



Molecular Mechanisms and Intervention Strategies in Breast Cancer Associated with Obesity



Ying Zhou and Guanghua Luo*

Comprehensive Laboratory, Third Affiliated Hospital of Soochow University, China

*Corresponding author: Guanghua Luo, Comprehensive Laboratory, Changzhou, Changzhou Key Lab of Individualized Diagnosis and Treatment Associated with High Technology Research, the Third Affiliated Hospital of Soochow University, China

Submission: 📅 November 09, 2018; Published: 📅 November 15, 2018

Abstract

Breast cancer (BC) has become one of the most concerned diseases among women for high incidence and poor prognosis, which also increases the attention from all over the world. Besides, a large number of researches show that the increased BMI is consistently associated with BC recent years. While the intervention strategies of obese BC patients are incomplete and unspecific now, and there is no better treatment for the complexity of BC typing, especially for triple-negative BC. This paper will review the status of BC, the current situation of obesity, the connection between BC and obesity, as well as the possible intervention strategies. The molecular mechanisms about how obesity promotes breast cancer development are comparatively comprehensive illustrated, and the probable solutions for intervention of BC patients with obesity are suggested.

Introduction

Breast cancer (BC) is a prevalent disease that is diagnosed through imaging, clinical examination, or self-identification [1]. According to a systematic analysis, the incidence of global BC increased from 641,000 cases in 1980 to 1,643,000 cases in 2010, an annual rate of rise of 3.1%. Meanwhile, mortality from breast cancer has increased at an annual rate of 1.8% [2]. Furthermore, nearly 2.4 million new cases were diagnosed as BC in 2015 [3]. In China, the situation is no exception. The incidence and mortality of breast cancer has been sustained increasing, which also makes the female's concern about their health. The incidence rate in urban areas is higher than that in rural areas, and higher in eastern areas, followed by central and western regions [4]. There is a tendency for breast cancer patients to get younger, which could happen from the ages of 15 to 30 years, increase rapidly beyond 30 years, and reach a peak until the age of 45-49 [5]. In order to access to early diagnosis, monitor the tumor progression, and improve the quality of medical management, new prognostic biomarkers involved in BC are urgent to be identified. The golden standard for breast cancer is molecular classification. Basing on gene expression, there are four molecular subtypes of breast cancer including luminal A, luminal B, HER2 and basal type [6]. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki67, Bcl-2 and p53 are immunohistochemical markers, separately and combined distinguishing the four subtypes. While traditional analysis of tumor markers is still widely accepted and used in clinic. The status of hormone receptors regulating the growth and differentiation of breast epithelium plays a significant role in indicating the prognosis of invasive cancer. For example, triple-negative breast cancer (TNBC) which lacks the expression of ER, PR and HER2, has a very aggressive disease course [7] and a poor prognosis, with the risk of increasing local recurrence and distant

metastasis [8-10]. The incidence of TNBC in breast cancer is about 12%-26% [10].

Obesity defined by the World Health Organization (WHO) is a body mass index (BMI) more than 30kg/m². It is an abnormal or excessive fat accumulation in adipose tissue, resulting in impaired health [11]. In 2015, with 108 million obese children and 604 million obese adults, the obesity rates were 5% and 12%, respectively [12]. In China, data displayed that the prevalence of overweight increased from 37.4% in 2000, to 39.2% in 2005, 40.7% in 2010, and 41.2% in 2014, even raised with 0.27% per year approximately [13].

The mechanisms underlying BC associated with obesity

As some epidemiologic studies demonstrated, the increased BMI is consistently associated with the development of chronic health conditions [14], such as hypertension, hyperlipemia, stroke, angiocardopathy, diabetes, musculoskeletal diseases, malignant tumors and so on [15-17]. The relationships between obesity and diabetes, and between obesity and heart disease are well accepted [18,19], while the impact of obesity on cancer is still ongoing. It is reported that obesity is inversely associated with the risk of premenopausal breast cancer [20-22]. On the contrary, the obesity of postmenopausal women makes the risk of breast cancer increasing by 30%, which accounts for 21% of all breast cancer deaths in the world [23-25]. Generally, sexual organs synthesize estrogen, while the main source of estrogen synthesis is adipose tissue in obese postmenopausal [26]. Obesity alters the expression of hormones, growth factors, inflammatory, cytokines and adipokines, which consequently promote cancer cell survival, metastasis and angiogenesis, and decrease the apoptosis of cancer cell [26]. The following are the molecular mechanisms concerning how obesity promotes breast cancer development.

Adipokines

Adipokines secreted mainly by adipocytes from white adipose tissue, are small peptide hormonal growth factors, and primarily lead to breast cancer with obesity. The two most important adipokines associated with breast cancer development [27], are leptin and adiponectin [26].

Leptin

Leptin is produced mainly by adipocytes [28] and also by various peripheral tissues, such as skeletal muscle, placenta, mammary epithelial cells, and ovaries [29]. Studies have shown that overexpression of leptin and leptin receptor (Ob-R) is correlated with a high risk of tumor recurrence and keep a close connection with the poor prognosis of breast cancer [30,31]. Leptin level is proportional to BMI [26]. On the menopausal status, the risk of breast cancer is determined by the level of leptin. As a result, plasma leptin is inversely associated with breast cancer risk in premenopausal obese women [32], whereas its level increases breast cancer risk in postmenopausal women with obesity [33]. Increased expression of adipose-associated aromatase in human breast tissue was recently found, partly for the expression of aromatase in adipose stromal cells (ASCs) increasing *in situ*. Leptin, converging to regulate metabolic pathways and aromatase in ASCs, leads to a hormonal environment conducive to tumor growth [34].

Adiponectin

Adiponectin (also referred to as GBP-28, apM1, AdipoQ and Acrp30) is a collagen-like protein, which is exclusively synthesized in white adipose tissue. Adiponectin is induced during adipocyte differentiation and circulates at relatively high concentrations in the serum. It regulates the modulation of glucose and lipid metabolism in insulin-sensitive tissues in both humans and animals [35]. Due to increased TNF- α and other adipocytokines, the adiponectin content is decreased in obese patients. Therefore, adiponectin levels have been shown to increase with weight loss [36] and strongly associated with increased BC risk in premenopausal and postmenopausal women [37]. According to a meta-analysis, low serum adiponectin levels connect with the increased risk of breast cancer, and what is needed is that further investigation should be carried out to explore a threshold of adiponectin for a protective effect against BC [37]. Therefore, more investigation should be carried out for more explanation of the mechanism of adiponectin with BC.

Insulin-like growth factor-1

Several studies have supported that leptin regulates hepatic insulin-like growth factor-1 (IGF-1) production and that a positive relationship between leptin and IGF-1 expression [38-40]; it showed that leptin activates the AP-1 cis-acting element upstream of IGF-1 transcription initiation site from -39 to -27, which stimulates the expression of IGF-1 gene, and the above is the mechanism of leptin regulating IGF-1 [38]. IGFs are mitogens distributed throughout the body, playing the role of regulating cell proliferation, differentiation, apoptosis, and metastasis [41]. According to a recent meta-analysis, there is a positive connection between high concentrations of IGF-1 and increased breast cancer risk [42], which demonstrated that IGF-

1 is a key growth factor during the development of breast cancer. A pooled individual data analysis of 17 prospective studies showed that circulating IGF1 has a positive association with breast-cancer risk. IGF binding protein 3 (IGFBP3) doesn't substantially modify the association, and menopausal status does not differ markedly, but this connection seems just confined to estrogen-receptor-positive tumors [42].

Inflammatory cytokines

According to a report, obesity is characterized by a state of chronic low-grade inflammation. Furthermore, chronic inflammatory state is determined by adipose tissue, which is mainly reflected by the levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) [43]. Several documents showed that IL-6 is associated with BC cell proliferation. The mechanism is that IL-6 stimulates the activity of estrogen-producing enzymes, which consequently contributes the growth of breast cancer tissues [44]. TNF- α increasing matrix metalloproteinase (MMP)-9 expression and human breast cancer cell invasion, thereby enhancing migration and invasive capacity [45]. In addition, the expression of IL-11 increases in node-positive, high-grade breast cancer and leads to poor survivals [46]. More documents illustrate the influence of inflammatory cytokines in breast cancer, but the mechanism is still ongoing to be discovered.

The probable intervention strategies

Many studies have focused on finding a link between weight loss and breast cancer risk. One using multivariable cox proportional hazard regression models demonstrates that weight loss in postmenopausal women is associated with lower breast cancer risk. These findings suggest that interventions for weight loss in postmenopausal women may result in a reduction in breast cancer risk [47]. For breast cancer survivors, insulin resistance is a risk factor owing to the increased risk of recurrence and poor prognosis. However, if one survivor managed a minimum of 5% weight loss, she would have significantly lower insulin resistance, lower fasting insulin levels as well as the chances decreasing negative breast cancer outcomes [48].

As we all know, exercise or physical activity benefits us a lot with regard to physical and mental well-being. One for that, it can prevent excess weight gain; and the other is that, it can decrease the levels of serum lipid [49]. The lowering of serum lipid attributes to the tumor's slow growth. Besides of this, exercise can reduce or inhibit cardiac toxicity, bone loss, cardiotoxicity of chemotherapy, which contributes to an improvement of the quality of life [50].

A study with Multivariable Cox proportional hazards models showed that breast cancer patients was associated with higher risk of death when decreasing diet quality after breast cancer diagnosis [51]. Epidemiologic studies suggest that an enrich flavonoids diet is linked to a decreased risk of breast cancer. The flavonoids are abundant in daily fruits and vegetables. Besides, they alter numerous signaling pathways to play a protective role in cancer-related phenomena such as inflammation and proliferation. Although natural flavonoids play a leading role in the synthesis of cancer chemical prophylaxis and/or therapeutic agents, there is a

lack of clinical approval of natural flavonoids for the treatment of breast cancer [52]. Additionally, actions such as reducing the intake of alcohol, decreasing the consumption of fats and red meat, as well as increasing the amount of fiber in the diet may be protective against breast cancer [53].

The role of leptin in adipose tissue has been illustrated [30,31]. The leptin/ObR system is overexpressed in cancer specifically and might have connection with breast tumorigenesis, which is reflected by an existing data. But several questions do need to be settled down. If it is true that the leptin/ObR system is involved in breast cancer development and progression, we couldn't wait to discuss the role of leptin targeted drugs in the treatment of breast cancer [54].

A study showed that AMPK pathway is enhanced by vitamin D compounds and inhibits local estrogen synthesis which is increased for the reason of obesity in breast microenvironment. The result also suggested that the supplementation of calcitriol or dietary vitamin D benefits the treatment of ER⁺BC in obese postmenopausal patients [55]. The intake of vitamin D is limited, and one way is exposed under sunlight. Another data indicated that breast cancer risk may be affected by vitamin D status and genetic variations in the vitamin D-3 receptor (VDR, the biologically active form of vitamin D-3). Besides, the VDR, a gene modulating growth-regulatory, may represent a molecular target for chemoprevention of breast cancer [56].

Last, obesity is considered as a state of chronic low-grade inflammation, and many inflammatory cytokines are involved in such process [44-46,57]. As a result, a pan-anti-inflammatory approach is more likely to make success in reduce inflammation of breast tissue and subsequent tumorigenesis with obesity. And, increased n-3 PUFA intake could play a role in obesity-associated BC [57].

Conclusion

Collectively, considering the current state of breast cancer with obesity all over the world, more effective and universally solutions or therapy are urgently to be inquired and put into clinic, which will bring good news to those suffering from breast cancer. Besides, it is ongoing that the mechanism of obesity associated with breast cancer should be uncovered, which could help identify some biologic targets and provide an explicit guideline for treatment prescriptions. While the greatest need that we can manage is to obtain a stable weight and stop the obesity epidemic [58]. Furthermore, statistics emphasizes the importance of making effective ideal body weight maintenance practices, in order to maximize health benefit [59]. In contemporary times, one of the greatest health care challenges is to reduce obesity on a public health level [58].

Acknowledgment

This work was supported by the Changzhou High-Level Medical Talents Training Project (No: 2016ZCLJ002) and Changzhou International Scientific and Technological Cooperation Project (CZ20180018).

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