EC.

Future research is needed in larger and more diverse populations of women with EC to further elucidate the relationship between modifiable and nonmodifiable risk factors, such as obesity, age, race, diet, and physical activity on EC stage, as well as their effect on survival. This information would be useful for better management and treatment of EC, as well as improved EC outcomes.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: M.A. Bittoni, J.L. Fisher, E.D. Paskett.
Development of methodology: M.A. Bittoni, J.L. Fisher
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Fowler, G. Maxwell
Analysis and interpretation of data (e.g., statistical analysis, bioinformatics, computational analysis): M.A. Bittoni, J.L. Fisher, G. Maxwell
Writing, review, and/or revision of the manuscript: M.A. Bittoni, J.L. Fisher, J. Fowler, G. Maxwell, E.D. Paskett
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.A. Bittoni
Study supervision: M.A. Bittoni

Grant Support
This study was funded by the Department of Defense Telemedicine and Advanced Technology Center, Award Number W81XWH-05-2-00065. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Received August 5, 2012; revised October 5, 2012; accepted October 22, 2012; published OnlineFirst November 1, 2012.

References


Assessment of the Effects of Severe Obesity and Lifestyle Risk Factors On Stage of Endometrial Cancer

Marisa A. Bittoni, James L. Fisher, Jeffrey M. Fowler, et al.

Cancer Epidemiol Biomarkers Prev  Published OnlineFirst November 1, 2012.

Updated version  Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-12-0843