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# Range of Body Mass Index and the risk of breast cancer

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## Abstract

**Introduction.** Obesity leads to an increased incidence of many diseases. The research subject of scientists is the impact of obesity on breast cancer as one of the most commonly diagnosed cancers among women.

**Aim of the study.** Analysis of the relationship between overweight and obesity with the risk of invasive breast cancer.

**Material and method**. Review of studies on the association of obesity with the incidence of breast cancer published in the last 10 years.

**Results**. The study conducted in 67142 women who were measured at baseline weight is noteworthy. Overweight and obese women showed an increased risk of invasive breast cancer with a positive estrogen and progesterone receptor (HR 1.86; CI 1.60-2.17). The presented analysis of 1017 cases of women suffering from breast cancer showed that the BMI above 25kg/m2 in both the period before and after menopause was associated with a larger tumor size, shorter period of disease (DFS), overall survival (OS) (P <. 001) and a higher risk of recurrence and death due to illness (P <0.05). In a study analyzing the relationship of BMI and various subtypes of breast cancer in which 657 women participated, the high BMI in postmenopausal women is most strongly associated with a more benign form of breast cancer, which immunohistochemical appearance is as follows: ER +, PR +, HER2-, Ki67low, Bcl-2 + and p53- (HR per 5 kg / m2: 1.44 [1.10 1.90], p = 0.009).

**Conclusions.** The above analysis unequivocally convinces that the promotion of a healthy lifestyle and the development of obesity prevention programs may contribute to reducing the risk of breast cancer in women.

**Streszczenie**

**Wprowadzenie.** Otyłość prowadzi do zwiększonej zachorowalności na wiele chorób. Przedmiotem badań naukowców jest wpływ otyłości na raka piersi.

**Celem pracy** jest analiza związku nadwagi i otyłości (wyrażane w poziomie BMI) z ryzykiem wystąpienia inwazyjnego raka piersi.

**Materiał i metoda.** Przegląd badan dotyczących związku otyłości z zachorowalnością na raka piersi opublikowanych ostatnich 10 latach.

**Wyniki.** Na uwagę zasługuje badanie przeprowadzone u 67142 kobiet, u których zmierzono wyjściową masę ciała. Kobiety z nadwagą i otyłością wykazywały zwiększone ryzyko inwazyjnego raka piersi z dodatnim receptorem estrogenu i progesteronu (HR 1,86; CI 1,60-2,17). Analiza 1017 przypadków kobiet cierpiących na raka piersi wykazała, że BMI powyżej 25 kg / m2 zarówno w okresie przed menopauzą, jak i po menopauzie było związane z większym rozmiarem guza, krótszym okresem choroby (DFS), całkowitym przeżyciem (OS) ( P <0,001) i większe ryzyko nawrotów i śmierci z powodu choroby (P <0,05).W badaniu analizującym zależność BMI od różnych podtypów raka piersi, w których uczestniczyło 657 kobiet, wysoki BMI u kobiet po menopauzie jest najsilniej związany z bardziej łagodną postacią raka piersi: ER +, PR +, HER2-, Ki67low, Bcl-2 + i p53- (HR na 5 kg / m2: 1,44 [1,10 1,90], p = 0,009).

**Wnioski.** Powyższa analiza jednoznacznie przekonuje, że promowanie zdrowego stylu życia i opracowywanie programów zapobiegania otyłości może przyczynić się do zmniejszenia ryzyka wystąpienia raka piersi u kobiet.

## Background

Breast cancer is the most common diagnosed malignant tumor in women, which arises from breast cells and often gives metastases to the lymph nodes and organs such as the lungs, liver, bones or the brain. It accounts for 23% of cancers diagnosed in women. However, when it comes to the cause of death, it is classified in second place. Most cases are recognized in highly developed countries - the USA, Canada, Australia, and the least in Asia or Africa. The most important risk factors are female sex, age (the most vulnerable are women between 50-69), genetic factors (the occurrence of cancer in the sister or mother), presence of BRCA1 / BRCA2 mutation, hormonal factors (use of hormonal contraception or hormone replacement therapy), mild changes previously occurring breasts such as hyperplasia ductalis atypica and hyperplasia lobularis atypica, high density of glandular tissue and lifestyle (alcohol consumption or obesity).

Obesity is a condition in which the amount of adipose tissue in women exceeds 25% of the total body weight and 20% in men, which significantly exceeds the need. This may result in a number of disorders in the functioning of the body resulting in numerous diseases such as type II diabetes, cardiovascular disease, obstructive sleep apnea and certain types of cancer. From the concept of obesity one should distinguish the concept of overweight, which determines the excessive body weight above the norm. Body mass index (BMI) allows detection of overweight or obesity in adults. It was created by dividing body weight in kilograms by the square of height given in meters.

## Aim of the study

Analysis of the relationship of overweight and obesity expressed in the BMI index with the risk of invasive breast cancer.

## Material and method

Standard criteria were used to review the literature data. The search of articles in English in the PubMed database and Google Scholar was carried out using the following keywords: BMI, obesity, overweight, breast cancer

## Description of the state of knowledge

During a clinical trial conducted on the initiative of the WHI (Women's Health Initiative) in 40 American clinical centers, it was decided to analyze the relationship between overweight and obesity and the risk of post-menopausal invasive breast cancer. The project involved 67142

women in the post-menopausal age from 50 to 79 years of age, who were measured at baseline, weight, and yearly or two-year mammography. The results of the study show, after 13 years of observation in 2010, 3388 invasive breast cancers. Overweight and obesity were associated with an increased risk of estrogen and progesterone receptor positive breast cancer in postmenopausal women. Particularly high risk was associated with 2 and 3 degree of obesity which was associated with a larger tumor size, (HR 2.12, 95% CI 1.67-2.69, P = 0.02), more frequent involvement of lymph nodes ( HR 1.89, 95% CI 1.46-2.45, P = 0.06) and a significant risk of death (HR 2.11, 95% CI 1.57-2.84, P <. 001). In women whose baseline BMI was below 25 and whose body weight increased by 5% during the observation period increased the risk of this disease (HR 1.36, 95% CI 1.1-1.65). On the other hand, among women whose initial BMI was overweight or obese, the change in body weight was not associated with a change in the risk of invasive breast cancer [1].

An analysis of 1017 patients with breast cancer treated in 2004-2012 was performed. Patients were divided into three groups according to BMI, for normal weight - BMI below 25kg/m2, overweight - BMI 25-30kg / m2, obesity- BMI above 30kg / m2. Prognosis in individual groups was analyzed in relation to the menopausal state of women at the time of the diagnosis. BMI over 25kg / m2 both before and after menopause was associated with a larger tumor size, a shorter disease free period (DFS), overall survival (OS) (P <.001) and a higher risk of recurrence and death due to disease (P <0.05) (Sun L, 2018) [2]. In another group of 337 819 women, of whom 4385 incidents of invasive breast cancer were found, the relationship between body mass index (BMI) and breast cancer was different depending on the woman's menopausal state. Weight control can reduce the risk in postmenopausal women (Van den Brandt PA, 2000) [3].

During the next study (Liu K, 2018), a study was conducted on 22 768 674 participants to examine the relationship between BMI and the risk of breast cancer. The 95% confidence intervals (CI) and the total relative risk (SRR) were used for the risk assessment. The results showed a slight positive relationship between an increase in BMI by 5 units and thus by 5 kg / m2 and a 2% increase in the risk of breast cancer (SRR): 1.02, 95% CI: 1.01-1.04, p <0.001). However, a higher BMI in premenopausal women may be a risk-reducing factor (SRR: 0.98, 95% CI: 0.96-0.99, p <0.001) [4].

Among 84 patients with brain metastases for breast cancer treated with intracranial radiotherapy, the body mass index above 25kg / m2 was associated with a reduction in overall survival (OS) (13.7 vs 30.6 months, p <0.001) and with a reduction of progression-free time within intracranial metastases. No differences were observed among the various subtypes of

breast cancer. In the analysis taking into account various risk factors, BMI ≥ 25 kg/m2 [HR 2.35 (1.39-3.98) was associated with higher mortality due to the disease (McCall NS, 2018) [5].

Using the Healthy Lifestyle Indicator (HLI), the dependence of various modifiable factors increasing the risk of disease such as smoking, alcohol, diet, physical activity and BMI on the risk of invasive breast cancer from the Women's Health Initiative was assessed. The research group consisted of 131 833 post-menopausal women, of whom 168 had breast cancer. An increase in the HLI index by one unit corresponded to a 4% decrease in the risk of breast cancer. Women with the highest HLI score were 30% less likely to develop breast cancer positive for ER + / PR + and HER2 + receptors (HR = 0.70; CI 0.64-0.76, 0.63, 0.57-0.69 and 0.70, 0.55-0.90, respectively). It should be noted that the majority of the risk factors studied were independently related to cancer (Arthur R, 2018) [6].

The next study (Guo W, 2018) compared the method of measuring the amount of body fat by means of impedance and BMI. The study involved 162 691 post-menopausal women. Body weight was measured using specialized techniques. Included were age, socioeconomic status, age at birth, age of menarche and menopause, smoking, alcohol consumption and physical activity. 2913 invasive breast cancers were observed during the 6-year follow-up period. Increased body weight was associated with an increased risk of breast cancer. On the other hand, the measurement of fat mass by impedance over BMI measurement in relation to the risk assessment was not shown. In addition, the highest risk has been demonstrated in women over 12 years after menopause [7].

Next, the compounds of individual breast cancer types and the risk of their occurrence due to increased body weight were analyzed. The division was based on the molecular profile on the basis of which the basaloidal, luminal and HER2 types were isolated. The observation period was 2 years in this case. The average age of patients was 46 years, of which 58% did not undergo menopause. The average BMI was 24.1, which in postmenopausal women was statistically higher (24.9 vs. 23.6, $p < 0.05$), while obesity was found only in 10% of the subjects. The relationship between BMI and breast cancer subtype has been demonstrated. The lowest values were obtained for the HER2 subtype, which amounted to 22.4, 23.9 for the basaloid subtype respectively, and the highest for 24.7 luminal breast cancer ($p < 0.01$). Also, the tumor size was related to the tumor subtype and was 4, respectively 02, 3.80 and 4.27 cm ($p = 0.158$) for the luminal, HER2 and basaloidal subtypes (Govind Babu K, 2018) [8].

The research group of the next study (Cho WK, 2018) was 5668 patients undergoing surgical treatment for breast cancer in 1996-2013. Disease-free survival (DFS) and overall

survival (OS) were analyzed in relation to patients with BMI ≥ 25 kg / m2 and <25 kg / m2 (P = 0.012 and 0.005 respectively). In all subtypes of breast cancer, BMI over 25 was an unfavorable factor only for OS (P = 0.030). Patients with HR + / HER2- cancer with BMI below 25 had longer DFS and OS, compared to patients with BMI above 25 (P = 0.012 and 0.005 respectively) [9].

Once again, it was examined whether there is a difference between different types of breast cancer depending on the weight of the body. For this purpose, 6 different immunohistochemical markers (ER, PR, HER2, Ki67, Bcl-2 and p53) were evaluated. 657 breast cancer incidents were analyzed. The relationship between BMI and breast cancer was assessed using Cox regression models. The menopausal status and the use of hormone replacement therapy were also taken into account. The results show that the high BMI in postmenopausal women who do not receive hormone replacement therapy is most strongly associated with more benign form of breast cancer, which immunohistochemical appearance is as follows: ER +, PR +, HER2-, Ki67low, Bcl-2 + and p53- (HR per 5 kg / m2: 1.44 [1.10 1.90], p = 0.009). However, no links to more aggressive subtypes of breast cancer have been demonstrated (Nattenmüller CJ, 2018) [10].

The next study (Goodwin PJ, 2018) found that obesity is associated with an increased risk of triple negative breast cancer after menopause and poor prognosis for most types of breast cancer. In obese people, breast cancer is often at more advanced stage, and may show biological differences from non-obese women. This is due to many factors underlying to the link between obesity and the emergence of cancer and obesity and systemic changes that promote cancer, enhance proliferation, invasion and metastasis [11].

In addition to obesity, the risk factor for breast cancer is the high mammography density of the breast, which often masks malignant lesions of this organ. The study was conducted among patients undergoing bariatric procedures (e.g. sleeve gastrectomy). The women had mammograms performed before and after the operation. The average weight loss was 28.7 kg, the average initial BMI was 44.3, and the average final BMI was 33.6 (range: 20-62, p <0.01). The reduction in body weight as a result of the treatments resulted in an increase in breast mammographic density in 14% of cases, and thus increased risk of breast cancer (Partain N, 2018) [12].

The hypothesis was analyzed - obesity in childhood protects against the development of breast cancer. Mammograms were performed among 365 premenopausal women at the University of Washington (St. Louis, MO) from 2015 to 2016. BMI at the age of 10 was analyzed using special software and data from the "Growing Up Today" study. The relationship between

mammography density and BMI in childhood was determined. Obesity at an early age turned out to be inversely proportional to breast mammography density. Each gain in BMI by one unit or 1kg / m2 at the age of 10 resulted in a 6.4% decrease in breast gland density and an increase of 6.9% in the amount of adipose tissue in the breast. The body mass of women determined at the age of 10 was divided into 6 groups starting from the lowest ending with the highest weight. Patients whose body weight was in group 3 or 4 showed a 16.8% decrease in density and a 26.6% increase in adipose tissue in the breast. Correspondingly, the group 5 was characterized by a density decrease of 32.5% and an increase in the amount of adipose tissue by 58.5%. In group 6, there was a 47.8% decrease in breast gland density and 80.9% increase in adipose tissue content ($P < 0.05$) (Alimujiang A, 2018) [13].

The mechanism which is responsible for the higher incidence of breast cancer among women with obesity and overweight is probably multifactorial. Noteworthy is the higher level of estrogen in people with more adipose tissue, and the fact that they have breast cancer positive for estrogen receptors. The relationship between body mass index and sex hormone estradiol concentration was examined in serum. The study group consisted of 624 women diagnosed with breast cancer and 1669 persons constituting a control group. The hypothesis was confirmed that the increase in BMI increases the risk of breast cancer and this is directly related to the higher level of estradiol in the blood. This dependence was particularly strong in postmenopausal women. In addition, obese patients tolerate surgical treatment worse and have more complications. This causes a delay in the inclusion of systemic treatment such as chemo- or hormone therapy, which in addition in people with BMI above 30 is less effective. It should be remembered that the relationship between body fat and body composition is not responsible for the relationship described, and the BMI index does not differentiate between lean and nonfat fat [14, 15].

The ethnicity of women can be important in the relationship between obesity and breast cancer in pre-menopausal women. An increase in body mass index of 5 kg was inversely related to the risk of breast cancer before menopause (RR = 0.95, 95% confidence interval [CI]: 0.94, 0.97), whereas this relationship was confirmed only among African Americans (RR = 0.95, 95% CI: 0.91, 0.98) and Caucasian women (RR = 0.93, 95% CI: 0.91, 0.95). In Asian women, weight gain resulted in an increased risk of breast cancer before menopause. It is worth mentioning the waist-hip index (WHR), in which an increase of 0.1 unit was associated with an increased risk of pre-menopausal breast cancer (RR = 1.08, 95% CI: 1.01, 1.16), which was most visible among women of Asian origin (RR = 1.19, 95% CI: 1.15, 1.24). A weaker relationship will be observed in the African race of 5% and white 6% (Amadou A, 2013) [16].

**Summary**

The results presented above suggest that the relationship between overweight and obesity and the risk of breast cancer may depend on many factors. It is necessary to mention the passage of menopause, hormone replacement therapy, fat distribution, subtype of cancer, breast mammography density, and even ethnicity. Obesity increases the risk of developing a positive estrogen receptor breast cancer characterized by relatively low aggressiveness. However, further studies are needed to confirm the relationship of BMI to other subtypes of breast cancer. To better understand the pathogenic mechanisms responsible for the described dependence, further analyzes are certainly necessary. This would help prevent, control and cure the disease better. Increased BMI results in a potentially higher risk of breast cancer in postmenopausal women. However, the research results that determine the relationship between obesity and breast cancer in pre-menopausal patients, which undoubtedly require further analysis, are unclear. It seems, therefore, that the menopausal status of a woman is very important here. The above analysis unequivocally convinces that the promotion of a healthy lifestyle and the development of obesity prevention programs may contribute to reducing the risk of breast cancer in postmenopausal women.

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