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Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer (Protocol)

Roberts KE, Rickett K, Vagenas D, Woodward NE

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[Intervention Protocol]

Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of exercise therapies on the prevention or management of aromatase inhibitor-induced musculoskeletal symptoms (AIMSS) in women with stage I-III hormone receptor-positive breast cancer.

BACKGROUND

Description of the condition

Breast cancer remains a major public health problem despite advances in screening and treatment. There was an estimated 1.67 million new cases diagnosed in 2012, making breast cancer the most common non-skin cancer in women (Ferlay 2012). With 522,000 deaths, breast cancer was the fifth most common cause of cancer death globally in 2012 (Ferlay 2012). In women in developed regions of the world, breast cancer is second to lung cancer as the leading cause of cancer death, and in less developed regions, breast cancer remains the leading cause of cancer death (Ferlay 2012). Hormone receptor-positive breast cancer, i.e. oestrogen receptor (ER)-positive, or progesterone receptor (PR)-positive, or both, accounts for about 80% of breast cancer, with women with early breast cancer usually having oestrogen or 'endocrine-sensitive' cancer (Nadji 2005). Treatment of postmenopausal women with hormone receptor-positive breast cancer with aromatase inhibitor (AI) medications is effective. Five years of AI therapy in early breast cancer improves disease-free survival (DFS) and breast cancer specific survival (BCSS) when compared to another hormonal therapy, tamoxifen (Aydiner 2013; EBCTCG 2015). However, AIs are commonly associated with joint and muscular symptoms, referred to as aromatase inhibitor-induced musculoskeletal symptoms (AIMSS) (Lintermans 2013). Nearly half of all women on AIs experience these side effects (Beckwee 2017).

AIMSS often presents as symmetrical pain or soreness in multiple joints, and is also often associated with early morning stiffness (Burstein 2007). Despite the survival advantage of AIs, these side effects are causing a quarter to half of all women on this treatment to discontinue (Chim 2013; Henry 2012; Kadakia 2016). An association between switching AIs and the development of new musculoskeletal pain has been identified (Kemp-Casey 2017). If AIMSS can be managed, then quality of life and adherence to treatment may improve, and the survival advantage from using AI therapy may not be compromised.

Description of the intervention

Exercise can be defined as "a subset of physical activity that is planned, structured, repetitive, and has as a final or an intermediate objective of the improvement or maintenance of physical fitness" (Caspersen 1985). The definition of therapy in the Merriam-Webster dictionary is the "therapeutic treatment especially of bodily, mental, or behavioral disorder" (Merriam-Webster). Exercise therapies investigated in this review involve a variety of therapeutic interventions intended to improve or maintain fitness. These include, but are not restricted to, cardiovascular and resistance exercises, yoga, tai-chi, aquatic exercise, walking and Pilates.

How the intervention might work

The cause of AIMSS is unknown, and therefore the mechanism for the effectiveness of exercise therapies on AIMSS cannot be ascertained. There has been a growing interest in conducting research into the effect of exercise on a wide variety of conditions, such as the effect on cancer mortality, recurrence and treatment-related adverse effects (Cormie 2017), cancer-related fatigue and mobility (Dennett 2016), quality of life in cancer survivors (Mishra 2012), the immune system (Szlezak 2016), and rheumatological conditions, such as osteoarthritis (Fransen 2014; Osteras 2017). There has been a large phase III randomised control trial (RCT) investigating the intervention of cardiovascular and resistance exercise in the treatment of AIMSS, which reported a clinically significant benefit with the use of exercise (Irwin 2015). Therefore, even though the mechanism of any potential benefit of exercise in this area is largely unknown, a positive result from a large phase III RCT, plus multiple other smaller studies in this field, warrants a comprehensive review of these therapies.

Why it is important to do this review

AIMSS has a clinical impact on the management of women with breast cancer, as studies have shown significant rates of suboptimal adherence to AIs (Brier 2017; Hadji 2014; Henry 2012; Hershman 2011; Partridge 2008; Presant 2007). Non-compliance with endocrine therapies in the adjuvant setting may impact on women's survival (Hershman 2011). To date, there is limited evidence regarding the best management options for AIMSS. With a growing emphasis on the management of survivorship issues for women with early breast cancer, this area of research is very topical, and of increasing importance. It has been identified that oncologists may feel ill-equipped to prescribe exercise to women with early breast cancer (Smaradottir 2017), and providing a stronger evidence base for the role of exercise in managing symptoms may assist with this issue.

OBJECTIVES

To assess the effects of exercise therapies on the prevention or management of aromatase inhibitor-induced musculoskeletal symptoms (AIMSS) in women with stage I-III hormone receptor-positive breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) looking at the prevention or management of AIMSS in women with stage I-III hormone receptor-positive breast cancer. AIMSS will be defined by the study authors of each trial. We will exclude animal and in vitro studies. We will consider studies in all languages for inclusion.

Types of participants

Women aged ≥18 years with stage I-III oestrogen receptor (ER)-positive, or progesterone receptor (PR)-positive breast cancer, or both, being treated adjuvantly with aromatase inhibitors (AIs).

Types of interventions

We will include all exercise therapy interventions, such as aerobic and resistance exercise, tai chi, yoga and aqua aerobics. We will exclude musculoskeletal manipulation therapies, such as massage and kinesiology. We will not impose any restriction on the type of comparator arm; comparator arms may include an alternative type of exercise, no exercise, or a waiting-list control.

Types of outcome measures

Primary outcomes

- Symptoms of AIMSS (pain, stiffness, and grip-strength) from baseline. These will preferably be assessed by validated questionnaires, such as the Visual Analogue Scale (VAS), Brief Pain Inventory (BPI), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Functional Assessment of Cancer Therapy - General (FACT-G), Medical Outcome Study Short Form 36 (SF-36), and the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH)
- Safety of the intervention, including adverse effects, such as injury

Secondary outcomes

- Incidence of AIMSS
- Persistence and compliance of women continuing to take their AI medication due to the intervention
- Participant health-related quality of life, also preferably assessed by validated participant-reported outcome questionnaires
- Breast cancer specific survival (BCSS)
- Overall survival (OS)

Search methods for identification of studies

Electronic searches

We will search the following databases.

- The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. We will extract and consider for inclusion in the review trials with the key words "breast cancer" and related terms, "aromatase inhibitors", "exemestane", "anastrozole", "letrozole", "exercise", "physical activity", "resistance training", "yoga", "walking", "T'ai chi".
- MEDLINE (via PubMed) from 1946 to present. (See Appendix 1).
- Embase (via Embase.com) from 1947 to present. (See Appendix 2).
- CENTRAL (the Cochrane Library, latest issue. (See Appendix 3).
- The WHO International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch) for all prospectively registered and ongoing trials. (See Appendix 4).
- Clinicaltrials.gov (clinicaltrials.gov). (See Appendix 5).
- CINAHL (via EBSCO) from 1937 to present. (See Appendix 6)

Searching other resources

Bibliographic searching

We will try to identify further studies from reference and citation lists of identified relevant trials or reviews. We will obtain a copy of the full article for each reference reporting a potentially eligible trial. Where this is not possible, such as with the inclusion of conference abstracts, we may source additional information from clinical trial databases, and we will attempt to contact authors to provide additional information.

Grey searching

We will screen conference abstracts from major conferences (i.e. San Antonio Breast Cancer Symposium (SABCS) and American Society of Clinical Oncology (ASCO)) via the Cochrane Breast Cancer Group's Specialised Register and Embase search results (see Electronic searches). We will also search Google Scholar by applying a two-year date limit.

Data collection and analysis

Selection of studies

Two review authors (KER and KR) will screen retrieved abstracts from the literature search and assess whether the abstracts meet the specified selection criteria. Subsequently, KER and KR will then review full-texts of all remaining studies to ensure that they still meet the selection criteria. Any disagreements on study selection will be resolved by a separate review author (NW). We will record the selection process in a PRISMA flow diagram (Liberati 2009). We will document the reason for excluding any studies in the 'Characteristics of excluded studies' tables. We will translate articles in languages other than English (where possible), when relevant to this review.

Data extraction and management

We will perform data extraction using a standard data extraction form that includes the following.

Characteristics of the study

- Study sponsors and author affiliations
- Study funding
- Methods, including study design, method of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome, participant attrition and exclusions, and selective outcome reporting
- Full-text availability versus abstract only

Characteristics of the study population

- Country of enrolment
- Inclusion/exclusion criteria
- Study definition of AIMSS
- Number of participants in each treatment arm
- Mean and range of participant ages
- Type of AI prescribed to the participant

Characteristics of the intervention

- Description of the intervention
  - Aerobic/resistance/combination/other
  - Exercise intensity: mild/moderate/vigorous
  - Frequency and duration of sessions
  - Duration of intervention period
  - Supervised versus home-based, group versus individual
- Details of control or waiting-list group
- Compliance with intervention
- Safety

Characteristics of the outcomes

- Scoring systems used (and documentation of participant-reported outcomes versus investigator-reported outcomes)
- Outcomes of pain, stiffness, grip-strength and health-related quality of life
- Change in incidence of AIMSS
- Timing of outcome data collection, including length of time between intervention and last collected outcome measurement
- Follow-up period

Two review authors (KER and KR) will perform data extraction and a third review author (NW) will resolve disagreements, if needed. KER will enter data into Review Manager 5 (Review Manager 2014). If there is more than one publication for a study, we will extract the data from all publications as required, but we will consider the most recent version of the study to be the primary reference. If possible, we will combine records relating to the same study under an overall trial name or ID.

Assessment of risk of bias in included studies

We will perform assessment of risk of bias for all RCTs using Cochrane's 'Risk of bias' assessment tool (Higgins 2011). This includes the assessment of seven specific domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. We will assess each trial domain as high risk, low risk or unclear risk. Two review authors (KER and KR) will independently assess studies for risk of bias and a third review author (NW) will resolve any disagreements. Where there is incomplete reporting of the conduct of a study, we will attempt to contact the authors of the study to clarify any uncertainties. We will incorporate a summary table, listing the 'Risk of bias' judgement for all studies into the review results.

Measures of treatment effect

We expect that studies will use a variety of different tools to measure the outcomes of interest (pain, stiffness, grip-strength and health-related quality of life) and will be reporting continuous outcomes. We therefore, plan to measure the treatment effect by performing a standardised mean difference (SMD) analysis, using a random-effects model to combine data from different instruments measuring the same domain. If we cannot obtain standard deviations (SDs) for studies, we will attempt to impute the standard deviation as per Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). By performing a SMD analysis, we run the risk of giving greater weight to the studies reporting change-from-baseline SDs, as the SDs in these studies may be more precise than studies only reporting final value SDs (Deeks 2011). Therefore, where possible, we will perform a separate analysis on final values and change-from-baseline values, and compare the results.

If studies report dichotomous outcomes, we will measure the treatment outcome by the risk ratio (RR), in combination with a 95% confidence interval (CI). We will report the ratio of treatment effect for the response so that a RR less than 1.0 favours the intervention group for relief of AIMSS symptoms and a RR greater than 1.0 favours the control group.

Unit of analysis issues

We will perform the analysis of studies with non-standard designs as per the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For cross-over trial designs, we will take the within-person design into account, so that we minimise the study receiving too little weight in the meta-analysis, and therefore risk potentially disguising clinically important heterogeneity. We will also adjust the analysis for correlation, if required. For multiple-arm studies, where possible, we will combine all intervention groups into a single intervention group, and combine all control groups into a single control group. We will then undertake a single pair-wise comparison, which will overcome the unit of analysis issue of a potential correlation between the estimated intervention effect of multiple comparisons. If we deem this method to be unsuitable, we will use one of the other recommended approaches from Chapter 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), such as undertaking a multiple treatments meta-analysis, or to include two or more correlated comparisons, and account for the correlation.

Dealing with missing data

In the case of missing data, we will source additional information through clinical trial registries or data repositories. If the required data are still not available, we will contact original investigators via email, or written correspondence, or both, and give three weeks to reply to the request. If we do not obtain a reply, we will attempt further contact with the original investigators, giving them an additional two weeks to reply. If we are unable to obtain missing data, we will explain this in the Discussion section of our review.

Assessment of heterogeneity

We will assess clinical heterogeneity using the I^2 statistic, Chi^2 test, and visual inspection of forest plots, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). An I^2 result of 30% to 60% may represent moderate heterogeneity, a result of 50% to 90% may represent substantial heterogeneity, and a result of 75% to 100% represents considerable heterogeneity (Higgins 2011). The importance of the I^2 result will depend on the magnitude and direction of effects, and the strength of evidence for heterogeneity. If there is significant heterogeneity, we will use a random-effects model for analysis of results. For the Chi^2 test, $P < 0.1$ indicates significant heterogeneity.

Assessment of reporting biases

We will assess reporting biases by visual examination of funnel plots for asymmetry. Testing for funnel plot asymmetry, and the limitations involved in this assessment will be guided by Chapter 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). As funnel plot asymmetry can be affected by sample size and reporting biases (Egger 1998), we may need to carry out additional sensitivity tests.

Data synthesis

We will perform statistical analysis using Review Manager 5 software (Review Manager 2014). We will assess for clinical heterogeneity (see Assessment of heterogeneity). If there is significant heterogeneity between studies, we will use a random-effects meta-analysis, using the inverse variance method to combine data results.

We will report the meta-analysis mainly by forest plots and the 'Summary of findings' table. If there is an insufficient number of studies for us to pool for meta-analysis, or we cannot combine the data, we will present the findings in a narrative manner.

'Summary of findings' table

We will develop a 'Summary of findings' table to assess the quality of evidence using the GRADE approach, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 12.2 (Schünemann 2011). The GRADE approach assesses the evidence using five considerations: study limitations, consistency of effect, imprecision, indirectness and publication bias. The key outcomes we will include in the 'Summary of findings' table are:

- overall change in worst pain scores;
- overall change in stiffness scores;
- overall change in grip-strength;
- overall change in quality of life scores;
- overall change in the incidence of AIMSS;
- adverse effects, secondary to the intervention; and
- persistence and compliance of participants continuing to take their AI medication due to the intervention.

We will develop the 'Summary of findings' table using GRADEpro GDT software (GRADEpro GDT 2015). Two review authors (KER, KR) will independently assess the evidence using the GRADE approach and a third review author (NW) will resolve any disputes.

Subgroup analysis and investigation of heterogeneity

Where possible, we will perform a subgroup analysis based on:

- type of exercise (i.e. aerobic/resistance/combination/other);
- supervised versus home-based; and
- intensity of treatment (i.e. mild/moderate/vigorous).

Sensitivity analysis

If there are adequate data available, we will undertake further sensitivity analyses to examine the robustness of our conclusions. We will do this by restricting the analysis to published studies, and also by restricting the analysis to those studies with a low risk of bias. We will assess this by summarising the risk of bias for an outcome across multiple domains.

ACKNOWLEDGEMENTS

We would like to acknowledge the contributions of the peer-reviewers for this protocol: Fran Boyle (external clinical reviewer), Rebecca Seago-Coyle (consumer) and Max Bulsara (statistical editor).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE

1. "exemestane"[Supplementary Concept])
2. "Aromatase Inhibitors"[Mesh])
3. "Aromatase Inhibitors"[Pharmacological Action]
4. "letrozole"[Supplementary Concept]
5. "Aminoglutethimide"[Mesh]
6. "anastrozole"[Supplementary Concept]
7. "atamestane"[Supplementary Concept]
8. "Fadrozole"[Mesh]
9. "formestane"[Supplementary Concept]
10."vorozole"[Supplementary Concept]
11.aromatase inhibitor*
12.anastrozole
13.arimidex
14.exemestane
15.letrozole
16.aromasin
17.femara
18.fadrozole
19.formestane
20.rivizor
21.cytadren
22.aminoglutethimide
23. 1 OR 2 OR 3 OR 4 OR 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
24. (breast* OR mammary) AND (cancer OR cancers OR cancerous OR carcinoma OR malignant* OR tumor OR tumors OR tumour OR tumours OR adenocarcinoma*)
25. ("Breast"[Mesh] OR Breast Diseases"[Mesh]) AND "Neoplasms"[Mesh]
26."Breast Neoplasms"[Mesh]
27. 24 OR 25 OR 26
28."Exercise Therapy"[Mesh]
29. "Exercise Movement Techniques"[Mesh]
30. "Sports"[Mesh]
31. "Dancing"[Mesh]
32. "Exercise"[Mesh]
33. "Resistance training"[MeSH Terms]
34. dhyan*[Text Word] OR pranayam*[Text Word] OR asana [Text Word] OR bikram [Text Word] OR vinyasa [Text Word] OR hatha [Text Word] OR ashtanga [Text Word] OR iyengar [Text Word] OR kundalini [Text Word] OR yoga OR yogi*
35. (sport OR sports* OR walk* OR swim* OR aquatic OR danc* OR running OR jogging OR aerobic* OR pilates OR qigong OR "qi gong" OR "chi kung" OR "chi gung" OR exercis* OR gym* OR isometric* OR "tai chi" OR "t'ai chi" OR taijiquan)
36. (exercise* AND (therap* OR program* OR training*))
37. (physical OR strength* OR resistance OR isometric) AND (exercis* OR activit* OR therapy OR therapies OR therapeutic OR program* OR training)
38. 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39. randomized controlled trial[Publication Type]
40. controlled clinical trial[Publication Type]
41. randomized[Title/Abstract]
42.randomised[Title/Abstract]
43.randomly[Title/Abstract]

44. placebo[Title/Abstract]
45.trial[Title/Abstract])
46.groups[Title/Abstract]
47. 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46
48. 23 AND 27 AND 38 AND 47
49. "Animals"[Mesh] NOT "Humans"[Mesh]
50. 48 NOT 49

Appendix 2. Embase

(((aromatase NEAR/2 inhibit* OR 'aromatase inhibitor'/exp OR anastrozole OR exemestane OR 'letrozole' OR aminoglutethimide* OR atamestane OR fadrozole OR formestane OR vorozole OR arimidex OR aromasin OR femara OR fadrozole OR lentaron OR rivizor OR cytadren)
AND
('breast cancer'/exp OR (breast OR mammary) NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo*r* OR adenocarcinoma*) OR ('neoplasm'/exp AND ('breast'/exp OR 'breast disease'/exp)))
AND
('sport'/exp OR 'dancing'/exp OR 'exercise'/exp OR 'walking'/exp OR 'physical activity'/exp 'resistance training'/exp) OR (sport* OR walk* OR swim* OR aquatic OR danc* OR running OR jogging OR aerobic* OR pilates OR exercis* OR gym* OR isometric*) OR (sport*:ti,ab OR walk*:ti,ab OR swim*:ti,ab OR aquatic:ti,ab OR danc*:ti,ab OR running:ti,ab OR jogging:ti,ab OR aerobic*:ti,ab OR pilates:ti,ab OR exercis*:ti,ab OR gym*:ti,ab OR isometric*:ti,ab) OR (exercise* NEAR/3 (therap* OR program* OR training*)):ti,ab OR ((physical OR strength OR resistance OR isometric) NEAR/3 (exercis* OR activity* OR therap* OR program* OR training)):ti,ab OR (qigong:ti,ab OR 'qi gong':ti,ab OR 'chi kung':ti,ab OR 'chi gung':ti,ab) OR ('tai chi' OR 't?ai chi' OR taijiquan) OR (yoga:ti,ab OR yogi*:ti,ab) OR (dhyan:ti,ab OR pranayam:ti,ab OR asana:ti,ab OR bikram:ti,ab OR vinyasa:ti,ab OR hatha:ti,ab OR ashtanga:ti,ab OR iyengar:ti,ab OR kundalini:ti,ab)))
AND
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

Appendix 3. CENTRAL

#1 MeSH descriptor: [Aromatase Inhibitors] explode all trees
#2 aromatase inhibit* (Word variations have been searched)
#3 anastrozole or exemestane or letrozole or aminoglutethimide* or atamestane or fadrozole or formestane or vorozole or arimidex or aromasin or femara or fadrozole or lentaron or rivizor or cytadren (Word variations have been searched)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Breast Neoplasms] explode all trees
#6 breast near cancer*
#7 breast near (tumour* or tumor*)
#8 breast near malignan*
#9 breast near (carcinoma* or adenocarcinoma*)
#10 #5 or #6 or #7 or #8 or #9
#11 (physical or strength* or resistance or isometric*)
#12 (exercise* or activit* or therap* or program* or training)
#13 #11 near #12
#14 exercise near (therap* or program* or training*)
#15 MeSH descriptor: [Exercise Therapy] explode all trees
#16 MeSH descriptor: [Exercise] explode all trees
#17 sport or sports* or walk* or swim* or aquatic or danc* or running or jogging or aerobic* or pilates or qigong or "qi gong" or "chi kung" or "chi gung" or exercis* or gym* or isometric*

#18 tai chi or t'ai chi or taijiquan or yoga or yogi* or dhyan or pranayam or asana or bikram or vinyasa or hatha or ashtanga or iyengar or kundalini
#19 #13 or #14 or #15 or #16 or #17 or #18
#20 #4 and #10 and #19 [in trials]

Appendix 4. WHO ICTRP

breast cancer AND aromatase AND exercise
breast cancer AND aromatase AND yoga
breast cancer AND aromatase AND training
breast cancer AND aromatase AND physical activity

Appendix 5. ClinicalTrials.gov

breast cancer AND aromatase | exercise OR physical OR yoga OR activity OR training OR walking | Studies with Female Participants

Appendix 6. CINAHL

S1 (MH "Aromatase Inhibitors+")
S2 TX (aromatase N3 inhibit*)
S3 TX exemestane
S4 TX letrozole
S5 TX Aminoglutethimide*
S6 TX atamestane
S7 TX fadrozole
S8 TX formestane
S9 TX vorozole
S10 TX arimidex
S11 TX aromasin
S12 TX femara
S13 TX fadrozole or TX anastrozole or TX rivizor or TX cytadren or TX lentaron
S14 TX hormon* W1 therapy*
S15 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16 (MH "Breast Neoplasms+")
S17 (MH "Breast+")
S18 (MH "Neoplasms+")
S19 S18 AND S19
S20 TX ((breast* OR mammary) N3 (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumo#r*))
S21 S16 or S19 or S20
S22 (MH "Therapeutic Exercise+")
S23 (MH "Exercise+")
S24 (MH "Resistance Training")
S25 (MH "Physical Activity")
S26 (MH "Physical Fitness") OR (MH "Physical Performance") OR (MH "Sports+")
S27 (MH "Walking+") or (MH "Swimming")
S28 (MH "Dance Therapy") OR (MH "Dancing+")
S29 (MH "Yoga+") OR (MH "Tai Chi")
S30 (MH "Qigong")
S31 TX sport OR sports* OR walk* OR swim* OR aquatic OR danc* OR running OR jogging OR aerobic* OR pilates OR qigong OR "qi gong" OR "chi kung" OR "chi gung" OR exercis* OR gym* OR isometric*
S32 TX ((physical OR strength* OR resistance or isometric*) N3 (exercis* OR activit* OR therap* OR program* OR training)) or TX (exercise W6 therap*)

S33 TX dhyan* OR pranayam* OR asana OR bikram OR vinyasa OR hatha OR ashtanga OR iyengar OR kundalini OR yoga OR yogi*
S34 TX "tai chi"
S35 TX "t'ai chi" or or TX (tai ji) or TX (taijiquan)
S36 S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S37 (MH "Clinical Trials+")
S38 PT Clinical trial
S39 TX clinic* n1 trial*
S40 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S41 TX randomi* control* trial*
S42 (MH "Random Assignment")
S43 TX random* allocat*
S44 TX placebo*
S45 (MH "Placebos")
S46 (MH "Quantitative Studies")
S47 TX allocat* random*
S48 S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47
S49 S15 and S21 and S36 and S48

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: KER, KR, NW, DV
- Study selection: KER, KR
- Extract data from studies: KER, KR
- Enter data into Review Manager 2014: KER, KR
- Carry out the analysis: KER, DV
- Interpret the analysis: KER, NW, DV
- Draft the final review: KER, KR, NW, DV
- Disagreement resolution: NW
- Update the review: KER, KR, NW, DV

DECLARATIONS OF INTEREST

KER: travel/accommodation/meeting expenses by Roche, Amgen, Bristol-Myers Squibb

KR: none to declare

DV: none to declare

NW: consultancy fees from Roche, Novartis; grants from Medivation; expert panel review for Roche; travel/accommodation/meeting expenses for Roche, Novartis; stock in CSL

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