RELATIONSHIP BETWEEN OBESITY AND BREAST CANCER

Relação entre obesidade e câncer de mama

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ABSTRACT

Obesity is a growing clinical condition around the world, considered a risk factor for numerous diseases such as hypertension, myocardial infarction, diabetes, and cancer. Among the neoplasms related to overweight, breast cancer stands out. Therefore, the objective of this review is to elucidate the impact of obesity on the most prevalent cancer among women, either as a direct risk factor for its onset or as a determinant of survival.

KEYWORDS: obesity; cancer; breast cancer; risk factor.

RESUMO

A obesidade aponta como condição clínica em ascensão pelo mundo, considerada fator de risco para inúmeras doenças como hipertensão, infarto, diabetes e câncer. Dentre as neoplasias relacionadas com o excesso de peso, destaca-se o câncer de mama. O objetivo desta revisão é, portanto, elucidar o impacto que a obesidade causa no câncer mais prevalente entre as mulheres, seja como fator de risco direto para seu aparecimento, seja como determinante na sobrevida.

PALAVRAS-CHAVE: obesidade; câncer; câncer de mama; fator de risco.

INTRODUCTION

Obesity causes a chronic state of systemic inflammation, which in turn is one of the conditions for the development of several types of neoplasms, including breast cancer[1-3]. Data from the Brazilian Association for the Study of Obesity and Metabolic Syndrome (*Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica* - ABESO) in 2013 indicate that approximately 56% of Brazilians are overweight[4]. Around 20% of this group are obese, that is, their body mass index (BMI) is greater than or equal to 30 kg/m². This percentage is increasing around the world, which is alarming since overweight alone is responsible for many diseases, such as hypertension, diabetes, myocardial infarction, dyslipidemia, and cancer. In the United States of America (USA), this situation is even more critical, with approximately 40% of the population considered obese[5]. The risk of breast cancer for obese post-menopausal women has been well defined, as expounded below, but for pre-menopausal women, it is still being established, covering only some histological subtypes such as the triple-negative[6]. Risks of recurrence and death also increased in the subgroup of patients who already were obese at diagnosis, seeming more determinant for women with BMI above 35 kg/m²[7].

DISCUSSION

Overweight and obesity have been associated with increased risk of hormone positive breast cancer (presence of progesterone and/or estrogen receptors) in post-menopause. On the other hand, the most consistent studies on pre-menopause show an inverse relationship between overweight, obesity, and the incidence of breast cancer in general[6,8], although the risk of the triple-negative histopathological subtype has been rising in this population. Such data have caused a strong impact on the Medical Society, which, in 2012, at the annual meeting between several North American medical entities, including the National Cancer Institute, concluded that obesity is responsible for a relative risk of 1.25 of developing breast cancer in post-menopause[9]. This same report established that physical activities and other weight loss efforts should be encouraged to avoid the growth of neoplasms in the USA.

A randomized clinical trial conducted by the North American group Women's Health Initiative (WHI), involving a 13-year follow-up of post-menopausal women, aged 50 to 79 years, showed a linear relationship between the risk of developing breast cancer and the various categories of body mass index (p<0.001)[6]. The group of women with BMI above 35 kg/m2 showed the strongest association. Their risk of developing invasive breast cancer was 58% higher compared to women with BMI lower than 25 kg/m². This same study analyzed a subgroup of women who developed breast tumors histologically positive for estrogen and progesterone receptors. The risk of developing this specific tumor was 56%

higher among grade I obese women (BMI between 30 and 35 kg/m²) and 86% among grade II obese women (BMI above 35 kg/m²) when compared to women with normal BMI, according to the categorization of the study. The growth of estrogen receptor positive tumors is under the direct influence of estrogen levels, which are higher in overweight and obese post-menopausal women[10,11]. This scenario is the result of the facilitated aromatization of androstenedione and testosterone into estrogens in the adipose tissue[12,13].

Still on the WHI study[6], we highlight an important fact: women who started the follow-up with BMI below 25 kg/m² and had a weight gain of 5% above usual had a relative risk of 1.36 of developing invasive breast cancer when compared to women who maintained a stable weight. Besides the role of aromatization in carcinogenesis, the inflammatory behavior of adipocytes stands out. These two potential causes might explain the increased risk of breast cancer in the specific population who gained weight. The result suggests that preventing weight gain in healthy women can reduce their risk of developing breast cancer.

In contrast, the same study could not determine if there was an increase or decrease in the risk of breast cancer for subgroups of overweight and obese women who gained or lost weight during the follow-up. As this is not a specific study to analyze weight loss and its effects, we could not draw inferences about these results, not least because an unintended weight loss might have occurred. The conclusion from this research is that further well-designed studies aimed at this weight loss strategy are necessary.

Death specifically related to breast cancer in the group with BMI above 35 kg/m² was also twice as high than in the one with normal BMI. In addition, obesity has been associated with tumors having a larger diameter, presence of nodal disease, and distant metastases at diagnosis[6].

Recently, two large meta-analyses[14,15] skillfully described the negative influence of obesity on the survival of breast cancer patients, but with limitations, since the patient samples were heterogeneous, and the degree of obesity was not determined.

A recent observational study[16] that analyzed 18,967 women with a 10-year follow-up revealed a higher risk of distant metastasis at diagnosis when their BMI was greater than or equal to 30 kg/m². The risk of developing distant metastasis after 10 years of follow-up and dying of breast cancer after 30 years of being diagnosed was 46 and 38%, respectively, for women with BMI greater than or equal to 30 kg/m² when compared to those with BMI lower than 25 kg/m².

A retrospective analysis of a randomized phase III clinical trial called SUCCESS[17], involving more than 3,700 patients, verified the influence of obesity on people with high-risk breast cancer, with a follow-up of 65 months. The definition of high-risk adopted was: histologically positive axillary lymph node metastasis (pN1-N3) or node-negative breast cancer with tumor size greater than or equal to pT2, grade 3, negative hormone receptor status, or age

lower than 35 years. The mean patient age was 53 years, ranging from 21 to 86 years.

In this study, severely obese patients (BMI greater than or equal to 40 kg/m²) had worse disease-free survival and overall survival rates, with a relative risk of 2.70 and 2.79, respectively, when compared to patients with normal weight. It is noteworthy that the study separated patients according to BMI in normal weight/underweight (BMI lower than 25 kg/m²), overweight (between 25 and 29.9 kg/m²), slightly obese (between 30 and 34.9 kg/m²), moderately obese (between 35 and 39.9 kg/m²), and severely obese (greater than 40 kg/m²). Besides severely obese patients, no other subgroup was statistically significant in relation to worse progression-free survival and overall survival.

In general, epidemiological studies[18,19] show that obesity is a protective factor for breast cancer in pre-menopause. For young women, the ovary is the main source of circulating estrogens. As obesity would cause less frequent and irregular menstrual cycles, women would have less systemic exposure to estrogen, which would reduce their risk of developing hormone receptor positive tumors[20,21]. Corroborating this hypothesis, a recent study that retrospectively analyzed 2,659 women diagnosed with invasive breast cancer showed that this protection might occur in cases of luminal A tumors, that is, obese women would have a lower chance of developing tumors with this histological subtype[22]. However, a subgroup analysis of the same study showed a positive relationship between obesity and triple-negative breast cancer in pre-menopause. For each 5 kg/m² increase in BMI, the risk of developing a triple-negative tumor rose 16%. Regarding post-menopausal women, for each 5 kg/m² increase in BMI, there was a decrease of 9 and 16% in the risk of triple-negative and HER2 positive tumors, respectively, but a higher chance of developing a hormone receptor positive tumor.

Even though three other large studies[23-25] did not show a statistically significant relationship, their results tended to suggest an increased risk of triple-negative breast cancer for young obese women, in contrast to the findings of the study cited above.

Works such as these, which study histopathological subtypes in breast cancer and determine the various degrees of obesity, show us that overweight alone cannot be considered an isolated risk factor for breast cancer since the menopausal status and degree of obesity are crucial for conclusions about each specific case.

With the advances in breast cancer diagnosis and treatment, patient survival has increased, so researches are turning to lifestyle changes as a way to avoid its recurrence and improve overall survival. Based on this assumption, a recent systematic review[26] emphasized the importance of combining diet with physical activity for weight loss and gain in quality of life. Didactically, this review lists in a table the main dietary and physical activity recommendations for patients survivors of breast cancer.

The ENERGY[27] study is a multicenter intervention trial with 692 breast cancer survivors who had received treatment for their tumor at least two years previously, including patients on hormone therapy. Patients were separated into two groups. One adopted a more interventionist approach, with customized newsletters about how to lose weight and phone advice, while the other group had less intensive assistance. After 12 months, the intervention group presented a mean weight loss of 6%, while in the control group, the loss was 1.5% (p<0.001). Data on recurrence-free survival and overall survival are still not available for this work, but the authors suggest that weight loss causes lower circulating levels of estrogens and cytokines, markers involved in worse general prognosis for breast cancer patients.

A multicenter randomized clinical trial called DIANA[28], which is currently in progress, intends to answer more appropriately whether changes in the lifestyle of overweight or obese survivors of breast cancer can result in less recurrence and better overall survival. The intervention group will be supervised on weekly physical activities and dietary adjustments, such as reduced intake of saturated fat, animal protein (except fish), and high glycemic index foods, and increase in the consumption of fruits and vegetables, with a focus on weight loss.

Regarding drug intervention, some studies[29-31] used metformin in obese non-diabetic breast cancer patients, but these works have methodological and phase II flaws, not allowing the drawing of conclusions that could change the medical practice at the moment. Many of these studies showed that administration of metformin decreased levels of glycated hemoglobin and insulin, indirect markers of inflammatory response.

CONCLUSION

Obesity is increasing around the world, becoming the cause of numerous cardiovascular diseases, in addition to being responsible for several types of neoplasms, particularly breast cancer, the most prevalent among women. Until a short time ago, obesity was considered a risk factor for breast cancer in post-menopausal women and worked as a protective factor for those in pre-menopause. However, recent studies have provided more detailed data, as demonstrated in this review. We underline the fact that severe obesity (BMI above 35 kg/m²) leads to an increased risk of breast cancer for post-menopausal women when compared to grade I obesity (BMI between 30 and 34.9 kg/m²), overweight (BMI between 25 and 29 kg/m²) and normal weight/underweight (BMI below 25 kg/m²).

Similarly, severely obese women receive more diagnosis of tumors with a larger diameter, nodal disease, and distant metastasis. With respect to pre-menopause, obesity has been increasingly associated with histologically triple-negative tumors, of worse prognosis. Considering these data, interventional studies have been developed to assist breast cancer survivors in losing weight and improving their life quality. Even though they present favorable data concerning weight loss, we need further

studies with wider sampling and long follow-up to draw definitive conclusions about gain in disease-free survival and overall survival. At any rate, all health professionals who follow breast cancer patients must recommend adjustments to their diet with reduced intake of saturated fat, animal protein (except fish), and high glycemic index foods, and higher consumption of fruits and vegetables, as well as physical activity monitored by a qualified physical educator.

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