The obese endometrial cancer patient: how do we effectively improve morbidity and mortality in this patient population?

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The relationship between obesity, metabolic syndrome, and endometrial cancer has been established and accepted for decades. However, despite this understanding, endometrial cancer patients continue to die of their obesity-related co-morbidities such as cardiovascular disease and diabetes. Furthermore, studies show that gynecologic oncologists, general obstetrician/gynecologists, and bariatric specialists do not appropriately address obesity as a risk factor for cancer and also do not provide appropriate counseling on weight loss and lifestyle modification during screening, diagnosis, and follow-up for endometrial cancer. Given the increasing numbers of obese women both in the United States as well as globally, it is imperative that this risk be addressed and mitigated during patient interactions. Therefore, this article reviews the literature on obesity, metabolic syndrome, and endometrial cancer, as well as the literature on causes of death in endometrial cancer patients. Given the increased cardiovascular and all-cause mortality, we provide a number of methods to address obesity as a risk factor for cancer during patient visits. These methods include self-directed diet and exercise, supervised diet and exercise programs, medical management with insulin-sensitizing agents and statins, as well as bariatric surgery in extreme cases. Furthermore, we also encourage collaboration between general obstetrician/gynecologists, gynecologic oncologists, and bariatric specialists in the care of obese endometrial cancer patients to ensure that they not only survive their diagnosis, but also go on to live long, healthy lives.

Key words: endometrial neoplasms, obesity, gynecologic surgical procedures, bariatric surgery

introduction

Endometrial cancer is the sixth most common malignancy in women and one of the first malignancies to be linked with obesity [1, 2]. In 2015, there were an estimated 54,870 newly diagnosed cases with ~10,170 deaths. Established risk factors include unopposed estrogen therapy, tamoxifen use, obesity, nulliparity, polycystic ovarian syndrome, Lynch syndrome, Cowden syndrome, early menarche, and late menopause [3]. Despite the increasing numbers of women diagnosed with endometrial cancer, the survival rate remains high, at 81.7% overall and 95.3% for localized disease [4]. Recent data show that women diagnosed with endometrial cancer are more likely to die of other causes. The objective of this article is to review these other causes of morbidity and mortality in endometrial cancer patients and to propose treatment interventions to mitigate these cases.

background

obesity and endometrial cancer

Overweight status and obesity are objectively measured using the body mass index (BMI) and are defined as excessive fat accumulation in relation to height. A BMI over 25 is defined as being overweight, whereas a BMI over 30 defines obesity. A BMI of 30.0–34.9 constitutes class I obesity, 35.0–39.9 class II obesity, and 40.0 or greater class III obesity. [5] In 2014, over 1.9 billion adults were overweight across the world, of which over 600 million were obese. [6] According to a 2009–2010 National Health and Nutrition Examination Survey (NHANES), over 68.8% of adults of age 20 years or older in the United States are overweight or obese, and over 35.7% are considered obese [7]. As shown in Figure 1, these numbers have been rapidly increasing among women and will only continue to increase over the next few years. Since obesity is a risk factor for endometrial cancer, it is imperative that the association of obesity with morbidity and mortality be better understood.

Danaei et al. [9] estimated that 20% of all deaths in the United States are caused by obesity and/or overweight and...
PTEN has been noted in 40% of cancer cases, with increasing weight [13]. One study showed that the odds ratio was 3.33, compared to 1.43, respectively. In obese women, the relative risk was 2.54, and the odds ratio for developing endometrial cancer in overweight women were 1.34 and 4.76, respectively. Reduced levels of these protective molecules have been found in individuals with obesity and hyperinsulinemia. Thus, both obesity and hyperinsulinemia are associated with endometrial cancer [12]. Along with obesity, comorbid conditions such as metabolic syndrome and hyperinsulinemia are associated with endometrial cancer. The relationship between these factors and endometrial cancer is demonstrated in Figure 2 below. An NHANES survey estimates the prevalence of metabolic syndrome as 30.6% among women 40–59 years old and 46.1% in women over 60 years in the United States [18]. Among premenopausal women with metabolic syndrome, there is an adjusted twofold increased risk of endometrial cancer, largely due to increasing waist sizes. After menopause, this jumps to a 60–230% elevated risk of endometrial cancer in women with metabolic syndrome [19].

A 2015 meta-analysis of 40 studies showed that compared with normal weight women, the relative risk and odds ratio for developing endometrial cancer in overweight women were 1.34 and 1.43, respectively, in obese women, the relative risk was 2.54, and the odds ratio was 3.33, confirming that the risk of endometrial cancer increases incrementally with increasing weight [13]. One of the earliest epidemiologic studies on obesity and endometrial cancer carried out in 1966 proposed weight reduction as the most practical preventive measure for endometrial cancer [2].

A recent prospective study showed that high BMI during childhood and adolescence had no significant association with endometrial cancer risk when adjusted for the most recent BMI; however, weight gain of >25 kg since the age of 18 was associated with endometrial cancer risk (HR 2.54) [14]. Furthermore, another study showed that adult weight gain was associated with an increased risk of endometrial cancer (RR 1.81) [15]. Similarly, a case–control study showed that not only do overweight and obese women have an increased risk of developing endometrial cancer (RR 1.54 and 4.76, respectively), but also women who were overweight in their 20s and 30s and maintained this weight throughout their life had a much greater risk of developing endometrial cancer than did women who became overweight later in life. Women with weight gain greater than 35% in early adulthood developed endometrial cancer 10 years earlier than other women [16]. The results of these studies suggest that both preventing obesity in young adulthood and maintaining a stable BMI throughout life are important.

Finally, obesity is not only a risk factor for developing endometrial cancer, but it may also impact treatment. Bouwman et al. retrospectively evaluated endometrial cancer patients managed with surgery. Obese women had significantly more perioperative complications, including wound complications and increased need for antibiotics. The risk of complications was even higher in those women who were morbidly obese [17]. This study did not take into consideration women who were unable to receive necessary treatment due to their morbid obesity.

**Figure 1.** Prevalence of overweight, obesity, and extreme obesity in USA adult women, 1960–2010 [8].
Further, after adjusting for overweight/obesity, the association with the other component factors remained [20]. Another study by Shou et al. [21] suggested that beyond metabolic syndrome, even abnormalities in systolic and diastolic blood pressures are associated with an increased occurrence of endometrial cancer. These results are supported by a larger study carried out in 2014 in which the risk estimates for endometrial cancer were independently calculated for the components of metabolic syndrome, including BMI and/or waist size (2.21), hyperglycemia (1.81), hypertension (1.81), and hypertriglyceridemia (1.17) [22]. These studies suggest that targeting even just one component of metabolic syndrome can mitigate an individual’s risk of developing endometrial cancer.

Due to the increasing prevalence of diabetes, it is also important to understand and address the relationship between insulin resistance and endometrial cancer. Shan et al. [23] found that insulin resistance and hyperinsulinemia are key events early on in endometrial hyperplasia and might even be initiating factors in the development of endometrial cancer. One large case–control study showed that patients with uncontrolled diabetes had a relative risk of 5.563 for developing endometrial cancer, whereas patients with controlled diabetes had less of an increased risk of developing EC (RR 1.331) [24].

For patients with diabetes and obesity, a stationary lifestyle can lead to even worse outcomes. In one study, the RR of developing endometrial cancer among obese diabetics compared with nonobese diabetics was found to be 6.39. Among diabetics with low physical activity, the RR was 2.80 compared with physically active nondiabetics. Obese diabetics with low physical activity had an RR of 9.61 compared with normal weight, nondiabetic women with high physical activity [25]. One study also showed that hyperinsulinemia and insulin resistance are both prevalent among overweight but nonobese women with endometrial cancer, and thus, it is imperative that even overweight patients be screened for insulin resistance and encouraged to maintain a normal weight [26].

what are the causes of death in women with endometrial cancer?

Women with endometrial cancer suffer from a number of comorbidities, including diabetes, osteoarthritis, hypertension, and cardiopulmonary diseases [27]. A study done by von Greunigen and the Gynecologic Oncology Group (GOG) showed that obesity does not increase disease recurrence rates. However, it does increase the risk of mortality in women with a diagnosis of early-stage endometrial cancer [28]. Similar studies show that obese endometrial cancer survivors with diabetes have decreased life expectancy compared with their counterparts without diabetes or obesity [27]. Although the mortality rate in endometrial cancer patients is low, the relative risk of dying for obese endometrial cancer patients is significantly higher than for those with normal BMI (RR 2.53 for BMI 30–34, RR 6.25 for BMI > 40) [29].

In 2007, the first cohort study on mortality in endometrial cancer patients in Britain found that 42% of death certificates listed endometrial cancer as an underlying cause of death. However, this cohort also had a fourfold increase in deaths due to ovarian cancer compared with the general population, as well as a twofold increase in mortality from breast cancer and a twofold increase in diabetes-related mortality [30].

More recent studies have pointed toward similar trends in mortality among endometrial cancer patients. A 2012 study focusing on cardiovascular mortality used SEER registries to show that endometrial cancer patients were most likely to die of cardiovascular disease (35.9%), followed by other causes, other malignancies, and finally, endometrial cancer. Due to the high survivorship in low-grade localized cancers, these patients were most likely to survive their cancer diagnosis and go on to develop and die of cardiovascular causes [31]. In the NIH-AARP Diet and Health Study, an increase in the BMI was related to an increase in 5-year all-cause mortality and endometrial cancer-specific mortality, but not in cardiovascular mortality. However, 10-year cardiovascular mortality as it is related to BMI became statistically significant (HR 4.08) when comparing the extremes of BMI [32]. These studies thus suggest that as survivorship from endometrial cancer increases, the risk of dying from cardiovascular disease also increases. In a majority of cases, early-stage endometrial cancer alone does not lead to death but, rather, women will have an increased all-cause and obesity-related mortality later in life.

improving obesity-related mortality in endometrial cancer patients

Today, the gynecologic oncologist’s role in endometrial cancer patient care has broadened to encompass:

1) Diagnosis and primary surgical management of disease
2) Participation in surveillance for disease recurrence
3) Provision of preventive care
4) Coordination with other disciplines for management of comorbidities
5) Help with informed decision-making regarding hormone therapy and sexual health options both before and after treatment [33].

Given these roles, the following methods of targeting obesity and its comorbidities should be incorporated into the care of endometrial cancer patients:

self-directed diet and exercise

Both dietary modification and physical activity have been proved to be associated with a decreased risk of endometrial cancer.
cancer. Furthermore, weight loss of 5–10% has been shown to reverse insulin resistance, decrease IGF-1 levels, and prevent the development of type 2 diabetes mellitus [12]. A 2008 study of 42,672 postmenopausal women enrolled in the American Cancer Society Cancer Prevention Study II Nutrition Cohort (1992–2003) showed that recreational and moderate physical activity was associated with a 33% decrease in endometrial cancer risk. This benefit was maximized in overweight or obese participants [34]. In terms of diet, a 2009 case–control study showed a significantly increased endometrial cancer risk in women who regularly consumed red meat (OR 2.07 per 1 serving per day) [35]. Another study focusing on exercise, BMI, and quality of life in survivors showed that lack of exercise and high BMI were associated with declines in quality of life. Furthermore, 70% of study participants were obese and were not meeting health exercise guidelines [36].

Unfortunately, despite the evidence suggesting that improving diet and increasing exercise can improve survival and quality of life, studies show that endometrial cancer patients are not able to undertake these lifestyle modifications on their own [26]. In one study on endometrial cancer patients’ changes in diet, exercise, and complementary medicine use, 86% of the participants were found to be obese. Between the preoperative and 6-month postoperative periods, weight, exercise, and fruit and/or vegetable intake did not change, but complementary medicine use significantly increased. This study shows that women who are obese or have a sedentary lifestyle before treatment of endometrial cancer are unlikely to change their lifestyle after treatment. Furthermore, the women included in the study turned to complementary medicine rather than lifestyle modification, suggesting that they may have received inadequate counseling by their gynecologist or find it difficult to successfully implement healthy lifestyle changes [37].

supervised diet and exercise programs

In a literature review carried out by Zhang et al., only 14.2% of endometrial cancer patients were found to be able to safely exercise without supervision based on their health at the time of diagnosis. Factors likely to lead to exclusion from unsupervised community and/or home-based exercise programs included older age at diagnosis and higher BMI [38].

There is considerable evidence showing that when placed in structured lifestyle intervention care groups, EC survivors are able to lose weight and incorporate healthy lifestyle changes. The SUCCEED trial showed that significant 6-month and 12-month changes were achievable, but recommended longer follow-up. The rate of adherence in this study was 84%, and follow-up data were available from 92% of participants at 6 months and 79% at 12 months, showing that survivors are more likely to follow diet and exercise regimens when enrolled in a supervised program [39]. As a follow-up to their study on complementary medicine use, von Gruenigen et al. randomized 45 overweight and obese endometrial cancer survivors into a control group and an intervention group that received counseling on weight loss, healthy diet, and physical activity. After 1 year, the intervention group lost significantly more weight than the control group. Furthermore, their physical activity increased by 16.4 metabolic equivalents compared with a decrease in 1.3 metabolic equivalents in the control group. Most importantly, the women in the intervention group also had increased quality-of-life scores compared with the control group [37].

medical management

The mainstay of medical management for women with endometrial hyperplasia without atypia is currently high-dose progestin therapy [40]. There is considerable evidence suggesting that medications meant to target hypercholesterolemia and type II diabetes can also be used to inhibit endometrial proliferation [33]. For those patients with endometrial hyperplasia, prescribing these medications not only will stabilize their obesity-related comorbidities, but also can prevent further malignant transformation. Furthermore, in those patients with endometrial hyperplasia who have failed high-dose progestin therapy and wish to avoid a hysterectomy, the prescription of these medications remains a viable option.

Statins: A 2015 retrospective cohort study of 985 endometrial cancer cases showed improved disease-specific survival (81%) in women taking statins at the time of diagnosis and staging compared with nonusers (74%). Furthermore, women taking aspirin in addition to a statin for cardiovascular health had particularly low disease-specific mortality (HR 0.25) relative to patients who used neither aspirin nor a statin [41].

Insulin-sensitizing agents: Metformin not only inhibits glucose-neogenesis but also improves insulin sensitivity and peripheral glucose uptake [33]. Although the exact effects of hyperinsulinemia on EC are not known, rat models show that the proliferative effect of estrogen on the endometrium is enhanced in obese, hyperinsulinemic rats [42]. Additional research suggests that metformin also activates growth inhibitory pathways, affects signal transduction pathways, and lowers sex-steroid hormone levels in postmenopausal women [43, 44].

Two separate case reports have shown that insulin-sensitizing agents such as metformin can cause regression in patients with atypical endometrial hyperplasia resistant to progestin therapy. In one of these reports, the patients were obese, insulin-resistant, and nulliparous. In both reports, endometrial biopsy after initiation of the insulin-sensitizing agents showed proliferative endometrium [45, 46].

In a recent interventional study, women with atypical hyperplasia or endometrioid adenocarcinoma of the endometrium were separated into an intervention group that received metformin twice daily for 4 weeks before surgery, or a control group. The results of this study revealed two key points. First, that presurgical metformin was associated with reduced proliferation. Second, that undiagnosed insulin resistance and/or diabetes were very common in the enrolled patients [47]. Thus, given what we know about the relationship between endometrial cancer and insulin resistance, the benefits of using metformin as a chemotherapeutic drug are clear. Considering all of the evidence, the questions that need further investigation are as follows: should metformin and potentially statins be regularly prescribed drugs for obese gynecologic patients with abnormal endometrial lining? Should guidelines be put in place for the regular screening of obese patients for insulin resistance at their annual gynecology exams?

bariatric surgery

On a molecular level, it has been shown that morbid obesity is associated with high hormone receptor expression in the
hyperplastic endometrium. Clinically, the lifestyle changes that are required to reduce this expression through sustained weight loss are often too difficult to maintain for many individuals. For these patients, bariatric surgery is associated with a significant reduction in hormone receptors and remains a viable option [48]. A systematic review and meta-analysis carried out in 2015 showed that there was a significant risk reduction for endometrial cancer associated with bariatric surgery (pooled RR 0.40) [49]. Furthermore, a large study of 6596 USA patients who underwent gastric bypass surgery showed that there was an overall reduction in cancer risk (HR 0.76). Interestingly, this study also found that the risk reduction was most pronounced in women (HR 0.73). The hazard ratio for endometrial cancer specifically also dropped significantly to 0.22 after bariatric surgery [50]. Ward et al. carried out a retrospective cohort study of women admitted with and without a diagnosis of obesity and/or a history of bariatric surgery. The results of this study showed that a history of bariatric surgery was associated with a 71% risk reduction for uterine malignancy, and an 81% risk reduction if the weight loss was maintained after surgery [51].

Current data clearly demonstrate that bariatric surgery can result in clinically significant weight loss that not only reduces the risk of development of endometrial cancer but also mediates cardiovascular comorbidities. Furthermore, cost-effective analysis of bariatric surgery compared with routine care in obese endometrial cancer patients shows that weight loss surgery is a cost-effective option and has an incremental cost-effectiveness ratio (ICER) of $26,080 per QALY when compared with routine care, a number that is well below the standard of $50,000 per QALY [52].

current counseling practices

Despite the current evidence supporting the benefits of weight loss in obese patients, gynecologic oncologists are not providing effective weight loss counseling during patient interactions. A 2014 survey of members of the Society of Gynecologic Oncology showed that despite reporting that over 50% of their patients were obese, only 10% of responders had any formal training (noted to be either in medical school or in residency) in weight loss counseling. Furthermore, over 90% of those surveyed stated that they believed that weight loss surgery is a feasible and more effective option than diet and medical management of obesity [52].

From a primary care perspective, general gynecologists should also be screening for and addressing obesity at annual exam visits. One study assessing screening methods and the usage of educational materials among members of the American College of Obstetrician and Gynecologists (ACOG) showed that in 2007, 91% of OB-GYN specialists screened their nonpregnant patients using BMI. However, only 55% stated that they usually counseled their patients on physical activity, and only 48% ever prescribed medications for weight loss. Furthermore, only 33% provided counseling on weight control during most visits, and many providers felt that their patients would not follow their advice regarding weight loss [53].

Similarly, one study of USA bariatric surgeons showed that despite the known association between obesity and endometrial cancer, only 21% had ever referred a patient for endometrial surveillance. Furthermore, although 80% obtained gynecologic histories from their patients, 56% did not require Pap smears, and 49% did not require mammograms before surgery. Most significantly, 20% of the surgeons stated that they did not consistently counsel patients on the relationship between obesity and cancer risk [54].

A few studies have also looked at patient perception and acceptance of obesity counseling. One such study in endometrial cancer survivors showed that gynecologic oncologists provided dietary counseling 25% of the time compared with 37% from a primary care physician (PCP), and exercise counseling 37% of the time versus 62% from a PCP. Only 29% of patients reported ever being told of the relationship between obesity and endometrial cancer. Despite this, over 50% of the patients reported attempting to lose weight through lifestyle changes after diagnosis. Those who were most likely to make lifestyle modifications were those who had received adequate counseling by a physician. Weight loss attempts were significantly associated with having received weight loss counseling [55]. A similar study showed that 91% of surveyed patients would be receptive to weight loss discussions with their gynecologic oncologists. Of the 106 women surveyed in this study, 6 were already seeing a bariatric specialist and an additional 43 agreed to a medical or surgical referral. Three months later, only 17 women had complied with the referrals. However, 59 women had initiated lifestyle changes to lose weight [56]. Thus, although a small percentage received weight loss counseling from their care providers, a majority of women were still willing and able to initiate these lifestyle changes if they were provided with the appropriate information. Gynecologic oncologists and bariatric surgeons should therefore collaborate to educate patients regarding their weight loss and cancer risk.

Given the long-standing relationship that women form with their obstetrician/gynecologist, counseling for obesity and weight loss should start at a woman’s first annual exam visit. The ACOG provides a number of resources to assist providers with these conversations. One such resource—a committee opinion published in 2014—outlines a number of different approaches and recommendations for OB/GYN specialists, including motivational interviewing techniques, providing educational materials on healthy food options, and advocating for exercise programs in the hospital [57]. Thus, general obstetrician/gynecologists have many tools at their disposal to target obesity among their patients and, in conjunction with bariatric surgeons and gynecologic oncologists, can make a large impact on their patients’ endometrial cancer risks.

conclusion

Despite the well-defined relationship between endometrial cancer and obesity, hyperinsulinemia, and metabolic syndrome, medical practitioners are not counseling their obese endometrial cancer patients on the benefits of weight loss. Furthermore, data show that endometrial cancer patients are most likely to suffer reduced quality of life and to eventually die of their medical comorbidities, rather than their cancer. Thus, it is imperative that gynecologic oncologists regularly incorporate weight-loss counseling during diagnosis, treatment, and follow-up care for endometrial cancer. Potential options include self-directed or supervised diet and exercise programs, medical management
with insulin-sensitizing agents and/or statins, and bariatric surgery. As medical and surgical care providers, gynecologic oncologists have a unique opportunity to provide weight loss counseling and continuity of care for their cancer patients. Given the growing number of women who are obese worldwide, this is an opportunity we cannot afford to miss.

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references
Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues

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Since the last two decades, the feasibility of fertility-sparing surgery (FSS) in early-stage epithelial ovarian cancer (EOC) has been explored by several teams and is reconsidered in this systematic review undertaken using the PRISMA guidelines. Borderline ovarian tumours and non-EOCs were excluded. This review comprises 1150 patients and 139 relapsing patients reported by 21 teams. This conservative treatment can be safely carried out for stage IA and IC grade 1 and 2 disease and stage IC1 according to the new FIGO staging system. Nevertheless, the number of patients reported with grade 2 disease is too small to definitively confirm whether FSS is safe in this subgroup. For patients with ‘less favourable’ prognostic factors (grade 3 or stage IC3 disease), the safety of FSS could not be confirmed, but patients should be informed that radical treatment probably may not necessarily improve their oncological outcome, because the poorest survival observed could be related to the natural history of the disease itself and not specifically to the use of conservative therapy. FSS could probably be considered in stage I clear-cell tumours but should remain contraindicated for stage II/III disease (whatever the histologic subtype). As the disease stage and the histologic data (tumour type and grade) are crucial to patient selection for this treatment, this implies careful and mandatory complete surgical staging surgery in this context and a pathological analysis (or review) of the tumour by an expert pathologist.

Key words: conservative treatment, early stage, epithelial ovarian cancer, fertility-sparing surgery, recurrence, survival