Nutritional Factors in Ovarian Cancer Survival

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Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States. Because symptoms tend to be nonspecific, early detection is difficult, and most ovarian cancers are diagnosed at an advanced stage when the prognosis is poor. Nonetheless, there is clinical evidence that even given the same tumor characteristics (histologic type, stage, and grade), some cases experience much better survival than others. This has led to extensive research on molecular prognostic factors to enable more efficient and targeted therapeutic regimens. However, little is known about the impact that lifestyle factors, such as diet or physical activity, may have in the prognosis of ovarian cancer, whether on disease-free survival or on the response to and complications from treatment. The role of obesity on ovarian cancer survival is unclear. Obesity may delay diagnosis, hinder optimal surgical and cytotoxic treatment, and cause postoperative complications. As overweight and obesity rates reach epidemic proportions, the impact of body mass index in the clinical management of ovarian cancer is increasingly significant, whereas current evidence of its impact is limited and inconclusive.

INTRODUCTION

Cancer of the ovary is the second most common gynecologic cancer and the leading cause of death from gynecologic malignancies in the United States, with an estimated 21,650 new cases and 15,520 new deaths that were expected in 2008 (1). Early detection of ovarian cancer remains a major challenge because disease symptoms of abdominal discomfort and bloating, vaginal bleeding, gastrointestinal, or urinary tract symptoms are nonspecific, and no reliable screening and diagnostic tests are currently available (2). Only 19% of ovarian malignancies are detected at a localized stage when the disease can be cured successfully with 5-yr survival rate of 92% (1). Most patients are diagnosed with regional or distant disease, which have 5-yr survival rates of 71% and 30%, respectively (1).

According to Surveillance Epidemiology and End Results (SEER) data (3), 5-yr survival rates ranged from 98% for “borderline” tumors to 18% for adenocarcinomas not otherwise specified. Overall, the 5-yr survival rate is 45% (4). More advanced tumor stage, residual disease, histologic grade, age at diagnosis, performance status, presence or absence of ascites, and histologic type of tumor have been shown to be important prognostic factors in ovarian cancer (5,6). Race has been shown to be an important factor, with lower survival rates for Black women compared to Whites (3,7).

Although advanced ovarian cancers tend to have a poor prognosis, cases with similar clinical and histopathological characteristics do not necessarily respond the same way to a given treatment, and some patients experience very long survival (8). Given the uncertainties regarding the etiology of ovarian cancer, the difficulties in early detection, and its current low survival rates, particularly when not diagnosed at an early stage, the identification of factors that could improve disease-free survival among women diagnosed with ovarian cancer is of great significance.

The role of reproductive factors on survival has been evaluated in several studies, reviewed by Nagle et al. (9). Overall, studies that have examined parity, hysterectomy, oral contraceptive use, age at menopause, or age at last birth found no association with ovarian cancer survival, whereas there is insufficient evidence for a role of tubal ligation, breastfeeding, or hormone replacement therapy use before diagnosis.

The role of lifestyle factors on ovarian cancer prognosis is largely unknown. The negative impact of current smoking on ovarian cancer survival found in two studies (10,11), was not confirmed in a more recent study conducted in Sweden (12). However, in this latter study, there were only 21 cases and 10 deaths among smokers of more than a pack per day. Therefore, this study may not have had enough statistical power to detect
an association. To our knowledge, only one study evaluated physical activity and ovarian cancer survival and found little indication of an association (12). In this study, when analyses were restricted to women diagnosed with early stage ovarian cancer, higher levels of physical activity during young adult life was associated with decreased ovarian cancer mortality. Although intriguing, these findings need replication.

Although little is known about the influence of food, nutrition, and physical activity on ovarian cancer prognosis, there is an extensive body of literature evaluating their impact on ovarian cancer prevention (13,14). The role of dairy products and lactose on ovarian cancer risk has been explored for over 20 yr. However, current epidemiologic literature for these and other dietary factors—such as vegetables, fruit, dietary fiber, dietary fats, and animal foods—is too inconsistent to draw any conclusions (13–15). A few studies have suggested that tea (16–19) and phytoestrogens (18,20,21) may reduce ovarian cancer risk. However, more studies are needed to confirm these findings. The evidence relating obesity to ovarian cancer risk has also been inconsistent (13,14). However, there are some data suggesting a role for central adiposity (14).

Physical activity has been shown in some studies to reduce ovarian cancer risk, whereas other studies have shown increased risk (14). The overall evidence was deemed by both the American Cancer Society (15) and the World Cancer Research Fund International/American Institute for Cancer Research (13) to be inconclusive.

The goal of this study was to review current evidence linking food intake, physical activity, and obesity to ovarian cancer prognosis.

METHODS

We followed standard methods to conduct systematic literature reviews (22). Studies were identified through searches on PubMed (1966 to September 2008) complemented with manual searches of bibliographies in published articles. We included original peer-reviewed publications in English that reported on consumption of dietary factors (foods, nutrients, beverages), anthropometry (body size, weight, body fat distribution), or physical activity and ovarian cancer survival. No papers were found evaluating physical activity. Cohort studies evaluating the role of prediagnosis dietary intake and/or obesity on ovarian cancer mortality were not included. In general, these studies have found elevated ovarian cancer mortality among obese women (23,24). However, in these types of studies, the observed increased mortality could have resulted from higher incidence or decreased survival.

RESULTS

Food and Nutrient Intake and Ovarian Cancer Survival

To our knowledge, only three studies have evaluated the role of dietary factors on ovarian cancer survival (12,25,26). Nagle et al. (25) reported on the mortality experience of cases from a case-control study conducted in Australia. Usual intake over the year prior to any symptoms was ascertained using a 119-item, semiquantitative, food frequency questionnaire. Higher intakes of vegetables, cruciferous vegetables, red meat, white meat, and vitamin E from foods were associated with better ovarian cancer survival. On the other hand, higher intakes of dairy foods and lactose were associated with poorer survival after adjusting for International Federation of Gynecology and Obstetrics (FIGO) stage, age, grade, total energy intake, and body mass index (BMI). Interestingly, the authors pointed out that the case-control analysis in this study revealed no association with dairy products or lactose intakes. An additional report from this study evaluated a possible interaction between manganese superoxide dismutase (MnSOD) Val9Ala polymorphism and dietary antioxidant intake in ovarian cancer survival and found no association (27).

The second study by Zhang et al. (26), conducted in China, focused on the effect of green tea on ovarian cancer survival. This study was also based on a case-control study by tracing cases \(n = 244\) by phone to ascertain vital status and obtaining postdiagnosis information on tea and alcohol drinking and smoking. Proxy interviews were conducted for 98 of the women because they were too ill or deceased. Ovarian cancer deaths were confirmed by obtaining medical records, from which relevant information was also obtained. Higher frequency and quantity of green tea consumption after diagnosis was associated with better survival. The hazard ratio (HR) for women consuming one or more cups of tea per day compared those consuming it never or seldom was 0.43 [95% CI = 0.20–0.92] after controlling for age at diagnosis, locality (urban/rural), prediagnosis BMI, parity, FIGO stage, grade, ascites (yes/no), residual lesions (≤2 cm, >2 cm), and chemotherapy (yes/no). An additional study in Sweden, based on a population-based case-control study (635 cases), evaluated alcohol intake and found little evidence of an association with ovarian cancer survival (12).

Studies that have followed cases from case-control studies, such as the study by Nagle et al. (25) described above, can be limited in that only cases that were not too sick or did not die soon after diagnosis might be included. Therefore, women with more advanced disease and worse prognosis would be underrepresented. Other studies, such as the one by Zhang et al. (26), rely on information obtained from proxy interviews, which may not be accurate. Also, some studies, such as the study by Nagle et al. (25), relied on cases’ recall of prediagnosis dietary intake, which may thus be subject to some measurement error. Furthermore, the study by Nagle et al. (25) did not attempt to ascertain dietary intake after diagnosis (during treatment and after treatment), which may be highly relevant to prognosis (28). There is a clear need for prospective studies evaluating dietary factors on ovarian cancer prognosis, as what we know from ovarian cancer prevention studies cannot be easily extrapolated to ovarian cancer prognosis.
Obesity and Ovarian Cancer Survival

The increasing rates of obesity are a significant global concern (29), with approximately 60% of the U.S. female population currently being overweight or obese, the latter consisting of 32% of the population (30). Studies have shown that obesity has a detrimental effect in breast cancer prognosis (31), which has been attributed to several factors including a tendency to underdose obese patients in chemotherapeutic regimens (32) or the impact of body weight on the metabolism of several drugs (33,34). However, the role of obesity on ovarian cancer survival is unclear, and only a few studies have attempted to evaluate this issue.

Obesity may affect ovarian cancer survival by having a negative impact on optimal surgical and cytotoxic treatment and increasing the likelihood of postoperative complications (35). In addition, the greater prevalence of other chronic diseases among obese women, such as cardiovascular disease and diabetes, may also impair their tolerance to chemotherapy, affecting their survival (36).

The evaluation of the impact of obesity on stage of disease at diagnosis, as well as its effect on survival, is of great interest. Survival analyses need to include important covariates, such as age, stage, grade, histologic type, presence of ascites, and treatment information. Of relevance is not just weight or BMI prediagnosis or at the time of diagnosis but also during and after treatment. Only 10 studies have evaluated the role of aspects of weight/BMI on ovarian cancer survival (11,12,25,36–42). Their findings are summarized in Table 1 and described following.

Body size before diagnosis and ovarian cancer survival. The role of weight or BMI before diagnosis has been evaluated in 6 studies (11,12,25,41–43). These 6 studies followed cases in a case-control study for recurrence or death. Three of these studies, conducted in Australia (25) and the United States (42,43), evaluated self-reported "usual BMI before diagnosis" (25,42) or "usual weight as an adult" in relation to height (43) and found no association with ovarian cancer survival as shown in Table 1. The ambiguity of the time frame may have led to considerable random error, affecting the study's ability to detect an association. In contrast, the two studies (11,41) that evaluated BMI 5 yr before diagnosis found it to be an independent prognostic factor in ovarian cancer. Zhang et al. (41), in a study in China, found lower ovarian cancer survival for higher BMI 5 yr before diagnosis and at age 21 yr, with an adjusted HR of 2.33 (95% CI = 1.12–4.87) and 3.31 (95% CI = 1.26–8.73), respectively. Similarly, a study by Kjaerbye-Thygesen et al. (11) in Denmark limited to stage III ovarian cancer cases found decreased survival for those with higher BMI 5 yr before diagnosis and at age 20 to 29 yr, with an adjusted HR of 1.83 (95% CI = 1.38–2.42) and 1.30 (95% CI = 0.81–2.10), respectively. The remaining study, conducted in Sweden, did not find a clear association between BMI 1 yr before diagnosis and ovarian cancer survival (12). However, being overweight or obese at age 18 yr was associated with decreased survival (HR = 1.56; 95% CI = 1.04–2.36).

Body size at the time of diagnosis and ovarian cancer survival. In contrast to prediagnosis body size, studies have shown little evidence for a role of BMI or weight around the time of diagnosis on ovarian cancer survival. This could be explained in part with the confounding effects of the presence of ascites, which typically has not been taken into account in analyses. Two of the studies used baseline body size data from randomized clinical trials designed to evaluate chemotherapeutic regimens and ovarian cancer survival (37,38) and found no association between weight at the initiation of chemotherapy and ovarian cancer survival. The study by Zhang et al. (41), discussed above, based on a case-control study, also failed to find an association with BMI at diagnosis. Three retrospective cohort studies (36,39,40) also evaluated BMI/weight at diagnosis as a prognostic factor in ovarian cancer, with conflicting results.

Body size after diagnosis and ovarian cancer survival. The evaluation of weight changes after diagnosis, particularly during treatment, is complex: Cancer treatment may result in changes in weight, and normal weight patients may tolerate treatment better than underweight patients (39). At the same time, advanced ovarian cancer patients may experience cachexia from symptoms related to advanced disease (e.g., bowel obstruction, metabolic changes) and suffer weight loss (38,44,45). Little is known about weight changes in ovarian cancer patients after diagnosis and during and after treatment. One study found weight loss occurring after surgery, being regained gradually over the year following surgery (46). This weight regain tended to be body fat and not lean mass.

To our knowledge, only 1 study has evaluated the role of weight changes during treatment on ovarian cancer survival, using data from a phase III Gynecologic Oncology Group randomized trial of cisplatin and paclitaxel versus carboplatin and paclitaxel in optimal stage III epithelial ovarian cancer (38). After adjustment for age, race, performance status, histology, tumor grade, tumor residual, and treatment, there was no evidence of an association between pretreatment or end of treatment (after 6 cycles) weight on overall survival or progression-free survival. However, this study suggested a 7% decrease in risk of death per 5% increase in weight during treatment. Although these findings are intriguing, they need replication in a more general series of cases of ovarian cancer (including not only advanced cases and not just volunteers in clinical trials) and with a longer follow-up period.

Obesity and chemotherapy dosing. An important aspect of ovarian cancer management in obese women is the uncertainty regarding their optimal chemotherapy dosing. At the present time, standardized guidelines for dosing in the obese patient do not exist and, to our knowledge, there are no studies evaluating outcomes on chemotherapy treatment in obese patients. Oncologists have been using body surface area (BSA) for calculation of chemotherapy doses for more than 40 yr, even though it is now recognized that this method is inaccurate (47). Several formulas have been proposed to calculate BSA, with the one proposed by DuBois and Dubois being widely used, even
<table>
<thead>
<tr>
<th>Author, Yr (Ref)</th>
<th>Location</th>
<th>Design</th>
<th>Sample Size</th>
<th>Time of BMI Data</th>
<th>Contrast</th>
<th>HR (95% CI) or Summary of Results</th>
<th>Covariates Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schildkraut et al., 2000 (43)</td>
<td>United States</td>
<td>Follow-up of cases in a case-control study</td>
<td>197 invasive cases</td>
<td>“Usual weight as an adult” in relation to height</td>
<td>≥27.9 vs. &lt;27.9</td>
<td>1.1 (0.7–1.7)</td>
<td></td>
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<tr>
<td>Nagle et al., 2003 (25)</td>
<td>Australia</td>
<td>Follow-up of cases in a case-control study</td>
<td>609 cases</td>
<td>Weight and height before diagnosis</td>
<td>“Usual BMI” before diagnosis &gt;25.8 vs. &lt;22.2</td>
<td>0.96 (0.74–1.23)</td>
<td>FIGO stage, age, grade, total energy intake, ascites, smoking status, parity, and length of oral contraceptive use</td>
</tr>
<tr>
<td>Zhang et al., 2005 (41)</td>
<td>China</td>
<td>Follow-up of cases in a case-control study</td>
<td>214 cases</td>
<td>Self-reported height and weight at diagnosis, 5 yr before diagnosis, and at age 21 yr</td>
<td>BMI at diagnosis: ≥25 vs. &lt;20</td>
<td>0.76 (0.38–1.52)</td>
<td>Age at diagnosis, energy intake, menopausal status, stage, grade, ascites (yes/no), residual lesions (&lt;2 and ≥2 cm), and chemotherapy (yes/no)</td>
</tr>
<tr>
<td>Moysich et al., 2005 (42)</td>
<td>United States</td>
<td>Follow-up of cases in a hospital-based case-control study</td>
<td>395</td>
<td>Self-reported height and weight</td>
<td>BMI at baseline and during treatment (every 21 days for 6 cycles)</td>
<td>Weight pretherapy (per 1 kg)</td>
<td>1.0 (0.99–1.01)</td>
</tr>
<tr>
<td>Hess et al., 2007 (38)</td>
<td>United States</td>
<td>Participants in a GOG phase III randomized study of chemotherapeutic agents in stage III epithelial ovarian cancer</td>
<td>685 advanced cases</td>
<td>BMI at baseline and during treatment (every 21 days for 6 cycles)</td>
<td>Weight posttherapy (per 1 kg)</td>
<td>1.0 (0.99–1.00)</td>
<td>Relative weight change (per 5%)</td>
</tr>
<tr>
<td>Kjaerbye-Thygesen et al., 2006 (11)</td>
<td>Denmark</td>
<td>Follow-up of cases in a population-based, case-control study</td>
<td>295 cases (stage III epithelial cases)</td>
<td>Premorbid BMI (average over the last 5 yr before diagnosis) and BMI at age 20–29 yr</td>
<td>BMI 5 yr before diagnosis ≥25 vs. 18.5–24.9</td>
<td>1.83 (1.38–2.42)</td>
<td>Adjusted for current age, radicality of surgery, histology, and platinum-based chemotherapy</td>
</tr>
</tbody>
</table>

(Continued on next page)
## TABLE 1
Studies evaluating BMI and ovarian cancer survival\(^a\) (Continued)

<table>
<thead>
<tr>
<th>Author, Yr (Ref)</th>
<th>Location</th>
<th>Design</th>
<th>Sample Size</th>
<th>Time of BMI Data</th>
<th>Contrast</th>
<th>HR (95% CI) or Summary of Results</th>
<th>Covariates Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pavelka et al., 2006 (40)</td>
<td>United States</td>
<td>Retrospective cohort (cases from Cedar Sinai Medical Center from 1996–2003)</td>
<td>216 cases</td>
<td>Height and weight from first postoperative visit</td>
<td>Median survival time was lower for obese than normal weight patients</td>
<td>1.05 (1.005–1.097)</td>
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<tr>
<td>Skirnisdottir et al., 2008 (36)</td>
<td>Sweden</td>
<td>Retrospective cohort (cases from regional database of all gynecologic cancer patients, 1975–2004)</td>
<td>635 cases, FIGO stages IA–IIC</td>
<td>Weight and height at the start of adjuvant treatment</td>
<td>BMI ≥30 vs. BMI &lt;18.5</td>
<td>1.7 ((P = 0.26))</td>
<td></td>
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<tr>
<td>Munstedt et al., 2008 (39)</td>
<td>Germany</td>
<td>Retrospective cohort Cases from a single institution (1986–2005) Follow-up to December 2006 (medical records)</td>
<td>824 cases, 221 with tumor samples</td>
<td>Preoperative weight at diagnosis</td>
<td>Suggestion of better survival in obese patients ((&gt;25 \text{ kg/m}^2))</td>
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<tr>
<td>Barrett et al., 2008 (37)</td>
<td>83 sites, including, Scotland, United Kingdom, Australia</td>
<td>Participants in a phase III randomized trial (SCOTROC) I- for stages IC–IV ovarian cancers</td>
<td>1,077 cases (ovarian or peritoneal carcinoma)</td>
<td>Height and weight recorded at first treatment</td>
<td>No association between BMI and tumor stage, tumor grade, or extent of debulking surgery</td>
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<tr>
<td>Yang et al., 2008 (12)</td>
<td>Sweden</td>
<td>Follow-up of cases in a case-control study</td>
<td>635 cases</td>
<td>Self-reported weight and height 1 yr before diagnosis and at age 18</td>
<td>Age at diagnosis, FIGO stage, and WHO grade of differentiation</td>
<td>1.22 (0.86–1.71)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Abbreviations are as follows: BMI, body mass index; HR, hazard ratio for overall survival; CI, confidence interval; FIGO, Federation Internationale de Gynecologie et d’Obstetrique (International Federation of Gynecology and Obstetrics); GOG, gynecologic oncology group; PFS, progression free survival; OS, overall survival; WHO, World Health Organization.
though this formula was only based on 9 individuals and had not been validated (48). More recently, an equation proposed by Mosteller (49) was recommended and is commonly used in clinical practice to calculate BSA. According to Mosteller’s formula, BSA (m²) is calculated as \[\text{BSA} = \frac{\text{Wt(in)}}{3600} \times \frac{1}{2}.\]

When compared to estimates based on Mosteller’s equation, BSA calculation based on the DuBois formula underestimated BSA in obese female patients by 5% (50). In chemotherapy dosing, errors in calculation of BSA may result in underdosing or toxic effects. For obese women, this issue may be particularly troublesome, as oncologists may commonly cap the dose, afraid of overdosing the obese patient (35). Other oncologists base dosing on true BSA, BSA based on ideal weight, or the average of the two (35). Whether the choice of one over the other has an impact on ovarian cancer survival, to our knowledge, has not been evaluated.

**CONCLUSION**

Ovarian cancer presents unique challenges to epidemiologists trying to understand risk and prognostic factors as well as to the oncologist aiming to its optimal management. At the present time, very few studies have evaluated the influence of lifestyle factors (e.g., diet, physical activity, smoking) in ovarian cancer prognosis. The role of obesity on ovarian cancer survival is complex and not well understood at the present time. Obesity might delay diagnosis, hinder optimal surgical and cytotoxic treatment, and cause postoperative complications that delay initiation of cytotoxic treatment. Furthermore, optimal chemotherapy dosing of obese patients may not be reached. Several mechanisms involving hormonal pathways have also been postulated to explain a possible role of obesity on ovarian cancer survival. These include effects on insulin resistance and insulin-like growth factor (IGF)-I increased aromatization of androstenedione to estrone in peripheral adipocytes, thus increasing the bioavailability of sex steroids (11), and increased adrenal and ovarian secretion of androgens (35). Higher circulating estrogen levels may stimulate ovarian cancer proliferation, resulting in faster growth of metastatic tissue (11). Furthermore, IGFBP-2, a binding protein for IGF, has been shown to promote invasion in ovarian cancer (40).

Although early detection of ovarian cancer continues to be a challenge, and survival rates remain low, the identification of factors that could influence disease-free survival of women with ovarian cancer is of critical importance. Large cohort studies evaluating the role of dietary factors, physical activity, and obesity on ovarian cancer survival are clearly needed.

**REFERENCES**


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