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Efeitos da dieta após o tratamento do câncer de mama

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Orientadora: Daniela Dornelles Rosa

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RESUMO

Introdução: Ensaios clínicos randomizados são inconclusivos sobre o papel de intervenções dietéticas em desfechos de pacientes tratadas com intuito curativo para câncer de mama em estágio inicial.

Objetivos: Avaliar os efeitos de intervenções com dieta na sobrevida livre de doença (SLD) e sobrevida global (SG) e nas medidas antropométricas de pacientes tratados para câncer de mama em estágio inicial.

Material e Métodos: Conduzimos uma revisão sistemática e meta-análise de ensaios clínicos randomizados de pacientes com câncer de mama inicial comparando intervenções dietéticas (aconselhamento dietético individualizado, prescrição de dieta específica ou outro) com cuidados usuais, através da pesquisa de registros nos bancos de dados EMBASE, MEDLINE, Cochrane Database of Systematic Reviews (CDSR) e Cochrane Central Register of Controlled Trials (CENTRAL). Os desfechos primários foram SLD e SG e os secundários, alteração em medidas antropométricas.

Resultados: Identificamos 12 ensaios clínicos randomizados elegíveis para análise, dos quais sete foram incluídos na análise quantitativa (meta-análise). Somente dois reportaram dados de SG e de SLD. Seis estudos reportaram dados de índice de massa corporal (IMC). O *hazard ratio* (HR) para SG e SLD foi 0,91 (intervalo de confiança (IC) 95% 0,77-1,07, p=0,25) e 0,92 (IC 95% 0,79-1,08, p=0,31) para o grupo intervenção comparado ao grupo controle, respectivamente. Intervenção dietética foi associada com redução do IMC nos sujeitos que receberam uma dieta específica ao invés de aconselhamento ou outro tipo de intervenção (-0,67 IC 95% -1,14 a -0,21).

Conclusões: Apesar do aumento da sobrevida entre paciente com câncer de mama decorrentes de melhores tratamentos oncológicos, ainda não há dados suficientes de estudos prospectivos em relação aos efeitos de intervenções dietéticas nesta população. Identificamos uma associação positiva entre prescrição de dietas específicas em termos de alterações em medidas antropométricas, mas não identificamos diferenças em SG nem em SLD.

Palavras-chave: Câncer de mama; Dieta; Sobrevida Global; Ensaio clínico randomizado; Meta-análise.

ABSTRACT

Introduction: Randomized clinical trials are inconclusive regarding the role of dietary interventions in the outcomes of patients with early stage breast cancer after curative treatment.

Aim: To assess the effects of dietetic interventions on overall survival (OS), disease-free survival (DFS), anthropometric measures, metabolic markers and quality of life in patients treated for early breast cancer.

Methods: EMBASE, MEDLINE, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials comparing dietary interventions (individualized dietary counseling, prescription of specific diets or others) with usual care in women treated for early stage breast cancer. Primary outcomes were overall survival (OS) and disease-free survival (DFS); secondary outcome was change in body mass index.

Results: We found 12 clinical trials eligible for analysis, of which seven were included in the quantitative analysis. Only two of them reported OS and DFS, whereas six reported data for body mass index. The hazard ratio (HR) for OS and DFS was 0.91 (95% CI 0.77-1.07, p=0.25) and 0.92 (95% CI 0.79-1.08, p=0.31) for the intervention group compared to the control group, respectively. Dietetic interventions were associated with body mass index reduction in those subjects who received a specific diet instead of counseling or other types of intervention (-0.67 95% CI -1.14 to -0.21).

Conclusions: Despite increasing survival among breast cancer patients due to better oncologic treatments, there is still a lack of prospective data regarding the

effects of dietary interventions in this population. We found a positive association between prescription of specific diets in terms of anthropometric measures. There were no differences in OS or DFS.

Keywords: Breast Cancer; Diet; Overall Survival; Randomized Clinical Trials; Meta-Analysis.

LISTA DE ABREVIATURAS

SG: Sobrevida Global

SLD: Sobrevida Livre de Doença

IMC: Índice de Massa Corporal

UICC: *Union for International Cancer Control*

GCO: Observatório Global do Câncer

OMS: Organização Mundial da Saúde

AJCC: *American Joint Committee on Cancer*

RE: Receptor de Estrogênio

RP: Receptor de Progesterona

PI3K: Fosfatidilinositol-3-quinase

HER2: Receptor do fator de crescimento epidérmico humano 2

SERM: Modulador seletivo do receptor de estrogênio

IGF-1: Fator de crescimento insulina-símile 1

WINS: *Women's Intervention Nutrition Study*

WHEL: *Women's Health Eat and Living study*

TRH: Terapira de Reposição Hormonal

SUMÁRIO

1 REFERENCIAL TEÓRICO

O câncer de mama é a neoplasia maligna mais frequente entre as mulheres em todo o mundo, quando excluídos os cânceres de pele do tipo não melanoma. Segundo o Globocan (*World Health Organization*, 2018), banco de dados *online* da *Union for International Cancer Control* (UICC), o qual fornece as estimativas de incidência e mortalidade de 36 tipos de câncer em 185 países, incluindo o Brasil, 2.088.849 novos casos de câncer de mama foram diagnosticados em todo o mundo em 2018, de um total de 18.078.957, alcançando o segundo lugar em frequencia. No Brasil, com 85.620 de novos casos, o câncer de mama foi o primeiro na lista, superando o número de novos casos de câncer de próstata (84.992).

1.1 Estadiamento e Prognóstico

A mortalidade pelo câncer de mama guarda estreita relação com o estadiamento da doença, que é fornecido pelo sistema TNM (Tumor, Linfonodo, Metástases) da *American Joint Committe on Cancer* (AJCC) (Hortobagyi et al. 2018). O TNM é um sistema internacionalmente reconhecido e amplamente utilizado para determinar o prognóstico e a escolha terapêutica. Consiste do tamanho do tumor primário (T: Tx, T0, Tis, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c), da quantidade de linfonodos regionais acometidos (N: Nx, N0, N1, N1mi, N2 e N3) e da presença ou não de metástases à distância (M: Mx, M0, M1). Na última revisão do TNM (8ª edição), foram incorporados biomarcadores ao sistema de estadiamento, tais quais, o grau do tumor (1, 2,

3), a positividade para receptores de estrogênio (RE) e progesterona (RP) no espécime tumoral, e a expressão do receptor do fator de crescimento epidérmico humano 2 (HER2). A composição dos componentes do sistema de estadiamento permitem classificar o paciente em estágios prognósticos: 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC e IV. São considerados iniciais os estágios I e II, localmente avançado o estágio III e metastático o estágio IV; a presença de metástases à distância determina a incurabilidade da doença. Devido às constantes atualizações do sistema de estadiamento da AJCC, pode haver diferenças entre os grupos estudados quando comparados estudos mais antigos como os mais atuais. As curvas de mortalidade demonstram que, quanto maior o estadiamento, menor a sobrevida global e, consequentemente, maior a chance de morrer pelo câncer de mama. A sobrevida global pode variar de 97% em 5 anos para pacientes com melhor prognóstico em estágio clínico I a 33% em 5 anos para pacientes com doença em estágio IIIC.

1.2 Tratamento

O tratamento para o câncer de mama é multimodal. A cirurgia é o pilar terapêutico nos tumores não metastáticos. A quimioterapia pode ser oferecida de forma neoadjuvante (antes da cirurgia), adjuvante (após a cirurgia) ou paliativa (para doença metastática). A radioterapia possui papel no tratamento locorregional de forma adjuvante e no tratamento de metástases sintomáticas. Além disso, o uso de bloqueadores hormonais, como inibidores de aromatase, moduladores seletivos do receptor de estrógeno (SERM) e dos inibidores diretos do receptor de estrógeno desempenham função fundamental no

tratamento adjuvante e paliativo nos casos de tumores que expressam receptores hormonais. Existem ainda os bloqueadores do receptor HER2 e as novas classes de medicamentos para doença metastática, como inibidores de ciclina quinase 4 e 6, inibidores de PI3K, inibidores de PARP e imunoterapia que, progressivamente, estão sendo incorporadas ao rol de opções terapêuticas.

1.3 Sobrepeso, Obesidade e Câncer de Mama

Aproximadamente metade das mulheres ocidentais portadoras de câncer de mama têm sobrepeso ou obesidade. Destas, cerca de 60% ganharão peso durante o tratamento. Estes fatores estão relacionados a piores taxas de sobrevida livre de progressão e de sobrevida global pelo câncer de mama (Camoriano et al., 1990; Chlebowski, Aiello e McTiernan 2002; Goodwin e Boyd, 1990; Schapira et al., 1991; Zumoff et al., 1982; Playdon et ai., 2015).

O sobrepeso e a obesidade em mulheres na idade fértil são fatores de proteção ao desenvolvimento de câncer de mama tanto na pré-menopausa (Ritte et al., 2012; Michels, Terry e Willett; 2016) quanto na menopausa (Baer et al., 2010; Fagherazzi et al., 2013; Huang et a., 1997; Palmer et al., 2007; Morimoto et al., 2002). Esse benefício aplica-se somente para os tumores com positividade para RE e RP.

No entanto, mulheres com sobrepeso e obesidade na pós-menopausa apresentam risco aumentado para o desenvolvimento de câncer de mama com expressão de RE e RP. O risco parece ser maior em mulheres acima dos 65 anos de idade (Ritte et al., 2012). Os estrogênios derivados do tecido adiposo

estão implicados no aumento do risco de câncer de mama em mulheres com baixos níveis endógenos destes hormônios. A terapia de reposição hormonal (TRH) também aumenta o risco de câncer de mama nesta população, mas este risco é independente do Índice de Massa Corporal (IMC). Desta forma, infere-se que a produção aumentada de estrogênio pelo tecido adiposo desempenhe papel na carcinogênese somente em mulheres que não realizam TRH (Munsell et al., 2014).

Além da produção aumentada de estrogênio, a obesidade está relacionada a maior quantidade de hormônios anabólicos, que possuem relação com o desenvolvimento de câncer de mama. Como visto anteriormente, níveis elevados de estrogênio aumentam o risco de câncer de mama em mulheres na pós-menopausa, e a perda ponderal pode influenciar positivamente esta relação (Wu, Pike e Stram, 1999). Outros fatores como leptina (Niu et al., 2013), IGF-1 (Renehan et al., 2004) e insulina em mulheres obesas podem desempenhar papel importante na carcinogênese mamária. Enquanto isso, níveis elevados de adiponectina circulante parecem desempenhar fator protetor quanto ao desenvolvimento de câncer de mama, principalmente em mulheres na menopausa (Ye et al., 2014).

À medida que mais dados foram reforçando a associação entre a obesidade e desfechos piores após tratamento de câncer de mama, houve interesse crescente em se investigar a possibilidade de perda de peso e medidas comportamentais reduzirem o risco de recidiva da doença ou morte por câncer de mama. Além da prática regular de exercício físico, o seguimento de uma dieta equilibrada é um dos pilares fundamentais da manutenção de um peso saudável (Asghari et al., 2017). Levando-se em consideração o risco

aumentado de obesidade após o tratamento de câncer de mama em estágio inicial, a associação desta complicação com piores desfechos do câncer e os benefícios potenciais de um programa de exercícios e dieta, tornou-se necessário que os profissionais envolvidos nos cuidados desta população reconheçam a importância destas medidas e abordem estes aspectos sempre que possível com as pacientes (Rock e Demark-Wahnefried, 2002).

1.4 Dieta

Uma dieta rica em vegetais e frutas provavelmente diminua o risco de câncer de mama, ao passo que uma dieta rica em gorduras totais possivelmente aumente o risco (Glade, 1999). No entanto, evidências a partir de estudos epidemiológicos de que haja associação entre dieta rica em vegetais e frutas e pobre em gordura total com prevenção de recidiva e progressão do câncer de mama são contraditórias (Harashima et al., 2007; Ingram, 1994; Jain, Miller e To, 1994; Kroenke et al., 2005; Mai et al., 2005; Pierce et al., 2007; Rock e Demark-Wahnefried, 2002; Rohan, Hiller, e McMichael, 1993; Taaffe, 2018; Zhang et al., 1995, Aune et al., 2012). Dados do *Women's Intervention Nutrition Study* (WINS), um estudo randomizado para avaliar se dieta muito rica em vegetais, frutas e fibras e pobre em gordura reduz os riscos de recorrência ou novo câncer de mama primário assim como risco de mortalidade por todas as causas em mulheres previamente tratadas para câncer de mama precoce, demonstraram que a intervenção foi associada a uma melhoria marginal, mas estatisticamente significativa, da sobrevida livre de recidiva (Chlebowski et al., 2006).

O outro estudo randomizado de maiores proporções, o *Women's Health Eating and Living* (WHEL), com mais de 3000 participantes, não demonstrou diferença estatisticamente significativa na taxa de recorrência do câncer de mama para o grupo que foi randomizado para uma dieta rica em frutas e verduras e pobre em gordura (Pierce et al., 2007). Por outro lado, uma meta-análise de 41 estudos observacionais chegou à conclusão de que uma dieta "saudável", ou seja, rica em frutas, verduras e fibras e pobre em carne vermelha ou processada, estava associada com redução de 24% no risco de mortalidade global (Schwedhelm et al., 2016).

Mesmo que os dados relativos aos benefícios da dieta na redução de recidivas de câncer e mortalidade específica pela doença não sejam conclusivos, não há circunstância em que não se deva recomendar uma dieta considerada saudável para uma paciente sobrevivente de câncer de mama. Uma mudança comportamental deste tipo não tem efeitos adversos nem riscos maiores, pode ser considerada de baixo custo, relativamente a outras intervenções, e traz benefícios múltiplos além daqueles puramente oncológicos.

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3 OBJETIVOS

3.1 Objetivo Geral

Avaliar os efeitos da prescrição de intervenções dietéticas a pacientes com câncer de mama em estágio inicial tratadas com intenção curativa através da realização de revisão sistemática e meta-análise de ensaios clínicos randomizados.

3.2 Objetivos Específicos

a) Avaliar os efeitos na sobrevida global e na sobrevida livre de recidiva (5 anos após o tratamento ou até follow-up máximo do estudo).
b) Avaliar os efeitos em medidas antropométricas:
    i. Mudança de peso;
    ii. Mudança no índice de massa corporal;
    iii. Mudança na relação cintura-quadril;
    iv. Mudança no percentual de gordura corporal.

4 ARTIGO CIENTÍFICO REDIGIDO EM INGLÊS

Effects of diet after early breast cancer treatment: systematic review and meta-analysis of clinical trials

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Purpose: Randomized clinical trials are inconclusive regarding the role of dietary interventions in anthropometric measurements and survival in breast cancer patients. Our aim was to conduct a systematic review and meta-analysis to assess the effects of diet on these outcomes in women treated for early stage breast cancer.

Methods: EMBASE, MEDLINE, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials comparing dietary interventions (individualized dietary counseling, prescription of a specific diet or other) with usual care in women that were treated for early breast cancer. Primary outcomes were overall survival (OS) and disease-free survival (DFS); secondary outcome was change in body mass index.

Results: We found 12 clinical trials eligible for analysis, of which 7 were included in the quantitative analysis. Only two of them reported OS and DFS, whereas six reported data for body mass index. The hazard ratio (HR) for OS and DFS was 0.91 (95% CI 0.77-1.07, p=0.25) and 0.92 (95% CI 0.79-1.08, p=0.31) for the intervention group compared to the control group, respectively. Diet intervention was associated with body mass index reduction in those subjects who received a specific diet instead of counseling or other types of intervention (-0.67 95% CI -1.14 to -0.21).

Conclusions: Despite increasing survival among breast cancer patients due to better oncologic treatments, there is still a lack of prospective data regarding the effects of dietary interventions in this population. We found positive association between prescription of specific diets in terms of anthropometric measures; there were no differences in OS no DFS.

PROSPERO registry: CRD42014008743.

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Introduction

Breast cancer is the major cause of cancer among women worldwide and is the leading cause of death in many countries.(1,2) Despite advances in medical, surgical and radiation treatments as well as in screening methods, around 30% of all initial breast cancer cases will recur.

Approximately half of breast cancer patients in Western countries are overweight or obese at the time of diagnosis (3). Moreover, up to 60% of women will gain weight during oncologic treatment (4). Obesity and weight gain after the diagnosis are related to poor overall (OS) and disease-free survival (DFS) (5,6). Physical activity and dietary interventions limit weight gain among breast cancer patients (7) what may improve outcomes and may contribute in reducing breast cancer specific mortality, according to observational studies (8). There are one clinical trial assessing physical interventions and mortality in early breast cancer showing better OS and DFS with the interventions (9,10).

Observational studies showed that quality of the diet could reduce the risk of breast cancer recurrence, but none of them assessed the risk of death (11,12). There are scant data about dietary interventions and their relationship with outcomes in early breast cancer patients.

In the present study, we aimed to conduct a systematic review and meta-analysis to assess the effects of dietary interventions in anthropometric measures and survival in women after treatment of early breast cancer.

Methods

Protocol and registration

The protocol of this systematic review and meta-analysis was previously published (13) (PROSPERO registry number CRD42014008743). The systematic review was conducted according to Cochrane Handbook for Systematic Reviews of Interventions (14) and the manuscript was reported according to PRISMA recommendations (15).

Data sources and searches

The electronic databases EMBASE, MEDLINE, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) were consulted for indexed literature including papers, abstracts or reports up to February 2019. We also have searched in the grey literature in annals of meetings and ongoing trials at ClinicalTrials.gov.

Study selection

We included in the analysis randomized trials that evaluated the effects of dietary interventions (individualized dietary counseling, prescription of a specific diet or other) compared to usual care in women who went through treatment for stages I-III breast cancer. We excluded studies that applied the intervention after 5 years from the diagnosis and studies whose patients were on neoadjuvant chemotherapy and/or radiation therapy; hormone therapy was allowed.

The primary outcomes were OS and DFS (5 years after treatment or until the maximum follow-up period). Secondary endpoint was body mass index (BMI) (kg/m^2). Other endpoints, included in the protocol report (13), were waist-hip ratio (WHR), estradiol levels, insulin levels, testosterone levels, SHBG levels and quality of life; these variables will be reported for the qualitative analysis.

The evaluation of titles and abstracts for eligible studies, the inclusion of papers and data extraction were conducted by HAVT, FSF, FKA and MRRF in pairs, independently, and using a standardized form. All disagreements were solved through discussion with the senior author.

Data extraction

The data used for meta-analysis and comparison between usual care and intervention were the same as our previous study (10). Briefly, we used the final values of both groups after the intervention, since these were the data most frequently found, in order to minimize the need for imputations. Studies without both initial and final values were excluded from the analysis. For studies that presented only values of the difference between final results and initial results, the final values were calculated from a simple sum of the variation with the initial value. In this case, the values of the standard deviations used were the same as the initial values of the variables. Some values of final standard deviation were not reported, as was the case of studies of Parekh et al. (16) and Ramirez et al. (17). In this case, we used the initial standard deviation. For the study of Chlebowski et al. (18) we used the imputation formula based on confidence interval to obtain the final standard deviation. The studies of Holm et al. (19), Chlebowski et al. (20) and Zuniga et al. (21) were excluded from the meta-analysis due the lack of data for analysis or imputations; the study of Thomson et al. (22) was excluded since it described a population that probably was already described by Rock et al. (23).

Quality assessment

The quality evaluation of all studies was carried out in the same way as for study selection and data extraction, always paired and in accordance to Cochrane Handbook of Systematic Reviews (14) through the Cochrane risk of

bias tool. The overall quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (24), and was classified as ‘high,’ ‘moderate,’ ‘low,’ or ‘very low`.

Data synthesis and analysis

The data were combined using the random-effect meta-analysis model, with DerSimonian–Laird estimator as variance estimator, and the treatment effect was estimated using the mean difference (MD) as summary measure for continuous outcomes. All analyzes were performed using software R, version 3.2.1, *meta* packages version 4.9-2. Statistical heterogeneity was assessed in each meta-analysis using the statistics I^2 and heterogeneity was considered substantial if the I^2 was greater than 50%. Publication bias was assessed using funnel plot and its effect on the interpretation of the results was evaluated by a trim-and-fill computation.

Results

Literature search

A total 21,748 records were identified through database search. There were 3,982 duplicated records, lasting for title and abstract analysis 17,766; 78 studies were selected for full text analysis. After that, 12 studies provided data for qualitative analysis, of which 7 were included in the meta-analysis. The flowchart of the search is presented in Figure 1. The studies characteristics are presented in Table 1. The risk of studies bias is summarized in Figures 2 and 3.

Study characteristics

A total of 6,087 patients were allocated in 7 studies. The mean duration of interventions was 15.7 months (ranged from 2 months to 60 months). The maximum follow-up period was 108 months and the minimum was 2 months. Two studies reported OS and DFS data.

WINS (*Chlebowski 2006*, *Blackburn 2007* and *Chlebowski 2008*)

The Women's Intervention Nutrition Study (WINS) is a phase III randomized clinical trial designed to assess the effects of a low-fat dietary intervention on OS and DFS among early breast cancer patients. A total of 2,437 women were randomized either to receive low-fat eating plan (< 20% of total calories intake) for up to 60 months or usual care. The first report of OS and DFS was published in 2006 (18) and its update was published as an abstract in 2008 (25). At 108 months of follow-up the OS did not differ between groups with adjusted HR = 0.83 (95% CI = 0.59 - 1.03, p=.146). However, in the 362 women with estrogen receptor (ER)-negative and progesterone receptor (PR)-negative disease, a significant OS benefit was seen for the intervention group (7.5% vs. 18.1%, cumulative mortality, RR 0.41, p=0.003). DFS was reported in 2006, after 60 months of follow-up. There was a benefit for patients enrolled to the intervention group. These participants had a 24% lower risk of relapse than those allocated at control group (HR = 0.76; 95% CI = 0.60 – 0.98, p = 0.034). The greater benefit was seen in patients with ER-negative tumors (HR = 0.58; 95% CI 0.37 - 0.91, p=.018). In 2007 a sub analysis of 53 patients of 3 centers of WINS study trial was published assessing metabolic parameters, including fasting insulin levels. There were no differences in all measures among the intervention and the control groups (26).

WHEL (*Rock 2004*, *Thomson 2005*, *Pierce 2007*)

The second trial, The Women’s Healthy Eating and Living (WHEL) trial, published by Pierce et al. aimed to assess whether a diet high in vegetables, fruit and fiber and low in fat was effective to reduce breast cancer survival and recurrence in early breast cancer patients (27). Intervention consists of

prescription of a diet with increased fibers, vegetables and fruits and reduced fat intake (5 vegetable servings/day, 3 fruit servings/day, around 475 milliliter vegetable juice/day, 30 grams fibers/day, and 15 to 20% total calorie intake from fat), while control group participants were advised to consume general dietary recommendations based on nutritional guidelines (5 servings of fruits and vegetables per day, 20 grams/day fiber, and ≤ 30% energy from fat). After 7.3 years of follow-up, there were no differences between the control and the intervention groups in terms of breast cancer-related events, despite the significant differences in the pattern of dietary changes. This is the largest randomized clinical trial assessing OS and DFS, with 3,088 participants. There were 315 deaths during the follow up, 160 in the control group and 155 in the intervention group; adjusted HR 0.91 (95% CI 0.71 – 1.15, p = .43). During the follow up, 518 patients had a breast cancer-related event: 256 in the intervention group and 262 in the control group (adjusted HR 0.96; 95% CI 0.80 – 1.14, p = .63).

Rock et al. reported an analysis of a WHEL trial subgroup of 291 women in which serum concentration of steroids were assessed (23). The intervention group experienced a significant change in estradiol concentration in comparison to the control group. There were no differences in terms of weight loss in both groups. Thomson et al. reported the results of 52 participants of the Arizona site of WHEL study (22). No differences between the groups were seen after 48 months of follow-up in terms of weight, BMI, WHR, percentage of body fat, and lean body mass, despite the increased intake of fibers at 6 and 12 months.

NAS (*Chlebowski 1987*)

Other smaller studies also assessed the effects of a dietary intervention as adjuvant therapy for early breast cancer patients. The Nutrition Adjuvant Study (NAS) published in 1987 by Chlebowski et al. reported the initial patient's adherence to a low-fat diet, in which the caloric intake in the intervention group were no more than 15% of the total calories (20). NAS is a two-arm randomized clinical trial, in which 49 women were treated for stage II (at least 1 positive lymph node) breast cancer with randomization within 60 days from mastectomy.

The endpoints were change in dietary fat intake, total fat gram intake, total caloric intake and body weight. There were no differences between groups in terms of change in body weight, but there was a significant reduction in fat and caloric intake in the intervention group.

(*Holm 1990*)

Holm et al. published a feasibility study to evaluate the effects of a low-fat diet as adjuvant treatment (20-25% of total caloric intake) for women who had been operated for breast cancer (19). After 24 months of follow up, the total energy intake in both groups were reduced and the fat intake reduced in the intervention group, remaining around 20% of total caloric energy. There was a significant reduction in body weight in the intervention group compared to the control group, (-0.4 kg vs. +1.3 kg, p=0.05, respectively, after 24 months).

(*Zuniga 2018, Ramirez 2016*)

The adherence to a Mediterranean-style, anti-inflammatory diet was evaluated by Zuniga et al. (21), whose trial protocol has been described by Ramirez (28). There was an increased adherence to a more Mediterranean-style diet among intervention group participants. There was minimal difference in weight after 6 months of follow up in both groups. Previously, Ramirez et al. reported the initial results of an anti-inflammatory dietary prescription for obese and overweight stage 0 to III breast cancer patients (17). There was a significant reduction in BMI in the intervention group (-1.7 kg/m^2; median 32.3 kg/m^2 to 30.6 kg/m^2 after 12 months). In contrast, the control group experienced minimal change in BMI (0.5 kg/m^2; median 30.0 kg/m^2 to 30.5 kg/m^2 after 12 months).

(*Cho2014*)

Cho et al. assessed whether a 8-week intervention based on dietary counseling may increase fruit and vegetables intake, improve quality of life, increase serum antioxidant levels, and change anthropometric measures (29).

Sixty-one stage I to III breast cancer patients were enrolled. There were no differences in BMI, weight and quality of life in both groups. The intervention group consistently increased fruit and vegetables intake at the end of the study.

HEAL-BCa (*Parekh 2018*)

An educational intervention aiming to improve nutritional literacy among breast cancer survivors was designed by Parekh et al. in order to provide healthy eating habits in this subset of patients. This pilot study suggested that this approach is feasible and could improve not just nutrition literacy but anthropometric measures too (16).

Outcomes

Regarding the primary outcomes, the interventions studied did not promote significant mortality reduction for all subset of patients (HR 0.91; 95% CI 0.77-1.07, p=0.25, I^2= 7%, high quality of evidence), as seen in figure 4. Similarly, there was no improvement in DFS for the intervention group (HR 0.92; 95% CI 0.79-1.08, p=0.31, I^2=52%, high quality of evidence), as shown in figure 5. Due to a trend of better DFS for ER-negative and PR-negative patients allocated in the intervention group in WINS trial, we performed a subgroup analysis stratifying participants with hormone receptor (HR)-positive and HR-negative tumors. This analysis showed no benefits of dietary interventions in DFS (HR 0.87; 95% CI 0.68 – 1.1, p=0.23, I^2 = 62%, high quality of evidence; figure 6).

General dietary interventions were not associated with BMI reduction (-0.32 kg/m^2; CI 95% -0.95 to 0.30, p=0.31, I^2= 21%, very low quality of evidence; figure 7), but there was a significant BMI reduction for those subjects who received a specific diet instead of counseling or other types of intervention (-0.67; CI 95% -1.14 to -0.21), with very low quality of evidence, as shown in figure 8.

Egger test for asymmetry and publication bias was not conducted since there was less than 10 trials. Visual asymmetry was used as described by Sterne et al. (30,31). Since there were few outcomes, trim and fill analysis was performed for all the outcomes and can be seen in the Supplementary Material. Trim-and-fill computation resulted in gain of statistical significance when publication bias was corrected for BMI . After this correction, the effect of the intervention on BMI reduction was – 0.75 kg/m^2 (95% CI − 1.43 to – 0.08, p = 0.02), Supplementary Material.

Discussion

Besides their impact in the general health and quality of life of patients, weight gain and obesity might affect OS and DFS of patients treated for breast cancer (5). There is lack of prospective data evaluating the effects of dietary interventions in this population.

We have previously published a meta-analysis assessing the effects of physical activity combined or not to diet on OS and DFS and in anthropometric changes among women who had finished adjuvant treatment for early stage breast cancer. The present study is the first meta-analysis of randomized clinical trials that reported data on OS and DFS of dietary interventions exclusively, without combining physical activity or other intervention. Other meta-analysis assessed the same outcomes, but they included observational studies (6). Our goal was to collect the best evidence available, therefore we chose to include only randomized trials comparing the impact of dietary interventions against usual care.

We separated the type of intervention in 3 groups: prescription of a specific diet, individual dietary counseling and other. We noticed a slight difference in terms of BMI reduction favoring the intervention group.

The present meta-analysis provides data on OS and DFS of 5,525 patients of two studies, WINS and WHEL trials (25,27). There were no differences in both outcomes compared to usual care in regard to OS or DFS, even when stratifying by hormonal receptor status. For this reason, there is a

clear lack of guidance on which diet or dietary intervention should be recommended to patients after they finished treatment for breast cancer.

Our meta-analysis has several limitations. First, there was a lack of good quality data on anthropometric measures accordingly to GRADE quality assessment (very low quality of evidence). Second, the type of interventions and their duration were heterogeneous among the studies. Third, some of the studies did not reported the histologic features of tumors, such as HR and HER2 status. Fourth, two studies (17,21) included only overweight or obese women whereas the great majority of studies included patients in all BMI groups. Fifth, despite of the great numbers of subjects included in OS and DFS analysis (5,525), it was not possible to run Egger test, since the number of studies was low. We think this could have compromised bias evaluation and could have implications on the quality of evidence.

Considering all limitations, our meta-analysis provided data on OS and DFS of early breast cancer survivors who underwent dietetic interventions after completion of breast cancer treatment. We found no differences in OS and DFS in the groups probably because the interventions did not reduce significantly BMI. Clinical trials assessing intensive weight control are necessary to answer this question. Despite the lack of evidence supporting diet or dietary interventions after treatment of early breast cancer, survivors are oriented to maintain or reduce weight through high quality food diet and low caloric intake because this intervention is cheap and has no significant adverse effects. Therefore, interventions targeting weight control and healthier behaviors must be assessed by high quality evidence studies.

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Table1. Studies characteristics n = 12

Study	Sample	Intervention characteristics	Outcomes
Chlebowski 1987 USA 7 centers	49 women Stage II breast cancer with at least 1 positive axillar node after surgery Hormone receptor status: ER positive: 32; RP positive: 10; unknown: 7 Mean age, 60.3 years Mean % ideal BMI, 114,5%	3 months intervention (1) Intervention: prescription of diet with a target of 15% of caloric intake derived from fat. Nutritional counseling every 2 weeks for 3 months. After, monthly appointments until 12 months. (2) Control: maintenance of basal fat intake around 38% of total calories. Nutritional counseling every 3 months for 1 year.	Chance from baseline to 6 months: (1) Weight: -2.4 kg $\pm$ 2.96 p=0.001 (2) Weight: -1.2 kg $\pm$ 3.74 p: NS

Holm 1990 Sweden 3 centers	240 women Stages I (33%) and II (61%) breast cancer patients who had been previously operated Pre-menopausal: 12% Post-menopausal: 85% Mean age, 58 years BMI ≥25 kg/m^2, 34%	24 months intervention (1) Intervention: individualized dietary counseling to reduce fat to 20-25% of total caloric intake while increasing carbohydrate intake. No change in total energy intake. A Nutritionist monitored the dietary changes every 3 months with help of the food records during the first year. (2) Control: usual care to maintain baseline fat intake	Change from baseline to 24 months: (1): Weight: - 0.4 kg (2): Weight: 1.3 kg P <0.05

Rock 2004 USA 7 centers WHEL study subgroup	291 women Stages I to IIIA breast cancer patients who went through surgery, lymph node dissection and radiotherapy Mean age, 54.9 years Mean BMI, 27.6 kg/m^2	12 months intervention (1) Intervention: prescription of diet with increased fibers, vegetables and fruits and reduced fat intake (5 vegetable servings/day, 3 fruit servings/day, around 475 milliliter vegetable juice/day, 30 grams fibers/day, and 15 to 20% total calorie intake from fat) (2) Control: advised to consume general dietary recommendations (5 servings of fruits and vegetables per day, 20 grams/day fiber, and ≤ 30% energy from fat)	*Sub-analysis of WHEL study* Change from baseline to 12 months: (1) Energy: -79 kcal/d % energy from fat: -7% Weight: 0.0 kg BMI: 0.0 kg/m^2 Estradiol: -27 pmol/L Testosterone: 0.0 nmol/L SHBG: +0.05 umol/L (2) Energy: -146 kcal/d % energy from fat: -1% Weight: + 1.0 kg BMI: + 0.1 kg/m^2 Estradiol: +5.0 pmol/L Testosterone: 0.0 nmol/L SHBG: - 0.03 umol/L

Thomson 2005 USA 1 center WHEL trial subgroup	52 women Stages I to IIIA breast cancer patients who went through surgery, lymph node dissection and radiotherapy from Arizona site of WHEL study Mean age, 53,6 years	48 months intervention (1) Intervention: prescription of diet with increased fibers, vegetables and fruits and reduced fat intake (5 vegetable servings/day, 3 fruit servings/day, around 475 milliliter vegetable juice/day, 30 grams fibers/day, and 15 to 20% total calorie intake from fat) (2) Control: advised to consume general dietary recommendations (5 servings of fruits and vegetables per day, 20 grams/day fiber, and ≤ 30% energy from fat)	*Sub-analysis of a WHEL study center* Change from baseine to 48 months (1) BMI: +0.7 kg Waist-hip ratio: +0.03 cm Body fat: + 1.0 % (2) BMI: + 2.1 kg Waist-hip ratio: + 0.02 cm Body fat: + 2.0 %

Chlebowski 2006 USA 39 centers WINS study	2437 women Stage I and II unilateral total resected breast cancer patients Baseline fat intake 20%+ of total calories Pre-menopausal 34.8%, Post-menopausal 64.2%, Unknown 1% Hormone receptor status: ER positive: 80% PR positive: 66% Mean age, 58.5 years Mean BMI, 27.5 kg/m^2	60 months intervention (1) Intervention: low-fat eating plan (< 20% of total calories intake) with registered dieticians with regular appointments. Instructed to keep written record of fat intake daily. (2) Control: One baseline dietitian's visit. Received written information on nutritional adequacy.	60 months follow-up (1):(2) – total group OS HR 0.89 (0.65-1.21, p=0.56) DFS HR 0.81 (0.65-0.99, p=0.007) (1):(2) – ER- group RFS 0.58 (0.37-0.91) Change from baseline to 12 months (1) Weight: -2.1kg BMI: -0.8 kg/m^2 (2) Weight: + 0.2 kg BMI: +0.1 kg/m^2
Blackburn 2007 USA 3 centers WINS study subgroup	53 women Stage I and II unilateral total resected breast cancer patients Baseline fat intake 20%+ of total calories	60 months intervention (1) Intervention: low-fat eating plan (< 20% of total calories intake) with registered dieticians with regular appointments. Instructed to keep written record of fat intake daily. (2) Control: One baseline dietitian's visit. Received written information on nutritional adequacy.	Change from baseline to 24 months: (1) Insulin: -6.1 uU/mL (2) Insulin: - 7.7 uU/mL

Pierce 2007 USA 7 centers WHEL trial	3088 women Stages I to IIIA breast cancer patients who went through surgery, lymph node dissection and radiotherapy Stage I: 1191 (38.5%), Stage II: 1743(56.5%), Stage III: 154 (5%) Hormone receptor status: ER positive: 2269 (73.5%), PR positive: 2032 (55.8%), ER/PR negative: 619 (20%) Mean age, 53.1 years Mean body weight, 73.4 kg	12 months intervention (1) Intervention: prescription of diet with increased fibers, vegetables and fruits and reduced fat intake (5 vegetable servings/day, 3 fruit servings/day, around 475 milliliter vegetable juice/day, 30 grams fibers/day, and 15 to 20% total calorie intake from fat) (2) Control: advised to consume general dietary recommendations (5 servings of fruits and vegetables per day, 20 grams/day fiber, and ≤ 30% energy from fat)	87.6 months follow-up (1):(2) OS HR 0.91 (0.72-1.15,p=0.43) IBCE* HR 0.96 (0.80-1.14, p=.63) Change from baseline to 72 months: (1) Weight: +0.6 kg (2) Weight: +0.4 kg

Chlebowski 2008 USA 39 centers WINS study ABSTRACT	2437 women Stage I and II unilateral total resected breast cancer patients Baseline fat intake 20%+ of total calories	60 months intervention (1) Intervention: low-fat eating plan (< 20% of total calories intake) with registered dieticians with regular appointments. Instructed to keep written record of fat intake daily. (2) Control: One baseline dietitian's visit. Received written information on nutritional adequacy.	108 months follow-up: (1):(2) – total group OS HR 0.83 (0.59-1.03,p=0.14) (1):(2) – ER-/PR- patients Cumulative mortality: 7.5% vs. 18.1%, RR 0.41, p=0.003
Cho 2014 South Korea 1 center	61 women Stage I to III breast cancer patients who completed treatment Pre-menopause: 10 (16%), Post-menopause: 41 (84%) Mean age, 46.1 years Mean BMI, 22.9 kg/m^2	8-week intervention (1) Intervention: 2 nutrition counseling and 1 cooking sessions, to encourage participants to eat at least 10 servings of fruits and vegetables per day (2) Control: brochures with recommendations of rich phytochemical diet	Change from baseline to 8-weeks (1) Weight: + 0.2 kg BMI: +0.1 kg/m^2 FACT-B QoL: +0.7 points (2) Weight: +0.3 kg BMI: +0.1 kg/m^2 FACT-B QoL: +1.8 points

Ramirez 2016 USA 1 center	153 women Overweight or obese stage 0 to III breast cancer patients Mean age, 56,5 years Mean BMI, 31.7 kg/m^2	6 months intervention (1) Intervention: individualized anti-inflammatory dietary prescription and monthly behavior-change workshops, motivational interviewing, and tailoring newsletter (2) Control: nutritional information at baseline and monthly American Institute for Cancer Research brochures with nutritional information. Received 2 telephone calls during the follow-up	Change from baseline to 12 months (1) BMI: - 1.3 kg/m^2 (2) BMI: - 1.1 kg/m^2
Parekh 2017 USA 1 center HEAL-Bca study	59 women Early-breast cancer patients who had completed prescribed treatment (surgery, chemotherapy, and/or radiation therapy) Mean age, 58.1 years Mean BMI, 31.5 kg/m^2	3 months intervention (1) Intervention: educational intervention to improve nutritional literacy among breast cancer survivors based on training over a period of 3 months (6 sessions; 12 hours in total) (2) Control: nutritional information throughout brochures developed by American Institute for Cancer Research for cancer survivors	Change from baseline to 3 months (1) BMI: - 0.69 kg/m^2 (2) BMI: - 0.02 kg/m^2

Zuniga 2018 USA 1 center	125 women Overweight or obese stage 0 to III breast cancer patients Stage 0: 12 (8%), Stage I: 35 (23%), Stage II: 38 (25%), Stage III: 21(14%), Unknown: 19 (12%) Mean age, 56,5 years Mean BMI, 31.7 kg/m^2	6 months intervention (1) Intervention: individualized anti-inflammatory dietary prescription and monthly behavior-change workshops, motivational interviewing, and tailoring newsletter (2) Control: nutritional information at baseline and monthly American Institute for Cancer Research brochures with nutritional information. Received 2 telephone calls during the follow-up	Change from baseline to 6 months (1) Weight: - 0.2 kg (2) Weight: + 0.06 kg

* IBCE = invasive breast cancer event

Figure 1. Prisma flow diagram

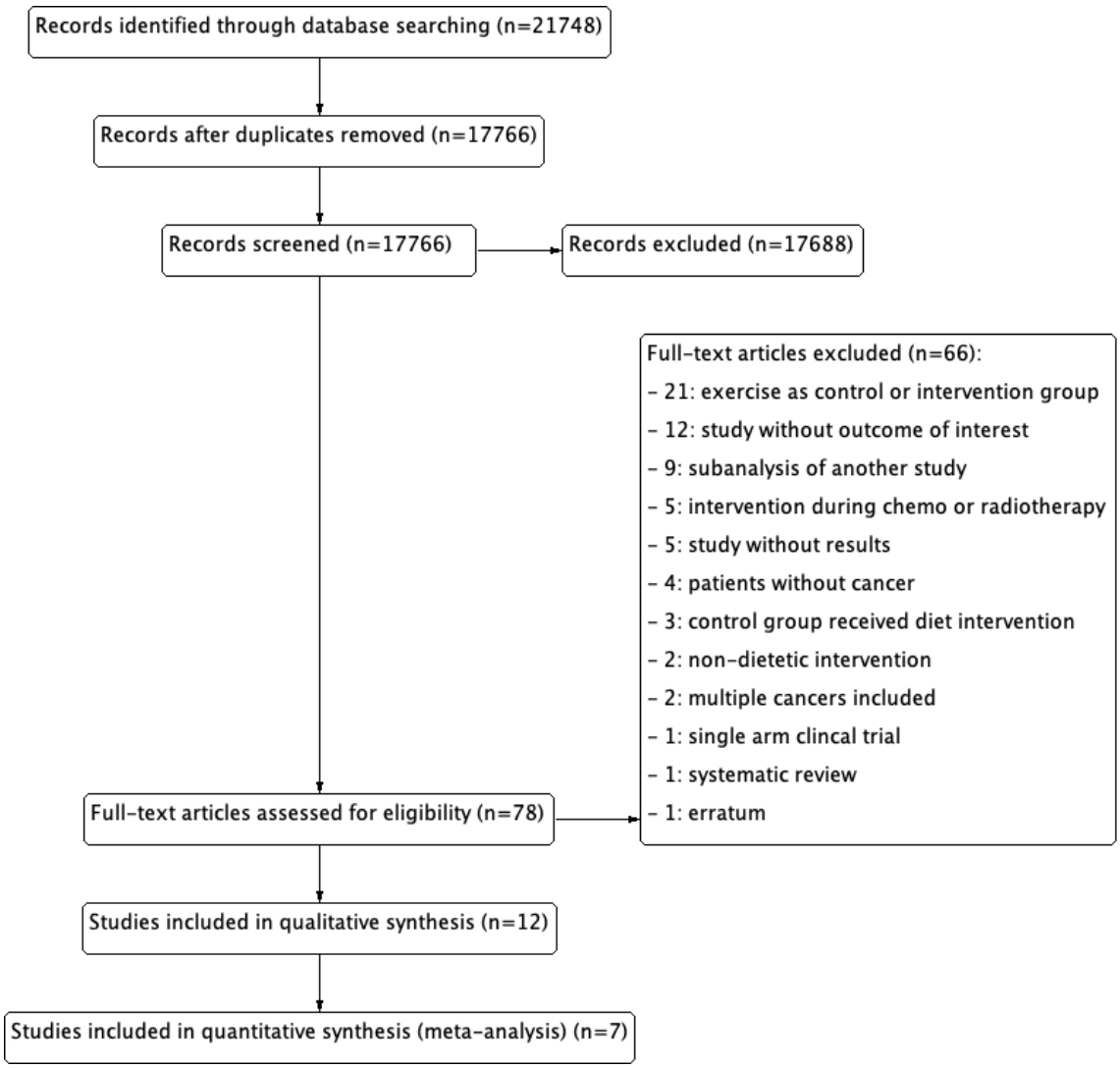
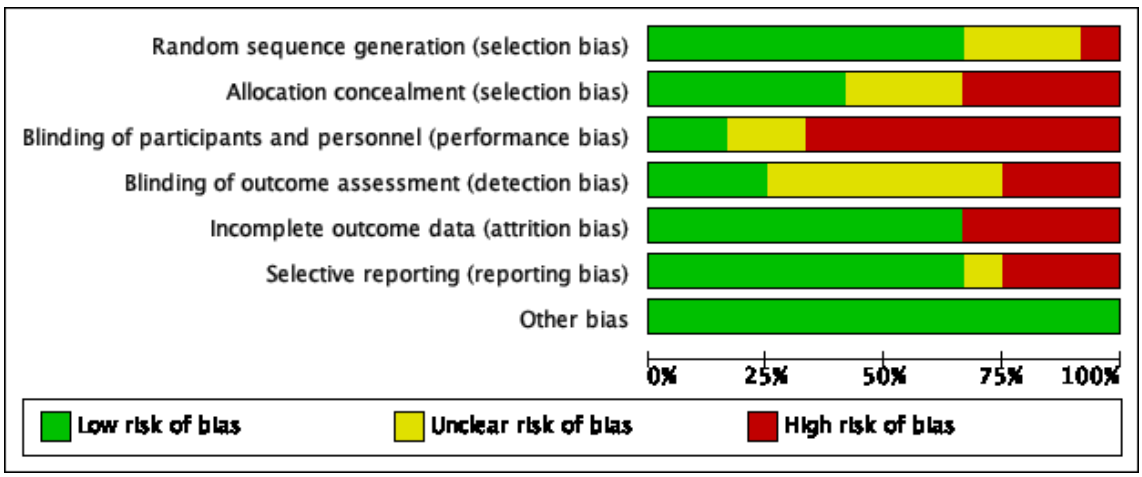


Figure 2. Risk of bias graph



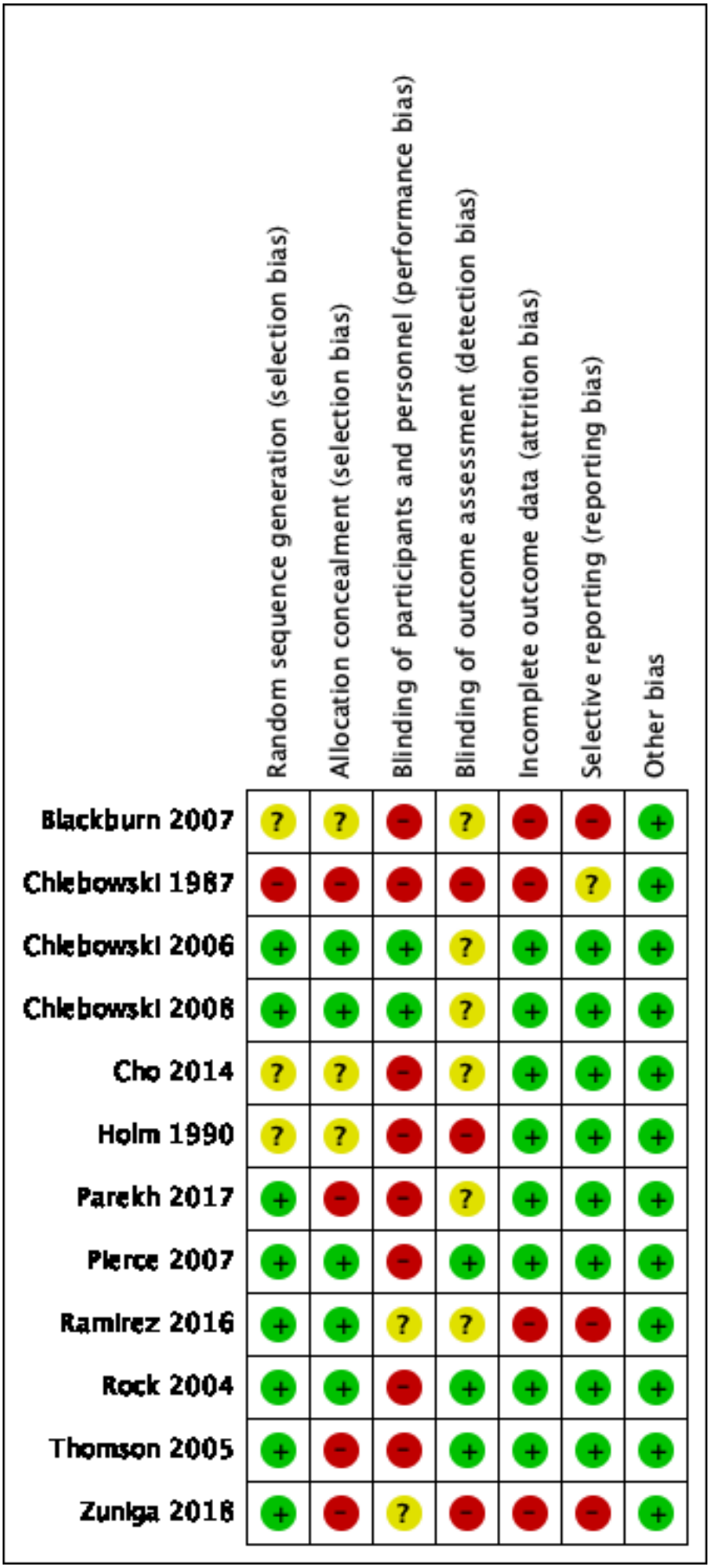


Figure 3. Risk of bias summary

Figure 4. Forest plot for overall survival

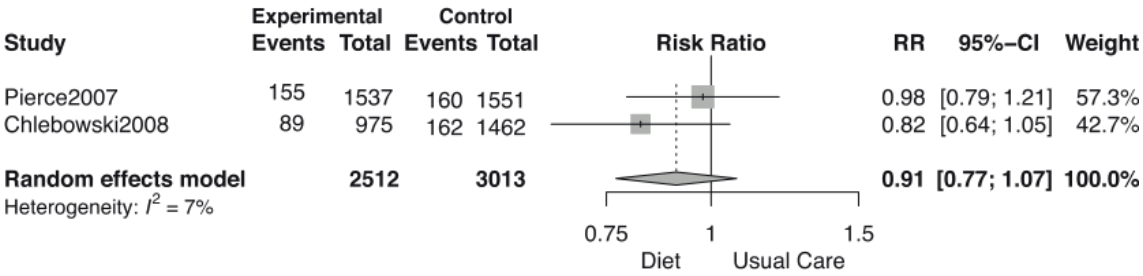


Figure 5. Forest plot for disease-free survival

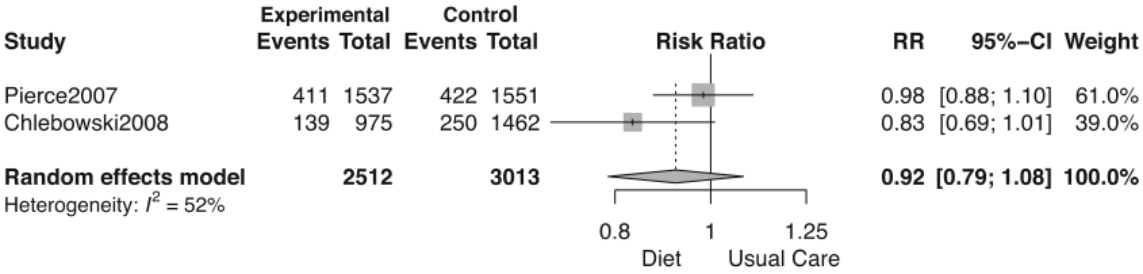


Figure 6. Forest plot DFS sorted by HR status (ER+ and/or PR + vs HR negative)

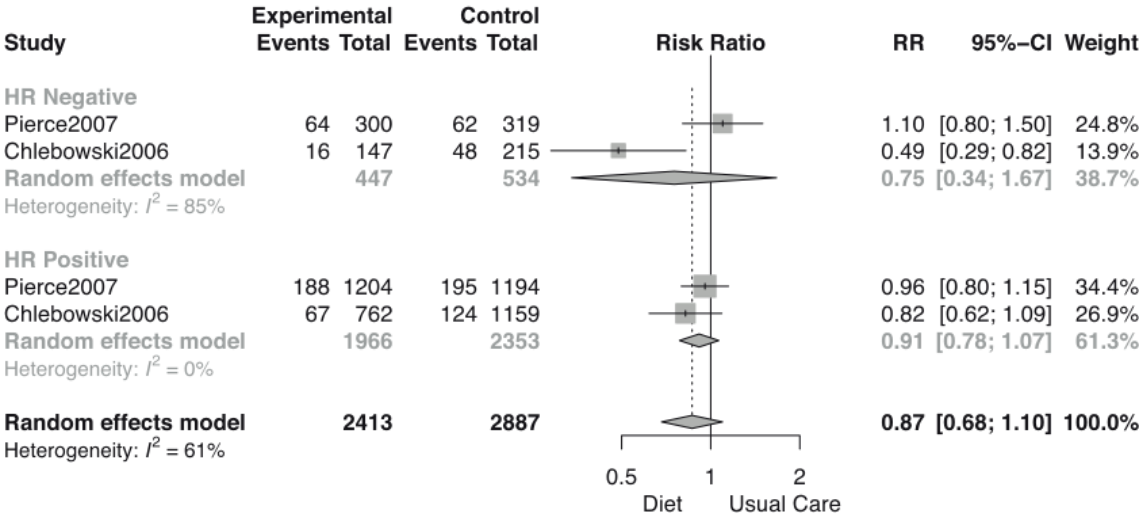


Figure 7. Forest plot for BMI reduction

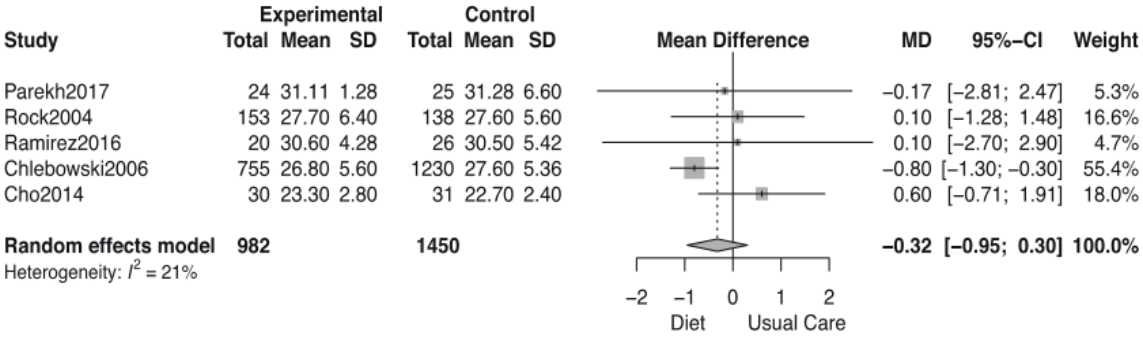


Figure 8. Forest plot for BMI reduction sorted by type of intervention

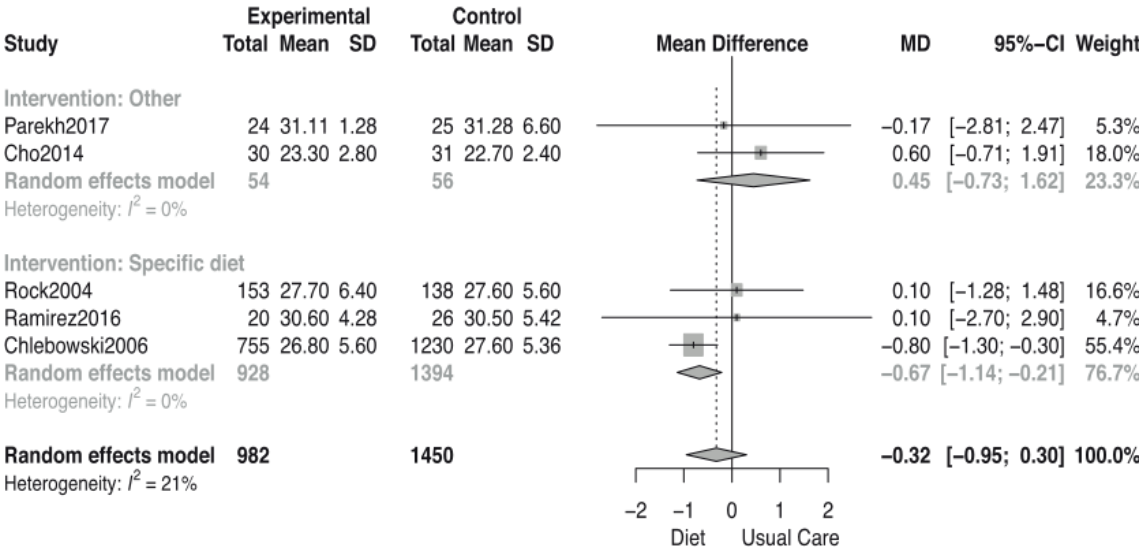


Figure 9. GRADE summary

Diet compared to usual care for early breast cancer

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet	Usual care	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (follow up: range 87 months to 108 months)												
2	randomised trials	serious [a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2512 participants	3013 participants	**HR 0.91** (0.77 to 1.07) [Overall Survival]	**9 fewer per 1.000** (from 24 fewer to 7 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
							-	10.7%		**9 fewer per 1.000** (from 24 fewer to 7 more)		
Disease-free Survival (follow up: range 87.6 months to 108 months)												
2	randomised trials	serious [a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2512 participants	3013 participants	**HR 0.92** (0.79 to 1.08) [Relapse from breast cancer]	**28 more per 1.000** (from 25 fewer to 83 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet	Usual care	Relative (95% CI)	Absolute (95% CI)		
							-	22.3%		**28 more per 1.000** (from 25 fewer to 83 more)		

Body Mass Index (follow up: range 2 months to 60 months)

5	randomised trials	serious [a,b,c,d]	serious [d]	not serious	serious [a,b,d]	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [c]	982	1450	-	MD **0.32 kg/m2 lower** (0.95 lower to 0.3 higher)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. Diet adherence unknown

b. Interventions varied widely across different studies

c. Evidence that publication bias is present

d. Wide confidence intervals

5 CONCLUSÕES

Devido ao maior acesso aos exames de rastreamento do câncer de mama, é notável que houve um aumento do diagnóstico e consequentemente da incidência desta doença, principalmente em estágios iniciais, ao longo dos últimos anos. O tratamento para a doença em estágio inicial tem melhorado, aumentando o número de sobreviventes. Desta forma, doenças crônicas presentes na população não oncológica têm aumentado entre os sobreviventes de câncer de mama, como obesidade e síndrome metabólica. Dados retrospectivos sugerem que o ganho de peso e a obesidade podem ter impacto negativo na SG e na SLD. Atualmente, há escassos dados prospectivos referentes a intervenções dietéticas nesta população.

Nossa meta-análise é a primeira a avaliar, através de ensaios clínicos randomizados, os efeitos de intervenções dietéticas em desfechos de sobrevida e medidas antropométricas em pacientes com câncer de mama em estágio inicial tratadas com intuito curativo. Outras meta-análises avaliaram a mesma questão, mas incluíram somente estudos observacionais.

Conseguimos demonstrar uma discreta diferença em relação à redução do IMC em pacientes que receberam prescrição de dieta específica (grupo intervenção) em comparação aos cuidados usuais (grupo controle). Esta diferença não foi demonstrada com os outros dois tipos de intervenção (aconselhamento dietético individual e outros). Em relação à SG e à SLD, dois estudos foram selecionados, com total de 5525 pacientes. Apesar do grande número de sujeitos incluídos, não identificamos diferenças nestes desfechos, mesmo ao estratificar a amostra pelo *status* hormonal.

Nossa meta-análise possui algumas limitações. Primeiro, a baixa qualidade da evidência segundo o GRADE para as medidas antropométricas compromete a análise destes desfechos. Segundo, os tipos de intervenções e suas durações foram heterogêneas entre os estudos. Terceiro, alguns estudos não reportaram dados histológicos importantes, como os *status hormonal* e a expressão do HER2. Quarto, dois estudos incluíram somente mulheres com sobrepeso e obesidade, enquanto os demais incluíram mulheres de todos os estratos de IMC.

Apesar das limitações, nosso trabalho forneceu dados que corroboram que intervenções dietéticas, que não visam a redução da ingesta calórica, mas sim a melhora da qualidade da alimentação, não possuem impacto na SG e na SLD, uma vez que não houve diferença em relação a mudanças no peso e no IMC. Estudos prospectivos que visem o controle intensivo do peso são necessários para responder a esta questão. Apesar da falta de evidência robusta que recomende intervenções dietéticas para a redução de mortalidade relacionada ao câncer de mama, as sobreviventes são sempre orientadas a manterem ou reduzirem o peso através da prática de exercícios físicos e através de alimentação de alta qualidade, pois são intervenções baratas e com mínimos efeitos adversos. Com isso, acreditamos que intervenções visando à redução intensiva do peso e os hábitos de vida saudáveis devem ser avaliados através de estudos de alta qualidade de evidência.

6 BIOGRAFIA

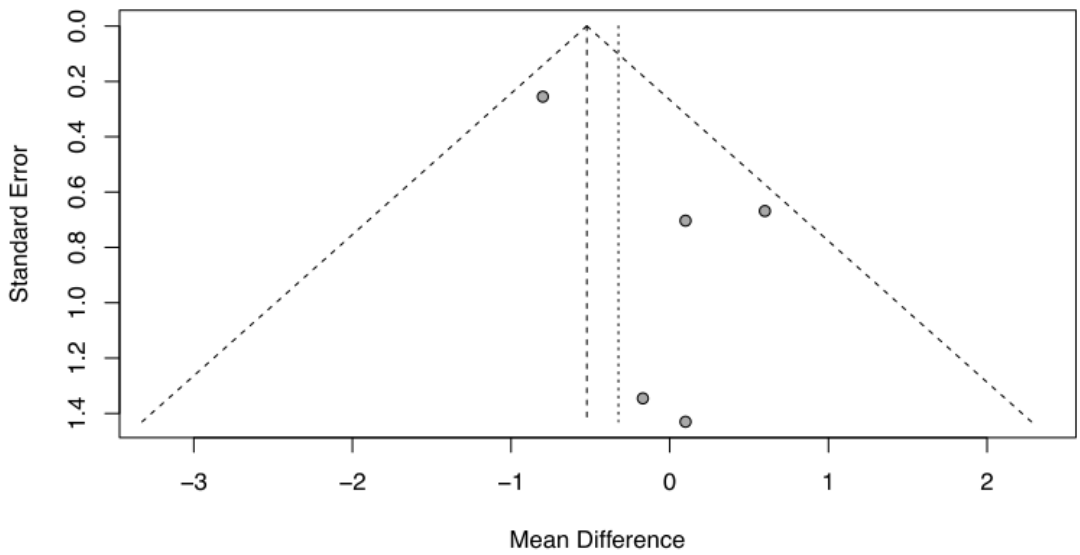
Produção relacionada ao trabalho:

1. Soares Falcetta, F., de Araújo Vianna Träsel, H., de Almeida, F.K. et al. Breast Cancer Res Treat (2018), Effects of physical exercise after treatment of early breast cancer: systematic review and meta-analysis. 170: 455. https://doi.org/10.1007/s10549-018-4786-y
2. De Almeida, F.K., De Jesus, R.G., Falcetta, F.S., Trasel, H.d.A.V., dos, Santos, F.X.S., de, Almeida, W.J., Staldschmidt, R., Barletta, D.V., Pereira-Lima, M.N. and Rosa, D.D. (2020). Brain imaging and treatment modality of central nervous system metastasis: A single-institution cohort. Breast J. doi: 10.1111/tbj.13650

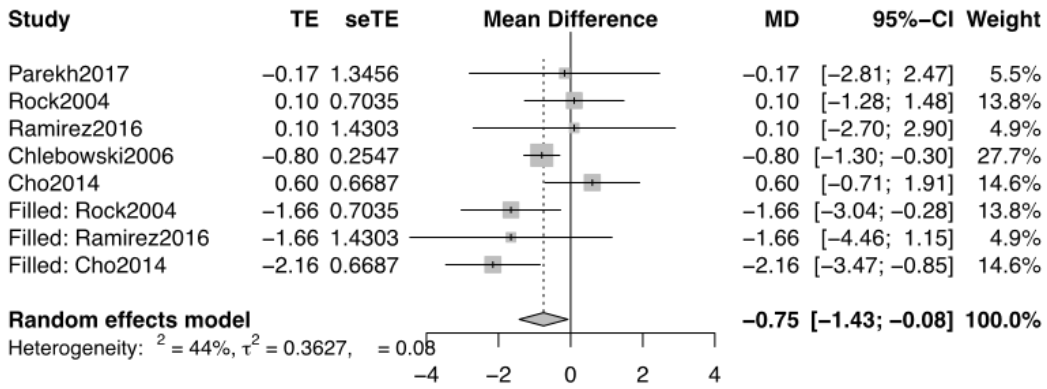
APÊNDICE

A. Material Suplementar

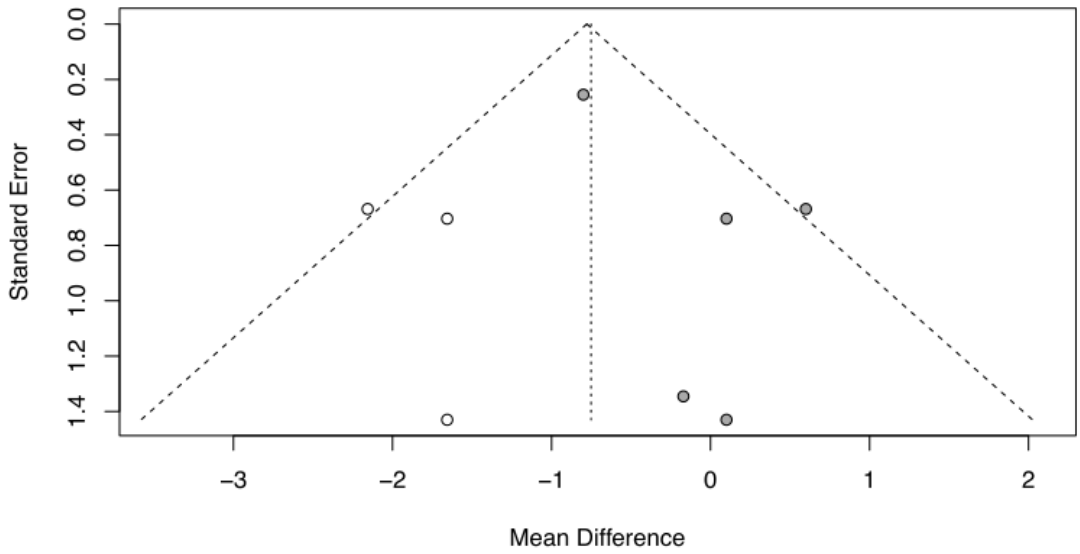
1. Funnel plot for BMI reduction



2. Forest plot of Trim-and-Fill for BMI reduction



3. Funnel plot of Trim-and-Fill for weight reduction



B. Estratégia Eletrônica Para Busca em Banco de Dados

CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees

#2 breast near cancer*

#3 breast near neoplasm*

#4 breast near carcinom*

#5 breast near tumour*

#6 breast near tumor*

#7 breast near malignan*

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 MeSH descriptor: [Health Behavior] explode all trees

#10 MeSH descriptor: [Health Promotion] explode all trees

#11 MeSH descriptor: [Exercise] explode all trees

#12 MeSH descriptor: [Exercise Therapy] explode all trees

#13 MeSH descriptor: [Sports] explode all trees

#14 MeSH descriptor: [Physical Fitness] explode all trees

#15 MeSH descriptor: [Diet Therapy] explode all trees

#16 MeSH descriptor: [Feeding Behavior] explode all trees

#17 MeSH descriptor: [Diet] explode all trees

#18 MeSH descriptor: [Physical Education and Training] explode all trees

#19 MeSH descriptor: [Life Style] explode all trees

#20 MeSH descriptor: [Health Education] explode all trees

#21 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 (lifestyl* or life styl*):ti,ab,kw

#23 (health* near (behav* or educ* or promot*)):ti,ab,kw

#24 (exercis* or physic* activit* or exert* or physic* fit* or sport*):ti,ab,kw

#25 (walk* or jog* or swim* or bicyc* or cycling or weight lift* or gymnastic or danc*):ti,ab,kw

#26 ((strength or resistance or circuit or enduran* or aerob* or physic* or fit*) next train*):ti,ab,kw

#27 (nutri* or diet*):ti,ab,kw

#28 #22 or #23 or #24 or #25 or #26 or #27

#29 #21 or #27

#30 #8 AND #29

MEDLINE (OVID)

#1 exp breast neoplasms/

#2 exp breast/

#3 breast.tw.

#4 2 or 3

#5 exp neoplasms/

#6 exp lymphedema/

#7 exp radiotherapy/

#8 or/5-7

#9 4 and 8

#10 (breast adj25 neoplasm$).tw,ot.

#11 (breast adj25 cancer$).tw,ot.

#12 (breast adj25 tumour$).tw,ot.

#13 (breast adj25 tumor$).tw,ot.

#14 (breast adj25 carcinoma$).tw,ot.

#15 (breast adj25 adenocarcinoma$).tw,ot.

#16 (breast adj25 ductal).tw,ot.

#17 (breast adj25 infiltrating).tw,ot.

#18 (breast adj25 lobular).tw,ot.

#19 (breast adj25 medullary).tw,ot.

#20 exp mammary neoplasms/

#21 (mammary adj25 neoplasm$).tw,ot.

#22 (mammary adj25 cancer$).tw,ot.

#23 (mammary adj25 tumour$).tw,ot.

#24 (mammary adj25 tumor$).tw,ot.

#25 (mammary adj25 carcinoma$).tw,ot.

#26 (mammary adj25 adenocarcinoma$).tw,ot.

#27 (mammary adj25 ductal).tw,ot.

#28 (mammary adj25 infiltrating).tw,ot.

#29 (mammary adj25 lobular).tw,ot.

#30 (mammary adj25 medullary).tw,ot.

#31 exp mastectomy/

#32 or/10-31

#33 1 or 9 or 32

#34 exp Health Behavior/

#35 exp Health Promotion/

#36 exp exercise/

#37 exp exercise therapy/

#38 exp Sports/

#39 exp Physical Fitness/

#40 exp Diet Therapy/

#41 exp Feeding Behavior/

#42 exp Diet/

#43 exp "Physical Education and Training"/

#44 exp Life Style/

#45 exp Health Education/

#46 (lifestyl$ or life styl$).tw,ot.

#47 (health$ adj6 (behav$ or educ$ or promot$)).tw,ot.

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#49 (walk$ or jog$ or swim$ or bicyc$ or cycling or weight lift$ or gymnastic or danc$).tw,ot.

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#51 (nutri$ or diet$).tw,ot.

#52 or/34-51

#53 Randomized Controlled Trials as Topic/

#54 randomized controlled trial/

#55 Random Allocation/

#56 Double Blind Method/

#57 Single Blind Method/

#58 clinical trial/

#59 clinical trial, phase i.pt

#60 clinical trial, phase ii.pt

#61 clinical trial, phase iii.pt

#62 clinical trial, phase iv.pt

#63 controlled clinical trial.pt

#64 randomized controlled trial.pt

#65 multicenter study.pt

#66 clinical trial.pt

#67 exp Clinical Trials as topic/

#68 (clinical adj trial$).tw

#69 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw

#70 PLACEBOS/

#71 placebo$.tw

#72 randomly allocated.tw

#73 (allocated adj2 random$).tw

#74 or/53-73

#75 case report.tw

#76 letter/

#77 historical article/

#78 or/75-77

#79 74 not 78

#80 33 and 52 and 79

EMBASE (OVID)

#1 exp breast neoplasms/

#2 exp breast/

#3 breast.tw.

#4 2 or 3

#5 exp neoplasms/

#6 exp lymphedema/

#7 exp radiotherapy/

#8 or/5-7

#9 4 and 8

#10 (breast adj25 neoplasm$).tw,ot.

#11 (breast adj25 cancer$).tw,ot.

#12 (breast adj25 tumour$).tw,ot.

#13 (breast adj25 tumor$).tw,ot.

#14 (breast adj25 carcinoma$).tw,ot.

#15 (breast adj25 adenocarcinoma$).tw,ot.

#16 (breast adj25 ductal).tw,ot.

#17 (breast adj25 infiltrating).tw,ot.

#18 (breast adj25 lobular).tw,ot.

#19 (breast adj25 medullary).tw,ot.

#20 exp mammary neoplasms/

#21 (mammary adj25 neoplasm$).tw,ot.

#22 (mammary adj25 cancer$).tw,ot.

#23 (mammary adj25 tumour$).tw,ot.

#24 (mammary adj25 tumor$).tw,ot.

#25 (mammary adj25 carcinoma$).tw,ot.

#26 (mammary adj25 adenocarcinoma$).tw,ot.

#27 (mammary adj25 ductal).tw,ot.

#28 (mammary adj25 infiltrating).tw,ot.

#29 (mammary adj25 lobular).tw,ot.

#30 (mammary adj25 medullary).tw,ot.

#31 exp mastectomy/

#32 or/10-31

#33 1 or 9 or 32

#34 exp Health Behavior/

#35 exp Health Promotion/

#36 exp Exertion/

#37 exp exercise/

#38 exp exercise therapy/

#39 exp Sports/

#40 exp Physical Fitness/

#41 exp Diet Therapy/

#42 exp Feeding Behavior/

#43 exp Diet/

#44 exp "Physical Education and Training"/

#45 exp Life Style/

#46 exp Health Education/

#47 (lifestyl$ or life styl$).tw,ot.

#48 (health$ adj6 (behav$ or educ$ or promot$)).tw,ot.

#49 (exercis$ or physic$ activit$ or exert$ or physic$ fit$ or sport$).tw,ot.

#50 (walk$ or jog$ or swim$ or bicyc$ or cycling or weight lift$ or gymnastic or danc$).tw,ot.

#51 ((strength or resistance or circuit or enduran$ or aerob$ or physic$ or fit$) adj6 train$).tw,ot.

#52 (nutri$ or diet$).tw,ot.

#53 or/34-52

#54 Clinical trial/

#55 Randomized controlled trial/

#56 Randomization/

#57 Single blind procedure/

#58 Double blind procedure/

#59 Crossover procedure/

#60 Placebo/

#61 Randomi?ed controlled trial$.tw.

#62 Rct.tw.

#63 Random allocation.tw.

#64 Randomly allocated.tw.

#65 Allocated randomly.tw.

#66 (allocated adj2 random).tw.

#67 Single blind$.tw.

#68 Double blind$.tw.

#69 ((treble or triple) adj (blind$)).tw.

#70 Placebo$.tw.

#71 Prospective study/

#72 Or/54-71

#73 Case study/

#74 Case report.tw.

#75 Abstract report/

#76 letter/

#77 Or/73-76

#78 72 not 77

#79 32 and 53 and 78

C. Artigos Publicados

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-018-4786-y

REVIEW

Effects of physical exercise after treatment of early breast cancer: systematic review and meta-analysis

Frederico Soares Falcetta[1] · Henrique de Araújo Vianna Träsel[1] · Fernando Kude de Almeida[1] · Mariana Rangel Ribeiro Falcetta[2] · Maicon Falavigna[2] · Daniela Dornelles Rosa[1,3]

Received: 27 January 2018 / Accepted: 9 April 2018

Abstract

Purpose Randomized clinical trials are inconclusive regarding the role of physical exercise in anthropometric measurements, quality of life, and survival in breast cancer patients. Our aim was to conduct a systematic review and meta-analysis to assess the effects of physical exercise on these outcomes in women who went through curative treatment of early-stage breast cancer.

Methods Pubmed, Embase, Cochrane Library were searched for randomized clinical trial comparing physical exercise (counseling or structured programs with supervised/individualized exercise sessions) with usual care in women that went through for breast cancer treatment. Primary outcomes were overall survival and disease-free survival, while secondary outcomes were weight loss, body mass index, waist–hip ratio, percentage of body fat, and quality of life.

Results We found 60 randomized clinical trials, only one of them showed mortality data; the HR for mortality was 0.45 (95% CI 0.21–0.97) for the intervention group when compared to the control group. Physical exercise was associated with weight reduction (− 1.36 kg, 95% CI − 2.51 to − 0.21, $p = 0.02$), lower body mass index (− 0.89 kg/m^2, 95% CI − 1.50 to − 0.28, $p < 0.01$), and lower percentage of body fat (− 1.60 percentage points, 95% CI − 2.31 to − 0.88, $p < 0.01$). There was an increase in the quality of life (standardized mean difference of 0.45, 95% CI 0.20–0.69, $p < 0.01$).

Conclusions The articles found had heterogeneous types of intervention, but they showed significant effects on anthropometric measures and quality of life. Among them, only one study had mortality as outcome and it showed physical exercise as a protective intervention. Despite these findings, publication bias and poor methodological quality were presented. Physical exercise should be advised for breast cancer survivors since it has no adverse effects and can improve anthropometrics measures and quality of life. PROSPERO registry: CRD42014008743.

Keywords Breast cancer · Meta-analysis · Physical exercise · Quality of life

Introduction

Breast cancer is the most common malignant neoplasm among women in much of the world, even in more developed countries, when cases of non-melanoma skin cancer are excluded. Incidence and mortality make breast cancer a very important health problem. This is associated with the fact that the majority of newly diagnosed cases are in early stages, which are highly curable with surgical and adjuvant treatment. This is the result of significant advances in the diagnosis and treatment of the disease. At the same time, high rates of cure lead to a growing contingent of women survivors of breast cancer [1]. This is a population with different medical and social needs, to which the different health systems are neither trained nor prepared to attend [2]. Caring

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-4786-y) contains supplementary material, which is available to authorized users.

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for breast cancer survivors is therefore a matter of growing importance for health professionals.

Obesity is also a growing problem that requires attention from multiple healthcare professionals. There is evidence that obese women and women who gain weight after breast cancer diagnosis have twice the risk of recurrence and death from breast cancer in 5 years and 60% higher risk of death over 10 years, when compared to women normal weight [3, 4]. More than half of women diagnosed with breast cancer experience an increase in body weight associated with menopause and related to chemotherapy and hormonal treatment [5]. In this setting, regular physical activity can help control body weight and has already been shown to reduce the risk of breast cancer [6, 7]. Recent studies suggest that physical activity can also halve the risk of death in patients with breast cancer [8]. The Nurses' Health Study, one of the largest cohorts in the field, showed that physically active women (from 2987 patients with early breast cancer) had half the risk of recurrence and death when compared to sedentary women [8].

Unlike studies involving chemotherapeutic treatments, physical exercise studies are consistently smaller, with shorter follow-up and different assessments regarding the type of physical exercises whether aerobic or strength exercises. In addition, the existing randomized clinical trials were inconclusive regarding the role of this intervention in anthropometric measurements or quality-of-life outcomes [9].

In this study, we aim to conduct a systematic review and meta-analysis to assess the effects of physical exercise (with or without dietary interventions) in body composition, quality of life, and survival in women after treatment of early-stage breast cancer.

Methods

Protocol and registration

We conducted this systematic review and meta-analysis using a previously published protocol [10] (PROSPERO registry number CRD42014008743) for the research question related to physical activity. We conducted this systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions [11] and reported the manuscript according to PRISMA recommendations [12].

Data sources and searches

The following electronic databases were used to evaluate the indexed literature: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. We conducted the electronic search and up to July 2017; it was limited to papers in English (see Supplementary Material). We have also searched gray literature in annals of major meetings and ongoing studies at ClinicalTrials.gov.

Study selection

We included randomized trials that evaluated physical exercise interventions (counseling or structured programs with supervised/individualized exercise sessions). The intervention should have been compared with usual care in women treated for stage I–III breast cancer. We included studies that performed the intervention after the end of adjuvant treatment (excluding hormone therapy) and excluded studies that applied the intervention after 5 years from the diagnosis.

The following primary outcomes were considered in the evaluation of the studies: overall survival and disease-free survival (5 years after treatment or until the maximum follow-up study). The secondary endpoints were weight loss (kg), BMI (kg/m^2), waist–hip ratio, percentage body fat (%), and quality of life. Adverse events, such as exercise-induced lesions, were also been considered.

The evaluation of titles and abstracts for potentially eligible studies was conducted in paired and independently. Inclusion and data extraction were conducted for the full texts in the same manner, using a standardized form. Disagreement was solved through discussion.

Data extraction

The data used for meta-analysis and comparison between usual care and intervention were the final values of the groups after the intervention, since these were the data most frequently found. This method was used to minimize the number of errors and minimize the need for imputations. In the studies that presented only the values of the difference between final results and initial results, the final values were calculated from a simple sum of the variation with the initial value. In this case, the values of the standard deviations used were the same as the initial values of the variables. We preferred the EORTC QLQ-C30 quality-of-life score, since this was the most frequently used instrument among the studies. For studies such as Harrigan 2016 [13], Demark-Wahnefried 2014 [14], and Vallance 2007 [15] with two or more intervention groups, the data from all intervention groups were combined into a single group. Finally, some values of standard deviation of the quality-of-life data were not described by the authors in their works (Herrero 2006 [16], Lee 2014 [17], Heim 2007 [18], Rogers 2009 [19], Baruth 2015 [20] and Fields 2016 [21]); in these cases, the standard deviation was used as a weighted mean of the other studies that used the same scale.

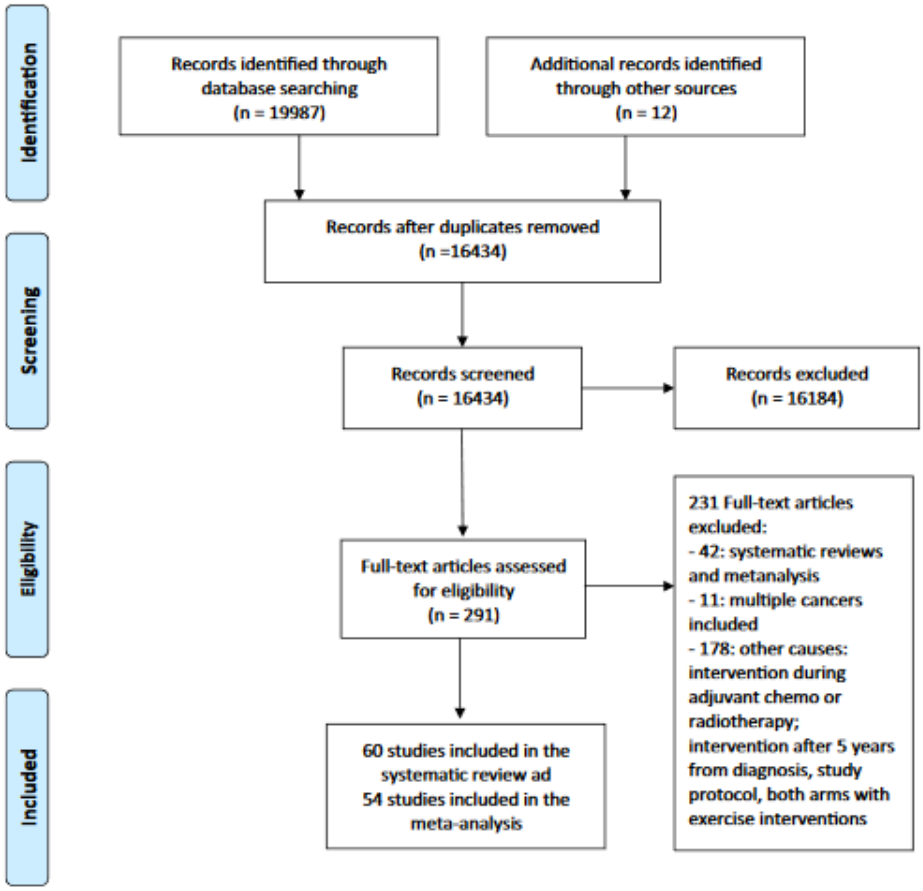

Fig. 1 Prisma flow diagram

Quality assessment

We also carried out a paired methodological quality evaluation of the individual studies, according to the Cochrane Handbook of Systematic Reviews [11] using the Cochrane risk of bias tool. Disagreement was solved through discussion. The overall quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [22], and verified by a third reviewer. The quality of evidence was classified as 'high,' 'moderate,' 'low,' or 'very low.'

Data synthesis and analysis

The data were combined using the random-effect meta-analysis model, with DerSimonian–Laird estimator as variance estimator. We estimated the treatment effect using the mean difference (MD) as summary measure for continuous outcomes. For continuous outcomes presented in different scales, we used the standardized mean difference (SMD). Data were presented with 95% confidence intervals (CI). All analyzes were performed using software R, version 3.3.2, *meta* packages version 4.8-4.

Statistical heterogeneity was assessed in each meta-analysis using the statistics I^2. Heterogeneity was considered substantial if the I^2 was greater than 50%. Heterogeneity was explored through subgroup analysis. We assessed publication bias using funnel plot and the Egger test. A significant publication bias was considered if $p < 0.10$. We estimated the effect of publication bias on the interpretation of results by a trim-and-fill computation.

Results

Literature search

In total, 19,987 titles were located, of which 3553 were duplicates. In the review of titles and abstracts 16,434 studies were excluded 291 were fully read for assessment

Table 1 Characteristics of the included studies

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Anderson 2015 (Australia) [27]	12-Week program instructions and healthy lifestyle readings, with a book containing weekly exercise planning and special parts to record data on diet, aerobic exercise, strength exercises, pelvic floor exercises, weight, waist circumference, and climacteric symptoms and diary supply to help participants achieve their goals	3	3	51	48.9
Baruth 2015 (USA) [20]	Home walking program for 12 weeks. First a face-to-face orientation session on exercise and week 1, 2, 4, and 10-week guidelines	3	3	32	56.7
Cadmus 2009 (USA) [28]	Supervised exercises 3×/week plus exercises on their own 2×/week; heart rate monitoring during sessions with a goal of maintaining between 60 and 80% of the expected maximum frequency	6	6	75	56.0
Campbell 2017 (Canada) [29]	150 min per week of aerobic activity (moderate to vigorous): two 45-min sessions at a research facility gym and 2 30-min sessions of unsupervised exercise of patient preference	6	6	19	52.6
Casla 2015 (Spain) [30]	Exercise program consisted of supervised exercise sessions twice a week (aerobic + resistance) with progressive increase of intensity. Patients also received nutritional guidance	3	3	94	47.9
Courneya 2003 (Canada) [31]	Training 3×/week on ergonomic bikes for 15 weeks. Duration of training gradually increased and intensity was adjusted according to the ventilatory equivalent for carbon dioxide	3.75	3.75	52	58.7
Daley 2007 (UK) [32]	Moderate-intensity exercises 3×/week for 8 weeks lasting 50 min under the supervision of a specialist	2	2	72	51.4
De Luca 2016 (Italy) [33]	Two weekly sessions of 90 min, corresponding to 10 min of warm-up (onset) and cooling (final) followed by 40 min of resistance exercise followed by 30 min of aerobic exercise for 24 weeks. The exercises were progressive during the protocol	6	6	20	48.8

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Demark-Wahnefried 2014 (USA) [14]	Individualized books with guidelines for weight loss and dietary changes followed by six leaflets over a year. Patients in the two intervention groups received individualized information or individualized information plus information about other participants in the group	12	12	68	61.3
Demark-Wahnenfried 2015 (USA) [34]	Physical exercise group sessions of 1 h/week for 4 months, then sessions of 15/15 days and then monthly for 1 year, as well as telephone and e-mail between sessions. They also received dietary information on diet to physical exercise	12	24	692	56.1
Do 2015 (South Korea) [35]	Heating, aerobic exercise, strength exercise, core stability exercise, and cooling 5×/week for 4 weeks under the supervision of a physical therapist	1	1	62	47.5
Duijts 2012 (Netherlands) [36]	Unsupervised exercises, at home, lasting 2.5–3 h per week for 12 weeks aiming to achieve 60–80% Karvonen (Max heart rate equivalent). Physiotherapist assisted the patient to choose the most appropriate exercise modality (bicycle, running, swimming)	3	6	207	47.7
Fairey 2003 (Canada) [37]	Treadmill 3×/week in ergometers at a VO2 of 70–75%. Exercise started for 15 min in the first 3 weeks and progressed in 5 min every 3 weeks to 35 min	3.75	3.75	52	58.7
Fields 2016 (UK) [21]	Nordic walks (two-stick walk) supervised by the first ones for 12 weeks. Exercise was a group under supervision at weeks 1–6 with gradual increase in frequency, in weeks 7–12 the patients were instructed to perform 4 sessions of 30 min per week on their own	3	3	40	62.0
Fillion 2008 (Canada) [38]	Supervised walk for 1 h associated with management sessions for fatigue symptoms once a week for 4 weeks. Patients were given a heart monitor (Polar) to receive objective feedback from walking	1	4	87	52.7
Galiano-Castillo 2016 (Spain) [39]	Three sessions of 90 min per week on non-consecutive days for 8 weeks. Exercises consisted of an aerobic part and a part of resistance	2	6	81	48.0

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Ghavami 2017 (Turkey) [40]	Moderate-intensity aerobic exercise sessions under supervision 3–5 days per week throughout 24 weeks. Each session comprised a 10-min light aerobic exercise and a gentle range of motion exercises (warm-up period), followed by 30 min of aerobic exercise at an intensity of 70–85% of maximum heart rate and a reduction of caloric intake to 600 kcal below calculated energy requirements	6	6	80	49
Giallauria 2015 (Italy) [41]	Aerobic training with treadmill or bicycle 3×/week for 3 months and after 1×/week for another 9 months; patients also received information leaflets on exercise, diet, and weight loss with a goal of performing exercises for 210 min per week. Patients also participated in feeding classes and meetings	12	12	51	52.5
Goodwin 2014 (USA, Canada) [42]	Patients received in the whole 19 connections over 24 months with guidelines on reduction of caloric intake, weight loss, increase in the amount of vegetables and fruits consumed, and reduction in fats; goal of gradual increase in the practice of aerobic physical exercises to a goal of 150–200 min per week; between 30 and 60 min	24	24	338	61.2
Greenlee 2013 (USA) [43]	Patients were enrolled in a physical training center where they were recommended to attend 5×/week; strength and aerobic exercises for 15–30 min per session; also received dietary recommendations in a nutrition course	6	12	42	51.3
Guinan 2013 (Ireland) [44]	Aerobic exercises (biking, treadmill, rowing) supervised 2×/week + exercises at home up to 5×/week. Lesson duration and intensity increased every two weeks	2	3	26	48.7
Hagstrom 2016 (Australia) [45]	Resistance training 3×/week for 60 min for 16 weeks; movements with the use of machines in the first 8 weeks and movements without weights in the last 8 weeks	4	4	39	51.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Harrigan 2016 (USA) [13]	Counseling by telephone [1] or live [2] focusing on weight loss: reduced caloric intake and moderate-intensity exercise for 150 min/week; also received a book on the LEAN method of weight loss. Weekly meetings in the first month; biweekly in the second and third months; monthly thereafter	6	6	66	58.6
Hayes 2017 (Australia, New Zealand) [23]	Described as a translational exercise intervention delivered either face-to-face or over the telephone	8	101	337	Not described
Heim 2007 (Germany) [18]	Brochure and guidelines on stretching and muscle exercises; instructions for aerobic (walking), coordination, and relaxation	During rehabilitation	3 months after finishing rehabilitation	63	Not described
Herrero 2006 (Spain) [16]	Three weekly sessions of 90 min with endurance and aerobic exercises	2	2	20	50.3
Irwin 2009 (USA) [46]	Supervised aerobic exercise 3×/week plus home exercise 2×/week; duration of 15–30 min according to tolerance; mode of exercise of the patient's preference	6	6	75	56.0
Irwin 2013 (USA) [47]	Supervised aerobic and strength exercises 2×/week plus home exercises for 150 min/week. Intensity of the exercise was adjusted according to heart rate	12	12	121	61.5
Karimi 2013 (Iran) [48]	Aquatic aerobic exercises 4×/week lasting 40–80 min per session	1.5	1.5	20	Not described
Kim 2011 (South Korea) [49]	Patients received counseling by phone, book, and a prescription of diet and exercise. The goal was to perform exercises 5×/week for at least 30 min	3	6	45	45.4
Kim 2017 (South Korea) [50]	Three times a week of warm-up consisting whole body stretching and flexibility exercises for 10 min followed by step aerobics for 20 min followed by the strength training using body weight and elastic bands for 20 min. The exercise intensity and the resistance of elastic band were progressively increased. At the end of the session, subjects performed cool-down involving easy walking and stretching exercises for 10 min	3	3	24	52

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Kwiatkowski 2013 (France) [51]	Admission to a SPA for 2 weeks, where 2 h of physical activity (strength, resistance, elasticity, and water aerobics) were performed daily. They also received baths, massages, prepared diet, and esthetic care	0.5	12	222	52.0
Lahart 2016 (UK) [52]	Stimulating exercise; phone call at the end of the first, second, and third month to maintain exercise; leaflet by mail at the end of the fourth and the fifth month with encouragement to practice. Order to maintain the practice of exercises 3–5×/week for 30 min at least. Patients also received a brochure with information and a DVD.	6	6	80	53.2
Lee 2014 (South Korea) [17]	Self-management web-based exercise and diet program. The intervention incorporates strategies of transtheoretical model as stage of change, process of change, balance of decision, or self-efficiency	3	3	59	42.1
Ligibel 2008 (USA) [53]	Strength and cardiovascular training at home for 16 weeks. Two weekly training sessions of 50 min supervised strength + 1 cardiovascular training of 90 min weekly at home	4	4	100	52.3
Matthews 2007 (USA) [54]	Guided home walks on a 30-min visit, followed by short phone calls after 1, 2, 4, 7, and 10 weeks. Hiking in the first 4 weeks 3×/week (20–30 min/session); at weeks 5–7, 4×/week (30–40 min/session); in the last 5 weeks, 5×/week (30–40 min/session) at moderate intensity	3	3	36	52.9
Mefferd 2007 (USA) [55]	Cognitive-behavioral group therapy, physical activity, and dietary guidelines. Physical activity: promotion and encouragement of daily aerobic exercises, with progression of time and intensity. Strength exercises 2–3× per week. Providing a pedometer to encourage and record physical activity on a daily basis	4	4	76	56.3
Milne 2008 (Australia) [56]	3 times per week supervised physical activity sessions in rehabilitation clinic. The program contains aerobic/cardiovascular and endurance, as well as stretching	3	6	58	55.2

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Nuri 2012 (Iran) [57]	Supervised walking program for two times per week in a time-progressive duration protocol plus 60 min resistance training during the 15 weeks of intervention	3.75	3.75	29	58.3
Nyrop 2017 (USA) [26]	Participants were asked to walk on their own or with others at a pace that was safe, comfortable, and sustainable for 150 min per week	1.5	1.2	29	63.8
Ohira 2006 (USA) [58]	Supervised strength and resistance training exercises using resistance machines and free weights for thorax muscles, back, shoulders, and arms as well as the buttocks, hips, and thighs. In addition, participants were taught stretching exercises to perform before and after each weight training session	6	6	81	53.1
Pakiz 2011 (USA) [59]	Cognitive-behavioral therapy based on 24 group sessions for weight loss. Weekly for 4 months and monthly up to 12 months. Aim to promote regular physical activity and reduce caloric intake to facilitate weight loss	4	4	68	56.0
Pinto 2005 (USA) [60]	Participants received instructions on how to exercise at moderate intensity, heart rate monitoring, and how to perform warm-up and cooling after exercise. Received pedometer and exercise table. Oriented to exercise for at least 10 min 2× per week, with gradual increase up to 30 min 5× per week at the end of 12 weeks. Weekly phone calls from the team to monitor. They received weekly workout tips	3	9	86	53.2
Rahnama 2010 (Iran) [61]	60 min of resistance exercise (weight lifting) 2× in the week + walks (minimum time 25 min) 2× in the week (alternate days)	3.75	3.75	29	Not described
Reeves 2017 (Australia, USA) [62]	Participants received detailed workbook of lifestyle recommendations, monitoring diary, digital scales, calorie count book, and 16 phone calls (by lifestyle coaches, nutritionists specializing in motivation for physical training), calorie deficit diet of 2000 kJ, orientation for increase walks to at least 30 min/day, and a pedometer	6.5	6	90	55.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Rock 2015 (USA) [63]	Weekly meetings of 1 h in the first 4 months, then every 15 days for another 2 months and after monthly; in the meetings were taught exercises and provided guidance as to achievement. Orientation of 60 min/day. Diet recommendation with caloric deficit of 500–1000 kcal	24	24	692	56.0
Rogers 2009 (USA) [19]	Goal of reaching 150 min of moderate-intensity walking per week. Participants attended 6 group sessions for time management, importance of physical activity, and behavioral change and goals. They also attended 12 supervised exercise sessions and 3 session sessions with exercise specialists	3	3	41	52.7
Roveda 2016 (Italy) [64]	A program conducted by 2 sport therapy experts and included 2 sessions of 1-h brisk walking per week for 3 months	3	3	40	56.8
Saarto 2012 (Finland) [65]	Supervised on-site training and home-based exercise counseling. The supervised training was 1×/week, with up to 15 individuals and was performed circuit training and aerobic with walking, with progressive intensity. The home part could be walks, Nordic walks, step exercises or jump (patient preference), oriented to perform preferably 3×/week and at least 2×/week	12	12	473	52.3
Schmitz 2005 (USA) [66]	In the first 3 months of intervention: supervised exercises with trainer enabled in groups of maximum 4 people. In the other 3 months, participants were encouraged to continue performing physical activity on their own	6	12	81	53.1
Scott 2013 (UK) [67]	Three sessions per week supervised 30 min of aerobic exercise plus 10–15 min of muscle strengthening, using free weight. In addition, consultation with nutritionist for a caloric deficit of 600 kcal/day	6	6	90	55.7
Sheppard 2016 (USA) [68]	Supervised 30-min physical activity group sessions and 60 min educational sessions every 2 weeks comprising. On weeks when participants did not meet as a group they had individual telephone coaching sessions led by a trained survivor coach.	3	3	22	54.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Shobeiri 2016 (Iran) [69]	Exercises of 40–60 min 2× per week for 10 weeks involving the HEATING (5–10 min walk slow and moderate stretching), moderate aerobic exercise (15 min of slow walking, stretching, and specific movements of the arms and shoulders), and 5 min of cooling down (slow walk). Increase of 2% of aerobic exercise time each week, resulting in 35 min in the tenth week	2.5	2.5	53	43.0
Speck 2010 (USA) [70]	Group instructions 2×/week for 90 min for 13 weeks followed by a further 13 weeks of 2×/week exercises without supervision. Sessions included stretching, cardiovascular warm-up, abdominal and back strengthening exercises, and weight lifting	12	12	234	56.5
Sturgeon 2016 (USA) [71]	The exercise component required 160 min/week of exercise (3 days/week of progressive resistance exercise, 2 days/week of interval aerobic exercise, and 1 day/week of active recovery aerobic exercise)	12	12	35	46.1
Swisher 2015 (USA) [72]	Supervised exercise of moderate intensity for 3×/week in physical activity environment and other 2×/week in home environment without supervision. Consultation with nutritionist with dietary guidelines of caloric reduction	3	3	28	53.7
Thomas 2017 (USA) [73]	Twice-weekly supervised resistance training (total body program for the lower and upper extremities) and 150 min of moderate-intensity aerobic at home (brisk walking on a treadmill or outside, but cycle ergometers and elliptical trainers were permitted). Exercise started at 50% of predicted maximal heart rate (220-age) and was gradually increased to approximately 60–80% of predicted maximal heart rate (verified by heart rate monitors)	12	12	121	61.2
Tirado-Gomez 2015 (Spain) [74]	Study of three groups in which one received written materials adapted to the culture of the patient with orientation of physical exercise, another group receiving materials not adapted to their culture and a placebo group	4	4	38	58.0

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Vallance 2007 (Canada) [15]	The participants received a standard public health recommendation for physical activity (PA), previously developed breast cancer-specific PA print materials, a step pedometer, or a combination of breast cancer-specific print materials and step pedometers	3	3	190	57.0
Winters-Stone 2013 (USA) [75]	Participants received supervised classes (30–60/min) 2 days/week and were instructed to repeat at home 1×/week for 12 months. The intervention group performed resistance activities with weights (shin guards and weight vests, dumbbell, kettlebell, barbells) with 8–15× repetition orientation and modulation of weight depending on individual capacity	12	12	71	46.6

of eligibility. After that, 169 studies were excluded, and 60 studies entered the phase of data extraction, of those *54 studies provided quantitative data for meta-analysis*. The flowchart of the search is presented in Fig. 1, and the initial characteristics of the studies are presented in Table 1.

Study characteristics

The total number of patients in all of the studies was 6303. The follow-up ranged from 1 to 101 months and the duration of the intervention ranged from 4 weeks to 24 months. The mean age of the patients across the trials was 47.4 years, and the time from breast cancer surgery or from finishing the adjuvant treatment to intervention ranged from 1 month to 4 years. We found multiple types of physical exercise interventions but the most frequent modality was structured or individualized programs (found in 41 trials).

Outcomes

We found only one trial that reported disease-free survival in an abstract. This was an Australian trial that randomized 337 women 6 weeks after surgery for breast cancer to 8 months of physical exercise counseling (either in person or by telephone) or to usual care. After a follow-up of 101 months, the HR for overall survival in the intervention groups compared to placebo was 0.45 (95% CI 0.21–0.97); there was no difference in disease-free survival between the groups (HR 0.66 [95% CI 0.38–1.17]). Despite not establishing causality, the study suggests the potential of physical activity to influence survival.

For the secondary outcomes we found that physical exercise interventions, whether by orientation or by structured programs, promote statistically significant weight reduction in breast cancer patients (−1.36 kg; 95% CI −2.51 to −0.21; $p=0.02$; $I^2=17\%$; very low quality of evidence) (Fig. 2) and BMI reduction (−0.89; CI 95% −1.50 to −0.28; $p<0.01$; $I^2=51\%$; low quality of evidence) especially for the diet and exercise counseling group (Fig. 3). Physical exercise also showed a statistically significant decrease of −1.60 in body fat percentage points (95% CI −2.31 to −0.88; $p<0.01$; $I^2=28\%$; low quality of evidence) especially in the structured or individualized exercise program (Fig. 4).

The overall quality of life was significantly modified by physical exercise interventions showing a standardized mean difference of 0.45 (95% CI 0.20–0.69, $p<0.01$; $I^2=83\%$; very low quality of evidence) (Fig. 5). The same can be said about the effect on the physical domain of quality

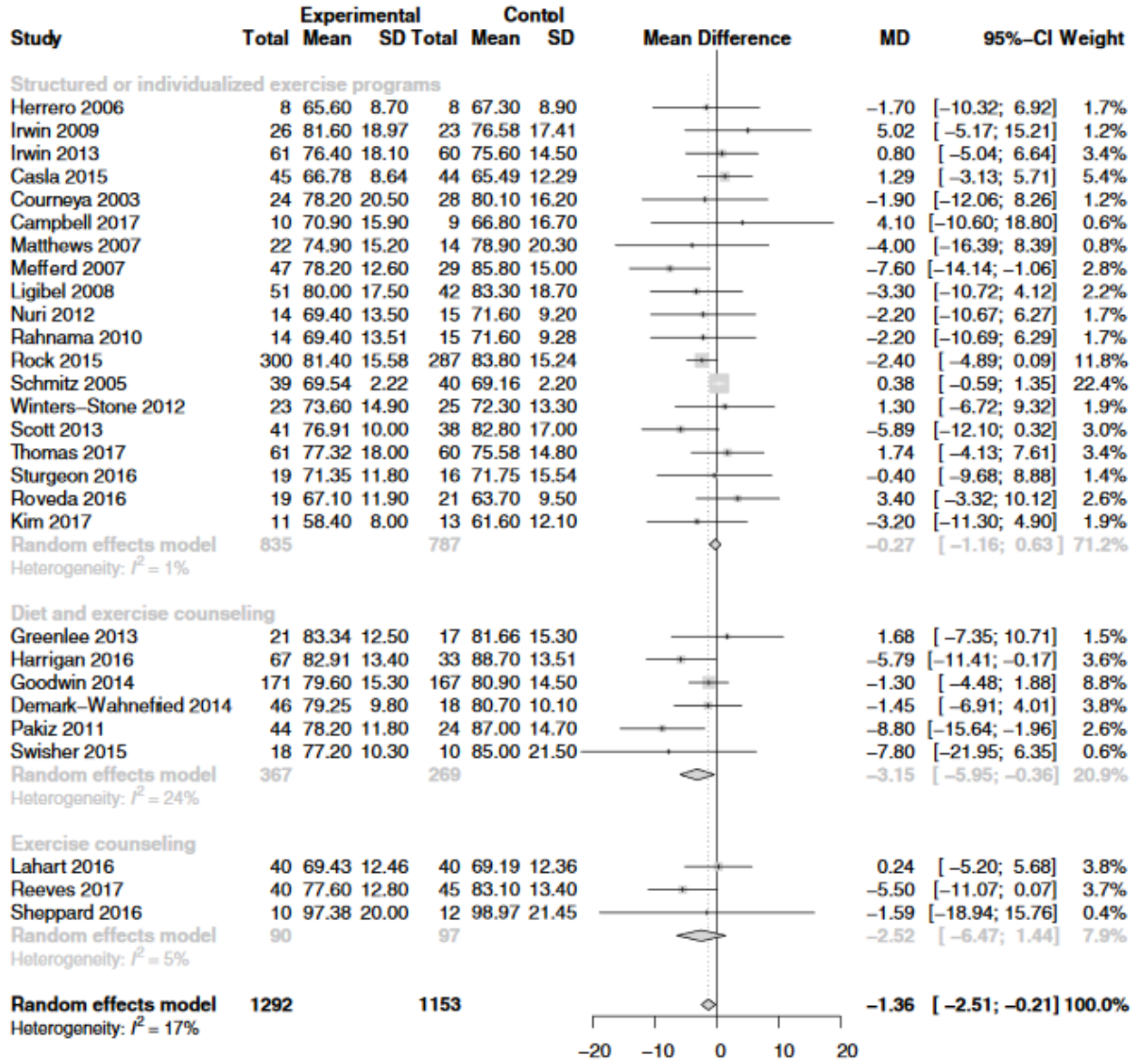

Fig. 2 Forest plot for weight reduction

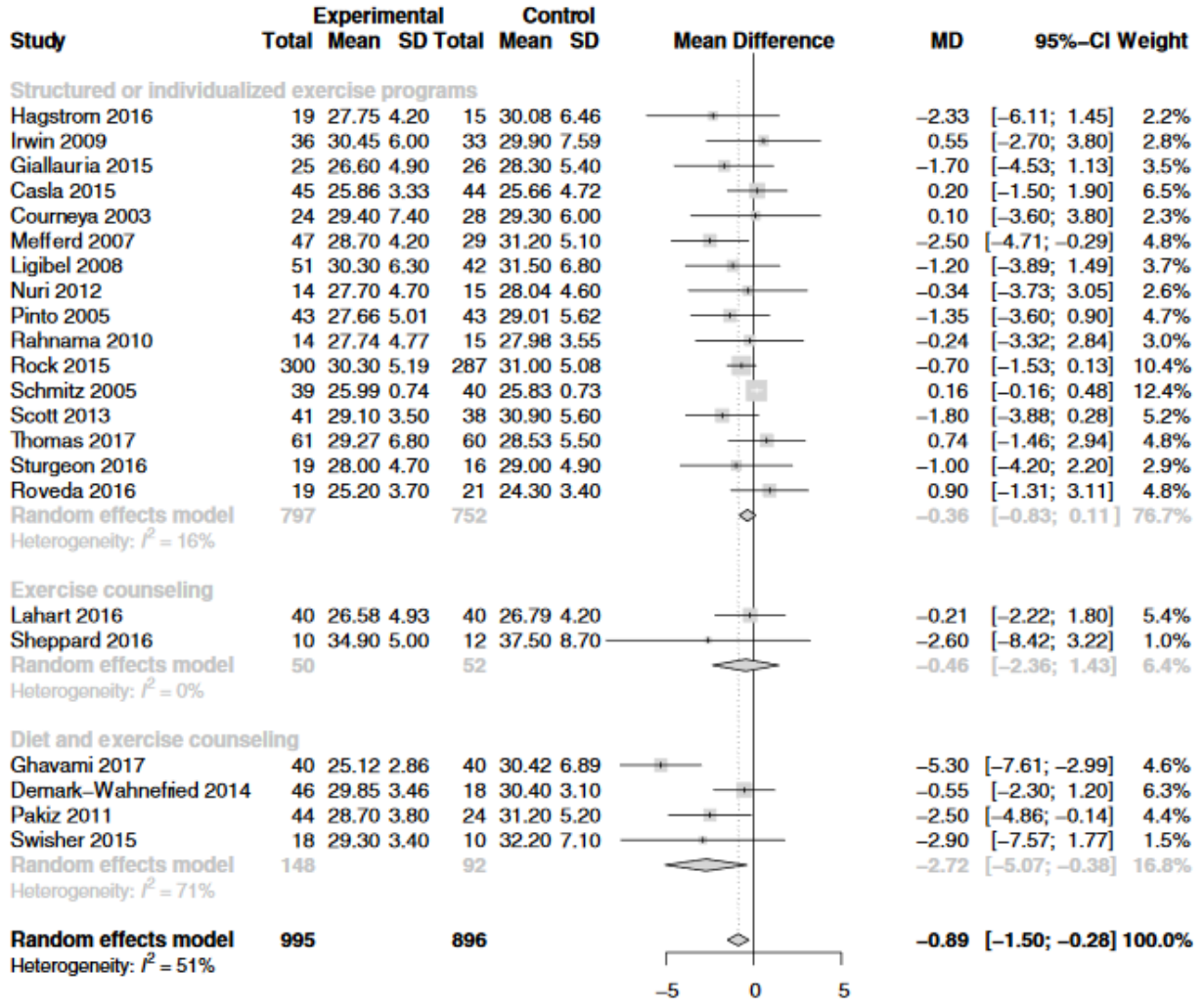

Fig. 3 Forest plot for BMI reduction

of life, showing a standardized mean difference of 0.51 (95% CI 0.23–0.79; $p<0.01$; $I^2=86\%$; very low quality of evidence) (Supplementary Material) and the mental domain, showing a standardized mean difference of 0.28 (95% CI 0.06–0.50; $p=0.013$; $I^2=71\%$; very low quality of evidence) in favor of the intervention groups (Supplementary Material). No significant effect of physical exercise could be seen on HOMA-IR (−0.03; 95% CI −0.20 to 0.13; $p=0.68$) (see Supplementary Material).

We performed subgroup analysis for all the anthropometric outcomes according to type of intervention and for the different quality-of-life scales (as seen in Figs. 2, 3, 4, 5, and

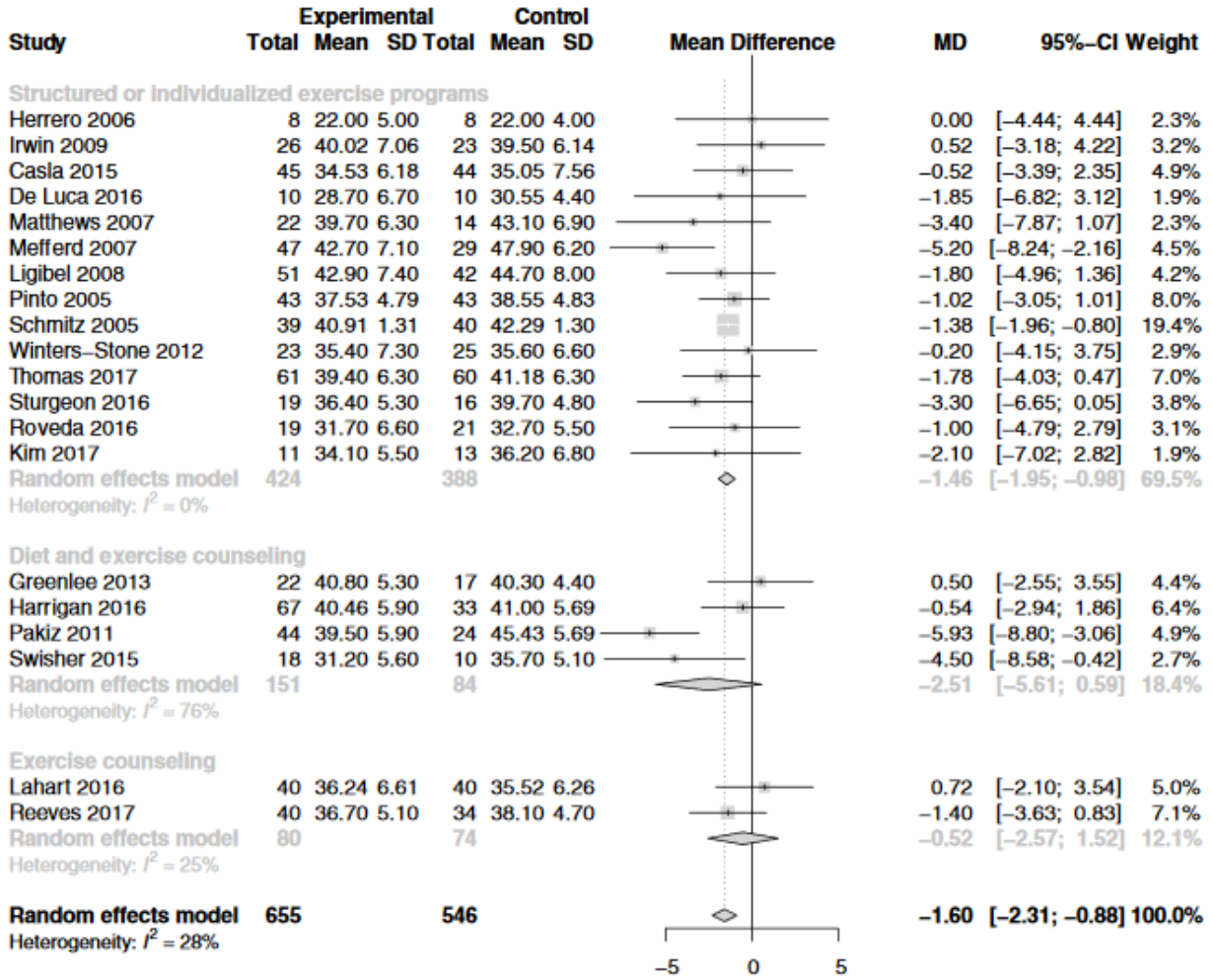

Fig. 4 Forest plot for fat percentage reduction

in the Supplementary Material). Meta-regression analysis showed no association between duration of intervention and all outcomes.

The Egger test showed significant publication bias for all outcomes, except for fat percentage reduction or the mental domain of quality of life. Funnel plots for all the outcomes can be seen in the Supplementary Material. Trim-and-fill computation resulted in loss of statistical significance when publication bias was corrected. After this correction, the effect of the intervention on weight was −0.18 (95% CI −1.52 to 1.15), on BMI was −0.04 (95% CI −0.67 to 0.60), on the general quality of life was 0.08 (95% CI −0.2 to 0.36), and on physical quality of life was 0.09 (95% CI −0.22 to 0.40).

Quality evaluation

The risk of bias according to Cochrane risk of bias tool is presented in Figs. 6 and 7. Serious methodological flaws were found such as poor randomization methods and poor outcome assessments. Noteworthy, most of the studies

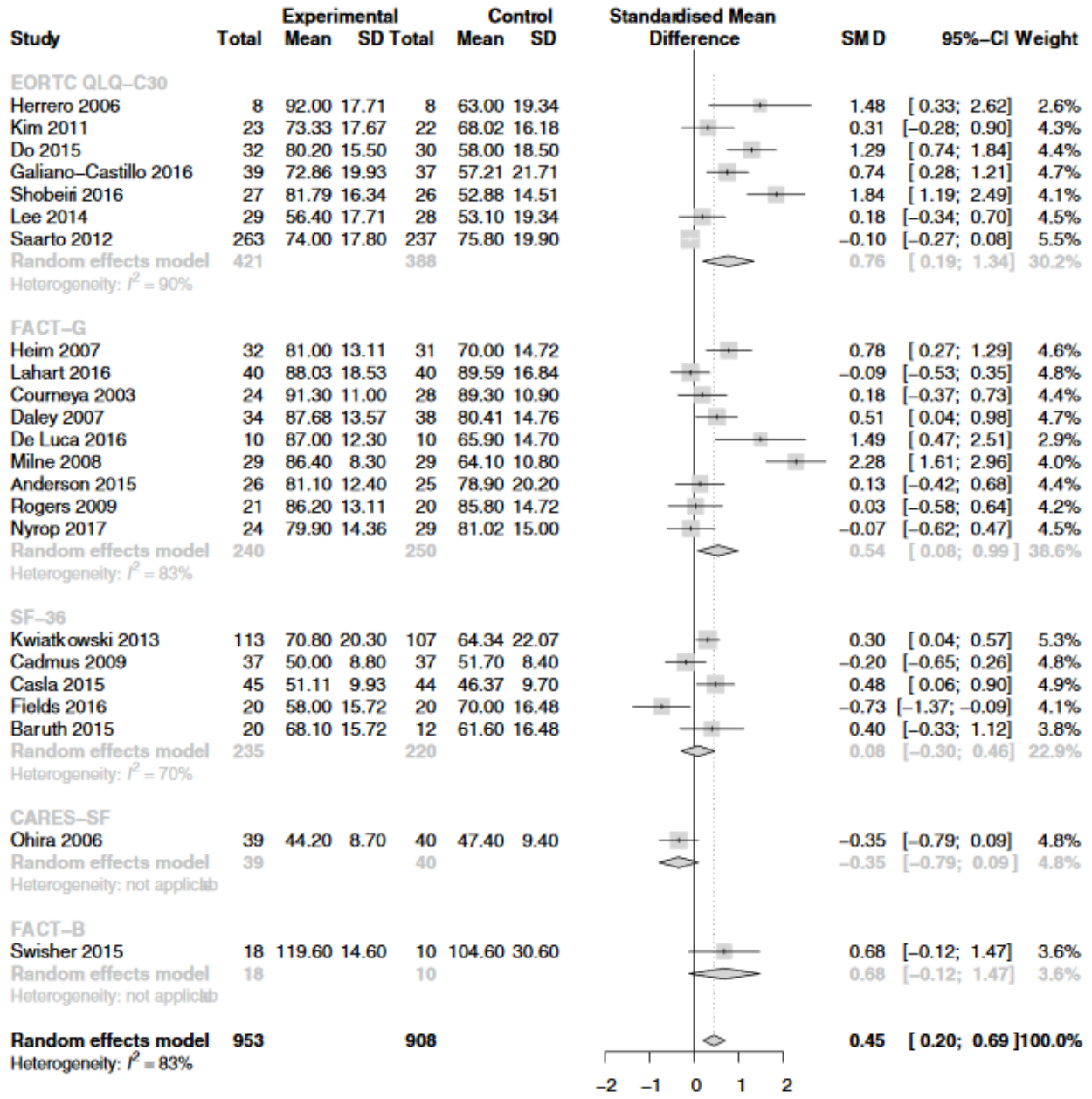

Fig. 5 Forest plot for quality of life (general) for different scales

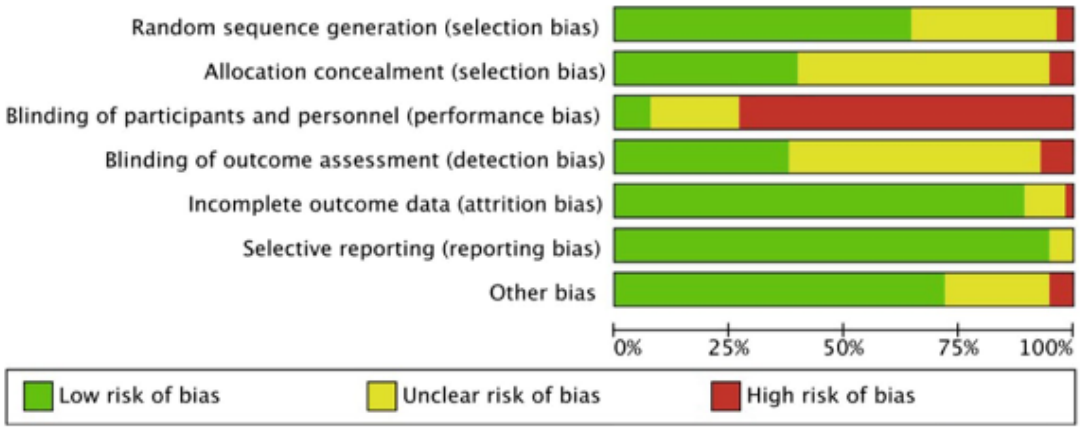

Fig. 6 Risk of bias graph

were relatively small and just one study, published as an abstract, evaluated outcomes such as overall mortality or disease-free survival [23]. The GRADE summary of findings table is shown in Fig. 8.

Discussion

The diagnosis of breast cancer affects patients' quality of life and has long-lasting consequences. Both the diagnosis itself and the treatments that those patients are submitted to have significant influence in mental and physical health for years to come. The incidence of breast cancer in its earlier stages is increasing due to improved screening. In the same way, treatments for the disease are becoming more effective, and so the number of survivors is expected to increase in the next years [24]. Many of these women might live for many years and have time to develop chronic conditions just as the general population [25]. Therefore, high-quality evidence for survivorship guidance will be necessary. Physical activity is key to improve health and quality of life in any population, and here it is not an exception.

Our goal was to collect the best evidence regarding the impact of physical activity on the body composition and quality of life of patients who had been treated for breast cancer with curative intent. We have searched for randomized clinical trials only, considering them to be the best source of evidence for the question. To avoid confusion regarding quality of life, we exclude trials that assessed patients during treatment with chemotherapy or radiation; the included patients may have been receiving adjuvant hormone therapy. Also, trials evaluating patients with metastatic disease were not included, since treatment goals and prognosis are significantly different in more advanced stages of the disease. We may say that we have collected the best evidence about this issue.

The results of this meta-analysis demonstrated a significant decrease in body weight and BMI and an improvement in quality-of-life outcomes, but a serious bias effect was demonstrated. Publication bias was found in almost all

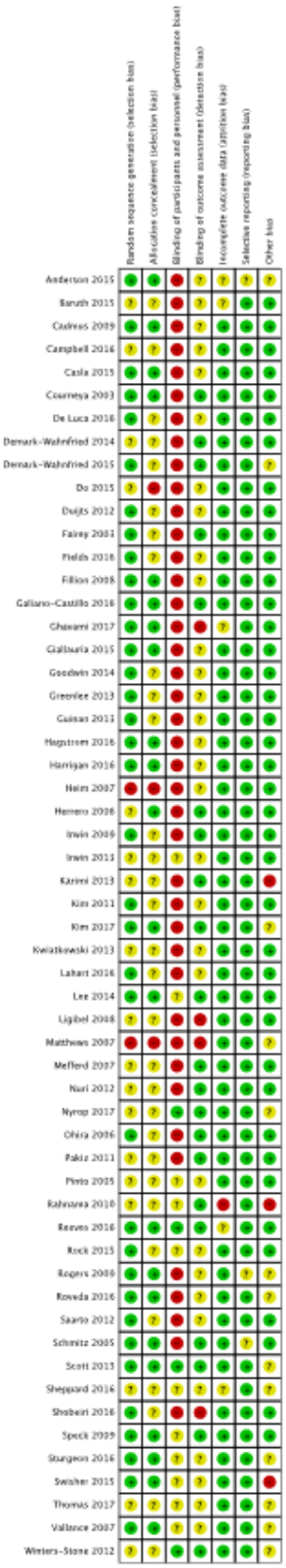

Fig. 7 Risk of bias summary

outcomes and is a concern regarding physical activity trials, since all of them lost statistical significance after correction.

We found only one study that described overall survival and progression-free survival: it was from an Australian population of 337 newly diagnosed breast cancer women showing lower mortality rates in the physical activity group [23].

Nonetheless, our meta-analysis has several limitations. First, most of the included studies were small and many of them had significant methodological flaws. In some studies reducing pain was the main outcome in aromatase inhibitors users, such as Nyrop 2017 [26] and Fields 2016 [21], so some selection bias was expected from this population. Second, the interventions were very different among the studies, making it very difficult to select any one of them as the best. The interventions varied in duration and quality, since they comprised from exercise counseling to structured and supervised exercise programs. Because of this we chose to compare exercise interventions as a single group. It was also not possible to determine if any of the interventions should have been considered ineffective at all. Third, quality of life was assessed using different scales, which may have influenced the results, since these scales correspond to different metrics assessing the same underlying outcome. Finally, long-term data are seldom available, and conclusions about the possible impact in outcomes such as overall survival or disease-free survival were not possible. High-quality randomized trials with larger numbers of patients are required, and patients should be followed for longer periods of time to assess if the benefits of the interventions are long lasting or temporary.

It is also worth commenting that the studies included were broadly heterogeneous, with variations in the type of intervention (counseling, face-to-face orientation, practicing, phone call orientation), therefore we cannot classify all these interventions under the same label, once they are not equivalent. This study shows that any intervention towards encouraging physical activity is valid and promotes good life habits that might affect the quality of life, the metabolic profile, and mortality.

With all the limitations considered, clinical trials of physical activity as an intervention for breast cancer survivors are highly justifiable, especially because exercise is a cheap intervention, is easy to apply, and practically has no contraindications or adverse effects. Even though a strong and solid evidence relating physical activity and reduced risk of recurrence and death from breast cancer is lacking, survivors are oriented to avoid a sedentary lifestyle and seek to exercise regularly. The potential benefits of this practice can help maintaining a healthy weight, improve fitness and tolerance to treatment, stimulate healthy lifestyles, and prevent other chronic diseases for which this population is particularly vulnerable.

Physical exercise compared to not realize physical exercise for breast cancer

Bibliography:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with not realize physical exercise	Risk difference with Physical exercise
Weight	2445 (24 RCTs)	⨁◯◯◯ VERY LOW a,b,c,d	-	The mean weight was **0** kg	MD **1.36 kg lower** (2.51 lower to 0.21 lower)
Body mass index	1891 (19 RCTs)	⨁⨁◯◯ LOW d	-	The mean body mass index was **0**	MD **0.89 lower** (1.5 lower to 0.28 lower)
Body fat percentage	1201 (16 RCTs)	⨁⨁◯◯ LOW b,e	-	The mean body fat percentage was **0** % points	MD **1.6 % points lower** (2.31 lower to 0.88 lower)
Quality of life - General	1861 (22 RCTs)	⨁◯◯◯ VERY LOW a,d,f	-	-	SMD **0.45 SD higher** (0.2 higher to 0.69 higher)
Quality of life - physical	1716 (20 RCTs)	⨁◯◯◯ VERY LOW a,d,f,g	-	-	SMD **0.51 SD higher** (0.23 higher to 0.79 higher)
Quality of life - mental	1326 (14 RCTs)	⨁◯◯◯ VERY LOW a,f,g	-	-	SMD **0.28 SD higher** (0.06 higher to 0.5 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Impact on outcome varied greatly across studies.
b. Interventions varied widely across different studies. Interventions, in general, not tailored for the target patients. Excercise adherence unknown.
c. Confidence interval ranging from important effect (-1.5) to no clinical significant effect (-0.28)
d. Publication bias detected through Egger test. Trim and fill computation resulted in loss of statistical significance.
e. Confidence interval ranging from important effect (-2.31) to no clinical significant effect (-0.88)
f. Confidence intervals varied greatly across studies and across the different quality of life scales
g. Outcome assessed through different quality of life scales

Fig. 8 GRADE summary

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest to carry out this work.

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COMMENTARY

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Brain imaging and treatment modality of central nervous system metastasis: A single-institution cohort

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Breast cancer is usually curable in early stages, but when it has metastasized to distant organs it is usually considered incurable and leads to high morbidity and mortality. As metastatic disease is not considered amenable to be cured, benefit of early detection of metastasis is controversial, and most medical organizations and expert committees do not recommend periodic screening for metastatic disease during follow-up due to this alleged lack of benefit.[1,2]

This is particularly the case for central nervous system (CNS) metastasis, which is related to a median survival usually below six months.[3] In the last few decades, treatment for brain metastasis has advanced to some extent and stereotactic radiosurgery (SRS), a treatment in which focused radiation beams are directed to the tumor sparing the surrounding tissue, has largely supplanted whole-brain radiotherapy (WBRT) for patients with a limited number of brain lesions.[4,5]

We conducted a retrospective analysis of patients treated with radiation therapy for brain metastasis of breast cancer in our institution to investigate if routine imaging was associated with more conservative treatments like SRS in relation to WBRT.

We searched for all patients treated with radiation therapy for breast cancer metastatic to the brain in our institution from October 2011 to November 2018. Patients were included if they had (a) brain metastasis from breast cancer of any histologic or molecular subtype; (b) started some modality of radiotherapy to the brain; and (c) diagnosis, treatment, and follow-up were performed in our institution. Metastasis from unknown primary was all excluded, as were all male patients.

Patients were analyzed according to the treatment modality received, being the two groups (1) Radiosurgery, including SRS or fractionated stereotactic radiotherapy (FSRT); and (2) Whole-brain radiotherapy. Surgery for decompression before radiation was permitted in both groups. The strategy for the detection of brain metastasis was defined as (a) Routine brain imaging in the absence of symptoms; or (b) symptoms leading to diagnosis.

A total of 417 patients were treated with radiation for disease in the central nervous system (CNS) at our institution in the given period. The number of patients that had breast cancer and fulfilled all the above criteria was 47.

Twenty-six patients (55,3%) received exclusively WBRT, and 21 patients (44,7%) received radiosurgery. Both groups had similar age at cancer diagnosis (51.38 vs 52.45, respectively) and had about the same probability of having been submitted to neurosurgery before radiotherapy (23.1% vs 23.8%). Patients who received focused treatment had more frequently HER2-positive disease (71,5% vs 38,5%), more metastatic disease at diagnosis (28.6% vs 15.4%) and had a shorter time from cancer diagnosis to CNS metastasis (48.71 vs 63.08 months) when compared to those who received exclusively WBRT. Patients submitted to WBRT, on the other hand, were more likely to have triple-negative disease (19.2% vs 4.8%) and stage III disease at diagnosis (42.3% vs 19%). Nonetheless, only the association between disease stage at initial diagnosis and treatment modality was considered statistically significant (Table 1).

Only one patient in the radiosurgery group had a lesion larger than 3 cm (4.7%), and most of them had lesions smaller than 3 cm in their largest diameter (81%). Patients submitted to WBRT were more likely to have five or more CNS lesions than those in the focused

TABLE 1 Comparisons according to treatment modality

Treatment	Whole-brain radiation therapy—n (%)	Radiosurgery—n (%)	*P*-value
Mean age at diagnosis	50.77	51.95	.8847
Detection method of CNS metastases			
Routine examination in asymptomatic patient	5 (19.23)	8 (38.10)	.1506
Symptoms	21 (80.77)	13 (61.90)	
Metastasis at diagnosis of breast cancer			
Yes	4 (15.38)	6 (12.77)	.1567
No	22 (84.62)	15 (71.43)	
HER2-directed therapy			
Yes	7 (28.00)	10 (52.63)	.0965
No	18 (72.00)	9 (47.37)	
Molecular subtype of breast cancer			
Luminal/HER2-negative	10 (40.00)	5 (23.81)	.2037
HER2+	6 (24.00)	9 (42.86)	
HER2+ luminal	4 (16.00)	6 (28.57)	
Triple negative	5 (20.00)	1 (4.76)	
Disease stage at diagnosis			
I	2 (8.00)	1 (5.26)	.0079
II	8 (32.00)	11 (42.11)	
III	11 (44.00)	4 (21.05)	
IV	4 (16.00)	6 (31.58)	
Neurosurgery before radiotherapy			
Yes	6 (23.10)	5 (23.8)	.9530
No	20 (76.90)	16 (76.2)	
Largest CNS lesion			
Not measured	20 (76.92)	3 (14.29)	.1080
<1 cm	0 (0.00)	1 (4.76)	
1-3 cm	4 (15.38)	16 (76.19)	
>3 cm	2 (7.69)	1 (4.76)	
Number of CNS lesions			
Unknown	3 (11.50)	1 (4.80)	<.0001
1	2 (7.70)	9 (42.90)	
2-3	2 (7.70)	7 (33.30)	
4-5	0 (0.00)	3 (14.30)	
>5	19 (73.10)	1 (4.80)	

treatment group (73.1% vs 4.8%) (Table 1). Patients in the radiosurgery group were treated with SRS and FSRT (61.9% and 33.3%, respectively). One patient in this group had the option to be submitted to SRS for a single brain metastasis, but decision was made to perform a conventional neurosurgery followed by adjuvant WBRT; he was kept in this group according to the above criteria.

More patients in the radiosurgery group had detected the metastasis due to a routine asymptomatic examination than patients who were subsequently treated with WBRT (38,1% × 19,2%), but this difference was not statistically significant ($P = .15$). None of the molecular subtypes examined was statistically related to the probability of being submitted to focal treatment (Table 1), even though having been submitted previously to HER2-directed therapy showed a trend to be associated with more focused treatments (52.63% vs 28% when compared to WBRT, respectively; $P = .09$).

Patients treated with radiosurgery lived longer than patients treated with WBRT, what was attributed to the more favorable clinical characteristics at baseline (Figure 1). Median overall survival was not reached in the focused treatment group and was calculated as 9 months in the WBRT-only group.

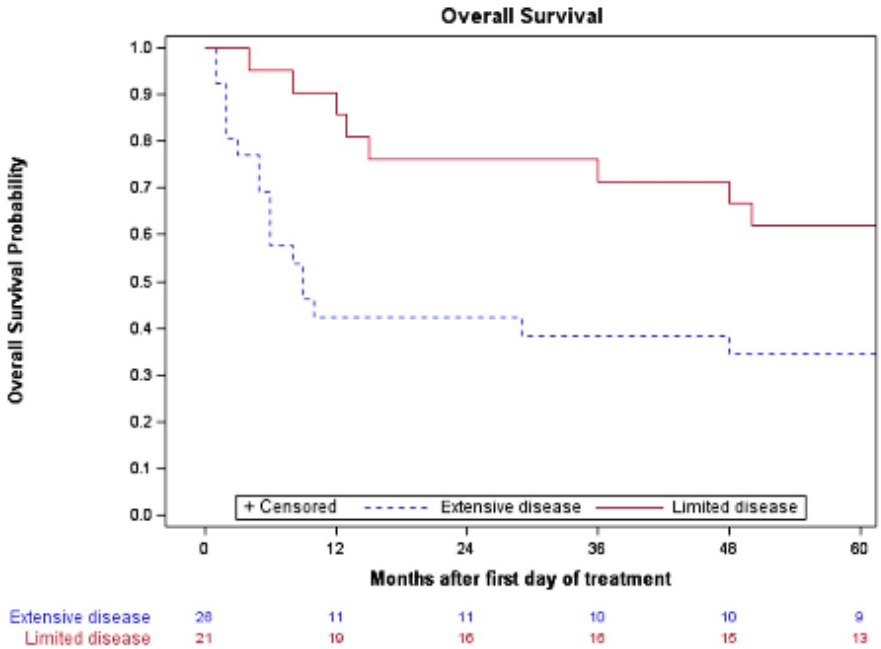

FIGURE 1 Overall survival according to type of CNS treatment

Asymptomatic patients with cerebral metastasis in our cohort study were more frequently submitted to focus treatments to the brain and had an overall better prognosis. Patients whose tumors had HER2-overexpression were more frequently treated in the focused group. These results may suggest that routine screening of brain metastasis in asymptomatic breast cancer patients could be of benefit for some subgroups of patients.

Our study is limited by its retrospective design and for being single-institution based. Furthermore, we could not include patients that died before or were not eligible for any kind of treatment. Despite recognizing its limitations, we consider our results provocative. Larger prospective studies on the detection and treatment of breast cancer CNS metastasis are in need.

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