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Olga Adamczyk-Gruszka<sup>1,A,D-</sup>F, Jakub Gruszka<sup>2,D,F</sup>, Adrianna Frydrysiak - Brzozowska<sup>3,A,D-F</sup>, Anna Zwierzyńska<sup>4,D,F</sup>

# WPŁYW ODŻYWIANIA NA ROZWÓJ NOWOTWORÓW TRZONU MACICY

## The influence of nutrition on the development of endometrial cancer

- <sup>1</sup>Katedra Ginekologii i Położnictwa, Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska
- <sup>2</sup> II Katedra i Klinika Położnictwa i Ginekologii, Wydział Lekarski, Warszawski Uniwersytet Medyczny, Polska
- <sup>3</sup> Collegium Medicum, Wydział Nauk o Zdrowiu, Katedra Zintegrowanej Opieki Medycznej, Zakład Pielęgniarstwa, Akademia Mazowiecka w Płocku, Polska
- <sup>4</sup>Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska

A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

## Abstract (in Polish):

Wstęp: Nowotwory żeńskich narządów płciowych są problem światowym. Najczęstszą grupą schorzeń u kobiet w wieku rozrodczym są mięśniaki macicy. Mogą on powodować całe spektrum objawów klinicznych od nieprawidłowych krwawień macicznych, bólu miednicy, zaburzeń ze strony pęcherza moczowego do niepłodności. Nowotworem złośliwym najczęściej diagnozowanym u kobiet jest rak trzonu macicy. Stanowi niejednorodną histologicznie i klinicznie grupę. Zazwyczaj rozpoznawany jest we wczesnym stadium zaawansowania klinicznego, rzadko tworzy miejscowe wznowy i przerzuty odległe. Z reguły wiąże się z dobrym rokowaniem.

Cel i metody: Celem pracy jest przedstawienie wpływu odżywiania na rozwój nowotworów trzonu macicy na podstawie przeglądu aktualnego piśmiennictwa.

Wnioski: Odżywianie ma wpływ na ekspresję genów. Przez zmiany genetyczne i epigenetyczne wpływa na ludzki genom. Składniki diety aktywują geny supresorowe nowotworów, apoptozę komórki, translację białek. MikroRNA (miRNA) odgrywa rolę w matrycowym RNA (mRNA) odpowiedzialnym za stabilność i translację.

## Abstract (in English):

Introduction: Female genital cancers are a global problem. The most common group of diseases in women of childbearing age are uterine fibroids. They can cause a spectrum of clinical symptoms from abnormal uterine bleeding, pelvic pain, bladder disorders to infertility. The most common malignant tumor diagnosed in women is endometrial cancer. It is a histologically and clinically heterogeneous group. It is usually diagnosed at an early clinical stage and rarely causes local recurrences and distant metastases. It is usually associated with a good prognosis.

Purpose and methods: The aim of the study is to present the influence of nutrition on the development of endometrial cancer based on a review of the current literature.

Conclusions: Nutrition affects gene expression. Through genetic and epigenetic changes, it affects the human genome. Dietary components activate tumor suppressor genes, cell apoptosis, and protein translation. MicroRNA (miRNA) plays a role in messenger RNA (mRNA) responsible for stability and translation.

Keywords (in Polish): dieta, odżywianie, składniki odżywcze, nowotwory trzonu macicy.

Keywords (in English): diet, nutrients, nutrition, endometrial cancer.

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**Krótki tytuł** Odżywianie a nowotwory ginekologiczne

## Autor do korespondencji

Anna Zwierzyńska Collegium Medicum, Uniwersytet Jana Kochanowskiego w Kielcach, Polska; email: anna.zwierzynska@ o2.pl Telefon: +48666047755

## Skrócona lista autorów

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#### Introduction

Diseases of the female genital organs are a general social problem. They concern both benign and malignant tumors of the female genital organs. Education about a healthy lifestyle is aimed at reducing the incidence of this group of cancers. Nutrition affects the human genome by genetic and epigenetic changes and gene expression. Dietary components activate protein translation, cell apoptosis, tumor suppressor genes. MicroRNA (miRNA) plays a role in messenger RNA (mRNA) responsible for stability and translation [1,2].

#### Aim and methods

The aim of the study is to present the influence of nutrition on the development of endometrial cancer based on a review of the current literature.

#### Literature review

Uterine fibroids are mostly benign gynecologic tumors that are most common in women of childbearing age. They can cause numerous ailments such as abnormal uterine bleeding, pelvic pain, bladder dysfunction, and infertility that must be distinguished from endometrial cancer. Despite the high incidence of this cancer, its pathophysiology is not fully understood. Risk factors include obesity, early menarche, nulliparity, vitamin D3 deficiency, African American ancestry, and poor diet [3, 4]. Diet can alter endogenous hormone levels. Trans fatty acids affect metabolism. A reduction in dietary fat intake results in lower serum estradiol levels. Uterine fibroids develop about 15 years later in white women than in African American women. This is due to the lower fat intake from fish and meat compared to dairy products [4, 5, 6].

Based on clinical studies, Wise et al. found that omega-3 polyunsaturated fatty acids (PUFA) were independent of total fat content, except for total monounsaturated fatty acid (MUFA) intake, where a positive relationship was observed. It was found that the risk of uterine fibroids increased with intake. In their work, they showed that a higher intake of polyunsaturated fatty acids  $/\omega$ -3 PUFA/ from marine fish is associated with a 21% increased risk of uterine fibroids [7]. Harris et al. examined the level of fatty acids in the erythrocyte membrane among women of childbearing age 25-42 years. They showed an inverse relationship between the total content of  $\omega$ -3 PUFA and the positive association of trans fats and the development of uterine fibroids. They indicated the existence of an estrogenic or inflammatory effect of fats in the diet, causing a decrease in the quality of life of women through the increase of cytokines, chronic inflammation and the growth of fibrous tissue [8]. An Italian study involving 843 women did not confirm the relationship between the consumption of food products, i.e. butter, margarine, oil, and the risk of uterine fibroids [4, 9]. Similar results were reported by Islam et al. Achieved. This indicates that the myometrium has a higher proportion of arachidonic acid than fatty acids. This study did not reflect changes in mRNA expression of extracellular matrix (ECM) components. The authors concluded that omega-3 fatty acids modulate lipid profile and mechanosignaling. A diet rich in dairy, vegetables, and fruit plays a protective role in development, but high consumption of red meat increases this risk [4, 10].

Wise et al. assessed the relationship between fruit and vegetable consumption and the risk of uterine fibroids. The study looked at the effects of vitamins A, C, E, carotenoids, folic acid and fiber on the risk of developing uterine fibroids. The results showed that the greatest reduction in fibroids was observed with the consumption of citrus fruits. On this basis, a hypothesis was made

that the mechanism of action is related to the pathways in which sex hormones participate [11]. He et al. confirmed a reduced risk of fibroids with high fruit and vegetable consumption. They found that the protective role of these products may be related to the content of fiber and lycopene. Fiber may affect the metabolism of sex hormones and bile acids by inhibiting enterohepatic circulation. Another substance that affects uterine fibroids is phytoestrogens. Found in soy, they have moderate estrogenic and anti-estrogenic activity being a bioactive nutrient. The presence of a phenolic ring in soy isoflavone may bind to the estrogen receptor and compete with estradiol [12].

Another study examined the effects of quercetin and indole-3-carbinol (I3C) on ECM expression, cell migration, and proliferation of human myometrial cells and fibroids. Quercetin is found in tea, lemons, tomatoes, onions, and strawberries. A flavonoid with anti-fibrotic effects. I3C is a natural glucosinolate found in vegetables. Both substances decrease the expression of the ECM markers type I collagen and fibronectin. Blueberries, raspberries, and strawberries contain water-soluble flavonoid pigments, anthocyanins, which have anti-inflammatory, antioxidant, and antiproliferative properties [4, 13].

Islam et al. studied the effects of Aruba strawberry on apoptosis, fibrosis and oxidation of fibroid cells and fibroids. The results showed that strawberry induced apoptosis, inhibited glycolysis and fibrosis of uterine fibroid cells, and increased the level of reactive oxygen species. Anthocyanins in strawberries decreased fibronectin mRNA and collagen expression in myoma cells. When testing different varieties of strawberries, the authors observed that Alba and Romina varieties reduced mRNA expression of collagen 1A1, fibronectin, versican and activin A the most [14]. Another substance is curcumin found in turmeric. By regulating the apoptosis pathway, it prevents the growth of fibroids by inhibiting cell proliferation. On the other hand, genistein contained in soybeans has a stimulating effect at lower concentrations and an inhibitory effect at higher concentrations. By affecting the proliferation of fibroid cells, it reduces the proliferating cell nuclear antigen (PCNA), increases the apoptosis of uterine fibroid cells. Inversely associated with the proliferation of fibroids is resveratrol present in mulberries, peanuts, grapes. It induces cell apoptosis in vitro [4, 15].

Ciebiera et al. showed that the consumption of green tea extract reduces the size of fibroids. This was attributed to the inhibitory effect of epigallocatechin gallate EGCG on the proliferation of fibroid cells and the induction of apoptosis [16].

Dairy products contain calcium, vitamin D and butyric acid, which have been shown to have anti-cancer properties. Milk may also contain cancer-causing hormones such as estrogen and progesterone. Wise et al. Their study found that women who consumed four or more servings of dairy products per day had a 30% lower risk of developing uterine fibroids [17]. Al Hendy et al. showed that vitamin D, as an anti-estrogen, reduced the expression of sex steroid receptors, reduced fibroid size, and was a potent anti-proliferative agent for fibroid cells. Vitamin D exerts its action by inducing genes involved in DNA repair, thereby reducing DNA damage in both fibroid cells and those at risk of developing it [4, 18, 19].

Many pollutants resemble steroid hormones and thus affect their receptors. This applies to phthalates, parabens, phenols, alternative plasticizers, diethylstilbestrol and organophosphorus esters. The U.S. National Institute of Environmental Health Sciences (NIEHS) defines EDCs as "chemicals that disrupt the body's endocrine system and have adverse developmental, reproductive, neurological, or immunological effects. EDCs bind to the nuclear estrogen receptor and alter hormone function by mimicking endogenous hormones or blocking their interaction with the receptor. Epidemiological studies have shown that some EDCs increase the risk of developing uterine fibroids. Heavy metals

in cigarette smoke, polluted air, seafood, and leafy green vegetables are associated with an increased risk of uterine fibroids. Heavy metals (metalloestrogens) activate estrogen receptors in the absence of estradiol and, like endocrine disruptors, affect the hypothalamic-pituitary-ovarian axis [4, 20].

In addition to uterine fibroids in women, endometrial cancer is a growing public health concern because of its prevalence and associated medical burden. Endometrial cancer (EC) is the most common malignancy of the female reproductive tract. It is a histologically and clinically heterogeneous group. It is usually diagnosed at an early stage of clinical advancement, rarely causes local recurrences and distant metastases. It is usually associated with a good prognosis. Patients diagnosed at an early stage have a survival rate of approximately 75% to 90%. Surgery is the basic treatment. It occurs mainly in postmenopausal women. Risk factors include older age, childlessness, diabetes, use of estrogen-only hormone replacement therapy, and obesity. These tumors fall into her two types. Type I presents as endometrial adenocarcinoma, often preceded by endometrial hyperplasia. Its development is influenced by long-term estrogen stimulation on the endometrium. Type II tumors are most often estrogen-independent serous carcinomas. Their formation can be observed from the atrophic endometrium [21].

Bandera et al. noticed an inverse correlation of the risk of developing endometrial cancer with the consumption of carotenes, ascorbic acid and tocopherols. They found that a diet high in fat was associated with an increased risk of endometrial cancer, but energy from carbohydrates and proteins did not increase this risk. However, overweight and obesity were associated with a higher risk of precancerous lesions [22].

The pathophysiology of endometrial cancer has often been assessed in the context of inflammation. Elevated levels of prostaglandins may be the basis for the transformation of normal endometrium into neoplastic tissue, which is associated with cell divisions caused by inflammation, with the subsequent possibility of ineffective DNA repair and mutations. It can be assumed that the polyunsaturated fatty acids available in seafood have an anti-inflammatory effect and play a beneficial anti-cancer role. Brasky et al. showed that the risk of cancer development increased by 80% with a high intake of eicosapentaenoic acid and docosahexaenoic acid in the diet in relation to a lower intake of these acids [4, 23].

Epidemiological studies have shown that high intakes of fish oil or omega-3 PUFAs reduce the risk of uterine cancer.  $\omega$ -3 PUFA, docosahexaenoic acid (DHA), exhibits anticancer activity by inducing apoptosis of some human cancer cells without toxicity to normal cells. It induces oxidative stress and the formation of oxidative DNA adducts by depleting intracellular glutathione (GSH) and reducing the function of the mitochondria of cancer cells. DHA has a variable inhibitory effect on the growth of cancer cells depending on the molecular properties of the cells and the degree of malignancy. It affects DNA repair processes, including DNA-dependent protein kinases and mismatch repair in cancer cells. Moreover, it increases the effectiveness of anti-cancer drugs by increasing drug uptake and inhibition of survival pathways in cancer cells [24].

Alcohol increases the risk of cancer by increasing the concentration of sex steroids. Rinaldi et al. showed that compared to non-alcohol consumers, sex hormone binding globulin levels are about 15% lower in alcohol drinkers [25].

Flavonoids, having antioxidant and antimutagenic properties, may reduce the risk of cancer. Ollberding et al. showed that higher consumption of food containing isoflavones (soy) is associated with a reduced risk of body cancer in postmenopausal women [26]. Isoflavones have a selective estrogen receptor modulating effect with different estrogenic and antiestrogenic potential, depending on the receptor of the target tissue. Similar conclusions were drawn by Zhang et al. In their research, they showed that soy consumption may be associated with a lower risk of endometrial cancer, emphasizing that the exact mechanisms are unknown [4, 27].

Vitamin B12 intake is negatively associated with endometrial cancer. In the study, it contributed to an increase in the risk of endometrial cancer, but in overweight women it significantly increased this risk. The negative relationship between endometrial cancer and vitamin B12 intake may be due to altered expression of cancer-related genes by reducing DNA synthesis, leading to cancer development [28].

Li et al. in their meta-analysis noted a lower risk of endometrial cancer associated with the consumption of dairy products in women with a higher BMI, while a higher risk was associated with the consumption of butter. Dairy products contain saturated fatty acids and estrogens that are positively associated with the risk of endometrial cancer, on the other hand, several nutrients in dairy products can inhibit carcinogenicity. Calcium contained in dairy products is described as an element significantly associated with a reduced risk of endometrial cancer, through a metabolic correlation with vitamin D, which may reduce cellular expression of osteopontin and increase E-cadherin levels to reduce tumor development [29].

Dairy products are an excellent source of conjugated linoleic acid, which is significantly associated with a reduced risk of endometrial cancer. Conjugated linoleic acid (CLA) Cis-9, trans-11 can induce apoptosis of endometrial cancer cells. Type II endometrial cancer usually has distant metastases and a poor prognosis. It has been demonstrated that there is an inverse relationship between UV radiation and the generation of EC. Considering the multidirectional effects, a possible positive effect of vitamin D is suspected. Kaempferol, a natural flavonoid with anticancer, anti-inflammatory, and antioxidant properties, inhibits cell proliferation through various mechanisms [30]. Yan et al. showed little or no association between green tea consumption and endometrial cancer risk [31]. Around et al. The lower risk is thought to be due to the significantly higher catechin content in green tea compared to black tea. Catechins like EGCG can regulate estrogen-induced activation of endometrial cells, induce apoptosis of cancer cells, and cause cell cycle arrest [32].

## Conclusions

The available data on the effect of nutrients on the pathophysiology of uterine fibroids are satisfactory but insufficient for endometrial cancer. This makes it possible to discover new natural products for the prevention or treatment of certain people. Gynecological diseases are causally related to several environmental factors. These factors can be physical and/or social. Therefore, in the clinical treatment of gynecological diseases, it is recommended to pay attention to the factors that increase the success rate of treatment.

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