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Review article

The association between obesity and gynecological cancer

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ABSTRACT

Obesity is a growing problem and has significant implications for a variety of diseases, including human cancers. A positive association between obesity and incidence of many gynecological cancers, including endometrial cancer, ovarian cancer, and breast cancer has been observed. The mechanism proposed to connect obesity and these cancers was sex hormone, insulin resistance, and certain adipokines. Obesity adversely affects survival in most studies. For endometrial cancer, the obesity was associated with increased risk and unfavorable outcome. With regard to ovarian cancer and cervical cancer, the evidence was inconsistent. The positive association between obesity and the risk of postmenopausal breast cancer has been consistently observed but it is not the same story in premenopausal breast cancer. But the prognosis for both pre- and postmenopausal breast cancer was substantially worse among obese than normal-weight individuals. In this article, we review the current evidence linking obesity with risk and outcome of gynecological cancers.

Introduction

Currently, obesity has become a major public issue in most developed and developing countries. Overweight and obesity have been known to be associated with the risk of cardiovascular disease and type 2 diabetes mellitus. More recently an epidemiological connection between obesity and the prevalence of a variety of cancers has been revealed. A body mass index (BMI) > 30 is associated with increased risk for many female cancers, including endometrial, gallbladder, esophageal, renal, leukemia, thyroid, and breast cancers.[1] Obesity also increases cancer-related morbidity and mortality. In esophageal cancer, the increased risk may be associated with the increase of acid reflux from obesity leading to chronic local inflammation, Barrett's, esophagus, and eventually adenocarcinoma.[2] Colon cancer has been known to associate with high caloric intake and low fiber diet. The energy balance and BMI are intricately connected with diet content.[3,4] There is increasing awareness of the effect obesity also may have on cancer, as new evidence suggests that overeating along with obesity may be the largest preventable causes of cancer among nonsmokers and may account for one in five cancer deaths among women.[5] A higher BMI leads to a worse outcome in cancer patients. Women with obesity may have shorter survival secondary to delay in cancer screening or suboptimal dosage of chemotherapy.[6,7] Several mechanisms have been proposed to link the association between obesity and cancer promotion including insulin resistance, estrogen, adiposity, and low-grade chronic inflammation.[8] Here we review the literature to identify the effect of obesity on several gynecologic cancers.

Obesity and endometrial cancer

Incidence rates of endometrial cancer are much higher in Western countries than in Asia or rural Africa.[9] The evolution of the industrial development and migration from low- to high-risk areas has shown that endometrial cancer has strong environmental or nongenetic risk factors. Several risk factors have been proposed, including postmenopausal unopposed estrogen use, nulliparity, diabetes mellitus, and obesity. Obesity has been estimated to account for up to 40% of endometrial cancer incidence in developed countries.[10] The interaction between obesity, estrogen, insulin resistance, and carcinogenesis has been extensively investigated (Figure 1). Adipose tissue converts androstenedione to estrone and is a major source of circulating estrogen in postmenopausal women. From the perspective of histological and molecular pathology, at least two major subtypes of endometrial cancer can be defined. Type I cancers are categorized as endometrioid carcinoma, which represent up to 80% of endometrial cancers and are usually

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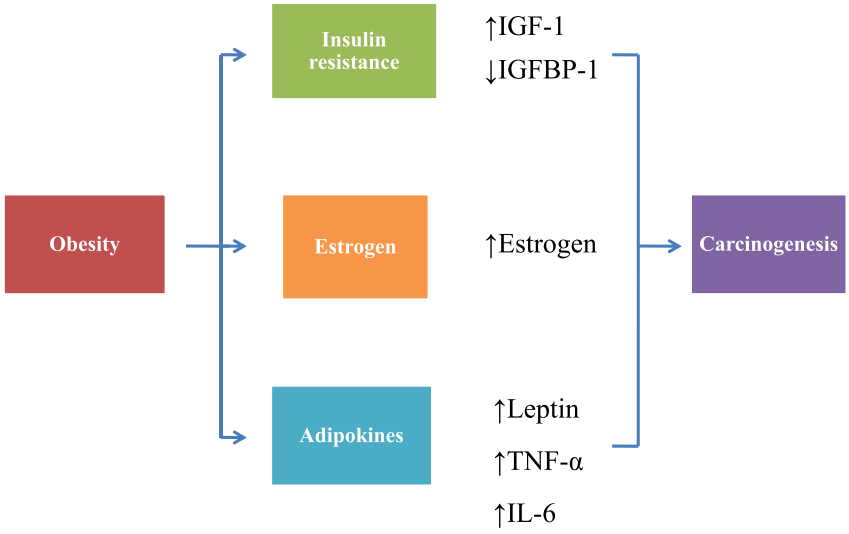

Figure 1. The interaction between obesity and carcinogenesis.

associated with endometrial hyperplasia.[11,12] Type II cancers are serous papillary, clear cell, or squamous cell subtypes and often result from atrophic endometrial tissue in older women.[13] There is some evidence that endocrine and nutritional lifestyle factors, including obesity, influence the risk of type I, but not of type II cancers.[11,12]

Excess weight is associated with insulin resistance, which leads to type II diabetes mellitus. In the insulin-resistant state, elevated plasma insulin develops even during fasting. Insulin resistance induced by overweight leads to a state of increased plasma concentration of fatty acids, which are released from adipose tissue. The increase of free fatty acids leads to limitation of glucose absorption of liver and muscle for energy metabolism. These cascading processes include a reduction of insulin receptor levels and postreceptor defects in insulin signaling.[14] Insulin resistance and aberrant elevation of plasma insulin levels, in turn, lead to various effects on the insulin growth factor (IGF) and insulin growth factor-binding protein (IGFBP) system. These include decreases in the hepatic production and plasma levels of IGFBP-1 and IGFBP-2, and a rise in plasma levels of free IGF-I. Plasma free IGF-I correlates directly with BMI and levels of insulin, and inversely with levels and IGFBP-1 and IGFBP-2.[15] Epidemiological studies have shown an increased risk of endometrial cancer in both pre- and postmenopausal women with noninsulin-dependent diabetes. One large case–control study disclosed that endometrial cancer risk to be associated with serum level of C-peptide a marker of pancreatic insulin secretion.[16] Several mechanisms have been proposed to link the elevated insulin and endometrial cancer development. Insulin can act as a growth factor and tumor tissues including endometrial tumors, generally have an increased level of IGF-I receptors.[17] Furthermore, insulin can increase IGF-I activity in endometrial tissue by suppressing gene expression of endometrial IGFBP-1.[18] Finally, insulin is also a major regulator of the sex hormone binding globulin (SHBG). Downregulating SHBG level is a direct determinant of bioavailable E2 unbound to SHBG.[19] In a rat model of hyperinsulinemia, estrogen induced higher expression of the proliferative genes, including *cyclin A* and *c-myc*, in endometrium of obese rats, as compared with in lean ones.[20] Adipose tissue has been considered as a complex endocrine organ because it secretes both anti- and proinflammatory factors classified as adipokines. Tumor necrosis factor alpha (TNF-alpha), one of the important adipokines, disrupts insulin receptor signaling by inducing the inhibitory phosphorylation of insulin receptor substrate (IRS) proteins.[21]

The effect of obesity on endometrial cancer survival is not yet well defined. Higher prediagnosis BMI was significantly associated with poorer cancer-specific and overall survival in patients with endometrial cancer reported from the result of the National Institutes of Health-AARP Diet and Health Study.[22] In a small study of 147 women with primary treatment of endometrial cancer in Mexico, obese women had the same survival as normal or underweight women.[23] In the endometrial cancer study of Women's Health Initiative, no association has been observed between BMI and disease stage or grade.[24] Regarding the surgical outcome and perioperative complications, obese patients have longer surgical time, but intraoperative and overall postoperative complication rates do not differ among different BMI.[25,26] For women who are moderately or severely obese receiving adjuvant radiotherapy for endometrial cancer, a wider planning target margin is required to reduce the magnitude of setup error.[27] Furthermore, 4-year cancer-specific survival in obese women (BMI $\geq$30 kg/m^2) was 10% higher than all-cause deaths, compared with 6% in nonobese women.[28]

Obesity and cervical cancer

The incidence of and mortality from cervical cancer have decreased with the advent of the Papanicolaou test for cervical cancer screening.[29] It has been found that many cytokines and chemokines play important roles in stimulating immune system to regulate cervical carcinoma and integrate as a part of potential cancer therapy.[30] However, obese women in the United States were reported to have a higher mortality from cervical cancer.[5] A meta-analysis review suggested that obese women were less likely to report being screened for cervical cancer than their lean counterparts. Less screening may partly explain the higher cervical cancer mortality seen in obese white women.[31] Cervical adenocarcinoma was found to be strongly associated with obesity rather than squamous cell carcinoma. This finding implied that obesity may have a particular influence on the risk of glandular cervical carcinoma.[32] Few data are available regarding treatment outcome of patients with cervical cancer and obesity. For 404 women with cervical cancer underwent definitive chemoradiation therapy,

underweight patients (BMI < 18.5 kg/m^2) with local advanced cervical cancer had diminished overall survival and more complications that normal weight and obese patients.[33] Many gynecologic oncologists believed that obese women are often poor candidates for radical surgery, not only the perception of a more difficult surgical technique but also associated with increased rate of intra- and postoperative complications. One study regarding completion surgery after concurrent chemoradiation in obese women with local advanced cervical cancer, the survival benefit in individuals with different BMIs was uncertain.[34] In addition, the survival benefit was not compromised in patients with obesity and cervical cancer treated with radical hysterectomy. The surgery in obese patients was associated with longer duration of surgery and greater blood loss.[35,36] Without adequate evidence, obesity is not a negative prognostic factor in women with cervical cancer who underwent surgery.

Obesity and ovarian cancer

Ovarian cancer is a highly fatal disease, with only 40% of women with ovarian cancer alive >5 years after diagnosis. One of the reasons contributing to the poor prognosis of ovarian cancer is that approximately 75% of patients with ovarian cancer receive a diagnosis of metastatic spread beyond the pelvis.[37] The rationale for increased risk of ovarian cancer in women with obesity focuses on the hormonal effect of obesity. In 2001, the International Agency for Research on Cancer group found that the "evidence from the relatively few studies has been inconsistent and does not allow any conclusion to be drawn on a possible association".[38] However, a 30% increased risk of ovarian cancer in obese women (BMI of >30 kg/m^2) has been reported from a meta-analysis. It has been hypothesized that in menopausal women, adiposity enhances ovarian cancer risk partly through the mitogenic effects of excess endogenous estrogen synthesized in the adipose tissue.[39] Among different histological subtypes of ovarian cancer, obesity was positively associated with clear cell tumors, but less correlated with invasive endometrioid or mucinous tumors.[40] Few studies focused on the association between obesity and ovarian cancer survival provided conflicting results. A recent meta-analysis found that women with ovarian cancer with obesity during early adulthood or before diagnosis had worse survival.[41] However, the effect of obesity on surgical morbidity in primary ovarian cancer after optimal primary tumor debulking remains controversial. Either peri- or postoperative morbidity was not affected by BMI.[42,43] However, in patients with ovarian cancer treated with carboplatin-based chemotherapy, the carboplatin dosing is traditionally based on the Jelliffe formula, which lacks dose adjustment for weight. Women with obesity experienced a lower relative decrease in their platelet counts and hemoglobin levels. There was a trend toward increased risk for disease progression in women with a BMI $\geq$ 30.[44]

Obesity and breast cancer

There is growing evidence to link between obesity and breast cancer. For postmenopausal women, prospective cohort studies have associated increasing BMI with increasing breast cancer incidence in postmenopausal women, especially in those with hormone-positive breast cancer.[45] Regarding the influence of obesity and hormone replacement therapy on mammary carcinogenesis, the strength of estrogenic risk attenuated by obesity is stronger than with hormone replacement therapy. A review analysis showed that hormone replacement therapy does not increase the risk of breast cancer in postmenopausal women with obesity [relative risk (RR) 1.02 for BMI > 25 kg/m^2], though it is a significant risk for breast cancer in women of normal weight (RR 1.73).[46–48] By contrast, studies of obesity and premenopausal breast cancer have had conflicting results. Both prospective cohort and case–control studies in premenopausal women consistently report a modest decreased risk of breast cancer in women with obesity compared with women of normal weight, but with similar risks for women with obesity and those of normal weight.[49,50] However, a positive association between increased BMI and premenopausal breast cancer was found only in the Asia-Pacific population.[1] There is a substantial body of research showing that obesity is a risk factor for breast cancer recurrence and poor survival. A meta-analysis estimated overweight or obese was associated with a 78–91% increased risk of recurrence and a 36–56% increased risk of death in women with breast cancer. A detailed review by Chlebowski et al[51] concluded that a significant association between being obese and increased recurrence or mortality was seen in 26 of 40 studies including 29,460 women with breast cancer.[51] The effect of obesity on clinical presentation and detection was investigated by a retrospective review. It was disclosed that women with obesity that is clinically present at an older age with mammographically detected breast cancer at more advance stages than women without obesity.[52] In recent case–case analyses within a large consortium, obesity was more frequent with hormone receptor negative than hormone receptor positive disease in women younger than 50 years, but was more frequent only with progesterone receptor-positive tumor in older women.[53] Triple-negative breast cancer is a subtype of breast tumor with unique characteristics in terms of clinical-pathological presentation, response to therapy, and poor outcome. By a case–case comparison from a systemic review, a significant association between triple-negative breast cancer and obesity was identified (odds ratio: 1.20; 95% confidence interval: 1.03–1.40).[54]

Several studies have investigated the interactions between obesity and adjuvant therapy effectiveness. A National Surgical Adjuvant Breast and Bowel Project analysis of 3385 clinical trial patients from a randomized, placebo-controlled trial evaluating tamoxifen for lymph node-negative, estrogen receptor-positive breast cancer showed that women with obesity had greater all-cause mortality and increased risk of contralateral breast cancer compared with women of normal weight.[55] Chemotherapy is one of the important treatments in breast cancer patients to improve survival. From a retrospective review of 735 patients with stages II and III primary breast cancer, patients with obesity tended to have a higher risk of disease recurrence after receiving adjuvant chemotherapy.[56] However, in metastatic breast cancer, BMI was not associated with outcome of patients treated with first-line chemotherapy from a recent retrospective trial report.[57]

Conclusion

Obesity has become an emerging challenge in human diseases including malignancy. However, it is not surprising that in no circumstance was obesity found to exert a positive benefit. With increasing evidence of the effect of obesity in gynecological malignancy, the better approach to prevent and manage obesity-related gynecological malignancy should be addressed in the future.

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