OBESITY AND BREAST CANCER: ADIPOKINES' ROLE

Obesidade e câncer de mama: o papel das adipocinas

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ABSTRACT

Objective: Obesity and overweight are risk factors, and also prognostic factor for cancer, including breast cancer. Studies have accessed adipokines, adiponectins and leptins as keymediators in obesity and breast cancer. **Methods**: This is a systematic review of observational epidemiological cohort, case-control and survival studies related adiponectin and leptin with obesity and breast cancer over the past 15 years. Fourteen studies met the inclusion criteria, assessing the relationship of adiponectin and leptin as a risk factors and prognostic in breast cancer. **Results**: The studies showed an inverse relationship of adiponectin and direct relationship of leptin with body mass index (BMI) and were consistent in assigning lower serum levels of adiponectin to an increased risk of breast cancer, independently of BMI and variables of insulin resistance. Patients with breast cancer have low serum levels of adiponectin and higher levels of leptin in comparison to healthy patients. Low concentration of adiponectin increases the risk of breast cancer, and low concentrations of adiponectin and high of leptin are worse prognosis no matter the factors for breast cancer in women. **Conclusion**: The adipokines, in complex and interrelated mechanisms, probably drive breast cancer initiation and progression.

KEYWORDS: Breast cancer; obesity; adiponectin; leptin.

RESUMO

Introdução: A obesidade e o sobrepeso são fatores de risco e prognóstico para o câncer em diferentes sítios, incluindo a mama. Estudos têm avaliado o papel das adipocinas, adiponectina e leptina, como mediadores-chave entre a obesidade e o câncer de mama. **Métodos**: Foi realizada uma revisão sistemática da literatura de estudos epidemiológicos observacionais do tipo coorte, caso-controle e de sobrevida que relacionavam a adiponectina e/ou a leptina com obesidade e câncer de mama nos 15 anos anteriores à pesquisa. Quatorze estudos preencheram os critérios de inclusão, avaliando a adiponectina e a leptina como fatores de risco e prognóstico para o câncer de mama. **Resultados**: Os estudos demonstraram uma relação inversa da adiponectina e uma relação direta da leptina com o índice de massa corporal (IMC), e foram concordantes em atribuir menores níveis séricos de adiponectina a um aumento no risco de câncer de mama, independentes do IMC e das variáveis de resistência à insulina. As pacientes com câncer de mama apresentaram níveis séricos baixos de adiponectina e altos de leptina, em relação às pacientes saudáveis; níveis séricos baixos de adiponectina e altos de leptina são fatores de pior prognóstico independentes para câncer de mama em mulheres. **Conclusão**: As adipocinas, em mecanismos complexos e inter-relacionados, provavelmente dirigem o aparecimento e a progressão do câncer de mama.

PALAVRAS-CHAVE: Câncer de mama; obesidade; adiponectina; leptina.

INTRODUCTION

Obesity is a current public health problem directly related to the modern "obesogenic" environment, which stimulates the "fast" and exaggerated consumption of high-calorie food and a sedentary lifestyle[1]. Overweight and obesity are risk factors for cancer in different primary sites, including the breast[2]. Obese women are 50% more likely to develop breast cancer than non-obese ones[2]. When diagnosed with breast cancer, obese women tend to present tumors with biological characteristics of greater aggressiveness[3], as well as higher rates of relapse and progression of the disease in their evolution and reduction in survival, in relation to non-obese women[4].

Epidemiological evidence correlates obesity as a worse prognosis risk factor for breast cancer, although the mechanisms related to carcinogenesis are still being studied and are not fully understood. It is postulated that the increased estrogenic stimulus related to obesity[5] and the adipose tissue dysfunction — determining metabolic disorders such as insulin resistance, chronic inflammation and alteration in the adipokine secretion by adipocytes — are the keymediators of breast cancer and obesity[6,7]. Adiponectin and leptin are adipokines responsible for controlling the energy metabolism of the body, satiety, insulin sensitivity, lipid metabolism and acute inflammatory response[8]. They have been related to the risk of cancer, including endometrial, rectum and breast cancer[9,10]. The imbalanced leptin and adiponectin secretion in obesity is implicated in pro-tumorigenic growth and proliferation activation pathways — such as PI3K, ERK and JAK/STAT3 —, angiogenesis stimulation, invasion and metastasis by tumor cells[11,12].

The adipokine's action potential in breast cancer has been studied, and may offer, in addition to understanding the pathophysiology of the disease, new perspectives for cancer prevention, the detection of biomarkers and possible future therapeutic targets[13].

This article had the objective of reviewing epidemiological studies on obesity and adipokines — adiponectin and leptin — on the risk and prognosis of breast cancer, among pre- and post-menopausal women, in the 15 years prior to the survey.

METHODS

It is a systematic review of the literature, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model[14] of epidemiological studies on the relation between obesity, breast cancer and adipokines. The PubMed database was searched for articles published between 1990 and 2016 using the descriptors *breast cancer*, *obesity* and *adiponectin* or *leptin*. The search resulted in 260 articles for the descriptors *breast cancer*, *obesity* and *leptin*; for the descriptors *breast cancer*, *obesity* and *adiponectin*, there were 142 articles.

Articles, written in English, referring to observational, cohort, case-control and survival epidemiological studies were selected, which assessed adiponectin and/or leptin as risk factors or prognosis for breast cancer with obesity, presenting an association measure as relative risk, *odds ratio* (OR) or hazard risk (HR). Basic research, clinical trials, review articles and meta-analyses were disregarded. At the end of the selection and evaluation, only 18 articles were observational epidemiological studies. Of these, four were descriptive ones and did not present the aforementioned association measures, thus being excluded. Finally, 14 studies met the inclusion criteria for the analysis, which was carried out considering the specific information of each article, related to serum levels of leptin and adiponectin or the expression of leptin or adiponectin receptors in tumor pieces, resulting in the relation between risk and/or breast cancer prognosis (Figure 1).

RESULTS

The studies evaluated included Asian, European and American populations. Serum levels or the expression of receptors in tumor pieces of adiponectin and leptin with risk or prognosis of breast cancer were correlated with covariables such as the body mass index (BMI) and anthropometric measures related to obesity; serum markers for insulin peripheral resistance (serum insulin dosage, HOWA calculation — homeostasis model assessment for insulin resistance —, blood glucose, insulin-like growth factor level and globulin-bound); inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNFA), interleukin-6(IL-6); and serum estradiol dosages (Table 1). HOWA = HOWA-IR homeostasis model assessment for insulin resistance

In the Asian population, the study by Miyoshi et al. (2003)[15], of retrospective case-control nature, observed that women
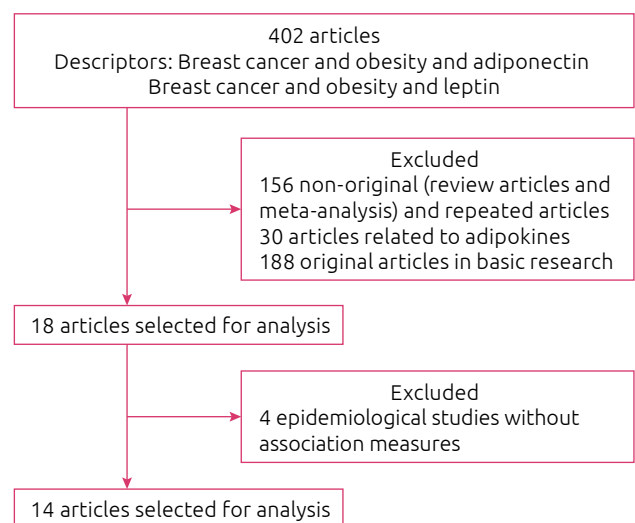

Figure 1. Review article selection flowchart.

with breast cancer had significantly lower levels of serum adiponectin when compared to control patients. The evaluation of serum levels of adiponectin by tertile, adjusted according to age and BMI, evidences that low levels increased the risk for breast cancer: in the lowest tertile, the OR was 3.63 (confidence interval of 95% – 95%CI 1.61–8.19, p<0.005), and in the intermediate tertile, 2.79 (95%CI 1.23–6.35, p<0.050), when compared to the highest serum adiponectin level. Premenopausal women do not have a significant higher risk of breast cancer in intermediate and low adiponectin tertiles, while postmenopausal ones have a significantly higher risk of breast cancer. As for prognosis factors, women with breast cancer and lower adiponectin levels (low tertile) presented a significant higher risk for tumors larger than 2.0 cm (p=0,005) and high grades (p<0.050), which are factors of worse prognosis for this pathology.

The case-control study by Tian et al.[16], with 488 women, related anthropometric measures and serum adiponectin dosage with breast cancer risk. It was observed that central adiposity anthropometrical measures (waist-hip ratio) and the BMI significantly increase the risk of breast cancer only in the postmenopausal period. The BMI was inversely correlated to, statistically significant, serum adiponectin levels, as well as the waist circumference and the waist-hip ratio. Women with elevated serum adiponectin levels had significantly lower risk of developing breast cancer in the postmenopausal period and non-significant risk of it in the premenopausal one, regardless of anthropometric measures. A significant negative association between adiponectin levels and breast cancer was detected in positive estrogen receptor tumor (OR=0.53; 95%CI 0.27–0.98).

The case-control study by Minatoya et al.[17] addressed the association of breast cancer, BMI, insulin levels and serum

Table 1. Distribution of epidemiological studies according to authors, type of study, number of patients, outcomes and covariables.

Author and year	Type of study	N	Adipokine (serum level)	Outcome OR (95%CI) Recurrence, mortality and survival (OS e DDFS)	Covariables
Miyoshi et al., 2003[15]	Case-control	202	Low adiponectin	OR=3.63 (1.61–8.19) Post-M OR=3.90 (1.23–12.44) Pre-M OR=3.48 (0.89–13.50)	BMI
Tian et al., 2007[16]	Case-control	488	High adiponectin	OR=0.55 (0.23–0.97) Post-M OR=0.55 (0.23–0.97) Pre-M OR=0.84 (0.46–1.52)	BMI, anthropometric measures and HR
Minatoya et al., 2014[17]	Case-control	66	High adiponectin	Post-M OR=0.13 (0.03–0.57) Pre-M OR=0.01 (0.00–0.26)	BMI, insulin
Oh et al., 2011[18]	Survival	747	Low adiponectin	Recurrence HR=2.82 (1.03–7.68)	BMI, HOWA-IR, HR
Mantzoros et al., 2004[19]	Case-control	341	High adiponectin	OR=0.84 (0.71–0.99) Post-M OR=0.81 (0.68–0.96) Pre-M OR=0.92 (0.66–1.27)	IGF-1, IGFBP-3
Macis et al., 2012[20]	Survival	214	High adiponectin	Recurrence HR=0.87 (0.79–0.95)	BMI, HOWA-IR, IGF-1, mammographic density HDL
Cust et al., 2008[21]	Case-control	1,122	High leptin	Stages II-IV OR=1.39 (0.65–2.96)	BMI, menopausal status, HR Hb1Ac
Gunter et al., 2015[23]	Case-control	1,714	High adiponectin	OR=0.76 (0.59–1.12) univariate OR=0.81 (0.59–1.12) multivariate	BMI, estradiol
Korner et al., 2007[22]	Case-control	150	High adiponectin	OR=0.35 (0.14–0.88)	BMI, menopausal status
Tworoger et al., 2007[24]	Case-control	3,673	Adiponectin	Post-M OR=0.73 (0.55–0.98) Pre-M OR=1.30 (0.80–2.10)	BMI, IGF-1, IGFBP-3
Harris et al., 2011[25]	Case-control	974	Leptin (interquartile)	OR=0.66 (0.40–0.96)	BMI
Duggan et al., 2010[26]	Survival	1,183	High adiponectin	Mortality reduction 61%	BMI
Gross et al., 2013[27]	Case-control	544	Low adiponectin High leptin	Adiponectin OR=1.63 (1.02–2.60) Leptin OR=2.44 (1.30–4.58)	BMI, TNF
Goodwin et al., 2012[28,29]	Survival	520	High leptin	OS HR=1.92 (1.00–3.69) DDFS HR=1.58 (0.90–2.79) Recurrence HR=1.41 (0.85–2.35)	BMI, insulin

OR: *odds ratio*; 95%CI 95% confidence interval; OS: overall survival; DDFS: distant disease-free survival; Post-M: postmenopausal; Pre-M: premenopausal; BMI: body mass index; HR: hormonal receptors; HOWA-IR: homeostasis model assessment for insulin resistance; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor-binding protein factor 3; HR: hazard risk; HDL: high density lipoprotein; Hb1Ac: glycated hemoglobin; TNF: tumor necrosis factor.

adiponectin. The study showed that serum adiponectin levels were significantly higher in the control group, both in pre- and postmenopausal periods. Adiponectin levels were inversely related to the BMI both in pre- and postmenopausal periods (p=0.001 and 0.002, respectively). There was an association between BMI and breast cancer risk both in premenopausal (OR=1.17; 95%CI 0.23–6.10) and postmenopausal periods (OR=1.39; 95%CI 0.50–3.86). The serum adiponectin level was inversely correlated with breast cancer: high serum adiponectin level reduced the risk of breast cancer in the postmenopausal (OR=0.13; 95%CI 0.03–0.57) and premenopausal periods (OR=0.01; 95%CI 0.00–0.26).

The study by Oh et al.[18] evaluated the recurrence of breast cancer in 747 women, correlating it to levels of serum adiponectin, leptin, insulin resistance markers and metabolic syndrome. The study showed that patients with positive hormone receptor (HR) have significantly higher adiponectin and estradiol levels, and low leptin and homeostasis model assessment for insulin resistance — HOWA-IR levels. In patients with negative HR, the serum adiponectin level had an inverse relation with recurrence (p=0.009), and the group with the lowest adiponectin level presented a 2.8 times higher risk of recurrence (1.03–7.68), even after adjusted by BMI and HOWA-IR. The metabolic syndrome, when evaluated in the negative HR patients group, was associated with a higher recurrence of breast cancer. However, this association fades after adjustment for the HOWA-IR and adiponectin variables. Leptin was not associated with prognosis factor for recurrence in this study.

In Europe, the study by Mantzoros et al.[19], of case-control nature, evaluated women with breast cancer (174 cases) and healthy women (167 controls), correlating measures of adiponectin, leptin, insulin-like growth factor 1 (IGF-1) and IGF bound to protein factor 3 (IGFBP-3). The study found a significant inverse association of breast cancer risk in the premenopausal period with levels of IGF-1 and IGFBP-3 (p=0.06 and 0.01, respectively), but not in the postmenopausal one. Leptin had no significant association with the risk of breast cancer in neither the pre- nor the postmenopausal period. There was significant association of low levels of adiponectin and increased risk of breast cancer in the postmenopausal period (OR=0.81; 95%CI 0.68–1.27; p=0.02).

The study by Macis et al.[20] exclusively included premenopausal women who had an increased risk of breast cancer or diagnosis of *in situ* or micro-invasive breast cancer, comparing four different chemoprevention groups with tamoxifen or placebo, with the objective of evaluating the recurrence of breast cancer and calculating the disease-free survival (DFS) in these groups. The levels of adiponectin and leptin were analyzed, as well as the leptin/adiponectin relation, IGF-1, glucose, insulin and insulin sensitivity by the HOWA criteria, related to the covariables of BMI and mammographic density percentage. Women with *in situ* and micro-invasive neoplasia

had significantly low adiponectin levels, and the leptin/adiponectin relation was significantly higher. Serum adiponectin levels were significantly lower, and the leptin/adiponectin relation was significantly higher in patients who experienced new events, while high serum adiponectin levels reduced the events (HR=0.87; 95%CI 0.79–0.95) of intraepithelial neoplasia and breast cancer by 8%, for each statistically significant increase in the adiponectin unit. The association of adiponectin with reduced risk of breast cancer in women was independent of BMI and the percentage of mammographic density. There was significant association, statistically significant (p=0.02), of adiponectin levels with DFS.

Cust et al.[21] carried out a case-control study with 1,121 women, evaluating the relation between BMI, levels of leptin, adiponectin, glycosylated hemoglobin (HbA1c) and CRP with risk of breast cancer. There was no association between BMI, levels of leptin, adiponectin, HbA1c and CRP with risk of breast cancer adjusted by age (≤55 years of age or less than 55 years of age), as well as their HR status. The study displayed a positive association between BMI, leptin and HbA1c with greater risk of breast cancer related to staging of the disease. For stage I, the highest and lowest leptin strata had an inverse relation with the risk of breast cancer (OR=0.45; 95%CI 0.22–0.91; p=0.03). There was a trend in stages II to IV of increased risk of breast cancer related to the highest and lowest strata of BMI (OR=1.89; 95%CI 0.99–3.59; p=0.05) and HbA1c (OR=1.91; 95%CI 1.00–3.66; p=0.05), although not significant to leptin (OR=1.39; 95%CI 0.65–2.96; p=0.40).

The study by Korner et al.[22] evaluated the levels of adiponectin, leptin and insulin and the expression of adiponectin receptors (Adipo R1/R2) in tumor tissue in women diagnosed with breast cancer. The study showed that women with higher adiponectin levels had a statistically significant reduction of 65% in the risk of death by breast cancer, regardless of the variables — age, BMI, reproductive and hormonal (estrogen) factors. Premenopausal and obese women were more prone to this benefit when compared to postmenopausal and non-obese women. Still in this study, the *in vitro* evaluation of adiponectin effects in normal and neoplastic cells cultures demonstrated that the exposure of breast cancer cells with positive estrogen receptors to adiponectin inhibited proliferation in 86% of malignant cells in the samples, in comparison to only 10% inhibition in normal cells.

The case-control study on postmenopausal women (875 cases and 839 controls)[23] in the United States had the objective of evaluating the role of adipokines along with inflammatory markers in the development of breast cancer. The study did not show any statistically significant association between adiponectin, leptin, resistin and inflammatory markers such as IL-6, TNFa and CRP with risk of breast cancer, in adjusted models. There was association between the reduced risk of breast cancer in high-level

serum quartiles (OR=0.76; 95%CI 0.59–1.12; p=0.06) for serum adiponectin levels, but this association was not significant in a multivariable analysis including insulin levels (OR=0.81; 95%CI 0.59–1.12; p=0.222). The CRP levels varied among patients who did and who did not undergo hormone replacement therapy (HRT), which reflected on the relation with the risk of breast cancer. Among patients who underwent HRT, the high levels of CRP was not related to the increased risk of breast cancer (OR=0.90; 95%CI 0.53–1.53; p=0.509); on the other hand, among patient who did not undergo HRT, the elevated levels of CRP correlated with the increased risk of breast cancer (OR=1.98; 95%CI 1.25–3.13; p=0.003) and maintained a significant positive association, even after adjusted in multivariate analysis[23].

Tworoger et al.[24] conducted a case-control study with 3,673 women with the objective of evaluating the association between serum adiponectin levels and the overall and menopausal risk of breast cancer. The study did not find any association between adiponectin levels and overall breast cancer, though it did observe a significant slight association to the menopausal status (p=0.008) between the highest and lowest serum adiponectin quartiles. This risk was of HR=1.3 (95%CI 0.80–2.10; p=0.09) in the premenopausal period; and HR=0.73 (95%CI 0.55–0.98; p=0.08) in the postmenopausal one, adjusted to the variables BMI, age, IGF-1 and IGFBP-1 levels. There was no difference between the adiponectin levels and the development of *in situ* or invasive cancer and HR expression in cancer. The study observed a non-statistically significant inverse relation between adiponectin levels and the risk of postmenopausal breast cancer, which was independent of estrogen levels and was maintained after adjusting the covariates for insulin resistance markers (C-peptide), IGF-1 and IGFBP-124.

Harris et al.[25] carried out a case-control study with 936 women evaluating the association of serum leptin levels and the risk of breast cancer. Association was observed between the levels of leptin and unadjusted breast cancer levels between the highest and lowest quartiles of serum leptin level (OR=0.66; 95%CI 0.40–0.96; p=0.05) and between leptin and breast cancer levels adjusted by the BMI (OR=0.55; 95%CI 0.31–0.99). The author concluded that the study demonstrated a significant borderline association between serum leptin levels in the largest quartile and the risk of breast cancer, although, after adjusted by the BMI model, there was no significance (p=0.26).

A cohort of 1,183 American women diagnosed with breast cancer and with doses of adiponectin, leptin, fasting plasma glucose and insulin was evaluated for mortality due to overall cancer and to breast cancer[26]. The study showed that serum adiponectin levels inversely correlated with HOWA-IR, BMI and leptin; more elevated levels of adiponectin reduced mortality due to breast cancer by 61%, and there was a positive association with survival. The HOWA-IR insulin resistance marker was associated to increased overall mortality, and the relation with breast cancer mortality and in overweight women was more evident in higher quartiles. The study concluded by demonstrating the importance of the role of hyperinsulinemia as an independent factor of worst prognosis for women diagnosed with breast cancer and their association with low levels of adiponectin and shorter survival to breast cancer.

Gross et al.[27] conducted a case-control study on women with postmenopausal breast cancer correlated with BMI, levels of serum leptin, adiponectin and tumor necrosis factor receptor (TNF-R2) evaluated with the risk of breast cancer. The study showed that the cases had significantly higher BMI, serum leptin and TNF-R2 levels, in relation to the control group. Elevated levels of leptin and TNF-R2 were significantly related to a higher risk of breast cancer; the relation between high quartiles and low leptin level had OR=2.44 (95%CI 1.30–4.58; p=0.05), and low adiponectin levels were significantly related to the increased risk of breast cancer (OR=1.63; 95%CI 1.02–2.60; p=0.08). The high TNF-R2 inflammatory level (comparing the highest quartile to the lowest TNF-R2 serum level) was the strongest association factor with the risk of breast cancer (OR=2.44; 95%CI 1.30–4.58), with a significant response dose between the highest levels and the risk of breast cancer (p=0.008).

The Canadian study by Goodwin et al.[28] evaluated leptin levels in the breast cancer prognosis of 520 women. Women with stage I to III breast cancer had their leptin, blood glucose and insulin levels collected and followed prospectively, with the objective of evaluating leptin as a prognosis factor and their relationship with the survival rates of these patients. The results showed that the leptin was strongly correlated with BMI and serum insulin levels. Higher leptin levels were pointed out as factor of worse tumor prognosis: larger tumor size (p=0.0050), high histological grade (p=0.0023) and negative HR (for estrogen p=0.0470 and progesterone p=0.0023 receptors). There was no association of leptin levels with distant disease-free survival (DDFS) (HR=1.58; 95%CI 0.90–2.79) and risk of distant recurrence (HR=1.41; 95%CI 0.85–2.35; p=0.19). The association with worse overall survival (OS) was non-significant (HR=1.92; 95%CI 1.00–3.69; p=0.049), more evident in the postmenopausal period. In this same cohort of Canadian women, in a 12-year follow-up[29], variables related to insulin resistance (fasting insulin, HOWA-IR empirical estimate of insulin resistance, fasting glucose and peptide-C), to obesity (BMI, waist-hip ratio) and to serum leptin dosage in women with diagnosis of breast cancer were evaluated. The study showed a strong prognostic linear association with a worse prognosis in relation to DDFS and OS, in the first five years of breast cancer, with statistically significant factors related to insulin resistance. The BMI and serum leptin levels, in a univariate analysis, were significantly associated with prognosis in breast cancer[29].

DISCUSSION AND CONCLUSION

The epidemiological studies included in this review showed association between breast cancer and adipokines levels (adiponectin and leptin) and their prognostic relationship with one another. The studies which correlated adiponectin and leptin levels with BMI demonstrated inverse adiponectin relation and direct leptin one with this variable[16,20,21,26,28], and were consistent in assigning lower serum adiponectin levels to an increased risk of breast cancer among women in general — and in the postmenopausal period[15,16,24,25] —, regardless of BMI and variables related to insulin resistance markers. Two recent meta-analyses, by Macis et al.[30] and Liu et al.[31], evaluating the relation of serum adiponectin levels alone with the risk of breast cancer, had divergent results. The first one[30] showed inverse association between adiponectin levels and the risk of breast cancer, detecting 34% risk reduction for higher levels of serum adiponectin in general, in the postmenopausal period and in the premenopausal one. The later one[31] does not suggest association of adiponectin levels with breast cancer among women in general, although, in a subgroup analysis, there would be evidence of inverse association between serum adiponectin levels and the risk of breast cancer among postmenopausal women.

The quantification of serum adiponectin levels was correlated with differences in the risk of breast cancer: the lower the serum adiponectin levels, the higher the risks of breast cancer[15-17,19]. These findings have also been demonstrated in the meta-analysis by Ye et al.[32], which showed association of significantly lower levels of adiponectin and higher risk of breast cancer.

The studies by Korner et al.[22] and Duggan et al.[26], which evaluated the role of adiponectin in breast cancer prognosis, showed the relation of higher serum adiponectin levels with a better prognosis. In the study by Korner et al.[22], positive estrogen receptor cancer cells, when exposed to adiponectin, had inhibition of malignant cell proliferation as a response in 86% of the samples, compared to only 10% of inhibition effect on normal cells. The inhibition effect of tumor cell growth and the stimulation of apoptosis pathways by adiponectin in breast cancer tumor cells were observed in other *in vitro* studies, and in negative and positive HR tumor cells samples[32,33].

Although there is no consensus on the relation of high serum leptin levels and increased risk of breast cancer — as is the case of adiponectin —, studies demonstrated a positive correlation of high serum leptin levels with high BMI and insulin resistance parameters in patient with breast cancer — when compared to control ones[20,21,28]; and the relation of significantly high leptin/adiponectin in cases of breast cancer compared to healthy control ones[20]. The relation between serum leptin levels and the greater expression of their OB-R receptor (leptin) in larger breast cancer tissue samples was also related to a worse prognosis of the disease, translated into larger tumors and more advanced staging at diagnosis, as well as by the difference in recurrence and survival[34].

Serum leptin levels are representative of body fat mass: the serum leptin concentration increases in obesity and decreases during fasting. Adiponectin is reduced in obesity and in insulin resistance cases and increases in response to weight loss[35]. Low adiponectin levels are related to dyslipidemia, regardless of conditions of peripheral resistance to insulin and chronic inflammation[36]. Some studies have shown that the adiponectin stimulates peripheral tissue sensitivity to insulin, and the decreased serum levels would be related to an increase in serum insulin and peripheral insulin resistance parameters[37]. The study by Oh et al.[18] concluded that serum adiponectin levels may have a prognostic effect on patients with negative HR breast cancer, regardless of obesity and insulin resistance, postulating that adiponectin may be the connection between obesity, hyperinsulinemia and insulin resistance in the development and progression of breast cancer.

The heterogeneity of the studies and their results indicate there is probably no single stimulation pathway associated to a risk factor or prognosis that directs the onset of breast cancer and determines their biological behavior[23]. Hyperinsulinemia in obesity may or may not be associated to a diabetes mellitus (DM) diagnosis; studies are controversial in trying to establish the role of DM, increasing the risk of breast cancer[38]. Some studies evaluated the impact of Metformin use in the reduction of peripheral insulin resistance, impacting the reduction of risk and improving the prognosis of breast cancer, though with still contradictory results[39]. A more recent study by Calip et al.[40], with 10,050 diabetic women in treatment, did not detect, in a multivariate analysis adjusted for confounding factors with BMI, any decrease in the risk of breast cancer among patients using Metformin.

The adipose tissue is an active endocrine organ, which among other function secretes biomarkers, such as adipokines (adiponectin and leptin), involved in cancer activation pathways and proliferation. Epidemiological studies show that the metabolic dysregulation of obese patients with breast cancer, both in pre- and postmenopausal periods, expressed by low serum adiponectin and high serum leptin levels, increases the risk of breast cancer in patients with low adiponectin levels and worsens their prognosis, reducing the survival of patients with high serum leptin levels and low adiponectin ones. However, the metabolic dysregulation relation to unbalanced adipokines levels is not a single pathway for stimulation and progression of cancer. The interaction of the pathways related to insulin resistance and inflammation, to which the role of adipokines is associated, contributes or determines the development of breast cancer in women.

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