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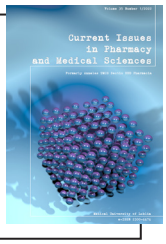

Obesity, diet, and endometrial cancer

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ABSTRACT

Endometrial cancer is the most common gynaecological malignancy in developed countries, and its increasing incidence is strongly associated with obesity. In most cases, the disease is driven by prolonged oestrogen exposure without adequate progesterone — a hormonal imbalance that is often linked to excess adipose tissue. Obesity contributes to more than half of all cases and is considered the leading modifiable risk factor. Dietary patterns can affect the risk of developing endometrial cancer not only through their impact on body weight, but also by modulating hormone levels, insulin resistance, and chronic inflammation. Lifestyle interventions that promote healthy nutrition and regular physical activity, and that prevent obesity, diabetes, and metabolic disorders, are essential components of prevention strategies. An appropriate diet may also improve prognosis, alleviate symptoms and reduce adverse effects of treatment. Future research should focus on tailored dietary approaches for specific histological and molecular subtypes, as well as high-risk populations. Current evidence suggests that a healthy diet is particularly important for women with obesity as part of endometrial cancer prevention.

INTRODUCTION

Endometrial cancer is currently the most common cancer of the female reproductive system in developed countries. It results from the uncontrolled proliferation of cells within the endometrial lining. Prolonged stimulation of the endometrium by estrogen in the absence of adequate progesterone activity is the primary factor contributing to its development and accounts for approximately 80-90% of cases. This hormonal imbalance often occurs in obese women, whose excess adipose tissue increases estrogen production and contributes to carcinogenesis.

Poland is among the countries with the highest incidence rates of endometrial cancer. Between 2013 and 2022, more than 6,000 new cases and approximately 1,600 deaths were recorded annually [1]. Endometrial cancer is the second leading cause of death from gynecological malignancies after ovarian cancer, and current prevention and treatment strategies remain insufficient. The disease most commonly occurs in postmenopausal women, particularly those between 55 and 70 years of age [1].

The recent increase in incidence has largely been attributed to lifestyle factors that lead to obesity. Studies indicate that obesity is associated with more than half of endometrial cancer cases, making it the leading modifiable risk factor. Given this strong association, diet and lifestyle appear to play a central role in the etiology of this malignancy. Understanding the relationship between dietary habits and endometrial cancer risk could lead to the development of effective

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Table 1. Major risk factors for endometrial cancer [1]

Category	Risk factor	Notes
Hormonal	Long-term exposure to unopposed estrogens (e.g., estrogen therapy without progestin)	Increases endometrial proliferation
	Anovulatory cycles, polycystic ovary syndrome (PCOS)	Chronic estrogen stimulation
	Early menarche and late menopause	Longer lifetime estrogen exposure
Reproductive	Infertility, nulliparity	Higher risk compared with multiparity
Metabolic	Obesity	Aromatization of androgens to estrogens in adipose tissue
	Type 2 diabetes mellitus	Frequently coexists with obesity and insulin resistance
	Arterial hypertension	Associated with metabolic syndrome
Genetic	Lynch syndrome (HNPCC)	Significantly increased risk; prophylaxis recommended
	Family history of endometrial cancer	Predisposing factor
Drugs	Tamoxifen (used in breast cancer therapy)	Acts as an estrogen receptor agonist in the endometrium
Lifestyle	High-fat diet, low physical activity	Promotes obesity and metabolic disorders
	Tobacco smoking (controversial)	Some studies suggest a protective effect
Other	Age (>50 years)	Highest incidence among postmenopausal women

preventive and chemopreventive strategies. Additional risk factors for endometrial cancer are summarized in Table 1.

METHODS

This narrative review is based on an analysis of scientific literature examining the relationship between obesity, diet, and endometrial cancer risk. Relevant publications were identified through searches of the PubMed, Scopus, and Web of Science databases. The review included epidemiological studies, clinical trials, and meta-analyses, primarily published in English. This study aimed to summarize the current knowledge of the metabolic, hormonal, and dietary factors involved in endometrial cancer development.

Biological mechanisms linking obesity and endometrial cancer

Obesity contributes to endometrial carcinogenesis through several biological mechanisms involving hormonal imbalance, metabolic disturbances, and chronic inflammation. From both histological and clinical perspectives, endometrial cancers represent a heterogeneous group. Two major types are distinguished: Type I and Type II. Type I tumors, including endometrioid carcinomas, develop on the basis of estrogen-stimulated endometrial hyperplasia.

Several factors may contribute to relative hyperestrogenism; however, obesity remains the most significant determinant of elevated estrogen levels. Adipose tissue is now recognized as a complex endocrine organ composed of adipocytes, preadipocytes, macrophages, stromal cells, and stem cells. These cells secrete various adipokines that act locally and systemically, stimulating endometrial cell proliferation and promoting carcinogenesis.

Adipokines regulate metabolism and induce chronic inflammation associated with visceral obesity. Pro-inflammatory adipokines, such as leptin, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), impair insulin signaling and contribute to insulin resistance while simultaneously promoting endometrial cell proliferation. Adipokines also regulate the expression of sex hormone-binding globulin (SHBG), thereby affecting circulating levels of bioavailable estrogen.

Adiponectin, a potent anti-inflammatory adipokine, has been shown to stimulate SHBG synthesis, thereby reducing estrogen bioavailability. In contrast, obesity-related pro-inflammatory cytokines are associated with decreased SHBG concentrations and increased endometrial cancer risk. Chronic inflammation mediated by adipokines also contributes to cellular stress and genetic instability, as reactive oxygen species generated by inflammatory cells may induce DNA strand breaks. Under these conditions, harmful mutations may accumulate and lead to endometrial hyperplasia.

Adipose tissue additionally produces aromatase, an enzyme responsible for converting androgens into estrogens, and this process intensifies with increasing obesity severity. Mesenchymal stem cells present within adipose tissue have also been demonstrated to promote tumor growth and progression. A meta-analysis conducted by the American Institute for Cancer Research found that each 5-unit increase in body mass index (BMI) increased endometrial cancer risk by 50% [2]. Recent evidence has further linked obesity with more aggressive, non-endometrioid subtypes of uterine cancer, including serous carcinoma, clear cell carcinoma, and carcinosarcoma [2].

Obesity is also associated with poorer prognosis among patients diagnosed with endometrial cancer. Compared with women with normal BMI, disease-specific mortality risk is 2.53 among women with BMI values between 30 and 34.9 kg/m² and 6.25 among those with BMI values exceeding 40 kg/m² [3].

Women with obesity frequently develop additional metabolic disturbances that activate carcinogenic pathways. One of the most common obesity-related comorbidities is type 2 diabetes mellitus. The association between endometrial cancer risk, hyperinsulinemia, and type 2 diabetes has been well documented. This condition is characterized by elevated insulin, insulin-like growth factor 1 (IGF-1), and blood glucose concentrations.

In healthy premenopausal women, estrogen-driven cyclic fluctuations in IGF-1 signaling regulate endometrial cell growth throughout the menstrual cycle. In endometrial hyperplasia, the expression of insulin and IGF-1 receptors is increased, making cells more sensitive to these hormones and intensifying the activation of metabolic pathways such as MAPK and PI3K/AKT/mTOR, which are frequently implicated in endometrial carcinogenesis [4]. Furthermore, hyperglycemia supports the growth of metabolically active tissues, including hyperplastic endometrium.

Studies also indicate that visceral obesity, defined as a higher proportion of visceral adipose tissue relative to total body fat, is associated with poorer prognosis in patients with endometrial cancer. Therefore, visceral adipose tissue percentage may represent a useful prognostic indicator in this malignancy.

Endometrial cancer and diet

Diet plays a crucial role in maintaining healthy body weight. Dietary habits may contribute to reduced estrogen levels and modulation of chronic inflammation, thereby lowering endometrial cancer risk.

Fatty acids

Dietary fatty acids influence the risk of various chronic diseases, including cardiovascular diseases and cancer. Two major groups of fatty acids include omega-3 and omega-6 fatty acids, which differ in their chemical structure and biological activity. Omega-3 fatty acids are generally characterized by anti-inflammatory properties, whereas omega-6 fatty acids may be metabolized into pro-inflammatory compounds.

Due to the significant role inflammation plays in the initiation and progression of cancer, omega-3 fatty acids have received considerable attention in cancer prevention research. Current evidence suggests that a higher omega-3-to-omega-6 dietary ratio is associated with a lower risk of endometrial cancer [5].

In a study involving 556 women with endometrial cancer and 533 healthy controls, higher intake of omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) was associated with significantly lower

endometrial cancer risk. Women who consumed fish rich in EPA had a 43% lower risk of developing endometrial cancer, while those with higher DHA intake had a 36% lower risk. Similar findings were observed among women using fish oil supplements, in whom a 37% lower disease risk was reported [5].

Additional studies have demonstrated that polyunsaturated fatty acids present in seafood exert anti-inflammatory effects and may contribute to cancer prevention. A study involving more than 3,500 women found that consumption of omega-3-rich fatty fish reduced endometrial cancer risk by 40% [6].

Omega-3 fatty acids are believed to prevent carcinogenesis through modulation of gene expression, estrogen metabolism, insulin sensitivity, and inflammatory processes. These findings suggest that consumption of fatty fish and maintenance of a favorable omega-3-to-omega-6 ratio may be beneficial in reducing endometrial cancer risk.

Cholesterol intake may also influence endometrial carcinogenesis. Recent evidence indicates a positive association between cholesterol consumption and increased endometrial cancer risk. Dietary compounds such as cholesterol and 27-hydroxycholesterol may act as exogenous estrogens or substrates for estrogen synthesis, thereby promoting endometrial cell proliferation.

Dairy products and calcium

Dairy products represent another dietary factor potentially influencing endometrial cancer risk. In a meta-analysis conducted by Li *et al*., dairy intake among women with elevated BMI was associated with reduced endometrial cancer risk [7]. In contrast, butter consumption was associated with increased risk.

Dairy products contain saturated fats and estrogens that may contribute to carcinogenesis. However, they also contain compounds that may inhibit tumor development [8]. Calcium plays a central role in numerous metabolic pathways associated with cell proliferation and survival, including protein kinase C (PKC) signaling.

Studies have demonstrated that endometrial cancer risk is significantly lower among women consuming calcium supplements or calcium-rich foods. Both dairy sources, including milk, cheese, and yogurt, and non-dairy sources, such as seafood, leafy green vegetables, legumes, dried fruits, and tofu, have been associated with reduced disease risk [9].

These findings support the need for further research into the role of calcium supplementation in the prevention and treatment of endometrial cancer. Calcium may additionally exert protective effects through its metabolic relationship with vitamin D, which inhibits osteopontin expression and increases E-cadherin levels, thereby suppressing tumor development.

Dairy products are also an important source of conjugated linoleic acid (CLA), which has been associated with a lower risk of endometrial cancer. Experimental studies have shown that CLA (cis-9, trans-11) induces apoptosis in endometrial cancer cells.

Phytoestrogens and flavonoids

Flavonoids are another group of dietary compounds with potential anticancer properties. Due to their antioxidant and antimutagenic effects, they may reduce cancer risk.

Ollberding *et al*. demonstrated that increased intake of isoflavone-rich foods, particularly soy products, was associated with decreased endometrial cancer risk among postmenopausal women [10]. Isoflavones exert selective modulatory effects on estrogen receptors. Similarly, Zhang *et al*. reported that soy consumption may significantly reduce endometrial cancer risk, although the exact underlying mechanisms remain unclear [11].

Kaempferol, a natural flavonoid with antioxidant, anti-inflammatory, and anticancer properties, has recently been shown to inhibit proliferation of endometrial cancer cells during the G1 and G2/M phases of the cell cycle. It also blocks estrogen receptor alpha (ERα) signaling in hormone-dependent endometrial cancer cells, thereby reducing cell viability.

The detrimental effects of excessive alcohol consumption on cancer risk are well established. In endometrial cancer, alcohol may increase risk by altering sex hormone concentrations. Rinaldi *et al*. demonstrated that alcohol consumers had SHBG concentrations approximately 15% lower than those observed in non-drinkers [12].

Vitamins and micronutrients

Vitamins and trace elements may also significantly influence cancer prevention. Wang *et al*. evaluated the effects of 15 micronutrients, including vitamins A, B6, B12, C, D, and E, β-carotene, calcium, copper, iron, magnesium, phosphorus, selenium, and zinc, adjusted for macronutrient intake, on endometrial cancer risk.

Their findings indicated that vitamin C intake was strongly associated with reduced endometrial cancer risk. Several studies have demonstrated that vitamin C may inhibit the activity of hypoxia-inducible factor 1 alpha (HIF-1α), a protein involved in survival of endometrial cancer cells. In addition to its direct effects, vitamin C may indirectly affect cancer cells through stimulation of the immune system.

Research has shown that ascorbic acid supplementation may reduce both the risk and progression of endometrial cancer. Bandera *et al*. reported that intake of as little as 50 mg of vitamin C per 1,000 kcal reduced endometrial cancer risk by 15%, whereas intake equal to or exceeding 72.7 mg reduced the risk by 20%. Women in the lowest intake group (≤29.8 mg/1,000 kcal/day) demonstrated the highest disease risk [13].

These findings suggest that foods rich in vitamin C should constitute an important component of the daily diet. Vitamin A, another antioxidant nutrient, belongs to the carotenoid family. The best-known carotenoid, beta-carotene, is converted into active vitamin A.

Vitamin A and its derivatives interact with retinoic acid receptors, thereby regulating transcription of genes involved in cancer cell growth, invasion, and apoptosis. Increased vitamin A intake has been associated with reduced endometrial cancer risk. Combined intake of beta-carotene and vitamin C may reduce endometrial cancer risk by approximately 50% [4]. Therefore, patients with endometrial cancer

should be encouraged to increase consumption of vegetables rich in beta-carotene.

Dietary patterns – Mediterranean diet

The Mediterranean diet is widely regarded as one of the healthiest dietary patterns in the world. This traditional dietary model emphasizes whole grains, vegetables, fruits, olive oil, and fish, while permitting moderate consumption of dairy products and wine.

Numerous studies have demonstrated that the Mediterranean diet reduces the risk of obesity, cardiovascular disease, and cancer. Accordingly, endometrial cancer incidence rates in Mediterranean countries are lower than in the United States and Western Europe. It has been estimated that at least 10% of endometrial cancer cases could be prevented by adopting a Mediterranean-style diet, which is characterized by lower consumption of red meat, animal fats, and pro-inflammatory foods. Additionally, long-term consumption of high-carbohydrate diets leading to hyperinsulinemia may increase insulin-like growth factor 1 (IGF-1) concentrations and stimulate the proliferation of endometrial epithelial cells.

A meta-analysis reported a 51% increase in endometrial cancer risk associated with red meat consumption; no such association was observed with white meat or fish intake. These findings support the potential protective role of Mediterranean dietary patterns. However, other cohort studies, including the Iowa Women's Health Study, failed to confirm a relationship between red meat consumption and endometrial cancer risk.

Current evidence remains inconclusive regarding whether vegetarian or vegan diets prevent endometrial cancer development. Nevertheless, in a case-control study involving 297 women with newly diagnosed endometrial cancer and 307 controls, Ricceri et al. demonstrated that higher intake of fruits and vegetables and stronger adherence to a Mediterranean-style diet were associated with lower endometrial cancer risk [15].

Reducing red meat consumption is also recommended because it may prevent other cancers, support weight loss, and improve metabolic health. The Mediterranean diet is also rich in phytoestrogens, which are compounds with estrogen-like activity that may compete with estrogen for binding to receptors.

Vegetables, particularly non-starchy vegetables, may have anticancer effects by modulating steroid hormone levels, activating antioxidant mechanisms, regulating detoxification enzymes, and stimulating the immune response. Previous studies have shown that dietary components such as vegetables and coffee may reduce endometrial cancer risk. Conversely, pro-inflammatory foods, particularly processed animal products, may increase C-reactive protein concentrations and induce chronic, low-grade inflammation. This inflammation can promote insulin resistance, cell proliferation, and apoptosis inhibition.

Aarestrup et al. investigated the relationship between whole grain and dietary fiber intake and endometrial cancer incidence in Danish women and found no significant associations. However, McCann et al. reported that diets rich in plant-based foods are associated with a reduced risk of endometrial cancer [17].

Table 2 summarizes the main dietary factors that potentially influence endometrial cancer risk and their biological mechanisms.

CONCLUSION

Current evidence suggests that diet significantly impacts the development of endometrial cancer by affecting body weight, hormonal balance, insulin resistance, and chronic inflammation. Therefore, promoting a healthy lifestyle that prevents obesity, insulin resistance, and diabetes, and encourages healthy nutrition and regular physical activity should be an essential part of endometrial cancer prevention.

Educating individuals about healthy lifestyle behaviors can reduce disease incidence, improve prognosis, and delay disease progression. An appropriate diet is an important part of modern preventive medicine and can help prevent disease, alleviate symptoms, and reduce adverse effects of treatment.

It is important to note that nutritional management in endometrial cancer involves more than just selecting appropriate foods; it also requires comprehensive, individualized planning tailored to the patient's needs. Future studies should focus on the histological variants and

Table 2. Dietary factors and their potential effects on endometrial cancer risk

Dietary factor	Main bioactive components	Proposed mechanisms	Effect on endometrial cancer risk
Omega-3 fatty acids	EPA, DHA	Anti-inflammatory effects, modulation of estrogen metabolism, improved insulin sensitivity	Reduced risk
Omega-6 fatty acids	Linoleic acid	Conversion to pro-inflammatory mediators	Possible increased risk when consumed excessively
Fatty fish	EPA, DHA	Anti-inflammatory activity, reduction of oxidative stress	Reduced risk
Dairy products	Calcium, CLA, vitamin D	Regulation of cell proliferation, induction of apoptosis, hormonal modulation	Potential protective effect
Calcium	Calcium ions	Regulation of intracellular signaling and cell proliferation	Reduced risk
Phytoestrogens	Isoflavones	Modulation of estrogen receptor activity	Possible protective effect
Flavonoids	Kaempferol and other polyphenols	Antioxidant activity, inhibition of cancer cell proliferation	Potential protective effect
Vitamins A and C	Retinoids, ascorbic acid	Antioxidant effects, regulation of gene expression and immune response	Reduced risk
Cholesterol derivatives	27-hydroxycholesterol	Estrogen-like activity stimulating endometrial cell proliferation	Increased risk
Mediterranean diet	Fruits, vegetables, olive oil, fish	Anti-inflammatory dietary pattern, improved metabolic profile	Reduced risk
Red and processed meat	Saturated fats, heme iron	Pro-inflammatory effects, oxidative stress	Possible increased risk
High carbohydrate intake	High glycemic load	Hyperinsulinemia, increased IGF-1 signaling	Potential increased risk

molecular profiles of endometrial tumors, as well as on populations at increased risk for obesity-associated endometrial cancer. Nevertheless, the current evidence strongly supports the promotion of healthy nutrition, particularly among obese women, as an important element of endometrial cancer prevention and potential chemoprevention.

From a practical perspective, preventive strategies should emphasize maintaining a healthy body weight, promoting balanced dietary patterns rich in fruits, vegetables, and whole grains, and encouraging regular physical activity. Public health interventions aimed at reducing obesity and improving metabolic health may substantially lower endometrial cancer incidence.

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