Chapter

Obesity and Endometrial Cancer

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Abstract

Obesity is a very common health problem in almost all societies. Although obesity is a problem especially in high-income or upper-middle-income countries, it is predicted that obesity will increase rapidly in the future in developing countries. Excess body weight is associated with an increased risk for many malignancies and its impact on cancer incidence and mortality is well established. The role of obesity in the pathogenesis of endometrial cancer has been proved. The incidence of endometrial cancer is increasing due to an increasing prevalence of obesity. Approximately 57% of endometrial cancers in the United States are thought to be attributable to being overweight and obese. The mechanisms underlying the relationship between obesity and endometrial cancer have not been fully defined, however adipokines are known to stimulate cell proliferation in endometrial carcinoma. By preventing obesity and reducing its prevalence, deaths from endometrial cancer can be reduced.

Keywords: endometrial cancer, obesity, global epidemic, prevention

1. Introduction

Obesity is a very common health problem in almost all societies. Although obesity is a problem especially in high-income or upper-middle-income countries, it is predicted that obesity will increase rapidly in the future in developing countries. The worldwide prevalence of obesity has more than doubled among women and tripled among men over the past four decades [1]. Excess body weight is associated with an increased risk for many malignancies and its impact on cancer incidence and mortality is well established [2]. This makes obesity an important public health problem. Despite clear evidence linking endometrial cancer and obesity, public awareness is poor [3, 4]. Weight, weight gain, and obesity account for about 20% of all cancer cases. Although the role of obesity in the pathogenesis of endometrial cancer has been proved, its importance in the esophagus, thyroid, colon, kidney, liver, melanoma, multiple myeloma, rectum, gallbladder, leukemia, lymphoma, and prostate in men and breast cancer in postmenopausal women is also demonstrated [5, 6].

Endometrial cancer is the most common female genital tract malignancy in high-income countries and the second most common gynecological cancer in low-middle-income countries. Endometrial carcinoma is a histological diagnosis based on characteristic findings in an endometrial biopsy, curettage, or hysterectomy specimen. A woman's lifetime risk of endometrial cancer in the general population is 3%. The incidence peaks between the ages of 60 and 70, but less than 5% of cases emerge before age of 40. The incidence of endometrial cancer is increasing due to an increasing prevalence of obesity, decreased use of menopausal hormone therapy with progestins, increased prevalence of diabetes, and changes in reproductive behavior (eg, nulliparity) [7, 8]. Most patients are diagnosed at an early

stage and therefore have a five-year survival rate of more than 90%. Unfortunately, approximately 30% of women have stage III or IV disease, with 5-year survival rates significantly worse than in early-stage patients, 60% and 20%, respectively [9].

The primary complaint is abnormal uterine bleeding in 70% to 90% of endometrial carcinoma cases [10]. Premenopausal patients with abnormal uterine bleeding have a lower risk of cancer than postmenopausal women with the same complaint. In patients younger than 45 years of age, abnormal uterine bleeding tends to be persistent and is more likely to occur if there is a history of unopposed estrogen exposure (eg. obesity, chronic anovulation). The emergence of endometrial carcinoma in postmenopausal women requires evaluation of endogenous and exogenous estrogen sources because unopposed estrogen (estrogen therapy, obesity, selective estrogenic receptor modulators, some herbs, sex cord-stromal tumors) is a risk factor for the disease.

Endometrial carcinoma is sometimes discovered incidentally when a hysterectomy is performed for benign disease. To minimize this coincidence and optimize the surgical procedure performed, patients with abnormal uterine bleeding should always undergo endometrial sampling before performing a hysterectomy, and the results should be evaluated to determine the extent of surgery before the operation. Occult uterine cancer risk is significantly associated with race/ethnicity, obesity, comorbidity, personal history of malignancy, and cause of hysterectomy [11].

Typically, a pelvic examination is usually normal in patients with early-stage endometrial carcinoma. In women with more advanced disease, the uterus can be palpated as larger and fixed for the age of the patient. With blind endometrial sampling, the sensitivity is 90% or higher. History of colorectal cancer, endometrial polyps, and morbid obesity are risk factors for false-negative endometrial sampling [12]. In case of high clinical suspicion, hysteroscopy and targeted lesion-directed biopsy can be performed to reduce the false-negative rate. It is important to repeat endometrial sampling to exclude endometrial hyperplasia or carcinoma, especially in patients with risk factors for malignancy (eg. obesity, chronic anovulation).

More than 90% of uterine cancers originate from the endometrium, with most of the remainder originating from the myometrial muscle or less frequently from the endometrial stroma [13]. Adenocarcinoma of the endometrium is the most common histological type. The prognosis of endometrial carcinoma is primarily determined by the stage, grade, and histology of the disease. Most patients have a favorable prognosis as the majority of the histological type is the endometrioid type and presents with early-stage disease. Serous and clear cell types and other uterine cancers are associated with poor prognosis. Most women with low-risk endometrial cancer die from another cause, and cardiovascular disease is the leading cause of death among endometrial cancer patients [14]. The endometrioid type is the subtype predominantly associated with obesity; however, more aggressive subtypes (such as serous, clear cell, and carcinosarcoma) have recently been stated to increase with obesity [15].

Endometrial carcinomas are divided into two categories that differ in incidence, response to hormones, clinicopathological features, and risk factors [16, 17]. However, this approach does not adequately address the complexity of these neoplasms. Because 25% of high-grade endometrioid carcinomas progress like serous carcinomas [18].

Type 1: It accounts for about 80 percent of endometrial carcinomas. Includes tumors with grade 1 or 2 endometrioid histology; It may result from intraepithelial neoplasm (atypical and/or complex endometrial hyperplasia), typically has a favorable prognosis, is estrogen-induced, and responsive to progestins on therapy. While estrogen excess is important in its etiology, unexposure to progesterone is probably equally important. The increasing prevalence of obesity, decreased use of menopausal hormone therapy with progestins, and decreased propensity to delivery in women explain the increasing prevalence of type 1 endometrial carcinoma.

Type 2: Accounts for 10 to 20 percent of endometrial carcinomas. Includes grade 3 endometrioid tumors as well as histological types of non-endometrioid types: serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated. These patients generally have lower body mass indexes and are older than type 1 patients. These neoplasms are insensitive to estrogen, often occur in the atrophic endometrium, and have a poor prognosis. The reason for the increased incidence of type 2 neoplasms is unknown.

The Cancer Genome Atlas (TCGA) Research Network has significantly improved our understanding of the molecular level of endometrial cancer and introduced not two but four molecular subtypes [18];

1. POLE (ultra mutated) tumors,

2. Microsatellite unstable tumors,

3. Tumors with high copy number, mostly with TP53 mutations,

4. The group remaining without these changes.

2. Risk factors for endometrial cancer

The main risk factor for type I (endometrioid) endometrial carcinoma is an excess of endogenous or exogenous estrogen that is not adequately opposed with progestin [19]. In a woman with a uterus, oral, transdermal, and vaginal systemic estrogen therapy without the administration of progestin results in a marked increased risk of developing endometrial premalignant lesions and endometrial carcinoma. Unopposed estrogen increases the risk of endometrial cancer by 2–10 times [20]. Studies have reported an increased risk of endometrial cancer in patients using estrogen alone, depending on the dose and duration of use [21–23]. The risk of endometrial cancer in postmenopausal patients is estimated to be approximately 1 in 1000; therefore, studies have shown that patients receiving unopposed estrogen have an increased absolute risk of up to 1 in 100 [24]. Other risk factors include tamoxifen therapy, chronic anovulation, obesity, nulliparity, early menarche, late menopause, ovarian granulosa cell tumor, Cowden syndrome, having a first-degree relative with endometrial cancer, history of pelvic radiotherapy, diabetes mellitus and hypertension, and Lynch syndrome. A history of breast cancer is a risk factor for the development of endometrial cancer, partly because of the use of tamoxifen in the treatment of breast cancer, the increased risk of breast cancer in conditions such as obesity, and Cowden syndrome. As patients with hypertension and diabetes mellitus are generally obese, much of the risk these two comorbid conditions have in developing endometrial cancer may be attributable to obesity [25]. However, there are also studies stating that each has an independent risk factor [26, 27].

3. Obesity

Obesity is a chronic disease that is considered a global epidemic today. Obesity is defined by the World Health Organization (WHO) as excessive accumulation of fat in the body to the extent that it impairs health. According to WHO estimates, 39% of adults worldwide were overweight and 13% were obese in 2016. Obesity is defined as an excess weight rather than excess fat, as it is impractical to determine body fat percentage. Based on the body mass index (BMI) of the

definition and grading of obesity, it is evaluated with the formula (BMI=Weight (kg)/Height (m^2)). BMI provides a better estimate of total body fat compared to bodyweight alone [28]. According to the World Health Organization (WHO) standards, someone with a body mass index (BMI) >30 kg/m^2 is classified as obese. Obesity classification according to body mass index in adults is demostrated in **Table 1** [29–31]. According to the World Food Security and Nutrition Status 2019, obesity rates are increasing day by day in almost every country and the global adult obesity rate has reached 13.2% [32]. Today, overweight and obesity are considered to increase the overall health burden more than smoking. Obesity is associated with a significant increase in morbidity (including diabetes mellitus, hypertension, dyslipidemia, cardiovascular diseases, cerebrovascular accident, sleep apnea, and cancer) and mortality [33]. Weight loss reduces obesity-related morbidity. Due to the potential stigma risk of obesity, routine screening, diagnosis, and management are rare, and there is insufficient awareness of the health problems caused by obesity in the population.

The type of obesity with increased waist circumference or waist/hip ratio is called central (abdominal, visceral, android, or male-type obesity) obesity. According to WHO, a waist circumference of 88 cm or more in women and 102 cm or more in men indicates the presence of central obesity. Patients with central obesity have higher mortality rates [34] because these patients are at high risk for heart disease, diabetes, hypertension, dyslipidemia, and non-alcoholic fatty liver disease [34, 35]. Central obesity is a component of metabolic syndrome. The association of metabolic syndrome with endometrial cancer has also been reported [36, 37]. However, there is no data to suggest that outcomes can be improved with more effective management of associated medical conditions. In the Prospective Studies Collaboration analysis, in the upper BMI range (25 to 50 kg/m^2), every 5 kg/m^2 increase in BMI is associated with coronary heart disease (CHD), stroke, diabetes, chronic kidney disease, and cancer (liver, kidney, breast, endometrial, prostate and colon) have been demonstrated to result in a significant increase in deaths [38].

Most cases of obesity are related to behaviors such as a sedentary lifestyle and increased calorie intake. Obesity develops with excessive fat accumulation in the body secondary to high energy intake. Energy homeostasis is impaired due to an increase in energy intake or a decrease in energy expenditure [39]. Interactions between genetic/epigenetic factors and behavioral/social factors and chronic stress regulate energy balance. High-calorie diet, physical inactivity, sedentary lifestyle, and in addition, eating disorders accelerate the development of obesity. In addition, hypertrophy, hyperplasia and inflammation in adipocytes cause many changes in the structure of adipose tissue and the secretion of adipokines such as leptin, interleukin-6, and

Underweight	BMI <18.5 kg/m^2
Normal weight	BMI ≥18.5 to 24.9 kg/m^2
Overweight	BMI ≥25 to 29.9 kg/m^2
Obesity	BMI ≥30 kg/m^2
Obesity class 1	BMI 30 to 34.9 kg/m^2
Obesity class 2	BMI 35 to 39.9 kg/m^2
Obesity class 3	BMI ≥40 kg/m^2 (also referred to as severe, extreme, or massive obesity)

BMI, body mass index.

Table 1.
Classification of body mass index.

tumor necrosis factor-a. With the increasing prevalence of obesity, there is a growing awareness of its impact on cancers. Obesity has been defined as a risk factor affecting the severity of the disease and mortality in people with cancer.

4. The relationship between endometrial cancer and obesity

Obesity is known to increase the risk of endometrial cancer in women [40, 41]. Approximately 57% of endometrial cancers in the United States are thought to be attributable to being overweight and obese. The incidence of endometrial cancer increases as body mass index (BMI) increases [42]. More importantly, obesity and overweight can increase the likelihood of dying from cancer. A review of the literature states that most of the associations between adiposity indices and endometrial cancer are supported by strong or highly suggestive evidence. A review (IARC) from a comprehensive meta-analysis of weight, physical activity, and cancer incidence by the International Agency for Research on Cancer demonstrated that it is the cause of 39% of endometrial cancer cases [43].

The cause and effect relationship between obesity and endometrial cancer can be explained by 3 mechanisms; first; in obese patients, the adrenal glands secrete more androgen precursors for conversion to estrogen in peripheral tissues. An androgen, androstenedione, (A) is converted to estrone (E1) mainly in peripheral adipose tissue, and this conversion is increased in adipose tissue of obese patients. Plasma SHBG levels that bind estradiol (E2) are reduced in obese subjects and therefore higher-than-normal amounts of serum estradiol are present in the circulation, thereby increasing the estrogenic stimulus in target tissues [44]. Proinflammatory cytokines such as tumor necrosis factor-a in obesity are associated with low plasma SHBG levels [45]. Obese patients also have changes in the concentration of insulin-like growth factors and their binding proteins and insulin resistance, all of which may contribute to an increased risk of endometrial cancer in these patients [46]. The triad of obesity, insulin resistance, and adipokine aberrations is linked to cancer [47], since adipokines impair insulin signaling and contribute to insulin resistance [48]. Other mechanisms in pathophysiology are subclinical chronic low-grade inflammation, oxidative stress, and sex hormone biosynthesis [6]. Adipokine-mediated chronic inflammation and cellular stress cause genetic instability and DNA damage [42]. All of these mechanisms lead to endometrial hyperplasia and cancer. Despite all these conditions, obese patients who do not have metabolic problems seem to have an increased risk of endometrial cancer [49].

The mechanisms underlying the relationship between obesity and endometrial cancer have not been fully defined. However, estrogens and proinflammatory adipokines are known to stimulate cell proliferation in endometrial carcinoma. In addition to stimulating cell proliferation, estrogen also has mutagenic properties. Genotoxic metabolites of estrogen react with DNA and contribute to DNA breaks and genetic instability [50]. Although the role of estrogen metabolites in the pathogenesis of breast cancer is well defined, their role in the context of endometrial cancer has not been fully understood. However, defects in DNA mismatch repair genes were detected in one-third of endometrial cancer cases. Visceral fat is a complex endocrine organ composed of adipocytes, preadipocytes, macrophages, stromal, nerve, and stem cells [42]. Adipokines secreted by these cells increase endometrial proliferation and promote tumor formation [51], even mesenchymal stem cells support tumor growth and progression [52, 53].

Cyclic secretion of ovarian estrogen and estrogen-induced cyclic secretion of insulin-like growth factor 1 (IGF1) in premenopausal women stimulates endometrial proliferation [54, 55]. In postmenopausal women, especially adipose tissue

is the main site of estrogen synthesis [56]. Aromatase enzyme, which provides estrogen synthesis from androgens, is mainly found in adipose tissue [57]. As body adiposity increases, the amount and activity of aromatase increases [58]. Steroid hormone synthesis from cholesterol and estrogen synthesis from androgens by aromatase enzyme is shown in **Figure 1**.

In a pooled analysis of individual patient data from 10 cohort and 14 case–control studies, including more than 14,000 endometrial cancer cases and more than 35,000 controls, for type I endometrial cancer, by body mass index (BMI): overweight (BMI) 25.0 to <30.0 kg/m^2) OR 1.5, OR 2.5 (30.0 to <35.0 kg/m^2) for class 1 obesity, OR 4.5 for class 2 obesity (35.0 to 39.9 kg/m^2) and calculated as 7.1 for class 3 obesity (≥40.0 kg/m^2). For type 2 endometrial cancer, the ORs were calculated as 1.2 for overweight, 1.7 for class 1 obesity, 2.2 for class 2 obesity, and 3.1 for class 3 obesity [59]. Higher BMI is associated with the development of endometrial cancer at a younger age (<45 years old) [60]. In another meta-analysis, body mass index and waist-to-hip ratio were associated with increased cancer risk in premenopausal women (RR 1.49 per 5 kg/m^2; CI 1.39–1.61) and for total endometrial cancer (RR 1.21 per 0.1 unit; CI 1.13–1.29), respectively [61].

Severely obese patients (BMI ≥40 kg/m^2) who develop endometrial cancer are more likely to have a less aggressive histological subtype (endometrioid 87% vs. serous or clear cell 75%) compared to patients with BMI <30 kg/m^2 [62]. Therefore, patients with severe obesity are more likely to present with stage I disease (77 versus 61%) or low-grade histology (44% vs. 24%), but severe obesity is associated with an increased risk of death in endometrial cancer patients [63, 64]. After being diagnosed with endometrial cancer, being obese indicates worse outcomes. Obesity has a negative effect on all-cause mortality. A retrospective study found that morbidly obese women with early-stage disease had higher mortality rates compared with women with a normal body mass index, accounting for 67% of these deaths. It has been determined that there are obesity-related causes unrelated to cancer [65]. Increased mortality may be due to sustained stimulation of metastatic cells by endogenous estrogen or may result from obesity-related conditions such as diabetes or cardiovascular disease [66, 67].

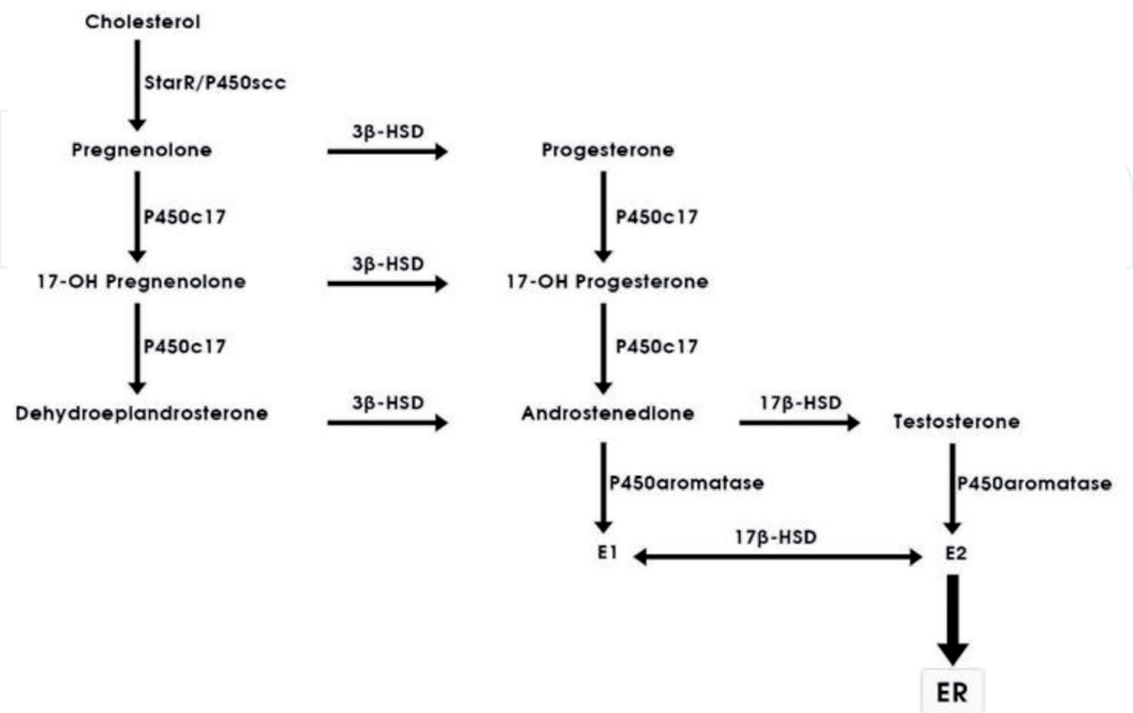

Figure 1.
Steroid hormone synthesis.

After obese women are diagnosed with endometrial cancer, clinical management strategies can be complex. As the operations of obese patients are technically more difficult it takes a longer time than normal-weight individuals. Since these patients also have many co-morbid medical problems, both perioperative and postoperative complication rates are increased. Even though the patients have early-stage cancer, they may not be able to be operated on due to concomitant systemic diseases such as cardiovascular and diabetes mellitus, and they may have to undergo primary radiotherapy. Robotic surgery may provide an advantage over conventional laparoscopy in such patients [68, 69].

Meta-analyses show that increased physical activity reduces the risk of endometrial cancer [70–72]. Exercise may provide moderate protection against endometrial cancer [73]. Physical activity benefits by reducing obesity and making positive changes in immune function, endogenous sexual and metabolic hormone levels, and growth factors [74]. Losing weight through lifestyle changes such as diet and physical activity or bariatric surgery can reduce obesity. Bariatric surgery has been associated with a 50% to 80% reduction in the occurrence of endometrial cancer in a meta-analysis of controlled trials [75, 76]. Obesity-related hormonal and metabolic disorders and drugs aimed at correcting insulin resistance can also be used as a prevention strategy. Losing weight has health benefits beyond protecting the endometrium. Preventing or treating obesity can provide significant lifelong health benefits. Public health interventions may be beneficial to reduce the incidence of endometrial cancer in the community. Obese patients should receive counseling about health risks, lifestyle changes, obesity treatment options, and risk factor reduction.

5. Conclusion

By preventing obesity and reducing its prevalence, deaths from endometrial cancer can be reduced. Prevention strategies should focus on changing the environmental and lifestyle risk factors that cause endometrial cancer. General lifestyle recommendations include being physically active and maintaining a healthy weight. Healthy weight is considered a risk reducer and has a positive effect on blood pressure, glucose metabolism, cardiac and vascular function. Therefore, reducing obesity reduces morbidity and mortality from endometrial cancer. More public awareness is needed regarding the cause and effect relationship between obesity and endometrial cancer. Public health education including obesity prevention is of great importance.

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