Mammographic density, endocrine therapy and breast cancer risk: a prognostic and predictive biomarker review (Protocol)

Atakpa EC, Thorat MA, Cuzick J, Brentnall AR

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Mammographic density, endocrine therapy and breast cancer risk: a prognostic and predictive biomarker review

Emma C Atakpa[1], Mangesh A Thorat[1], Jack Cuzick[1], Adam R Brentnall[1]

[1]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Contact address: Adam R Brentnall, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK. a.brentnall@qmul.ac.uk.

ABSTRACT

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

Endocrine therapy for breast cancer prevention has been shown to reduce risk, and for treatment of early stage oestrogen receptor-positive (ER-positive) breast cancer to reduce breast cancer mortality. The objective of the review is to synthesise available evidence on whether mammographic density reduction in these settings is (i) a prognostic biomarker and (ii) a predictive biomarker, as defined in the Introduction. We will explore sources of heterogeneity to identify the impact of differences in participants, measures of mammographic density, follow-up length and study design. Within the prognostic and predictive biomarker reviews, our analysis will consider prevention and treatment populations separately, and within these, selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) separately.

BACKGROUND

Description of the condition and intervention

Breast cancer is the most common cancer in women worldwide, the second most frequent cause of cancer death in women from high-income regions and the most common cause of death in low-income regions (Ferlay 2013). Two types of drugs have shown efficacy for both prevention and treatment of certain subtypes of the disease. The first are called selective oestrogen receptor modulators (SERMS). They prevent breast cancer (Cuzick 2013; Cuzick 2015), and are also used in adjuvant settings to reduce the chance that breast cancer will reoccur when it has been diagnosed at an early stage (Davies 2011; EBCTCG 1998). The second are called aromatase inhibitors (AIs). AIs are suitable for postmenopausal women only, and they confer greater average reductions in the risk of breast cancer (Cuzick 2014; Visvanathan 2013), and recurrence than SERMs (EBCTCG 2015).

Description of the biomarker

The breast is made up of glandular and supportive tissue. Glandular tissue is the network that produces and transports milk to the nipple; the supportive tissue is largely fat but also contains fibrocollagenous tissue called glandular stroma. Glandular tissue and glandular stroma appear as a white area on a mammogram (breast x-ray), which is called mammographic density (Assi 2011). Breast density is a strong risk factor for breast cancer, and women with mostly dense breasts have approximately four times the risk of breast cancer than women of the same age and weight with mostly fatty breasts (Huo 2014; McCormack 2006). Mammographic density is also associated with classical reproductive risk factors, and it is lower in women who have had children and breast fed (Boyd 1998).

How the biomarker might be related to treatment response

Hormonal treatment can change a woman's mammographic density. Density increases during use of hormone replacement therapy (HRT) and HRT is also a risk factor for breast cancer (McTiernan 2005; Rutter 2001). After cessation of HRT, mammographic density may decrease in as little as four weeks (Harvey 1997), and it is likely that within a couple of years the woman will have the same level of risk as a woman who has never used HRT (Beral 2011). Breast density may also decrease during SERM therapy above that expected due to age (Cuzick 2004), but the evidence for AIs is less clear (Engmann 2017; Vachon 2013).

The association between hormonal treatment and density change is well documented, and there is also direct evidence that the increased risk from combination HRT is mediated by mammographic density (Boyd 2006; Byrne 2017; Martin 2009). Findings for prevention (Cuzick 2011a), and treatment (including Kim 2012; Ko 2013; Li 2013; Nyante 2015; Vachon 2013), also suggest that change in breast density is an appropriate biomarker for response to SERMs. A working hypothesis is therefore that mammographic density reductions in women receiving endocrine therapy for treatment or prevention might indicate who is responding to therapy, making it a reliable surrogate outcome. The precise mechanism is still unclear and is an area of active research, but one theory is that decreases in density arise when a woman is able to metabolise the drug effectively (Jordan 2007).

Why it is important to do this review

The first aim of this review is to assess the evidence that change in mammographic density is a prognostic biomarker (Altman 2001). We define the term prognostic biomarker to be a measure that is associated with a clinical outcome of interest in a defined group of patients. This terminology is standard when the group of patients has a health condition such as breast cancer, but it perhaps is less

frequently used for risk factors in healthy patients when the clinical outcome is breast cancer.

Several prognostic factors for women diagnosed with breast cancer have been identified. These include classical factors such as tumour size, grade and lymph node involvement, and biomarkers including Ki67 and commercial genetic signatures such as OncotypeDX (Cuzick 2011b; Harris 2007). Prognostic factors for healthy women without breast cancer (or risk factors) include age, a family history of the disease, and hormonal and reproductive factors including weight and age at first child (Tyrer 2004). Quantifying the effect of potential prognostic factors on outcomes is important for many reasons. It may be used to help guide clinical decision making, improve understanding of disease, improve the design and analysis of trials, and improve risk assessment (Riley 2013).

The second aim of this review is to assess the evidence that change in mammographic density is a predictive biomarker, which is taken to be a measure that is differentially associated with response to treatment (Hingorani 2013). Some, but not all, prognostic biomarkers are predictive biomarkers. Two examples for women with breast cancer are human epidermal growth factor receptor (HER-2) and oestrogen receptor (ER) status. HER-2 was identified as a prognostic factor for breast cancer and provided a target for a treatment (trastuzumab), which was subsequently shown to be effective for women with HER-2 breast cancer. ER status is a prognostic biomarker and a predictive biomarker for SERM and AI treatments: they have been shown to improve clinical outcomes only in ER-positive patients.

There is currently no systematic review that focuses on the evidence that mammographic density reductions in women receiving endocrine therapy are prognostic or predictive biomarkers. However, some other reviews on the topic have been published, most recently the Shawky 2017 study. This reported seven studies of density change as a prognostic factor for women receiving a SERM or AI, but no data from a randomised trial or otherwise to evaluate change in mammographic density after initiation of adjuvant tamoxifen treatment as a predictive biomarker. For prevention there has been one study to evaluate density change as a prognostic and predictive biomarker for prevention, which was a case-control study from within a randomised trial.

It is important to undertake this review because findings are likely to be important to: clinicians and their patients undergoing or considering endocrine therapy, such as by helping to define risk groups and to better predict outcomes; regulators and ethics boards considering trials of products that use mammographic density reductions as an endpoint; those with an interest in mechanisms by which endocrine therapy improves clinical outcomes. Additionally, as discussed in the Mullooly 2016 study, had the randomised trials of SERMS and AIs included density change as a potential prognostic or predictive biomarker, then different conclusions might have been reached regarding their effectiveness: it is possible that women with density reductions from a SERM might

have greater benefits from this treatment than from an AI. Another possibility is that women who see density increases following a short-term decrease might show resistance to the treatment.

OBJECTIVES

Endocrine therapy for breast cancer prevention has been shown to reduce risk, and for treatment of early stage oestrogen receptor-positive (ER-positive) breast cancer to reduce breast cancer mortality. The objective of the review is to synthesise available evidence on whether mammographic density reduction in these settings is (i) a prognostic biomarker and (ii) a predictive biomarker, as defined in the Introduction. We will explore sources of heterogeneity to identify the impact of differences in participants, measures of mammographic density, follow-up length and study design. Within the prognostic and predictive biomarker reviews, our analysis will consider prevention and treatment populations separately, and within these, selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) separately.

METHODS

We will write this review according to PRISMA guidelines (Liberati 2009), while supplemented as necessary for a predictive and prognostic biomarker review, and will follow the REMARK guidelines (Altman 2012; McShane 2005). We plan to conduct a literature-based analysis to identify relevant studies and then meta-analytic methods. Subsequently, we will seek individual-level data from those studies included in order to conduct further analysis that may better account for heterogeneity between the studies in aspects such as definition of the biomarker and cutpoints used. We will develop a separate protocol for data extraction and statistical analysis of this subsequent study.

Criteria for considering studies for this review

Our review question will include studies with the following designs, participants, interventions, biomarkers and outcomes.

Types of study designs

We will include the same study designs for both the prognostic and predictive review. We will include randomised and non-randomised observational studies (prospective and retrospective cohort and case-control studies). We will separately treat exploratory biomarker studies in the analysis, where density is one of several biomarkers considered simultaneously (this is unlikely).

Types of participants

We will include the same type of participant for the prognostic and predictive biomarker reviews. We will include all adult women aged 18 years or more, with or without breast cancer (denoted respectively as treatment, prevention), based on the following criteria.

Treatment: women with early stage hormone receptor- (oestrogen (ER) or progesterone (PgR)) positive breast cancer. This is defined to be women who have had histologically-proven operable invasive hormone receptor-positive breast cancer or ductal carcinoma in situ (DCIS), and were candidates to receive endocrine adjuvant therapy; there was no clinical evidence of metastatic disease. In addition, women are ineligible if breast density measurements were not possible on a contralateral breast or if they had bilateral breast cancer.

Prevention: women who have not previously been diagnosed with invasive breast cancer or DCIS. There are no exclusions for level of increased risk due to genetic factors (including BRCA1/2 gene mutations or a family history of the disease, or both) or otherwise assessed by an absolute or relative risk prediction model. We will exclude women with breast implants or those who have undergone risk-reducing mastectomies because accurate breast density estimation is not possible.

Women must be at risk for at least the length of time between baseline and follow-up mammogram. We will include women who might have changed treatment or discontinued treatment throughout follow-up, but will exclude women who changed treatment between the mammograms for density change (we will not exclude those who discontinued). We will exclude women who received another selective oestrogen receptor modulator (SERM) or aromatase inhibitor (AI) before treatment.

For AI comparisons women must be postmenopausal at the start of treatment; for SERM comparisons they may be pre or postmenopausal. Postmenopausal women will include women having had a bilateral oophorectomy; or aged more than 60 years; or aged 40 to 59 years with an intact uterus and amenorrhoeic for at least 12 months. We will exclude women rendered temporarily postmenopausal through medical interventions (e.g. gonadotropin-releasing hormone (GnRH) analogues).

We will include studies that include subsets of relevant participants in the main analysis, provided results are given for the subset that includes relevant participants.

Types of interventions

Interventions

We will define the same types of intervention for the prognostic and predictive biomarker reviews.

We will include women receiving SERMs at the following minimum doses (Komm 2014): Tamoxifen, 20 mg daily; Raloxifene,

60 mg daily; Lasofoxifene, 0.25 mg daily; Arzoxifene, 20 mg daily; Droloxifene, 40 mg daily; Bazedoxifene, 20 mg daily; and Fulvestrant, 250 mg monthly.

We will include women receiving AIs at the following minimum doses: Anastrozole, 1 mg daily; Letrozole, 2.5 mg daily; and Exemestane, 25 mg daily. All treatments are oral, except Fulvestrant (intramuscular). Women must receive treatment for at least the length of time between baseline and follow-up mammogram (i.e. at least 1 year). We will include studies of women receiving doses lower than these doses for a secondary dose-response analysis, but will exclude them from the main analysis. We will include studies that are a mix of women including SERMs and AIs in the primary analysis if we can separate results; otherwise we will include them only in secondary analyses.

Cointerventions

We will allow the same types of cointervention for the prognostic and predictive biomarker reviews.

For treatment, women are ineligible if they had not completed primary locoregional (surgery or radiotherapy, or both) treatment and systemic (chemotherapy or targeted therapy) treatment (where indicated) with curative intent (either in neoadjuvant or in adjuvant setting). Women are ineligible if there was a gap of more than eight weeks between different treatment interventions, for example, between surgery and start of radiotherapy. Women are also ineligible if they had received endocrine therapy for breast cancer prevention before diagnosis of breast cancer or if endocrine treatment was started before surgery and received for more than 28 days.

We will include studies if some women use or used (up to 2 years before baseline) hormone replacement therapy (HRT) (prevention and treatment), but we will note this, including in the 'Risk of bias' assessment. We will permit other cointerventions, including exercise and diet advice, but we will identify them where possible, including in the 'Risk of bias' assessment.

Comparators

The main difference between the prognostic and predictive biomarker review is the comparator.

Prognostic biomarker review

The comparison is within each intervention group (SERM or AI), where the outcome is related to the change in density over the period. This will help assess whether the biomarker is associated with the outcome in those receiving SERM or AI interventions, i.e. a prognostic biomarker.

Predictive biomarker review

The predictive biomarker review will make a comparison between the intervention group and a control group from the same study. The within-study comparator group will be a corresponding randomised placebo group, or a non-randomised control group of women not receiving endocrine therapy.

Biomarker

We will use the same definition of biomarker for the prognostic and predictive reviews.

A measure of mammographic density is required at baseline (start of endocrine therapy or study entry in those from the control group) and follow-up. We will include studies with baseline mammograms obtained before or after diagnosis and before the start of therapy (treatment) and up to two years before the diagnosis, and a follow-up mammogram performed 90 days to three years after therapy start (or study entry), with the density closest to one year from the start of endocrine therapy, if there is a choice. We will record the range and average time between baseline mammogram and diagnosis, between diagnosis and start of endocrine therapy (or study entry), and between start of endocrine therapy (or study entry) and the follow-up mammogram.

We will include any density method that has been shown in more than one study, outside of the review studies, to have a relationship with breast cancer risk. This will include, but not be limited to, the following percentage methods: (i) visual assessment by expert in 5% bands; (ii) visual assessment by expert in 20% bands (Boyd categories); (iii) visual assessment by expert as continuous percentage (%); (iv) semi-automated thresholding such as using CUMULUS software (Byng 1994) by expert (or trained) reader; (v) fully-automated (based on area of density); and (vi) fully-automated volumetric percentage (e.g. Volpara, Highnam 2010). We will also consider the following categorical measures: (i) BI-RADS density (D'Orsi 2013); (ii) Wolfe grade (Wolfe 1976); and (iii) Tabar grade (Gram 1997). We will also consider absolute dense area or volume from: (i) semi-automated methods (including CUMULUS); (ii) automated area-based methods; and (iii) fully-automated volumetric methods.

We will also consider information on reliability of density measures, including correlation between repeated measures from repeat mammograms, intraclass correlation coefficients and Bland-Altman limits of agreement (Bland 1999), whether different interpreters of density were used, whether the same reader assessed change in density, whether the reader was blinded to case status, whether the reader was blinded to treatment allocation, whether randomisation was per mammogram (mammograms read independently) or per woman (mammograms for each woman read with the knowledge of her other mammograms), and whether the order of per woman mammograms was sequential or random and assessed one at a time or simultaneously. We will use these for a

qualitative assessment of potential bias due to measurement of the biomarker.

We will not include women or studies that have different definitions or measures of mammographic density between the time points used to assess change.

Types of outcome measures

We will use the same outcome measures for the prognostic and predictive reviews.

Primary outcomes

Potential benefits from treatment

- Treatment: breast cancer mortality (time to death caused by breast cancer)
- Prevention: incidence of invasive breast cancer and DCIS

Potential harms from treatment

- Treatment and prevention: rate of all serious adverse events. These include serious side effects noted for Tamoxifen (cataracts, pulmonary embolism or deep vein thrombosis and endometrial cancer) and Anastrozole (osteoporosis and bone fractures).

Secondary outcomes

Potential benefits from treatment

- Treatment: recurrence
- Treatment: incidence of a secondary primary breast cancer (e.g. in the contralateral breast)
- Treatment: any recurrence or any death (disease-free survival)
- Treatment: distant metastases
- Treatment: death from all causes (all-cause mortality)
- Treatment: recurrence of invasive cancer only
- Treatment: recurrence of DCIS cancer only
- Prevention: incidence of invasive cancer only
- Prevention: incidence of DCIS cancer only

Potential harms from treatment

- Treatment and prevention: troublesome but not serious side effects observed for SERMs and AIs, including vasomotor symptoms and joint or muscle pain.

'Summary of findings' table for assessing the quality of the evidence

We will produce different 'Summary of findings' tables for the prognostic and predictive biomarker reviews, but based on the same outcomes. We will apply methods following the approach outlined by GRADE (Schunemann 2011), using GRADEpro GDT software (GRADEpro GDT). The seven main outcomes to be reported are as follows.

- Treatment: breast cancer mortality (time to death caused by breast cancer).
- Prevention: incidence of invasive and DCIS.
- Treatment and prevention: the rate of all serious adverse events. These include serious side effects noted for Tamoxifen (cataracts, pulmonary embolism or deep vein thrombosis and endometrial cancer) and Anastrozole (osteoporosis and bone fractures).
- Treatment: recurrence.
- Treatment: any recurrence or any death (disease-free survival).
- Treatment: death from all causes (all-cause mortality).
- Treatment and prevention: troublesome but not serious side effects observed for SERMs and AIs, including vasomotor symptoms and joint or muscle pain.

Search methods for identification of studies

Electronic searches

We will search the following databases.

- 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 website (breastcancer.cochrane.org/specialised-register). We will extract and consider for inclusion in the review trials with the key words "Tamoxifen, Raloxifene, Lasofoxifene, Arzoxifene, Droloxifene, Bazedoxifene, Fulvestrant, Anastrozole, Letrozole, Exemestane, selective estrogen receptor modulator, aromatase inhibitor".
- CENTRAL (the Cochrane Library, latest issue). See Appendix 1.
- MEDLINE (via OvidSP) from 1996 to present. See Appendix 2.
- Embase (via OvidSP) from 1996 to present. See Appendix 3.
- The World Health Organization (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.

Searching other resources

- Bibliographic searching

We will try to identify further studies from reference 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, we will make attempts to contact study authors to provide additional information.

Data collection and analysis

Selection of studies

Two review authors (AB and EA) will independently review all titles and abstracts retrieved to assess eligibility against inclusion criteria. If a review author has published a potentially eligible study, two other authors (EA and MT) will review the study for eligibility. One author (AB or EA) will obtain full-text copies of all papers and two review authors (AB and EA) will review the full texts. Any disagreement at this stage will be resolved by one review author (MT) and the included and excluded studies will be recorded. We will contact authors of primary studies for clarification, if necessary. We will record duplicate studies as one reference (e.g. the same study but multiple papers with slightly different aims or follow-up). We will only include studies published in English. We will record the selection process in a PRISMA flow diagram (Liberati 2009) in Review Manager 5 software (Review Manager 2014). We will record the process using the Covidence system (Covidence 2018).

Data extraction and management

Two review authors (AB and EA) will independently complete data extraction using custom forms. One review author (MT) will resolve disagreement. We will automatically extract the forms into a custom database. We will collect the following information.

- Study design: type of study. For example, a nested case-control study from a randomised trial, or a non-randomised cohort study, or a case-control study. If there is matching, then what was matching by and to what level (e.g. age to plus/minus 2 years). Control group: yes/no (women without treatment). Whether prognostic or predictive study, or both. For prognostic factor study, what phase (following Altman 1998; Riley 2009).
- Participants: demographic information, including number of participants, age, body mass index (BMI), ethnicity, education. Summary statistics such as mean, interquartile range (or standard deviation) and range for age, BMI and absolute or relative baseline risk, or both, from a risk model (e.g. Gail model (Gail 1989), Tyrer-Cuzick (Tyrer 2004), BCSC (Tice 2008)). Total number and total number (percentage) postmenopausal,

perimenopausal or premenopausal. For a predictive review, the previous variables are to be split by treatment or control group.

- Biomarker: whether mammograms were from film (digitised for density or not) or full field digital mammography. Manufacturer of digital mammogram machine. Whether any preprocessing was carried out for quality control of mammographic density. Density measure(s), and the range and average time between baseline mammogram and diagnosis, between diagnosis and start of endocrine therapy (or study entry), and between start of endocrine therapy (or study entry) and the follow-up mammogram.
- Setting: country, whether in a high-risk clinic, a treatment clinic, time period, urban/rural.
- Cointerventions: HRT use, chemotherapy use (treatment), targeted therapy use (treatment), radiotherapy use (treatment), neoadjuvant endocrine therapy use (treatment).
- Follow-up time period: minimum, mean, median, interquartile range, standard deviation, maximum follow-up.
- Sources of funding and stated conflicts of interest: descriptive text copied from sections in each paper.

When publications pertain to more than one publication, we will extract the data from all publications and record them in the database as such. We will consider the most recent or up-to-date reference (largest number of participants, or longest follow-up time, or correction to previous analysis) as the primary reference.

Assessment of risk of bias in included studies

For the prognostic review, we will use a version of the QUIPS tool (Hayden 2013), modified for our study (Table 1), in order to assess the risk of bias (Hayden 2006). This tool will assess six important domains that might affect bias from included studies: (i) study participation, (ii) attrition, (iii) measurement of density, (iv) measurement of the outcomes, (v) confounding, and (vi) statistical analysis.

For the predictive biomarker review, we will augment the QUIPS tool with the ROBINS-I tool (Sterne 2016; Table 2; Table 3). This tool will assess the risk of bias in estimation of an interaction between mammographic density change and treatment. Two review authors (AB and EA) will independently assess the studies with disagreements resolved by another review author (MT). If a review author is an author of an included study, two other review authors (EA and MT) will independently complete data extraction and assess the study for risk of bias for that study.

For both prognostic and predictive biomarker reviews, we plan to consider the included studies together but with a narrative identifying the risk in different domains across studies. We will exclude studies that have substantial potential for bias in a sensitivity analysis of results.

Measures of biomarker response

Effect measure

In both reviews, the primary measure we will look for will be the mean effect over a five-year follow-up period. We will allow other time periods, but if split into different periods (e.g. 0 to 5 years; 5 to 10 years) then periods outside the initial five years would be in a secondary analysis. Meta-analysis results will be subgroups by similar cutpoints and by those using continuous trends. We will report the ratios so that less than 1.0 favours a risk reduction associated with a decrease in mammographic density and greater than 1.0 indicates a risk increase.

Prognostic biomarker review

The primary measure will be a hazard ratio (cohort study with time to event) or an odds ratio (case-control study) for the effect of density change. We will treat an odds ratio as an equivalent measure of the hazard ratio, unless rates are high. In this case, we would include the odds ratio estimates in a secondary analysis.

Predictive biomarker review

The primary measure will be the interaction between treatment and the biomarker, expressed as a relative hazard (cohort study) or odds ratio (case-control study).

Adjustment

Prognostic biomarker review

The primary effect estimate will be adjusted. We will include unadjusted estimates if adjusted estimates are not available. To measure the prognostic ability of factors it is commonly accepted that effect estimates that are adjusted for potential confounders are more relevant than unadjusted ones (Riley 2013). However, when adjusted estimates are not available then unadjusted estimates will be used because we do not expect the change in density to be associated with the baseline value of most other prognostic factors, although we acknowledge that changes in BMI may also occur, and since BMI is negatively associated with breast density and a prognostic factor one would ideally adjust for this in the analysis.

Predictive biomarker review

The primary effect estimate will be adjusted. There are currently no established predictive biomarkers for either prevention or treatment in the groups of women to be included that were defined above.

Dealing with missing data

Where data are missing, we will contact study authors in an attempt to obtain the data.

Assessment of heterogeneity

We will measure heterogeneity using the estimated variance in a random-effects model (Tau^2). We will assess publication bias using a funnel plot and Egger's test (Egger 1997).

Subgroup analysis and investigation of heterogeneity

When sufficient studies exist, we will conduct the following a priori subgroup analysis to explore reasons for heterogeneity within the predefined homogeneous groups above.

Between-studies

- Drug within SERM (Tamoxifen, Raloxifene, Lasofoxifene, Arzoxifene, Droloxifene, Bazedoxifene, Fulvestrant) and AI grouping (Anastrozole, Letrozole, Exemestane)
- Type of study: case-control, observational cohort, randomised trial (nested case-control)
- Type of cancer at baseline (treatment): (percentage DCIS)
- Severity of cancer at baseline (treatment): stage (percentage regional spread)
- Cointerventions (treatment): chemotherapy/targeted therapy
- Hormone therapy use during therapy (yes/no, percentage if available), or in previous two years (yes/no, percentage if available)
- Time between start of therapy (or study entry) and follow-up mammogram (mean and range)
- Menopausal status (percentage premenopausal)
- Age (mean)
- BMI (mean)
- Digital or film mammography (percentage digital)
- Distribution of density at baseline (some studies may exclude women with low density)

Within-study estimates of effect

- Type of cancer at baseline (treatment): DCIS versus invasive
- Severity of cancer at baseline (treatment): stage (percentage regional spread)
- Cointerventions (treatment): chemotherapy/targeted therapy
- Hormone therapy use: no HRT prior to endocrine therapy, some HRT two years or more than two years prior to endocrine therapy, some HRT less than two years prior to endocrine therapy, some HRT during endocrine therapy
- Menopausal status (pre, peri or postmenopausal)
- Age group (< 50 years or ≥ 50 years) as a proxy for menopausal status
- BMI (both within-study (< 25, 25 to < 30, 30 to < 35, > 35 kg/m^2) and between-studies (mean))
- Baseline density

Data synthesis

Heterogeneity between studies is expected in this review because in general it is common in reviews of prognostic biomarkers (Riley 2013). To address this we will only consider to undertake meta-analysis for studies within predefined groups that we believe homogenous enough in advance to be meaningful for data synthesis. Namely, those with the same class of drug, same outcome, same density measure, same effect measure (same cutpoint or continuous variable assessment). Where more than one study is available we will combine estimates using an inverse-variance weighting (fixed-effect estimation); if there is substantial variability then we will present the result but state that the overall effect estimate has very limited interpretation, while we will seek subgroups (above) that best explain the heterogeneity.

Meta-analysis of the studies using individual data from patients may overcome many of the expected issues arising in this review of published data, including heterogeneity in the biomarker used and cutpoints (Riley 2009; Riley 2013). We will use the review to identify relevant studies, and invite the best quality studies (using information from the 'Risk of bias' analysis) to share data for an individual participant-level review.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1.   Adapted QUIPS 'Risk of bias' assessment instrument for prognostic factor studies

Biases	Issues to consider for judging overall rating of risk of bias
Instructions to assess the risk of each potential bias	**These issues will guide your thinking and judgement about the overall risk of bias within each of the six domains. These issues are taken together to inform the overall judgement of potential bias for each of the six domains**
1. Study participation	Goal: to judge the risk of selection bias (likelihood that relationship between density reductions and outcome is different for participants and eligible non-participants)
Source of target population	The source population or population of interest is adequately described for: a) treatment: (i) proportion with DCIS, (ii) cointerventions (chemotherapy/targeted therapy), (iii) severity of cancer at baseline (stage, % regional spread); b) prevention: level of risk in population, including whether some or all are BRCA1/2 mutation carriers, (ii) prior hormone replacement therapy use, (iii) cointerventions such as diet or exercise regimens, or both
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias
Recruitment period	Period of recruitment is adequately described.
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described.

Table 1. Adapted QUIPS 'Risk of bias' assessment instrument for prognostic factor studies *(Continued)*

Adequate study participation	There is adequate participation in the study by eligible individuals
Baseline characteristics	The baseline study sample (i.e. individuals entering the study) is adequately described for (treatment and prevention) age, menopausal status, cointerventions; (treatment) % DCIS, disease severity; (prevention) breast cancer risk, prior hormone replacement therapy use
Summary study participation	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between density change and outcome
2. Study attrition	Goal: to judge the risk of attrition bias (likelihood that relationship between density reductions and outcome are different for completing and non-completing participants)
Proportion of baseline sample available for analysis	Response rate (i.e. proportion of study sample allocated treatment who received treatment) is adequate
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for age at entry and cointerventions (if any), and for a) treatment: (i) DCIS, (ii) disease severity; b) prevention: (i) risk of breast cancer including BRCA1/2 carriers and testing. Whether loss to follow-up or inability to retrieve mammograms, or both, was likely related to the study outcome
Study attrition summary	There are no important differences between these characteristics in participants who completed the study and those who did not. Loss to follow-up (from baseline sample to study population analysed) is not associated with key characteristics (i.e. the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between density change and outcome
3. Prognostic factor measurement	Goal: to judge the risk of measurement bias related to how mammographic density was measured (differential measurement of mammographic density related to the level of outcome)

Table 1. Adapted QUIPS 'Risk of bias' assessment instrument for prognostic factor studies (*Continued*)

Definition of the prognostic factor	A clear definition or description of mammographic density is provided (e.g. including the method of measurement, if subjective then who undertook it, if treatment then whether contralateral breast assessed)
Valid and reliable measurement of prognostic factor	Method of mammographic density change measurement is adequately valid and reliable to limit misclassification bias (e.g. may include relevant outside sources of information on measurement properties; also characteristics, such as measurement blinded to case status)
	Continuous variables are reported or appropriate cutpoints (i.e. not data-dependent (except for percentiles)) are used
Method and setting of prognostic factor measurement	The method and setting of measurement of mammographic density is the same for all study participants. The same mammogram type (film/digital) is used for both baseline and follow-up. The time at which baseline and follow-up mammograms have low variability between participants
Proportion of data on prognostic factor available for analysis	Adequate proportion of the study sample has complete data for the change in mammographic density variable
Method used for missing data	Appropriate methods of imputation are used for missing mammographic density data
Summary	Prognostic factor is adequately measured in study participants to sufficiently limit potential bias
4. Outcome measurement	Goal: to judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the density reductions)
Definition of the outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct
Valid and reliable measurement of outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias
Method and setting of outcome measurement	The method and setting of outcome measurement is the same for all study participants, including by age and obesity groups
Outcome measurement summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias

Table 1. Adapted QUIPS 'Risk of bias' assessment instrument for prognostic factor studies   *(Continued)*

5. Study confounding	Goal: to judge the risk of bias due to confounding (i.e. the effect of density reductions is distorted by another factor that is related to density reductions and the outcome)
Important confounders measured	Age, BMI, or another measure of adiposity are measured.
Definition of the confounding factor	Clear definitions are provided.
Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable
Method and setting of confounding measurement	The method and setting of confounding measurement are the same for all study participants
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data
Appropriate accounting for confounding	The primary analysis will be adjusted for at least age, either through the study design and analysis, or through adjustment in the analysis only; and other prognostic factors
Study confounding summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between prognostic factor and outcome
6. Statistical analysis and reporting	Goal: to judge the risk of bias related to the statistical analysis and presentation of results
Presentation of analytical strategy, model development strategy	There is sufficient presentation of data to assess the adequacy of the analysis
Model development strategy	The strategy for model building (i.e. inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model
Reporting of results	The selected statistical model is adequate for the design of the study. There is no selective reporting of results
Statistical analysis and presentation summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results

BMI: body mass index
DCIS: ductal carcinoma in situ

Table 2. ROBINS-I tool (stage 1): treatment

List of confounding domains relevant to all or most studies (prognostic factors that predict whether an individual receives a SERM/AI versus no SERM/AI)
Age Menopausal status Body mass index Hormone replacement therapy ER status Tumour size Nodal status HER-2 status
List of cointerventions that could be different between intervention groups and that could impact on outcome
Hormone replacement therapy Anti-HER2 therapy Chemotherapy Radiotherapy Mastectomy

ER: oestrogen receptor
HER: human epidermal growth factor receptor
SERM/AI: selective oestrogen receptor modulator/aromatase inhibitor

Table 3. ROBINS-I tool (stage 1): prevention

List of confounding domains relevant to all or most studies (prognostic factors that predict whether an individual receives a SERM/AI versus no SERM/AI)
Age Menopausal status Body mass index Family history of disease Hormone replacement therapy use Benign breast disease Previous cancer other than breast cancer Ethnicity
List of cointerventions that could be different between intervention groups and that could impact on outcome
Hormone replacement therapy Risk-reducing surgery

SERM/AI: selective oestrogen receptor modulator/aromatase inhibitor

A P P E N D I C E S

Appendix I. CENTRAL

#1 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
#2 MeSH descriptor: [Aromatase Inhibitors] explode all trees
#3 MeSH descriptor: [Tamoxifen] explode all trees
#4 tamoxifen
#5 MeSH descriptor: [Raloxifene Hydrochloride] explode all trees
#6 raloxifene or lasofoxifene or arzoxifene or droloxifene or bazedoxifene or fulvestrant or anastrozole or letrozole or exemestane
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Breast Density] explode all trees
#9 (mammogr* or breast or mammary) near dens*
#10 MeSH descriptor: [Mammography] explode all trees
#11 MeSH descriptor: [Mammary Glands, Human] explode all trees
#12 dens*
#13 (#10 or #11) and #12
#14 #8 or #9 or #13
#15 #7 and #14

Appendix 2. MEDLINE via OvidSP

1	exp Selective Estrogen Receptor Modulators/
2	exp Aromatase Inhibitors/
3	exp TAMOXIFEN/
4	tamoxifen.mp.
5	exp Raloxifene Hydrochloride/
6	raloxifene.mp.
7	lasofoxifene.mp.
8	arzoxifene.mp.
9	droloxifene.mp.
10	bazedoxifene.mp.
11	fulvestrant.mp.
12	anastrozole.mp.
13	letrozole.mp.

(Continued)

14	exemestane.mp.
15	or/1-14
16	exp Breast Density/
17	exp MAMMOGRAPHY/
18	exp Mammary Glands, Human/
19	((mammogr* or breast or mammary) adj6 dens*).tw.
20	dens*.tw.
21	(17 or 18) and 20
22	16 or 19 or 21
23	15 and 22
24	Animals/ not Humans/
25	23 not 24
26	limit 25 to yr="1996 -Current"

Appendix 3. Embase via OvidSP

#	Searches
1	exp selective estrogen receptor modulator/
2	exp aromatase inhibitor/
3	exp tamoxifen/
4	tamoxifen.ti,ab.
5	exp raloxifene/
6	raloxifene.ti,ab.
7	exp lasofoxifene/
8	lasofoxifene.ti,ab.

9	exp arzoxifene/
10	arzoxifene.ti,ab.
11	exp droloxifene/
12	droloxifene.ti,ab.
13	exp bazedoxifene/
14	bazedoxifene.ti,ab.
15	exp fulvestrant/
16	fulvestrant.ti,ab.
17	exp anastrozole/
18	anastrozole.ti,ab.
19	exp letrozole/
20	letrozole.ti,ab.
21	exp exemestane/
22	exemestane.ti,ab.
23	or/1-22
24	exp breast density/
25	((mammogr$ or breast or mammary) adj6 dens$).ti,ab.
26	dens$.ti,ab.
27	exp mammography/
28	exp mammary gland/
29	26 and (27 or 28)
30	24 or 25 or 29
31	23 and 30
32	limit 31 to (human and (conference abstracts or embase) and yr="1996 -Current")

Appendix 4. WHO ICTRP

Basic search:
1. breast density OR mammographic density
Advanced search:
Title: density
Condition: breast cancer
Intervention: selective oestrogen receptor modulator OR serm OR aromatase inhibitor OR tamoxifen OR raloxifene OR lasofoxifene OR arzoxifene OR droloxifene OR bazedoxifene OR fulvestrant OR anastrozole OR letrozole OR exemestane
Recruitment status: ALL

Appendix 5. ClinicalTrials.gov

Advanced search:
Condition or disease: breast cancer
Other terms: breast density OR mammographic density
Study type: All studies
Study results: All studies
Sex: All
Intervention/treatment: selective oestrogen receptor modulator OR serm OR aromatase inhibitor OR tamoxifen OR raloxifene OR lasofoxifene OR arzoxifene OR droloxifene OR bazedoxifene OR fulvestrant OR anastrozole OR letrozole OR exemestane

CONTRIBUTIONS OF AUTHORS

The objectives and aims of the review were discussed and agreed by all authors. ARB drafted the protocol. It was updated to address critiques from EA, MT, JC and peer-reviewers. All authors agreed the final version.

DECLARATIONS OF INTEREST

JC has previously received research funding from AstraZeneca and is a member of the scientific advisory board for Atossa Genetics. JC and ARB report royalty payments through Cancer Research UK for use of the Tyrer-Cuzick breast cancer risk assessment algorithm. EA and MT declare no conflicts of interest.

If any eligible studies are co-authored by any of the Cochrane review authors, these authors will not be involved in the risk of bias assessment or data extraction of these articles.