REVIEW ARTICLE
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Association between obesity and triple-negative breast cancer: a systematic qualitative review

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ABSTRACT

Introduction: The relation between obesity and triple-negative breast cancer (TNBC) is not totally elucidated. TNBC represents a heterogeneous group of aggressive growth neoplasms. The concepts related to the development of hormone receptor-positive tumors cannot be directly extended to this group. To evaluate the association between obesity and TNBC, considering as primary outcome the assessment of the incidence of this tumor subtype in this population and as secondary outcomes the specific pathophysiology, prognosis, and treatment in this context. Methods: This was a systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses — PRISMA statement. PubMed/MEDLINE and Cochrane were the databases used as primary paper sources. Inclusion according to titles and abstracts allowed a secondary selection by reference list revision. The final full-text review was done on the most opportune studies identified. Results: A total of 52 articles were included. Epidemiology: A higher frequency of obesity among TNBC patients compared to other subtypes and TNBC in obese women was observed in the literature. It is uncertain whether premenopausal status is an aggravating factor. Pathophysiology: Several studies identified the production of different factors by obese adipose tissue and their regulation of genes related to the expression of stem-like cell properties, mainly leptin, IL-6, and IL-8. Prognosis: Most studies pointed out that disease-free survival and overall survival are independent of body mass index. Treatment: Weight reduction showed no significant power in improving prognosis but may favor primary incidence prevention. Drugs based on obesity-related pathways are still in research, and various potential targets were raised. Conclusions: Obesity is a risk factor for TNBC. Obese-related inflammatory cytokines may contribute to tumor development. Once TNBC is established, the prognosis does not differ according to initial body mass index changes. No target drug for obesity-related tumorigenic pathways is currently available for clinical use.

KEYWORDS: obesity; breast neoplasm; triple negative breast cancer.

INTRODUCTION

The relationship between obesity and breast cancer is an old topic of discussion and investigation. Over years of epidemiological research and observation, it has become clear that the interaction of body mass index (BMI) with breast tumorigenesis could not be simplified into one unique conclusion. This binomial showed itself to be complex and heterogeneous. Different associations were found depending on multiple context factors such as ethnicity, menstrual status, and anatomopathological tumor type.

The well-established association is obesity in postmenopausal women as a risk factor for hormone receptor-positive breast cancer. Pathophysiology justifying this influence was initially well-understood and supposedly simple. The higher and maintained estrogenic synthesis, by aromatase enzyme conversion of adrenal androgens in adipose tissue, could stimulate the breast cells proliferation that expressed those hormone receptors[1]. However, past decade data already point to other factors synthesized by adipose tissue that could have a synergistic carcinogenic effect on the breast and other organs, as well.

The connection between triple-negative breast cancer (TNBC) and obesity is not entirely intuitive. TNBC consists of the most aggressive subtype and stands for 20% of breast cancer cases. The absence of hormone or HER2 expression reflects the difficulty to treat the cancer, as no targeted therapy has been developed to date[2].

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Recently, numerous lines of research have been interested in this subtype of tumor. Pro-inflammatory activity related to adipose tissue has brought to light more consistent data concerning the possibility of obesity as a risk factor for TNBC development.

This systematic review aimed to concentrate on and explore the prior global knowledge already published in the scientific literature about the association between obesity and TNBC.

As a primary outcome, we intended to evaluate whether the incidence of TNBC is proportionally higher in the obese population. As secondary outcomes, we evaluated the pathophysiology that could explain such an association, the prognostic effect of obesity in a patient with this tumor subtype, and the targeted treatments that could be applied in this specific associative context.

The data presented in this article were designed to concisely report to generalists and specialists what is known about this issue so that they can improve their practice based on available evidence.

METHODS

This review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[3] (Figure 1). A systematic search was conducted to determine relevant articles published until July 1, 2022, using two primary biomedical literature databases: PubMed/MEDLINE and Cochrane. The following terms were used to access papers of interest broadly: ((triple-negative breast cancer) OR (basal-like)) AND ((BMI) OR (obesity)). No limits were placed on the country or publication date. All types of studies, descriptives or analytics were accepted. Studies in process or only published in conference annals were not included.

Only articles in English were selected. Studies in which TNBC was analyzed, among other types of breast tumor, were also considered. Studies with women across both premenopausal and postmenopausal status were considered for analysis. Animal model studies were also included. After the initial exclusion of duplicates, titles and abstracts were revised, allowing the first filtration of our bibliography, selecting the articles with probably the highest impact for the full-text review.

A secondary selection of opportune papers for analysis was performed. Additional studies were identified by reviewing the reference lists of the first listed studies that met the inclusion criteria.

After full-text evaluations, the last refinement was concluded, finishing the selection process of adequate literature for this topic review. This systematic review was performed from this condensed but relevant group of articles. Thereafter, the study's samples, methods, results, and conclusions were qualitatively described. No statistical analysis was conducted on these data.

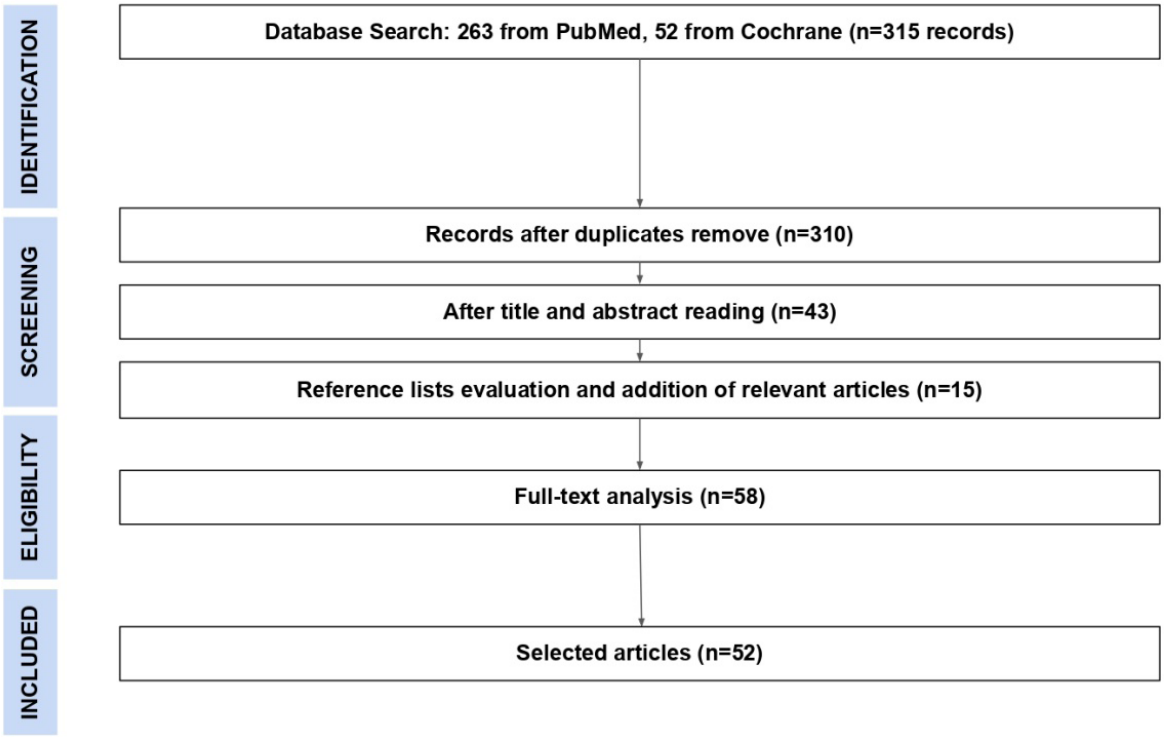

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for systematic review articles selection.

This article's discussion of the relationship between obesity and TNBC was carefully and objectively detailed based on the most consistent data available. Aiming for a straightforward approach, we organized epidemiology, pathophysiology, prognosis, and interventions.

RESULTS

The primary literature search yielded 310 articles, considering 263 from PubMed, 52 from Cochrane, and the removal of five duplicates. After the title and abstract reading, 43 studies directly related to the association between obesity and TNBC were selected. We added 15 other opportune studies by their reference lists evaluation, reaching 58 articles for full-text analyses. After reading all 58 texts, we ended up with 52 primary studies covering epidemiology, pathophysiology, prognosis, and treatment subtopics.

Epidemiology

There are multiple studies concerning TNBC patients' characteristics. However, the pathophysiology of this tumor subtype has not been elucidated yet. Therefore, populational analyses have always been a first step in bringing to light this disease mechanism.

Through extensive sample studies, including initially its different subtypes, breast cancer incidence showed itself to be directly related to obesity frequency, and over years of detailed research comparing individual characteristics between breast cancer subtypes, TNBC alone also presented a frequent association with obesity in concordance with general tendency.

Millikan et al. found an increasing waist-hip ratio positively associated with basal-like tumors, even though no relation was observed with BMI[4]. After that, several studies pointed to a higher frequency of obesity among TNBC patients compared to other subtypes or obesity as a significant risk factor for TNBC[5-12]. Somali et al., Enger et al., and Maiti et al., found no relationship between obesity and TNBC[13-15].

Pierobon's meta-analysis with 3,845 patients diagnosed with TNBC, which evaluated breast cancer, obesity, and menopausal status, concluded that this association between obesity and TNBC was only valid for women with premenopausal status[10]. This corroborated a previous study by Gaudet, which comprised women under 56 years old and restricted its conclusion of TNBC increased risk by obesity only to premenopausal status[9]. Also, in a pooled analysis of 34 studies comprising 35,568 patients, of which 1,997 had TNBC, Yang et al. identified an association between obesity and breast cancer confined to TNBC cases in women younger than 50 years old[8]. An epidemiological difference was then established with the protective effect obesity imposes over hormone receptor-positive tumors in premenopausal women[11].

Concerning racial differences in this context, Siddharth et al. suggested a higher frequency of obesity among African-American women compared to European-American ones as one of the factors that could explain the TNBC earlier onset and more advanced stage at diagnosis in that population. Other factors related would be a genetic risk, low income, and inadequate screening[16].

In Table 1, we listed and summarized the main epidemiological studies that evaluated the association between TNBC and obesity. It is observed that the correlation is positive in the majority of the studies (8 out of 11), with a particular emphasis on the premenopausal period.

Pathophysiology

Obesity has already been linked to the development of different types of cancer. Concerning TNBC, a couple of articles examined molecular factors and pathways that may favor this tumor's emergence in obese patients, as summarized in Figure 2. Most of these studies are ***in vivo*** research using TNBC cells inoculated in animal models.

The main primary changes in an obese organism described as possible triggers for TNBC tumorigenesis are adipose tissue mechanical stress and hypoxia, with adipocyte death and consequent systemic inflammation. A second pathway recurrently explored is the high leptin levels observed in obese individuals, being directly associated with TNBC severity[15,17,18].

Adipose tissue is responsible for inflammatory cytokines release, including IL-6, IL-8, IL-12, CCL2, and IL-1β[19]. Leptin and IL-6 are related to increased macrophage migration to adipose tissue and their subtype change from type 1 to type 2. Type 2 macrophages secrete IL-6 (dependent on NADPH oxidase 2 activity), IL-8, TGF-β, and EGF. Also, leptin stimulates T cell release of IL-2 and IFN-γ[20,21].

Leptin, IL-2, and IFN-γ from T cells, IL-6, and TNF-α (through glycoprotein 130) from type 2 macrophages can activate STAT3/JAK2, NF-κB, and Wnt/EZH2[17,20,21]. These transcription factors regulate the expression of NANOG, SOX2, and OCT4 — genes that are shown to induce stem-like properties in TNBC cells, including renewal capacity[18,21].

In addition, obese individuals present low natural killer (NK) cell number and activity that have already been associated with poor prognosis in TNBC[22]. NK cells play a role against tumor cells' survival, and chronically elevated leptin levels can decrease leptin receptor sensibility, resulting in the downregulation of cytotoxic activity[23]. Naik et al. described this immune pathway by which obesity could favor TNBC progression[24].

Teslow et al. reported that inflammation and reactive oxygen species derived from the obesity context can regulate splicing factor serine/arginine-rich splicing factor 2 (SRSF2), which augments the expression of methyl-CpG-binding domain variant 2 (MBD2-v2) that is another inductor of NANOG overexpression[25]. Additionally, Kolb et al. presented that inflammation enhances the

Table 1. Previous articles that evaluated the association of triple-negative breast cancer incidence with obesity.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Enger et al.[14]	U.S.A.	1,184 cases; 272 TNBC	Case-control (two groups: pre and postmenopause)	Body mass index was not associated with TNBC, including BMI>27	No association was found regarding BMI	Low cut point regarding BMI>27
Milikan et al.[4]	U.S.A.	1,424 cases; 225 basal-like	Case-control	Elevated WHR was associated with increased risk of basal-like breast cancer in pre and postmenopausal women compared to luminal A cases and controls.	WHR 0.77–0.83: OR 2.3 (95%CI 1.5–3.5)/≥0.84: OR 2.3 (95%CI 1.4–3.6) (referent to controls)	Higher incidence of basal-like tumors among African-Americans
Vona-Davis et al.[5]	U.S.A.	620 cases; 117 TNBC	Retrospective cohort	Obesity was present in 49.6% of those with triple-negative tumors but in only 35.8% of those with non-triple-negative tumors.	p=0.0098	No analysis according to age subgroups
Kwan et al.[7]	U.S.A.	2,544 cases; 288 TNBC	Prospective cohort	Compared with luminal A cases, triple-negative cases tended more likely to be overweight or obese if premenopausal	Overweight: OR 1.82 (95%CI 1.03–3.24)/Obese: OR 1.97 (95%CI 1.03–3.77)	Higher incidence of TNBC among African-Americans
Maiti et al.[15]	U.S.A.	176 cases; 86 TNBC	Retrospective cohort	Triple-negative breast cancer is associated with a higher prevalence of the metabolic syndrome but not with higher BMI	No association was found regarding BMI	Reduced population, retrospective study
Trivers et al.[6]	U.S.A.	476 cases, 135 TNBC	Case-control	Women with TN tumors were more likely to be obese than normal/ underweight	OR 1.89 (95%CI 1.22–2.92)	Tumor specimens were available only on a subset of eligible cases
Yang et al.[8]	U.S.A.	35,568 cases; 1,997 TNBC	Pooled analysis 34 studies/Case control	Association in women <50 years between obesity and breast cancer confined to TNBC cases	OR 1.80 (95%CI 1.42–2.29)/ p=0.000002	Differences in study populations, designs and methods of collecting risk factors, and marker data
Gaudet et al.[9]	U.S.A.	890 cases; 246 TNBC	Case-control	Larger body size among premenopausal women was associated with higher risk of luminal B and TNBC	OR 1.67 (95%CI 1.22–2.28)/p=0,026 (compared to luminal A)	Biased observed findings for unmeasured risk factors, staining obtained by a single pathologist
Pierobon et al.[10]		24,479 cases; 3,845 TNBC	Systematic review and meta-analysis	The case-case and case-control comparisons showed a significant association between TNBC and obesity	Case-case: OR 1.2 (95%CI 1.03–1.4)/ p=0.003 Case-control: OR 1.43 (95%CI 1.23–1.65)/p=0.913	

Continue...

Table 1. Continuation.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Somali et al.[13]	Turkey	882 cases; 132 TNBC	Retrospective cohort	No significant difference was observed in terms of BMI between postmenopausal and premenopausal patients in the TNBC group	p=0.08	Patients with unknown menopausal status, >50 years old were considered postmenopausal
Chen et al.[11]	U.S.A.	2,659 cases; 1,275 TNBC	Case-case-control	Obese premenopausal women had an increased risk of TNBC while obese postmenopausal women had a reduced risk of TNBC	Pre: OR 1.82 (95%CI 1.32–2.51)/ p=0.004 Post: OR 0.74 (95%CI 0.54–1)/ p=0.032	Case-case comparison should not be extended to a cancer-free population

U.S.A.: United States of America; TNBC: triple-negative breast cancer; BMI: body mass index; CI: confidence interval; WHR: waist-hip ratio; OR: odds ratio.

upregulation of angiopoietin-like 4 (ANGPTL4) in adipocytes. This condition leads to angiogenesis and progression of breast cancer[19].

High levels of leptin and leptin receptor activity have also been shown to promote Serpine-1 gene expression that codifies serine protease inhibitors in vascular epithelial cells. Through binding vitronectin, this protein favors the detachment of cancer cells, facilitating metastasis. Leptin knockdown resulted in a diminution of metastasis[26].

A third pathway described by which obesity could be associated with TNBC development is chronic hyperglycemia. D'Esposito et al. showed that TNBC cells become more invasive when cultivated with adipocytes and even more when exposed to a hyperglycemic environment. Hyperglycemia increases CCL5 produced by adipocytes that bind to CCR5, which activates STAT3/JAK2, mTOR, and p38MAP kinase. CCL5 presence in adipose tissue was associated with lymph node positivity and metastasis[27]. In concordance, Dietze et al. showed that hyperglycemia through induced hyperinsulinemia and IGF-1 raise could activate AKT/mTOR cascade, resulting in elevated glucose uptake by the cell ending on the Warburg effect[20].

Prognosis

Previously, it has already been shown that obesity appears to be a factor in poor prognosis for breast cancer in general. Ewertz et al., in a large sample Danish study with 18,967 patients, revealed an increase in metastasis and death frequency in obese patients with breast cancer compared to non-obese ones; however, cancer subtypes were not discriminated[28].

Despite a general investigation of obesity and breast cancer development, researchers have been specifically interested in evaluating the influence of obesity according to each cancer subtype. In the last decade, a couple of studies were dedicated to analyzing if obesity could or could not be confirmed as a possible factor for a poor prognosis in TNBC. The results found were not always homogeneous.

In a systematic review and meta-analysis including nine studies comprising 4,412 TNBC patients, Mei et al. concluded that disease-free survival (DFS) and overall survival (OS) were independent of BMI[29]. This was consistent with other studies not included in this meta-analysis[30-34]. It is valid to point out that Dawood et al. and Tait et al. analyzed their sample by menopausal status and still found no significant influence of BMI over TNBC prognosis between pre and postmenopausal groups[31,33]. Schmidt et al., however, presented similar results but with a 70% postmenopausal sample[34]. Also, Mowad et al., despite finding larger tumor size and grade staging, DFS and OS remained indifferent among obese and non-obese individuals[32].

In counterpoint, some authors found a positive association between obesity and TNBC's poor prognosis, including DFS and OS. Through these studies, attention should be taken to Turkoz et al. presenting an all-premenopausal sample and Loi et al. a 74% one[35,36]. Also, Hao et al., Bao et al., and Al Jarroudi et al. found a worse prognosis exclusively among the premenopausal group[37-39]. However, Choi et al. described no difference according to menopausal status, comprising only 50 patients[40]. Chen et al., independent of menopausal status, similarly presented a decrease in DFS and OS in the obese group and were the first, to our knowledge, to include in the analyses the abdominal circumference, not only the weight, finding a worse prognosis in the group with both general obesity associated with central obesity[41].

Additionally, Maehle et al. described a better prognosis for their obese negative hormone receptor group than the non-obese one, considering that the sample was 75% composed of postmenopausal women and TNBC individuals were not isolated[42].

Treatment

Since there is no available well-established target therapy for TNBC, modifiable risk factors, such as weight intervention, have been a source of interest in the last years for prevention or even cancer progression impairment.

Eliassen et al., in a large prospective cohort study within the Nurses' Health Study, including 87,143 postmenopausal patients followed up for 24 years, observed an increased risk for general breast cancer associated with weight gain since the age of 18

years. This pointed to weight maintenance or loss as a possible prevention method. However, TNBC was not evaluated separately[43].

Enger et al. precisely found a tendency of risk increase of breast cancer by weight gain during the menace restricted to hormone receptor-positive tumors. Hormone receptor-negative tumor risk was independent of weight change, and physical activity frequency was also evaluated. Weight loss or physical activity after diagnosis was not evaluated[14].

First, *in vivo* studies showed reverse TNBC progression and delayed tumor latency in obese mice submitted to weight loss on a low-fat diet. This phenomenon was associated with a reduction in kinases (PKC-α, PKD1, PKA, and MEK3) and an increase in AMPKα activity[44,45].

However, studies with TNBC patients did not show that clear correlation. In a 518 Chinese patients study, weight loss was associated with higher tumor recurrence and mortality than stable weight[38]. In a second study with 173 patients, weight change — gain or loss — did not correlate with Ki67 or pathologic complete response change during neoadjuvant chemotherapy[46]. In counterpoint, Wang et al. described JAK/STAT3-regulated fatty acid β-oxidation as critical for cancer stem cell self-renewal and chemoresistance, which could be more evident in obese patients[47].

Finally, some authors tested therapeutic drug alternatives for TNBC related to obesity pathophysiology. Otvos et al., in a mouse xenograft model for TNBC, found a significant average survival increase by subcutaneous Allo-aca (a leptin receptor antagonist) administration compared to conventional intraperitoneal cisplatin[48]. Similarly, Gourgue et al. described a reduction in TNBC growth with apelin antagonist F13A. This substance reduces apelin activity, an adipokine increased in adipose tissue of obese mouse tumors[49].

Naik et al., in an extensive discussion about immune pathways related to TNBC development and progression in obese organisms, suggested some hypothetical points of possible therapeutic interventions to be studied:

1) PD-1/PD-L1 suppression, since in a study with 250 patients, obese ones got the major benefit of this intervention than lean individuals. Being PD-L1 a mark of immunosuppression, it becomes a possible target for blocking;
2) Adoptive NK cell therapy, since obese have low NK cell number and activity;
3) Inhibition of IL-6 or its receptor related to a tumorigenic pathway;
4) Inhibition of CCL2/CCR2 and CSF/CSF-1R related to macrophage type 2 polarization and accumulation, also favoring stem cell properties development;
5) Blocking of myeloid-derived suppressor cells that also express PD-L1 and are stimulated by obesity-related cytokines; and
6) TGF-β1 blocking since its increment in obese individuals hinders a sustained effective T cell response against tumor cells[24].

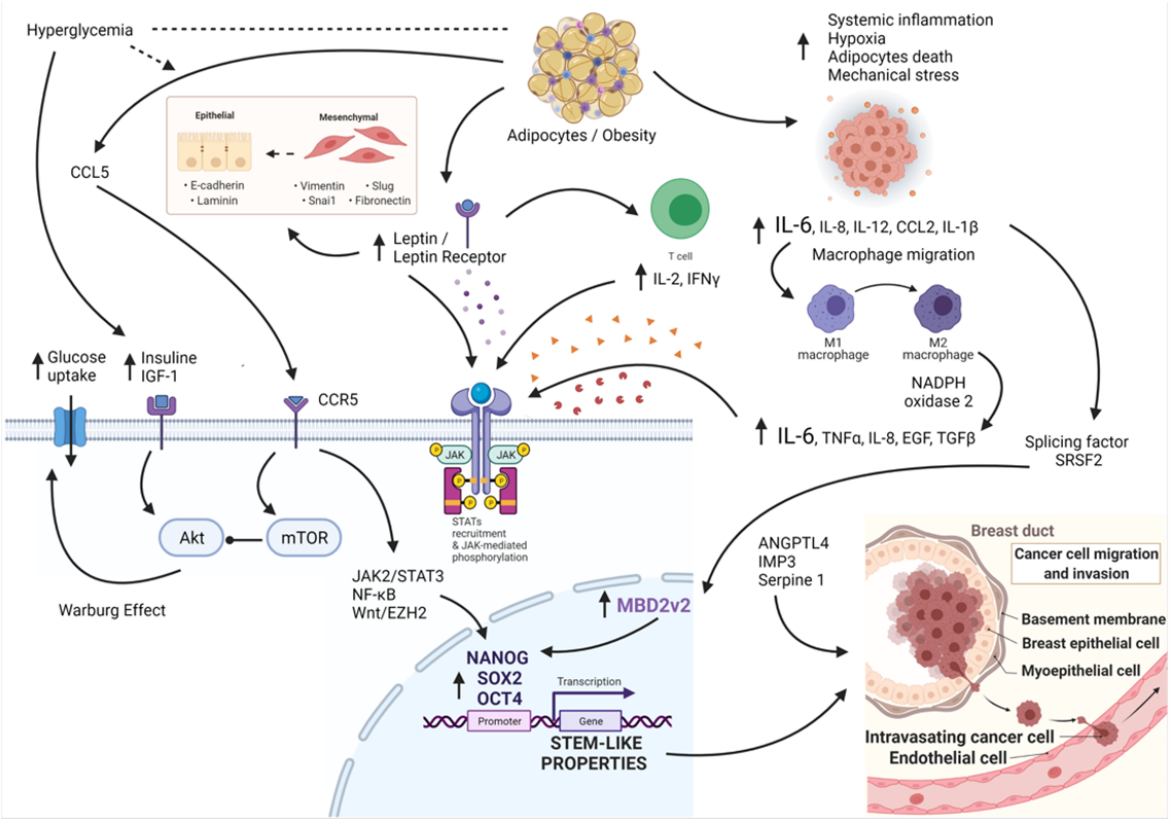

Figure 2. Pathways linking obesity and breast cancer development (created with BioRender).

DISCUSSION

After some years of research and many studies focused on exploring the specific effect of obesity on TNBC development and progression, we are beginning to identify concordant results that point to the establishment of initial consistent knowledge on this topic. In the past, breast cancer was considered a unique disease. Today, we understand that different subtypes make breast cancer notably a heterogeneous disease.

Concerning TNBC, the majority of studies agree that obesity is a risk factor for tumor development. Just one study focused on evaluating menopausal status directly, and it suggested that this association is limited to the premenopausal period[10]. The authors gave no hypothesis to explain why the prejudicial effect of obesity would be reduced after menopause, especially considering its supposed independence from hormone influence.

A temporality bias, however, could be a reasonable hypothesis. TNBC presents itself as an early-onset tumor, possibly based on the significant influence of genetic factors. Thereby, incidence at older ages would naturally be lower, as most susceptible individuals had already developed and manifested it at a younger age. Also, a higher incidence of obesity and TNBC among African-Americans should be considered as a possible bias regarding the influence of confounding genetic and social factors in this population.[4,7]

Mamidi et al. identified the main pathways activated in premenopausal women with TNBC in a whole genome transcriptome analysis, including unfolded protein response, endoplasmic reticulum stress, B cell receptor, and autophagy signaling[50]. Despite that, more investigation should be conducted to explain the possible influence of hormonal status on these specific mechanisms. As for hormone receptor-positive breast cancer, it is valid that the opposite association is observed: obesity showed itself as a protective factor among premenopausal women. Potischman et al. suggested that in premenopausal women, obesity is associated with a more significant number of anovulatory cycles, thus, lower estradiol levels and less incidence of hormone-dependent tumors[51].

Inflammation is a new focus of interest for all diseases epidemiologically associated with obesity. Pathophysiology studies revealed a world of obesity-related inflammatory and genetic cascades that could justify developing cancers independently of estrogen, such as TNBC. Almost all of the articles consisted of *in vivo* research and elucidated different pathways that could be more investigated to offer new potential therapeutic targets.

Studies related to obesity and TNBC prognosis presented conflicting findings. The authors do not exclude possible bias considering the aggressiveness of this tumor subtype. Once this cancer is established, its progression is possibly little or nothing different comparing an obese or not-obese environment. However, some authors found a worse prognosis, especially in premenopausal groups. This condition may be associated with significant incidence of TNBC in premenopausal obese women.

Concerning the still absence of specific treatment, lifestyle modifiable factors have been evaluated. Sun et al. pointed to the maintenance of an optimal body weight as a valuable primary prevention for TNBC — the only clear, effective measure currently available[52].

Even though obesity seems to favor the development of TNBC, studies investigating weight loss as a possible factor for tumor control after diagnosis did not reach concordant conclusions; tumor stage, chemotherapy side effects, or diet may influence weight loss. Further investigation in more homogeneous groups is necessary to differentiate cases in which diet and consequent weight loss could be used to break the disease from those in which weight loss occurs due to advanced tumor itself or palliative treatment. Weight loss could contribute to the reduction of hormones and inflammatory cytokines that eventually figure as stimulants for tumor cell perpetuation.

The impact of physical activity still needs to be specifically better evaluated for TNBC. Few studies analyzed it as a risk reducer for this tumor incidence. No consistent evidence has been observed, as it was reported by The Women's Health Initiative concerning breast cancer in general[53].

The complexity of inflammatory pathways and immune system regulation is a current challenge and an opportunity for improving or developing treatment for different types of cancer. Little literature is currently available, but specific targets for obese-related environmental factors seem promising, including leptin, IL-6, PD-1/PD-L1, and NK cells.

As a qualitative review, we emphasize that this study presents the risk of bias related to a subjective joint analysis of articles. The absence of a meta-analysis weakens the power of its evidence. Results remain based on the global impression of a team of experts over a systematic selection of studies.

CONCLUSIONS

There is consistent evidence supporting obesity as a risk factor for TNBC. Inflammatory cytokines related to an obese environment may contribute to tumor development. It is uncertain if the premenopausal status is a worsening factor. Obese patients with already diagnosed TNBC have a similar prognosis to t non-obese ones, and their weight loss does not seem to be a disease course modifier. Few target drugs directed to obesity-related tumorigenic pathways began to be tested and showed initial encouraging results. More investigations concerning the pathophysiology and new treatment possibilities need to be performed.

AUTHORS' CONTRIBUTIONS

LLI: data curation, formal analysis, visualization, writing – original draft, writing – review & editing. SRM: investigation, software, writing – review & editing. JRF: funding acquisition, resources, supervision, validation. EB: funding acquisition, project administration, resources. SMO: conceptualization, methology, project administration.

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