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Review Article

The role of overweight and obesity in selected gynecological malignancies

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Summary

A review of literature data related to the effects of overweight and obesity on the development and course of selected gynecological malignancies: endometrial, breast and ovarian cancer is presented. Three hypotheses are included in an attempt to explain this relationship: the adipokinine hypothesis, a hypothesis involving the effects of excessive estrogen levels, and the insulin hypothesis.

Key words: Obesity; Endometrial cancer; Breast cancer; Ovarian cancer.

Introduction

Obesity is a 21st century global health and social problem, affecting both economically developed and developing countries [1, 2]. According to the WHO classification, overweight and obesity are defined on the basis of body mass index (BMI). To calculate the BMI value, body mass [kg] is divided by the square of body height (m^2); BMI= kg/m^2. Overweight is defined as a situation in which BMI value exceeds 25, obesity is when BMI $\geq$ 30, and extreme obesity occurs when the value of BMI $\geq$ 40. Another index linked to obesity is the waist-hip ratio (WHR), in women the normal value amounts to $\leq$ 0.8; while higher values point to central (visceral) obesity [3]. In 2012, over half of the population in European Union was estimated to be overweight while one in every six was obese. In the population of women aged 45- 64 years in the Czech Republic, Lithuania, and UK, over 60% are overweight or obese. Among women aged 65 to 70 years living in Lithuania, Slovakia, UK, and Greece, over 70% suffer from obesity or overweight. Similarly in Poland: 60% of women aged 45 to 64 years, and as many as 70% of women aged 65 to 70 years are overweight or obese. The lowest proportion of women with excessive body weight was encountered in France, Italy, and Romania [2].

Excessive body weight is linked to increasing incidence of several malignant tumours of the esophagus, large intestine, gall bladder, pancreas, breast cancer in postmenopausal women, ovarian cancer, prostate cancer, and kidney cancer. Around 4% to 38% of the cancers were found to manifest a correlation with overweight [2, 4]. The meta-analysis of data originating from ten European countries fully confirmed the relationship between cancer development and obesity [5]. Reneham *et al.* [6] pointed to a relationship between the development of cancers in the breast, ovary, and endometrium and BMI in postmenopausal women. Prospective studies on a population of over 495,000 women monitored for 16 years demonstrated that the value of BMI (at least 40 kg/m^2) was linked to an increased incidence of deaths due to cancers of the esophagus, large intestine, liver, gall bladder, pancreas, and kidney (HR 1.62). Significant trends toward increased mortality of obese women were also demonstrated in women with endometrial cancer, cancers of the breast, and ovary [7]. The elevated mortality due to malignant tumours in obese women additionally reflected numerous coexisting diseases such as strokes, cardiovascular diseases, and metabolic syndrome, resulting in an 88% increase in mortality in obese women suffering from cancer [7, 8].

The role of obesity in the development and progression of certain malignant tumour types remains to be fully clarified but several relevant hypotheses which have been suggested are presented below.

Adipokine hypothesis

Adipose tissue consists mainly of adipocytes and the stroma fraction, formed by pericytes, endothelial cells, monocytes, macrophages, and multipotential stem cells. Both adipocytes and the accompanying stroma cells secrete adipokines, including leptin, adiponectin, and pro-inflammatory cytokines, mainly TFNα, IL-6, IL-8, plasminogen activator inhibitor type 1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1). They also generate reactive oxygen species (ROS) which manifest mitogenic

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properties, PDGF, TGF, EGF, and VEGF, as well as insulin-like growth factor (IGF1), the recognised inducers of proliferation, metastases, and angiogenesis [9-12]. Adipose tissue of obese individuals manifests chronic inflammation and anoxia, additionally provoking the secretion of pro-inflammatory cytokines and hypoxia-induced factor 1 (HIF), which stimulates angiogenesis [13].

According to Nieman *et al.* [12], during interaction with cancerous cells (in anatomic vicinity), adipocytes undergo dedifferentiation, forming cancer associated adipocytes (CAA), which acquire functions supporting the development of cancer. They influence the migration and invasion of cancerous cells and release fatty acids in the process of lipolysis which are subsequently used for energy production by tumour cells. Thus, adipose tissue remains metabolically active, supporting the development and progression of cancer in obese individuals.

Insulin hypothesis

Epidemiological studies have demonstrated a relationship between obesity, diabetes type 2, insulin resistance, secondary hyperinsulinemia, increased levels of insulin-like protein factor-1 (IGF-1) on one hand, and the development of cancers on the other. Insulin manifests a mitogenic property, stimulating mitogen-activated protein kinases (MAPK) and in this way increasing cell proliferation and inhibiting apoptosis. It also augments the secretion of IGF and reduces the production of sex hormone binding globulin (SHGB), which binds estrogens, with the resulting increase in the level of active estrogens. Both insulin and IGF-1, as well as the growth factors secreted by adipocytes, activate the PI3K/AKT and mTOR pathways, involved in cell metabolism, proliferation, and apoptosis, thereby promoting cancer development [14-16].

Hypothesis of excessive estrogen level

Estrogens and mainly estradiol, are stimulators of cell division. IGF1 is also linked to cell proliferation. In contrast, progesterone inhibits cell division through a decrease in the number of estrogen receptors as well as stimulating the conversion of estradiol to less active estrogen forms (estrone and estrogen sulphates). It also inhibits the production of IGF1-binding peptide [17]. Extensive exposure to endogenous estrogens (early menarche, late menopause), the application of hormone-substitutive therapy (HST) and aromatization of androgens to estrogens in adipose tissue by aromatase P450 contained within, result in an alteration of hormonal homeostasis [18]. The elevated amount of cytokines in adipose tissue of obese individuals (particularly of TNF and IL6) increases the synthesis of estrogens as well activates the JAK/STAT pathway, which controls the concentration of aromatase. Therefore, the resulting pool of estrogens is excessive compared to the levels of progesterone [5, 19].

There is an increasing amount of epidemiological proof which indicates that cancers of the endometrium, postmenopausal breast cancers, and ovarian cancers develop more frequently in overweight or obese women.

Endometrial cancer

According to the Globocan world register for 2012, endometrial cancer is the second most frequently (following cancer of the uterine cervix) diagnosed malignant tumour of the female genital tract. In 2012, a total of 319,605 new cases were discovered which accounts for 4.8% cases of malignant tumours in women, causing 76,160 relevant deaths (2.1% of all deaths due to tumours in women). Among all European countries, Poland is ranked tenth in respective incidence [20]. In 2012, 5,426 cases of endometrial cancer were detected in Poland (a standardized coefficient of 15.13), which accounted for 7.1% of incidence manifested by all malignant tumours in women. The respective number of deaths amounted to 1,162 (a standardized coefficient of 2.73), which accounted for 2.76% of all deaths due to cancer [21].

Out of the two main types of endometrial cancer (types I and II), endometrioidal, estrogen-dependent type I comprised 80% of all cases [22, 23]. Epidemiological studies proved that cancer was linked to excessive body weight. Evaluation based on data originating from the Women's Health Initiative showed that BMI provided an independent risk factor stronger than diabetes or obesity [24].

Cohort (population) studies in over 62,000 women, including 226 patients with endometrial cancer demonstrated a four- to five-fold increase in the risk of developing this cancer in females with a BMI exceeding 30 kg/m^2 [25]. Between 2008 and 2013, the relationship between obesity and the incidence of endometrial cancer was subjected to questionnaire studies within research by the European Organization for Research and Treatment of Cancer (EORTC) conducted in 158 women. In 40% of obese women, BMI amounted to $\geq$ 30-39.9, and in 19% of women with morbid obesity BMI amounted to $\geq$ 40, which was associated with reduced life quality (physical efficacy, social functioning) and with somatic complaints [26].

As mentioned above, endometrial type I cancer is associated with hormonal disturbances in the form of excessive estrogen levels (duration of the hormonally active period, application of hormonal substitutive therapy), a complex relationship between estrogen and progesterone receptors, and metabolism in active adipose tissue. In obese individuals the secreted cytokines, hyperinsulinemia, an elevated level of IGF, which reduces the pool of estrogen-binding SHGB, assist in increasing the amount of estrogens [5, 15, 16, 23]. According to Setiawan *et al.* [27], on the basis of ten cohort studies and 14 case-controlled studies from the Consortium of Endometrial Cancer Epidemiology (including over 14,000 cases of endometrial cancer and over 35,000 women in the

control group), among whom 7,246 endometrial cancers of type I and 508 serous endometrial cancers (type II) were diagnosed, the profiles of risk factors for the cancers proved to be similar; obesity also proved to be a risk factor regarding type II endometrial cancers. Obesity in women with endometrial cancer is linked to an augmented mortality. Schouten *et al.* [25] evaluated that the risk is directly related to the BMI value; where BMI was > 40, the risk ratio (HR) amounted to 6.25, where BMI = 35-39.9 it was 2.77 and it was the lowest for a BMI of 25-29.9, and amounted to 1.5. On a large prospective study of the Women's Health Initiative covering over 161,000 women aged 50 to 79 years from 40 clinical centres, the relationship between obesity and mortality was statistically significant [28].

Data obtained from a review of 45 articles proved that in prophylaxis against endometrial cancer, a reduction of the obesity-linked IGF-1 concentration was important [29]. On the other hand, the significance of metformin used for the treatment of diabetes in women with endometrial cancer requires further studies due to the low numbers of data related to type I and II cancers [30].

Breast cancer

In 2012, in Poland, 17,000 new breast cancer cases were discovered (a standardized index of 51.9), which accounted for 22.2% of the incidence involving all malignant tumours in women. The respective mortality amounted to 5,574 (a standardized index of 14.11), accounting for 13.26% of all deaths due to the tumour [21].

The risk of developing breast cancer is most pronounced in the postmenopausal period. The evidence for the premenopausal period is not so clear, but some data indicate that visceral obesity (a VHR high value) likewise represents a risk factor in the premenopausal period [31, 32].

At the time of diagnosis involving breast cancer, 50% of the patients manifested overweight or obesity [33]. Meta-analyses indicate that an increase in body weight of five kg/m² in BMI increased the risk for postmenopausal breast cancer by around 12%, depending on the histological subtype of the cancer. Additionally, patients frequently manifest a predisposition to increase their body weight during oncological therapy [33, 34]. In such patients obesity is associated with an augmented risk of relapse in the disease, mortality, development of another tumour and deterioration quality of life (QOL) due to an increased risk of lymphedema in the upper extremities, following axillar lymphadenectomy, arterial hypertension or diabetes [33].

Following a diagnosis of breast cancer, obese women manifested lower survival, as compared to women with normal body weight [33, 35, 36]. In comparison to women with normal body weight, obese women exhibited a 41% increased risk of death for any reason during the timeframe of < 12 months and a 23% increase at > 12 months following diagnosis of the tumour. The risk of death due to breast cancer was also higher by 35% and 25%, respectively [35]. In addition, they are more frequently diagnosed as carrying a tumour with a higher primary dimension (trait T) and with metastases to the draining lymph nodes (trait N+) [36, 37]. Patients with metastases to the draining lymph nodes manifested a statistically distinct disease-free survival (DFS) and overall survival (OS) when obese patients and patients with normal body weight were considered. The differences were most evident in postmenopausal women and women with hormone-positive breast cancers [36]. The mechanism of the phenomenon remains incompletely recognised, and it is therefore difficult to evaluate if a loss in body weight following the diagnosis of breast cancer extended the OS of the patients. There is no reason then for which women should attempt to lose weight following the diagnosis of breast cancer [38]. On the other hand, it was proved that patients on a low lipid diet manifested a decreased risk in breast cancer relapse as compared to patients using no dietary restrictions [39].

The amplification or overexpression of HER-2 plays a significant role in the development and progression of certain subtypes of breast cancer; this group encompasses around 15% to 20% of breast cancers. An inverse correlation was documented between BMI and overexpression of HER-2 in breast cancers, particularly in patients with breast cancer over the age of 50 years [33, 40].

A study by the Eastern Cooperative Oncology Group E1199 proved that obesity failed to affect OS among women with HER-2-positive breast cancer, in contrast to women with hormone-positive and HER-2-negative breast cancers. However, other retrospective studies yielded reciprocal conclusions [41, 42].

The relationship between obesity and the triple negative breast cancer (TNBC) was also studied. No correlation could be detected between BMI and mortality due to TNBC. Regrettably, the studies were conducted in a small group of patients and the period of observation was short. The study was therefore statistically insignificant and unable to appropriately document the correlation described above [45]. In 2015, a meta-analysis was published involving Chinese women, among whom obese women carried a larger tumour more frequently, particularly evident in triple-negative cancers, likewise in the premenopausal period [43]. Obese patients with a diagnosis of triple-negative breast cancer less frequently manifested a complete response following the application of inductive therapy as compared to patients with normal body weight [44-46].

The report by Niraul *et al.* [35] indicated that obesity is linked to an augmented risk of breast cancer, not just the hormone-dependent cancer, but also cancer with a negative hormonal status ($p = 0.31$). The risk is similar, irrespective of menopausal status. Similar conclusions were presented by Protani *et al.* [32].

The poorer results of treatment in obese patients with diagnosed breast cancer may reflect a reduction in the appropriate cytostatics dose calculated per square meter (m²). As

doctors fear patients may experience toxicity due to the dose of cytostatics calculated on the basis of the patient's body height and weight, the dose applied is reduced to one calculated per two m^2 of body surface area (BSA). The presented studies failed to confirm the thesis that women with a BSA above two m^2, who received a suitable dose of cytostatic drugs experienced a more pronounced or more frequent toxicity after administration of cytostatic drugs [44]. Another question involves the fact that obese patients frequently receive reduced doses of cytostatic drugs due to their coexisting morbidities, i.e. arterial hypertension, diabetes or renal insufficiency.

According to the recommendations of the American Society for Clinical Oncology (ASCO), full calculated doses of cytostatic drugs should be administered to obese female patients since this augments their chances for survival, and does not aggravate the toxicity of the treatment [47].

Adjuvant hormonal therapy is effective and broadly used in patients with a diagnosis of estrogen receptor (ER)-positive (60% to 75% of all breast cancers) and progesterone-receptor positive (65% of ER-positive) breast cancers. Tamoxifen manifests the same efficacy in patients with breast cancer, independently of their body weight [33, 44].

Inhibitors of aromatase block cytochrome 450, thus not permitting the transformation of androgens into estrogen, inhibit cell proliferation and antiapoptotic activity. Therefore, in obese patients, anastrozol treatment is accompanied by decreased efficacy and a higher risk of death linked to breast cancer than in patients with a normal body weight [48].

The ALIQUOT study proved that letrozol, as compared to anastrozol, warranted a more pronounced suppression of estradiol/estrogen levels, particularly in patients with a high BMI [49], while the BIG-1.98 study demonstrated the same DFS and OS in patients with hormonally positive breast cancers independently of their BMI [50].

In obese females treated with aromatase inhibitors, side effects are more pronounced and manifest more frequently such as arthralgias, particularly in the hand region, which may be associated with an irregular administration of drugs in the group and, therefore, with less favourable prognosis [51]

The available literature on the subject presents two hypotheses of the less favourable results of treatment of obese patients with breast cancer. According to the first, obese patients may develop biologically more aggressive forms of cancer because obesity may dysregulate cell proliferation pathways, as described above. This may result in more intense tumour cell proliferation and more pronounced metastatic activity. For example, leptin and adipocytokin act as growth factors in tumour cells, including breast cancer cells. The second hypothesis is linked to IGF-1 activity. Obesity influences the amount of free IGF-1 available for cells but it does not affect the total levels of IGF-1 in the blood. IGF-1 represents an important mitogen in the breast gland. Binding between IGF-1 and its receptor, IGF-1R, motorizes the cascade of events leading to an augmented proliferation and anti-apoptotic events [52].

Summing up the above: the IGF-1 system is involved in the development, progression, and metastases of breast cancer. A potential mechanism linking obesity with an augmented risk of breast cancer is associated with resistance to insulin, hyperinsulinemia, hyperglycemia, glucose intolerance, and the production of adipocytokines. Adipose tissue produces factors, such as estrogens and adipokines, which act as mediators in metabolism, angiogenesis, and in cell proliferation [31]. It was also postulated that adipose tissue produces estrogens which may predispose post-menopausal females to biologically more aggressive forms of ER-positive breast cancer, since a direct correlation was documented between the level of circulating estrogens and BMI [38].

Obesity is known to predispose humans to coexisting diseases, such as type 2 diabetes mellitus or arterial hypertension. Metformin represents the first anti-diabetic drug, which allows a reduction in insulin, BMI, glucose, leptin, and CRP protein levels, independently of the original BMI. It is also linked to a reduced risk of breast cancer development and reduced mortality due to cancer in patients suffering from diabetes [53].

Physical exercise promotes a reduction in body weight and it is linked to a 10–25 % reduction in the risk of developing breast cancer [54].

Literature data indicate that obesity is associated with a deterioration of prognosis in pre- and post-menopausal patients affected by breast cancer. In this respect. no extensive difference could be noted between hormone-positive and hormone-negative tumours.

Even if standards of treatment remain the same, i.e. the applied dose of cytostatic drugs is calculated per body surface area and the adjuvant hormonal therapy with tamoxifen is administered in hormonally-positive patients for ten instead of five years, in cases of patients with contraindications preventing the use of tamoxifen, it seems that letrozol may prove more valuable in obese patients than anastrazol, but more respective studies should be conducted. In cases of breast cancer diagnosis, oncologists should encourage the patients to maintain a normal body weight, take advantage of physical exercise, and to follow a healthy lifestyle. Further studies are necessary to identify the most favourable model of exercise, their frequency, and duration in patients with breast cancer [34, 37, 54].

Ovarian cancer

In 2012, 3,544 cases of ovarian cancer development were detected in Poland (a standardized coefficient of 10.8), which accounted for 4.6% of malignant tumour developments in females. The number of deaths amounted to 2.432 (a standardized coefficient of 6.4), which accounted for 5.78% of all deaths due to cancer [21].

Ovarian cancer represents a heterogenous group of tumours, manifesting an extensive variability in clinical be-

haviour, histology, and molecular traits. Serous ovarian cancers manifesting a histopathological differentiation of G1 (low-grade serous epithelial ovarian cancer, LGSC) account for around 10% of all ovarian cancers [55]. Malpica *et al.* [56] in 2004 suggested a two-grade system for the classification of ovarian cancer, the high grade was reserved for G2 and G3 tumours and the low grade for tumours manifesting G1 histopathological differentiation. In line with the suggestion of Kurman and Shih [57], low grade serous ovarian cancers encompass a single subtype of type 1 ovarian cancers (epithelial ovarian cancer, EOC). Patients with a diagnosis of LGCS are younger, live longer, and in most cases the disease is restricted to the ovary only [58, 59].

The protective variables against the development of ovarian cancer include a higher number of pregnancies, use of oral contraception in the past, oophorectomy, bilateral ligation of the oviducts, and earlier hysterectomy. On the other hand, the development of ovarian cancer is promoted by hormonal substitutive therapy, a high lipid diet, smoking, alcohol consumption, and a lack of exercise [60].

Relationships between BMI, obesity, and development of ovarian cancer remain uncertain and few studies concerning such relationships are available. Literature on the role of obesity in ovarian cancer yielded contradictory data.

Earlier works pointed to a lack of differences in survival and in time before relapse was noted in obese women and women with normal body weight [61]. In another study, high stature was linked to a high risk of ovarian cancer, particularly among pre-menopausal women. BMI was linked to the manifestation of ovarian cancer in pre-menopausal women, while no such a relationship was detected in post-menopausal women [62].

It is quite possible that certain histological types of ovarian cancer are more related to obesity. It has been noted that obesity and overweight in young women are linked to higher chances of developing ovarian cancer. Also tall women below 60 years of age have a greater risk of developing ovarian cancer (particularly endometrioidal cancer) [63-65]. In 2013, Olsen *et al.* [66] on the grounds of a performed meta-analysis, demonstrated that obese patients exhibit a higher risk of developing serous ovarian cancer of marginal malignancy (HR 1.24), invasive endometrioidal cancer (HR 1.17), and invasive mucous cancer (HR 1.19). No relationship could be noted between BMI, and an invasive serous cancer (HR 0.98), with the exception of pre-menopausal women (HR 1.11). The risk of developing LGSC increases with an increase in BMI (HR 1.13). Obese patients suffering from LGSC manifest an abbreviated total survival [67]. Nagle *et al.* [68], in 2015, published a study indicating that obese women suffering from ovarian cancer manifest shorter duration of total survival (BMI: 30-34.9 HR 1,10; BMI > 35 HR 1.12). Similar results were related to the period of relapse development in ovarian cancer. It has also been shown that obese patients with LGCS or endometrioidal cancer do not live as long (HR 1.12; 1.08). A less strict relationship between BMI, and the duration of survival was demonstrated in patients with high grade serous ovarian cancer.

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