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REVIEW

Cancer and comorbidity: The role of leptin in breast cancer and associated pathologies

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Abstract

Obesity is an important risk factor for postmenopausal breast cancer and also a poor prognostic factor among cancer patients. Moreover, obesity is associated with a number of health disorders such as insulin resistance/type-2 diabetes mellitus, hypertension, and other cardiovascular diseases. Frequently, these health disorders exhibit as components/complications of the metabolic syndrome. Nevertheless, obesity-related diseases may coexist with postmenopausal breast cancer; and these comorbid conditions could be substantial. Therefore, it may be assumed that different diseases including breast cancer could originate from a common pathological background in excessive adipose tissue. Adipocyte-released hormone-like cytokine (or adipokine) leptin behaves differently in a normal healthy state and obesity. A growing body of evidence suggests an important role of leptin in our major obesity-related health issues such as insulin resistance, hypertension, and neoplasia. In this context, this review describes the relationships of the abovementioned pathologies with leptin.

Key words: Hypertension; Obesity; Postmenopausal breast cancer; Comorbidity; Diabetes

Core tip: Obesity and associated pathologies such as insulin resistance and metabolic syndrome are interrelated health disorders wherein a chronic low-grade inflammation persists. Perhaps this inflammatory condition is associated with the etiology and disease course of postmenopausal breast cancer, like other obesity-related diseases such as type-2 diabetes mellitus and hypertension. Often these diseases may coexist, and comorbidity worsens the prognosis of cancer patients. Leptin is an important adipokine (mainly released by fat cells), which may play a crucial role in these obesity-related diseases.

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INTRODUCTION

Obesity has been emerging as an important public health problem since about 1980, and currently almost all nations are affected by this health disorder. As per the World Health Organization, global estimates in 2016 revealed that more than 1.9 billion adults (39%, 18 years and older) were overweight; of these, over 650 million (13%) were obese. Logically, this health disorder is closely linked with lifestyle changes such as inappropriate diets and widespread physical inactivity: Both are currently prevalent in many societies. It may be worth mentioning that obesity promotes several pathological conditions, including dyslipidemia, insulin resistance or type-2 diabetes mellitus, hypertension and other cardiovascular diseases, and certain cancers.

Evidence shows that obesity is associated with an increased risk of postmenopausal breast cancer, which occurs more frequently compared to premenopausal cases[1,2]. Furthermore, obesity is a poor prognostic factor among cancer survivors. Obesity in postmenopausal women may influence the disease process in several ways. For instance, aromatase enzyme present in adipose tissue converts androgens to estrogens; therefore, more aromatase activities and estrogens are expected in subjects having excessive adipose tissue. Moreover, decreased levels of sex hormone-binding globulins (SHBG) in obese postmenopausal women may increase free/bioavailable estrogens and breast cancer risk. It has also been suggested that an excess of local adipose tissue may play a critical role in disease progression by providing various substances such as fatty acids and pro-inflammatory cytokines[3].

Systemic low-grade inflammation and insulin resistance are two related mechanisms assumed to play a role in the association between obesity and relevant pathologies[4,5]. On the other hand, it is now fairly understandable that adipose tissue acts as an endocrine organ and releases several hormone-like substances/cytokines (adipokines) such as leptin, resistin, adiponectin[6]. The majority of these adipokines, including leptin, participates in the pro-inflammatory processes in obesity and perpetuates the state of insulin resistance. Adult obesity is commonly associated with higher blood levels of leptin[7,8]. In regard to carcinogenesis, several studies have indicated that leptin potentiates the growth of breast cancer cells[3,9,10].

Leptin, a 16 kDa protein, is primarily released from adipocytes and maintains energy homeostasis by influencing the central/hypothalamic anorexigenic pathway. Nevertheless, in obesity, leptin possibly acts differently and helps create a pro-inflammatory situation. Leptin exerts its effects through at least six alternatively spliced isoforms of leptin receptor (Ob-R), including the long form Ob-Rb and secretory form Ob-Re/sOb-R. Perhaps Ob-Rb plays a key role in both physiologic and pathologic conditions[2].

LEPTIN IN BREAST CANCER

A number of studies documented higher blood levels of leptin among patients with breast cancer, particularly postmenopausal cases[11-17]. Furthermore, circulating leptin concentration has been shown to correlate with different prognostic indicators, such as tumor grade, TNM stage, and receptor status[18-20]. In postmenopausal patients, studies also detected a correlation between blood levels of leptin and aromatase activity[21,22]. Leptin's association with aromatase, which catalyzes the conversion of androgen to estrogen, reasonably suggests an involvement with estrogen biosynthesis. Interestingly, Jardé *et al*[23] observed that Ob-R expression in breast cancer tissue was positively correlated with estrogen receptor (ER) expression. On the other hand, high tissue expression of leptin has been reported to be associated with tumors that were ER(-), progesterone receptor (PR)+, and human epidermal growth factor receptor-2 (HER2)(-)[24]. In another study, investigators found that increased Ob-R mRNA expression was associated with the triple negative phenotype, *i.e.*, ER(-), PR(-), and HER2(-)[25]. They also noticed that higher serum leptin levels were linked with prognosis, such as recurrence and mortality.

In many studies, high levels of leptin and/or Ob-R were detected in malignant tissue compared to non-cancerous breast tissue samples[26-29]. In an initial study that immunohistochemically analyzed the tumor specimens, Ishikawa *et al*[30] observed that distant metastasis was detected more frequently in Ob-R and leptin overexpressing tumors, but in none of the tumors that lacked Ob-R or leptin overexpression. Similarly, Miyoshi *et al*[31] reported that high intra-tumoral mRNA levels of both Ob-Rb and short isoform Ob-R were significantly associated with a poor prognosis for patients with high serum leptin or high intra-tumoral leptin mRNA levels, but not in the subset of patients with low serum leptin or low intra-tumoral leptin mRNA levels. In addition, in a study conducted by Révillion *et al*[32], high Ob-R mRNA expression in breast tumor samples was associated with a shorter relapse-free survival. In an interesting study, mRNA expression of leptin in mammary adipose tissue and Ob-R in tumor tissue was significantly higher in patients with metabolic syndrome compared to obese only or normal weight cancer patients[33]. It is worth mentioning that metabolic syndrome or its components may affect the pathologic course of breast cancer in different phases, such as the risk for disease development, comorbidities, and prognosis.

METABOLIC SYNDROME AND COMORBIDITY IN BREAST CANCER

In general, characteristics of metabolic syndrome include abdominal obesity, hyperglycemia/insulin resistance, dyslipidemia, and hypertension, which result in an increased risk for the development of type-2 diabetes and cardiovascular disease. Many studies revealed that the presence of metabolic syndrome increased the risk of postmenopausal breast cancer[34-36]. Remarkably, an important environmental factor for both hypertension and type-2 diabetes is obesity. Furthermore, it has been observed that obesity, in combination with the metabolically unhealthy condition, was associated with the highest risk of postmenopausal breast cancer[37]. Mechanistically, in an environment of metabolic syndrome, pathological phenomena such as insulin resistance, pro-inflammatory cytokines and subacute chronic inflammation may influence the risk and prognosis of breast cancer[38,39].

On the other hand, comorbid conditions could be substantial in breast cancer patients, and prevalent comorbidities usually include various disorders, *e.g.*, diabetes, hypertension, arthritis, osteoporosis, and psychological difficulties[40-43]. Reports from different geographical areas demonstrated that type-2 diabetes increased breast cancer risk and can affect patients' prognosis (Table 1)[44-56]. Interestingly, studies have demonstrated different impacts of type-1 and type-2 diabetes on breast cancer risk. Liaw *et al*[57] analyzed the entire adult female population in Taiwan and found that the breast cancer incidence rate was significantly higher in patients with type-2 diabetes compared to type-1 diabetes patients and persons without diabetes. Conversely, some investigators reported a decreased risk of breast cancer in women with type-1 diabetes[58,59]. Regarding the quality of life among breast cancer survivors, a worse condition was revealed in patients with type-2 diabetes than those with type-1[60]. However, obesity and diabetes probably act synergistically for a worse outcome in breast cancer[61-63].

Another important comorbid condition among cancer patients is hypertension. In general, it is the most common cardiovascular disease and a risk factor for several other cardiovascular problems, such as atherosclerosis, coronary artery disease, and cerebrovascular accident. Nevertheless, a significant proportion of postmenopausal breast cancer patients with hypertension have been detected in different studies[64-66]. In addition, certain antihypertensive drugs have been shown to increase the risk of breast cancer[67-69]. Biological mechanisms linking hypertension and breast cancer risk are clearly intricate. However, a number of factors may play a key role in this link, such as obesity, adipokines like leptin, angiogenic factors like vascular endothelial growth factor (VEGF), macrophages, and insulin resistance[67,70-74].

ROLE OF LEPTIN IN DIABETES AND HYPERTENSION

A number of investigators documented higher blood levels of leptin in patients with type-2 diabetes[75-78]. Furthermore, higher leptin concentrations were detected in saliva samples from type-2 diabetes patients compared to healthy controls[79]. It has been demonstrated that leptin positively correlated with different cardiometabolic risk factors, *e.g.*, body mass index (BMI), waist circumference, blood pressure, dyslipidemia, and insulin resistance index[80-83]. Therefore, hyperleptinemia can be considered a critical link between obesity and insulin resistance[84]. It is thought that leptin upregulates pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, and these are associated with insulin resistance and type-2 diabetes[85].

In human subjects, different studies observed that hyperleptinemia was associated with hypertension[86-89]. Furthermore, hyperleptinemia could be involved in arterial stiffness[90] and cardiac autonomic dysfunction[81]. Interestingly, human subjects or animal models with loss-of-function mutations in leptin/Ob-R or melanocortin receptor genes exhibit lower blood pressure despite severe obesity[91,92]. Of note, in the hypothalamic anorexigenic pathway, leptin binds to Ob-R on the pro-opiomelanocortin-expressing neurons, which leads to the release of alpha melanocyte-stimulating hormone that subsequently binds to melanocortin receptors[93]. Overall, leptin activates the sympathetic nervous system *via* the melanocortin system, and this effect particularly involves the renal sympathetic outflow in order to increase blood pressure[94-96]. Apart from the sympatho-excitatory actions, leptin may influence the blood pressure *via* a number of mechanisms, such as the renin-angiotensin and aldosterone system[95-97]. Furthermore, leptin is thought to be associated with other hypertension-related phenomena, *e.g.*, endothelial dysfunction, impairment of nitric oxide-mediated vasodilation, atherosclerosis, cardiomyocyte hypertrophy, cardiac disorders, and kidney damage[98-104]. However, the precise mechanisms by which the hyperleptinemia state influences hypertension remains poorly understood.

APPROACHES FOR OBESITY MANAGEMENT

Clinical laboratories play a significant role in the metabolic assessment and early diagnosis of complications associated with obesity. Due to the fact that obesity acts like a chronic low-grade inflammatory process, an alteration can be expected in the circulating levels of various metabolic components and biomolecules, including leptin (Table 2)[105-115]. Nonetheless, laboratory values of different nutritional parameters are useful in all levels of prevention[116]. In order to prevent various

Table 1 Selected recent reports on diabetes and epidemiological/clinical characteristics of breast cancer

Authors and report time	Study types, geographical areas and patients	Findings in brief
Bronsveld *et al*[44] 2017	Population-based cohort study among British population, 2371 breast cancer cases during approximately 1.6 million person-years	Approximately 2880 women with T2D are diagnosed with breast cancer per year in the United Kingdom
Charlot *et al*[45] 2017	1621 African-American women with invasive breast cancer (232 had T2D) were followed	A positive association of T2D with breast cancer mortality
Dankner *et al*[46] 2016	Israel, 2186196 individuals (prevalent diabetes: 159104 and incident diabetes: 408243) were followed for various cancers	Diabetes posed an increased risk of breast cancer in postmenopausal women
Gini *et al*[47] 2016	Retrospective population-based cohort study, Italy, 32247 T2D patients	T2D patients are at increased risk of several cancers, and of premature death in women with breast cancer
Lipscombe *et al*[48] 2015	Retrospective cohort study, Ontario, Canada, 38407 women with breast cancer (6115 had diabetes)	Diabetes was associated with more advanced-stage breast cancer
Luo *et al*[49] 2014	Women's Health Initiative, United States, 8108 women with breast cancer	T2D increased risk of total mortality among women with breast cancer
Ma *et al*[50] 2014	China, 865 early stage triple-negative breast cancer cases	T2D exhibited a significantly lower disease-free survival; increased likelihood of recurrence and metastasis
Maskarinec *et al*[51] 2017	Multiethnic cohort, Among 103721 women with 14558 T2D cases, 6692 women developed breast cancer	T2D status was primarily associated with higher breast cancer risk in Latinas
Palmer *et al*[52] 2017	Prospective cohort of African-American women, 1851 breast cancer cases during 847934 person-years of follow-up	Women with T2D were at increased risk of developing ER(-) breast cancer
Pan *et al*[53] 2018	Prospective study in China, 17463 incident cases (various cancers) among 508892 participants	Participants with T2D had increased risks of breast cancer
Samson *et al*[54] 2016	Retrospective cohort study, South Carolina, 7310 participants (3835 European-origin and 3475 African-American women)	Negative association between T2D and breast cancer was stronger in African-American women
Wu *et al*[55] 2015	Multiethnic cohort, California, 8952 breast cancer cases	Risk of mortality increased among cases with diabetes
Xu *et al*[56] 2015	Population-based retrospective cohort study, China, 36379 T2D patients	Elevated risk of breast cancer

T2D: Type-2 diabetes; ER(-): Estrogen receptor negative; Person-years: Amount of total time in years contributed by all participants.

obesity-related complications, a number of reports have advised different strategies, which are primarily connected with physical activity and healthy eating practice[117,118]. Apart from caloric restriction, regular intake of certain dietary constituents such as garlic and fenugreek are perhaps helpful[119-123]. It is clearly understood that there is an urgent need to develop appropriate therapeutic strategies for the treatment of obesity. It may be worth noting that the currently available anti-obesity pharmaceutical agents include monotherapy options, such as orlistat and lorcaserin, as well as combination products, such as phentermine/topiramate and naltrexone/bupropion[124].

On the other hand, surgical options may help extremely obese individuals. Bariatric or obesity surgery encompasses many types of weight-reduction procedures, such as gastric bypass, gastric banding or sleeve gastrectomy, and involves structural and physiologic alterations of the gastrointestinal tract. A number of studies have been performed to document the quality of life after weight-loss surgery. In a few reports, bariatric procedures were performed after the diagnosis of cancer[125-127]. In a retrospective cohort study, the investigators concluded that long-term mortality after gastric bypass surgery was significantly reduced, particularly deaths from diabetes, heart disease, and cancer[128]. Similarly, other studies found that bariatric surgery resulted in a decreased risk for the development of cancers, including breast cancer[129,130]. However, a national population-based cohort study from the United Kingdom noticed that individuals who had undergone a bariatric procedure exhibited a decreased risk of hormone-related cancers such as breast and endometrial cancers, while gastric bypass was associated with an increased risk of colorectal cancer[131]. In contrast, a similar study from the United Kingdom recorded that prior obesity surgery was not associated with an increased colorectal cancer risk[132]. In their study, the risk of breast cancer was reduced, while the risk of endometrial and kidney cancers remained elevated. In line with the conflicting trends, a nationwide population-based cohort study in Sweden found increased mortality from rectal cancer following obesity surgery[133]. Conversely, in a Dutch population-based study, which collected information on colorectal cancer cases, no differences were observed between hospitals performing bariatric surgery and hospitals that did not[134].

In general, studies have demonstrated a significant decrease in blood levels of leptin after bariatric surgery[135,136]. One study has shown that Ob-R expression

Table 2 Levels of circulating leptin in various pathophysiological conditions

Investigators	Subjects and salient findings
Al-Daghri *et al*[105] 2007 (Saudi Arabia)	308 adults participated [type-2 diabetes = 142 (female- 45), prediabetes = 86 (female- 37), normal controls = 80 (female- 35)]. Serum leptin levels among male subjects with type-2 diabetes (BMI- 27.3 ± 4.1 kg/m^2) were 12.4 (3.2-72) ng/mL; among pre-diabetes (BMI- 28.5 ± 4.3 kg/m^2) - 7.6 (1.2-72) ng/mL; and in controls (BMI- 29.2 ± 7.3 kg/m^2) - 3.9 (0.8-20) ng/mL. Leptin levels among female subjects with type-2 diabetes (BMI- 32.5 ± 10.3 kg/m^2) were 13.3 (3.6-49.1) ng/mL; among pre-diabetes (BMI- 32.5 ± 8.4 kg/m^2) - 14.09 (2.8-44.4) ng/mL; and in controls (BMI- 30.4 ± 6.4 kg/m^2) - 10.2 (0.25-34.8) ng/mL
Al-Harithy[106] 2004 (Saudi Arabia)	Females (n = 57) had higher serum leptin concentration (6.04 ± 4.71 ng/mL *vs* 1.72 ± 0.95 ng/mL) than males (n = 65). BMI values showed a strong association with leptin levels in both genders
Al Maskari and Alnaqdy[107] 2006 (Oman)	Overall, there was a significant difference in serum leptin between the obese group (n = 35, 34.78 ± 13.96 ng/mL) and the control non-obese subjects (n = 20, 10.6 ± 4.2 ng/mL). Obese females (n = 25): age- 29.2 ± 1.6 yr, BMI- 39.6 ± 1.5 kg/m^2, leptin- 38.2 ± 2.5 ng/mL; Obese males (n = 10): age- 30.0 ± 3.1 yr, BMI- 39.0 ± 2.9 kg/m^2, leptin- 27.0 ± 4.9 ng/mL
Kazmi *et al*[108] 2013 (Pakistan)	Obese and overweight group: n = 40, female- 33, age- 34.8 ± 4.6 yr, BMI- 31.7 ± 3.1 kg/m^2; and non-obese group: n = 50, female- 32, age- 32.7 ± 6.1 yr, BMI- 21.2 ± 1.5 kg/m^2. Serum leptin concentrations were higher in obese subjects (52.8 ± 24.6 ng/mL) than in non-obese subjects (6.3 ± 3.1 ng/mL)
Laimer *et al*[109] 2002 (Austria)	18 morbidly obese women were studied before and one year after SAGB. In addition, eight lean women were examined as a control group. Serum leptin levels decreased from 44.6 ± 18.0 ng/mL in pre-SAGB subjects (age- 40.3 ± 9.8 yr, BMI- 42.9 ± 5.6 kg/m^2) to 20.0 ± 13.1 ng/mL in post-SAGB state (BMI- 32.9 ± 6.0 kg/m^2). Control subjects: age- 38.3 ± 9.8 yr, BMI- 22.9 ± 2.2 kg/m^2, leptin- 6.3 ± 3.3 ng/mL
Miyawaki *et al*[110] 2002 (Japan)	During four weeks, ten obese subjects (five men and five premenopausal women: age- 33 ± 13 yr, BMI- 35.4 ± 2.4 kg/m^2, plasma leptin level- 46.2 ± 14.6 ng/mL) underwent 800 kcal/day LCD. In addition, ten obese subjects (five men and five premenopausal women: age- 31 ± 11 yr, BMI- 32.3 ± 2.1 kg/m^2, leptin- 14.9 ± 3.5 ng/mL) consumed a 1400 kcal/day BDD for the same period. Plasma leptin levels in the LCD group markedly decreased (13.2 ± 3.6 ng/mL) with the decrement in BMI (33.1 ± 2.2 kg/m^2); while in the BDD group, BMI and leptin concentrations were 31.0 ± 2.5 kg/m^2 and 13.4 ± 2.8 ng/mL, respectively
Osegbe *et al*[111] 2016 (Nigeria)	80 obese females (BMI- 39.1 ± 7.2 kg/m^2) were examined. Prevalence of hyperleptinemia was 92.5% and serum leptin levels- 48.4 ± 24.4 ng/mL
Sinorita *et al*[112] 2010 (Indonesia)	57 obese persons (female- 33) were divided into obese class Ⅰ (BMI > 25 kg/m^2 to < 30 kg/m^2) and obese class Ⅱ (BMI > 30 kg/m^2). Leptin concentration in obese class Ⅰ was 13.998 ± 13.486 ng/mL, and in obese class Ⅱ was 31.074 ± 26.158 ng/mL
Tasaka *et al*[113] 1997 (Japan)	In BMI < 25 kg/m^2, plasma leptin was 2.24 ± 0.25 ng/mL in males (n = 29) and 3.01 ± 0.39 ng/mL in females (n = 13); in BMI 25-30 kg/m^2, levels were 3.14 ± 0.31 ng/mL in males (n = 10) and 10.66 ± 2.86 ng/mL in females (n = 7) and in BMI > 30 kg/m^2, levels were 8.98 ± 1.5 ng/mL in males (n = 11) and 11.74 ± 2.2 ng/mL in females (n = 6)
Tong *et al*[114] 2005 (United States)	The subjects consisted of nondiabetic Japanese-American population (n = 518, male- 51%) enrolled in the Japanese-American Community Diabetes Study. The mean plasma leptin level for men (BMI- 25.2 ± 3.0 kg/m^2) was 4.0 ± 2.7 pmol/L and 11.6 ± 7.3 pmol/L for women (BMI- 22.9 ± 3.1 kg/m^2) (1 pmol/L = 0.445 ng/mL)
van Rossum *et al*[115] 2000 (United States)	54 postmenopausal obese women before and after a 6-mo hypocaloric diet - the women lost an average of 7.1% of body weight and 14.5% serum leptin levels during the 6-mo weight loss intervention (initial BMI- 32.0 ± 4.5 kg/m^2, leptin- 30.9 ± 20.2 ng/mL; and after weight loss BMI- 29.8 ± 4.7 kg/m^2, leptin- 24.3 ± 14.8 ng/mL)

BMI: Body mass index; SAGB: Swedish adjustable gastric banding; LCD: Low-calorie diet; BDD: Balanced deficit diet.

was increased, while adipocyte size was decreased following surgical obesity reduction[137]. After a direct comparison of the effect of caloric restriction and bariatric surgery on circulating levels of different inflammatory cytokines including leptin, the investigators concluded that caloric restriction seemed to have more favorable effects[138]. In the same way, another study found that caloric restriction plus exercise resulted in weight loss of similar magnitude to a matched group of subjects following bariatric surgery[139]. On the other hand, anti-obesity pharmacotherapy such as orlistat (or in combination with other conservative methods) has been shown to exert beneficial effects on weight loss and inflammatory cytokines including leptin[140-142].

CONCLUSION

There are substantial comorbidities among postmenopausal breast cancer patients, which include obesity-related diseases such as type-2 diabetes mellitus, hypertension, and other cardiovascular disorders. The abovementioned health issues possibly originate from a state of chronic low-grade inflammation that is associated with a dysregulation of pro-inflammatory adipokines like leptin. A growing body of evidence has shown that leptin can impact different obesity-related pathologies and patients' prognosis. Overall, there is an urgent need to understand the precise functions of leptin, its interactions with various adipokines and classical hormones, and methods to develop a nontoxic and clinically effective leptin antagonist.

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