ŻYCHOŃ, Piotr, PRAJWOS, Eryk, JANAWA, Kamil, TOMASZEK, Michał, DOMAGAŁA, Małgorzata, CĘKALSKA, Klaudia and STENKA, Wiktoria. An overview of endometrial cancer risk factors. Journal of Education, Health and Sport. 2024;76:56569 eISSN 2450-3118.
https://dx.doi.org/10.12775/JEHS.2024.76.56569
https://apcz.umk.pl/JEHS/article/view/56569

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.12.2024. Revised: 16.12.2024. Accepted: 18.12.2024. Published: 20.12.2024.

An overview of endometrial cancer risk factors

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Abstract
In developed countries, endometrial cancer is the most common form of invasive gynecological cancer. Endometrial cancer is rare in less developed countries where there are fewer common

risk factors, but the specific mortality rate is higher. The histological types of endometrial cancers show significant differences in prognosis. The first type of lesions is usually responsive to hormones, at a low stage, and has an excellent outlook, while the second type consists of high-grade tumors that are prone to recurrence, even at an early stage. The majority of endometrial cancers are influenced by hormones, with estrogen playing a role in promoting cancer through its interaction with estrogen receptor α (ER). Obesity is one of the most significant and common risk factors for endometrial cancer. Women who are obese have a three times higher risk of developing endometrial cancer. Many nonobese women can develop PCOS despite obesity being a risk factor, and many obese women may not show signs of PCOS. PCOS involves more than just a decrease in progesterone; progesterone levels may not always be lowered, and other hormone levels can also be impacted. Women affected by infertility may be more at risk for endometrial cancer, particularly if affected by ovulatory disorders. The expression of G-protein coupled estrogen receptor 1 (GPER-1) explains the estrogen-agonistic effect of tamoxifen in endometrial cancers. Tamoxifen and other "antiestrogens" act as pure agonists for GPER-1, a membrane-bound estrogen receptor. Besides genetic predisposition syndromes such as Lynch syndrome and Cowden syndrome, the development of endometrial cancer is associated with risk factors related to estrogen signaling as the main contributing factor. It's important to create prevention strategies by understanding the key risk factors and how they are involved in the formation of tumors.

Key words: “endometrial cancer” ; “risk factors”; “obesity”; “polycystic ovary syndrome”

Introduction

Endometrial cancer is the most prevalent invasive type of gynecological cancer in developed countries, with a staggering 417,367 cases diagnosed globally in 2020 alone. [1] According to global statistics, the incidence rate of endometrial cancer among women, adjusted for age, is approximately 8.7 cases per 100,000 women. [2] The growing importance of endometrial cancer as a leading cause of death partly reflects the marked declines in mortality rates from stroke and coronary heart disease, compared to cancer, in many countries. [1] Endometrial cancer is a hormonally driven type of cancer, with around 80% of cases thought to be caused by an imbalance of estrogen and progesterone hormones, either excessive estrogen or insufficient progesterone. [3] This situation can be caused by various endogenic and exgenic factors, the significance of which will be the main focus of this work.

Epidemiology

By 2020, uterine cancer ranked as the fourth most prevalent cancer among women in Europe, with an incidence rate ranging from 12.9 to 20.2 cases per 100,000 women and a mortality rate between 2.0 and 3.7 deaths per 100,000 women. [2,4] The rate of endometrial cancer is rising swiftly. [1] The elevated incidence rate of endometrial cancer in North America and Western Europe may be due to a high prevalence of lifestyle risk factors, particularly obesity, which is linked to approximately 50% of endometrial cancer cases. [5] A pooled analysis of epidemiological studies from 1971 to 2014, conducted in 2016, found that mortality related to endometrial cancer has risen by an average of 1.9% annually. [6] If current trends persist, the number of women diagnosed with endometrial cancer in the United States is projected to double to 122,000 cases annually by 2030. [7]

Pathophysiology

Endometrial cancer can be categorized into two types based on epidemiology, histopathology, prognosis, and treatment: type 1 (endometrioid), which affects around 80% of patients, and type 2 (non-endometrioid), which affects roughly 20% of patients. [8–10] Type 1 tumors originate from atypical glandular hyperplasia and are associated with prolonged unopposed estrogen exposure, often being preceded by endometrial hyperplasia.[11,12] Hormones like estrogen have a mitogenic effect on endometrial cells. [13] Cells that proliferate more rapidly are more susceptible to errors during DNA replication, and these mutated cells can potentially undergo malignant transformation, most often resulting in adenocarcinomas. In a healthy endometrium, progesterone typically counteracts estrogen's proliferative effects. However, when progesterone is absent, estrogen can promote oncogenesis, a risk that is heightened in conditions of excess estrogen. [3] Type 2 tumors primarily consist of unspecified endometrial cancer, clear-cell carcinoma, carcinosarcoma, high-grade endometrial cancer, and mixed variants, which typically combine endometrioid and high-grade non-endometrioid patterns. [14] Most cases of endometrial cancer are due to sporadic mutations, but about 5% result from inherited genetic mutations. Endometrial cancer linked to genetic predispositions usually appears 10 to 20 years earlier than sporadic cases. The following syndromes are known to predispose individuals to endometrial cancer: Lynch syndrome, Cowden syndrome. [12]

Methods

This paper examines the current understanding of how various factors influence the risk of developing endometrial cancer. We selected articles without date restrictions from several

databases, including PubMed, Google Scholar, and Web of Science. Only English-language articles with full-text availability were included in the review, with no limitations on the type of article.

Overweight and obesity

High fat consumption and being overweight (defined as a body mass index [BMI] of 25 kg/m² or higher) are significant risk factors found in nearly 50% of women with endometrial cancer.[13,15] A body mass index (BMI) over 25 kg/m² doubles a woman's risk of developing endometrial cancer, while a BMI exceeding 30 kg/m² triples the risk.[5] Obesity primarily promotes endometrial carcinogenesis by increasing estrogen production. Adipocytes convert androgens to estrogen, which then stimulates endometrial proliferation and potentially leads to hyperplasia and cancer. [16] Moreover, obesity-associated hyperglycemia and insulin resistance can lead to abnormalities in IGF-1 signaling and activation of the Mammalian target of rapamycin (mTOR) pathway, resulting in increased cell proliferation. Associated inflammation and oxidative stress, as well as alterations in cytokines, steroid hormones and adipokine pathophysiology, and cellular and vascular perturbations, can also promote endometrial oncogenesis in women with obesity. [17] Hyperinsulinemia raises the risk of endometrial cancer primarily by binding insulin to insulin receptors on endometrial cells, stimulating the growth of endometrial stromal cells, and through additional pathways. [13]

Intentional weight loss has shown promising results as an effective preventive measure. After adjusting for baseline BMI, post-menopausal women who lost at least 5% of their body weight experienced an approximately 30% reduction in endometrial cancer risk, with this reduction increasing to 66% for women with obesity. [18]

Genetic factors

The following syndromes are known to increase the risk of developing endometrial cancer:

Lynch syndrome

Lynch syndrome (LS), an autosomal dominant disorder caused by a germline mutation in one of four DNA mismatch repair genes (MLH1, MSH2, MSH6, or PMS2), is linked to a significantly increased lifetime risk of colorectal cancer, endometrial cancer, and several other cancers. [12,19] Lynch syndrome occurs with a frequency of 1 in 100 to 1 in 180 individuals. [20] Because it involves colorectal carcinomas, Lynch syndrome is also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC). However, the initial pedigrees of Lynch syndrome

(LS) already demonstrated a high incidence of uterine cancers. [21,22] Endometrial tumors in Lynch syndrome patients are often poorly differentiated, typically exhibit tumor-infiltrating lymphocytes, and frequently involve the lower uterine segment. [23] In contrast to patients with sporadic low-grade endometrioid tumors, those with Lynch syndrome typically do not have a particularly high body mass index. [24] Data from the Prospective Lynch Syndrome Database (PLSD) indicate that heterozygotes have a high average lifetime risk of developing LS-associated endometrial cancers. By age 75, the risk is 37% (30–47%) for MLH1 variant carriers, 49% (40–61%) for MSH2 variant carriers, 41% (29–62%) for MSH6 variant carriers, and 13% (5–50%) for PMS2 variant carriers. [25] These risk estimates are comparable to those for colorectal cancer and are 3–4 times higher than the risk for ovarian cancer. [25,26]

Cowden syndrome

Cowden syndrome (CS), an autosomal dominant disorder characterized by PTEN mutations, is associated with a 19% to 28% risk of developing endometrial cancer by the age of 70. [12] Cowden syndrome is a hamartoma and cancer syndrome affecting approximately 1 in 200,000 individuals, increasing the lifetime risk for cancers of the breast, thyroid, kidney, endometrium, colon, and melanoma.[27] Immunohistochemistry reveals a loss of PTEN staining in endometrial cancers of CS patients. However, somatic mutations in PTEN and subsequent loss of PTEN expression are also frequently observed in sporadic endometrial cancer. [28,29]

The evidence supporting general endometrial cancer screening in LS and CS patients remains weak. However, there is evidence that annual endometrial biopsy (EB) is more effective than transvaginal ultrasound (TVS) for identifying endometrial cancer and other premalignant endometrial lesions. [30] A group of European experts recommends screening all mutation carriers using transvaginal ultrasound (TVS) and endometrial biopsy (EB) starting at age 35 to 40. [31]

POLE and POLD1

Dominantly inherited germline variants within the exonuclease domains of the DNA replication and proofreading polymerases POLD1 and POLE have been identified as predispositions for colorectal cancer and have also been associated with increased susceptibility to endometrial cancer. [32–36] A recent study has demonstrated that germline missense mutations in the POLE and POLD1 genes result in the development of polymerase proofreading-associated polyposis, which resembles Lynch syndrome in its tumor spectrum and

includes an increased risk of endometrial cancer. [37] At the presently low numbers, the relative risks for endometrial cancer have not yet been quantified but pedigrees were consistent with a hereditary predisposition. [30]

MUTYH

The MUTYH gene encodes a protein involved in the base excision repair system responsible for repairing oxidative DNA damage. MUTYH-associated polyposis is an autosomal recessive condition predisposing individuals to adenomatous polyposis and colorectal cancer. Biallelic variants are linked to a 75% lifetime risk of colon cancer, while monoallelic variants carry a 7% lifetime risk. [38] Some findings suggest that heterozygotes for MUTYH variants may have an approximately two-fold increased risk of developing endometrial cancer. [39,40]

NTHL1

The NTLH1 gene encodes a protein involved in the base excision repair system, and mutations in this gene have been reported as an autosomal recessive predisposition to adenomatous polyposis and colorectal cancer. Homozygosity for a germline nonsense variant in NTLH1 was found in multiple polyposis-affected patients from three unrelated families, all of which included women who developed endometrial cancer. [41] A later study involving 17 additional families with biallelic NTLH1 variants revealed a high occurrence of polyposis coli and breast carcinomas, and also found cases of endometrial cancer in 4 of the families. [42] These findings indicate that a constitutional deficiency in NTHL1 is responsible for a high-risk hereditary multitumor syndrome, predisposing individuals with homozygous mutations to colon, breast, and endometrial cancers. It remains uncertain whether monoallelic NTHL1 variants also increase cancer risk, as suggested for MUTYH heterozygotes, but current evidence suggests that if there is any increased risk for heterozygotes, it is probably minimal. [30]

BRCA1

A multinational study conducted by the Breast Cancer Linkage Consortium, which included 11,847 carriers of BRCA1 variants, found a significant increase in the risk of endometrial cancer, showing a two-to-three-fold higher risk. [43] However, interpreting these results is challenging because BRCA1 variant carriers might use tamoxifen, a medication that is known to raise the risk of endometrial cancer. [44] Evidence suggests that BRCA1 variant carriers who undergo risk-reducing salpingo-oophorectomy might face a higher risk of

developing the more aggressive but less common serous or serous-like endometrial cancers, although there is no significant increased risk for the endometrioid subtype. [45]

Infertility

Several previous studies have suggested a link between nulliparity and an increased risk of endometrial cancer. [46] Two extensive cohort studies revealed an increased risk of endometrial cancer in infertile patients compared to the general population. Venn observed a standardized incidence ratio (SIR) of 2.47 in untreated IVF clinic patients, while Modan documented an SIR of 4.8 in patients who had undergone infertility treatment. [47,48] Given that infertility treatment has been linked to a possible impact on the risk of endometrial cancer, it is crucial to acknowledge its potential role as a confounding factor and to factor it into consideration. [49] When interpreting the findings, it is important to take into account potential confounding risk factors that must be recognized and managed, including age at the onset of menstruation, past use of contraceptives or hormone replacement therapy, number of childbirths, age at first childbirth, and family history of breast and ovarian cancer. [50]

Polycystic ovary syndrome (PCOS)

Patients with PCOS experience hormonal imbalance due to anovulation, which is linked to unopposed estrogen activity. [46] The proliferation and differentiation driven by estrogen could potentially result in the occurrence of endometrial hyperplasia and eventually lead to endometrial cancer. According to data of moderate quality, it was found that women diagnosed with PCOS have a 2.7 times higher risk of developing endometrial cancer over their lifetime. Women diagnosed with PCOS have been found to have an increased risk of endometrial cancer in several studies, although many of these studies did not consider BMI, which is a well-known and significant risk factor for endometrial cancer. Additionally, the interpretation of the data was constrained by the variability among the studies. The authors proposed that the higher likelihood of endometrial cancer in women with PCOS could be affected by the higher occurrence of obesity. [49]

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), is approved by the US Food and Drug Administration (FDA) for adjuvant treatment of invasive or metastatic breast cancer with hormone receptor (HR)–positive tumors, typically for 5 to 10 years. It is also

approved for reducing the risk of future breast cancers in certain high-risk individuals, with a treatment duration of 5 years. Additionally, Tamoxifen is sometimes used off-label for conditions like cyclic mastodynia. [51] In the breast, tamoxifen exerts an antiestrogenic influence, and it can function as a mild estrogen agonist on the endometrium. [52] Changes related to tamoxifen usage may involve the development of endometrial hyperplasia, atypical changes, and malignancy. [53] The likelihood of getting endometrial cancer increases with higher cumulative doses and longer exposures, showing a dose and time-dependent relationship. However, the positive impact of tamoxifen in preventing breast cancer far outweighed the risk of developing endometrial cancer. [54] Postmenopausal women with higher body mass and pre-existing endometrial pathology before starting tamoxifen treatment have the highest risk of developing tamoxifen-associated endometrial cancer. In contrast, the risk of developing this cancer for premenopausal women is very low. [55] Minimizing this risk involves the early detection and treatment of endometrial pathologies before starting tamoxifen treatment. [56]

Conclusions

In this review, we have summarized the evidence on the association between overweight and obesity, different genetic factors, infertility, PCOS, use of tamoxifen, and the risk of endometrial cancer. Studies indicate that there is a direct correlation between higher consumption of dietary fat and obesity, indicating that increased fat intake is linked to a higher likelihood of developing endometrial cancer. Adjuvant tamoxifen therapy significantly reduces breast cancer mortality, even though it has a slightly increased risk of endometrial cancer. The connection between infertility, PCOS, and endometrial cancer is a subject of debate because of the unclear impact of various confounding factors and requires further exploration.

Understanding the crucial risk factors and their involvement in tumor formation is essential for creating prevention strategies. In this case, we consider it particularly important because we do not have any screening tests to detect endometrial cancer. The growing incidence of endometrial cancer underscores why this is especially crucial.

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All authors have read and agreed with the published version of the manuscript

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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