

# Role of adipokines in ovarian cancer epidemiology and prognosis

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## ABSTRACT

Ovarian cancer is one of the most serious problems in modern oncological gynecology. The link between obesity (expressed in BMI, WHR, waist circumference, body weight) and ovarian cancer has been poorly studied. Obesity is defined as an excessive accumulation of bodily fat, exceeding its physiological needs and adaptability. Study results suggest a link between specific histological types of ovarian cancer with increased patients' BMI. Adipose tissue is hormonally active and secretes biologically active proteins called adipokines. Resistin and leptin may show proliferative and anti-apoptotic effects. There is currently increasing attention to adipokine levels in ovarian cancer research. The influence of adiponectin on the secretion of angiogenic factors by ovarian cancer cells has been shown. It has been proven that leptin is associated with a worse prognosis for patients treated with platinum compounds combined with paclitaxel/docetaxel. The relation has been observed between the level of resistin and the growth of neoplastic cells, their spread and the resistance to chemotherapy. The level of AdipoR1 may be independent prognostic factor in the case of epithelial ovarian cancer. The role of adipokine in the neoplasm development requires further investigation, in the view of fact that results of current research are still inconclusive. Considering increasing number of people suffering from obesity as well as the current analysis results, it is necessary to extend experimentation on the influence of obesity on the development and prognosis of ovarian cancer.

**Key words:** ovarian cancer; adiponectin; leptin; resistin; visfatin; adipokines

Ginekologia Polska 2022; 93, 6: 496–500

## INTRODUCTION

Ovarian cancer poses a significant problem in modern oncological gynecology. Globally, it is the eighth most diagnosed cancer among women. A total of 312,800 new diagnoses and 206,800 deaths were recorded in 2020 worldwide [1].

Due to the growing number of scientific reports concerning the link between obesity and metabolic disorders with the risk of cancer, it has become necessary to determine the molecular and metabolic factors involved in the process of creating neoplasms including ovarian cancer.

## OVARIAN CANCER

The American Cancer Society estimates that in 2021 in the United States, 21,410 women will be diagnosed with ovarian cancer, and 13,770 will die there from [2]. In Poland, ovarian cancer is the fifth most common cancer among women and the fourth in terms of mortality [3]. The high

mortality rate concerning ovarian cancer is primarily caused by late diagnosis (at the time of diagnosis approx. 75% of patients are already in clinical stage III or IV) [4].

In population studies, an increased risk of ovarian cancer is observed among women experiencing early puberty, entering menopause late, among nulliparous women, as well as those taking advantage of ovulation-stimulating therapy. The link between obesity (expressed in BMI, WHR, waist circumference, body weight) and the risk of ovarian cancer remains much less studied [5]. At the same time, there is an indicated relation between metabolic changes concerning glucose management in the entire body and in the tumor's surrounding, including the expression of glucose transporters (mainly GLUT-1) as a marker of malignancy, invasiveness, and advancement, as well as a prognostic factor concerning many malignant neoplasms, including ovarian cancer [6].

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Received: 22.12.2021 Accepted: 22.03.2022 Early publication date: 4.05.2022

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## OBESITY DEVELOPMENT MECHANISMS

Obesity is defined as an excessive accumulation of bodily fat, exceeding its physiological needs and adaptability, carrying the risk of adverse effects on health [7].

There is a genetic predisposition for developing obesity with a hereditary tendency to obesity whose level is 40–70% [8].

The arcuate nucleus of the hypothalamus is the center for integrating signals that regulate appetite.

In it, there are two opposing systems that regulate energy consumption. The first one — the orexigenic system reduces the use of energy in conditions of hunger and stimulates the intake of meals. The second one consists in the anorexigenic system that suppresses appetite and increases the use of energy in the event of its excess [9].

Currently, it is known that white adipose tissue is hormonally active and secretes numerous biologically active proteins with multidirectional action, called adipokines. So far, approx. 50 active substances produced by adipose tissue cells have been described, many of whom have the properties of hormones, for example: leptin, adiponectin, resistin, visfatin, apelin, chemerin, and omentin. The relation with ovarian cancer has been studied in terms of the above, and proven mainly for leptin, adiponectin, resistin, and visfatin.

Leptin is one of the most important proteins secreted by adipocytes. It is created mainly in mature cells of white adipose tissue (WAT) of mammals, and its biosynthesis and secretion depend on adipose tissue mass and constitutes a reflection of the energy reservoir in this tissue [10]. It turns out that leptin also affects fetal development, puberty, lactation, hematopoiesis, and the body's immune response.

Adiponectin is a peptide secreted by adipose cells. Adiponectin acts through a membrane receptor (two receptor isoforms differing in gene and organ location). It plays an important role in regulating the metabolism of glucose, lipids, has an impact on appetite control, and has a strong vasoprotective effect by acting directly on the vascular endothelium. Adiponectin leads to vasodilation, inhibition of adhesion molecule expression, inhibition of inflammatory cytokine (TNF $\alpha$ ) inflammation, increasing the production of nitric oxide (NO), stimulation of angiogenesis, inhibition of proliferation and migration of endothelial cells and smooth muscle cells. Obesity, type 2 diabetes, hypertension, coronary artery disease, and stroke are accompanied by a decrease in adiponectin levels, while its high values have been recorded among long-lived people [11]. At the same time, lower adiponectin concentrations and higher leptin concentrations are observed among patients with polycystic ovary syndrome [12].

Resistin is an adipokine that reduces tissue sensitivity to insulin, and in case of high insulin concentrations, a fac-

tor for developing insulin resistance. It has been proven that, in addition to modulating insulin sensitivity, resistin participates in the development of inflammation, regulates carbohydrate and lipid metabolism, and stimulates endothelial cell proliferation. Additionally, it directly affects the adipose tissue through proliferation and differentiation of adipocytes. By controlling food intake, it participates in establishing energy balance. Furthermore, resistin stimulates and facilitates angiogenesis. Resistin has also been shown to affect endothelial cells of blood vessels — both in terms of proliferation and endothelial cell migration. It has also been established that resistin modulates the activity of female gonads by participating in the regulation of steroidogenesis, folliculogenesis, and cellular proliferation of follicular layer cells in some animal species. Resistin has also been proven to regulate the synthesis and secretion of sex hormones — progesterone and estradiol [13].

Visfatin is a protein produced by visceral adipose tissue. An experiment confirming the origin of visfatin consisted in a demonstration of a correlation between the concentration of this protein and the amount of visceral adipose tissue and the lack of such a relation with the amount of subcutaneous adipose tissue. Summarizing the research concerning visfatin conducted so far, it should be stated that it shows some similarities in action with insulin (hypoglycemic effect, activation of the insulin pathway by an insulin receptor). A low concentration of visfatin compared with insulin — as well as the lack of change in concentration after a meal — results in a relatively low hypoglycemic effect of this protein under physiological conditions. However, it seems that in conditions of excessive amount of visceral adipose tissue, and thus with higher production of pro-inflammatory cytokines, the participation of visfatin in glycemic-lipemic homeostasis increases. Visfatin constitutes one of the elements of the relation between adipose tissue and an inflammatory response, although this mechanism constitutes a challenge for further research [14].

## THE RELATION OF OBESITY WITH CANCER

In a study published in "Lancet", Bhaskaran K., Douglas I. et al. [15] showed a link between obesity (increased BMI) and 17 out of 22 examined cancers, including primarily endometrial, gallbladder, kidney, cervical, and thyroid cancer, as well as leukemias. They also associated elevated BMI with cancer of the liver, colon, ovary, and breast in the postmenopausal period.

Epidemiological and clinical data point to the key role of hormones, cytokines, and other mediators as metabolic markers of obesity, expressed in pro-proliferative and pro-inflammatory activity, linking the activity of adipose tissue cells (adipocytes, macrophages etc.) with the appearance and expansion of cancer cells [16].

Resistin and leptin may show proliferative, anti-apoptotic, pro-inflammatory effects, stimulate angiogenesis, which makes them a potential diagnostic and prognostic biomarker of cancer. At the same time, attention is drawn to the protective nature of adiponectin, which possesses anti-inflammatory, anti-atherosclerotic, anti-diabetic, and anti-cancer properties. Studies have shown low levels of adiponectin in breast, liver, pancreatic, prostate, colon, and ovarian cancer [17].

### **LINK BETWEEN OBESITY AND OVARIAN CANCER**

The link between obesity and the risk of ovarian cancer remains much less studied.

In UK 512 in 7011 new cases of ovarian cancer per year are considered attributable to overweight and obesity, while 125 extra cases per year are projected with concomitant 1 kg/m<sup>2</sup> population wide increase in BMI [15].

Study results suggest a link between specific histological types of ovarian cancer — serous with low malignancy potential and invasive mucous tumors with increased patients' BMI [18].

Studies have been carried out concerning the simultaneous use of quantification of osteopontin, IGF-II, leptin, prolactin, and Ca 125 as markers of early ovarian cancer — not giving any positive results [19].

For patients suffering from ovarian cancer with elevated levels of leptin in the serum and excessive receptor expression (Ob-R), this was related with an aggressive course of the disease [20]. It was possible to prove the stimulating effect of leptin on the growth of OVCAR-3-line ovarian cancer cells with simultaneous inhibition of apoptosis by increasing the share of cyclin D1 and Mcl-1 expression by activating the PI3K/Akt and MEK/ERK1/2 pathways [21]. Studies concerning the expression of leptin receptors in ovarian cancer cell lines and its impact on proliferation, activating the JAK2/STAT3, IRS1/2-PI3K/AKT, SHP2/ERK, and COX-2 pathways, as well as the inhibition of apoptosis, suggest that leptin may be a regulating factor for ovarian cancer [22].

Adiponectin stimulates the secretion of CXCL1 from cancer cells in ovarian cancer, leading to VEGF-independent angiogenesis. Studies suggest that it is a key factor initiating angiogenesis in ovarian cancer. At the same time, it may become a new therapeutic target in the treatment of ovarian cancer. However, the role of adiponectin in angiogenesis, tumor development, and metastasis formation, requires further research as the current results are often inconclusive or even contradictory [23].

The levels of adiponectin and leptin among patients with ovarian cancer were lower compared to the control group. However, no significant differences have been found in terms of the stage of the disease. The decreased level

of adiponectin and leptin in ovarian cancer compared to other gynecological neoplasms may be of diagnostic importance [24].

In a study with AdipoRon — a synthetic agonist of AdipoR1 and AdipoR2 receptors, an anti-proliferative and pro-apoptotic impact on cells was demonstrated in high grade serum ovarian cancer. AdipoRon activates AMPK, disrupts the cell cycle and activates caspase 3. This suggests that the same pathways may be activated with the use of exogenous adiponectin, which plays a significant role in the survival of tumor cells [25].

It has been determined that adiponectin reduces cell proliferation in epithelial ovarian cancer and is a phenomenon independent of apoptosis. At the same time, it reverses the stimulating effect of estradiol and IGF-1 on cell proliferation. Progesterone increases the sensitivity of cancer cells to adiponectin by increasing the expression of its receptors. These dependencies suggest that there is a link between adiponectin and ovarian steroid hormones and growth factor pathways in ovarian cancer cells [26].

### **IMPACT OF OBESITY ON SURVIVAL PARAMETERS AMONG PATIENTS WITH OVARIAN CANCER**

It has been proven that leptin is associated with a worse prognosis for patients treated with platinum compounds combined with paclitaxel/docetaxel. Leptin reduces the sensitivity of ovarian cancer cells to paclitaxel/docetaxel. Flow cytometry showed that the administration of exogenous leptin reduced the proportion of ovarian cancer cells in the G2/M phase, the titre of which was increased as a result of treatment with paclitaxel/docetaxel [27].

The studies explained the relation on the leptin/Ob-Rb axis and the role of the estrogen receptor  $\alpha$  in tumor growth and confirmed the estrogen-dependent effect of ER $\alpha$  on leptin-induced cell growth in ovarian cancer, which may contribute to discovering a new mechanism of leptin-dependent progression in ovarian cancer [28].

Serum leptin levels, although, according to most researchers, decreased among patients with ovarian cancer, has not become a prognostic marker. Higher leptin levels were found among obese patients, which was associated with shorter survival times. The concentration of leptin in ascites in combination with the Ca 125 marker has been considered an important prognostic factor in terms of resistance to first-line chemotherapy [29].

Research has been carried out concerning the OB3 protein, which could play a metabolic role similar to leptin, without its oncogenic potential. The OB3 protein in ovarian cancer could prevent neoplasm initiation and progression by disrupting leptin-dependent proliferative signals through STAT3 phosphorylation and ER $\alpha$  activation.

Taking advantage of OB3 protein in case of obese individuals should be taken into consideration as a prophylaxis of leptin-induced cancers [30].

Studies have revealed that blocking the action of leptin as a factor activating the epithelial-mesenchymal transformation of ovarian cancer cells by activating the PI3K/Akt/mTOR pathway is related to a significant reduction in peritoneal metastasis, which provides new therapeutic possibilities [31].

It has also been determined that leptin plays a key role in expressing urokinase plasminogen activator via the OB-Rb, RhoA/ROCK, PI3K/AKT, JAK/STAT, and NF- $\kappa$ B pathways, which constitute a new mechanism of ovarian cancer expansion [32].

In ovarian cancer, the inductive effect of resistin on the growth of cancer cells, their spread, resistance to cisplatin through the transformation of epithelial into mesenchymal stem cells (EMT) is indicated, which with the simultaneous suppression of miRNA, let-7a, miR-200c, and miR-186 lies at the base of producing chemoresistance [33].

## CONCLUSIONS

Taking into consideration the global increase in the number of obese people as well as the current research results, it is necessary to deepen the research concerning the mechanisms linking obesity with the increased risk of ovarian cancer development and its impact on the prognosis and course of the disease among female patients.

### Conflict of interest

All authors declare no conflict of interest.

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