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Inflammation, dysregulated metabolism and aromatase in obesity and breast cancer

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Obesity is associated with an increased risk of estrogen-dependent breast cancer after menopause. Adipose tissue undergoes important changes in obesity due to excess storage of lipids, leading to adipocyte cell death and the recruitment of macrophages. The resultant state of chronic low-grade inflammation is associated with the activation of NFkB signaling and elevated levels of aromatase, the rate-limiting enzyme in estrogen biosynthesis. This occurs not only in the visceral and subcutaneous fat, but also in the breast fat. The regulation of aromatase in the breast adipose stromal cell in response to inflammatory mediators is under the control of complex signaling pathways, including metabolic pathways involving LKB1/AMPK, p53, HIF1α and PKM2. Interventions aimed at modifying weight, including diet and exercise, are associated with changes in adipose tissue inflammation and estrogen production that are likely to impact breast cancer risk. This review will present an overview of these topics.

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Obesity and breast cancer

Adipose tissue is the largest endocrine organ in the body and plays an important role in maintaining energy homeostasis. Understanding the underlying biology of adipose tissue is important for understanding how obesity contributes to tumor development. It is well known that obesity is associated with excess storage of lipids [1]. In addition to lipid storage, adipose tissue also produces adipokines and steroid hormones, including estrogens. Obesity affects the production of these factors and is associated with a chronic state of low-grade inflammation, having profound effects on tumor development and progression.

According to the World Health Organization, 55% of women worldwide are overweight or obese [2]. Higher obesity rates are associated with an increased prevalence of obesity-associated diseases, such as cardiovascular disease, diabetes and number of cancers, including breast cancer [3,4•,5]. Breast cancer is the most diagnosed cancer in women in developed and developing countries. In the United States, one in eight women will be diagnosed with breast cancer during their lifetime. Of these, two-thirds will develop estrogen receptor-positive (ER+) tumors that depend on estrogens for growth [6]. The main source of estrogen in premenopausal women is the ovaries, while in postmenopausal women, it is the adipose tissue [7].

In postmenopausal women, obesity and weight gain have been associated with significantly higher risk of ER+/progesterone receptor-positive (PR+) breast cancer (Table 1; [8–10]), attributable in part to increased local estrogen production from the breast adipose tissue. In ER+ breast cancer survivors, a 10% increase in body weight is also associated with increased risk of recurrence after 5 years [11]. Additionally, higher BMI is associated with poor prognosis and worse overall survival and breast cancer-specific survival in women with ER+/PR+/human epidermal growth factor receptor 2 (HER2) negative breast cancers [12•,13]. In premenopausal women, although no significant effect of BMI on breast cancer risk is observed [14], higher body mass index (BMI) is associated with larger tumors, higher incidence of lymph node metastases and higher histological grade [15,16]. In pre and postmenopausal women, obesity has been found to be positively associated with breast cancer-specific mortality [17,18] (Figure 1).

This review will discuss the role of obesity-associated inflammation in driving the local expression of aromatase, the rate-limiting enzyme in estrogen biosynthesis, via effects on metabolic pathways.

Obesity and adipose tissue inflammation

Adipose tissue is composed of multiple cell types, including adipocytes and cells of the stromal vascular fraction (e.g. preadipocytes, immune and endothelial cells). In adipocytes, a positive energy balance leads to the storage of excess calories as triglycerides, causing their expansion.

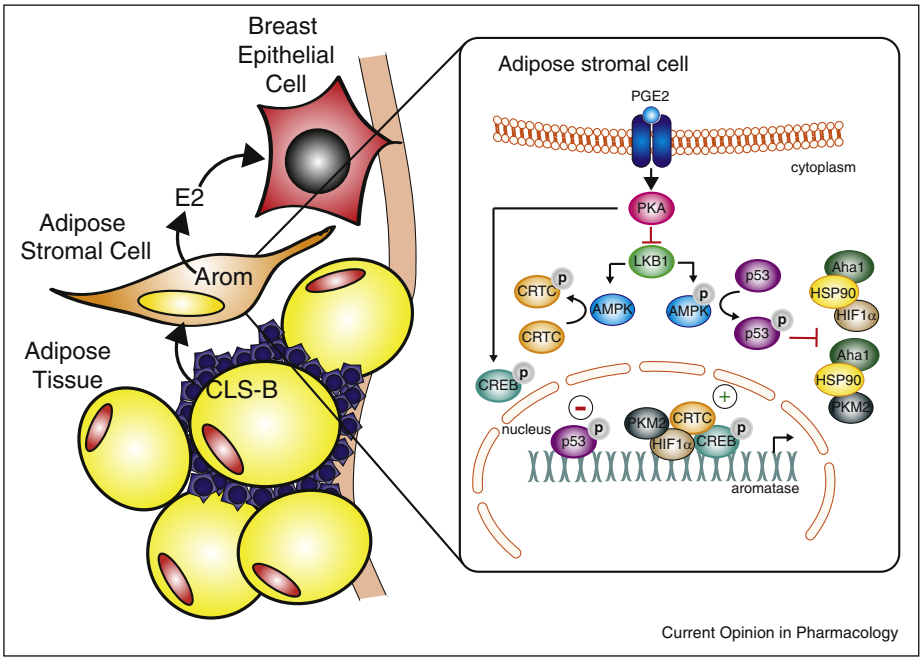
Table 1

Effect of BMI on breast cancer risk in postmenopausal women.

Type of study	Number of studies	Years	BMI (kg/m^2)	RR (95% CI)	References
Meta-analysis	25	1997–2014	25	1.02 (0.98–1.06)	[8]
			30	1.12 (1.01–1.24)	
			35	1.26 (1.07–1.50)	
Meta-analysis	11	1997–2011	Obese	1.25 (1.07–1.46)	[9]
Meta-analysis	39	1980–2012	25–29.9	1.10 (1.06–1.13)	[10]
			≥30	1.18 (1.12–1.25)	

With obesity, the unhealthy expansion of adipose tissue is associated with endoplasmic reticulum stress, adipose tissue fibrosis and localized hypoxia [1]. This, in turn, is associated with adipocyte cell death and initiation of an inflammatory response [19••]. An increase in monocyte chemoattractant protein-1 (MCP-1), also known as CCL2, in adipose tissue contributes to the infiltration of macrophages [20] and their accumulation around dead or dying adipocytes, leading to the formation of a distinct histological structure referred to as 'crown like structure' (CLS). In contrast to lean adipose tissue, which predominantly contains alternatively activated M2 macrophages, obese adipose tissue is characterized by the infiltration of classically activated M1 macrophages which promote inflammation, generate reactive oxygen species and release cytokines such as tumor necrosis factor-α (TNFα) and interleukin 6 (IL-6) [21]. Hypoxia inducible factor 1α (HIF1α) is a key driver of this response, as loss of HIF1α in adipocytes leads to the reduced expression of TNFα and MCP-1 mRNA, resulting in reduced macrophage infiltration and attenuation of the pro-inflammatory milieu [22]. The adipokine leptin, which is elevated with obesity, also stimulates the production of TNFα, IL-6 and other cytokines, and promotes monocyte phagocytic function (reviewed in [23]). Studies of CLS have been undertaken in mouse models of diet-induced and genetic-induced obesity, as well as in humans, where increased weight has been shown to be associated with a greater

Figure 1



Obesity, breast inflammation and the regulation of aromatase by metabolic pathways. Obesity is associated with increased breast white adipose tissue inflammation, characterized by an increase in the presence of CLS-B. Inflammatory mediators, including PGE_2, stimulate the expression of aromatase in adipose stromal cells via effects on metabolic pathways involving LKB1/AMPK, CREB/CRTC, p53, HIF1α and PKM2. Aromatase catalyzes the conversion of androgens into estrogens, known to drive the growth of obesity-related breast cancer cells. Large yellow cells represent adipocytes; blue cells represent infiltrating macrophages forming CLS. CLS-B: crown-like structure of the breast; Arom: aromatase; E2: estradiol; PGE_2: prostaglandin E_2; PKA: protein kinase A; LKB1: liver kinase B1; AMPK: AMP-activated protein kinase; CREB: cAMP response element binding protein; CRTC: CREB-regulated transcription coactivator; HSP90: heat shock protein 90; Aha1: activator of heat shock 90 kDa protein ATPase homolog 1; HIF1α: hypoxia inducible factor-1α; PKM2: protein kinase M2.