**KWIATKOWSKA, Anita, MAŁEK, Natalia, EMERLA, Sara, BROŻYNA, Aleksandra, BYDLIŃSKI, Arkadiusz, KARŁOWICZ, Konrad, HERMANOWSKA, Maria, LUBOMIRSKA, Julia, FIGUROWSKA, Patrycja and CIULKIEWICZ, Łukasz. Role of metabolic syndrome and lifestyle factors in endometrial cancer risk and prevention. Quality in Sport. 2024;32:55862 eISSN 2450-3118.**
**https://dx.doi.org/10.12775/QS.2024.32.55862**
**https://apcz.umk.pl/QS/article/view/55862**

The journal has been 20 points in the 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 assig589 ned: 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: 30.10.2024. Revised: 12.11.2024. Accepted: 18.11.2024. Published: 18.11.2024.

# Role of metabolic syndrome and lifestyle factors in endometrial cancer risk and prevention

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## ABSTRACT

**Introduction:** The incidence of endometrial cancer, the sixth most common cancer among women, has been rising, especially in developed countries, possibly due to the obesity and diabetes pandemic. The aim of this review is to investigate the connection between metabolic syndrome, its individual components and endometrial cancer risk and to explore the role of lifestyle factors in endometrial cancer prevention.

**Materials and methods:** For this review, we included studies regarding endometrial cancer and metabolic syndrome, obesity, diabetes and hyperglycemia, hypertension, dyslipidemia and several lifestyle factors, from 1994 to 2024.

**State of knowledge:** This paper reviews existing literature on the relationship between metabolic syndrome and endometrial cancer, highlighting the significant role of central obesity, hyperglycemia and diabetes, dyslipidemia, and hypertension as risk factors. Evidence consistently demonstrates that individuals with metabolic syndrome, and its components individually, are at a heightened risk of developing endometrial cancer compared to those without metabolic abnormalities. Biological mechanisms linking metabolic syndrome's components to endometrial cancer involve complex interplays between metabolic, hormonal or inflammatory factors and signalling pathways.

Lifestyle interventions focusing on weight management, physical activity, and eating habits play an important role in reducing endometrial cancer risk and improving overall health outcomes.

**Conclusion:** An understanding of the relationship between metabolic syndrome and endometrial cancer is crucial for improving risk stratification, early detection, and prevention strategies. Addressing metabolic abnormalities and promoting healthy lifestyle behaviours are essential actions against the rising incidence and burden of endometrial cancer.

**Keywords:** endometrial cancer, metabolic syndrome, lifestyle, prevention, risk factors

## INTRODUCTION

In 2022, around 417,000 new cases of endometrial cancer were detected globally, making it the sixth most common cancer in women.[1] Over the last three decades, the incidence rate has risen by 0,69% annually.[2]

Endometrial cancer is classified into two histological subtypes. Type I cancers are endometrioid, low-grade tumours with good prognosis. Type II is characterised by non-endometrioid histology, high grade and high risk of metastatic disease.[3] Pathogenesis of the most common subtype - endometrioid cancer is associated with long-term exposure to unopposed estrogens leading to endometrial hyperplasia.[4] The main risk factors include nulliparity, early menarche, late menopause, hormone-replacement therapy, history of breast cancer, and tamoxifen therapy.[5] The most common symptom - postmenopausal abnormal uterine bleeding, is present in 90% of women with endometrial cancer. Diagnostic pathway include transvaginal ultrasound as an initial assessment. In case of thickened endometrium, endometrial biopsy with optional hysteroscopy is recommended.[6] Early diagnosis is crucial for a good prognosis. In most cases, endometrial cancer is detected in the early stages with 5 year overall survival from 74% to 91%.[3]

Developed countries are characterised by higher endometrial cancer incidence than developing countries.[2] The increasing incidence has been attributed to the obesity and diabetes pandemic.[7] Among 20 other types of cancer in women, endometrial cancer has the strongest connection to obesity.[8] While obesity has been recognised as a major risk factor for endometrial cancer, emerging evidence suggests that metabolic syndrome may also play a critical role in the pathogenesis of this disease.[9] A meta-analysis from 2020, showed an association of metabolic syndrome with a higher risk of endometrial cancer, with OR: 1.62 (95% CI = 1.26–2.07).[10] Metabolic syndrome is a copresence of several cardiovascular risk factors including central obesity, hyperglycemia, dyslipidemia and hypertension.[11]

The aim of this analysis is to investigate the connection between metabolic syndrome, its individual components and endometrial cancer risk. We will explore the underlying biological mechanisms and discuss the implications for the prevention of this disease.

## METHODS

For this review, we searched the databases such as PubMed and Google Scholar with the term „endometrial cancer" combined with the terms: „metabolic syndrome", „obesity", „BMI", „diabetes", „hyperglycemia", „hypertension", „dyslipidemia", „adipokines", „physical activity", „diet", „metformin", „weight loss", „epidemiology", „diagnosis". We included results from the studies from 1994 to 2024.

## STATE OF KNOWLEDGE

### Hyperglycemia and diabetes

Many studies suggest a connection between endometrial cancer, hyperglycemia and diabetes mellitus.[12–17] The meta-analysis of 22 case-control and cohort studies demonstrated that the presence of diabetes mellitus was linked to a higher risk of developing endometrial cancer with the RR = 1.72 (95% CI 1.48–2.01).[18] Moreover, diabetes is related to worse survival outcomes in endometrial cancer patients. Patients with pre-existing diabetes faced a 15% higher risk of cancer-specific mortality and a 23% higher risk of disease progression or recurrence of endometrial cancer.[19] Another study showed a significant association between diabetes and the risk of developing endometrial cancer without adjusting for BMI. However, this association weakened and became statistically insignificant after including BMI in the analysis.[20] These findings suggest that the connection between diabetes and the occurrence of endometrial cancer might primarily be influenced by body weight.

Various biological mechanisms have been suggested as potential explanations for the onset of endometrial cancer in women with diabetes.[21] One of the factors is hyperinsulinemia, which is frequently observed in individuals with diabetes. Estrogens and insulin-like growth factor 1 (IGF-1) stimulate the proliferation of endometrial cells. High levels of insulin decrease concentrations of insulin-like growth factor binding protein 1 and circulating sex hormone binding globulin (SHBG), which leads to increased levels of circulating free IGF-1 and bioactive estrogens. It is also shown that insulin can promote the growth of endometrial stromal cells by interacting with insulin receptors present in endometrial cells.[22] Furthermore, high glucose levels were shown to stimulate endometrial cell growth.[23]

### Obesity

Overweight and obesity emerge as strong risk factors for endometrial cancer.[24–26] The risk of developing endometrial cancer increases by 60% for every 5 kg/m2 rise in body mass index (BMI).[27] Regardless of BMI, higher waist circumference is also associated with greater endometrial cancer risk.[28] Elevated BMI harms the prognosis of individuals with endometrial cancer.[29] However, the increased mortality might be a result of other conditions related to obesity, as obesity is linked with all-cause mortality, but did not significantly affect endometrial cancer-specific mortality. Body mass index greater than or equal to 30 kg/m2 was associated with higher rates of cancer recurrence.[30]

There are several mechanisms explaining this connection. First of all, excess adipose tissue results in hormone imbalance. In postmenopausal women, adipose tissue becomes the main origin of estrogens. It produces aromatase, an enzyme which is responsible for converting androgens to estradiol and estrone.[31,32]

Therefore, obesity leads to increased levels of estrogen. Furthermore, obesity is associated with lower levels of SHBG, which transports and regulates the activity of estrogens. With decreased SHBG levels, there is a higher concentration of free estrogen available in circulation.[33] Estrogen exposure in postmenopausal occurs without the natural regulatory influence of cyclical progesterone.[33] Estradiol activates both the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which are involved in cellular proliferation.[34] It also stimulates the production of IGF-1 which induces cell growth and tumor progression.[33]

Moreover, the function of adipose tissue involves the secretion of various hormones and signaling molecules, a.o. leptin, TNF, IL-6, adiponectin, known as adipokines. Leptin encourages angiogenesis by stimulating endothelial cells and activating vascular endothelial growth factor (VEGF) and promotes chronic inflammation by enhancing pro-inflammatory cytokine secretion.[35] TNFα and IL-6, cytokines secreted by macrophages, affect tumour formation by their pro-inflammatory properties. TNFα stimulates cell growth and inhibits apoptosis by acting through NFκB pathway.[36] Moreover, IL-6 stimulates aromatase activity and indirectly affects the level of estrogens.[33] As opposed to other adipokines, adiponectin suppresses cell proliferation, angiogenesis and stimulates apoptosis of cancerous cells.[36] Moreover, it expresses an anti-inflammatory effect and inhibits TNFalfa and IL-6 synthesis.[35,37] As adiposity increases, the adiponectin concentration decreases.[34] The number of main adiponectin receptors, AdipoR1 and AdipoR2, is decreased in obesity-linked insulin resistance and diabetes.[38] Regardless of adiposity, low serum levels of adiponectin correlate with hyperinsulinemia and insulin resistance.[39] Reduced levels of adiponectin are linked with a higher risk of developing endometrial cancer.[40,41]

**Hypertension**

The study collecting data from 15,631 endometrial cancer cases matching with 42,239 controls from 29 studies showed that hypertension increases the risk of endometrial cancer by 14%, independently of factors such as BMI or diabetes.[42] Since hypertension usually co-exists with other civilization-related medical conditions and is closely related to lifestyle factors, there is a possibility that confounding variables might influence the noted connection between hypertension and endometrial cancer risk. In another study from Sweden hypertension was associated with higher endometrial cancer risk only in obese women.[43] The meta-analysis from 2017, which investigated the association between hypertension and endometrial cancer after adjusting for BMI, and smoking, demonstrated it as weaker, but still significant.[44] Hypertension was found to reduce the survival rate among endometrial cancer patients.[45]

The mechanisms underlying the potential impact of hypertension and endometrial cancer risk remain unclear.[44] Studies indicate that hypertension may result in the suppression of apoptosis. [42]

**Dyslipidemia**

A meta-analysis of 6 studies including 3,132 cancer cases presented a 17% increased risk of cancer in patients with elevated triglycerides levels. An association between low HDL-cholesterol levels and cancer wasn't significant.[46] Another study revealed a connection between endometrial cancer and triglycerides, total cholesterol, and the TG/HDL ratio.[47] On the other hand, a cohort study investigating 233 cases of endometrial cancer showed no significant relationship between lipids (including triglycerides, HDL and LDL-cholesterol) and endometrial cancer.[48]

The possible explanation for the connection between dyslipidemia and endometrial cancer risk may involve the deregulation of peroxisome proliferator-activated receptors (PPAR). These nuclear receptors play a role both in regulating lipid levels and cancer cell proliferation.[49]

**Lifestyle factors and prevention**

The meta-analysis of 13 studies showed that deliberate reduction of body weight, as well as avoiding weight fluctuations can reduce the risk of endometrial cancer. According to this meta-analysis, weight loss achieved through bariatric surgery also lowers this risk by 59%.[50] A study from 2022 of women with BMI ≥40 undergoing bariatric surgery or implementing a low-calorie diet under medical supervision, analysed blood and endometrial samples before and after a body weight loss intervention. They observed a significant decrease in systemic inflammation markers such as CRP and IL-6. Moreover, a significant increase of CD8+ cells in endometrial tissue samples was noted.[51] CD8+ cells recognize and selectively eliminate neoplastic cells and play a crucial role in the immune response against cancer formation.[52]

Also, eating habits may have an impact on endometrial cancer prevention. Following the Dietary Risk Reduction Diet (DRRD), rich in fibre, coffee, nuts, with a high intake of polyunsaturated fats, a low glycemic index (GI), and minimal consumption of red and processed meats, sugar-sweetened beverages, and trans fats, was linked to a decreased risk of developing endometrial cancer. Women who highly adhered to the DRRD presented a 27% lower risk of developing endometrial cancer compared to those with moderate to low adherence.[53] In another study, which included 1411 endometrial cancer cases and 3668 controls, the Mediterranean diet was found to reduce the risk of endometrial cancer by 50% for women with high adherence to diet compared to those with low adherence. The Mediterranean diet, taken as a whole, plays a more significant role in determining the risk of endometrial cancer compared to individual dietary components.[54] Meta-analysis of 21 case-control studies and 6 cohort studies proved that a diet rich in fruits, and vegetables has a positive impact on lowering the risk of endometrial cancer.[55] Glycemic index, which influences insulin secretion and plays a role in the etiology of diabetes, was also studied for the association with endometrial cancer risk. An Australian case-control study of 1,290 women diagnosed with endometrial cancer and 1,436 population controls presented a moderate positive relation between high dietary GI and risk of endometrial cancer, but no significant association with high GL.[56]

Metformin, as a medicine, which is a common drug used as initial treatment in type II diabetes, was investigated for its potential benefits on endometrial cancer prevention and treatment. In in vitro studies, metformin was shown to inhibit the proliferation of endometrial cancer cells.[57,58] However, the meta-analysis of 7 studies, did not show any positive impact of metformin therapy on lowering the risk of endometrial cancer.[59]

Through reducing adipose tissue and enhancing insulin sensitivity, physical activity can be an important preventive tool for the metabolic syndrome-related disease.[60] A randomised clinical trial indicated that 12-month moderate-intensity exercise can reduce levels of estrogens and raise levels of SHBG in obese postmenopausal women.[61] The meta-analysis investigating 19,558 endometrial cancer cases found out that physical activity reduces the risk of endometrial cancer. This connection was particularly significant among obese women and postmenopausal women.[62] Regardless of the intensity of exercise, also excess of sitting time is linked to a higher risk of developing endometrial cancer.[63]

In 2007, the World Cancer Research Fund/American Institute for Cancer Research announced recommendations concerning cancer prevention, emphasising the importance of maintaining an optimal body weight, following a healthy diet and avoiding alcohol.

A multi-centred study demonstrated that high adherence to these indications was related to a 60% reduction in endometrial cancer risk.[64]

## CONCLUSION

The data presented in this review highlights the significant association between the presence of metabolic syndrome and elevated endometrial cancer risk. Multiple studies demonstrate that the individual components of metabolic syndrome, including central obesity, insulin resistance, dyslipidemia, and hypertension, have each been independently linked to an increased risk of endometrial cancer.

The underlying biological mechanisms contributing to this association involve complex interplays between metabolic, hormonal, or inflammatory factors and signalling pathways. Metabolic abnormalities exacerbate the carcinogenic environment. Adipokines and inflammatory mediators secreted by adipose tissue, insulin and IGF-1, estrogens play important roles in this process.

The recognition of metabolic syndrome as a significant risk factor for endometrial cancer has implications for clinical practice and public health. Healthcare professionals should identify individuals with metabolic abnormalities and implement appropriate preventive measures, including lifestyle interventions for weight management, physical activity promotion, and dietary modification. Early detection and treatment of metabolic abnormalities may result in reducing the risk of endometrial cancer and improving overall health outcomes in women.

Unfortunately, many patients are not aware of the link between obesity and endometrial cancer. In a survey study of women diagnosed with endometrial cancer, less than half (44.4%) of surveyed patients recognised obesity as a risk factor.[65] In another study, 91% of surveyed women had never been educated about endometrial cancer risk factors by a gynaecologist or a primary care doctor.[66]

Efforts to raise awareness of the association between metabolic syndrome and endometrial cancer among healthcare professionals and the general population are important for implementing preventive strategies.

An understanding of the relationship between metabolic syndrome and endometrial cancer is crucial for improving risk stratification, early detection, and prevention strategies. Addressing metabolic abnormalities and promoting healthy lifestyle behaviours are essential actions against the rising incidence and burden of endometrial cancer.

## DISCLOSURES

**Author's contribution:**

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Writing-review and editing: Anita Kwiatkowska, Natalia Małek;
Supervision: Anita Kwiatkowska, Natalia Małek.

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

**Funding Statement:**

This Research received no external funding.

**Institutional Review Board Statement:**

Not applicable.

**Informed Consent Statement:**

Not applicable.

**Data Availability Statement:**

Not applicable.

**Conflicts of Interests:**

The authors declare no conflict of interest.

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