BMJ Open

Bisphosphonate and risk of cancer recurrence: protocol for a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials

Yupeng Liu,[1] Chen Du,[2] Yuxue Zhang,[3] Shu Zhao,[4] Lina Zhao,[4] Pengfei Li,[5] Fulan Hu,[1] Lin Zhu,[1] Yanlong Liu,[6] Da Pang,[7] Yashuang Zhao[1]

To cite: Liu Y, Du C, Zhang Y, *et al*. Bisphosphonate and risk of cancer recurrence: protocol for a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials. *BMJ Open* 2015;**5**:e007215. doi:10.1136/bmjopen-2014-007215

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2014-007215).

YL, CD, YZ and SZ contributed equally to this protocol and should be considered as co-first authors.

Received 15 November 2014
Revised 4 March 2015
Accepted 27 March 2015

For numbered affiliations see end of article.

Correspondence to
Dr Yashuang Zhao;
zhao_yashuang@263.net

ABSTRACT

Introduction: No consensus exists on the associations between adjuvant treatment with bisphosphonates and cancer recurrence risk among patients with primary early-stage cancers. We plan to perform a comprehensive systematic review, study-level meta-analysis and trial sequential analysis of randomised controlled trials to comprehensively summarise evidence of the bisphosphonate treatment for difference cancers.

Methods and analyses: We will report our results according to the PRISMA guideline. The primary outcomes include any cancer recurrence and bone metastasis and secondary outcomes include events of local recurrence, regional recurrence or non-skeletal distant metastasis, disease-free survival and overall survival. We will perform systematic electronic searches and other manual searches. To be conservative, all statistical analyses will be conducted with random-effects models. Cumulative meta-analyses and trial sequential analyses will be performed to assess whether and when firm evidence is reached. Various sensitivity analyses and rigid publication bias analyses will be performed to challenge the consistency and robustness of results. We will also grade the quality of evidence with the GRADE system.

Ethics and dissemination: Ethical approval is not required in this study. The findings will be submitted for publication in a peer-reviewed journal and also presented at relevant national and international conferences.

Trial registration number: PROSPERO CRD42014014699.

INTRODUCTION

Cancer has already been a major public health problem worldwide.[1] There were 32.6 million people with a history of cancer and 8.2 million cancer deaths in 2012 worldwide.[2] In the USA, the number of cancer survivors continues to grow and it is estimated that 14.5 million persons lived with cancer in 2014 and that the number will increase to nearly 19 million.[3] Cancer recurrence is common among cancer survivors.[4–6] Bone metastasis causes major mobility in metastatic cancer.[7–9] Since metastatic cancer is unlikely to be cured and commonly results in significant decline of the quality of life, an efficient and safe strategy to prevent against cancer recurrence is therefore urgently necessary.

Bisphosphonates are widely prescribed for the prevention and treatment of osteoporosis[10] and recommended as the standard care for bone loss or skeletal-related complications caused by malignancies.[11] Recently, an increasing body of evidence[12–28] has shown that bisphosphonates could decrease the recurrence risk of various cancers including breast cancer, lung cancer, prostate cancer, multiple myeloma and so on. Nonetheless, the findings from current studies have been inconsistent.

Several meta-analyses[29–38] have assessed whether bisphosphonates are associated with reduced risk of cancer recurrences; however, all of them only investigated a particular type of cancer and most only evaluated the effect of a particular type of bisphosphonates. Some meta-analyses examined the effect of either zoledronic acid[31 32 35 37] or clodronate[29 34] on breast cancer recurrence, and others[31–33 35–37] incorporated results from trials with non-bisphosphonate treatment or delayed bisphosphonate treatment as controls, and yet another meta-analysis[31] combined both early-stage breast cancer cases and metastatic breast cancer cases and included studies with denosumab treatment as controls. The formal publication of another large individual patient meta-analysis[39] conducted by the Early Breast Cancer Trialists' Collaborative Group's

Bisphosphonate Working Group (EBCTCG) on all adjuvant trials in early breast cancer is ongoing and this individual-patient meta-analysis will answer some questions in a better way than study-level meta-analysis. None of these previously published reviews have assessed the impact of differences in lengths of follow-up, and none of them have taken into account the accumulated information size or random errors that may be due to sparse data and multiple testing in subgroup analyses. Additionally, several unanswered questions remain, including whether the effects hold for less common cancers, whether the effects differ at different time points of follow-up, how long the effects could last, and whether the effects attenuate or become more pronounced with time. Therefore, we will conduct this systematic review, study-level meta-analysis and trial sequential analysis of randomised controlled trials (RCTs) in order to quantify effects of adjuvant treatment with bisphosphonates on cancer recurrence among people with primary early-stage cancers.

OBJECTIVES

The primary objectives of this study are to comprehensively summarise current evidence to determine whether the adjuvant treatment with bisphosphonate could decrease the risk of any cancer recurrences in people with different primary early-stage cancers, to evaluate whether the evidence for effects of bisphosphonates is conclusive for any particular type of cancer, to assess how long the effects of bisphosphonates could persist and whether these effects disappear, attenuate or become more pronounced with time, and then to compare the effects across different cancers using meta-analysis and trial sequential analysis. The secondary objectives of this study are to determine the effects of bisphosphonates on outcomes of local recurrence, regional recurrence, bone metastasis and non-skeletal distant metastasis, and to determine the effects on recurrence-free survival (RFS), disease-free survival (DFS) and overall survival (OS). We will further compare the effects across different types of bisphosphonates and explore which group of population could obtain the benefits from bisphosphonates and what is the optimal duration of bisphosphonate treatment in decreasing the risk of cancer recurrence.

METHODS

This meta-analysis and trial sequential analysis will be reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline.[40] This protocol was prepared according to the recommendations within PRISMA-P.[41]

Eligibility criteria

Study designs

RCTs will be included in this review with no restriction of language, sample size or blinding. Single group designed clinical trials and non-randomised allocation trials will be excluded.

Participants

We will include studies on participants who are histologically diagnosed with any primary cancer and without evidence of any relapse before follow-up in original studies. Studies on patients with clinical evidence of advanced or late-stage cancer or any recurrence will be excluded from our analyses.

Interventions

Interventions include any type of bisphosphonates that were given to participants in the intervention arm. Interventions should clarify the dosage, frequency and duration of bisphosphonate treatment. If a trial only mentioned an intervention of bisphosphonate therapy with no detailed statement about the treatment dosage, frequency or duration, it will be excluded.

Controls

Control groups include placebo controls, observation controls and other non-bisphosphonate controls. Delayed bisphosphonate therapy controls and denosumab treatment controls will be excluded from the present study.

Other criteria

Inclusion criteria: (1) Events of cancer recurrence should be designated as the primary or secondary outcomes in individual RCTs; (2) RCTs should report either the effect estimates, such as HRs with 95% CIs, or sufficient information to calculate these values; (3) when multiple reports from the same study are published at different time points of follow-up, we will include the data after the longest follow-up period in primary analyses, while in subgroup analyses, cumulative meta-analyses and trial sequential analyses according to the follow-up duration, we will use all the data sets of diverse follow-up periods from the same study; (4) RCTs with zero events during study periods will not be included in initial analyses, but we will included these studies in sensitivity analyses.

Exclusion criteria: RCTs are not initially designed to study cancer recurrences, which are not designed as outcomes in the protocol or are not mentioned in the Methods section, even though events of cancer recurrence are provided in the results.

Outcomes

Primary outcomes

1. Any recurrence events that are defined as any local recurrence, regional recurrence or distant recurrence after the first diagnosis or study randomisation.
2. Bone metastasis events, or bone metastasis-free survival that is defined as time from randomisation to the first occurrence of bone metastasis during follow-up.

Secondary outcomes

1. Events of local recurrence, regional recurrence or non-skeletal distant metastasis after the first diagnosis or study randomisation.

2. RFS, which is defined as any local recurrence, regional recurrence or distant recurrence after the first diagnosis or study randomisation.
3. DFS, which is defined as the time from random assignment to the first occurrence of any recurrence (including a local or regional recurrence, distant metastasis), second primary carcinoma or death from any cause.
4. OS, which is defined as the time from random assignment to death from any cause.

Search methods

Electronic searches

We will systematically search MEDLINE, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) for relevant studies using a combination of Medical Subject Headings (MeSH) terms and corresponding free-text terms as follows: ((diphosphonates [MeSH Terms]) or diphosphonate or bisphosphonate or alendron* or etidron* or clodron* or zoledron* or risedron* or ibandron* or pamidron* or tiludron* or neridron* or olpadron*) and ((neoplasms[MeSH Terms]) or neoplasm or cancer or tumor or carcinoma). We will also search the ClinicalTrials.gov[42] and the Clinicaltrialsregister.eu[43] for potentially eligible studies including completed and ongoing RCTs, which could possibly post their interim results online.

Additional searches

The reference sections and citation lists of the retrieved literature, including original research articles, reviews, editorials and letters, will be also reviewed for potentially relevant studies.

Study selection and data extraction

Identification and selection of studies

After screening titles and abstracts, reviewing the full text of potentially eligible articles will be independently performed by two reviewers to assess whether studies meet the aforementioned criteria.

Data extraction

Two reviewers will independently extract data from each study with uniform electronic forms specifically created for this study and the following data will be recorded: trial characteristics (country, details of study procedure, sample size, study period, follow-up duration and funding), intervention characteristics (type, dose, frequency and duration of interventions applied), patient characteristics (inclusion criteria, background treatment, age, gender, proportion of postmenopausal women, body weight, body mass index (BMI), etc). Both the maximally adjusted and unadjusted effect sizes with 95% CIs will be recorded, if available. Any discrepancies will be resolved by discussion or consensus with a third reviewer. The extracted data from each study will be carefully checked by another reviewer before performing final analyses. When necessary, we will contact authors of studies for missing information.

Risk of bias assessment

The bias risk of individual studies will be assessed with the domains recommended by the Cochrane Collaboration tool including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), baseline imbalance bias and other bias (eg, academy bias). The results of bias risk assessment of each trial will be presented as figure 1 (risk of bias summary).

Data synthesis and statistical analysis

Measures of treatment effect

Data will be summarised as HR with 95% CI for time-to-event outcomes. Dichotomous data (adverse effects) will be determined by using risk ratio (RR) with 95% CI. Characteristics of included studies will be presented descriptively.

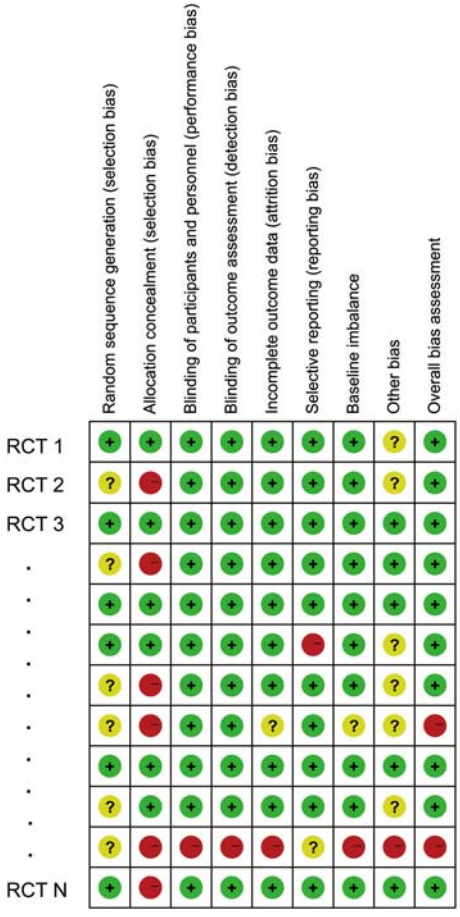

Figure 1 Risk of bias summary displaying review authors' judgements about each risk of bias domain for each included trial (RCT, randomised controlled trial).

Unit of analysis issues

The unit of analysis will be an individual study from which we will extract the aggregate data. For time-to-event outcomes, the maximally adjusted and unadjusted HRs with 95% CIs will be extracted. For adverse effects, the number of participants in the intervention and control arms will be extracted.

Data synthesis

The aggregate data (study level) from each study will be summarised using random-effect models in a conservative manner. The summarised effect estimates will be presented by HRs with 95% CIs. In the primary meta-analyses, we will use the maximally adjusted effect sizes and 95% CIs. To correct for random errors and repetitive testing, which are possibly produced in the conventional meta-analysis, and to assess whether the current evidence is conclusive, we will therefore perform trial sequential analysis.[44 45] We will conduct cumulative meta-analyses and trial sequential analyses by publication year and sample size. To determine whether the effect of bisphosphonates will disappear, persist, attenuate or be more pronounced with the time of follow-up, we will conduct subgroup analyses, cumulative meta-analyses and trial sequential analyses according to the follow-up periods, using all the data sets reported after different follow-up periods from the same trials.

Sensitivity analysis

For sensitivity analyses, we will perform meta-analyses using fixed effect models and assess the consistency of our results across random-effect models and fixed effect models. We will remove the most relatively weighted study from each subgroup analysis. A sensitivity analysis including zero event trials will be conducted with an application of constant continuity correction to the no-event trial. In addition, to test whether the underlying confounders, which could have been very little or nil in theory because of random assignments in RCTs, could have influenced the results, we will conduct sensitivity analyses using the unadjusted data and then analyse the confounding RR,[46] which is defined as the ratio of the pooled results of the maximally adjusted and unadjusted data.

Subgroup analysis

Subgroup analyses will be conducted based on the type of bisphosphonates, underlying disease, treatment duration and dose intensity, follow-up duration, recurrence site, risk of bias evaluated by the Cochrane Collaboration's tool, gender, ethnicity, age at baseline, BMI at baseline, sample size (with a median sample size as the cut-off point) for any type of cancer, and subgroup analyses by menopausal status at baseline will be conducted for female cancers. To correct for the potential random errors because of few data and repetitive testing of subgroup analyses, we will conduct trial sequential analyses for each subgroup.

Heterogeneity analysis

We will assess the between-trial heterogeneity using the Q test and the I^2 statistic.[47] We will conduct subgroup analyses by some factors (eg, age, gender, ethnicity, etc) and meta-regression analyses by other factors (eg, sample size, publication year, mean age, etc) to explore potential sources of the between-trial heterogeneity and potential effect modifiers in this study.

Publication bias assessment

We will use funnel plots for asymmetry and formally use Begg's rank correlation and Egger's linear regression tests to detect potential publication bias.[48] Furthermore, we will rigidly adjust for the summarised results with Duval and Tweedie's trim and fill method[49] to challenge the robustness of our results.

Grading quality of evidence

We will apply the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the overall quality of evidence.[50] The quality of evidence for each outcome will be classified as high, moderate, low or very low based on the evaluation for study design, bias risk, inconsistency, indirectness, imprecision, publication bias and confounding bias. The results of the GRADE assessment will be presented as table 1.

Statistical analysis

RevMan V.5.3 will be used to assess the risk of bias of individual trials. Comprehensive Meta Analysis V.2.0 (Biostat, Englewood, New Jersey, USA) will be used for meta-analyses, meta-regression analyses, cumulative meta-analyses, sensitivity analyses, heterogeneity analyses and publication bias analyses. Trial Sequential Analysis Viewer V.0.9 β (Copenhagen Trial Unit, Copenhagen, Denmark) will be used for trial sequential analyses. GRADEpro V.3.6 will be used for grading the overall quality of evidence.

ETHICS AND DISSEMINATION

Ethical approval is not required in this study. This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, Registration number CRD42014014699).[51] The results of this study will be submitted for publication in a peer-reviewed journal in this field and also presented at relevant national and international conferences.

LIMITATIONS

This systematic review may have several limitations. Currently, the vast majority of randomised trials have investigated the role of bisphosphonates in early breast cancer or multiple myeloma. There are only a limited number of studies on other cancers. Additionally, we could not conduct an individual-patient meta-analysis.

Table 1 GRADE quality of evidence

Quality assessment								Patients (n)		Effect			
Studies (n)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Any blood pressures	Non-users	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Primary outcomes													
Outcome 1													
Outcome													
Secondary outcomes													
Outcome 1													
Outcome													

Author affiliations
[1]Department of Epidemiology, School of Public Health, Harbin Medical University, Harbin, China
[2]Department of Urology Oncology, The Third Affiliated Hospital, Harbin Medical University, Harbin, China
[3]Department of Preventive Medicine, School of Public Health, Harbin Medical University, Harbin, China
[4]Department of Medical Oncology, The Third Affiliated Hospital, Harbin Medical University, Harbin, China
[5]Department of Radiology, The Third Affiliated Hospital, Harbin Medical University, Harbin, China
[6]Department of Colorectal Cancer Surgery, The Third Affiliated Hospital, Harbin Medical University, Harbin, China
[7]Department of Breast Cancer Surgery, The Third Affiliated Hospital, Harbin Medical University, Harbin, China

Contributors YZ is the guarantor. YL, CD, YZ, SZ and YZ conceived and designed the review. YL, CD, YZ and SZ wrote the first draft of this protocol. The electronic and manual searches, article screening, data extraction and quality assessment will be conducted by YL, YZ, SZ and CD. YL, YZ and YZ provided statistical expertise. CD, SZ, LZ, PL, YL and DP provided expertise on cancer treatment with bisphosphonates. All authors contributed considerably to the writing of the final manuscript of this protocol and approved publication of the protocol.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Siegel R, Ma J, Zou Z, *et al*. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
2. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. http://globocan.iarc.fr
3. DeSantis CE, Lin CC, Mariotto AB, *et al*. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252–71.
4. Aghili M, Izadi S, Madani H, *et al*. Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer. *Asia Pac J Clin Oncol* 2010;6:35–41.
5. Heney NM, Ahmed S, Flanagan MJ, *et al*. Superficial bladder cancer: progression and recurrence. *J Urol* 1983;130:1083–6.
6. Cheng L, Swartz MD, Zhao H, *et al*. Hazard of recurrence among women after primary breast cancer treatment—a 10-year follow-up using data from SEER-Medicare. *Cancer Epidemiol Biomarkers Prev* 2012;21:800–9.
7. Barrett-Lee P, Casbard A, Abraham J, *et al*. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. *Lancet Oncol* 2014;15:114–22.
8. Oster G, Lamerato L, Glass AG, *et al*. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. *Support Care Cancer* 2013;21:3279–86.
9. Oster G, Lamerato L, Glass AG, *et al*. Use of intravenous bisphosphonates in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. *Support Care Cancer* 2014;22:1363–73.
10. Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med* 2005;353:595–603.
11. Aapro M, Abrahamsson PA, Body JJ, *et al*. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008;19:420–32.
12. Gnant M, Mlineritsch B, Stoeger H, *et al*. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011;12:631–41.
13. Aft R, Naughton M, Trinkaus K, *et al*. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast

cancer: an open label, randomised, phase 2 trial. *Lancet Oncol* 2010;11:421–8.
14. Coleman R, Cameron D, Dodwell D, *et al*. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol* 2014;15:997–1006.
15. Banys M, Solomayer EF, Gebauer G, *et al*. Influence of zoledronic acid on disseminated tumor cells in bone marrow and survival: results of a prospective clinical trial. *BMC Cancer* 2013;13:480.
16. Von Minckwitz G, Mobus V, Schneeweiss A, *et al*. German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. *J Clin Oncol* 2013;31:3531–9.
17. Paterson AH, Anderson SJ, Lembersky BC, *et al*. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. *Lancet Oncol* 2012;13:734–42.
18. Kristensen B, Ejlertsen B, Mouridsen HT, *et al*. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. *Acta Oncol* 2008;47:740–6.
19. Powles T, Paterson A, McCloskey E, *et al*. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. *Breast Cancer Res* 2006;8:R13.
20. Saarto T, Vehmanen L, Virkkunen P, *et al*. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncol* 2004;43:650–6.
21. Diel IJ, Solomayer EF, Costa SD, *et al*. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998;339:357–63.
22. Leal T, Tevaarwerk A, Love R, *et al*. Randomized trial of adjuvant zoledronic acid in postmenopausal women with high-risk breast cancer. *Clin Breast Cancer* 2010;10:471–6.
23. Denham JW, Joseph D, Lamb DS, *et al*. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol* 2014;15:1076–89.
24. Murakami H, Yamanaka T, Seto T, *et al*. Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group. *Cancer Sci* 2014;105:989–95.
25. Smith MR, Halabi S, Ryan CJ, *et al*. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol* 2014;32:1143–50.
26. Musto P, Petrucci MT, Bringhen S, *et al*. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer* 2008;113:1588–95.
27. Aviles A, Nambo MJ, Neri N, *et al*. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol* 2007;24:227–30.
28. Attal M, Harousseau JL, Leyvraz S, *et al*. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006;108:3289–94.
29. Zhu J, Zheng Y, Zhou Z. Oral adjuvant clodronate therapy could improve overall survival in early breast cancer: results from an updated systematic review and meta-analysis. *Eur J Cancer* 2013;49:2086–92.
30. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev* 2012;2:CD003474.
31. Huang WW, Huang C, Liu J, *et al*. Zoledronic acid as an adjuvant therapy in patients with breast cancer: a systematic review and meta-analysis. *PLoS ONE* 2012;7:e40783.
32. Yan T, Yin W, Zhou Q, *et al*. The efficacy of zoledronic acid in breast cancer adjuvant therapy: a meta-analysis of randomised controlled trials. *Eur J Cancer* 2012;48:187–95.
33. Mauri D, Valachis A, Polyzos NP, *et al*. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. *J Natl Compr Canc Netw* 2010;8:279–86.
34. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007;96:1796–801.
35. He M, Fan W, Zhang X. Adjuvant zoledronic acid therapy for patients with early stage breast cancer: an updated systematic review and meta-analysis. *J Hematol Oncol* 2013;6:80.
36. Ben-Aharon I, Vidal L, Rizel S, *et al*. Bisphosphonates in the adjuvant setting of breast cancer therapy—effect on survival: a systematic review and meta-analysis. *PLoS ONE* 2013;8:e70044.
37. Valachis A, Polyzos NP, Coleman RE, *et al*. Adjuvant therapy with zoledronic acid in patients with breast cancer: a systematic review and meta-analysis. *Oncologist* 2013;18:353–61.
38. Mhaskar R, Redzepovic J, Wheatley K, *et al*. Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database Syst Rev* 2012;5:CD003188.
39. Early Breast Cancer Trialists' Collaborative Group's Bisphosphonate Working Group (EBCTCG). Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: a meta-analysis of individual patient data from randomised trials. *Abstract S4–07. The 36th Annual San Antonio Breast Cancer Symposium (SABCS)*; 2013.
40. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
41. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
42. ClinicalTrials.gov. http://clinicaltrials.gov/
43. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search
44. Miladinovic B, Mhaskar R, Hozo I, *et al*. Optimal information size in trial sequential analysis of time-to-event outcomes reveals potentially inconclusive results because of the risk of random error. *J Clin Epidemiol* 2013;66:654–9.
45. Wetterslev J, Thorlund K, Brok J, *et al*. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75.
46. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987;9:1–30.
47. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
48. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
49. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
50. Schünemann H, Bro?ek J, Guyatt G, *et al*. *GRADE handbook for grading quality of evidence and strength of recommendations*. Updated October 2013. The GRADE Working Group, 2013. http://www.guidelinedevelopment.org/handbook
51. Liu YP, Zhang Y, Zhao S, *et al*. Bisphosphonate and risk of cancer recurrence: a systematic review, meta-analysis, and trial sequential analysis of randomized controlled trials. PROSPERO 2014: CRD42014014699. http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42014014699