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Obesity and breast cancer in premenopausal women: Current evidence and future perspectives

Daniela Laudisio[1], Giovanna Muscogiuri[1], Luigi Barrea, Silvia Savastano, Annamaria Colao*

Department of Clinical Medicine and Surgery, University "Federico II", Naples, Italy

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ABSTRACT

There is raising evidence reporting an increased incidence of breast cancer over the past decades. Every year approximately 1.4 million new cases of breast cancer are diagnosed worldwide, with a mortality rate of approximately 450,000/year. Out of these cases, 6.6% are diagnosed in premenopausal women with a median age at diagnosis of 40 years: in premenopausal women breast cancer seems to be more aggressive than in post-menopausal women. Obesity has been reported to increase the risk of developing breast cancer and to worsen the prognosis. This seems to be due to several obesity-related mechanisms. Insulin resistance that often occurs with obesity may results in compensatory hyperinsulinemia. Insulin cross-binds insulin-like growth factor-I receptors expressed on breast cells, resulting in proliferative stimuli on breast cancer cells. Besides, hyperinsulinemia up-regulates the growth hormone receptor (GHR) thus increasing GHR stimulation and resulting in an increased hepatic IGF-I synthesis. Moreover, insulin decreases the hepatic expression of binding proteins of IGF-I, such as insulin-like growth factor binding proteins (IGFBP)-1 and IGFBP-2, thus leading to high circulating and bioavailable free IGF-I. Additionally, obesity is associated to chronic low-grade inflammation that has been reported to be an additional stimulus for tumor growth. This review shows the current evidence regarding to the association of obesity and breast cancer in premenopausal state focusing on both human and basic studies; showing that the obesity is a risk factor for breast cancer also among premenopausal women, especially for the molecular subtype Triple Negative Breast Cancer.

Introduction

Breast cancer (BC) is a growing public health problem. Although current efforts in preventing BC, the incidence is increasing in most developed and developing countries [1–4]. Each year about 1.4 million new cases of BC are diagnosed worldwide, with a mortality rate of approximately 450,000/year [5]. Of these, 6.6% are diagnosed in premenopausal women, with a median age at diagnosis of 40 years [6,7]. In premenopausal women BC seems to be more aggressive than in post-menopausal women, showing higher histological grading, increased proliferation rate, higher rates of vascular invasion [8] and a higher proportion of triple-negative breast cancer (TNBC) [9]. Further, BC in premenopausal women has been associated to an increased risk of recurrence and mortality rate compared to postmenopausal women [9,10]. Several risk factors for BC have been identified, such as age, genetic mutations (BRCA 1 and BRCA 2) [11], younger age at menarche, first pregnancy after the age 30, nulliparity, older age at menopause, dense breast tissue [12], hormone replacement therapy, use of oral contraceptives [13], personal and family history of BC or other breast diseases [14]. Recently, it has been also highlighted that obesity could represent an important risk factor of developing BC [15,16]. This seems to be due to several metabolic derangements associated to obesity. First, obesity is often associated to insulin resistance that could result in secondary hyperinsulinemia with consequent cross-binding of insulin-like growth factor-I (IGF-I)

Abbreviations: BC, breast cancer; BMI, body mass index; TNBC, Triple Negative Breast Cancer; GHR, growth hormone receptor; IGF-1, insulin-like growth factor-I IGFBP Factor Binding Protein; ER, estrogenreceptor; IL, interleukin; NF-kB, nuclear factor-kappa B; MMP-9, metalloproteinase-9; MCP-1, monocyte chemoattractant protein-1; HIF-1, hypoxia inducible factor-1; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor.

* Corresponding author at: Department of Clinical Medicine and Surgery, University "Federico II", Via S. Pansini 5, 80131, Napoli, Italy.
E-mail address: colao@unina.it (A. Colao).

[1] These authors equally contributed to this manuscript.

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receptors, thus exerting a mitogen effect on both normal and neoplastic breast epithelial cells [17]. Furthermore, obesity has been associated to a subclinical, chronic, low-grade inflammation that represents an additional predisposing factor for cancer [18]. Thus, the aim of this manuscript is to provide a general overview of the current evidence on the association of BC and obesity in premenopausal state, reviewing both clinical and basic studies.

Obesity and Breast Cancer

Clinical evidence

Several studies investigated the association between obesity and BC [19–21], providing conflicting results [22,23]. In a longitudinal study Michels et al. reported an inverse association between body mass index (BMI) and the risk of BC ($p < 0.001$) in premenopausal women [22]. The women included in the study aged 25–42 years and were asked to reply to a self-administered questionnaire about their medical history and lifestyle. They were followed for 14 years and were asked to update questionnaires information on demographic variables, lifestyle factors, and medical events every two years. This study reported interesting result but the self-administration of the questionnaire represents an important bias [22]. Same results were reported by Cecchini et al. in a chemoprevention study finding that BMI had a significant relation with increased risk of BC among premenopausal women >35 years of age, although this result was not confirmed in postmenopausal women [23]. This study used data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 (Breast Cancer Prevention Trial) and STAR (Study of Tamoxifen and Raloxifene) that were 2-arms, double-blinded, randomized clinical trials investigating the use of chemoprevention for BC. The women included in the study were aged >35 years, did not have history of invasive BC but presented a high risk of developing BC evaluated by Gail score (Gail score $\geq$ 1.66). Increased risk of invasive BC was significantly associated with high BMI ($p = 0.01$) in premenopausal women [23]. Furthermore, the authors found a statistically significant association between BMI and estrogen receptor (ER)-positive BC, with hazard ratios for the 2 upper categories of BMI of 1.41 and 1.78 ($p = 0.04$) [23]. This trend was not confirmed for ER-negative BC and this could be due to the small number of BC events in this group. In this study, however, the assessment of BMI was performed only at the study beginning so preventing to draw firm conclusions on the long-term effect of high BMI [23]. The effect of obesity on premenopausal BC risk differs across disease subtypes. Several studies have reported a positive association between obesity and the risk of developing TNBC in premenopausal women [24–26]. TNBC subtype is particularly aggressive and frequently occurs in premenopausal women [24,26,27]. In a recent retrospective study, Sahin et al. evaluated the association between BMI and immunohistochemical subtypes in BC for premenopausal and postmenopausal women [25]. In the study population BMI was stratified into 3 groups according to BMI as normal-weighted (BMI <25 kg/m^2), over-weighted (BMI 25–29.9 kg/m^2), and obese (BMI 30 kg/m^2), immunohistochemical classification of the tumors was categorized into 4 groups: luminal-like, HER2/luminal-like, HER2-like, and TNBC according to the ER/PR and HER2 status. This study demonstrated that there was a high prevalence of obesity at diagnosis of BC in both premenopausal and postmenopausal women ($p < 0.001$ and $p < 0.001$, respectively) TNBC subtype was significantly more common in obese premenopausal women compared to women with BMI <30 kg/m^2 ($p = 0.007$). In addition, obese premenopausal patients experienced less common luminal-like subtype ($p = 0.033$), and more frequently presented with higher tumor stage ($p = 0.012$) and tumor grade ($p = 0.004$) at diagnosis when compared to patients with BMI <25 kg/m^2 [25]. These data confirm the results obtained by a case–case study, which has reported the positive association of risk for TNBC with both weight and BMI in premenopausal women ($p = 0.012$ and 0.004, respectively) with a 5% increase in risk observed for 5 kg increase in weight and a 16% increase in risk per 5 kg/m^2 increase in BMI [26]. The Cancer and Steroid Hormone (CASH) population-based, case-control study, found an increased risk for TNBC in premenopausal women reporting a strong positive association between BMI and premenopausal TNBC risk (OR (odds ratio) = 1.67, 95% CI (confidence interval) 1.22–2.28; $p = 0.026$) [28]. Conversely Yang et al. reported that obesity in younger women was associated with an increased risk of developing ER-positive or PR-positive tumors rather than TNBC suggesting that BMI seems to be more associated with hormone receptor positive tumors [29]. However, the results of this study were limited by the fact that data were pooled from different studies that were not totally comparable in terms of enrolled subjects and experimental design [29]. The association between BC and obesity seems to be mediated by intra-abdominal visceral fat that is the main responsible for obesity-related metabolic and hormonal changes promoting the development of BC [30]. Another prospective study, evaluated the association between abdominal fat, measured as waist and hip circumferences and by the waist-to-hip ratio, and the risk of BC in premenopausal women [31]: 116.430 women were included and during a 12-years follow up 630 cases of premenopausal invasive BC were recorded. Abdominal adiposity was not significantly associated with overall incidence of premenopausal BC: however, but adiposity was associated with risk of developing of ER-negative BC more strongly than with the risk of ER–positive BC. Although these results were promising, they should be interpreted with caution due to the fact that the assessment of anthropometric measurements was self measured by the patients. Further, the measurement of waist circumference is an indirect measurement of visceral adipose tissue, not providing an accurate evaluation [31]. Further research with more detailed measurements of abdominal fat with methods not investigator-dependent is required to elucidate the exact role played by total and abdominal fat mass in determining BC risk so identifying potential targets for treatment intervention.

Pathogenesis

Several mechanisms are involved in the association of obesity and increased risk of developing BC. In lean premenopausal women, estrogens are mainly produced by ovarian granulosa cells and only a little part is produced by other peripheral tissues especially the adipose one [32] while in obese premenopausal women, most of estrogens derive from the conversion of androgens into estrogens by aromatase in the adipose tissue [32]. High levels of estrogens released into the circulation from the adipose tissue activate the negative feedback in the hypothalamus pituitary axis leading to reduced gonadotrophin secretion [33], thus resulting in amenorrhea and reduced ovarian activity with a markedly reduced synthesis of progesterone [34]. Initially, this mechanism has been considered as protective against the risk of BC in obese premenopausal women, because it was hypothesized that progesterone would increase proliferation of breast cells in the luteal phase when progesterone levels are usually high [35]. However, this theory has not been supported by subsequent studies that have hypothesized that progesterone is neutral or even protective for BC [36]. In fact it has been hypothesized to either decrease BC risk, by mitigating the estrogen-induced proliferation in breast epithelial cells [37]. Cohort studies have examined circulating progesterone levels and BC risk in premenopausal women and have reported inverse association between circulating progesterone levels and risk of BC. The European Prospective

Investigation on Cancer and Nutrition (EPIC), investigated the association between sex steroid hormones and BC occurrence in premenopausal women, reporting a statistically significant inverse relationship between serum levels of progesterone and BC incidence OR for highest versus lowest quartile (OR = 0.61, 95% CI = 0.38–0.98; $p = 0.06$) [38]. In another prospective nested case-control study Schernhammer et al. have investigated the association between circulating sex steroids and BC risk in premenopausal women finding that endogenous progesterone was not statistically associated with BC (OR, 1.16; 95% CI, 0.60–2.27; $p = 0.75$) [39]. In addition to hormonal mechanisms, metabolic factors have been hypothesized to be involved in the link between obesity and BC. Several studies have confirmed that insulin resistance and compensatory hyperinsulinemia have been associated with increased risk of BC and with a worse prognostic outcomes both in premenopausal and postmenopausal women [40–43]. IGF-I receptors are the main mediators of proliferative effects of insulin. This could be due to the high homology (more than 50%) of the insulin receptor (IR) and IGF-I receptor (IGF-IR) that is even 84% at the α-subunit of the tyrosine kinase domain [44]. Further, insulin and IGF-I share 40–50% homology. Because of this, insulin and IGF-I can interact either with IR or with IGF-IR [45], and both of these receptors have been associated with tumor development [46]. It has also been reported an overexpression of IGF-IR in BC that is functional for establishing an enhanced anabolic state necessary for cell proliferation, differentiation, and anti-apoptosis via deregulating or over-activating multiple downstream signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways. This overexpression seems to be stimulated by high IGF-I and insulin levels [47–49]. Instead, the indirect effects of hyperinsulinemia on carcinogenesis are attributable to the action of insulin on circulating endogenous growth factors and their binding proteins. In hyperinsulinemic states, the growth hormone receptor (GHR) is upregulated by the increase of insulin concentrations in portal circulation thus the increase of GHR stimulation result in an increased hepatic IGF-I synthesis [50]. Moreover, insulin decreases the hepatic expression of binding proteins of IGF-I, such as insulin-like growth factor binding proteins (IGFBP)-1 and IGFBP-2 [51], thus leading to high plasma levels and bioavailability of free IGF-I [52]. In this context, IGFBP-1 inhibits the growth of BC cells in mice with MCF-7 BC xenografts, as well as hepatocellular cancer growth in mice over-expressing IGF-I and IGF-II [53,54]. Additionally, obesity is accompanied by increased circulating levels of pro-inflammatory mediators, such as interleukin (IL)-6, tumor necrosis factor alpha (TNFα), matrix metalloproteinase (MMP)-9 and IL-1β, that have been reported to promote tumorigenesis [55]. Additionally obesity enhances the secretion of monocyte chemo-attractant protein (MCP)-1, which stimulates the recruitment of macrophages to adipose tissue, including the breast one. These tumor-associated macrophages likely contribute to tumor growth by increasing local and/or systemic inflammatory and angiogenic factors and generating reactive oxygen species [56]. Thus, the increase of pro-inflammatory cytokines secretion creates a favorable environment inducing tumor cells to acquire a phenotype with major invasiveness and aggressiveness [57–60] (Fig. 1). Furthermore, the progressive hypertrophy of white adipocytes and the expansion of the white adipose tissue make the same adipocytes more away from the vascular network, with the reduction of the oxygen availability [61]. In hypoxia state the adipose tissue generates an increased state of oxidative stress, able to make the white adipocytes hypertrophic/hypoxic and to secrete inflammatory proteins and to induce brown adipocytes dysfunction [62]. Hypoxia, furthermore, induces a status of insulin resistance [63,64], ischemia and necrosis of white adipocytes [65]; production and release of inflammatory cytokines and angiogenic factors [66]. The decrease oxygen tension activates the transcription factor hypoxia inducible factor (HIF)-1 generating a series of negative effects as inhibition of production of adiponectin by white adipocytes and increased level of leptin [67]. In fact adiponectin appears to have a regulatory role in insulin resistance and to exert antineoplastic activities, a

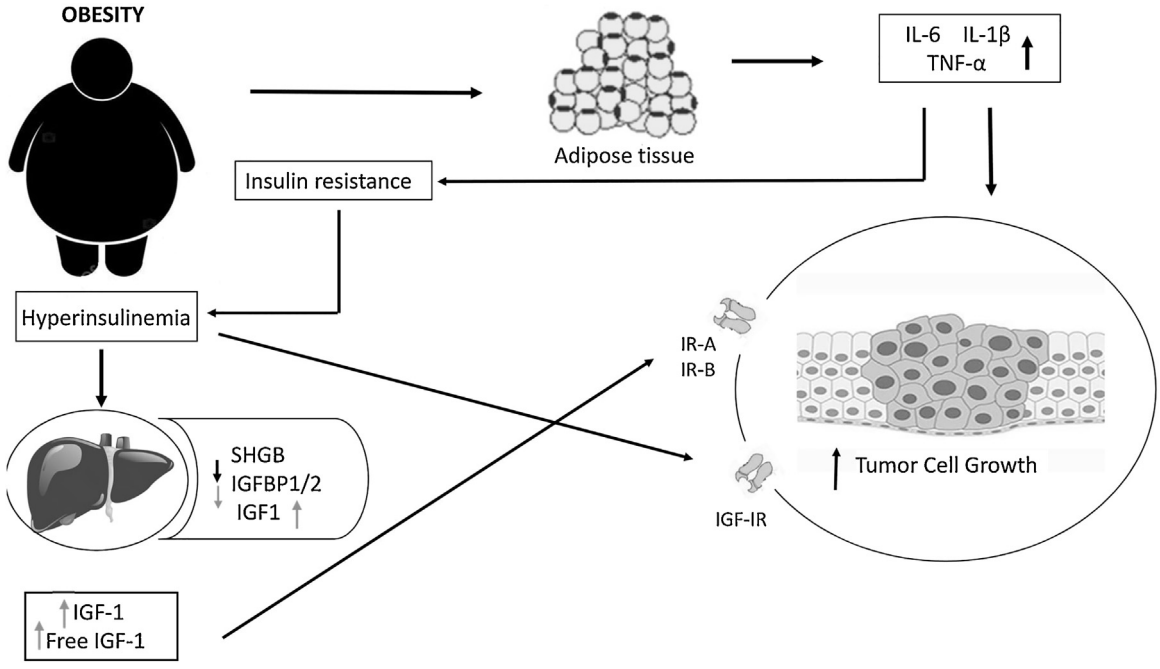

Fig. 1. Potential Mechanisms of obesity leading to cancer development. Schematic representation of aspects of obesity that shows how insulin resistance and inflammation may promote, directly and indirectly, breast cancer growth. IGF-1: insulin-like growth factor-1; IR-A: insulin receptor type A; IR-B: insulin receptor type B; SHBG: sex binding protein; IGFBP 1/2: insulin-like growth factor binding protein 1/2; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

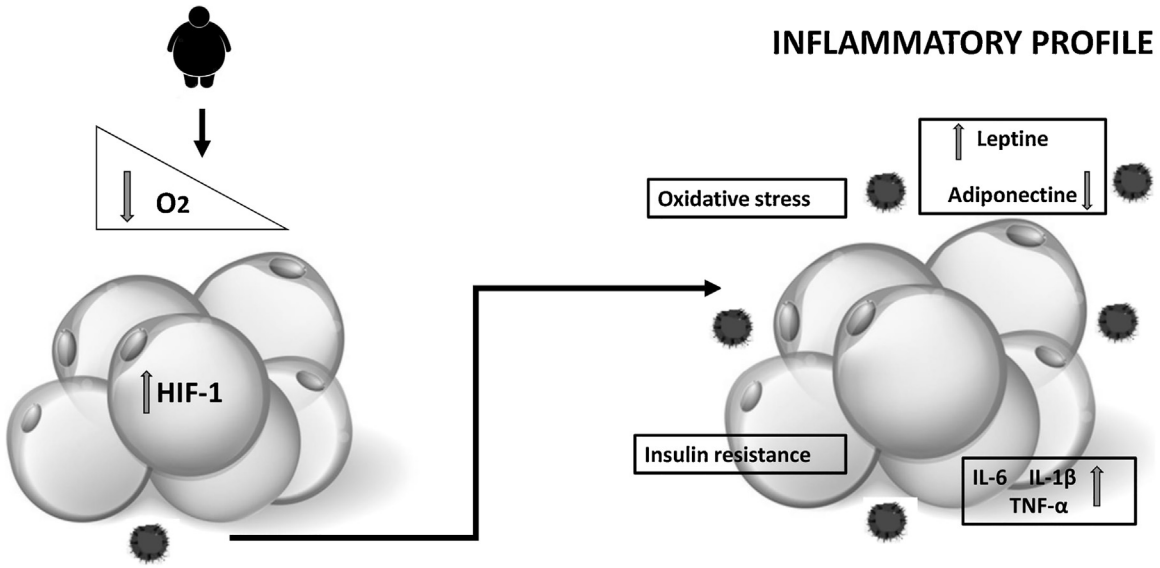

Fig. 2. Potential mechanisms of obesity leading to cancer development. Schematic representation of aspects of obesity that shows how the changes in adipose tissue during weight gain. During obese adipose tissue expansion, preadipocyte differentiation is impaired, and hypoxia activates hypoxia-inducible factor 1 (HIF-1) with consequently decrease adiponectin expression and upregulat leptin, secretion of inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), induction a status of insulin resistance and icreased of oxidative stress.

reduction in the proliferation of adipocyte cells, endothelial cells and tumor cells [68]. In addition, adiponectin has been reported to block angiogenesis by decreasing the expression of vascular endothelial growth factor (VEGF) and Bcl-2 (anti-apoptotic) and increasing the activity of p53, Bax and caspase (pro-apoptotic), with resulting in apoptosis of endothelial cells. Likewise, adiponectin was shown to reduce TNF-**α** induced effects on cell proliferation and migration [69,70]. Conversely low levels of adiponectin exert pro-inflammatory effects rising the secretion of several proinflammatory cytokines including TNF-**α** and IL-6, leading to the onset of a tumorigenic microenvironment promoting tumor development [71]. Leptin, closely related to adipose tissue mass and volume of adipocytes [72], has instead been shown to have carcinogenic properties, increasing the expression of anti-apoptotic proteins, inflammatory markers (TNF-**α**, IL-6), angiogenic factors (VEGF), and also the hypoxia-inducible factor-1a (HIF-1**α**) by promoting cancer cell survival, proliferation and migration [73]. (Fig. 2).

Conclusion

Epidemiological studies indicate progressively increased number of cases with BC in most developed and developing countries. Premenopausal state at diagnosis is highly associated with a significantly increased risk of recurrence and higher mortality rate. Obesity has been reported to be a risk factor for BC, especially for the molecular subtype TNBC. The effects of obesity on the risk of breast cancer in premenopausal are mediated by molecular mechanisms as compensatory hyperinsulinemia to insulin resistance and high levels of insulin and IGF-1, increased pro-inflammatory cytokines secretion (TNF-α and IL-6), changes in the leptin and the hypoxia. This information is important either for Oncologist and Nutritionists to increases the knowledge on the possible relationships between obesity and breast cancer in premenopausal women, with the aim not only to reduce the risk of breast cancer in obese patient but also for delineating the risk profile for metabolic risk factors that may result from obesity. Being obesity a multifactorial disease and an important risk factor for BC, further study should be focused to implement individual lifestyle recommendations based on both prevention of cancer risk and weight management.

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