NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

PIETRASZKIEWICZ Patrycja, ŻAK Paula, MICHALSKA Inez, KORBEL Zuzanna, PINKOWSKA Katarzyna, TACIAK Zuzanna, GLISTA Filip, GRZECZKA Anna-Maria, JASZOWSKI Mikołaj, DĄBROWSKA Agnieszka, NAWROCKA Weronika Klara. Obesity as a Risk Factor for Endometrial Cancer – Pathophysiological Mechanisms. Quality in Sport. 2026;54:70644. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70644

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a 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 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 interest regarding the publication of this paper.
Received: 07.04.2026. Revised: 14.04.2026. Accepted: 14.04.2026. Published: 19.04.2026.

Obesity as a Risk Factor for Endometrial Cancer – Pathophysiological Mechanisms

Patrycja Pietraszkiewicz [PP], ORCID https://orcid.org/0009-0007-4371-6999

E-mail: patrycjapietraszkiewicz7@gmail.com

Poznan University of Medical Sciences: Poznan, Greater Poland, PL

Paula Żak [PŻ], ORCID https://orcid.org/0009-0001-1251-432X

E-mail: zak.paula2000@gmail.com
Collegium Medicum in Bydgoszcz: Bydgoszcz, Kujawsko-Pomorskie, PL

Inez Michalska [IM], ORCID https://orcid.org/0009-0009-0116-0405
E-mail: inezmichalska33@gmail.com
Collegium Medicum in Bydgoszcz: Bydgoszcz, Kujawsko-Pomorskie, PL

Zuzanna Korbel [ZK], ORCID https://orcid.org/0009-0009-9863-1663
E-mail: zuwiko@gmail.com
Medical Center HCP 28 Czerwca 1956 r. 194, 61-485 Poznan, Poland

Katarzyna Pinkowska [KP], ORCID https://orcid.org/0009-0005-5048-0393
E-mail: pinkowska90@gmail.com
Medical Center HCP 28 Czerwca 1956 r. 194, 61-485 Poznan, Poland

Zuzanna Taciak [ZT], ORCID https://orcid.org/0009-0004-3101-009X
E-mail: taciakzuzanna@gmail.com
Medical Center HCP 28 Czerwca 1956r. 194, 61-485 Poznan, Poland

Filip Glista [FG], ORCID https://orcid.org/0000-0002-4456-6095
E-mail: filipg090700@gmail.com
Poznan University of Medical Sciences: Poznan, Greater Poland, PL

Anna-Maria Grzeczka [AMG], ORCID https://orcid.org/0009-0009-7623-3007
E-mail: am.klaus21@gmail.com
Józef Struś Multi-Specialist Municipal Hospital, Szwajcarska 3, 61-285, Poznan, Poland

Mikołaj Jaszowski [MJ], ORCID https://orcid.org/0009-0008-1433-6425
E-mail: mikolaj.jaszowski@gmail.com
Jan Biziel University Hospital No. 2 in Bydgoszcz: Bydgoszcz, Poland

Agnieszka Dąbrowska [AD], ORCID https://orcid.org/0009-0006-6517-3406
E-mail: aga.dabrowska@outlook.com
District Public Hospital, Juraszów 7-19, 60-479 Poznan, Poland

Weronika Klara Nawrocka [WN], ORCID https://orcid.org/0009-0000-3917-1884
E-mail: WeronikaKlaraNawrocka@gmail.com
Stefan Żeromski Specialist Hospital in Krakow: Krakow, Poland

Corresponding author

Patrycja Pietraszkiewicz [PP], E-mail: patrycjapietraszkiewicz7@gmail.com

Abstract

Background. Endometrial cancer is the most common gynecological malignancy in developed countries. Obesity is a major modifiable risk factor, promoting inflammation, hyperinsulinemia, increased estrogen production, and metabolic disturbances that contribute to carcinogenesis.

Aim. This narrative review summarizes current evidence on the pathophysiological mechanisms linking obesity with endometrial cancer and highlights the relevance of molecular classification and lifestyle-related prevention.

Material and methods. A narrative analysis of open-access publications (2008–2026) was conducted, focusing on epidemiology, metabolic and hormonal pathways related to obesity, and molecular subtypes of endometrial cancer described by The Cancer Genome Atlas (TCGA).

Results. Obesity contributes to endometrial cancer through estrogen excess, insulin resistance, IGF-1 signaling, chronic inflammation, and adipokine imbalance. Four molecular subtypes are recognized: POLE ultramutated, mismatch repair deficient, p53-abnormal, and non-specific profile. Physical activity may reduce cancer risk.

Conclusions. Understanding obesity-related molecular pathways in endometrial cancer may improve risk stratification and treatment decisions. Preventive strategies, including weight control and regular physical activity, may reduce disease burden.

Key words: endometrial cancer, obesity, molecular classification, TCGA, physical activity.

Content

1. Introduction

Endometrial cancer is currently the most frequently diagnosed gynecological malignancy in developed countries, and its incidence has steadily increased over recent decades (Baker-Rand & Kitson, 2024; Siegel, Giaquinto & Jemal, 2024). Epidemiological data indicate that this rising trend is strongly associated with the global increase in obesity, metabolic disorders, and sedentary lifestyle patterns observed in many populations worldwide (Ordeanu et al., 2025; Onstad, Schmandt, & Lu, 2016).

Among all known risk factors, obesity is considered one of the most significant and potentially modifiable contributors to endometrial carcinogenesis. Numerous epidemiological studies have demonstrated a strong association between elevated body mass index (BMI) and

the risk of developing endometrial cancer. Women with obesity have a substantially higher incidence of the disease compared with women of normal body weight (Crosbie et al., 2010). The biological relationship between obesity and endometrial cancer is complex and involves multiple interacting hormonal, metabolic, and inflammatory mechanisms. One of the most important pathways is the increased production of estrogens within adipose tissue. In postmenopausal women, peripheral conversion of androgens to estrogens through aromatase activity in adipose tissue becomes the primary source of circulating estrogens. Consequently, prolonged exposure of the endometrium to unopposed estrogen stimulation promotes continuous cellular proliferation and increases the risk of malignant transformation (Onstad, Schmandt, & Lu, 2016; Setiawan et al., 2016).

In addition to hormonal alterations, obesity is frequently associated with insulin resistance and chronic hyperinsulinemia. Elevated insulin levels activate the insulin-like growth factor (IGF-1) signaling pathway, which stimulates cellular proliferation and inhibits apoptosis in multiple tissues, including the endometrium (Gallagher & LeRoith, 2020). Activation of downstream signaling cascades, particularly the PI3K/AKT and MAPK pathways, further promotes tumor cell survival and growth.

Another important mechanism linking obesity and cancer is the role of adipose tissue as a metabolically active endocrine organ. Adipocytes secrete numerous biologically active molecules, including adipokines and inflammatory mediators, which influence metabolic regulation and immune responses (Ray et al., 2021; Ellis, Barron & Bermano, 2020). In obesity, dysregulation of these signaling pathways contributes to a chronic low-grade inflammatory state that may facilitate tumor initiation and progression.

Recent advances in genomic research have significantly improved the understanding of endometrial cancer heterogeneity. The molecular classification introduced by The Cancer Genome Atlas (TCGA) distinguishes four main molecular subtypes: POLE ultramutated, mismatch repair deficient, p53-abnormal, and non-specific molecular profile (Levine, 2013). This classification provides important prognostic information and increasingly influences therapeutic decision-making.

Lifestyle factors should also be considered in the context of cancer prevention. Regular physical activity has been shown to improve metabolic regulation, enhance insulin sensitivity, and reduce systemic inflammation. These effects may partially counteract metabolic disturbances associated with obesity and may therefore contribute to lowering the risk of endometrial cancer development (Friedenreich, Ryder-Burbidge & McNeil, 2020).

The aim of this narrative review is to summarize current knowledge regarding the pathophysiological mechanisms linking obesity with endometrial cancer, with particular emphasis on hormonal and metabolic pathways, chronic inflammation, molecular classification, and the potential preventive role of lifestyle-related factors.

2. Research Materials and Methods

This study was conducted as a narrative review of current scientific literature addressing the relationship between obesity and endometrial cancer. The analysis focused on studies describing epidemiology, metabolic and hormonal mechanisms associated with obesity, molecular classification of endometrial cancer, and the potential role of lifestyle factors in disease prevention.

Scientific publications were identified through searches of electronic databases including PubMed, Google Scholar, and other open-access scientific platforms. The search strategy included combinations of the following keywords: *"endometrial cancer", "obesity", "molecular classification", "TCGA", "insulin resistance", "adipokines",* and *"physical activity"*.

Inclusion criteria consisted of peer-reviewed original research articles and review papers available in full-text open-access format that addressed the relationship between obesity, metabolic dysregulation, and endometrial carcinogenesis. Studies languages other than English were excluded. No time criterion was used.

Studies focusing on molecular subtypes of endometrial cancer and their clinical implications were also included. Publications not directly related to obesity-associated mechanisms in endometrial cancer or lacking full-text availability were excluded.

3. Research results

3.1 Epidemiology of obesity-related endometrial cancer

Endometrial cancer represents the most common malignancy of the female reproductive tract in developed countries. Over the past several decades, the incidence of this disease has been steadily increasing, particularly in regions characterized by high prevalence of obesity and metabolic disorders (Baker-Rand & Kitson, 2024; Siegel, Giaquinto & Jemal, 2024). Epidemiological observations suggest that the global rise in obesity is closely associated with the growing burden of endometrial cancer.

Numerous population-based studies have demonstrated a clear relationship between body mass index (BMI) and the risk of developing endometrial cancer. Women with obesity have been reported to have a two- to four-fold higher risk of endometrial cancer compared with women with normal body weight (Crosbie et al., 2010). Importantly, the risk appears to increase progressively with increasing BMI values, suggesting a dose–response relationship between excess body weight and carcinogenesis.

In addition to total body weight, the distribution of adipose tissue may also play an important role in cancer risk. Visceral adiposity has been strongly associated with metabolic abnormalities such as insulin resistance, chronic inflammation, and dysregulation of adipokine secretion (Ordeanu et al., 2025; Deng et al., 2016). These metabolic disturbances create a biological environment that may support the development and growth of tumors.

Obesity is frequently accompanied by several metabolic comorbidities, including type 2 diabetes mellitus, hypertension, and dyslipidemia. These conditions share common pathophysiological mechanisms with obesity, particularly insulin resistance and chronic inflammatory activity, both of which may contribute to endometrial carcinogenesis (Onstad, Schmandt, & Lu, 2016).

Furthermore, the relationship between obesity and endometrial cancer appears to be particularly strong for estrogen-dependent endometrioid tumors. These cancers are often associated with metabolic and hormonal disturbances, whereas non-endometrioid subtypes may arise through different molecular pathways (Setiawan et al., 2013).

Taken together, these epidemiological findings emphasize the importance of obesity as a major modifiable risk factor for endometrial cancer and highlight the need for preventive strategies aimed at improving metabolic health.

Mechanism	Key biological changes	Main molecular pathways	Effect on endometrium
Estrogen excess	Increased aromatase activity in adipose tissue	ER signaling	Increased proliferation
Insulin resistance	Hyperinsulinemia and increased IGF-1	PI3K/AKT, MAPK	Enhanced cell survival

Chronic inflammation	Increased TNF-alfa, IL-6, CRP	NF-κB pathway	DNA damage and tumour promotion
Adipokine imbalance	Increased leptin, decreased adiponectin	JAK/STAT, PI3K/AKT	Angiogenesis and tumour growth
Metabolic dysregulation	Altered glucose and lipid metabolism	mTOR signaling	Increased oncogenic growth

Table 1. Biological mechanisms associated with obesity that promote endometrial carcinogenesis and their principal molecular pathways.

3.2 Estrogen excess and aromatase activity

Obesity contributes to endometrial carcinogenesis through a complex network of hormonal and metabolic mechanisms. One of the most important mechanisms linking obesity with endometrial carcinogenesis is chronic exposure to elevated estrogen levels. In postmenopausal women, adipose tissue becomes the main site of estrogen production due to increased aromatase activity converting androgens into estrogens. Consequently, women with obesity exhibit significantly higher circulating concentrations of estradiol compared with individuals with normal body weight (Onstad, Schmandt, & Lu, 2016).

In the absence of progesterone-mediated regulation, prolonged estrogen exposure leads to continuous stimulation of endometrial epithelial cells. Activation of estrogen receptors promotes transcription of genes responsible for cell cycle progression, angiogenesis, and inhibition of apoptosis. Over time, this persistent proliferative signaling increases the probability of genetic mutations and malignant transformation (Iyengar et al., 2016).

3.3 Insulin resistance and IGF-1 signaling

Obesity is strongly associated with insulin resistance and compensatory hyperinsulinemia, both of which contribute to carcinogenesis. Elevated insulin concentrations stimulate the insulin-like growth factor-1 (IGF-1) axis by increasing circulating IGF-1 levels and reducing IGF-binding proteins (Gallagher & LeRoith, 2020).

Activation of IGF-1 receptors triggers several intracellular signaling pathways, particularly PI3K/AKT/mTOR and MAPK pathways, which promote cellular proliferation, inhibit apoptosis, and enhance tumor cell survival. These molecular alterations represent a key link between metabolic disturbances and oncogenic transformation in endometrial tissue.

Furthermore, hyperinsulinemia reduces hepatic synthesis of sex hormone-binding globulin (SHBG), increasing the bioavailability of circulating estrogens and further amplifying estrogen-dependent proliferative signaling (Gallagher & LeRoith, 2020).

3.4 Chronic inflammation and adipokine imbalance

Adipose tissue expansion in obesity leads to macrophage infiltration and the development of chronic low-grade systemic inflammation. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein promote genomic instability and activate oncogenic pathways including NF-κB signaling (Deng et al., 2016).

Obesity is also associated with altered secretion of adipokines. Circulating levels of leptin are increased, whereas adiponectin concentrations are reduced. Leptin promotes angiogenesis, cellular proliferation, and migration through activation of signaling pathways such as JAK/STAT, PI3K/AKT, and MAPK. In contrast, adiponectin exhibits anti-inflammatory and anti-proliferative properties. Reduced adiponectin levels therefore remove an important protective mechanism against tumor development (Pérez-Pérez et al., 2020; Słabuszewska-Jóźwiak et al., 2022).

This imbalance between pro-tumorigenic and protective adipokines may contribute to a microenvironment that favors tumor development. In addition, obesity-related metabolic disturbances may influence oxidative stress, mitochondrial dysfunction, and DNA damage, which further increase the likelihood of malignant transformation.

3.5 Molecular pathways and genomic alterations

Advances in molecular oncology have demonstrated that endometrial cancer is a heterogeneous disease characterized by distinct genomic alterations. The TCGA classification identifies four molecular subtypes: POLE ultramutated, mismatch repair deficient (MMR-d), copy-number low (NSMP), and copy-number high (p53-abnormal) (Levine, 2013).

Metabolic disturbances associated with obesity may particularly influence pathways frequently altered in endometrioid endometrial carcinoma. Mutations affecting genes such as PTEN, PIK3CA, KRAS, and alterations in the PI3K/AKT/mTOR pathway are commonly observed in obesity-associated tumors. These findings highlight the close relationship between metabolic dysregulation and oncogenic signaling in endometrial carcinogenesis.

3.6 Molecular classification of endometrial cancer

Advances in genomic research have significantly improved the understanding of the biological heterogeneity of endometrial cancer. Molecular analyses conducted within The Cancer Genome Atlas project identified four major molecular subtypes of the disease (Levine, 2013).

The POLE ultramutated subtype is characterized by mutations in the exonuclease domain of the DNA polymerase epsilon gene. Despite often presenting with high-grade histological features, tumors in this group are associated with an excellent prognosis and strong immune cell infiltration (Vrede et al., 2022).

The mismatch repair deficient subtype exhibits microsatellite instability and increased mutation rates resulting from defects in DNA mismatch repair mechanisms. Tumors in this category often demonstrate high immunogenicity and may respond favorably to immune checkpoint inhibitors (Le et al., 2017).

The p53-abnormal subtype is characterized by extensive genomic instability and mutations in the TP53 gene. These tumors frequently correspond to serous or high-grade endometrial carcinomas and are generally associated with more aggressive clinical behavior and poorer outcomes (Levine, 2013).

The non-specific molecular profile subtype represents a heterogeneous group lacking the defining alterations observed in the other categories. These tumors are often associated with endometrioid histology and may be linked with hormonal and metabolic risk factors, including obesity (Talhouk et al., 2015).

Integration of molecular classification with traditional clinicopathological factors has significantly improved risk stratification and may guide therapeutic decision-making in clinical practice.

3.7 Lifestyle factors and physical activity

Lifestyle factors may play an important role in the development and prevention of obesity-related cancers. Sedentary behavior and low levels of physical activity contribute to weight gain, metabolic dysfunction, and insulin resistance, which are key elements in obesity-associated carcinogenesis (Friedenreich, Ryder-Burbidge & McNeil, 2020).

Regular physical activity has been shown to improve insulin sensitivity, regulate glucose metabolism, and support body weight control. Exercise may also reduce systemic inflammation and improve immune function, which could influence biological pathways involved in tumor development (McTiernan, 2008).

Additionally, physical activity contributes to the reduction of visceral adiposity, which is closely associated with metabolic disturbances linked to endometrial cancer risk. By improving metabolic homeostasis, regular exercise may therefore inhibit some of the biological mechanisms associated with obesity-related carcinogenesis. Epidemiological studies suggest that women who maintain healthy body weight and engage in regular physical activity have a lower incidence of endometrial cancer. Although the precise mechanisms remain under investigation, improved metabolic regulation and reduction of chronic inflammation are considered key mediators of this protective effect.

Although physical activity alone cannot eliminate the risk of cancer, increasing evidence suggests that it may represent an important component of lifestyle-based preventive strategies aimed at reducing the burden of obesity-related malignancies.

A healthier lifestyle, measured using the Healthy Lifestyle Index (HLI) including diet, physical activity, BMI, alcohol consumption, and smoking, was associated with a reduced risk of endometrial cancer. Each standard deviation increase in HLI score corresponded to approximately 14% lower risk of endometrial cancer (HR 0.86; 95% CI 0.78–0.94). Among lifestyle components, BMI and physical activity were identified as the strongest contributors to the protective association between healthy lifestyle and endometrial cancer risk (Burkett et al.,2023).

Lifestyle-related interventions may influence several biological pathways involved in endometrial carcinogenesis, including estrogen signaling, insulin resistance, chronic inflammation and adipokine imbalance (Table 2).

Mechanism	Key biological effects	Lifestyle intervention and potential impact
Estrogen excess (aromatase activity)	Increased estrogen levels and stimulation of endometrial proliferation	Weight reduction through diet and physical activity may lower circulating estrogen levels
Insulin resistance/IGF-1 signaling	Hyperinsulinemia and activation of PI3K-AKT-mTOR pathway	Physical activity and weight loss improve insulin sensitivity

Chronic inflammation (NF-κB, IL-6, TNF-α)	Pro-inflammatory microenvironment and angiogenesis	Reduction of adiposity and regular exercise decrease systemic inflammatory markers
Adipokine imbalance (leptin/adiponectin)	Increased leptin and decreased adiponectin promoting proliferation and angiogenesis	Weight loss and physical activity increase adiponectin and reduce leptin levels

Table 2. Effects of healthy lifestyle interventions on biological mechanisms associated with endometrial cancer risk.

3.8 Microbiome dynamics in obesity-associated endometrial cancer

Recent evidence suggests that the gut microbiome may play an important role in the relationship between obesity and endometrial cancer. Obesity is associated with reduced microbial diversity and an increased abundance of bacterial species that promote chronic low-grade inflammation and metabolic dysregulation. These microbiota alterations may influence host metabolism through the production of microbial metabolites, modulation of immune responses, and effects on intestinal permeability.

An important mechanism linking the microbiome with endometrial carcinogenesis is the regulation of estrogen metabolism. Certain intestinal bacteria possess β-glucuronidase activity, which allows them to deconjugate estrogens and facilitate their reabsorption into the circulation. This process increases systemic estrogen exposure and may contribute to the "unopposed estrogen" environment that promotes endometrial proliferation and carcinogenesis.

Furthermore, microbiome-related metabolic pathways may interact with insulin resistance, adipokine signaling, and inflammatory pathways that are characteristic of obesity. Dysbiosis can enhance systemic inflammation and alter immune surveillance, potentially facilitating tumor initiation and progression. Emerging studies therefore suggest that microbiome composition may represent both a modifiable risk factor and a potential therapeutic target in obesity-related endometrial cancer.

Although current evidence is still limited, understanding microbiome dynamics may help explain the complex metabolic interactions between obesity and endometrial carcinogenesis and may support the development of preventive strategies focused on diet,

metabolic regulation, and lifestyle modification (Burkett et al., 2023).
.

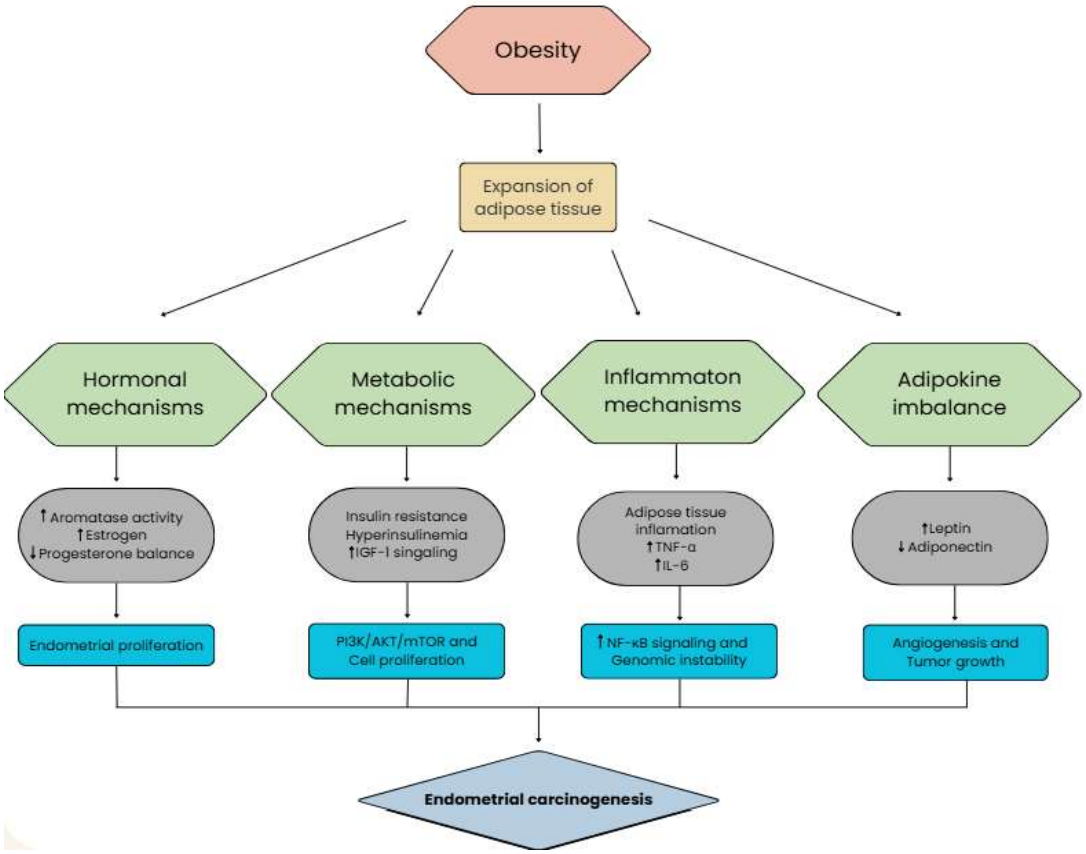

Figure 1. Pathophysiological mechanisms linking obesity and endometrial carcinogenesis.
Obesity promotes endometrial cancer development through several interacting biological pathways including increased estrogen production due to aromatase activity in adipose tissue, insulin resistance and activation of the IGF-1 signaling pathway, chronic inflammation mediated by cytokines, and imbalance of adipokines such as leptin and adiponectin. These mechanisms converge on oncogenic intracellular pathways including PI3K/AKT/mTOR and MAPK signaling, ultimately promoting endometrial cell proliferation, angiogenesis, and tumor development.

4. Discussion

This review summarizes current knowledge about the relationship between obesity and the development of endometrial cancer. The available literature clearly indicates that obesity is one of the most important risk factors associated with this malignancy. Epidemiological studies consistently show that women with higher body mass index have a significantly increased risk of developing endometrial cancer.

Several biological mechanisms may explain this relationship. One of the most important factors is increased estrogen production in adipose tissue. In postmenopausal women, adipose tissue becomes the main source of estrogen synthesis due to increased aromatase activity. As a result,

the endometrium is exposed to prolonged estrogen stimulation, which may lead to excessive cell proliferation and increase the risk of malignant transformation.

Metabolic disturbances associated with obesity also play an important role. Insulin resistance and elevated insulin levels are commonly observed in obese individuals. These metabolic changes may activate signaling pathways that stimulate cell growth and inhibit apoptosis, which may contribute to tumor development.

Another important mechanism is chronic low-grade inflammation. In obesity, adipose tissue becomes infiltrated by immune cells that produce inflammatory mediators. These molecules may influence cellular signaling pathways related to proliferation, angiogenesis, and tumor progression.

Recent advances in molecular research have also improved the understanding of endometrial cancer. The molecular classification proposed by The Cancer Genome Atlas identifies four major subtypes of the disease. These subtypes differ in prognosis and response to therapy, which may help clinicians choose more appropriate treatment strategies.

Lifestyle-related factors should also be considered when discussing cancer prevention. Low levels of physical activity are associated with obesity and metabolic dysfunction, whereas regular exercise improves insulin sensitivity, reduces systemic inflammation, and supports body weight control. Although physical activity alone cannot completely eliminate cancer risk, it may help reduce some of the metabolic disturbances linked to obesity.

Overall, the development of endometrial cancer appears to result from a combination of hormonal, metabolic, inflammatory, and genetic factors. Understanding these interactions may help improve prevention strategies and support earlier identification of individuals at increased risk.

5. Conclusions

The present narrative review highlights the complex relationship between obesity and endometrial cancer, emphasizing the interplay between metabolic, hormonal, and inflammatory pathways involved in tumor development. The available evidence clearly indicates that obesity is not only a coexisting condition but a major biological driver of endometrial carcinogenesis.

Epidemiological studies consistently demonstrate a strong association between increased body mass index and the risk of endometrial cancer. This relationship appears particularly pronounced for endometrioid tumors, which are strongly influenced by hormonal and

metabolic factors. The growing prevalence of obesity worldwide may therefore partly explain the rising incidence of this malignancy observed in many developed countries.

Several biological mechanisms have been proposed to explain the link between obesity and endometrial cancer. One of the most widely recognized pathways involves excess estrogen production in adipose tissue. Increased aromatase activity leads to enhanced peripheral conversion of androgens to estrogens, resulting in prolonged stimulation of the endometrial lining. In the absence of adequate progesterone opposition, this hormonal imbalance may promote endometrial hyperplasia and increase the risk of malignant transformation.

Metabolic disturbances associated with obesity also play an important role in carcinogenesis. Insulin resistance and hyperinsulinemia are frequently observed in obese individuals and may contribute to tumor development through activation of insulin and insulin-like growth factor signaling pathways. These pathways stimulate cell proliferation and inhibit apoptosis, thereby creating favorable conditions for tumor growth.

Another important aspect discussed in recent literature is the role of chronic inflammation. Adipose tissue expansion is associated with increased infiltration of immune cells and the production of inflammatory mediators such as interleukin-6 and tumor necrosis factor-α. Persistent inflammatory signaling may activate molecular pathways involved in cell survival, angiogenesis, and genomic instability, further contributing to cancer progression.

In addition to metabolic and inflammatory mechanisms, advances in genomic research have improved the understanding of endometrial cancer heterogeneity. The TCGA molecular classification distinguishes four major molecular subtypes that differ in prognosis and therapeutic response. Integrating molecular classification with traditional clinicopathological factors may therefore improve risk stratification and facilitate the development of more personalized treatment strategies.

Lifestyle-related factors should also be considered when discussing cancer prevention. Physical inactivity and sedentary behavior contribute to obesity and metabolic dysfunction, whereas regular physical activity has been shown to improve insulin sensitivity, regulate body weight, and reduce systemic inflammation. Although physical activity cannot completely eliminate the risk of cancer, it may play a supportive role in reducing obesity-related metabolic disturbances and improving overall health outcomes.

Taken together, the available evidence suggests that endometrial cancer arises from the combined effects of hormonal imbalance, metabolic dysregulation, inflammatory processes, and genetic alterations. A better understanding of these mechanisms may support the

development of more effective preventive strategies and may help identify individuals at increased risk of disease.

Disclosure

Author's Contribution:

Conceptualization: PP, PŻ, IM, ZT
Methodology: PP, KP, FG
Software: PP, PŻ, ZK
Check: PP, IM, ZK
Formal analysis: PP, PŻ, AMG
Investigation: PŻ, MJ, ZT
Resources: PP, AMG, MJ
Data curation: PŻ, ZK, AD
Writing–rough preparation: PP, PŻ, IM
Writing-review and editing: PP, ZT, AMG, MJ, WKN, AD
Visualization: PP, KP, FG
Supervision: PP, PŻ, ZT
Project administration: IM, KP, FG, WKN
All authors have read and agreed with the published version of the manuscript.

Funding:

This research received no external funding.

Institutional Review and Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

No new data were created or analyzed in this study.

Conflicts of Interest Statement:

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process:

In preparing this work, the authors used ChatGPT (OpenAI) for the purpose of language editing and grammar correction only. After using this tool, the authors reviewed and edited the text as needed and accept full responsibility for the substantive content of the publication

References

1. Baker-Rand, H., & Kitson, S. J. (2024). Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment. Cancers, 16(5), 1028. https://doi.org/10.3390/cancers16051028
2. Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. CA: A Cancer Journal for Clinicians, 74(1), 12–49. https://doi.org/10.3322/caac.21820
3. Ordeanu, I.-M., Busuioc, C. J., Văduva, C.-C., Pană, R.-C., Petrescu, A.-M., Văruț, R. M., Stanciu, M., & Popescu, M. (2025). Obesity as a Catalyst for Endometrial Hyperplasia and Cancer Progression: A Narrative Review of Epidemiology, Molecular Pathways, and Prevention. Biomedicines, 13(11), 2612. https://doi.org/10.3390/biomedicines13112612
4. Crosbie, E. J., Zwahlen, M., Kitchener, H. C., Egger, M., & Renehan, A. G. (2010). Body Mass Index, Hormone Replacement Therapy, and Endometrial Cancer Risk: A Meta-Analysis. Cancer Epidemiology, Biomarkers & Prevention, 19(12), 3119–3130. https://doi.org/10.1158/1055-9965.epi-10-0832
5. Onstad, M. A., Schmandt, R. E., & Lu, K. H. (2016). Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment. Journal of Clinical Oncology, 34(35), 4225–4230. https://doi.org/10.1200/jco.2016.69.4638
6. Setiawan, V. W., Yang, H. P., Pike, M. C., McCann, S. E., Yu, H., Xiang, Y.-B., Wolk, A., Wentzensen, N., Weiss, N. S., Webb, P. M., van den Brandt, P. A., van de Vijver, K., Thompson, P. J., Strom, B. L., Spurdle, A. B., Soslow, R. A., Shu, X., Schairer, C., … Horn-Ross, P. L. (2013). Type I and II Endometrial Cancers: Have They Different Risk Factors? Journal of Clinical Oncology, 31(20), 2607–2618. https://doi.org/10.1200/jco.2012.48.2596

7. Iyengar, N. M., Gucalp, A., Dannenberg, A. J., & Hudis, C. A. (2016). Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. Journal of Clinical Oncology, 34(35), 4270–4276. https://doi.org/10.1200/jco.2016.67.4283
8. Gallagher, E. J., & LeRoith, D. (2020). Hyperinsulinaemia in cancer. Nature Reviews Cancer, 20(11), 629–644. https://doi.org/10.1038/s41568-020-0295-5
9. Ray, I., Meira, L. B., Michael, A., & Ellis, P. E. (2021). Adipocytokines and disease progression in endometrial cancer: a systematic review. Cancer and Metastasis Reviews, 41(1), 211–242. https://doi.org/10.1007/s10555-021-10002-6
10. Pérez-Pérez, A., Sánchez-Jiménez, F., Vilariño-García, T., & Sánchez-Margalet, V. (2020). Role of Leptin in Inflammation and Vice Versa. International Journal of Molecular Sciences, 21(16), 5887. https://doi.org/10.3390/ijms21165887
11. Słabuszewska-Jóźwiak, A., Lukaszuk, A., Janicka-Kośnik, M., Wdowiak, A., & Jakiel, G. (2022). Role of Leptin and Adiponectin in Endometrial Cancer. International Journal of Molecular Sciences, 23(10), 5307. https://doi.org/10.3390/ijms23105307
12. Ellis, P. E., Barron, G. A., & Bermano, G. (2020). Adipocytokines and their relationship to endometrial cancer risk: A systematic review and meta-analysis. Gynecologic Oncology, 158(2), 507–516. https://doi.org/10.1016/j.ygyno.2020.05.033
13. Deng, T., Lyon, C. J., Bergin, S., Caligiuri, M. A., & Hsueh, W. A. (2016). Obesity, Inflammation, and Cancer. Annual Review of Pathology: Mechanisms of Disease, 11(1), 421–449. https://doi.org/10.1146/annurev-pathol-012615-044359
14. Levine, D. A. (2013). Integrated genomic characterization of endometrial carcinoma. Nature, 497(7447), 67–73. https://doi.org/10.1038/nature12113
15. Vrede, S. W., Kasius, J., Bulten, J., Teerenstra, S., Huvila, J., Colas, E., Gil-Moreno, A., Boll, D., Vos, M. C., van Altena, A. M., Asberger, J., Sweegers, S., van Weelden, W. J., van der Putten, L. J. M., Amant, F., Visser, N. C. M., Snijders, M. P. L. M., Küsters-Vandevelde, H. V. N., Kruitwagen, R., … Pijnenborg, J. M. A. (2022). Relevance of Molecular Profiling in Patients With Low-Grade Endometrial Cancer. JAMA Network Open, 5(12), e2247372. https://doi.org/10.1001/jamanetworkopen.2022.47372
16. Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., Aulakh, L. K., Lu, S., Kemberling, H., Wilt, C., Luber, B. S., Wong, F., Azad, N. S., Rucki, A. A., Laheru, D., Donehower, R., Zaheer, A., Fisher, G. A., Crocenzi, T. S., Lee, J. J., … Diaz, L. A., Jr. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science, 357(6349), 409–413. https://doi.org/10.1126/science.aan6733

17. Talhouk, A., McConechy, M. K., Leung, S., Li-Chang, H. H., Kwon, J. S., Melnyk, N., Yang, W., Senz, J., Boyd, N., Karnezis, A. N., Huntsman, D. G., Gilks, C. B., & McAlpine, J. N. (2015). A clinically applicable molecular-based classification for endometrial cancers. British Journal of Cancer, 113(2), 299–310. https://doi.org/10.1038/bjc.2015.190
18. Friedenreich, C. M., Ryder-Burbidge, C., & McNeil, J. (2020). Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Molecular Oncology, 15(3), 790–800. https://doi.org/10.1002/1878-0261.12772
19. McTiernan, A. (2008). Mechanisms linking physical activity with cancer. Nature Reviews Cancer, 8(3), 205–211. https://doi.org/10.1038/nrc2325
20. Coemans, E., van den Brandt, P. A., & Schouten, L. J. (2025). Healthy lifestyle and the risk of endometrial cancer. Cancer Epidemiology, 96, 102798. https://doi.org/10.1016/j.canep.2025.102798
21. Burkett, W. C., Clontz, A. D., Keku, T. O., & Bae-Jump, V. (2023). The interplay of obesity, microbiome dynamics, and innovative anti-obesity strategies in the context of endometrial cancer progression and therapeutic approaches. Biochimica et Biophysica Acta (BBA) – Reviews on Cancer, 1878(6), 189000. https://doi.org/10.1016/j.bbcan.2023.189000