Influence of Body Mass Index on Survival of Women with Different Subtypes of Breast Cancer: an Integrative Review

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Influência do Índice de Massa Corporal na Sobrevida de Mulheres com Diferentes Subtipos de Câncer de Mama: uma Revisão Integrativa

Influencia del Índice de Masa Corporal en la Supervivencia de las Mujeres con Diferentes Subtipos de Cáncer de Mama: una Revisión Integrativa

Rosilene de Lima Pinheiro[1]; Gina Torres Rego Monteiro[2]

Abstract

Introduction: Obesity is considered a negative prognostic factor for women with breast cancer, however, its influence on the course of the disease can be differentiated in molecular subtypes. **Objective:** To analyze the influence of the body mass index (BMI) on the survival of women with breast cancer according to the molecular subtype. **Method:** Integrative review using PICOS strategy for the design of the study, identification of keywords and definition of eligibility criteria. Studies that analyzed the influence of BMI on the survival of women with breast cancer, by tumor subtype, using COX regression and/or Kaplan-Meier published until June 2018 were identified in PubMed, VHL, Scopus and Web of Science databases. **Results:** There were selected 23 studies from 446 identified. Women with triple negative tumors in higher BMI categories presented worse survival in four of the seventeen studies including this subtype. In cases of luminal tumors, high BMI was a negative prognostic factor in seven of the eleven studies. For HER2 (Human Epidermal growth factor Receptor-type **2**) overexpressed, there was worse survival for higher BMI in two of the six studies. Among HER2 positive women regardless of hormone status, it was observed worse survival for women with higher BMI in two of the five studies. **Conclusion:** The effect of BMI on the survival of women with breast cancer appears to be differentiated according to the tumor subtype, and its effect is apparently greater in those with luminal tumors.

Key words: Breast Neoplasms/classification; Body Mass Index; Survival Analysis.

Resumo

Introdução: A obesidade é considerada fator prognóstico negativo para mulheres com câncer de mama; entretanto, sua influência sobre o curso da doença pode ser diferenciada nos subtipos moleculares. **Objetivo:** Analisar a influência do índice de massa corporal (IMC) na sobrevida de mulheres com câncer de mama segundo o subtipo molecular. **Método:** Realizada revisão integrativa de literatura utilizando estratégia PICOS para formulação da pesquisa, identificação de palavras-chave e definição dos critérios de elegibilidade. Estudos que analisaram a influência do IMC na sobrevida de mulheres com câncer de mama, por subtipo tumoral, utilizando risco proporcional de COX e/ou Kaplan-Meier, publicados até junho de 2018, foram identificados nas bases PubMed, BVS, *Scopus* e *Web of Science*. **Resultados:** Foram selecionados 23 estudos entre 446 identificados. Mulheres com tumores do tipo triplo-negativo nas maiores categorias de IMC exibiram pior sobrevida em quatro dos 17 estudos incluindo esse subtipo. Nos casos de tumores luminal, IMC elevado foi fator prognóstico negativo em sete entre 11 estudos. Para HER2 (receptor tipo 2 do fator de crescimento epidérmico humano) superexpresso, houve pior sobrevida quando IMC elevado em dois dos seis estudos. Entre os HER2 positivos, independente do *status* hormonal, observou-se pior sobrevida para mulheres com maiores IMC em dois dos cinco estudos. **Conclusão:** O efeito do IMC na sobrevida de mulheres com câncer de mama parece ser diferenciado de acordo com o subtipo tumoral, sendo seu efeito, aparentemente, maior naquelas com tumores luminais.

Palavras-chave: Neoplasias da Mama/classificação; Índice de Massa Corporal; Análise de Sobrevida.

Resumen

Introducción: La obesidad se considera un factor pronóstico negativo para las mujeres con cáncer de mama y su influencia sobre el curso de la enfermedad puede diferenciarse en los subtipos moleculares. **Objetivo:** Analizar la influencia del índice de masa corporal (IMC) en la supervivencia de las mujeres con cáncer de mama según subtipo molecular. **Método:** Realizada revisión integrativa utilizando estrategia PICOS para formulación de la investigación, identificación de palabras clave y definición de los criterios de elegibilidad. Los estudios que analizaron la influencia del IMC en la supervivencia, por subtipo tumoral, utilizando regresión de COX y/o Kaplan-Meier publicados hasta junio de 2018 fueron identificados en PubMed, BVS, Scopus y *Web of Science*. **Resultados:** Se seleccionaron 23 estudios. Las mujeres con tumores triple negativo en las mayores categorías de IMC mostraron peor sobrevida en cuatro de los diecisiete estudios incluyendo esse subtipo. Para casos de tumores lumínicos, IMC elevado fue factor pronóstico negativo en siete entre once estudios. Para HER2 (receptor tipo 2 del factor de crecimiento epidérmico humano) superexpresado, hubo peor sobrevida cuando IMC elevado en dos de los seis estudios. Entre los HER2 positivos independientes del *status* hormonal, se observó peor sobrevida para mujeres con mayores IMC en dos de los cinco estudios. **Conclusión:** El efecto del IMC en la supervivencia de las mujeres con cáncer de mama parece ser diferenciado de acuerdo con el subtipo tumoral, siendo su efecto, aparentemente, mayor en aquellas con tumores luminales.

Palabras clave: Neoplasias de la Mama/clasificación; Índice de Masa Corporal; Análisis de Supervivencia.

[1] Coordination of Teaching of Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Rio de Janeiro (RJ), Brazil. Orcid iD: https://orcid.org/0000-0002-7301-5452

[2] Escola Nacional de Saúde Pública da Fundação Oswaldo Cruz (Ensp/Fiocruz). Rio de Janeiro (RJ), Brazil. Orcid iD: https://orcid.org/0000-0002-9900-1825

Address for Correspondence: Rosilene de Lima Pinheiro. Rua Marquês de Pombal, nº. 125 – 3º andar – Centro. Rio de Janeiro (RJ), Brazil. CEP 20230-240. E-mail: rpinheiro@inca.gov.br

INTRODUCTION

The clinical course of breast cancer is influenced by a series of conditions related to the characteristics of the tumor, as size, nuclear grade, histological grade, status of hormone receptors (RH), for estrogen (RE) and progesterone (RP), status of receptor type 2 of the factor of human epidermal growth factor (HER2) and the clinical status from the disease to diagnosis as the commitment of axillary lymph nodes and the presence of remote metastasis that, conjointly, will determine the prognosis of the disease[1]. Recent progresses of the understanding about the biological characteristics of mammary tumors show that breast cancer is a complex and heterogeneous disease, including at least four molecular subtypes that show distinguished profiles of genic expression defined by the combination of RE, RP and HER2, with differentiated biological behavior associated to different therapeutic and prognostic responses[2].

Additionally, other prognosis factors of the breast cancer has been described in the literature, among them, the related to the immune, hormone and nutritional status of the patient, particularly obesity. Recent epidemiological studies show that breast cancer survival patients with obesity at the diagnosis have more odds of relapse and death; obesity is a negative prognostic factor[3,4]. A meta-analysis with 43 studies published between 1988 and 2009 noticed that obese women at the diagnosis had 33% more odds of dying of breast cancer when compared to non-obese[5]. A bibliographic review including 11 prospective studies and secondary analyzes of clinical trials published from 2010 indicated obesity at the diagnosis as a negative prognosis of breast cancer[6]. In another review, where 17 cohort studies were included, published between 1966 and June 2010, that investigated the association of body weight and prognosis of breast cancer, the authors concluded that there are convincing evidences that obesity, measured by the Body Mass Index (BMI) is associated to global mortality; that there is probable evidence of relation between obesity and specific mortality by breast cancer. The results are less clear in relation to the association between BMI and relapse of breast cancer[7]. The interference of obesity in the prognosis of breast cancer is being investigated in clinical trials in patients submitted to different types of treatment; however, despite many of these studies indicate an increase of the risk of death related to obesity, the results are still conflicting[8-14].

More recent investigations show that the influence of obesity over the course of the disease can be differentiated, contingent upon the biological interaction between the adipose tissue and the molecular subtypes of the tumor, which can explain the differences in the results encountered in distinct studies. Therefore, the search for clarification about the association between obesity and prognosis of different subtypes of breast cancer is mandatory. The objective of the present study was to analyze the scientific production about the influence of BMI over the survival of women with breast cancer, including disease-free survival (DFS), global survival (GS) and cancer-related survival (CRS) according to the tumor subtypes, utilizing as strategy an integrative review of the literature with the proposal of synthesis and narrative analysis of the scientific knowledge produced about the theme researched.

METHOD

This study was based in the methodological recommendations for integrative review proposed by Botelho et al.[15] and Whittemore and Knafl[16], and the guidelines for systematic reviews of observational studies about risk factors and prognosis proposed by the Ministry of Health[17].

The integrative review was systematized in six stages. In the first it was conducted the formulation of the research question; in the second, the location of the studies through bibliographic search in databases; the third stage comprehended the strategy of eligibility of studies with application of the inclusion and exclusion criteria; in the fourth, the extraction of data of the studies included; in the fifth, analysis, interpretation and discussion of the results and at last, the sixth, the elaboration of this document, which describes in detail the synthesis of the scientific knowledge produced. For a better interpretation of the findings, it was decided to describe and discuss the results jointly.

Research question

The research question was formulated through the strategy PICOS (Population; Intervention/Exposure; Control; Outcome; Study Design)[17]. As population of interest, women with breast cancer diagnosis classified per tumor subtype. As exposure, obesity determined through measurement of BMI. As control, low or normal weight determined through measurement of BMI. As outcome, relapse of the disease and death. As study design, cohort. The components PICOS were utilized to identify keywords utilized in the strategy of search and to define the criteria of eligibility to select the studies.

Location of the studies

The databases utilized to locate the studies were PubMed, BVS, Scopus and *Web of Science*, where searches were conducted with limit date until June 30, 2018,

including the following keywords: *breast cancer, molecular phenotype* (*molecular characteristics or molecular subtype or luminal or HER2 or Triple Negative Breast Neoplasm*), *Body Mass Index* (*BMI* or *overweight* or *obesity*), without application of filters. The references obtained in each one of the databases were listed in one Excel spreadsheet to identify the repeated citations among the databases and formation of a list of studies to obtain the abstracts and evaluation of eligibility.

Eligibility of the studies

The strategy to select the studies was conducted in two stages: screening and evaluation of the eligibility. The screening was done with the reading of the titles and abstracts to identify those who presented the following characteristics: address breast cancer in a female population, investigating survival through cohort analytical study, published in English, Portuguese or Spanish. The evaluation of the eligibility was performed with the reading of the full articles and application of the criteria of inclusion and exclusion. The inclusion criteria were: have analyzed the influence of BMI over survival per tumor subtype, utilizing Cox proportional hazards model as methods of statistical analysis to estimate the odds of relapse risk and death and/or Kaplan-Meier with *Log-rank* test. It were excluded the studies that did not describe the tumor subtypes, data of *odds ratio* for categories of BMI with confidence interval and values of *Log-rank* test, in addition to those whose population studied had been included in other selected study.

Extraction of data

From each study included, it were extracted: author, year and country of publication, methodological data, characteristics of the study population and main results. The methodological data addressed DFS, CRS and GS and its descriptions, survival time studied, tumor subtypes analyzed (measured or self-reported), moment the data were obtained (considering the status of RE, RP and HER2), how weight and height were obtained (measured or self-reported), how anthropometric data weight, height and/or BMI were obtained, BMI cut-off, method of analysis of survival (Cox proportional hazards and/or Kaplan-Meier) and the variables utilized to adjust the analyzes. It were collected the characteristics of the population studied: total women included in the study, mean and standard deviation (SD) or median and age range and menopausal status. The results extracted were: the median time of follow up, the values of hazard ratio with the respective confidence intervals for each category of BMI estimated by Cox proportional hazards model and the data of the curve of Kaplan-Meier with the *p* values of *Log-rank* test.

Each stage was conducted by two investigators separately and later compared. The discrepancies were discussed to reach a consensus.

RESULTS AND DISCUSSION

Based in the searches, 446 publications about the theme were obtained in the database investigated. While applying the eligibility criteria, 23 studies were included representing 5% of the total of abstracts obtained and to 32% of the articles read (Figure 1).

In Table 1, the main characteristics of the studies included are described[14,18-39]. The 23 studies were published between September 2011 and September 2018 showing that there are few studies with this object of investigation and that the theme is quite recent. Eight studies were conducted with the population of the United States of America, nine with Asian population (China 4, Turkey 3, Japan 1 and South Korea 1), five with European population (Italy, Spain, France and Germany) and one with Oceanian population (Australia), revealing the inexistence of studies with the South American population. The number of women included in each one of the studies varied between 112 and 41,021. The median time of follow up varied between 29 months and 11 years. Eleven studies estimated the effect of BMI over the survival through Cox proportional hazards, presenting the risk of mortality (global and/or cancer-related) and/or relapse of the disease. Two studies estimated the curves of survival of each category of BMI by the method Kaplan-Meier, comparing them with the *Log*-rank test; ten utilized both analyzes. The definitions of the types of survival considered in the methodology differed among some studies.

Of the 23 studies included in this review, only six reported clearly how the anthropometric data of weight and height were obtained: in four of them, height and weight were directly measured[18-21]; in one of them, height and weight were self-reported[23] and in one study, both were self-reported. The others did not explain how these indicators were collected. In eleven studies, BMI was obtained in the diagnosis[21,24-33], one, in a median of time of 21 days after the diagnosis[34]; in three, in the beginning of the study[19,22,23]; in three, after the surgery, before the chemotherapy treatment[14,20,35]; and five studies, failed to present information about how BMI was obtained[18,36-39]. Twenty two studies performed analyzes considering BMI as categorical variable, in 19, it were adopted one or more categories recommended by the World Health Organization (WHO) [14-20,22-30,32-34,36,37,39]: <18.5 kg/m² (low weight), 18.5-24.9 kg/m² (normal weight), 25.0-29.9 kg/m² (overweight) and ≥30 kg/m² (obesity), being sub-categorized in 30.0-34.9 kg/m² (mild

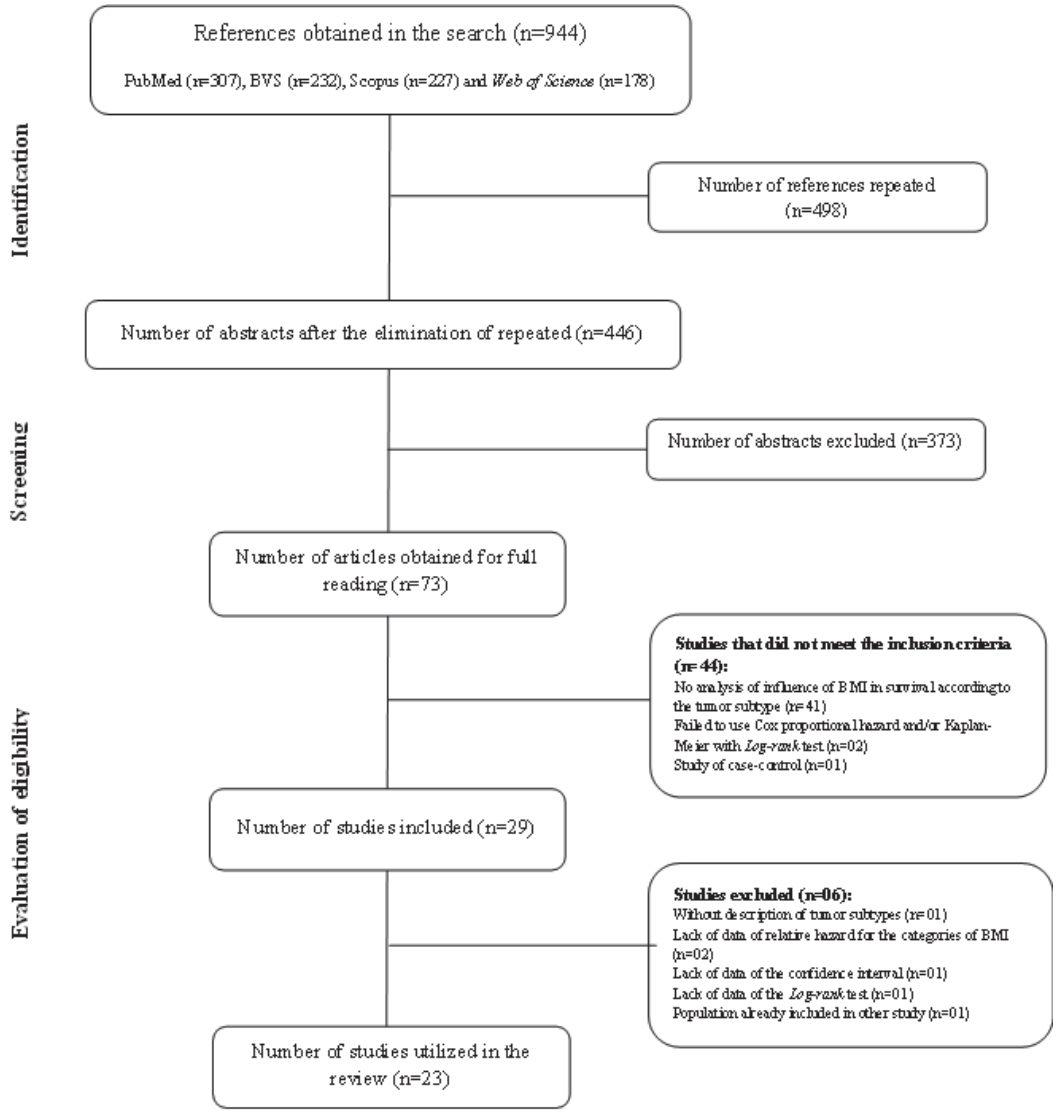

Figure 1. Flowchart of search and evaluation strategy of eligibility of the studies

obesity), 35-39.9 Kg/m² (moderate obesity) and ≥40 kg/m² (severe obesity); and in three studies, the categories were differentiated[21,31,38]. Only one study analyzed the BMI as continuous variable, with five units of BMI raise as cut-off[35] (Table 1).

The BMI is an important health indicator recommended by WHO to estimate the adequacy of weight/height and to monitor overweight of the population[40]. Its accuracy is directly dependent on the accuracy of weight and height though, in population studies, it is common the utilization of the self-reported information. Such strategy is being adopted to facilitate epidemiological studies in large groups, especially in field studies, granting agility to the process of data collection and economy of resources, since to directly verify weight and height, proper equipment and local are necessary to check the measurements, in addition to skilled staff. Despite the easiness provided by the use of self-reported weight and height, it is recommended caution with the method, because participants can tamper the information, which affects the accuracy of the data. A systematic review of the literature, which compared direct measurement *versus* self-reported weight and height and BMI, it was verified a tendency of under-estimation of weight and BMI and overestimation of height[41]. An integrative review to examine the accuracy of weight and height self-reported, including 35 studies with women, with height being investigated in 26 (n=39,244) and weight in 34 (n=57,172), showed that 21 of the 26 studies revealed that women overestimate height and that weight was underestimated in all the weight-related studies. The authors indicated that, despite the small average variation between self-reported and measured values, an important percent of women presented wide variation of values[42]. According to Martins et al.[43], some variables as gender, age

Table 1. Description of the main characteristics of the cohort studies included in the review

Authors/year/ country	General Characteristics	Definition of survival	Variables of adjustment	Tumoral subtype	Limitations indicated by the authors
Ademuyiwa et al. (2011)[24] USA	Retrospective cohort Number of women included: 418 Median of age: 54 years (26 to 92 years) Menopausal status: NI Survival in 5 years Median time of follow up: 37.2 months Time when BMI was obtained: at diagnosis How weight and height were obtained: NI	DFS: time between diagnosis and first recurrence or last follow up GS: time between the diagnosis and death or last follow up	Age, race, year of diagnosis, histological type, staging, tumoral grade, presence of vascular invasion and chemotherapy	TN (RE-/RP-/HER2-)	Reduced number of events, partially because of the short median time of follow up and preponderance of early stage of the disease; absence of information about alcohol intake and practice of physical activity
Dawood et al. (2012)[36] USA	Retrospective Cohort Number of women included: 2,311 Median age: NI Menopausal Status: pre and post-menopause Survival in 5 years Median time of follow up: 39 months Moment of measuring BMI: NI How height and weight were obtained: NI	DFS: time between the diagnosis date and the first recurrence or last follow up GS: time between the diagnosis and death or last follow up	Age, race, staging, vascular and lymphatic invasion, treatments: systemic adjuvant and radiotherapy	TN (RE-/RP-/HER2-)	Retrospective; short median time of follow up; absence of information about changes of BMI after diagnosis; absence of information about other factors modifiable related to the style of life as physical activity
Sparano et al. (2012)[14] USA	Cohort based in one clinical trial (not informed if prospective or retrospective) Number of women included: 4,770 Median age: NI Menopausal status: pre and post-menopause Survival in 8 years Median time of follow up: 7.9 years BMI: measured after surgery, before chemotherapy How height and weight were obtained: NI	DFS: time between randomization and the first event, including recurrence of the disease, contralateral breast cancer or death for any cause GS: time between the date of the randomization until death for any cause CRS: death attributed to breast cancer or preceded by recurrence of the disease, with follow up censored in the date of death by other causes	Age, race menopausal status, tumoral size, number of positive axillary lymph node, type of surgery, radiotherapy, chemotherapy and hormone therapy (depending on the arm of the treatment of the clinical trial)	Luminal (RE and/ or RP+/HER2- or unknown) HER2 overexpression (RE-/RP-/HER2+) TN (RE-/RP-/HER2-)	NI
Crozier et al. (2013)[22] USA	Cohort from one clinical trial (not informed if prospective or retrospective) Number of women included: 3,017 Median age: NI Menopausal status: pre and post-menopause Survival in 5 years Median time of follow up: 5.3 years BMI: beginning of the study How height and weight were obtained: weight measured and height reported	DFS: time between the diagnosis and the first disease-related event (recurrence of the local, regional or remote disease, contralateral breast cancer, a new cervix primary basal or squamous skin cancer in situ or breast lobular carcinoma in situ) or death by any cause)	Age and race	HER2 + (RH +/-)	Low power to detect minor statistic differences between the arms of the treatment and their interaction with the three categories of BMI
Mazzarella et al. (2013)[18] Italy	Retrospective cohort Number of women included: 1,250 Median age: NI Menopausal status: pre and post-menopause Survival in 5 years Median time of follow up: 8,2 years Timing BMI was obtained: NI How height and weight were obtained: measured	DFS: time between the surgery and the onset of the first event (recurrence, second primary cancer including breast cancer contralateral or death) GS: time between the date of the randomization until death for any cause	Age at diagnosis, menopausal status, number of positive lymph nodes, size of the tumor, tumor grade, percent of positive receptor estrogen cells. Perivascular invasion and type of surgery	Luminal (RE+/ HER2+)[a]	Natureza retrospectiva; pequeno número de pacientes obesos; ausência de informações sobre dose do tratamento

continue

Table 1. continuation

Authors/year/ country	General Characteristics	Definition of survival	Variables of adjustment	Tumoral subtype	Limitations indicated by the authors
Mowad et al. (2013)[25] USA	Retrospective cohort Number of women included: 183 Mean age: 49.8 years Menopausal status: NI Survival in 5 years Median time of follow up: 42.5 months. Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	DFS: time between the date of the diagnosis and the date of the first recurrence (local or remote) or date of the last follow up GS: time between the date of the diagnosis until death for any cause or last follow up	NI	TN (RE-/RP-/HER2-)	NI
Pajares et al. (2013)[19] Spain	Retrospective cohort from one clinical trial Number of women included: 5.683 Median age: NI Menopausal status: pre and post-menopause Survival in 10 years Median time of follow up: 93,4 months Timing BMI was obtained: beginning of the study How height and weight were obtained: measured	DFS: time until recurrence (local, regional or remote) or second primary breast cancer (except in situ) GS: time until death for any cause CRS: time until death by breast cancer	Age, menopausal status, tumor size, nodal status, histological grade, RH status, HER2 status, type of surgery, global sub-treatment, study (including nodal status)	Luminal (RE and/ or RP+/HER2-) HER2+ (RH +/-) TN (RE-/RP-/HER2-) Unknown	Retrospective, BMI measured only in the beginning of the follow up (modifications of BMI not measured); lack of information about HER2 in GEICAM/ 9805 trial, reducing the power of the statistical analysis
Turkoz et al. (2013)[26] Turkey	Retrospective cohort Number of women included: 733 Median age: NI Menopausal status: pre-menopause Survival in 5 years Median time of follow up: 29 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	DFS: time between the date of the diagnosis and date of recurrence (local or remote) GS: time between the date of the diagnosis until death by breast cancer (Considered CRS in this review)	Age, tumor size, nodal involvement, histological grade, perineural and lymphovascular invasion, extracapsular extension, hormone status	Luminal (RE and/or RP+/HER2-) HER2 overexpression (RH-/HER2+) TN (RE/RP-/HER2-)	Reduced number of cases TN and of HER2 overexpression; lack of measurement of central/abdominal adiposity and information about modification of the treatment during 10 years of follow up
Robinson et al. (2014)[23] Australia	Prospective cohort Number of women included: 1.155 Média de idade: 58,4 anos Menopausal status: NI Survival in 5 years Median time of follow up: 5,6 years Timing BMI was obtained: beginning of the study, average 0.8 months after diagnosis How height and weight were obtained: self-reported	For survival analysis, date of recurrence (relapse of the disease in the same breast, metastatic disease or cancer involving the other breast) or death by breast cancer constituted one event (Considered DFS in this review)	NI	Luminal (RE and/or RP+/HER2-)	Moment and form to measure BMI
Tait et al. (2014)[27] USA	Retrospective cohort Number of women included: 448 Median age: NI Menopausal status: pre and post-menopause Survival in 5 years Median time of follow up: 40,1 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	DFS: time between surgery and recurrence (local or remote) or death GS: time between the date of the diagnosis until death by any cause or date of the last follow up	Pathological staging	TN (RE-/RP-/HER2-)	Retrospective, relatively short follow up period, lack of information about modification of BMI after diagnosis, homogeneity of the patients about access the diagnosis, treatment and follow up, possible bias of selection
Xiao et al. (2014)[28] China	Retrospective cohort Number of women included: 5,785 Median age: NI Menopausal status: pre and post-menopause Survival in 5 years Median time of follow up: 70 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	CRS: time between the diagnosis and disease-related death or last follow up	NI	Luminal A Luminal B (HER2-/ neu+) Luminal B (Ki67 elevated)	Retrospective, differences of time of medication and number of drugs for the patients, glycemic control and extension of the disease was not clear for the patients

continue

Table 1. continuation

Authors/year/ country	General Characteristics	Definition of survival	Variables of adjustment	Tumoral subtype	Limitations indicated by the authors
Bonsang-Kitzis et al. (2015)[37] France	Retrospective cohort Number of women included: 326 Median age: 47 years (25 to 76) Menopausal status: pre and post-menopause Survival in 3 years Median time of follow up: 52 months Timing BMI was obtained: NI How height and weight were obtained: NI	DFS: time between the neoadjuvant chemotherapy treatment and recurrence of the disease or last follow up	NI	TN (RE-/RP-/HER2-)	NI
Cakar et al. (2015)[29] Turkey	Retrospective cohort Number of women included: 112 Median age: 50,4 Menopausal status: pre and post-menopause Survival: NI Median time of follow up: 29,4 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	DFS: time between the diagnosis and the first recurrence of the disease or metastasis GS: time between the date of the diagnosis until death or last follow up	*Menopausal status*	TN (RE-/RP-/HER2-)	Small number of patients
Fan et al. (2015)[30] China	Retrospective cohort Number of women included: 1.249 Median age: 49 years Menopausal status: NI Survival in 5 years Median time of follow up: 79 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	DFS: time between the date of the diagnosis and the date of the first recurrence (local or remote) or of the last follow up GS: time between the date of the diagnosis and date of death or last follow up	NI	TN (RE-/RP-/HER2-) Non TN	Retrospective, definition of obesity only by BMI, style of life, endocrine drugs and chemotherapy may affect the lipidic profile and can act as confounding factors in the analysis of association between HDL and survival
Hao et al. (2015)[31] China	Retrospective cohort Number of women included: 1.106 Median age: NI Menopausal status: pre and post-menopause Survival: NI Median time of follow up: 44,8 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	CRS: time between the surgery and date of breast cancer-related death. GS: time between the date of the surgery and date of death or date of last follow up	Age, menopausal status, size of the tumor, nodal status and systemic adjuvant therapy	TN (RE-/RP-/HER2-)	Proportion between low weight and obesity; classification of BMI in binary scale, without distinction between overweight and obesity; totality of patients in early staging with surgical treatment, not possible analysis of subgroup of patients with neoadjuvant treatment; study with only one ethnic group, not possible to extrapolate the results
Jeon et al. (2015)[32] Korea	Retrospective cohort Number of women included: 41,021 Median age: 48 years (18 a 93) Menopausal status: NI Survival: NI Median time of follow up: 92 months Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	GS: time between the date of the diagnosis and date of death by any cause CRS: time between the date of the diagnosis and date of death by breast cancer	Age, tumor size, nodal status, histological grade, surgical method, adjuvant treatment, Re and RP status and expression of HER2	Luminal (RE and/or RP+/HER2-) Luminal (RE and/or RP+/HER2+) HER2 overexpression (RE-/RP-/HER2+) TN (RE-/RP-/HER2-) Unknown	Limitation of the database (heterogeneity in the staging of the disease, in immunohistochemical and in presence of co-morbidity); registry of essential data (BMI and RH) available only in 62.84% of the patients, which could cause bias of selection; small sample size for low weight and obesity; ethnic homogeneity, limiting the generalization for other racial groups

continue

Table 1. continuation

Authors/year/ country	General Characteristics	Definition of survival	Variables of adjustment	Tumoral subtype	Limitations indicated by the authors
Ligibel et al. (2015)[35] USA	Retrospective cohort from one clinical trial Number of women included: 1,272 Median age: 50 years Menopausal status: pre and post-menopause Survival: NI Median time of follow up: 11 years Timing BMI was obtained: after surgery, before chemotherapy How height and weight were obtained: NI	DFS: time between the enrollment and the first recurrence (local or remote) or death without recurrence or date of the last follow up	Non adjusted	Luminal A Luminal B HER2 overexpression (RE-/RP-/HER2+) TN (RE-/RP-/HER2-)	Retrospective, sample size, PAM50 evaluated only for a subgroup of patients; lack of information about adherence to endocrine therapy, majority of the population, Caucasian
Widschwendter et al. (2015)[20] Germany	Retrospective cohort based in one clinical trial Number of women included: 3,670 Median of age: 53 years (21 to 86) Menopausal status: pre and post-menopause Survival: NI Median time of follow up: 65 months Timing BMI was obtained: prior to chemotherapy How height and weight were obtained: measured	DFS: period between the diagnosis and recurrence (local, contralateral and remote, primary/ secondary tumor) or death by any cause or date of last follow up GS: death by any cause or date of the last follow up	Age, tumor size, nodal status, tumor grade histological type, hormone receptor status, HER2 status, menopausal status, type of surgery, chemotherapy treatment, hormone therapy and chemotherapy sub-treatment	Luminal A like (RH+/HER2-/G1/ G2) Luminal B like (RH+/HER2-/G3) HER2 + (RH +/-) TN (RE-/RP-/HER2-)	Lack of information about Ki67; low number of patients with acute obesity, lack of data about metabolic syndrome
Bao et al. (2016)[21] China	Prospective cohort Number of women included: 518 Média de idade: 53,4 anos (DP±10,6) Menopausal status: pre and post-menopause Survival in 10 years Median time of follow up: 9,1 years Timing BMI was obtained: at diagnosis How height and weight were obtained: measured	DFS: time between the diagnosis and recurrence of the disease or metastasis and death by breast cancer GS: time between the diagnosis and death by any cause	Age, education level, menopausal status, Charlson co-morbidity index, participation in physical exercise, staging TNM, type of surgery, chemotherapy and radiotherapy	TN (RE-/RP-/HER2-)	Insufficient statistical analysis to explore interaction between BMI and other factors, which can explain the absence of significance
Kawai et al. (2016)[38] Japan	Retrospective cohort Number of women included: 20.090 Mean age: 57.3 years (SD±12.8) Menopausal status: pre and post-menopause Survival in 8 years Median time of follow up: 6,7 years Timing BMI was obtained: NI How height and weight were obtained: NI	DFS: time between the date of the first treatment and the date of recurrence (local or remote) or final of follow up CRS: time between the date of the first treatment and the date of death by breast cancer or end of the follow up	Age, place of domicile, method of detection, breast cancer family history, tumor stage, radiotherapy, chemotherapy, endocrine therapy, menopausal status and year of registry	Luminal A (RE+/ RP+/HER2-) Luminal B (RE+/ RP-/HER2- or RE+/ HER2+) HER2 overexpression (RE-/RP-/HER2+) TN (RE-/RP-/HER2-) Others[b]	When weight was measured; relatively low rate of follow up; lack of information about co-morbidities, body composition and confounding variables (tobacco, alcohol and physical activity); ethnics homogeneity compromising the external validation
Sendur et al. (2016)[39] Turkey	Retrospective cohort Number of women included: 826 Median age: NI Menopausal status: pre-menopause Survival in 3 years Median time of follow up: 37.5 months Timing BMI was obtained: NI How height and weight were obtained: NI	DFS: interval of time between the diagnosis and the first recurrence or death by any cause GS: interval of time between diagnosis and death by any cause	Non adjusted	Luminal (RH+ e HER2 +/-)	Retrospective, lack of information to compare the dose of chemotherapy among obese and non-obese, lack of information about change of weight during follow up, lack of analysis considering co-morbidities

continue

Table 1. continuation

Liu et al. (2018)[34] USA	Retrospective cohort Number of women included: 273 Median age: SI Menopausal status: NI Survival in 3 years Median time of follow up: 32,6 months Timing BMI was obtained: median time of 21 days after diagnosis How height and weight were obtained: NI	DFS: time between the diagnosis and the first event (any remote metastasis or local/regional, contralateral invasive breast cancer, any secondary invasive cancer) GS: time between the diagnosis and death by any cause	Non adjusted	Luminal (RE+ and/or RP+/HER2-)c HER2 + (RH +/-) TN (RE-/RP-/HER2-)	Retrospective, small sample size, incomplete evaluation of the menopausal status, utilization of hormone therapy
Martel et al. (2018)[33] Italy and other affiliated sites	Retrospective cohort Number of women included: 329 Median age: NI Menopausal status: pre and post-menopause Survival in 3 years Median time of follow up: 3 years Timing BMI was obtained: at diagnosis How height and weight were obtained: NI	GS: time between randomization and death by any cause	Staging IV at the diagnosis, disease-free interval, status of hormone receptor and histological grade	HER2 + (RH +/-)	Small sample size

Captions: NI = not informed; DFS = disease-free survival; GS = global survival; CRS = cancer-related survival; PFS = progression-free survival; TN = triple-negative; RE = receptor for estrogen; RP = receptor for progesterone; RH = hormone receptor (including RE and RP); HER2 = human epidermal growth factor; BMI = Body Mass Index; SD = standard deviation.

[a] Considered HER2 super express in this review, despite not having information about RP.

[b] Not specified.

[c] Analyzed per type of hormone therapy. Not considered in this review.

and economic status should be carefully evaluated to avoid potential bias of measurement of self-reported information about weight and height. Studies indicate that men tend to overestimate height [44-46], especially in elders[47], and women tend to underestimate weight[43,47-50]; education[51], family income[52] and some body characteristics [53] can also affect the accuracy of these information. Individuals in low socioeconomic levels and education verify their weight and height less often because of difficulties of accessing healthcare services, in-house scales and other places where these anthropometric measures are taken. When questioned about their measures, they report incorrect weight and height; weight is underestimated and height, overestimated[43,52,53]. The study of Dekkers et al.[53], with a population with overweight (n = 1,298) showed that the weight body was underestimated in 1.4 kg (SD ±1.9) and height, overestimated in 0.7 cm (SD ±1.5), both with statistical significance ($p<0.001$). According to the investigators, because overweight individuals measure their weight and height less frequently and do not know to report accurately, discrepancies between the information and actual measures may be the result of this characteristic. In addition, they consider there is influence of the standards of body characteristics dictated by the society where the ideal is to be tall and lean.

Furthermore, making a parallel with clinical practice in breast cancer, important questions must be considered in choosing the moment to check weight and validation: when done after a radical surgery, it will not reflect the total body mass properly, since there was the complete removal of the breast; when measured after the beginning of the chemotherapy treatment, either neoadjuvant or adjuvant, it can be overestimated because of the accumulation of fluid retention as a result of commonly used corticoids for symptoms management during chemotherapy; when measured months after the diagnosis, despite any type of treatment done, the body weight may have been altered, either by dietary guidance as recommended by healthcare professionals after the diagnosis or natural modification of food diet after being aware of the disease, that can be increasing or reducing the habitual food intake. Therefore, the BMI as an independent variable in studies that attempt to investigate its association with the disease relapse or with mortality, it is advisable that the anthropometric data, weight and height, are taken by direct measurement done with equipment and proper skills by trained staff and in the right moment. Further still, it is important to count with detailed and clear information in the publications because this can be an essential element for grouped analysis of the data, since it will be possible to determine the heterogeneity among the studies.

As reported by WHO[40], obesity is a condition of excessive accumulation of fat as adipose tissue where its extension may negatively affect health and recommends the classification of obesity through BMI and obesity is diagnosed when BMI is equal or higher than 30 kg/m^2. It is a health indicator accepted and utilized worldwide as an indirect indicative of body adiposity. Though it does

not allow distinguishing adipose from lean mass, it does not correctly reflect the distribution of body fat. Recently, it has been observed that the distribution of body fat is more predictive to health, and visceral fat is a potential risk factor for some metabolic dysfunction-related diseases [40,54], among them breast cancer. Considering the importance of visceral adiposity as inducer of metabolic dysfunctions, WHO recommends, in addition to BMI checking, the measurement of the waist circumference as an indicator of the distribution of body adiposity and, consequently, risk of metabolic complications[40]. So, measures of estimation of visceral fat must be incorporated in the evaluation of overweight and obesity, especially in studies that attempt to correlate body adiposity with the risk of complications or death by disease.

In relation to tumoral subtypes, 17 studies were identified, which included in the analysis the subtype triple-negative (TN)[14,19-21,24-27,29-32,34-38], 11, which included the subtype luminal and its variations[14,18-20,23,26,28,32,35,38,39] and six HER2 overexpression associated to negative RH[14,18,26,32,35,38]. Five studies conducted the analysis considering only the status of HER2, including the cases of positive HER2 independent of the status of RH[19,20,22,33,34], not being adopted the classifications traditionally utilized (Table 1).

Until the end of the decade of 1990, the classification of breast carcinoma was based in the morphological characteristics. However, it was observed that patients with similar clinical and pathological characteristics presented differentiated evolution and response to the treatment, and with dissimilar prognosis. Further, molecular subtypes with different prognosis were identified, revealing that breast cancer is a heterogeneous disease and that such subtypes should be considered in the diagnosis and therapeutic planning. Initially, the classification proposed to determine those subtypes was based in microarrays of deoxyribonucleic acid – DNA and standards of genic expression; however, despite this is considered as the gold standard for this determination, its complexity and high cost limit its routine utilization. In 2011, during the *12th St Gallen International Breast Cancer Conference Expert Panel*, the classification per clinical-pathological subtype, performed by immunohystochemical and hybridization fluorescence in situ subtype (FISH) and that approaches the classification based in microarrays of DNA and patterns of gene expression., however, simpler and of low cost, was adopted for the deliberations about therapeutic strategies, being considered the use of RE, RP, HER2 and of the antigen Ki67, an important marker of cellular proliferation and its cut-off for the classification of tumor subtypes. Later, it were adopted some alterations for the classification of the subtypes, supporting the use of the same tumoral markers subtype[55-57]. In this context, the studies included in the present review presented different classifications of tumoral subtypes in particular the luminal, hampering the comparison of its results. For that reason, the luminal subtypes were analyzed and discussed conjointly. The studies for positive HER2 that did not adopt the classification per subtypes proposed by the literature were presented separately.

The luminal subtypes are denominated as such because they originate in the epithelial cells of duct-lobular lumens naturally rich in RE. They are subdivided in luminal subtype A and B. In luminal A, there is negativity for HER2 with the presence of RE and RP in large quantity of cells and the analysis of Ki67 shows low rhythm of proliferation. Corresponds to nearly 50% to 60% of the cases of breast cancer and are quite sensitive to hormone therapy. The luminal subtype B also originates in luminal cells rich in RE. The RP can be present in low or high proportion of cells, HER2 can be detected and the analysis of Ki67 shows more elevated rhythm of proliferation. Represents 20% to 30% of the cases of breast carcinoma. This subtype is also sensitive to hormone therapy and, in case it presents positivity for HER2, trastuzumab can be indicated[58,59]. Among the ten studies that estimated the impact of BMI in the survival of women with breast cancer subtype luminal considering the risk analysis, six demonstrated inverse association between BMI and one or more types of survival (DFS, GS and CRS)[14,20,23,32,35,38]. Of the three studies that analyzed differences in the curves of survival shown in different categories of BMI, one showed difference between the curves of DFS[20] and one between the curves of GS[39]. Four studies did not present results statistically significant in any of the analyzes performed[18,19,26,28] (Table 2).

Subtype HER2 overexpression, defined as such when there is genetic amplification or elevated expression of oncoprotein HER2 and negativity for RH, affects approximately 15% to 20% of the patients with invasive breast carcinoma[58-60]. The HER2 belongs to the family of the receptors of growth. It codifies one protein of the membrane that stimulates the tumoral cells to develop faster and increase their capacity of duplication, which makes the tumors more aggressive; therefore, its expression is associated to higher biologic aggressiveness of the tumor and resistance to some types of treatment [61]. It is the subtype that represents the second worst prognosis when compared to the others[62]. Of the six studies that analyzed with subtype HER2 overexpression[14,18,26,32,35,38], two showed inverse association between BMI and survival with increase of the risk of global mortality for obese women[18,26]. Different result was observed in the study of Kawai et al.[38], that observed reduction of the risk of

death related to cancer for women with overweight[38]. In the study of Jeon et al.[32], unlike other results encountered, the increase of risk of global mortality was identified in low-weight women; this same study was the only that presented increase of risk of death, similarly, for the low-weight group of women[32]. Curves of DFS and GS among groups of BMI were compared in the study of Mazzarella et al.[18], evidencing significant statistic difference among the curves of GS[18] (Table 3).

Five studies analyzed HER2 positive independent of the status of RH of the tumor. Two of them presented increase of risk of recurrence of the disease[20,22]; in the study of Crozier et al.[22], the increase of risk of recurrence for the group of women with overweight and obesity was observed in the analysis, considering the whole population of the study. However, when the analysis was stratified per type of chemotherapy treatment, there was no statistically significant increase. The analyzes of survival curves of Widschwendter et al.[20] statistically significant differences were evidenced both for DFS and GS. The other three studies did not present results with statistical significance[19,33,34] (Table 3).

Though great advances have been reached either in the diagnosis or in therapeutics of breast cancer, incorporating more effective treatments, including target-therapy with blockade of RH and/or HER2, these are destined to cases of positive RH tumors and/or HER2 overexpression and not to TN[63,64]. This subtype corresponds to 15% to 20% of cases of breast cancer[58,59] and it is identified by the absence of expression for RE and RP and absence of HER2 overexpression, which limits the available therapeutic options. It is characterized by occurring in young women and is associated to an aggressive biological course, with more odds of early recurrence during the first three or five years after the diagnosis[65], leading to a worst diagnosis when compared to other tumoral subtypes [63-65]. So, efforts have been targeted to identify other prognosis factors, modifiable or not, that can be utilized to stratify

Table 2. Effect of the Body Mass Index in survival of women with luminal breast cancer

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	IC 95%	HR	CI 95%	HR	IC 95%	DFS	GS	CRS
Sparano et al. (2012)[a 14] USA	RH+/HER2- or unknown <30 kg/m^2 ≥30 kg/m^2	 1.00 1.24	 1.06-1.46	 1.00 1.37	 1.13-1.67	 1.00 1.40	 1.11-1.76	-	-	-
Mazzarella et al. (2013)[b 18] Italy	RE+/HER2+ <25 kg/m2 25.0-29.9 kg/m^2 ≥30 kg/m^2	 1.00 0.88 0.75	 0.63-1.23 0.43-1.31	 1.00 0.77 1.05	 0.46-1.26 0.53-2.09	-	-	p=0.55 §	p=0.85 §	
Pajares et al. (2013)[c 19] Spain	RE and/or RP+/HER2- <25.0 kg/m^2 ≥35 kg/m^2	 1.0 1.1	 0.8-1.6	 1.0 1.3	 0.9-1.8	 1.0 1.3	 0.9-2.0	-	-	-
Turkoz et al. (2013)[d 26] Turkey	RE and/or RP+/HER2- 18.5-24.9 kg/m^2 ≥30 kg/m^2	-	-	 1.00 1.5	 1.0-2.2	-	-	-	-	-
Robinson et al. (2014)[e 23] Australia	RH+/HER2- 25.0-29.9 kg/m^2 30-39.9 kg/m^2	 1.00 1.71	 1.12-2.62	-	-	-	-	-	-	-
Xiao et al. (2014)[f 28] China	Luminal A <25.0 kg/m^2 25.0-30.0 kg/m^2 ≥30.0 kg/m^2 Luminal B (Ki67 elevated) <25.0 kg/m^2 25.0-30.0 kg/m^2 ≥30.0 kg/m^2 Luminal B (HER2-/neu+) <25.0 kg/m^2 25.0-30.0 kg/m^2 ≥30.0 kg/m^2	-	-	-	-	 1.00 0.743 0.761 1.00 0.854 1.043 1.00 0.939 1.227	 0.491-1.124 0.522-1.109 0.698-1.046 0.846-1.286 0.680-1.295 0.890-1.692	-	-	-

continue

Tabela 2. continuation

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	IC 95%	HR	CI 95%	HR	IC 95%	DFS	GS	CRS
Jeon et al. (2015)[g 32] Korea	RE and/or RP+ and HER2-									
	<18.5 kg/m²	-	-	1.26	0.94-1.69	1.24	0.85-1.82	-	-	-
	18.5-24.9 kg/m²			1.00		1.00				
	25.0-29.9 kg/m²			1.32	1.18-1.48	1.30	0.96-1.76			
	≥30 kg/m²			1.48	1.18-1.85	1.31	1.13-1.52			
	RE and/or RP+ and HER2+									
	<18.5 kg/m²			1.07	0.63-1.83	0.61	0.25-1.48			
	18.5-24.9 kg/m²			1.00		1.00				
	25-29.9 kg/m²			1.02	0.81-1.28	1.18	0.90-1.55			
	≥30 kg/m²			0.94	0.55-1.61	0.62	0.27-1.39			
Ligibel et al. (2015)[h 35] USA	Luminal A									
	For each 5 units of BMI raise	1.23	1.08-1.40	-	-	-	-	-	-	-
	Luminal B									
	For each 5 units of BMI raise	1.00	0.87-1.16							
Widschwendter et al. (2015)[i 20] Germany	Luminal A like									
	<25.0 kg/m²	1.00		1.00		-	-	p=0.45[¥]	p=0.25[¥]	-
	25.0-29.9 kg/m²	1.21	0.81-1.82	0.86	0.48-1.52					
	30.0-34.9 kg/m²	1.10	0.66-1.83	1.32	0.71-2.47					
	35.0-39.9 kg/m²	1.42	0.65-3.09	1.72	0.69-4.30					
	≥30 kg/m²	0.82	0.11-6.06	1.51	0.20-11.42					
	Luminal B like									
	<25.0 kg/m2	1.00		1.00				p=0.03[¥]	p=0.15[¥]	
	25.0-29.9 kg/m²	1.18	0.72-1.93	0.87	0.44-1.75					
	30.0-34.9 kg/m²	1.46	0.78-2.74	1.29	0.55-3.00					
	35.0-39.9 kg/m²	0.76	0.29-2.00	0.58	0.17-2.07					
	≥30 kg/m²	3.32	1.17-9.46	2.84	0.71-11.40					
Kawai et al. (2016)[i 38] Japan	Luminal A									
	<18.5 kg/m²	1.24	0.93-1.64	-	-	1.39	0.77-2.49	-	-	-
	18.5-21.7 kg/m²	1.00				1.00				
	21.8-24.0 kg/m²	1.11	0.92-1.33			1.05	0.71-1.56			
	25.0-30.0 kg/m²	1.07	0.87-1.31			1.27	0.84-1.92			
	≥30 kg/m²	1.23	0.90-1.68			1.64	0.93-2.90			
	Luminal B									
	<18.5 kg/m²	0.97	0.70-1.37			1.32	0.75-2.35			
	18.5-21.7 kg/m²	1.00				1.00				
	21.8-24.0 kg/m²	1.01	0.83-1.24			1.07	0.73-1.54			
	25.0-30.0 kg/m²	0.87	0.68-1.12			1.14	0.75-1.74			
	≥30 kg/m²	1.16	0.77-1.75			2.59	1.51-4.43			
Sendur et al. (2016)[k 39] Turkey	RH+ and HER2+/-	-	-	-	-	-	-	p=0.39[£]	p=0.03[£]	
	18.5-24.9 kg/m²									
	≥25.0 kg/m²									

Captions: BMI = Body Mass Index; DFS = disease-free survival; GS = global survival; CRS = cancer-related survival; HR = hazard ratio; CI = confidence interval; RE = receptor for estrogen; RP = receptor for progesterone; RH = receptor hormonal (including RE and RP); HER2 = human epidermal growth factor.

[a] Adjusted to age, race, menopausal status, tumor size, number of positive axillary lymphatic node, type of surgery, radiotherapy, chemotherapy and hormone therapy (depending on the arm of the treatment of the clinical trial).

[b] Adjusted to age at diagnosis, menopausal status, number of positive lymph nodes, size of the tumor, tumor grade, percent of positive estrogen receptor cells, perivascular invasion and type of surgery.

[c] Adjusted to age, menopausal status, tumor size, nodal status, histological grade, RH and HER2 status, type of surgery, global sub-treatment, study (including nodal status).

[d] Adjusted to age, tumor size, nodal involvement, histological grade, perineural and lymphovascular invasion, extracapsular extension, hormone status.

[e,f] Variables of adjustment not informed.

[g] Adjusted to age, tumor size, nodal status, histological grade, surgical method, adjuvant therapy, status of RE and RP and expression of HER2.

[h,k] Non adjusted.

[i] Adjusted to age, tumor size, nodal status, tumor grade, histological type, status of hormone receptor, HER2 status, menopausal status, type of surgery, chemotherapy treatment, hormone therapy and chemotherapy sub-treatment.

[j] Adjusted to age, region of domicile, method of detection, breast cancer family history, tumor stage, radiotherapy, chemotherapy, endocrine therapy, menopausal status and year of registry.

[$] Time of survival in 5 years.

[¥] Time of survival not informed.

[£] Time of survival in 3 years.

the women in categories of risk[36]; among these factors, is obesity, considered a modifiable risk factor, which has been associated either to the increase of risk of breast cancer, including TN[66], or to the relapse of the disease and to mortality[4,36]. Of the 17 studies that analyzed the interference of BMI in the survival of women with subtype TN, 16 underwent risk analysis[14,19-21,24-27,30-32,34-38]. In three of them, it was observed increase of risk of recurrence of disease for women in the higher category of BMI [20,34,37]; in the study of Bonsang-Kitzis et al.[37], the increase of risk of recurrence was observed either for the group of women without lymph node commitment or to those with lymph mode commitment and grade III in pre and post menopause; two showed increase of risk for global mortality for women in the higher category of BMI[20,31]. It is worth noticing that in the study of Hao et al.[31], when the analysis was stratified per menopausal status, there was increase of risk only for women in pre menopause, group that also presented increase of risk of breast cancer mortality[31]. Eight studies analyzed the survival curves; in two of them, it was observed difference statistically significant in the curves of DFS[34]; in two, there was difference in the curve of GS[20,31] and in only one, it was observed difference in the curves of CRS[31]. Globally, in 13 of the 17 studies that did risk analysis it was not observed association between the BMI and relapse or death by

Table 3. Effect of the Body Mass Index in the survival of women with breast cancer HER2 overexpression and HER2 positive (negative or positive hormonal receptor)

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	IC 95%	HR	IC 95%	HR	IC 95%	DFS	GS	CRS
Subtype HER2 overexpression										
Sparano et al. (2012)[e 14] USA	<30.0 kg/m²	1.00		1.00	1.00	1.00		-	-	-
	≥30.0 kg/m²	1.06	0.82-1.38	0.99	0.73-1.34	1.00	0.71-1.40			
Mazzarella et al. (2013)[b 18] Italy	<25.0 kg/m²	1.00		1.00		-	-	p=0.17 §	p=0.04 §	
	25.0-29.9 kg/m²	0.99	0.7-1.39	1.16	0.75-1.79					
	≥30.0 kg/m²	1.34	0.84-2.13	1.79	1.03-3.10					
Turkoz et al. (2013)[c 26] Turkey	18.5-24.9	-	-	1.00		-	-	-	-	-
	≥30.0 kg/m²			1.4	1.1-2.1					
Jeon et al. (2015)[d 32] Korea	<18.5 kg/m²	-	-	1.67	1.12-2.47	1.79	1.11-2.90	-	-	-
	18.5-24.9 kg/m²			1.00		1.00				
	25-29.9 kg/m²			0.94	0.77-1.14	0.93	0.73-1.19			
	≥30.0 kg/m²			1.18	0.79-1.76	1.16	0.70-1.93			
Ligibel et al. (2015)[e 35]	Para cada 5 unidades de aumento de IMC	1.10	0.97-1.26	-	-	-	-	-	-	-
Kawai et al. (2016)[f 38] Japan	<18.5 kg/m²	0.95	0.61-1.47	-	-	0.99	0.52-1.89	-	-	-
	18.5-21.7 kg/m²	1.00				1.00				
	21.8-24.0 kg/m²	0.93	0.72-1,22			0.73	0.48-1.10			
	25.0-30.0 kg/m²	0.74	0.52-1.05			0.43	0.23-0.80			
	≥30.0 kg/m²	1.24	0.68-2.26			1.53	0.68-3.42			
HER2 positive (RH positive or negative)										
Crozier et al. (2013)[g 22] USA	Grupos A, B e C §			-	-	-	-		-	-
	<25.0 kg/m²	1.00						DND		
	25.0-29.9 kg/m²	1.30	1.06-1.61							
	≥30.0 kg/m²	1.31	1.07-1.59							
	Grupo A									
	<25.0 kg/m²	1.00						p=0.29 §		
	25.0-29.9 kg/m²	1.20	0.87-1.65							
	≥30.0 kg/m²	1.11	0.83-1.50							
	Grupo B									
	<25 kg/m²	1.00						p=0.11 §		
	25.0-29.9 kg/m²	1.40	0.97-2.03							
	≥30.0 kg/m²	1.42	1.00-2.01							
	Grupo C									
	<25.0 kg/m²	1.00						p=0.67 §		
	25.0-29.9 kg/m²	1.17	0.77-1.78							
	≥30.0 kg/m²	1.23	0.84-1.81							

continue

Table 3. continuation

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	IC 95%	HR	IC 95%	HR	IC 95%	DFS	GS	CRS
Pajares et al. (2013)[h 19] Spain	<25.0 kg/m²	1.0		1.0		1.0				-
	≥35.0 kg/m²	1.2	0.7-2.1	1.4	0.8-2.5	1.5	0.8-2.8			
Widschwendter et al. (2015)[i 20] Germany	<25.0 kg/m²	1.00		1.00		-	-	p=0.02	p=0.01	-
	25.0-29.9 kg/m²	1.08	0.68-1.69	0.86	0.46-1.62					
	30.0-34.9 kg/m²	0.81	0.44-1.50	0.82	0.37-1.80					
	35.0-39.9 kg/m²	1.09	0.43-2.79	1.36	0.43-4.35					
	≥30.0 kg/m²	3.28	1.14-9.48	2.78	0.75-10.34					
Liu et al. (2018)[i 34] USA	<30.0 kg/m²	1.0		1.0		-	-			-
	≥30.0 kg/m²	3.37	0.97-11.72	1.35	0.22-8.19					
Martel et al. (2018)[k 33]	<25.0 kg/m²			1.0		-	-	p=0.69 £	p=0.77 £	-
	≥25.0 kg/m²			0.88	0.59-1.31					

Captions: BMI = Body Mass Index; DFS = disease-free survival; GS = global survival; CRS = cancer-related survival; HR = hazard ratio; CI= confidence interval; RH = hormone receptor (including RE and RP); HER2 = human epidermal growth factor; DND = data not demonstrated.
[$] Groups of chemotherapy treatment.
[a] Adjusted to age, race, menopausal status, tumor size, number of positive axillary lymph node, type of surgery, radiotherapy, chemotherapy and hormone therapy (depending on the arm of treatment of the clinical trial).
[b] Adjusted to age at diagnosis, menopausal status, number of positive lymph nodes, size of the tumor, grade of the tumor, percent of positive estrogen cells receptor, perivascular invasion and type of surgery.
[c] Adjusted to age, size of the tumor, node involvement, histological grade, perineural and lymphovascular invasion, extracapsular invasion, hormone status.
[d] Adjusted to age, size of the tumor, nodal status, histological grade, surgical method, adjuvant therapy, status of RE and RP and expression of HER2.
[c, j] Not adjusted.
[f] Adjusted to age, region of domicile, method of detection, family history of breast cancer, tumoral staging, radiotherapy, chemotherapy, endocrine therapy, menopausal status and year of registration.
[g] Adjusted to age and race.
[h] Adjusted to age, menopausal status, tumor size, nodal status, histological grade, RH status, HER2 status, type of surgery, global sub-treatment, study (including nodal status).
[i] Adjusted to age, tumor size, nodal status, tumor grade, histological type, status of hormone receptor, status of HER2, menopausal status, type of surgery, chemotherapy treatment, hormone therapy and chemotherapy sub-treatment.
[k] Adjusted for staging IV at the diagnosis, disease free interval cancer, status of hormone receptor hormonal and histological grade.
[$] Time of survival, 5 years.
[¥] Time of survival not informed.
[£] Time of survival, 3 years.

breast cancer TN[14,19,21,24-27,29,30,32,35,36,38]; and in five of the eight studies that performed survival curves, there was no statistically significant difference, suggesting that BMI may not be a negative prognostic factor for women with this tumoral subtype (Table 4).

Obesity is associated to an increase of 88% of the rate of mortality by cancer in women[67]. The role of the adipose tissue in special, the adipocytes, in the tumor initiation and progression, it is a quite new area of investigation. Some mechanisms have been proposed to elucidate the relation of obesity and breast cancer; among them, the elevation of the levels of insulin and/or insulin-like growth factor (IGF) and deregulation of the levels of some adipocytokines, in addition to the alteration of sexual hormones[68]. In obesity, it occurs intense basal lipolysis with elevation of plasmatic levels of free fatty acids (FFA) and the storage of these in the interior of non-adipose cells, leading to lipotoxicity, with alteration of the function of insulin signalization and consequent insulin resistance, resulting in hyperglycemia and hyperinsulinemia. Insulin stimulates the DNA synthesis and in high concentrations, relates to the incidence, recurrence and mortality by breast cancer. In parallel, insulin contributes to the synthesis and activity of the insulin growth factor related to insulin IGF-1, also involved in the genesis and progression of the cancer. The body adiposity index is related to the blood concentration of IGF-1, to breast cancer and acts, stimulating the cellular proliferation and inhibiting the apoptosis, in addition to exerting synergy effect to other mitogenic factors [68-70]. Some products secreted by the adipose tissue called adipokines, in special the leptin, the tumor necrosis factor alpha (TNF-α) and interleukin -6 (IL-6), have been associated to cancer. Leptin has been characterized as a neoplastic cells growth factor stimulating cellular growth, migration, invasion and tumoral angiogenesis[71]. A immunohystochemical study verified that leptin receptors were not encountered in normal mammary epithelial cells, while in mammary carcinoma cells, there was a positive coloration in 83% of the cases[72]. It has been observed that the elevated plasmatic

Table 4. Effect of the Body Mass Index in the survival of women with triple-negative breast cancer

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	CI 95%	HR	CI 95%	HR	CI 95%	DFS	GS	CRS
Ademuyiwa et al. (2011)[a 24] USA	<25.0 kg/m² 25.0-29.9 kg/m² ≥30.0 kg/m²	1.00 0.74 0.81	 0.43-1.27 0.49-1.34	1.00 0.60 0.94	 0.32-1.14 0.54-1.64	-	-	p=0.93 §	p=0.57 §	
Dawood et al. (2012)[b 36] USA	<25.0 kg/m² 25.0-29.9 kg/m² ≥30.0 kg/m²	1.00 1.09 1.02	 0.92-1.29 0.86-1.20	1.00 1.00 0.97	 0.83-1.2 0.81-1.16	-	-	p=0.54 §	p=0.93 §	
Sparano et al. (2012)[c 14] USA	<30.0 kg/m² ≥30.0 kg/m²	1.00 1.02	 0.80-1.30	1.00 1.11	 0.85-1.46	1.00 1.00	 0.74-1.36			
Mowad et al. (2013)[d 25] USA	<25.0 kg/m² ≥30.0 kg/m² <25.0 kg/m² 25.0-29.9 kg/m² ≥30.0 kg/m²	1.00 1.01 -	 0.67-1.52 -	1.00 1.36 -	 0.77-2.42 -	-	-	 p=0.91 §	 -p=0.29 §	
Pajares et al. (2013)[e 19] Spain	<25.0 kg/m² ≥35.0 kg/m²	1.00 1.4	 0.9-2.3	1.00 1.4	 0.9-2.2	1.00 1.3	 0.8-2.3	-	-	-
Turkoz et al. (2013)[f 26] Turkey	18.5-24.9 kg/m² ≥30.0 kg/m²	-	-	1.00 1.4	 1.0-2.1	-	-	-	-	-
Tait et al. (2014)[g 27] USA	Global <25.0 kg/m² 25.0-29.9 kg/m² 30.0-34.9 kg/m² ≥35.0 kg/m² Post-menopause vs pre-menopause <25.0 kg/m² 25.0-29.9 kg/m² 30.0-34.9 kg/m² ≥35.0 kg/m²	 1.00 1.01 0.94 0.99 0.94 0.54 1.00 0.77	 0.65-1.56 0.60-1.47 0.63-1.57 0.49-1.82 0.29-1.01 0.53-1.91 0.38-1.56	 1.00 1.22 0.92 1.16 0.97 0.88 1.26 0.70	 0.78-1.91 0.59-1.43 0.70-1.90 0.50-1.89 0.45-1.74 0.63-2.52 0.33-1.50	-	-	p=0.84 §	p=0.82 §	-
Bonsang-Kitzis et al. (2015)[h 37] France	≤30.0 kg/m² >30.0 kg/m² pN - ≤30.0 kg/m² >30.0 kg/m² pN+ grade I-II ≤30.0 kg/m² >30.0 kg/m² pN+ grade III pre-menopause ≤30.0 kg/m² >30.0 kg/m² pN+ grau III post-menopause ≤30.0 kg/m² >30.0 kg/m²	1.00 1.71 1.00 2.64 1.00 1.29 1.00 9.68 1.00 3.57	 0.81-2.83 1.28-5.55 0.39-4.26 5.71-18.31 1.69-7.77	-	-	-	-	-	-	-
Cakar et al. (2015)[i 29] Turkey	<25.0 kg/m² 25.0-29.9 kg/m² ≥30.0 kg/m²	-	-	-	-			p=0.16 ¥ p=0.49 ¥	p=0.30 ¥ SA	
Fan et al. (2015)[j 30] China	<25.0 kg/m² ≥25.0 kg/m²	1.00 1.28	 0.81-2.02	1.00 1.13	 0.62-2.05	-	-	-	-	-

continue

Table 4. continuation

First author/ year/country	Cut-off for BMI	*Hazard ratio*						Kaplan-Meier		
		DFS		GS		CRS		*Log-rank test*		
		HR	CI 95%	HR	CI 95%	HR	CI 95%	DFS	GS	CRS
Hao et al. (2015)[k 31] China	All patients ≤24.0 kg/m² >24.0 kg/m²	-	-	1.00 1.46	1.04-2.06	1.00 1.34	0.90-2.01	-	p=0.01 [¥]	p=0.01 [¥]
	Pre-menopause ≤24.0 kg/m² >24.0 kg/m²	-	-	1.00 2.16	1.21-3.87	1.00 2.27	1.11-4.63	-	p=0.01 v	p=0.00 [¥]
	Post-menopause ≤24.0 kg/m² >24.0 kg/m²	-	-	1.00 1.07	0.70-1.64	1.00 0.96	0.58-1.58	-	p=0.35 [¥]	p=0.57 [¥]
Jeon et al. (2015)[l 32] Korea	<18.5 kg/mv 18.5-24.9 kg/mv 25.0-29.9 kg/mv ≥30.0 kg/m²	-	-	1.19 1.00 1.07 1.18	0.84-1.68 0.93-1.23 0.90-1.55	1.27 1.00 0.93 1.16	0.84-1.92 0.79-1.11 0.84-1.61	-	-	-
Ligibel et al. (2015)[m 35] USA	For each 5 units of BMI increase	1.11	0.97-1.28	-	-	-	-	-	-	-
Widschwendter et al. (2015)[n 20] Germany	<25.0 kg/m² 25.0-29.9 kg/m² 30.0-34.9 kg/m² 35.0-39.9 kg/m² ≥30.0 kg/m²	1.00 1.34 1.29 0.36 3.02	 0.91-1.97 0.77-2.17 0.09-1.48 1.50-6.08	1.00 1.41 1.27 0.51 3.85	 0.88-2.25 0.67-2.41 0.12-2.21 1.69-8.77	-	-	p<0.01 [¥]	p<0.01 [¥]	
Bao et al. (2016)[o 21] China	<18.5 kg/m² 18.5-23.9 kg/m² 24.0-27.9 kg/m² ≥28.0 kg/m²	1.28 1.00 1.38 1.53	0.57-2.89 0.88-2.17 0.84-2.77	1.16 1.00 1.19 1.36	0.54-2.50 0.79-1.81 0.78-2.40	-	-	-	-	-
Kawai et al. (2016)[p 38] Japan	<18.5 kg/m² 18.5-21.7 kg/m² 21.8-24.0 kg/m² 25.0-30.0 kg/m² ≥30.0 kg/m²	1.15 1.00 1.08 0.95 1.09	0.84-1.57 0.89-1.31 0.75-1.20 0.74-1.62	-	-	0.97 1.00 1.15 1.03 1.11	0.62-1.51 0.90-1.48 0.77-1.39 0.67-1.84	-	-	-
Liu et al. (2018)[q 34] USA	<30.0 kg/m² ≥30.0 kg/m²	1 2.62	 1.03-6.66	1 3.00	 0.95-9.51	-	-	p=0.04 [£]	p=0.06 [£]	-

Captions: BMI = body mass index; DFS = disease-free survival; GS = global survival; CRS – cancer-related survival; HR = Hazard ratio; CI = confidence interval; pN = commitment of lymph nodes in the histopathological test; NA= no analysis

[a] Adjusted to age, race, year of diagnosis, histological type, staging, tumor grade, presence of vascular invasion and chemotherapy.

[b] Adjusted to age, race, staging, lymphatic and vascular invasion, systemic adjuvant treatments and radiotherapy.

[c] Adjusted to age, race, menopausal status, tumor size, number of positive axillary lymph nodes, type of surgery, radiotherapy, chemotherapy and hormone therapy (contingent upon the arm of treatment of the clinical trial).

[d, h, j] Variables of adjustment not informed.

[e] Adjusted to age, menopausal status, tumor size, nodal status, histological grade, RH status d, HER2 status, type of surgery, global sub-treatment, study (including nodal status).

[f] Adjusted to age, tumor size, node involvement, histological grade, perineural and lymphovascular invasion, extracapsular extension, hormone status.

[g] Adjusted to pathological staging.

[i] Adjusted to menopausal status.

[k] Adjusted to age, menopausal status, tumor size, nodal status, systemic adjuvant therapy and grade.

[l] Adjusted to age, tumor size, nodal status, histological type, surgery method, adjuvant therapy, status of RE and RP and expression of HER2.

[m, q] Not adjusted.

[n] Adjusted to age, tumor size, nodal status, tumor grade, histological type, hormone receptor status, HER2 status, menopausal status, type of surgery, chemotherapy treatment, hormone therapy and chemotherapy sub-treatment.

[o] Adjusted to age, education level, menopausal status, Charlson comorbidity index, TNM staging, type of surgery, chemotherapy, radiotherapy.

[p] Adjusted to age, region of domicile, method of detection, family history of the breast cancer, tumor staging, radiotherapy, chemotherapy, endocrine therapy, menopausal status and year of registry.

[§] Time of survival in 5 years.

[¥] Time of survival not informed.

[£] Time of survival, 3 years.

level of leptin increases the risk of breast cancer in post-menopause women, while those in pre-menopause, it is encountered inverse association[73], showing that the menopausal status may influence the effect of leptin over the mammary carcinogenesis. Leptin induces the transcription of the enzyme aromatase, increasing the production of estradiol, the hormone promoter of breast cancer[68,71], and the effect of the increase of blood level can be differentiated contingent upon the menopausal status. It has been suggested that leptin is capable of inducing the proliferation of mammary neoplastic cells to increase the expression of proteolytic enzymes that are essential in the process of metastization and stimulation of angiogenesis necessary to the tumor growth[71], probably through the increase of the expression of the endothelial enzyme cyclooxygenase -2 (COX-2) and the of vascular endothelial growth factor (VEGF)[74]. TNF-α is associated to the mammary tumoral genesis especially for exacerbating the insulin resistance by the reduction of the expression of glucose transporter of cellular surface (GLUT-4) and by the specific phosphorylation of the insulin receptor. In addition, induces lipolysis, contributing to the lipotoxicity and correlated effects[68,75]. IL-6, an immunomodulatory cytokine produced in the adipose tissue, preferentially in the one located in the visceral region, increases its levels in obesity. It presents endocrine and post-inflammatory action[76], stimulates the expression of aromatase in the adipose tissue, provoking the biosynthesis of estrogen and acts as a antiapoptotic factor by inhibiting the activation of proteases involved in the apoptosis, further to promoting the cellular migration. In this direction, IL-6 can possibly contribute directly for the genesis and progression of breast cancer[68].

The mechanisms related to the alteration of sexual hormones involve both the synthesis and the bioactivity of the estrogens. The biosynthesis of the estrogen differs in pre and post-menopause women. In post-menopause, the adipose tissue assumes a relevant influence in the circulating estrogen levels, increasing the time of exposure of mammary cells to these hormones[77]. Additionally, the adipose cell influences the synthesis and bioactivity of the sexual steroid hormones through, at least, two mechanisms. The first related to the synthesis of estrogen, where the adipose tissue executed steroidogenic activity through tow biochemical ways related to the enzymes 17-β hydroxysteroid oxyreductase and aromatase P450, that participate in the conversion of androgenic precursors in estrogen, contributing significantly for the elevation of the blood levels of sexual steroids in post-menopause[76,78]. In post-menopause women, the increase of BMI is associated to a significant raise of the plasmatic levels of estrone and estradiol[79]. The second mechanism addresses the bioactivity of the estrogen. The excess of body adiposity results in an increase of blood level of insulin and bioactivity of IGF-1, both capable of inhibiting the synthesis of the sexual hormones biding globulin (SHBG), resulting in higher availability of free estrogen to act in the target-cell. The study conducted by McTiernan et al.[80] showed that women with BMI >30 kg/m^2 presented mean concentration of SHBG 50% lower than those with BMI <22 kg/m^2. The estrogen induces mitosis in the mammary epithelial cells and inhibits apoptosis; so, the exposure to estrogen and/or increase of the expression of the receptors of estrogen in the mammary epithelial cells increase the risk for either the development or the progression of breast cancer[68].

In regard to menopausal status, three studies analyzed pre and post-menopause separately[27,31,36]; in other eight, it was considered as variable of adjustment[14,18-21,29,37,38]; two studies included only women in pre menopause[26,39]; five only reported the quantitative of pre and post-menopause[22,28,33,35,36]; and six did not provide information[23-25,30,32,34] (Table 1). Considering the mechanisms that relate obesity to the risk and progression of breast cancer, the menopausal status is important factor for the determination of the influence of the obesity over the disease through leptin-related mechanisms and to the alteration of sexual hormones. Therefore, it is likely that the excess of body adiposity influences differently women in pre and post-menopause. So, this variable should be considered in the analyzes of the studies that attempt to verify the influence of the obesity over the survival in women with breast cancer.

An important factor observed in this review was the difference encountered in the definitions of survival among the studies. Classically, GS is defined as the period of time during which a patient remains alive after the diagnosis of the disease or beginning of the treatment; DFS, as the period where signs or symptoms of the disease are undetected after a curative treatment, and the outcome is identified when the recurrence of the disease occurs (local or remote) or death by any cause; and CRS, the time between the diagnosis and death by disease[81,82]. Only four, among the 23 studies included in this review adopted the classic definitions for survival[27,28,32,37], configuring methodological differences that hamper the comparison of results obtained and showing the necessity of uniformization of the terms.

This review was planned and executed according to specific protocols and established guidelines, following all the planned stages for a literature integrative review, which ensures the methodological strictness of the study. As the objective was to make a synthesis and narrative analysis of the knowledge produced about the

theme, it was chosen to not limit the selection of the studies because of methodological differences, but to describe and discuss them. To find the studies, it were searched four main databases; however, some bases were not included in the search strategy because of access restrictions, which was a limitation of the study and the language of publication.

CONCLUSION

Based in the results of the studies included in this review, the effect of overweight, in special obesity in the prognosis of women with breast cancer can be differentiated according to the tumoral subtype, obesity appears to have more influence in the survival of women with luminal tumors than in those with subtypes HER2 overexpression or TN. However, at present, data are still inconsistent, lacking enough body of evidence to respond to that question. The methodological differences observed in the definitions of survival, in the times of follow up, in the adjustment variables, in special, menopausal status, how and when the variables weight and height were obtained to estimate the BMI and in the classification of tumor subtypes, in particular the luminal tumors, hamper the comparison among the results published. More studies with methodological strictness matched to the objectives of the investigation are necessary to build up a strong body of knowledge that will not only respond to the question of the research, but also to steer specific nutritional intervention programs targeted to women with breast cancer.

CONTRIBUTIONS

Rosilene de Lima Pinheiro and Gina Torres Rego Monteiro contributed substantially to the conception and planning of the study, collection, analysis and interpretation of data as well as in the wording, critical review and final approval of the version published.

DECLARATION OF CONFLICT OF INTERESTS

There are no declaration of conflicts of interest to declare.

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