OBESITY AS A CIVILIZATION DISEASE AND RISK FACTOR FOR BREAST CANCER

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Abstract
Obesity belongs to civilization diseases and is a risk factor for the occurrence of a number of serious diseases, including colon and breast carcinoma. Clinical and epidemiological studies have identified many important breast cancer risk factors. Some of these factors are intangible or beyond our control; such as age or family history. However, several modifiable lifestyle factors have been associated with a higher risk of developing breast cancer. The aim of the minireview is summarisation of the effect of endogenous estrogen on breast cancer and these clinically meaningful findings should motivate programs for obesity prevention from the view of the selected current studies.

Key words: Obesity. Breast cancer. Endogenous estrogen. Prevention.

1 Introduction

All over the world, breast cancer remains a major issue for public health. Increasing numbers of new cases and deaths are observed in both developed and less developed countries, only partially attributable to the increasing population age. In the 28 member states of the European Union, there were 361,608 new breast cancer cases in 2012 and these are estimated to have increased to 373,733 in 2015 (+3.4 %); deaths were 91,585 and 95,357, respectively (+4.1 %) [1]. No major differences in this trend can be appreciated across European countries. However, in 2006–2012 the mortality for larger tumours remained greater than that for smaller tumours, significantly for the comparison of T1c and T1a stage, and was independent from nodal status.

Recent data demonstrate that the age-adjusted obesity (BMI ≥ 30.0 kg/m^2) prevalence in USA is 34.9% among all adults age 20 years and older while that for overweight plus obesity (BMI ≥ 25.0 kg/m^2) is 68.5% [2]. More recently, the 2012 Annual Report to the Nation on Cancer [3] concluded that overweight and obese women have a relative risk for postmenopausal breast cancer of 1.13 and 1.25, respectively vs. normal weight women [4].

2 Obesity

Obesity is a growing global health problem all over the world. The prevalence of obesity has been increasing globally over the past decades, resulting today in over 600 million adults worldwide with a BMI of 30 kg/m^2 or greater [5,6]. By 2030, the number of overweight and obese adults is projected to reach 2.16 and 1.12 billion, respectively, accounting for 57.8% of the world's adult population [7]. Recent data demonstrate that the age-adjusted obesity (BMI ≥ 30.0 kg/m^2) prevalence in USA is 34.9% among all adults age 20 years and older while that for overweight plus obesity (BMI ≥ 25.0 kg/m^2) is 68.5% [2]. More recently, the 2012 Annual Report to the Nation on Cancer [3] concluded that overweight and obese women have a relative risk for postmenopausal breast cancer of 1.13 and 1.25, respectively vs. normal weight women [4].

3 Etiology of breast cancer

The cause of breast cancer is multifactorial and includes hormonal, genetic and environmental causes [8]. The association between obesity and breast cancer risk is complex and can be different depending on menopausal status, the use of postmenopausal therapy, breast cancer subtype and racial/ethnic group [9]. However, there is abundant and consistent epidemiological evidence suggesting that obesity is associated with a higher risk of developing breast cancer in postmenopausal women, particularly for the hormone-dependent subtype of breast cancer [8]. Obesity, which is characterized by an excess accumulation of body fat, is at the origin of chronic inflammation of white adipose tissue and is associated with dramatic changes in the biology of adipocytes leading to their dysfunction. Inflammatory factors found in the breast of obese women considerably impact estrogen signaling, mainly by driving changes in aromatase expression the enzyme responsible for estrogen production, and therefore promote tumor formation and progression. There is thus a strong link between adipose inflammation and estrogen biosynthesis and their signaling pathways converge in obese patients [8, 13].

The development of breast cancer cells is linked to hypoxia. The hypoxia-induced factor HIF-1α influences metastasis through neovascularization. Hypoxia seems to decrease the responsiveness to hormonal treatment due

to loss of estrogen receptors (ERs). Obesity is discussed to increase hypoxia in adipocytes, which promotes a favorable environment for tumor cells in mammary fat tissue, whereas, tumor cells profit from good oxygen supply and are influenced by its deprivation as target regions within tumors show [10].

4 Obesity nad breast cancer

Neuhouser et al. investigated in their study the associations of overweight and obesity with risk of postmenopausal invasive breast cancer after extended follow-up in the Women's Health Initiative clinical trials [4]. Women who were overweight and obese had an increased invasive breast cancer risk vs women of normal weight. Risk was greatest for obesity grade 2 plus 3 (body mass index - BMI >35.0; hazard ratio - HR for invasive breast cancer, 1.58; 95% CI, 1.40-1.79). A BMI of 35.0 or higher was strongly associated with risk for estrogen receptor-positive and progesterone receptor-positive breast cancers (HR, 1.86; 95% CI, 1.60-2.17) but was not associated with estrogen receptor-negative cancers. Obesity grade 2 plus 3 was also associated with advanced disease, including larger tumor size (HR, 2.12; 95% CI, 1.67-2.69; P = .02), positive lymph nodes (HR, 1.89; 95% CI, 1.46-2.45; P = .06), regional and/or distant stage (HR, 1.94; 95% CI, 1.52-2.47; P = .05), and deaths after breast cancer (HR, 2.11; 95% CI, 1.57-2.84; P < .001). Women with a baseline BMI of less than 25.0 who gained more than 5% of body weight over the follow-up period had an increased breast cancer risk (HR, 1.36; 95% CI, 1.1-1.65), but among women already overweight or obese we found no association of weight change (gain or loss) with breast cancer during follow-up. There was no effect modification of the BMI-breast cancer relationship by postmenopausal hormone therapy, and the direction of association across BMI categories was similar for never, past, and current hormone therapy use.

Grill et al. [11] analysed in their study the relationship of the seemingly harmful lifestyle factors such as nicotine and alcohol indulgence, obesity, and physical inactivity, as well as a low socioeconomic status and increased cancer prevalence in a cohort of BRCA 1 and 2 mutation carriers. Study participants indicating a higher physical activity during their adolescence showed a significantly lower cancer prevalence ($p = 0.019$). A significant difference in cancer occurrence authors observed in those who smoked prior to the disease, and those who did not smoke ($p < 0.001$). Diseased mutation carriers tended to have a lower BMI compared to non-diseased mutation carriers ($p = 0.079$), whereas non-diseased revealed a significantly higher physical activity level than diseased mutation carriers ($p = 0.046$). Based on obtained data authors suggested that smoking and low physical activity during adolescence are risk factors for developing breast cancer in women with BRCA1 or BRCA2 mutation. Obesity may negatively affect survival in breast cancer, but studies are conflicting, and associations may vary by tumor subtypes and race/ethnicity groups.

Liu et al. [12] identified 273 women with invasive breast cancer administered Adriamycin/Taxane-based neoadjuvant chemotherapy from 2004 to 2016 with body mass index (BMI) data at diagnosis. Obesity was defined as BMI ≥30. Associations between obesity and event-free survival (EFS), using STEEP events, and overall survival (OS), using all-cause mortality, were assessed overall and stratified by tumor subtype [Hormone Receptor Positive (HR+)/HER2-, HER2+, and Triple-Negative Breast Cancer (TNBC])] in our diverse population. Overall, obesity was associated with worse EFS (HR 1.71, 95% CI 1.03-2.84, $p = 0.04$) and a trend towards worse OS ($p = 0.13$). In HR+/HER2- disease ($n = 135$), there was an interaction between obesity and hormonal therapy with respect to OS but not EFS. In those receiving tamoxifen ($n = 33$), obesity was associated with worse OS (HR 9.27, 95% CI 0.96-89.3, $p = 0.05$). In those receiving an aromatase inhibitor ($n = 89$), there was no association between obesity and OS. In TNBC ($n = 44$), obesity was associated with worse EFS (HR 2.62, 95% CI 1.03-6.66, $p = 0.04$) and a trend towards worse OS ($p = 0.06$). In HER2+ disease ($n = 94$), obesity was associated with a trend towards worse EFS (HR 3.37, 95% CI 0.97-11.72, $p = 0.06$) but not OS. Race/ethnicity was not associated with survival in any subtype, and there were no interactions with obesity on survival. Based on their results authors suggested that obesity may negatively impact survival, with differences among tumor subtypes.

5 Conclusion

Previous studies have indicated that obesity is one of the risk factors for postmenopausal women with breast cancer; in addition, weight gain is associated with poor prognosis of premenopausal breast cancer. However, the exact pathogenesis of obesity in the occurrence and development of breast cancer is still unclear. Currently, many risk factors are known, including abdominal obesity among the most important. This causes the release of endogenous estrogens and other health complications. Therefore, it is of utmost importance to understand the relationship between obesity in postmenopausal women and the development of breast cancer and, in particular, to target risk patients aged 50-70 years. Higher attention should be taken to informing (not only) the women to understand the importance of regular prenatal visits and to understand the importance of a healthy lifestyle.

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