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## **The Impact of Obesity on Endometrial Cancer: A Comprehensive Analysis**

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## ABSTRACT

**Introduction and purpose:** Endometrial cancer [EC] is the most common gynecological cancer in developed countries and its incidence is increasing worldwide. Obesity is a prominent risk factor associated with its incidence and progression.

**The aim of study:** The article aims to provide a thorough explanation of the mechanisms through which obesity can contribute to the development of EC. Additionally, it emphasizes the crucial role of combating excess adipose tissue as a significant component of cancer prevention specifically targeting endometrial cancer.

**Material and method:** The literature review applied standard criteria and focused on PubMed articles using keywords: Endometrial cancer, Obesity, Mortality, Prevention, Pathogenesis

**Description of the State of Knowledge:** Obesity significantly impacts EC development and prognosis, particularly in Type I cases. It modifies adipose tissue metabolism, affecting the release of various substances linked to tumor growth and mortality risk. The relative risks escalate with increasing BMI. Following an EC diagnosis, higher BMI, especially  $\geq 40$ , significantly associates with increased overall mortality risk. On a preventive front, exercise showcases its potential in reducing EC risk by moderating insulin and estrogen levels.

**Summary:** These findings underscore the critical role of obesity in both EC development and prognosis, emphasizing the potential for preventive measures. Without proactive measures, the worldwide obesity epidemic will persist, exerting a substantial effect on EC occurrences.

**Keywords:** Endometrial cancer, Obesity, Obesity risk, Obesity mortality, Obesity prevention, Obesity pathogenesis

## **INTRODUCTION**

Obesity has become a health pandemic of the 21st century. It is not only an individual problem, but also a social and global one, affecting an increasing number of people around the world. The number of overweight and obese people is constantly increasing. According to data from the World Health Organization in 2016 nearly 2 billion adults aged 18 years and older were overweight. Of these over 650 million adults were obese.[1]

Recent studies have honed in on the escalating incidence of endometrial cancer, particularly in countries undergoing rapid socio-economic transformations.[2] The anticipated rise in new endometrial cancer cases stems from an aging population and escalated presence of risk factors, notably obesity, contributing to around 41% of all endometrial cancers.[3, 4]

Despite evidence linking obesity to endometrial cancer, public awareness remains significantly inadequate. In a single study involving 43 women diagnosed with endometrial cancer or hyperplasia it was found that 46.5% of these women had no knowledge that obesity posed as a risk factor for endometrial cancer.[5] Additionally, doctors and healthcare providers often hesitate to talk to endometrial cancer patients about obesity. In a different study among 108 women diagnosed with endometrial cancer, merely 29% mentioned receiving information from their healthcare provider regarding the association between obesity and the development of endometrial cancer.[6]

This study aims to meticulously analyze the existing literature concerning the intricate relationship between obesity and the onset of endometrial cancer and demonstrate that combating obesity can be a significant preventive factor for endometrial cancer.

## **EPIDEMIOLOGY**

In the 2020 global cancer statistics, endometrial cancer (EC) accounts for 4.5% of malignancies in women, ranking as the sixth most common cancer among females. In 2020,

worldwide, 417,367 women were diagnosed with endometrial cancer, and 97,370 women died from it.[7][Fig.1] The countries with the highest rates of endometrial cancer are also those with high rates of obesity.[7] For example, in Poland endometrial cancer is the fourth most common cancer in women and the most common gynecological cancer. [Fig.2]

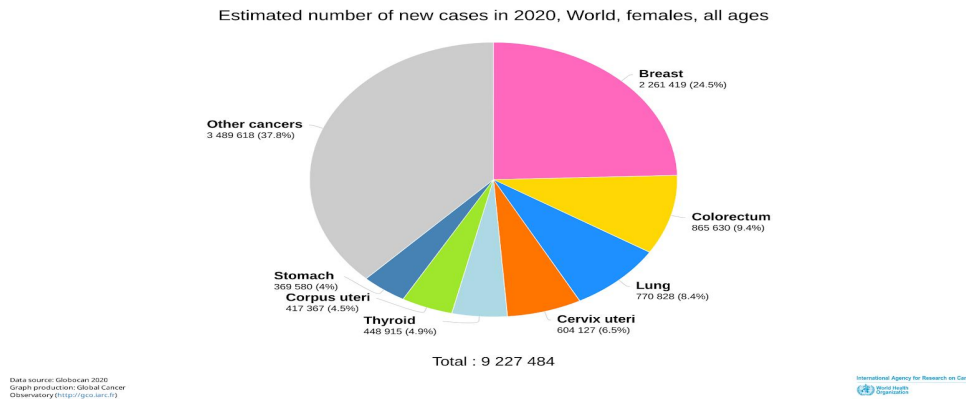


Figure 1. Estimated number of new cases in 2020, World, females, all ages. Data from the Globocan Registry.

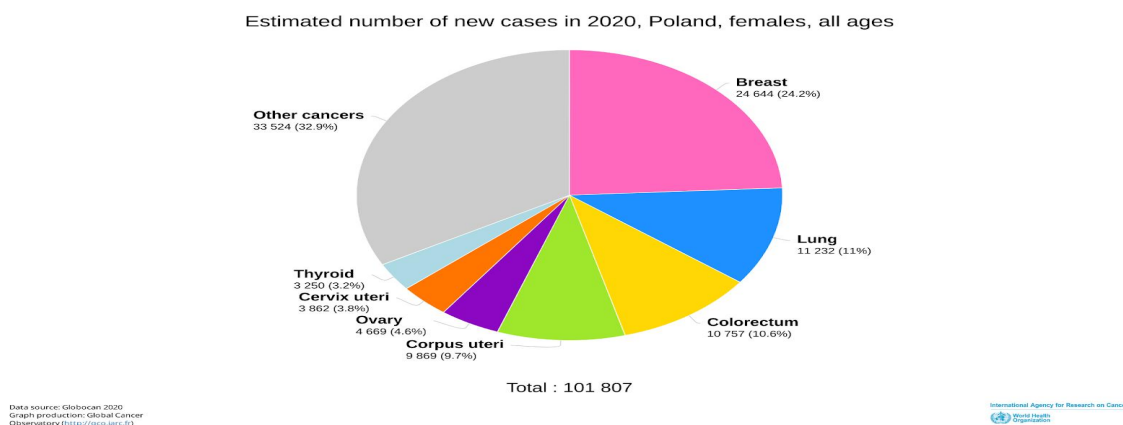


Figure 2. Estimated number of new cases in 2020, Poland, females, all ages. Data from the Globocan Registry.

Countries reporting the highest occurrences of endometrial cancer correspondingly exhibit elevated rates of obesity. The following figures illustrate the global incidence of endometrial cancer [Fig 3] and the prevalence of obesity worldwide [Fig.4]

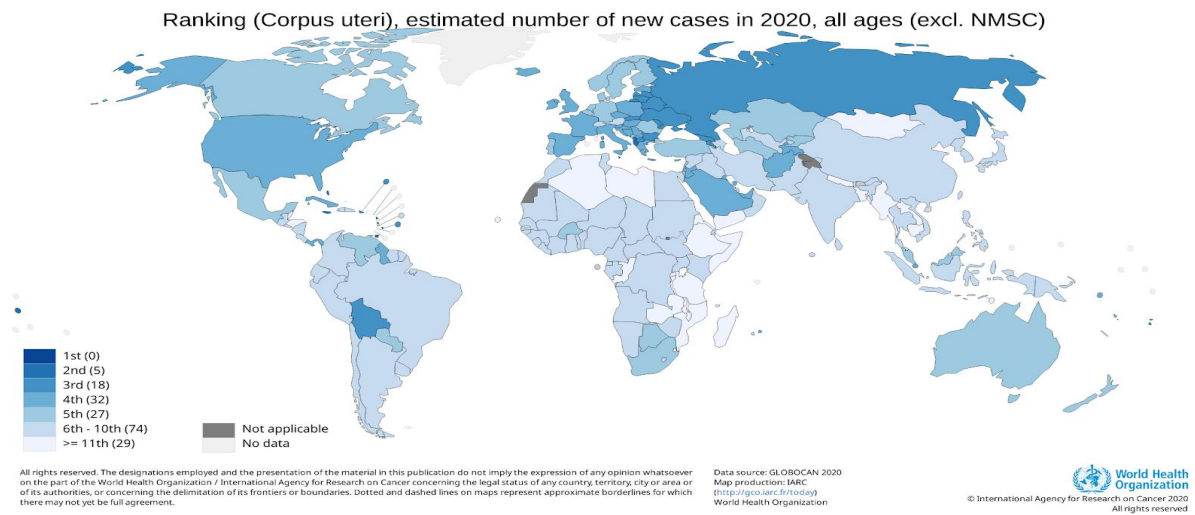


Figure 3. Worldwide incidence of cancers of the corpus uteri. Data from the Globocan Registry

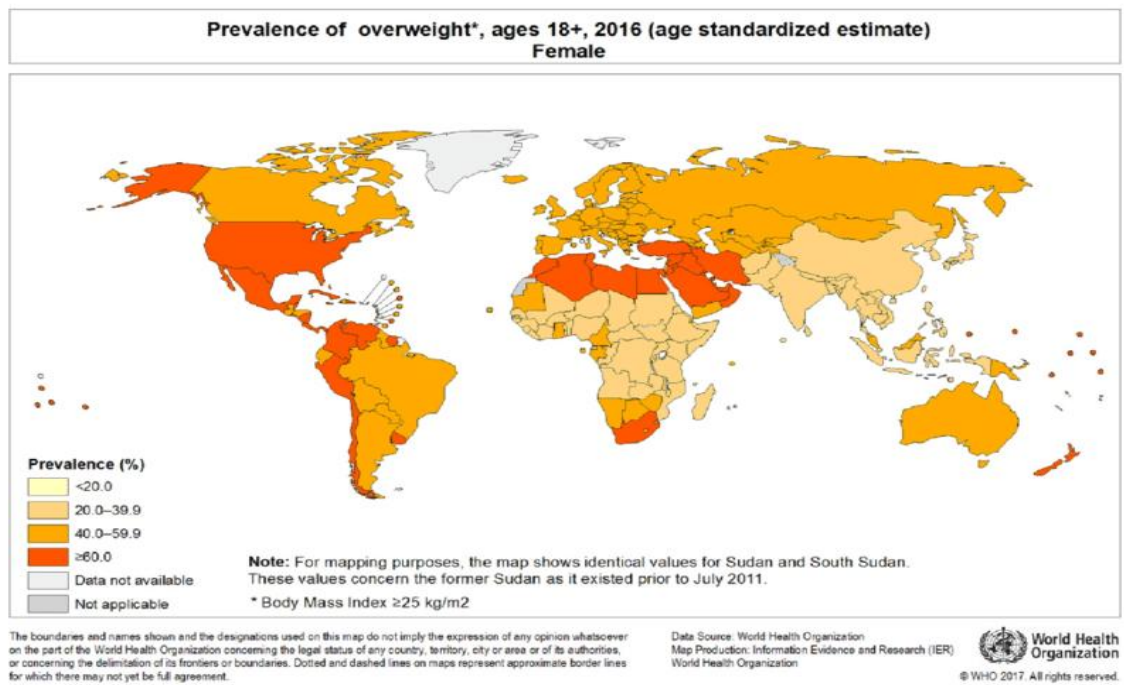


Figure 4. WHO world map of prevalence of overweight in adult female.

Over the last four decades, the incidence of overweight/obesity has been persistently increasing in both adults and children and has become a global pandemic. [8] In 2016, 39%

of adults aged 18 years and over (39% of men and 40% of women) were overweight. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The worldwide prevalence of obesity nearly tripled between 1975 and 2016. [9, 10]

## **ENDOMETRIAL CANCER - ETIOPATHOLOGY**

According to global statistics, endometrial cancer ranks as the second most commonly diagnosed malignant neoplasm of the female genital tract, following cervical cancer [11]. It primarily affects women over the age of 50 [12] and is linked to risk factors such as obesity, diabetes, and metabolic syndrome [13]. Common symptoms may involve vaginal bleeding and pelvic pain, although some women may not experience any noticeable symptoms [14].

Endometrial cancer (EC) is a malignancy of the inner epithelial lining of the uterus. [15] The tumor microenvironment surrounding these cells includes stromal cells, endothelial cells [16], and various immune cell types [17], all of which can impact cancer progression and response to treatment. While the majority of endometrial cancers (ECs) are in the early stage and confined to the uterus, some may spread by invading the myometrium and metastasizing to distant sites such as lymph nodes, liver, and lungs [18].

EC is categorized as Type I (association with unopposed estrogen stimulation, comprising low-grade cells that are more common and have a favorable prognosis) or Type II (not estrogen driven, comprising high-grade cells that are less common and have an unfavorable prognosis).[19] Type I cases are most often associated with obesity. They typically make up about 85% of EC cases and are glandular in structure. [20] Meanwhile, Type II is much rarer (making up the remaining 15%) and is believed to be rooted deeper in DNA error. [21]

## **OBESITY-INDUCED CARCINOGENESIS**

The literature describes mechanisms linking obesity and cancer, with several proposed connections to the development and progression of endometrial cancer (EC) [22, 23]. Obesity induces metabolic abnormalities in adipose tissue, influencing the release of various hormones, adipokines, inflammatory cytokines, growth factors, enzymes, and free fatty acids [24, 25]. These diverse metabolic substrates have been implicated as risk factors for cancer incidence and mortality [26, 27].

As a significant endocrine organ, adipose tissue produces and releases a variety of bioactive polypeptides, known as adipokines [28, 29]. The excessive expansion of adipose tissue in obesity modifies adipokine secretion, leading to chronic low-grade inflammation and

contributing to the development of metabolic disorders, including obesity and Type 2 Diabetes Mellitus (T2DM) (Fig. 1) [30]. Additionally, the dysregulation of adipose tissue-specific adipokines has a profound impact on the cellular physiology of various tumor cells, influencing cancer cell growth, proliferation [31], migration, invasion [32], epithelial-mesenchymal transition (EMT), angiogenesis, metastasis [33], and the development of multidrug resistance [34, 35]. These altered adipokine profiles are associated with a changed metabolic state and directly provide substrates to assist cancer cells in meeting their energy demands for the various biological processes mentioned above.

Insulin plays a crucial role in evolutionarily conserved pathways, participating in processes such as cell growth, proliferation, and differentiation. Additionally, insulin is instrumental in the synthesis of proteins and lipids, as well as in the processes of RNA and DNA synthesis. Insulin also acts as a mitogen with antiapoptotic activity, which is particularly concerning as many endothelial cell (EC) lines express high-affinity insulin receptors. [37] Often, obesity is linked to the development of insulin resistance. Insulin resistance, in turn, leads to elevated levels of blood insulin as the body continues to secrete insulin in an attempt to maintain homeostasis in a malfunctioning negative feedback loop. Studies indicate that the expression of insulin receptor subunits, particularly the ligand-binding domain, promotes the growth of endothelial (EC) cells. [38] Obesity may cause insulin resistance through promoting chronic inflammation in adipose tissue, and by increasing insulin secretion in the system, thereby activating multiple growth pathways.[24] [39] Therefore, insulin resistance induced by obesity plays a causative role in elevating both the incidence of cancer and cancer-specific mortality.

Obesity leads to estrogenic excess as adrenal androgens are aromatized to estrogen by adipose tissue. Additionally, women who are obese experience increased bioavailability of free estrogens due to low levels of sex hormone binding globulin (SHBG), a consequence of hyperinsulinemia. Estrogens directly bind to endometrial cell DNA, enhancing transcription, and interact with various growth factor signaling pathways, including the PI3K-Akt-mTOR and MAPK/ERK1,2 pathways, to promote proliferation. Excessive or 'unopposed' estrogen stimulation of the endometrium, particularly in postmenopausal or chronic anovulatory states (e.g., polycystic ovary syndrome, PCOS), contributes to tumorigenesis [40].

This hyperestrogenic and hyperinsulinemic state, along with insulin resistance, also heightens the bioavailability of insulin-like growth factor 1(IGF-1). IGF-1 has a direct effect on the endometrium, stimulating proliferation and activating the pro-oncogenic Ras/Raf/



mitogen-activated protein kinase (Ras-Raf-MAPK) and phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) pathways [40, 41, 42].

Obesity-associated chronic low-grade inflammation is recognized as a significant factor in the development of metabolic diseases and various types of cancer. [26] In healthy and lean adipose tissue, M2 macrophages secrete antiinflammatory interleukin 10 (IL-10) cytokines, and M2 marker genes such as arginase 1 (Arg-1), fizzled, and Ym1 to maintain adipose tissue homeostasis. In contrast to lean white adipose tissue, macrophages are recruited and infiltrated to white adipose tissue under obesogenic conditions and contribute to insulin resistance through promoting the secretion of proinflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, IL-1 $\beta$ , interferon  $\gamma$  (IFN- $\gamma$ ). Furthermore, in obese white adipose tissue, there is a shift in macrophage polarization. As obesity progresses, there is an increase in the levels of broadly defined pro-inflammatory M1 macrophages, leading to inflammation in adipose tissue and insulin resistance. [39, 43] Enhanced secretion of macrophage-derived pro-inflammatory cytokines in obese adipose tissue is a major contributor to the pathogenesis of tumor development by their direct and indirect effects on cells of the innate and adaptive immune systems, as well as through disturbed tissue homeostasis and increased oxidative stress. [40]

## **EPIDEMIOLOGICAL CORRELATION**

The correlation between obesity and EC is firmly recognized, especially evident in endometrioid EC. The estimated relative risks escalate: 1.5 for individuals in the overweight category, 2.5 for those with class 1 obesity (BMI 30.0-34.9 kg/m<sup>2</sup>), 4.5 for class 2 obesity (BMI 35.0-39.9 kg/m<sup>2</sup>), and notably, 7.1 for individuals in class 3 obesity (those with BMI  $\geq$ 40.0 kg/m<sup>2</sup>).[44]

Moreover, after being diagnosed with endometrial cancer, obesity signifies more adverse results. Higher BMI is significantly associated with increased overall mortality risk among women diagnosed with endometrial cancer, especially in those with a BMI  $\geq$  40. The analysis using random-effects models revealed higher mortality risks associated with increasing BMI among individuals with endometrial cancer. Specifically, the odds ratios were 1.01, 1.17, 1.26, and 1.66 for BMI categories of 25–29.9, 30–34.9, 35–39.9, and 40+. Comparing endometrial cancer patients with a BMI  $\geq$  40 to those with a BMI < 25, the odds ratio for all-cause mortality was 1.66 (CI: 1.10–2.51,  $p = 0.02$ ). The analysis concerning BMI changes indicated that a 10% increase corresponded to a 9.2% rise in overall mortality risk ( $p = 0.007$ ). [45]

## **PREVENTION**

Consistent exercise has demonstrated its ability to decrease the likelihood of developing endometrial cancer. This is achieved by lowering insulin and estrogen levels in the bloodstream, along with reduce weight or preventing weight gain. One comprehensive analysis revealed that when leisure-time physical activity rose by 3 MET-hours per week, there was a 2% decrease in the risk of endometrial cancer. Similarly, an increase of 1 hour per week in activity was linked to a 5% reduction in the risk of developing endometrial cancer.[46]

Although the available data solely originates from observational studies, it does suggest a significant discovery: deliberate weight loss of at least 5% of one's body weight is linked to a notable decrease in endometrial cancer risk (HR 0.61, 95%CI 0.42–0.88). [47]

Weight loss resulting from bariatric surgery holds greater significance and lasting effects compared to weight reduction from alterations in diet and physical activity. This surgical approach is transformative, albeit life-altering. [48] In one retrospective analysis, examining data from more than 850,000 women with obesity, findings revealed that those who had previously undergone bariatric surgery exhibited a significantly lower incidence of endometrial cancer, at 71% (95%CI, 68–74%), compared to women with obesity who did not undergo surgery. [49]

## **HEALTHCARE CHALLENGES IN OBESITY AND ENDOMETRIAL CANCER**

Apart from the direct effect of obesity on endometrial carcinogenesis, people with obesity may encounter barriers in accessing adequate healthcare. Accessibility to screening tests might be limited due to challenges in performing certain diagnostic procedures in obese individuals. This can lead to delays in detecting cancers, including endometrial cancer, subsequently impacting prognoses. Gynecologists face several challenges when examining patients with elevated BMI. The presence of excess fatty tissue around the perineum and labia can complicate gynecological examinations by increasing the distance between the vulva and the cervix. Additionally, the abdominal fold restricts the ability to manually examine the uterus.[50]

Furthermore, the stigmatization of obese individuals can affect their relationships with healthcare providers, potentially resulting in delays in seeking medical assistance. In a study assessing gynecological cancer screening in approximately 500 women with a BMI over 25 kg/m<sup>2</sup>, weight emerged as a notable obstacle to healthcare access. Among those with a BMI

exceeding 55 kg/m<sup>2</sup>, 68% admitted to postponing seeking medical attention due to their weight, while 83% acknowledged that their weight acted as a barrier preventing them from receiving suitable healthcare.[51, 52]

## **SUMMARY**

The number of new cases of endometrial cancer continues to increase. Obesity constitutes a substantial portion of the causes of such cancers. Despite evidence linking obesity to endometrial cancer, societal knowledge on this matter remains insufficient. Regular physical activity stands as a crucial factor in reducing the risk of endometrial cancer. Individuals with obesity encounter difficulties in accessing adequate healthcare, leading to delays in diagnosing diseases, including endometrial cancer. Gynecologists face challenges when examining patients with higher BMI, potentially hindering disease detection.

In summary, understanding the link between obesity and endometrial cancer is crucial for effective prevention, diagnosis, and treatment of such tumors. Effective interventions such as physical activity can play a significant role in reducing the risk of endometrial cancer among individuals with obesity. Efforts in public health, including education and obesity prevention, are crucial for enhancing outcomes in patients with endometrial cancer in the upcoming years.

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