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Review

Aromatase overexpression in dysfunctional adipose tissue links obesity to postmenopausal breast cancer

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ABSTRACT

The number of breast cancer cases has increased in the last a few decades and this is believed to be associated with the increased prevalence of obesity worldwide. The risk of breast cancer increases with age beyond menopause and the relationship between obesity and the risk of breast cancer in postmenopausal women is well established. The majority of postmenopausal breast cancers are estrogen receptor (ER) positive and estrogens produced in the adipose tissue promotes tumor formation. Obesity results in the secretion of inflammatory factors that stimulate the expression of the aromatase enzyme, which converts androgens into estrogens in the adipose tissue. Evidence demonstrating a link between obesity and breast cancer has led to the investigation of metabolic pathways as novel regulators of estrogen production, including pathways that can be targeted to inhibit aromatase specifically within the breast. This review aims to present some of the key findings in this regard.

Contents

Abbreviation: ASCs, adipose stromal cells; CLS, crown-like structures; COX-2, cyclooxygenase-2; WAT, white adipose tissue; EP receptors, E prostanoid receptors; ER, estrogen receptor; IGF-I, insulin-like growth factor-I; NF-κB, nuclear factor kB; STAT3, signal transducer and activator of transcription 3; JNK, c-jun-NH2 terminal protein-kinase; PGE_2, prostaglandin E_2; cAMP, cyclic AMP; PKA, protein kinase A; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase; mTOR, rapamycin; TNFα, necrosis factor α; IL, interleukin; FSK, forskolin; PMA, phorbol ester; AIs, aromatase inhibitors; AMPK, AMP-activated protein kinase; LKB1, liver kinase B1; CREB, cAMP response element-binding protein; CRTC, CREB-regulated transcription coactivator; LRH-1, liver receptor homologue-1; MAPK, mitogen-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; HIF1α, hypoxia inducible factor 1α.

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1. Breast cancer and obesity link

It is well established that obesity is a risk factor for different cancers and the increasing prevalence of obesity in women, especially in young and middle-age women, may lead to higher incidence of cancers such as postmenopausal breast cancer (reviewed in [1]. Breast cancer is the most frequent cancer among women in 140 of 184 countries worldwide (23% of all cancers) and it is also the most common cause of cancer death among women worldwide (522,000 deaths in 2012). According to GLOBOCAN 2012 from WHO, breast cancer incidence has increased by more than 20% and mortality has increased by 14% compared to 2008 [2]. Female gender, family history, genetic mutations and increasing age are the strongest risk factors for developing breast cancer. More than 70% of breast cancers occur in women aged between 40 and 69 years [3]. In postmenopausal women, where adipose tissue becomes the main site of estrogen biosynthesis, adiposity is positively correlated with a higher risk of breast cancer by increasing serum estradiol concentrations as well as breast estrogen levels (Table 1; [4,5]). Obesity-associated dysfunctional adipose tissue is the "source" of proinflammatory factors, excessive sex steroids and adipokines, which makes adipose tissue a fundamental factor driving the obesity-breast cancer link. The possible mechanisms and factors contributing to the associations between obesity and breast cancer have been reported in previous studies: dysregulation of growth signals, inflammation, bioavailability of sex steroid hormones, microenvironment and metabolic changes in the obese state can all enhance cancer risk and progression (reviewed in [6,7]).

1.1. Dysfunctional adipose tissue

Adipose tissue is composed of adipocytes, connective tissue matrix, nerve tissue, stromal cells and immune cells. These components function together as an integral unit which is not only responsible for energy storage but also acts as an endocrine organ that regulates metabolism via endocrine, autocrine and paracrine processes. Hypertrophy and hyperplasia of adipose tissue is seen in obesity, and adipose tissue dysfunction plays a crucial role in different obesity-linked diseases including inflammation, insulin resistance and cancer [12]. Studies have demonstrated that the expansion of abdominal adipose tissue increases cytokine secretion and insulin resistance, which leads to obesity-related morbidities and mortality [13,14].

The increased adipose tissue mass, especially white adipose tissue (WAT), produces adipokines and many inflammatory cytokines, such as leptin, tumor necrosis factor α (TNFα), interleukin (IL)-6, IL-8, IL-1β as well as the prostaglandin metabolising enzyme cyclooxygenase-2 (COX-2), all of which have been shown to be elevated both locally and/or systemically in obese women [15,16]. Excessive cytokine production in obesity will lead to the recruitment of immune cells, including adipose-derived macrophages, and the formation of crown-like structures (CLS). This process is accompanied by reduced differentiation of preadipocytes and increased desmoplasia of adipose stromal cells (ASCs) in the breast [14,15,17]. The process of macrophage infiltration associated with adipocyte hypertrophy and breast inflammation is also positively correlated with BMI and adipocyte size [18,19]. Since WAT has the capacity to produce sex hormones, adiposity can lead to an increase in estradiol and estrone levels by increasing the expression and activity of aromatase, which converts peripheral androgens into estrogen [20]. Furthermore, increased production of leptin from adipocytes is associated with obesity [6]. Taken together, the subsequent increased production of inflammatory cytokines and adipokines in combination with impaired mature adipocyte function can be defined as adipose tissue dysfunction. Obesity-associated dysfunctional adipose tissue also secretes pro-oncogenic factors such as TNFα, IL-6, IL-1β and provides a carcinogenesis-promoting microenvironment for breast cancer development and progression; it is therefore a fundamental factor of postmenopausal breast cancer development.

Table 1
Effect of high BMI on postmenopausal breast cancer risk.

Type of study	Relative risk (95%CI)	Reference
Meta-analysis	1.15 (1.07–1.24)	Cheraghi et al. [8]
Meta-analysis	1.02 (1.02, 1.03)	Bergström et al.[9]
Meta-analysis (Triple negative)	0.99 (0.79–1.24)	Pierobon et al. [10]
Meta-analysis	1.19 (1.05–1.34)	Key et al. [11]

1.2. Inflammation

Chronic inflammation increases the risk of several cancers and it is associated with cancer development and progression [21]; not surprisingly, inflammation of breast tissue is also observed in overweight and obese women. As mentioned previously, obesity leads to the formation of CLS, which are macrophages surrounding necrotic adipocytes that promote adipogenesis and inflammation in WAT [14,17,22]. Nearly 50% of obese women have CLS in their breast tissue [18,23]. Increased numbers of CLS are associated with higher levels of proinflammatory mediators such as cytokines, adipokines, and prostaglandins. These inflammatory factors modulate inflammation via increased intracellular signaling through nuclear factor kB (NF-κB)-, signal transducer and activator of transcription 3 (STAT3)-, and c-jun-NH2 terminal protein-kinase (JNK)–related pathways, which are pathways that are known to affect breast cancer and which can be inhibited by reduced food consumption in obese patients [24–26]. Pro-inflammatory cytokines alone can promote carcinogenesis by promoting cell proliferation and invasion. These cytokines are associated with an increased risk of cancer, cancer cell invasion and metastasis [27].

Furthermore, inflammation is also accompanied by elevated aromatase expression and activity mediated by inflammatory factors such as TNFα and prostaglandin E_2 (PGE_2), followed by enhanced estrogen synthesis within the mammary gland of obese women [16,18]. It is known that up-regulation of COX-2 leads to elevated levels of prostaglandins, and COX-2 is highly expressed in metastatic breast cancer [28]. Prostaglandins regulate cell migration and invasion in cancer and high prostaglandin levels are associated with many cancers including that of the breast. Interestingly, knocking out COX-2 in mice reduces mammary tumorigenesis and angiogenesis [29]. PGE_2 has been implicated in obesity, in which elevated levels of PGE_2 have been observed [30]. PGE_2 binds to EP receptors and which play a major role during inflammation [31]. The EP receptors are coupled to G proteins that can modulate the levels of Ca2+, cyclic AMP (cAMP) and inositol