Obesity and Endometrial Cancer: Mechanism and How to Deal with?

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Abstract
Obesity is strongly associated with development of endometrial cancer more than any other cancer type. The relationship between obesity and endometrial cancer risk is combination of inflammation, insulin resistance, and increased bioavailability of estrogen. Obesity can increase risk to develop endometrial cancer as exogenous estrogen has impact for tumorigenesis. The best method to reduce the risk of endometrial cancer in obese women is through progesterone medication and lifestyle intervention.

Keywords: Endometrial cancer, mechanism, obese women, obesity

Introduction
Endometrial cancer is the most common gynecological cancer in developed countries. Worldwide, there were 382,069 new cases and 89,929 deaths attributed to endometrial cancer according to GLOBOCAN in 2018. While more than 90% of endometrial cancers occur in women older than 50 years old, 4% are diagnosed in women younger than 40 years old. Cases in younger women could rise due to improvement of socioeconomic status in developing countries as it will decrease the fertility rate, increase obesity prevalence, and the use of estrogen-based contraception. Among these risk factors, obesity is the more prevalent; it is found in 39% adult over 18 years old.

Obesity is strongly associated with development of endometrial cancer more than any other cancer type. The relationship between obesity and endometrial cancer risk is combination of inflammation, insulin resistance, and increased estrogen bioavailability. Obesity causes macrophage accumulation and increased expression of pro-inflammatory cytokines. Pro-inflammatory cytokines contribute to insulin resistance and increased levels of insulin-like growth factor 1 (IGF-1) leading to promoting tumorigenesis via cell proliferation and reduction in apoptosis. They also increase inflammation and insulin with reduced sex hormone binding globulin (SHBG) which results in increased estrogen bioavailability. Increased estrogen exposure to endometrium results in DNA damage leading to tumorigenesis. Therefore, obesity-induced systemic inflammation, dysregulated hormone signaling, and aberrations in insulin signaling increase endometrial cancer risk.

The association follows a dose-response relationship with increased incidence of endometrial cancer associated with increased body mass index (BMI). American Institute for Cancer Research revealed that every increase of five BMI units would raise 50% risk of developing endometrial cancer (relative risk [RR] 1.50; 95% CI 1.42-1.59). Endometrioid endometrial cancer is the histologic subtype predominantly linked to obesity; while non-endometrioid subtypes such as serous, clear cell, and carcinosarcoma are more aggressive and not linked to increasing BMI.

This article will review the pathway of obesity to endometrial cancer and how to prevent it.

Mechanism Pathway of Obesity to Endometrial Cancer
Visceral fat is a complex endocrine organ consisting of adipocytes, preadipocytes, macrophages, stromal, nerve, and stem cells. They secrete adipokines that have localized and systemic effects to increase endometrial proliferation and promote tumorigenesis. In premenopausal women, cyclic expression of estrogen by ovaries will induce endometrial proliferation. After menopause, several
sites serve as estrogen synthesis, especially adipose tissue. Adipocytes, preadipocytes, and mesenchymal stem cell within fat tissue are believed as source of aromatase which converts androgens to estrogens.\textsuperscript{10,11} Furthermore, sex hormone-binding globulin (SHBG) levels decrease with increasing adiposity, it increases pool of bioactive estrogen in the absence of de novo estrogen synthesis.\textsuperscript{12}

Estrogen will bind to estrogen receptor-\(\alpha\) and/or -\(\beta\), it directly modulates transcription of several proliferative genes such as IGF1R and IGF1. G-protein coupled estrogen receptor 1 (GPER1) mediates ligand-dependent nongenomic signaling to stimulate endometrial proliferation via activation of MAPK and AKT signaling pathways.\textsuperscript{13} Estrogen acts as both mitogen and mutagen. Genotoxic metabolites of estrogen react with DNA to form depurinating adducts, especially producing an accumulation of dsDNA breaks and contributing to genetic instability.\textsuperscript{14} Approximately a third of endometrial cancers demonstrate DNA mismatch repair as a result of somatic methylation of MLH1 or less frequently Lynch syndrome. Localized exposure of endometrium to estrogen metabolites is more likely to produce genetic mutations contributing to tumorigenesis (Figure).\textsuperscript{15,16}

In normal premenstrual endometrium, progesterone counters estrogen-driven proliferation and induces glandular differentiation and decidualization of endometrial stroma. Prolonged progesterone deficiencies promote endometrial proliferation and increase risk of endometrial hyperplasia to cancer. Nulliparity, irregular menses, postmenopausal hormone replacement therapy with unopposed estrogen are associated with increased of endometrial cancer risk.\textsuperscript{17}

Adipose tissue is source of adipokines that regulate metabolism and modulate chronic inflammatory state associated with visceral adiposity. Obesity-associated proinflammatory adipokines such as leptin, interleukin-6, and tumor necrosis factor \(\alpha\), suppress normal insulin signaling and contribute to insulin resistance.\textsuperscript{18} It promotes endometrial proliferation and increases risk of endometrial cancer. In the context of adipokine-mediated chronic inflammation, cellular stress is associated with enhanced genetic instability and DNA damage. Mitochondrial reactive oxygen species produced by inflammatory cells can produce DNA strand breaks. Endometrial tissues with DNA mismatch repair defects are likely to accumulate deleterious genetic mutations, leading to endometrial hyperplasia and cancer.\textsuperscript{4}

**PREVENTION**

As a primary care provider, a physician should be aware and prevent obese patient from endometrial cancer by reducing their mass and correcting their metabolism. Several choices such as lifestyle intervention, medication, and surgical procedures can decrease fat and reverse metabolism derangement associated with obesity and insulin resistance.

**Lifestyle Intervention**

Lifestyle intervention including diet and exercise is the safest and first choice to reduce the risk of endometrial cancer in obese patients. Theoretically, weight reduction, diet modification, and physical activities will decrease circulating estrogen levels, reverse insulin resistance, and decrease regulation of inflammatory markers.\textsuperscript{17}

High BMI and glycemic load diet are correlated with some hormonal metabolism production. High glycemic diet and obesity will induce hyperinsulinemia and an increase expression of pro-inflammatory cytokines. Both contribute to insulin resistance and they will increase IGF-1 bioavailability. IGF-1 is known to promote cell proliferation and reduce cell apoptosis. Increased inflammation and high insulin level will also reduce SHBG production and increase the estrogen bioavailability, estrogen exposure to the endometrial cells will lead to tumorigenesis.\textsuperscript{19} Thus, weight loss by diet and exercise will decrease insulin resistance, lower IGF-1 levels, and increase SHBG production.\textsuperscript{19}

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\textsuperscript{4}Figure. Effects of obesity on endometrial proliferation and tumorigenesis\textsuperscript{4}
Even though it is theoretically promising, there are limited studies evaluating the effect of diet and physical activities to endometrial cancer risks. Some studies showed no evidence of correlation between good quality of diets and the risk of developing endometrial cancer. It also showed no change in endometrial proliferation in post-menopausal obese women.

**Medication**

Progesterone and synthetic progestin had been well known to decrease the risk of endometrial cancer. In post-menopausal women, oral combination hormone replacement therapy reduces the risk of endometrial cancer compared with estrogen only hormone therapy. Continuous combined therapy also provide more protection from endometrial cancer than sequential combined therapy. A meta-analysis also showed that for every 5 year of progestin-based contraceptives use, there was 24% risk reduction of developing endometrial cancer. It is expected to lower estrogen bioavailability in obese individuals, raise progesterone receptor expression in endometrial cancer cells. Therefore, it may amplify the protective risk of progesterone in metformin and progesterone combination therapy.

In practical use, metformin had conflicting result. In diabetic patient with endometrial cancer, it gives better survival rates and recurrence. In a case-control analysis, the use of metformin, sulfonylurea, thiazolidinedione, and insulin was not associated with altered risk of endometrial cancer. A systematic review has confirmed result in proving metformin usefulness due to lack of studies in PCOS patient. A biomarker study proved that metformin may induce minor changes in HbA1C and C-peptide in obese patients but it does not change endometrial proliferation histologically. Further data is needed to support metformin use to reduce endometrial cancer risk.

**Surgical Procedure**

Nowadays, people are difficult to change their diet and lifestyle consistently to promote weight loss. Thus, surgical procedure such as bariatric surgery can help and encourage patient. Bariatric surgery will reduce circulating estrogen levels by removing some adipose tissue, reduce insulin resistance and reduce insulin level, and removing excess adipose tissue will reduce inflammatory proteins. Overall, bariatric surgery could prevent and reduce the risk of developing cancer. In Swedish population study, bariatric surgery could reduce the risk of endometrial cancer (HR 0.56 95% CI 0.35–0.89; p=0.014). A meta-analyses also show that bariatric surgery reduce the risk until 60% among those obese control (RR 0.40, 95% CI 0.2 – 0.79). Unfortunately, bariatric surgery is not the main method to prevent endometrial cancer in obese women, this option is effective only in women who suffers morbid obesity, or obesity with comorbidities and fail to lose weight with medicine, diet, and lifestyle changes.

**CONCLUSION**

Obesity can increase risk to develop endometrial cancer as exogenous estrogen has impact for tumorigenesis. The best method to reduce the risk of endometrial cancer in obese women is through progesterone medication and lifestyle intervention. Medication such as insulin sensitizer is still debatable. In morbid obese women, bariatric surgery can be a choice for reducing visceral fat.

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