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Chapter

Obesity and Breast Cancer

Abdullah Şişik, Hasan Erdem, Muhammed Said Dalkılıç, Mehmet Gençtürk, Merih Yılmaz and Selim Sözen

Abstract

Obesity is associated with a higher risk of chronic diseases. Breast cancer is one of the malignancies, which has been related to obesity. Patients with a BMI more than 35 kg/m^2 had an 86% greater risk of having breast cancer than those with a normal BMI. Every 5 kg/m^2 rise in BMI has also been demonstrated to increase the risk of postmenopausal breast cancer. Obese people have poorer outcomes in terms of lymph node positivity, disease-free survival, and overall survival, according to research. Leptin, whose circulating levels rise in proportion to BMI and body fat reserves, is usually regarded as the primary driver of the intricate web that connects obesity and breast cancer. The number of studies examining the association between leptin activity and breast cancer genesis and behavior is growing. The effectiveness of bariatric surgery on lessening the risk of developing breast cancer has been proven.

Keywords: breast cancer, leptin, obesity, bariatric surgery

1. Introduction

Obesity prevalence is rapidly increasing in many developed and developing countries. Obesity is related to an increase in the risk of chronic diseases. Obesity is associated with type 2 diabetes, hypertension, cardiovascular disease, and a variety of cancers. Breast cancer is another malignancy that has been related to obesity [1, 2].

American Institute for Cancer Research (AICR) reported that 13 cancers, including postmenopausal breast cancer, colorectal cancer, endometrial/uterine cancer, esophageal adenocarcinoma, gallbladder cancer, stomach cancer, hepatocellular cancer, meningioma, multiple myeloma, ovarian cancer, pancreatic cancer, kidney cancer, and thyroid cancer, were associated with obesity [3, 4].

Breast cancer is one of the most frequently diagnosed cancers among women worldwide. It is known that breast cancer has a worse prognosis and higher mortality rates in obese women [5, 6]. Hyperinsulinemia, estrogen signaling, inflammation, and adipokine expression hypotheses have been proposed for the mechanism of action of obesity in breast cancer patients [7, 8]. At this point, the concept of adipokines is emerging. Despite being primarily produced by adipocytes, adipokines, which are endocrine, paracrine, and autocrine mechanisms produced in a variety of different cells, influence the development of malignancies in obese people [8]. Leptin, an adipokine, plays an important role in the relationship between obesity and breast cancer [9, 10].

2. Breast carcinoma

Classification of breast carcinoma is based on clinicopathological features and expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Approximately 70% of breast cancers consist of tumors that express hormonal receptors.

Genetic profile, age at menarche and menopause, parity, age of first child, past cancer occurrence, and lifestyle are the most important risk factors for breast cancer. However, BRCA1/2 mutations account for approximately 5–10% of cases [11]. Also, obesity, metabolic syndrome, alcohol, and hypercholesterolemia are the other risk factors for breast cancer [12]. Despite all the advances in medical oncology in people with breast cancer, fatal metastases may occur even years after surgical treatment [13, 14]. Bone, lung, and brain are the primary areas of metastasis. The invasion-metastasis process takes place in successive steps. These steps are defined as local invasion, intravasation, circulation survival, attachment and extravasation in distant organ regions, creation of micrometastases, and metastatic growth [15, 16]. Failure at any step will end the metastasis process.

3. Relationship between obesity and breast cancer

3.1 Epidemiology

It is worrying that the incidence of obesity has increased rapidly all over the world, and the relationship between obesity and different types of cancer has been revealed recently. According to WHO data, the incidence of obesity in women is above 35–40%. It has been shown that patients with class 2 and class 3 (class 2: body mass index (BMI) = 35–40 kg/m^2, class 3: BMI= > 40 kg/m^2) obesity have an 86% higher risk of developing breast cancer than patients with normal BMI [17]. The impact of obesity on breast cancer risk differs according to menopausal status and disease subtypes. Current evidence suggests that while increased BMI is associated with a reduced risk of breast cancer before menopause, it is strongly associated with an increased risk after menopause [18].

As is known, postmenopausal obesity is a risk factor for hormone receptor positive breast cancer in women [19–21]. Postmenopausal breast cancer risk has also been found to be positively associated with every 5 kg/m^2 increase in BMI [22].

Class 2 and class 3 obese individuals had more negative results in terms of tumor size and metastasis. There are also studies showing that obese individuals have worse outcomes in lymph node positivity, disease-free, and overall survival [23–30]. Secondary primary cancer formation and contralateral breast cancer formation have been reported to be increased in obese individuals [31]. On the other hand, adverse effects of obesity in adjuvant therapy have been demonstrated. Less response to treatment was obtained in obese individuals in both chemotherapy and aromatase inhibitor therapy.

3.2 Physiopathogenesis

In the presence of obesity, hypertrophy and hyperplasia are seen in white adipocytes, and accordingly pathophysiological changes such as increase in free fatty acid (FFA) and triglyceride levels increase in blood sugar and increase in insulin resistance occur.

Obese adipose tissue also produces inflammatory cytokines (e.g. tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and TGF-β) and factors called adipokines with important local and systemic functions. The release of these molecules can profoundly affect breast cancer progression, both through a direct effect on neoplastic epithelial cells and indirect effects on the tumor microenvironment [32]. Among the adipokines, leptin, whose circulating levels rise in proportion to the amount of BMI and body fat stores, has been widely accepted as the main driver of the complex web linking obesity and breast cancer.

3.2.1 Obesity, chronic inflammation, and breast cancer

Excessive calorie intake or low calorie expenditure leads to an increase in fat compartments. This causes dysregulation in the production of steroid hormones and adipokines and causes chronic subclinical inflammation. Such changes have been associated with carcinogenesis, tumor progression, and metastasis [33]. Adipose tissue inflammation may explain the physiological link between obesity and breast cancer. Inflamed adipose tissue is characterized by infiltrating macrophages surrounding dying adipocytes, termed crown-like structures (CLS) [34]. The presence of CLS in breast adipose tissue (CLS-B) is associated with activation of NF-κB and increased levels of pro-inflammatory factors, resulting in upregulation of estradiol (E2). In conclusion, locally produced estrogens can be considered the main driver for the development of hormone-dependent breast cancer in postmenopausal women.

Adipocytes produce adiponectin and leptin, which are involved in the regulation of calorie intake and metabolism, inflammation, angiogenesis, and cell proliferation. Breast cancer cells are surrounded and affected by this microenvironment. A strong role for leptin in breast carcinogenesis has been reported with abundant evidence. It may contribute to local pro-inflammatory mechanisms, especially in obese patients. There is a positive correlation between the BMI index and leptin levels, whereas adiponectin concentrations generally decrease with more adiposity. The increased leptin-adiponectin ratio seen in obesity has been associated with neoplastic transformation and tumor progression [35].

3.2.2 Leptin and breast cancer

Leptin is a molecule involved in appetite control, hematopoiesis, osteogenesis, angiogenesis, and proliferation of different cells such as breast cells [9, 10]. Studies showing the relationship between leptin activity and breast cancer formation and cancer behavior are increasing in the literature. Leptin may act as a molecular link between obesity and breast cancer [36]. Leptin exerts its effects through the transmembrane leptin receptor (ObR) expressed in various tissues. Many studies, both clinical and experimental, have shown that the leptin/ObR axis is involved in breast cancer progression and metastasis. Breast cancer cells overexpress the leptin receptor, thus rendering them highly susceptible to the effect of the high leptin levels typically seen in obese patients [37]. Leptin exerts pleiotropic effects in breast cancer cells, including inhibition of proapoptotic signals, sensitivity to estrogens, and modulation of the tumor microenvironment, contributing to local pro-inflammatory mechanisms and promoting breast tumor growth [37–39]. Increased leptin levels in breast cancer patients have been associated with the increased risk of metastasis and reduced survival [25].

Niu et al. showed the presence of higher leptin levels in people with breast cancer than in normal individuals in their epidemiological-based meta-analysis. In addition, people with breast cancer with lymph node metastases have been shown to have higher leptin levels than those without metastatic disease [40]. It has also been shown that serum leptin levels are higher in obese breast cancer patients [41]. In postmenopausal ER-positive breast cancer patients, serum leptin levels were higher at more advanced tumor stage (pT and TNM stage) and in the presence of distant metastases [42]. Similarly, leptin concentrations were significantly associated with TNM staging, tumor size, histological grading, lymph node involvement, and metastasis in postmenopausal breast cancer cases [43, 44]. Tumor size and lymph node metastasis have also been shown to correlate with increased leptin/adiponectin serum ratio in breast cancer patients. Ishikawa et al. observed that patients with overexpression of ObR and leptin in primary breast tumors developed more distant metastases [37]. In ER-negative breast cancer patients, ObR was found to be significantly overexpressed in metastatic lymph nodes compared to primary tumors or lymph nodes from ER-positive patients [45].

3.2.3 Dietary cholesterol intake/fat intake and breast cancer risk

In general, dietary-saturated fat intake is synonymous with cholesterol intake. It is well known that saturated fat raises low-density lipoprotein (LDL) cholesterol, a leading cause of atherosclerosis and cardiovascular disease [46]. Li et al. showed a relationship between daily cholesterol consumption of more than 370 mg and the development of breast cancer. The Mediterranean diet is a good example of a low-fat diet. It is characterized by moderate alcohol intake and low consumption of red meat, with high levels of extra virgin olive oil, vegetables, fruits, plant proteins, fish and other seafood, wholegrains, nuts, and low-fat dairy products [47]. The beneficial effects of the Mediterranean diet have been noted in reducing the risk of breast cancer and breast cancer recurrence while improving overall survival [48–50]. Being overweight and obese is closely associated with the development and recurrence of breast cancer. The interaction between obesity, inflammation, and the tumor microenvironment induces tumorigenesis primarily in hormone-sensitive and postmenopausal patients. Several meta-analyses have provided evidence that obesity carries a 35–40% increased risk of relapse and death, regardless of menopause or hormone receptor status. In this context, prevention of breast cancer requires raising awareness about monitoring body weight, especially in menopausal women. This can be achieved through a low cholesterol/low-saturated fat diet and regular exercise [51].

4. Obesity surgery and its effects on breast cancer

Today, bariatric surgery is the gold standard in the treatment of morbid obesity. Many studies have shown that only diet and exercise are insufficient in the fight against morbid obesity. In recent years, the rate of bariatric surgery has been increasing significantly all over the world. Laparoscopic sleeve gastrectomy, Roux en Y gastric bypass, and One anastomosis gastric bypass are the most frequently applied methods. Acceptable and sustainable weight loss has been reported with the implementation of appropriate postoperative lifestyle changes in all surgical techniques. In addition, remissions are possible in many obesity-related diseases.

It is not difficult to predict the reduction in breast cancer risk in individuals who have undergone bariatric surgery, due to effective weight loss, reduced fat tissue in the body, and correspondingly reduced inflammation, and reduced leptin effects. At the same time, the possibility of an earlier diagnosis of possible breast cancer increases due to both the examinations performed during the operation and the reduction in the volume of the breast tissue after the operation. Lovrics et al. found in their meta-analysis that surgical treatment of obesity in women was associated with a significantly reduced risk of developing breast cancer. In the same study, it was emphasized that previous bariatric surgery was associated with a lower-stage diagnosis in breast cancer [52].

The SPLENDID study examines obesity and obesity-related cancers. The patients included in the study had an average follow-up of 6.1 years. SPLENDID results showed that bariatric surgery was associated with a 32% reduction in obesity-related cancers and a 48% reduction in overall cancer-related mortality [53].

With regard to breast cancer specifically, bariatric surgery has been observed to reduce the risk of breast cancer in postmenopausal women, particularly ER-negative breast cancer, by 64% [54–56]. Moderate reductions in ER-positive [141] and HER2-positive breast cancer rates have been reported [57]. It has also been proven that thanks to bariatric surgery, possible later cancers are less aggressive and they are diagnosed earlier. At diagnosis of breast cancer in patients after bariatric surgery, the rate of diagnosis of stage I breast cancer increases, while stage III or IV decreases [52].

Conflict of interest

The authors declare no conflict of interest.

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