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Body weight management in overweight and obese breast cancer survivors

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[Intervention Protocol]

Body weight management in overweight and obese breast cancer survivors

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of different body weight management approaches in breast cancer survivors who are overweight or obese.

BACKGROUND

Description of the condition

Breast cancer is the second most common cancer worldwide, with 1.67 million new cases diagnosed in 2012 (Ferlay 2015). With early diagnosis and an increase in the use of neoadjuvant and adjuvant chemotherapy and hormonal therapy, survival rates have continued to improve (IARC of WHO 2012). The five-year survival rate for breast cancer is now 89% in North America (NCI 2014), and over 80% in England (Office for National Statistics 2013). In light of the rapid increase in the number of breast cancer survivors, there is a new emphasis on the need for appropriate survivorship care (Yu 2014).

In its broadest definition, a person becomes a cancer survivor when they are diagnosed with cancer, and remain a survivor for the rest of their life (Centers for Disease Control and Prevention 2011). Approximately 50% of breast cancer survivors worldwide are classified as overweight or obese (57% to 62% in the United States of America (Morimoto 2002; Imayama 2013), 55% in Switzerland (Eichholzer 2012) and 42% in Mexico (Ortiz-Mendoza 2014)). Many breast cancer survivors gain more body weight after primary neoadjuvant or adjuvant treatment (Arce-Salinas 2014; Kann 2014; Kim 2013) and hormonal therapy (Lorizio 2012).

Being overweight or obese is defined as having an abnormal or excessive amount of total body fat, that may affect health status (WHO 2015). It is usually measured by Body Mass Index (BMI (kg/m^2)), with overweight BMI classified as ranging from 25 to 29.9, obesity as a BMI of 30 and above, and morbid obesity as a BMI of 40 and above (WHO 1997).

Body fat is composed mostly of adipocytes and other cells including preadipocytes, fibroblasts, vascular endothelial cells and a variety of immune cells. It can store energy, and cushion and insulate the body. It has been recognised as a major endocrine organ

(Ferlay 2015; Kershaw 2004) as it produces hormones such as leptin, oestrogen, and the cytokine tumour necrosis factor - alpha (TNFα), which stimulates insulin secretion leading to insulin resistance (Rock 2013; Su 2013). Research has demonstrated that breast cancer survivors who have had a weight loss of < 5% of their initial weight have higher levels of oestrogen and leptin, and lower levels of adiponectin than those who achieved a weight loss of ≥5% of their initial weight (Rock 2013).

Studies suggest that women who are overweight or obese are at an increased risk of cancer recurrence, and higher all-cause mortality (Dignam 2003). Obesity has been found to increase the risk of total mortality by 17%, and 18% for breast cancer specific mortality, for every 5 kg/m^2 increment before their cancer diagnosis (Chan 2014). In addition, morbid obesity may be a prognostic factor for diabetes and cardiovascular disease (Vance 2011). Obesity also has a significant impact on a woman's quality of life (QOL) and ability to function in relation to everyday activities (Imayama 2013).

Description of the intervention

A number of interventions have been adopted into clinical practice for breast cancer survivors who are morbidly obese, to reduce body weight and maintain it within a healthy weight range (BMI of 18.5 to 24.9 kg/m^2). These include: physical activity programmes (Thomas 2013), dietary changes (Pierce 2009), medication (Goodwin 2011) and bariatric surgery (Wikipedia 2015). The weight loss approach selected needs to be matched to an individual patient's needs, comorbidities, and risk profile. The most common first-line strategy used for weight loss is comprehensive lifestyle modification. The basic components are to facilitate energy deficiency through increased physical activity and reduced calorie intake, generally with the goal of losing 3% to 5% of initial body weight for at least six months.

Individually-tailored physical activity programmes generally consist of a combination of aerobic resistance or weight load (strength training) with aerobic exercises (such as walking, jogging, running, cycling, swimming, dancing etc). Recommendations are to undertake at least 150 minutes per week of activity of moderate intensity (Rock 2012; Subirats Bayego 2012; U.S. Department of Health and Human Services 2008).

Weight loss diets have been designed to provide a balanced diet with low energy intake of 1200 to 1500 kilocalories (kcal) per day (d) for women and 1500 to 1800 kcal/d for men (Jensen 2014) (or 1000 to 1600 kcal/d for a low calorie diet (Commonwealth of Australia 2013)) for the management of overweight and obesity in adults. This can be achieved through a low-fat, high-fibre diet. A very-low-calorie diet (< 800 kcal/d) may be appropriate if supervised in a medical setting. Behavioural, psychological and/or social interventions are often used in conjunction with exercise and dietary interventions.

Physical activity and weight loss dietary programmes are usually administered in medical clinics, at home or in gyms. They can be conducted face to face, by telephone or through web sites (Rogers 2008).

Pharmacotherapy can be used either as an adjunct to comprehensive lifestyle modification, or in isolation for cancer survivors who cannot participate in lifestyle programmes due, for example, to comorbidities limiting their physical activity. Medications such as sibutramine and orlistat are most commonly used to achieve or maintain weight reduction in those with a BMI of 30 or above, or BMI of 27 or above in the presence of obesity related comorbidities (e.g. diabetes, cardiovascular diseases) (Jensen 2014). Sibutramine has been associated with an increased risk of elevated blood pressure and tachycardia (fast heart rate) while orlistat can lead to gastrointestinal side effects, deficiency of fat-soluble vitamins (e.g. vitamins A, D, E and K), and interactions with other medications, e.g. warfarin (National Health and Medical Research Council 2013).

Bariatric surgery may be considered for individuals with a BMI of at least 40, or a BMI of 35 or above with high-risk comorbidities (Jensen 2014) who have not responded to behavioural treatments, with or without pharmacotherapy. Bariatric surgery includes a variety of procedures where the aim is to achieve weight loss by reducing the size of the stomach using a gastric band, or removing a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch), or by resecting and re-routing the small stomach pouch (gastric bypass surgery) to the small intestine. Bariatric surgical interventions should be performed only in highly selected patients and in specialist centres by experienced surgeons. Patients need to be fully informed about the potential risks and side effects. Adverse effects include misplacement of the band, erosion of the gastric wall, port complications, anastomotic leak, wound complications, haemorrhage, pulmonary embolism, deep vein thrombosis, deficiency of nutrients or malnutrition, elevated parathyroid hormone, ventral hernia and, occasionally, death (Jensen 2014).

In this Cochrane review, we will include randomised controlled clinical trials (RCTs), in which the participants are randomly allocated to one or other of the different treatments under study. We will evaluate several types of comparator interventions such as placebo medications and supportive treatments (e.g. vitamins), as well as evidence-based positive controlled interventions (e.g. increased physical activity and diet modification regimens) (Pakiz 2011).

How the intervention might work

Obesity after a breast cancer diagnosis is known to be a poor prognostic risk factor, particularly for postmenopausal women (Chan 2014). This may be due to changes in energy metabolism secondary to the side effects of chemotherapy treatment (Gadea 2013). There is likely to be higher than normal oestrogen conversion and secretion in excess body fat tissue and less sex hormone

binding globulin in the circulation (Siiteri 1987), which will increase stimulation to breast tissue. Elevation of inflammatory cytokines such as TNF-α, interleukin-6 (IL-6) and adipokines (leptin) (Khandekar 2011) in adipose tissue can activate cancer cells by activating oncogenic transcription in breast tissue, and a fall in adiponectin decreases the inhibition of proliferation and metastasis of breast tumour cells. Finally, high insulin levels and insulin resistance (Oh 2011) may exacerbate the loco-regional metabolic microenvironment leading to an imbalance in homeostasis, with a depletion of oxygen, and energy dysfunction in localised breast lesions, which are considered to be an ideal microenvironment for tumour recurrence.

Under normal circumstances, obesity occurs when energy expenditure is less than the energy intake over a period of time (Davoodi 2013). However morbidly obese breast cancer survivors are often characterised by fat gain and loss of lean tissue (Vance 2011). The loss of muscle mass in the setting of increased body fat is known as sarcopenic obesity. This is a multifactorial condition. In addition to the metabolic and neuroendocrine alterations that may be induced by chemotherapy and genetics, other lifestyle-dependent factors such as inactivity are likely to be important risk determinants (Davoodi 2013). Other causes such as psycho-social and environmental factors may also play a role in the excess accumulation of adipose tissue (Deusinger 2012; Mastorakos 2010; Nahas 2012; Waxler-Morrison 1991).

There is a body of evidence finding that physical activity promotes blood circulation and oxygen concentration, and reduces the concentration of plasma cytokines and inflammatory factors (nuclear factor kappa B (NF-κB), IL-6, C-reactive protein (CRP)), insulin-like growth factor (IGF; Imayama 2013; Jones 2013), leptin (Iantorno 2014), and hormones (insulin and oestrogens; Borer 2014; Rock 2004). Exercise can also improve body composition (Guinan 2013). Studies of dietary modification suggest that exercise has positive effects on loss of excess body weight and weight loss maintenance for breast cancer survivors (Carpenter 2012; Reeves 2014). These changes may be helpful in improving the local breast microenvironment. In addition, management of body weight may have preventative effects on secondary events associated with breast cancer such as type 2 diabetes, cardiovascular disease, dyslipidaemia and other comorbidities (Jensen 2014; Patnaik 2011). Loss of body weight can also have a positive impact on psychosocial well being (Demark-Wahnefried 2012; Dignam 2003; Imayama 2013).

Although over the counter medications for obesity in the non-cancer population may reduce excess body weight by decreasing macronutrient absorption (orlistat) and suppressing appetite (sibutramine) (National Health and Medical Research Council 2013), and bariatric techniques through limiting food intake or diminishing the area available for digestion and absorption in the gastrointestinal tract (Bordalo 2011), there is a lack of evidence for use of these methods in breast cancer survivors.

Why it is important to do this review

Changes in body weight associated with cancer treatment (Vagenas 2015) have been noted for a number of decades (Dixon 1978). Studies indicate that body weight changes can occur in either direction, with weight gain or loss (Vagenas 2015). This heterogeneity maybe associated with complex factors in breast cancer survivors including: genetic predisposition (Slattery 2015), sociodemographic factors (Sedjo 2014; Thompson 2014), menopausal status (Irwin 2007), hormone receptor status (Ewertz 2012), clinical presentation (tumour size, histologic grade and degree of differentiation, lymph node metastasis) and treatment modality.

Cancer survivors gain weight mainly through sedentary and inactive lifestyles, with a peak in the third year when followed for six years after diagnosis (Makari-Judson 2014; Vagenas 2015). Studies suggest that body weight loss of more than 5% is feasible for obese or overweight breast cancer survivors (Davoodi 2013; Vitolins 2014). However, many studies have been observational in design (Makari-Judson 2014), with a paucity of high-quality evidence from clinical interventions to guide effective body weight management for cancer survivors. Consequently, body weight reduction is frequently not addressed in overweight breast cancer survivors (Chan 2014). There is a need to elucidate its effectiveness in terms of which modality to recommend, at what intensity, and for which group of participants. In this review, we aim to assess the benefits, risks and efficacy of different body weight loss approaches in overweight breast cancer survivors in order to guide the survivors, clinicians, and policy makers associated with survivorship care.

OBJECTIVES

To assess the effects of different body weight management approaches in breast cancer survivors who are overweight or obese.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs and randomised cross-over trials evaluating management of body weight for overweight and obese breast cancer survivors. There will be no restrictions based on the language of the publication. If studies are published in other languages, they will be translated into English.

Types of participants

We will include overweight or obese breast cancer survivors who have been diagnosed with early stage breast cancer (histopathologically confirmed), and who have no evidence of a recurrence of their cancer. Participants who have had surgery and/or are receiving or have received adjuvant chemotherapy and/or radiotherapy, adjuvant hormonal treatment and/or targeted therapies such as trastuzumab for women with Her 2 status will be eligible. There will be no restrictions based on participants' residence, race or ethnicity, occupation, gender, religion, education, socio-economic status (SES), or time from diagnosis.

Types of interventions

The experimental interventions can involve:

- Physical activity that includes exercise as well as other activities involving body movements that are done as part of playing, working, active transportation, household chores and recreational activities (WHO 1997). This may include physical activity programmes alone, or in combination with various other treatments. There are no limitations on the setting, duration and delivery of the physical activity programme, but the aim of the intervention needs to be weight loss.
- Dietary interventions that adhere to a foundation diet, with the goal of losing 3% to 5% of body weight, and/or sustaining weight loss for six months (Jensen 2014). Categories include a low-calorie diet (< 1200 kcal/d) and very-low-calorie diet (< 800 kcal/d), based on participants' needs and risk factors. There are no restrictions on dietary type.
- Drugs that are aimed primarily at reducing obesity such as: orlistat; sibutramine; L-carnitine, or other drugs such as metformin used for secondary event prevention.
- Social, psychological, and behavioral interventions that are aimed at improving the social environment, and cognitive and behavioural factors in relation to weight loss.
- Bariatric surgery, which may include a variety of surgical procedures including gastric banding, removal of a portion of the stomach, or gastric bypass surgery.
- Multifactorial interventions could include a combination of the following regimens: physical activity ± diet intervention ± obesity drug ± bariatric surgery ± social, psychological, and behavioural interventions.

The control interventions of comparisons will include: placebo, no treatment or waiting list, supportive treatments such as vitamins and/or minerals, conventional treatments or active control interventions to prevent the recurrence of cancer.

We will group the comparisons by interventions and controls in the pooling.

We will include studies with co-interventions if these co-interventions are applied in exactly the same way to both the control and intervention group.

Types of outcome measures

Primary outcomes

1. Overall breast cancer survival, defined as the percentage of breast cancer patients in a treatment group who are alive when the precise cause of death is not specified.
2. Incidence of cancer recurrence after diagnosis: defined as recurrence of any type of breast cancer in any region, after completing definitive surgery for the incident breast cancer.

Secondary outcomes

1. Body weight loss (% of baseline weight), and weight loss period (duration in days) for how long it took to lose the weight, and how long the weight loss was sustained.
2. Change in skinfold thickness and waist circumference.
3. Disease-free survival rate, defined as the interval from diagnosis to the date of first cancer recurrence.
4. Mortality (or crude death rate), defined as the total annual number of any death recorded relative to the total population of overweight and obese breast cancer survivors (usually expressed per 1000) between completing definitive surgery and the end of the data linkage. This will be categorised into breast cancer deaths and non-breast cancer deaths of breast cancer survivors.
5. Any potential adverse events such as exacerbation of symptoms (pain, fatigue, nausea, dyspnoea), falls and bone fractures.
6. Quality of life (QOL) and patient-reported outcomes, as defined by the perceived quality of an individual's daily life; that is, an assessment of their well being or lack thereof. This includes all emotional, social, and physical aspects of the individual's life. The patient-reported outcomes may be assessed using questionnaires or surveys used to collect data from the patient, such as the EORTC QLQ-C30 , FACT-G or SF-36 questionnaires. We will include data from self-administered structured questionnaires including participants' self-reported socio-demographic (race/ethnicity) and medical characteristics (lump before mammogram, menopausal status) and QOL.
7. Concentration of oestradiol, androgen, insulin, insulin-like growth factor (IGF), fasting glucose and lipids profile.
8. Adipokine levels concentrations (μg/mL): plasma leptin, adiponectin.
9. Inflammatatory marker concentrations (pg/ml) (IL-6, TNF-α, CRP).

Main outcomes for 'Summary of findings' table

The following outcomes will be included in the 'Summary of findings' table(s).

1. Overall breast cancer survival.
2. Incidence of cancer recurrence after diagnosis.

3. Any potential adverse events.
4. Body weight loss.
5. Disease-free survival rate.
6. Mortality.
7. Change in skinfold thickness and waist circumference.

Search methods for identification of studies

Electronic searches

We will search the following databases.

1. The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials with the key words 'breast cancer survivor', 'survivorship', 'breast cancer', 'obesity', 'overweight', 'body weight management', 'weight loss', 'weight reduction', 'body mass index', 'lifestyle intervention', 'lifestyle activity', 'exercise', 'diet', 'bariatric surgery', 'obesity medication', 'behavior', 'drug therapy' 'cognitive therapy' and 'surgery' will be extracted and considered for inclusion in the review.
2. Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, latest issue). See Appendix 1.
3. MEDLINE (2012 to present) (via OvidSP). See Appendix 2.
4. EMBASE (2016 to present) (via EMBASE.com). See Appendix 3.
5. The WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 4.
6. Clinicaltrials.gov (http://clinicaltrials.gov/). See Appendix 5.
7. Mainland Chinese academic literature databases using keywords in Chinese: CNKI (via http://www.cnki.net/) (1979 to present); VIP (http://edu.cqvip.com/) (1989 to present); Wan Fang Data (http://www.wanfangdata.com.cn/) (1980 to present); SinoMed (http://www.sinomed.ac.cn/zh/) (1978 to present).

Searching other resources

Bibliographic searching

We will attempt to identify further studies from reference lists of identified relevant trials or reviews. A copy of the full article for each reference reporting a potentially-eligible trial will be obtained. Where this is not possible, we will attempt to contact authors to obtain additional information.
We will handsearch the retrieved articles and bibliographies in order to identify other potentially-eligible studies and unpublished data.

Data collection and analysis

Selection of studies

Two authors (LXM and SYT) will independently screen the titles and abstracts. LXM and SYT will obtain full-text copies of the relevant articles and include the eligible studies in accordance with the above inclusion criteria. During this process any disagreement will be resolved by consensus and by the involvement of other review authors (MKB and JV). We will record excluded trials in the 'Characteristics of excluded studies' table.

Data extraction and management

Data will be collected in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) based on the inclusion criteria.
Data will be extracted from eligible studies using a data extraction form designed and pilot-tested by the authors. We will collect the following information: study design, participants, setting, interventions, outcomes, follow-up, and any other items relevant to this review (see Appendix 6 for a list of the categories of data collection). Where studies have multiple publications, the main trial report will be used as the primary reference and additional details supplemented from all papers. Two authors (LXM and SYT) will independently extract the data, and any uncertainties will be discussed with other authors (MKB and JV). Review authors will contact the study investigators if required.

Assessment of risk of bias in included studies

The risk of bias in the included studies will be assessed by two authors (LXM and SYT) using Cochrane's 'Risk of bias' assessment tool. Relevant items include: sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias. Two authors will assess these 'Risk of bias' domains independently, with any disagreements resolved by consensus or by discussion with other authors (MKB and JV). All judgments will be fully described in the 'Risk of bias' table and classified as 'low risk', 'high risk', and 'unclear risk'. The results will be incorporated into the interpretation of review findings by means of a sensitivity analyses.

Measures of treatment effect

Dichotomous outcomes, including the all cause mortality rate in overweight and obese breast cancer survivors will be expressed as risk ratios (RRs), and the adverse effects of the intervention will be expressed as odds ratio (OR), along with 95% confidence intervals (CIs). The number of events occurring in the control and intervention groups for each study will be used to calculate the outcomes.

Time-to-event outcomes including survival and local recurrence will be expressed as hazard ratios (HRs). If they are available, the observed number of events and expected number of events in both the experimental and control group of each study will be extracted directly from the trial publication. For data presented in Kaplan-Meier curves, a Cox proportional hazard model or in life tables, we will extract the HR and associated variances from published curves using methods described by Parmar (Parmar 1998). Censored participants will not be analysed as dichotomous variables.

Continuous data including body weight loss, skinfold thickness, waist circumference, levels of hormones, cytokines and adipokines, and metabolic effects will be expressed as the mean differences (MDs) between treatment groups with 95% CIs, when all studies report exactly the same outcomes. If similar outcomes are reported on different scales (for example, change in QOL) the standardised mean difference (SMD) will be calculated with 95% CIs.

When comparing the intervention benefits or risk effects, particular pooling outcomes will be displayed graphically as forest plots. A survival rate ratio of greater than 1.0 will be considered a positive response, favouring a body weight management regimen. The rate of cancer recurrence or incidence of adverse effects (e.g. incidence of fat soluble vitamin deficiencies) are detrimental responses, and a rate of less than 1.0 will favour a body weight management regimen.

Unit of analysis issues

Cross-over trial design will be eligible for inclusion, but only the data collected from the first stage will be used in the meta-analysis. For three-arm trials, we will combine groups to create a single pairwise comparison.

Dealing with missing data

In this review, missing data will be of significance as it is anticipated that many of the studies meeting the eligibility criteria for inclusion may not report the desired study outcomes of the participants. If the results of an RCT have been published but information on the outcome of interest has not been reported, an attempt will be made, whenever possible, to contact the trial authors for the missing information. All efforts made to obtain additional information will be reported in the completed review. Where possible, all analyses will be by intention-to-treat. If participants were allocated to one intervention, but after randomisation underwent a different intervention, they will be analysed according to their randomisation allocation. If the results for dichotomous variables are not reported in some participants, we will analyse based on both a worst possible outcome and a best possible outcome. Where results are unobtainable, multiple imputation of individual values will be undertaken for the primary outcomes only (Ellington 2015). If a standard deviation (SD) is missing we will use the method described by Hozo et al (Hozo 2015). A change in QOL will be assumed not to have occurred in participants with unreported outcomes. For other outcomes, only the available data will be analysed. We will discuss the impact of missing data in the 'Discussion' section of the review. Any imputation undertaken will be subject to sensitivity analysis.

Assessment of heterogeneity

Clinical characteristics, such as breast cancer subtypes and treatments, may not be randomly distributed across treatment and control groups, and/or not be described or accounted for in many studies. This may result in heterogeneity. In this review we will consider whether these clinical and other methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a meaningful summary. Visual inspection of the forest plots will be used to assess heterogeneity. In addition, a value of the I^2 statistic greater than 50% or the P value for Chi^2 less than 0.1 will indicate substantial heterogeneity (Higgins 2011). When there is consistency among the effect size of included studies, the fixed-effect model will be applied to quantitatively synthesise the evidence from the studies. If substantial heterogeneity is detected, we will use a random-effects model to pool the results. Possible explanations for the heterogeneity will be explored using subgroup and sensitivity analyses.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we will aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. If there are 10 or more studies for one effect outcome analysis, a funnel plot will be prepared to explore the possibility of small study effects (that is a tendency for the intervention effect to be more beneficial in smaller studies).

Data synthesis

For dichotomous outcomes, we will synthesise data using the Mantel-Haenszel analysis method for a fixed-effect model or the DerSimonian and Laird analysis method for a random-effects model. The Peto method will be used to pool odds ratios.The choice of model will be based on the assessment of heterogeneity.

For time-to-event outcomes, we will pool data using the generic inverse-variance method, allowing a mixture of log-rank and Cox model estimates to be obtained from studies.

For continuous outcomes, MDs and their 95% CI (body weight loss) or SMDs with 95% CI (for a QOL scale) will be calculated based on intention-to-treat data, available-case data and per-protocol data. As we assume that intention-to-treat data for continuous measures will not be available for a number of studies, we will use a preference approach for collecting data for the primary meta-analysis (first preference intention-to-treat data, second preference available-case data, and third preference per-protocol data).

We will perform meta-analysis using Review Manager 5.3 software (RevMan) and report the meta-analysis results mainly by forest plots and 'Summary of findings' tables.

We will use GRADEproGDT software (GRADEproGDT) to present a 'Summary of finding' (SoF) table to illustrate the main outcomes and grade the quality of the evidence.

We will grade the quality of the evidence for the two primary outcomes and the five secondary outcomes listed above in terms of the extent of our confidence in the estimates of effects. In the SoF table, findings will be grouped by outcome. We will record a summary of the estimated intervention effect, number of studies and participants, and justification of the evidence for each outcome. GRADE criteria for assessing the quality of the evidence will include study limitations, inconsistency, imprecision, indirectness, publication bias and other considerations (Schünemann 2011). Four grades of evidence will be used, as recommended by the GRADE Working Group, as follows:

1. High quality: Further research is very unlikely to change our confidence in the estimate of effect;
2. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
3. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
4. Very low quality: We are very uncertain about the estimate.

Two authors (CT and JV) will work on this assessment.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses to assess the heterogeneity of studies as well as the effect on clinical outcomes. Where there is heterogeneity we will explore its potential causes and discuss aspects of the study design, participant characteristics, interventions and outcome types. The main subgroup analyses will be as follows:

1. Hormonal receptor status (oestrogen, progesterone) and triple negative status;
2. Different races or ethnicity;
3. Age: < 45 years versus > 45 years;
4. Menopausal status: premenopausal versus postmenopausal;
5. Different types of diets;
6. Stage and status of tumour at diagnosis;
7. Body weight before commencing the study programme;
8. Different types of control groups;
9. Treatment status: chemotherapy: none, completed, ongoing; hormonal therapy: none, completed, ongoing; HER2-directed therapy: none, completed, ongoing.
10. The time of the weight gain (weight gain as a result of treatment versus obesity/overweight at the time of diagnosis).

Sensitivity analysis

Where data are available, sensitivity analyses will be performed to determine whether the pooling of results is robust in terms of the arbitrary decisions made regarding the eligibility of studies and the methods of meta-analysis. Sensitivity analysis will be conducted by excluding studies with a high risk of bias, by excluding unpublished studies or by using different pooling methods. We will exclude studies of poor overall methodological quality, i.e. quasi-randomisation, without adequate safeguards for allocation concealment, inadequate blinding, incomplete outcome reports and no intention-to-treat analysis, to determine the statistical stability of the results. Where forest plots and I^2 values suggest heterogeneity we will change from a fixed-effect model to a random-effects model or exclude the most outlying results in the forest plot and repeat the meta-analysis.

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REFERENCES

Additional references

Arce-Salinas 2014

Arce-Salinas C, Aguilar-Ponce JL, Villarreal-Garza C, Lara-Medina FU, Olvera-Caraza D, Alvarado MA, et al. Overweight and obesity as poor prognostic factors in locally advanced breast cancer patients. *Breast Cancer Research and Treatment* 2014;**146**(1):183–8. [10.1007/s10549–014–2977–8. Epub 2014 May 20]

Bordalo 2011

Bordalo LA, Teixeira TF, Bressan J, Mourão DM. Bariatric surgery: how and why to supplement [Cirurgia bariátrica: como e por que suplementar]. *Revista da Associação Médica Brasileira* 2011;**57**(1):113–20. [PUBMED: PMID: 21390468]

Borer 2014

Borer KT. Counterregulation of insulin by leptin as key component of autonomic regulation of body weight. *World Journal of Diabetes* 2014;**5**(5):606–29. [PUBMED: PMID: 25317239]

Carpenter 2012

Carpenter CL, Duvall K, Jardack P, Li L, Henning SM, Li Z, et al. Weight loss reduces breast ductal fluid estrogens in obese postmenopausal women: a single arm intervention pilot study. *Journal of Nutrition* 2012;**11**:102. [DOI: 10.1186/1475-2891-11-102]

Centers for Disease Control and Prevention 2011

Centers for Disease Control and Prevention (US). Cancer Survivors--United States, 2007. *MMWR. Morbidity and Mortality Weekly Report* 2011;**60**(9):269–72. [PUBMED: PMID: 21389929]

Chan 2014

Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Annals of Oncology* 2014;**25**(10):1901–14. [DOI: 10.1093/annonc/mdu042]

Commonwealth of Australia 2013

Commonwealth of Australia. Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia. http://www.nhmrc.gov.au/guidelines-publications/n57 2013:24.

Davoodi 2013

Davoodi SH, Malek-Shahabi T, Malekshahi-Moghadam A, Shahbazi R, Esmaeili S. Obesity as an important risk factor for certain types of cancer. *Iran Journal of Cancer Prevention* 2013;**6**(4):186–94. [PUBMED: PMID: 25250133]

Demark-Wahnefried 2012

Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer* 2012;**118**(Supplement):2277–87. [DOI: 10.1002/cncr.27466]

Deusinger 2012

Deusinger SS. Exercise intervention for management of obesity. *Pediatric Blood & Cancer* 2012;**58**(1):135–9. [DOI: 10.1002/pbc.23368]

Dignam 2003

Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *Journal of the National Cancer Institute* 2003;**95**(19):1467–76. [PUBMED: PMID: 14519753]

Dixon 1978

Dixon JK, Moritz DA, Baker FL. Breast cancer and weight gain: an unexpected finding. *Oncology Nursing Forum* 1978;**5**(3):5–7. [PUBMED: PMID: 248815]

Eichholzer 2012

Eichholzer M, Schmid SM, Bovey F, Jordan P, Rohrmann S, Huang DJ, et al. Impact of overweight and obesity on postmenopausal breast cancer: analysis of 20-year data from Switzerland. *Archives of Gynecology and Obstetrics* 2012;**285**(3):797–803. [10.1007/s00404–011–2022–7. Epub 2011 Aug 4]

Ellington 2015

Ellington EH, Bastille-Rousseau G, Austin C, Landolt KN, Pond BA, Rees EE, et al. Using multiple imputation to estimate missing data in meta-regression. *Methods in Ecology and Evolution* 2015;**6**:153-63. [DOI: 10.1111/2041-210X.12322]

Ewertz 2012

Ewertz M, Gray KP, Regan MM, Ejlertsen B, Price KN, Thurlimann B, et al. Obesity and risk of recurrence or death after adjuvant endocrine therapy with letrozole or tamoxifen in the breast international group 1-98 trial. *Journal of Clinical Oncology* 2012;**30**(32):3967–75. [DOI: 10.1200/JCO.2011.40.8666]

Ferlay 2015

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015;**136**(5):E359–86. [DOI: 10.1002/ijc.29210]

Gadea 2013

Gadea E, Thivat E, Wang-Lopez Q, Viala M, Paulon R, Planchat E, et al. Poor prognostic value of weight change during chemotherapy in non-metastatic breast cancer patients: causes, mechanisms involved and preventive strategies. *Bulletin du Cancer* 2013;**100**(9):865–70. [DOI: 10.1684/bdc.2013.1802]

Goodwin 2011

Goodwin PJ, Stambolic V. Obesity and insulin resistance in breast cancer--chemoprevention strategies with a focus on metformin. *Breast* 2011;**20**(Supplement 3):S31–5. [DOI: 10.1016/S0960-9776(11)70291-0]

GRADEproGDT

GRADEproGDT: GRADEpro Guideline Development Tool [software]. McMaster University, 2015 (developed by Evidence Prime, Inc). Available from www.gradepro.org.

Guinan 2013

Guinan E, Hussey J, Broderick JM, Lithander FE, O'Donnell D, Kennedy MJ, et al. The effect of aerobic exercise on metabolic and inflammatory markers in breast cancer survivors--a pilot study. *Supportive Care in Cancer* 2013;**21**(7):1983–92. [DOI: 10.1007/s00520-013-1743-5]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hozo 2015

Hozo Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2015;**5**(13):1–10. [DOI: 10.1186/1471-2288-5-13]

Iantorno 2014

Iantorno M, Campia U, Di Daniele N, Nistico S, Forleo GB, Cardillo C, et al. Obesity, inflammation and endothelial dysfunction. *Journal of Biological Regulators and Homeostatic Agents* 2014;**28**(2):169–76. [PUBMED: PMID: 25001649]

IARC of WHO 2012

IARC (International Agency for Research on Cancer) of WHO. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012-Cancer Fact sheet. World Health Organization 30 May 2015. [DOI: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx]

Imayama 2013

Imayama I, Alfano CM, Neuhouser ML, George SM, Wilder Smith A, Baumgartner RN, et al. Weight, inflammation, cancer-related symptoms and health related quality of life among breast cancer survivors. *Breast Cancer Research and Treatment* 2013;**140**(1):159–76. [PUBMED: PMID: 23797178]

Irwin 2007

Irwin ML, Aiello EJ, McTiernan A, Bernstein L, Gilliland FD, Baumgartner RN, et al. Physical activity, body mass index, and mammographic density in postmenopausal breast cancer survivors. *Journal of Clinical Oncology* 2007;**25**(9):1061–6. [DOI: 10.1200/JCO.2006.07.3965]

Jensen 2014

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. Journal of the American College of Cardiology 2014; Vol. 63, issue 25:2985–3023. [DOI: http://dx.doi.org/10.1016/j.jacc.2013.11.004]

Jones 2013

Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML. Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Prevention Research* 2013;**6**(2):109–18. [PUBMED: PMID: 23213072]

Kann 2014

Kann S, Schmid SM, Eichholzer M, Huang DJ, Amann E, Güth U. The impact of overweight and obesity on breast cancer: data from Switzerland, so far a country little affected by the current global obesity epidemic. *Gland Surgery* 2014;**3**(3):181–97. [DOI: 10.3978/j.issn.2227-684X.2013.12.01]

Kershaw 2004

Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *The Journal of Clinical Endocrinology & Metabolism* 2014;**89**(6):2548–56. [DOI: http://dx.doi.org/10.1210/jc.2004-0395]

Khandekar 2011

Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nature Reviews. Cancer* 2011;**11**(12):886–95. [PUBMED: PMID: 22113164]

Kim 2013

Kim A, Scharf K, Senthil M, Solomon N, Garberoglio C, Lum SS. The prevalence of overweight and obesity in a breast clinic population: consideration for weight loss as a therapeutic intervention. *Surgery for Obesity and Related Diseases* 2014;**10**(2):348–53. [10.1016/j.soard.2013.07.019. Epub 2013 Aug 30]

Lorizio 2012

Lorizio W, Wu AH, Beattie MS, Rugo H, Tchu S, Kerlikowske K, Ziv E. Clinical and biomarker predictors of side effects from tamoxifen. *Breast Cancer Research and Treatment* 2012;**132**(3):1107–18. [1107-1118. doi: 10.1007/s10549–011–1893–4]

Makari-Judson 2014

Makari-Judson G, Braun B, Jerry DJ, Mertens WC. Weight gain following breast cancer diagnosis: implication and proposed mechanisms. *World Journal of Clinical Oncology* 2014;**5**(3):272–82. [PUBMED: PMID: 25114844]

Mastorakos 2010

Mastorakos G, Valsamakis G, Paltoglou G, Creatsas G. Management of obesity in menopause: diet, exercise, pharmacotherapy and bariatric surgery. *Maturitas* 2010;**65**(3):219–24. [DOI: 10.1016/j.maturitas.2009.12.003]

Morimoto 2002

Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes & Control* 2002;**13**(8):741–51. [PUBMED: PMID: 12420953]

Nahas 2012

Nahas EA, de Almeida Bda R, Buttros Dde A, Vespoli Hde L, Uemura G, Nahas-Neto J. Metabolic syndrome in postmenopausal breast cancer survivors. *Revista Brasileira de Ginecologia e Obstetricia* 2012;**34**(12):555–62. [PUBMED: PMID: 23329285]

National Health and Medical Research Council 2013
National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Melbourne: National Health and Medical Research Council. www.nhmrc.gov.au/guidelines/publications/n57. Melbourn, 2013.

NCI 2014
National Cancer Institute (NCI). SEER Stat Fact Sheets: Breast Cancer. Surveillance, Epidemiology, and End Results Program (SEER). http://seer.cancer.gov/statfacts/html/breast.html 2014.

Office for National Statistics 2013
Office for National Statistics. Cancer survival in England: patients diagnosed 2007-2011 and followed up to 2012. Statistical Bulletin 2013. [http://www.ons.gov.uk/ons/dcp171778_333318.pdf]

Oh 2011
Oh SW, Park CY, Lee ES, Yoon YS, Lee ES, Park SS, et al. Adipokines, insulin resistance, metabolic syndrome, and breast cancer recurrence: a cohort study. *Breast Cancer Research* 2011;**13**(2):R34. [PUBMED: PMID: 21450081]

Ortiz-Mendoza 2014
Ortiz-Mendoza CM, de-la-Fuente-Vera TA, Pérez-Chávez E. Metabolic syndrome in Mexican women survivors of breast cancer: a pilot study at a general hospital. *Medical Archives* 2014;**68**(1):19–21. [PUBMED: PMID: 24783905]

Pakiz 2011
Pakiz B, Flatt SW, Bardwell WA, Rock CL, Mills PJ. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. *International Journal of Behavioral Medicine* 2011;**18**(4):333–41. [PUBMED: PMID: 21336679]

Parmar 1998
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34. [PUBMED: PMID: 9921604]

Patnaik 2011
Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Research* 2011;**13**(3):R64. [PUBMED: PMID: 21689398]

Pierce 2009
Pierce JP, Natarajan L, Caan BJ, Flatt SW, Kealey S, Gold EB, et al. Dietary change and reduced breast cancer events among women without hot flashes after treatment of early-stage breast cancer: subgroup analysis of the Women's Healthy Eating and Living Study. *The American Journal of Clinical Nutrition* 2011;**89**(5):1565S–71S. [PUBMED: PMID: 19339393]

Reeves 2014
Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. *Obesity Reviews* 2014;**15**(9):749–68. [PUBMED: PMID: 24891269]

RevMan [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rock 2004
Rock CL, Flatt SW, Thomson CA, Stefanick ML, Newman VA, Jones LA, et al. Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer. *Journal of Clinical Oncology* 2004;**22**(12):2379–87. [PUBMED: PMID: 15197199]

Rock 2012
Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journal for Clinicians* 2012;**62**(4):243–74. [PUBMED: PMID: 22539238]

Rock 2013
Rock CL, Pande C, Flatt SW, Ying C, Pakiz B, Parker BA, et al. Favorable changes in serum estrogens and other biologic factors after weight loss in breast cancer survivors who are overweight or obese. *Clinical Breast Cancer* 2013;**13**(3): 188–95. [PUBMED: PMID: 23375717]

Rogers 2008
Rogers LQ, Courneya KS, Verhulst S, Markwell SJ, McAuley E. Factors associated with exercise counseling and program preferences among breast cancer survivors. *Journal of Physical Activity & Health* 2008;**5**(5):688–705. [PUBMED: PMID: 18820344]

Schünemann 2011
Schunemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glaziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sedjo 2014
Sedjo RL, Byers T, Ganz PA, Colditz GA, Demark-Wahnefried W, Wolin KY, et al. Weight gain prior to entry into a weight-loss intervention study among overweight and obese breast cancer survivors. *Journal of Cancer Survivorship: Research and Practice* 2014;**8**(3):410–8. [PUBMED: PMID: 24599421]

Siiteri 1987
Siiteri PK. Adipose tissue as a source of hormones. *The American Journal of Clinical Nutrition* 1987;**45**(Supplement 1):277–82. [PUBMED: PMID: 3541569]

Slattery 2015
Slattery ML, Lundgreen A, John EM, Torres-Mejia G, Hines L, Giuliano AR, et al. MAPK genes interact with diet and lifestyle factors to alter risk of breast cancer: The Breast Cancer Health Disparities Study. *Nutrition and Cancer* 2015;**67**(2):292–304. [PUBMED: PMID: 25629224]

Su 2013
Su HI, Sue LY, Flatt SW, Natarajan L, Patterson RE, Pierce JP. Endogenous estradiol is not associated with poor physical health in postmenopausal breast cancer survivors. *Journal of Women's Health* 2013;**22**(12):1043–8. [PUBMED: PMID: 24111813]

Subirats Bayego 2012
Subirats Bayego E, Subirats Vila G, Soteras Martinez I. Exercise prescription: indications, dosage and side effects. *Medicina Clínica* 2012;**138**(1):18–24. [PUBMED: PMID: 21411113]

Thomas 2013
Thomas GA, Alvarez-Reeves M, Lu L, Yu H, Irwin ML. Effect of exercise on metabolic syndrome variables in breast cancer survivors. *International Journal of Endocrinology* 2013;**2013**:168797. [10.1155/2013/168797. Epub 2013 Nov 11]

Thompson 2014
Thompson CL, Owusu C, Nock NL, Li L, Berger NA. Race, age, and obesity disparities in adult physical activity levels in breast cancer patients and controls. *Frontiers in Public Health* 2014;**2**:150. [PUBMED: PMID: 25285306]

U.S. Department of Health and Human Services 2008
U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans. www.health.gov/paguidelines 2008.

Vagenas 2015
Vagenas D, DiSipio T, Battistutta D, Demark-Wahnefried W, Rye S, Bashford J, et al. Weight and weight change following breast cancer: evidence from a prospective, population-based, breast cancer cohort study. *BMC Cancer* 2015;**15**(1):28. [PUBMED: PMID: 25637285]

Vance 2011
Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obesity Reviews* 2011;**12**(4):282–94. [PUBMED: PMID: 20880127]

Vitolins 2014
Vitolins MZ, Milliron BJ, Hopkins JO, Fulmer A, Lawrence J, Melin S, et al. Weight loss intervention in survivors of ER/PR-negative breast cancer. *Clinical Medicine Insights. Women's Health* 2014;**7**:17–24. [PUBMED: PMID: 24987274]

Waxler-Morrison 1991
Waxler-Morrison N, Hislop TG, Mears B, Kan L. Effects of social relationships on survival for women with breast cancer: a prospective study. *Social Science & Medicine* 1991; **33**(2):177–83. [PUBMED: PMID: 1887281]

WHO 1997
WHO Consultation on Obesity, Division of Noncommunicable Diseases, Programme of Nutrition, Family and Reproductive Health. Obesity preventing and managing the global epidemic: report of a WHO consultation on obesity, 3-5 June 1997. World Health Organization, Geneva, 1998. [DOI: http://apps.who.int/iris/handle/10665/63854]

WHO 2015
World Health Organization. Obesity and Overweight. http://www.who.int/mediacentre/factsheets/fs311/en/ 15 July 2015.

Wikipedia 2015
Wikipedia. Bariatric Surgery. https://en.wikipedia.org/wiki/Bariatric_surgery 6 July 2015.

Yu 2014
Yu XQ, De Angelis R, Luo Q, Kahn C, Houssami N, O'Connell DL. A population-based study of breast cancer prevalence in Australia: predicting the future health care needs of women living with breast cancer. *BMC Cancer* 2014;**14**:936. [PUBMED: PMID: 25494610]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near neoplasm*
#3 breast near carcinom*
#4 breast near cancer*
#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: [Weight Reduction Programs] explode all trees
#10 weight reduction program* or weight near reduction near program*
#11 MeSH descriptor: [Weight Loss] explode all trees
#12 weight loss or weight near loss
#13 MeSH descriptor: [Body Weight Changes] explode all trees
#14 body weight chang* or body near weight near chang*
#15 MeSH descriptor: [Exercise] explode all trees
#16 MeSH descriptor: [Exercise Therapy] explode all trees
#17 exercis*
#18 exercise therap* or exercise near therap*
#19 MeSH descriptor: [Exercise Movement Techniques] explode all trees
#20 MeSH descriptor: [Physical Education and Training] explode all trees
#21 physical education and train*
#22 MeSH descriptor: [Physical Fitness] explode all trees
#23 physical near fitness or physical fitness
#24 MeSH descriptor: [Physical Exertion] explode all trees
#25 physical exertion or physical near exertion
#26 MeSH descriptor: [Sports] explode all trees
#27 sport*
#28 MeSH descriptor: [Motor Activity] explode all trees
#29 motor near activit* or physical activit* or physical near activit*
#30 MeSH descriptor: [Walking] explode all trees
#31 walk*
#32 MeSH descriptor: [Jogging] explode all trees
#33 jog*
#34 MeSH descriptor: [Swimming] explode all trees
#35 swim*
#36 MeSH descriptor: [Bicycling] explode all trees
#37 bicycl*
#38 MeSH descriptor: [Resistance Training] explode all trees
#39 (resistance or strength or weight) near train* or resistance train* or strength train* or weight train*
#40 MeSH descriptor: [Dancing] explode all trees
#41 MeSH descriptor: [Dance Therapy] explode all trees
#42 danc* near therap* or danc* therap* or danc*
#43 aerobic* near exercis* or aerobic exercis*
#44 MeSH descriptor: [Diet] explode all trees
#45 diet*
#46 MeSH descriptor: [Diet Therapy] explode all trees
#47 diet therapy or diet* near therap*
#48 MeSH descriptor: [Diet, Reducing] explode all trees

#49 body weight management or body near weight near manag* or weight management or weight near manag*
#50 MeSH descriptor: [Bariatric Surgery] explode all trees
#51 bariatric surger* or bariatric near surger*
#52 MeSH descriptor: [Bariatrics] explode all trees
#53 bariatrics
#54 MeSH descriptor: [Anti-Obesity Agents] explode all trees
#55 anti-obesity agent* or anti-obesity near agent* or anti-obesity drug* or anti-obesity near drug* or anti-obesity medic* or anti-obesity near medic*
#56 weight loss drug* or weight near loss near drug*
#57 weight loss medic* or weight near loss near medic*
#58 orlistat
#59 sibutramine
#60 L-carnitine or carnitine
#61 metformin
#62 weight loss intervention or weight near loss near intervention*
#63 MeSH descriptor: [Behavior Therapy] explode all trees
#64 behavior therap* or behavior near therap* or behaviour therap* or behaviour near therap*
#65 MeSH descriptor: [Cognitive Therapy] explode all trees
#66 cogniti* therap* or cogniti* near therap*
#67 MeSH descriptor: [Psychotherapy] explode all trees
#68 psychotherap*
#69 lifestyle modification or lifestyle near modif*
#70 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
#71 #8 and #70

Appendix 2. MEDLINE (via OvidSP)

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/

(*Continued*)

10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	(breast adj6 cancer$).tw.
14	(breast adj6 neoplasm$).tw.
15	(breast adj6 carcinoma$).tw.
16	(breast adj6 tumo?r$).tw.
17	or/12-16
18	exp Weight Reduction Programs/
19	weight reduc* program*.tw.
20	exp Weight Loss/
21	weight loss.tw.
22	exp body weight changes/
23	exp Exercise/
24	exercise.tw.
25	exp Exercise Movement Techniques/
26	exp Exercise Therapy/
27	exercise therap*.tw.
28	exp "Physical Education and Training"/
29	((physical adj6 education) and training).tw.
30	(physical and (education adj6 training)).tw.
31	((physical adj6 education) and training).tw.
32	(physical and (education adj6 training)).tw.
33	exp Physical Fitness/

(*Continued*)

34	physical fitness.tw.
35	(physical adj6 fitness).tw.
36	Physical Exertion/
37	exertion.tw.
38	exp Sports/
39	sport*.tw.
40	Motor Activity/
41	physical activit*.tw.
42	(physical adj6 activit*).tw.
43	exp Walking/
44	walk*.tw.
45	exp Jogging/
46	jog*.tw.
47	exp Swimming/
48	swim*.tw.
49	Bicycling/
50	bicycl*.tw.
51	weight training.tw.
52	(weight adj6 training).tw.
53	Dancing/
54	Dance Therapy/
55	danc*.tw.
56	(dance adj6 therap*).tw.
57	dance therap*.tw.

(*Continued*)

58	(aerobic adj6 exercis*).tw.
59	aerobic exercise.tw.
60	Resistance Training/
61	resistance train*.tw.
62	((resistance or strength) and train*).tw.
63	((resistance or strength) adj6 train*).tw.
64	strength train*.tw.
65	exp Diet Therapy/
66	exp Diet/
67	(diet adj6 therap*).tw.
68	diet therap*.tw.
69	diet*.tw.
70	Diet, Reducing/
71	body weight management.tw.
72	(weight adj6 manag*).tw.
73	exp bariatric surgery/
74	bariatric surger*.tw.
75	(bariatric adj6 surger*).tw.
76	exp Bariatrics/
77	exp Anti-Obesity Agents/
78	anti-obesity drug*.tw.
79	(anti-obesity adj6 drug).tw.
80	exp Appetite Depressants/
81	(obesity adj6 (drug* or medic*)).tw.

(*Continued*)

82	weight loss drug*.tw.
83	weight loss medic*.tw.
84	((weight and loss) adj6 (drug* or medic*)).tw.
85	((weight adj6 loss) and (drug* or medic*)).tw.
86	orlistat.mp.
87	sibutramine.mp.
88	L-carnitine.mp.
89	metformin.mp.
90	weight loss intervention.tw.
91	((weight and loss) adj6 intervention*).tw.
92	((weight adj6 loss) and intervention*).tw.
93	exp Behavior Therapy/
94	behaviour therap*.tw.
95	(behaviour adj6 therap*).tw.
96	exp Cognitive Therapy/
97	cogniti* therap*.tw.
98	(cogniti* adj6 therap*).tw.
99	exp Psychotherapy/
100	lifestyle modification.tw.
101	(lifestyle adj6 modif*).tw.
102	or/18-101
103	11 and 17 and 102
104	exp animals/ not humans/

(*Continued*)

105	103 not 104

Appendix 3. EMBASE (via Embase.com)

#1	random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp
#2	'breast'/exp OR 'breast disease'/exp AND 'neoplasm'/exp OR 'breast tumor'/exp OR (breast* NEAR/5 neoplas*):ab,ti OR (breast* NEAR/5 cancer*):ab,ti OR (breast* NEAR/5 carcin*):ab,ti OR (breast* NEAR/5 tumo*):ab,ti OR (breast* NEAR/5 metasta*):ab,ti OR (breast* NEAR/5 malig*):ab,ti
#3	'breast cancer'/exp OR 'breast cancer' OR 'breast neoplasm' OR 'breast carcinoma'/exp OR 'breast carcinoma' OR 'breast tumour' OR 'breast tumor'/exp OR 'breast tumor'
#4	#2 OR #3
#5	'weight reduction'/exp OR 'weight reduction' OR 'weight reduction' NEAR/6 program* OR 'weight loss' NEAR/6 program*
#6	'aerobic exercise'/exp OR 'aerobic exercise' OR aerobic NEAR/6 exercise*
#7	'exercise'/exp OR 'exercise'
#8	'kinesiotherapy'/exp OR 'exercise therapy' OR exercise* NEAR/6 therap*
#9	'movement therapy'/de OR 'movement therapy' OR movement NEAR/6 therap* OR 'exercise movement' OR exercise* NEAR/6 movement
#10	'physical education'/exp OR 'physical education and training' OR physical NEAR/6 education*
#11	'fitness'/exp OR 'physical fitness' OR physical NEAR/6 fitness
#12	'physical exertion'OR physical NEAR/6 exertion
#13	'sport'/exp OR 'sports' OR sport*
#14	'physical activity'/exp OR 'physical activity' OR physical NEAR/6 activit*
#15	'motor activity'/exp OR 'motor activity' OR motor NEAR/6 activit*
#16	'walking'/exp OR 'walking' OR walk*
#17	'jogging'/exp OR 'jogging' OR jog*

(*Continued*)

#18	'swimming'/exp OR 'swimming' OR swim*
#19	'cycling'/exp OR 'cycling' OR 'bicycling' OR bicycl*
#20	'weight lifting'/exp OR 'weight lifting' OR weight NEAR/6 lift* OR 'weight training' OR weight NEAR/6 train*
#21	'dance therapy'/exp OR 'dance therapy' OR danc* NEAR/6 therap* OR 'dance movement therapy' OR dance AND movement AND therap*
#22	'resistance training'/exp OR 'resistance training' OR resistance NEAR/6 train* OR 'strength training' OR strength NEAR/6 train*
#23	'diet therapy'/exp OR 'diet therapy' OR diet NEAR/6 therap*
#24	'diet'/exp OR 'diet'
#25	'body weight'/exp OR 'body weight' OR bod* NEAR/6 weight*
#26	'body weight management' OR 'body weight' NEAR/6 manag* OR weight* NEAR/6 manag*
#27	'bariatric surgery'/exp OR 'bariatric surgery' OR bariatric* NEAR/6 surger*
#28	'bariatrics'/exp OR 'bariatrics' OR bariatric*
#29	'antiobesity agent'/exp OR 'anti-obesity agent' OR 'anti obesity' NEAR/6 agent* OR 'anti-obesity drug' OR 'anti-obesity' NEAR/6 drug* OR 'anti-obesity medication' OR 'anti-obesity' NEAR/6 medic*
#30	'anorexigenic agent'/exp OR 'appetite suppressant' OR appetite NEAR/6 suppressant
#31	'weight loss medication'OR 'weight loss' NEAR/6 (medic* OR drug*) OR 'weight loss drug'
#32	orlistat
#33	sibutramine
#34	'carnitine'/exp OR 'carnitine' OR 'l-carnitine'
#35	'metformin'/exp OR 'metformin'
#36	'weight loss intervention'OR 'weight loss' NEAR/6 intervention
#37	'behavior therapy'/exp OR 'behavior therapy' OR behavior* NEAR/6 therap* OR 'behaviour therapy' OR behaviour* NEAR/6 therap*
#38	'cognitive therapy'/exp OR 'cognitive therapy' OR cognit* NEAR/6 therap*
#39	'psychotherapy'/exp OR 'psychotherapy' OR psychotherap*

(*Continued*)

#40	'lifestyle modification'/exp OR 'lifestyle modification' OR lifestyle* NEAR/6 modif*
#41	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#1 AND #4 AND #41
#43	#42 AND [humans]/lim AND [embase]/lim

Appendix 4. WHO ICTRP search portal

Basic searches:
1. breast cancer AND weight loss
2. breast cancer AND exercise
3. breast cancer AND physical activity
4. breast cancer AND diet
5. breast cancer AND bariatric surgery
6. breast cancer AND anti-obesity drug
7. breast cancer AND lifestyle modification
8. breast cancer AND behavior modification
9. breast cancer AND behaviour modification
Advanced searches:
1. Title: Body weight management in breast cancer survivors
Recruitment status: ALL
2. Condition: breast cancer OR breast neoplasm
Intervention: weight loss OR weight reduction
Recruitment status: ALL
3. Condition: breast cancer OR breast neoplasm
Intervention: exercis* OR exercise therap* OR sport* OR physical activit* OR walk* OR jog* OR swim* OR bicycl* OR weight training OR dancing OR dance OR resistance OR strength
Recruitment status: ALL
4. Condition: breast cancer OR breast neoplasm
Intervention: body weight management OR weight management OR diet OR diet therap* OR bariatric surger* OR weight loss surgery
Recruitment status: All
5. Condition: breast cancer OR breast neoplasm
Intervention: weight loss drug OR weight loss medic* OR anti-obesity drug OR anti-obesity medic* OR anti obesity agents OR orlistat OR sibutramine OR L-carnitine OR carnitine OR metformin
Recruitment status: All
6. Condition: breast cancer OR breast neoplasm
Intervention: behavior therap* OR behaviour therap* OR cognitive therap* OR psychotherap* OR lifestyle modification
Recruitment status: All

Appendix 5. Clinicaltrials.gov

Basic searches:
1. breast cancer AND weight loss
2. breast cancer AND exercise
3. breast cancer AND physical activity
4. breast cancer AND diet
5. breast cancer AND weight loss surgery
6. breast cancer AND anti obesity agents
7. breast cancer AND lifestyle modification
8. breast cancer AND behavior modification
Advanced searches:
1. Title: Body weight management in breast cancer survivors
Recruitment: All studies
Study Results: All studies
Study Type: All studies
2. Conditions: breast cancer OR breast neoplasm
Interventions: weight loss OR weight reduction
Recruitment status: All studies
Study type: All studies
3. Condition: breast cancer OR breast neoplasm
Intervention: exercis* OR exercise therap* OR sport* OR physical activit* OR walk* OR jog* OR swim* OR bicycl* OR weight training OR dancing OR dance OR resistance OR strength
Recruitment status: All studies
Study Results: All studies
Study type: All studies
4. Condition: breast cancer OR breast neoplasm
Intervention: body weight management OR weight management OR diet OR diet therap* OR bariatric surger* OR weight loss surgery
Recruitment status: All studies
Study Results: All studies
Study type: All studies
5. Condition: breast cancer OR breast neoplasm
Intervention: weight loss drug OR weight loss medic* OR anti-obesity drug OR anti-obesity medic* OR anti obesity agents OR orlistat OR sibutramine OR L-carnitine OR carnitine OR metformin
Recruitment status: All studies
Study Results: All studies
Study type: All studies
6. Condition: breast cancer OR breast neoplasm
Intervention: behavior therap* OR behaviour therap* OR cognitive therap* OR psychotherap* OR lifestyle modification* OR behavior modification*
Recruitment status: All studies
Study Results: All studies
Study type: All studies

Appendix 6. Data extraction table

Source: Study ID, review author ID, and citation and contact details (Correspondence).
For methods: study design, total study duration, sequence generation, allocation sequence concealment, blinding, and other concerns about bias (see 'Risk of bias' table).
For participants: Total numbers indicate whether excluded before or after Tx, and the numbers randomised, excluded, lost to follow-up, changed Tx and evaluated; in addition, setting, diagnostic criteria, age, sex, country, co-morbidity, social-demographics, ethnicity and date of study.
For interventions: total number of intervention groups, intervention details such as route, total dose or intensity, timing, duration, supervision; drug source (sufficient for replication, if feasible).
For outcomes: outcomes and time points (collected and reported), outcome definition (with diagnostic criteria), unit of measurement, for scales: upper and lower limits, and whether high or low score is good. For each outcome result: sample size, missing participants, summary data for each intervention group (e.g. 2×2 table for dichotomous data; means and SDs for continuous data), Estimate of effect with confidence interval and P value.
Investigator contacted for more information: Yes / No
If Yes, highlight on the form the information that was provided

CONTRIBUTIONS OF AUTHORS

1. Draft of protocol: JV, LXM, MKB, and SYT
2. Study selection: LXM, SYT, JV and MKB
3. Extract data from studies: LXM, SYT, JV and MKB
4. Enter data into RevMan: LXM, SYT, JV and MKB
5. Carry out the analysis: LXM, SYT, JV and MKB
6. Interpret the analysis: JV, LXM, SYT and MKB
7. Draft the final review: JV, LXM, SYT and MKB
8. Disagreement resolution: JV and MKB
9. Update the review: JV, LXM, SYT and MKB

DECLARATIONS OF INTEREST

LXM: None known.

MKB: None known.

SYT: None known.

JV: None known.

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Internal sources

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- Nutrition and Food Hygiene Department, Hebei University, Baoding, China.

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- Institute for Health Research, The University of Notre Dame Australia, Fremantle, Australia.

Salary

- Nutrition and Dietetics Department, Concord Repatriation General Hospital, Concord, Australia.

Salary

External sources

- The Commonwealth of Australia, Australia.

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