Current Problems in Cancer 43 (2019) 145–150

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Causal effect of obesity on gynecologic malignancies

Courtney Griffiths, DO, Edward Jimenez, DO, Eva Chalas, MD*

ARTICLE INFO

Keywords:
Obesity-related cancers
Obesity epidemic
Challenges of obesity
Cause-specific mortality
Postmenopausal breast cancer

ABSTRACT

Introduction: Gynecologic malignancies are estimated to affect 110,070 women and will be the cause of death in approximately 32,120 in 2018. Endometrial cancer is among the most prevalent with 63,320 estimated new cases and approximately 11,350 deaths, followed by ovarian cancer with an estimate of 22,000 new cases and 14,000 deaths annually. Obesity is one of the most modifiable risk factors. Providers should engage in a multifaceted approach to patient education and healthcare to decrease the projected cases of obesity-related cancers.

Background: The literature demonstrates a significant link between obesity and the development of certain malignancies such as endometrial, pancreatic, and renal cancer. Specific mechanisms found to play a role in the development of these malignancies include alterations of the metabolic pathway attributed to lipid accumulation as well as a chronic inflammatory process. Obesity also predisposes patients to other medical comorbidities as well as a poorer prognosis once a diagnosis of cancer is established. Factors contributing to poorer prognosis include challenges with treatment planning, specifically pertaining to inappropriate chemotherapy dosing and delivery of radiation therapy. Surgical approach and perioperative management are similarly challenging in obese patients and are associated with increased risk of complications.

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Winthrop Hospital, Mineola, NY

* Correspondence to: Eva Chalas, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Winthrop Hospital, 259 1st Street, Mineola, NY 11501.

E-mail address: eva.chalas@nyulangone.org (E. Chalas).

https://doi.org/10.1016/j.currproblcancer.2018.07.011

Conclusion: Obesity is a modifiable factor which is associated with an increased risk of cancer and poorer outcomes. Providers should educate patients on all health hazards of obesity, including increased risk of cancer, and encourage them to participate in a structured weight loss plan.

Introduction

Gynecologic malignancies are estimated to affect 110,070 women in the United States and will be the cause of death in approximately 32,120 in 2018. Endometrial cancer is among the most prevalent with 63,320 estimated new cases and approximately 11,350 deaths, followed by ovarian cancer with an estimate of 22,000 new cases and 14,000 deaths annually.[1] Predisposing risk factors for these malignancies include aging, family history, medical comorbidities, and environmental factors, particularly obesity.

Obesity is classified as either overweight (body mass index [BMI] 25-29.9 kg/m^2), obese (30-39.9 kg/m^2, divided into classes I and II), and morbidly obese (BMI 40 kg/m^2 and above).[2] Scientific literature supports a strong epidemiologic correlation between obesity and malignancy, particularly those of gynecologic origin.[3,4] Two-thirds of adults and one-third of children are currently classified as either overweight or obese as a result of an increase in obesity trends over the last few decades. According to the Centers for Disease Control, the number of weight-related cancers is expected to increase 30%–40% by 2020, with the exception of breast and colorectal cancers as a result of effective screening and greater access to high quality healthcare.[5] In addition, obesity contributes to cancer in 55% of women, while only affecting 24% of male patients, presumably due to excess endogenous estrogen effects of the adipose tissue, demonstrating strong associations with endometrial, postmenopausal breast, and colon cancers.[6,7] Obesity represents a modifiable risk factor, but trends in incidence represent lack of public awareness and action by healthcare providers. This review aims to discuss the challenges associated with obesity and the association with gynecologic cancer development, and to call for action by the public and healthcare providers to achieve decreased incidence of cancer, improve outcomes, and quality of life.

Background

Obesity is one of the most modifiable risk factors for cancer. The obesity epidemic began in the 1980s and has contributed to an increase in endometrial, pancreatic, and renal cancer incidence rates by 49%, 28%, and 24%, respectively, in the United States.[8] Hypotheses for this upward trend in prevalence of obesity include reductions in physical activity and food marketing practices.[9] Scientific literature supports the link between obesity and cancer. In the United Kingdom, the Million Women Study, designed as a prospective cohort study, demonstrated a correlation between obesity and a significant increase in the risk of cancer for 10 of 17 specific malignancies, including endometrial and ovarian cancers. The study estimated that among postmenopausal women, approximately 6000 cases annually in the United Kingdom were attributable to being overweight or obese, with obesity contributing to half the incidence of endometrial and esophageal cancers.[10] Associations between obesity and cancers have been made for liver, gallbladder, pancreatic, esophageal, colon, endometrial, renal cell, and breast (in postmenopausal women) cancers.[11] Estimates suggest that obesity will increase by at least 33% by 2030 with morbid obesity comprising 11% of the overall population.[12]

According to a comprehensive meta-analysis of the cancer incidence rate trends from 1992 to 2008 for those malignancies associated with obesity and lack of sufficient physical activity,

an increase in BMI by each 5 kg/m^2 is associated with a 30%–60% increased risk of endometrial, esophageal, and kidney cancers. Further, lack of physical activity was associated with a 30%–40% increased incidence of colorectal, postmenopausal breast, and endometrial cancers. In this same analysis, a relative risk (RR) of 2.2 was reported for endometrial cancer in patients with a BMI of greater than 30 kg/m^2 compared to those with similar risk factors and a BMI less than 25 kg/m^2 as well as a RR of 1.25 for postmenopausal breast cancer. Inactivity was found to predispose patients to a RR of 1.37 for endometrial cancer in the same BMI subgroups vs those who were active.[13] This study provides evidence that the combination of inactivity and obesity, both of which are modifiable risk factors, compounds the risk of malignancy.

Evidence from basic science suggests that obesity and/or diabetes contribute to carcinogenesis. Enlargement of adipose tissue deposits results in increased lipid accumulation as a result of chronic caloric excess which in turn, alters the normal metabolic pathway creating a signal transmission for nutrient excess to the cell. Glucose uptake, cell growth, and proliferation along with angiogenesis are activated and increase the risk of oncogenic transformation.[14] It is not surprising that diabetes, known to occur more often in the overweight and obese patient population, is associated with an increased risk of cancer. One particular study observed an increased risk (IR 1.77) for obesity-related cancer in diabetics 5 years prior to their diagnosis of diabetes compared to women in the general population.[15] In addition, obesity can lead to a chronic inflammatory process in both visceral and subcutaneous tissues secondary to an influx of proinflammatory cytokines and high activity levels of aromatase.[16] More specifically, necrotic adipocytes become surrounded by macrophages which form crown-like structures that in turn activate mediators such as TNF-alpha, IL-1 beta, and Cox-2. It is postulated that the resultant increased estrogen synthesis leads to carcinogenesis, specifically in the development of ER-positive breast cancer.[17]

Weight loss is a key intervention with strong data supporting a reduced cancer risk, especially in endometrial cancer. Recent data demonstrated a significantly lower endometrial cancer risk in women who lost weight (HR 0.71), with the strongest association found among women with intentional weight loss (HR 0.44). Conversely, a weight gain of greater than 10 pounds was correlated with a higher risk of endometrial cancer than those women with stable weight.[18] Bariatric surgery has been demonstrated to reduce the risk of developing a uterine malignancy by 71% with an 81% reduced risk if normal weight is maintained following surgery in one retrospective cohort study.[19]

Research in breast cancer has also identified a relationship between cancer development and obesity in postmenopausal women. Chlebowski et al. identified 61,335 postmenopausal women of whom approximately 3000 developed invasive breast cancer during an average follow up of 11.4 years. Of this sample size, 34% were overweight and 25% were obese. In these women, magnitude of weight loss was directly related to reduction of risk of breast cancer. Weight loss of $>$5% resulted in 12% lower risk and weight loss of $>$15% in a 37% risk reduction compared to those who maintained a stable weight.[20] Maintaining a healthy diet with a moderate amount of physical activity is of key importance, and may in turn affect prognosis for women diagnosed with a gynecologic or breast cancer. In a large randomized-control study, obese women with history of breast cancer assigned to a low-fat diet had an increased disease-free survival after 5 years.[21] The evidence for increased cancer risk with obesity, particularly when associated with inactivity, and poorer prognosis when diagnosed is strong. Therefore, weight loss by medical or surgical management, such as supervised or structured diet and/or bariatric intervention, in conjunction with exercise can be major determinants in cancer risk reduction and improved outcomes which represents an important strategy in maintaining health.

Of significant concern is the delay in diagnosis for obese patients, specifically seen in the breast literature. In one study, obese women were found to have more than a 20% increased risk of having false-positive mammography results compared to underweight or women with normal weight, related to limitations in image clarity and thicker volumes of breast tissue. In addition, women with larger breasts have been found to be less able to palpate breast abnormalities, increasing the likelihood of more advanced stage of disease at time of diagnosis. Secondary to the high costs and anxiety associated with additional unnecessary testing, obese women tend to

delay or avoid breast cancer screening altogether in comparison to the nonobese population. All of these factors can result in delay in care and higher stage disease at diagnosis.[22,23]

Obese patients with malignancy may have a poorer prognosis. A prospective mortality study by Calle et al. evaluated outcomes for 900,000 patients and found that morbid obesity was associated with a 1.62 RR of death from any cancer in comparison to the reference group of patients with a normal BMI. Negative trends in mortality were also noted for colorectal, liver, gallbladder, pancreatic, breast, endometrial, cervical, and ovarian cancers. Endometrial cancer was found to have the highest risk of mortality with a RR of 6.25 for women with a BMI of 40 kg/m^2 vs 1.50, 2.53, and 2.77 for BMI subgroups of overweight, low and moderate risk obesity, respectively (low risk defined as BMI 30-34.9 kg/m^2 and moderate risk 35-39.9 kg/m^2).[24] Further, a higher prediagnosis BMI was found to be significantly associated with poorer cancer-specific and overall survival in patients with endometrial cancer in the National Institutes of Health-AARP Diet and Health Study.[25] Despite less evidence of a link between obesity and cervical cancer risk, one case control study identified a positive correlation between obesity and the risk of cervical adenocarcinoma as well as a higher disease stage at diagnosis compared to women with squamous cell cervical cancer.[26]

Therapeutic interventions for malignancies include surgery, chemotherapy, including biologic agents, and radiation. Obese patients have an increased risk of morbidity as well as obvious technical difficulties of surgical intervention, such as prolonged intubation as well as difficulties with anesthesia. Analysis of the Gynecologic Oncology prospective randomized-controlled trial (GOG LAP2) of surgical treatment of endometrial cancer demonstrated that complications related to surgical staging were found to be increased by BMI for any grade >2 adverse event, with wound infection being predominant. Venous thrombophlebitis and lengthier hospital stay were also associated with obesity (BMI > 40 kg/m^2 as compared to normal BMI <25 kg/m^2).[27] Treatment planning including chemotherapy dosing and radiation therapy delivery have also been proven to be a challenge with this patient population, resulting in unnecessary reductions and possible worsened clinical outcomes. A systematic literature review demonstrated that 40% of obese patients received limited chemotherapy doses which were not based on actual body weight secondary to concerns for toxicity and overdosing. Chemotherapy dosing based on a patient's actual body weight has been found to be safe in obese patients. Higher mortality rates and poorer outcomes have been observed in those who have received dose reductions. Even in the circumstance of dose reduction used as a response to toxicity, full weight-based doses should be considered for subsequent cycles if the etiology for toxicity is identified and resolved.[28] The results of this study encouraged practitioners to use full-weight dosing for obese patients secondary to a lack of evidence of worsened toxicities. Delivery of radiation therapy may also prove to be technically difficult in the obese population. A BMI of >30 kg/m^2 has been found to have a significant impact on the rate of malpositioning during radiation treatments as well as margin of positioning errors. As with underdosing of chemotherapy, reduced delivery of fractions to targets also can lead to poorer outcomes. Bigger margins for planned target volumes are needed during planning to effect best clinical outcome.[29]

Lastly, obesity is associated with increased risk of medical comorbidities. Collaborative analysis by Whitlock et al. evaluated 57 prospective studies. Cause-specific mortality was increased for every 5 kg/m^2 increase over 25 in BMI. Specifically, obesity was associated with an HR of 1.39 for development of ischemic heart disease and stroke, HR 1.10 for malignancies and 1.20 for respiratory disease.[30] Causes of mortality include but are not limited to hypertension, diabetes, sleep apnea, and breathing difficulties as well as malignancies such as endometrial, breast, colon, kidney, gallbladder, and liver.

Conclusion

In summary, obesity is a significant risk factor for development of some of the most frequently diagnosed malignancies. Numerous studies have demonstrated a clear link between obesity and the increased risk for specific cancers. This specific patient population is at increased

risk of delay in diagnosis, complications related to surgical interventions, challenges in administration of chemotherapy and radiation, and face poorer prognosis. Available data support reduced cancer incidence and mortality for patients who undergo weight reduction either through diet and exercise or bariatric surgery. Early intervention is key, as prognosis can be positively affected by weight loss and proper nutrition. Future studies focusing on the link between obesity and molecular changes related to an increased risk of developing cancer may be able to identify those at highest risk and offer additional strategies to mitigate this risk. The providers should continue to educate patients on the health hazards of obesity, specifically including increased risk of cancer, and encourage them to participate in a structured weight loss plan. However, these efforts will not be successful without the cooperation of the public, who should not only be aware of relationship between obesity and cancer but should make every effort to follow national guidelines on diet and exercise.

Disclosures

Nothing to disclose.

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