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[Intervention Review]

Risk-reducing medications for primary breast cancer: a network meta-analysis

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ABSTRACT

Background

Breast cancer is the most frequently occurring malignancy and the second cause of death for cancer in women. Cancer prevention agents (CPAs) are a promising approach to reduce the burden of breast cancer. Currently, two main types of CPAs are available: selective estrogen receptor modulators (SERMs, such as tamoxifen and raloxifene) and aromatase inhibitors (AIs, such as exemestane and anastrozole).

Objectives

To assess the efficacy and acceptability of single CPAs for the prevention of primary breast cancer, in unaffected women, at an above-average risk of developing breast cancer.

Using a network meta-analysis, to rank single CPAs, based on their efficacy and acceptability (an endpoint that is defined as the inverse of CPA-related toxicity).

Search methods

We searched the Cochrane Breast Cancer Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), and ClinicalTrials.gov on 17 August 2018. We handsearched reference lists to identify additional relevant studies.

Selection criteria

We included randomized controlled trials (RCTs) that enrolled women without a personal history of breast cancer but with an above-average risk of developing a tumor. Women had to be treated with a CPA and followed up to record the occurrence of breast cancer and adverse events.

Data collection and analysis

Two review authors independently extracted data and conducted risk of bias assessments of the included studies, and assessed the certainty of the evidence using GRADE. Outcome data included incidence of breast carcinoma (both invasive and in situ carcinoma) and adverse events (both overall and severe toxicity). We performed a conventional meta-analysis (for direct comparisons of a single CPA with placebo or a different CPA) and network meta-analysis (for indirect comparisons).

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Main results

We included six studies enrolling 50,927 women randomized to receive one CPA (SERMs: tamoxifen or raloxifene, or AIs: exemestane or anastrozole) or placebo. Three studies compared tamoxifen and placebo, two studies compared AIs (exemestane or anastrozole) versus placebo, and one study compared tamoxifen versus raloxifene. The risk of bias was low for all RCTs.

For the tamoxifen versus placebo comparison, tamoxifen likely resulted in a lower risk of developing breast cancer compared to placebo (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.62 to 0.76; 3 studies, 22,832 women; moderate-certainty evidence). In terms of adverse events, tamoxifen likely increased the risk of severe toxicity compared to placebo (RR 1.28, 95% CI 1.12 to 1.47; 2 studies, 20,361 women; moderate-certainty evidence). In particular, women randomized to receive tamoxifen experienced a higher incidence of both endometrial carcinoma (RR 2.26, 95% CI 1.52 to 3.38; high-certainty evidence) and thromboembolism (RR 2.10, 95% CI 1.14 to 3.89; high-certainty evidence) compared to women who received placebo.

For the AIs versus placebo comparison, AIs (exemestane or anastrozole) reduced the risk of breast cancer by 53% (RR 0.47, 95% CI 0.35 to 0.63; 2 studies, 8424 women; high-certainty evidence). In terms of adverse events, AIs increased the risk of severe toxicity by 18% (RR 1.18, 95% CI 1.09 to 1.28; 2 studies, 8352 women; high-certainty evidence). These differences were sustained especially by endocrine (e.g. hot flashes), gastrointestinal (e.g. diarrhea), and musculoskeletal (e.g. arthralgia) adverse events, while there were no differences in endometrial cancer or thromboembolism rates between AIs and placebo.

For the tamoxifen versus raloxifene comparison, raloxifene probably performed worse than tamoxifen in terms of breast cancer incidence reduction (RR 1.25, 95% CI 1.09 to 1.43; 1 study, 19,490 women; moderate-certainty evidence), but its use was associated with lower toxicity rates (RR 0.87, 95% CI 0.80 to 0.95; 1 study, 19,490 women; moderate-certainty evidence), particularly relating to incidence of endometrial cancer and thromboembolism.

An indirect comparison of treatment effects allowed us to compare the SERMs and AIs in this review. In terms of efficacy, AIs (exemestane or anastrozole) may have reduced breast cancer incidence slightly compared to tamoxifen (RR 0.67, 95% CI 0.46 to 0.98; 5 RCTs, 31,256 women); however, the certainty of evidence was low. A lack of model convergence did not allow us to analyze toxicity data.

Authors' conclusions

For women with an above-average risk of developing breast cancer, CPAs can reduce the incidence of this disease. AIs appear to be more effective than SERMs (tamoxifen) in reducing the risk of developing breast cancer. AIs are not associated with an increased risk of endometrial cancer and thromboembolic events. However, long-term data on toxicities from tamoxifen are available while the follow-up toxicity data on unaffected women taking AIs is relatively short. Additional data from direct comparisons are needed to fully address the issues of breast cancer prevention by risk-reducing medications, with special regards to acceptability (i.e. the benefit/harm ratio).

PLAIN LANGUAGE SUMMARY

Medicines to prevent breast cancer in women at above-average risk of developing breast cancer

What is the issue?

Breast cancer is the most frequent type of cancer and the second cause of death by cancer in women. Therefore, any strategy which can reduce its burden is eagerly awaited. Cancer prevention agents (CPAs) are medicines that might fulfil this need. Currently, two main types of CPAs are available to combat breast cancer: selective estrogen receptor modulators (SERMs, such as tamoxifen and raloxifene) and aromatase inhibitors (such as exemestane and anastrozole). Women without personal history of breast cancer, but with above-average risk of developing this disease (that is, with a lifetime risk greater than 17%) represent the usual target population for CPAs.

Review question

This Cochrane Review aimed to summarize the evidence on the efficacy and toxicity of CPAs for the prevention of primary breast cancer.

Key messages

CPAs can reduce the incidence of breast cancer although at the cost of some toxicity. Aromatase inhibitors may be more effective than SERMs in reducing the risk of developing breast cancer. Aromatase inhibitors are not associated with the increased severe toxicity (i.e. cancer of the lining of the womb (endometrial cancer)) and thromboembolic events (blood clots)) that characterize the use of tamoxifen (although the lack of long-term data on aromatase inhibitors in unaffected women do not allow us to draw definitive conclusions). Additional data are needed to fully address the issues of breast cancer prevention by risk-reducing medicines, with emphasis on collecting information on side effects.

What was studied in the review?

The review authors found six studies enrolling 50,927 women to receive one CPA or placebo (a pretend treatment, e.g. a sugar pill). Three studies involving 23,013 women compared tamoxifen and placebo, two studies involving 8424 women compared aromatase inhibitors (exemestane or anastrozole) and placebo, and one study involving 19,490 women that compared tamoxifen and raloxifene.

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What are the main results of the review?

Based on the three studies that compared tamoxifen to placebo, tamoxifen probably reduced the risk of developing breast cancer by 32% compared to placebo. However, tamoxifen was associated with a 28% increased risk of severe side effects compared to placebo based on two studies involving 20,361 women. In particular, women taking tamoxifen experienced higher incidence of endometrial cancer and thromboembolism than women having no medicine.

For women who received either an aromatase inhibitor (exemestane or anastrozole) or placebo, aromatase inhibitors reduced the risk of breast cancer by 53% compared to placebo. Data from two studies involving 8352 women indicated that aromatase inhibitors increased the risk of severe side effects by 18% compared to placebo. These differences were sustained especially by endocrine (hormonal; e.g. hot flashes), gastrointestinal (e.g. diarrhea), and musculoskeletal (e.g. joint pain) side effects, whereas there were no differences in either endometrial cancer or thromboembolism rates.

For women who received either tamoxifen or raloxifene, raloxifene probably performed worse than tamoxifen in terms of breast cancer incidence reduction, but its use was associated with a 13% reduction of toxicity rates especially endometrial cancer and thromboembolism.

A specialized method named a 'network meta-analysis' allowed us to compare medications never directly compared to each other in a study. Based on this network meta-analysis, aromatase inhibitors may have led to a 23% additional risk reduction of developing breast cancer compared to tamoxifen. However, the reliability of the evidence was low meaning that further research is likely to have an impact on our confidence in this result. This analysis could not be performed on toxicity data.

How up-to-date is this review?

The review authors searched for studies that had been published up to 17 August 2018.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tamoxifen versus placebo

Tamoxifen compared with placebo for primary breast cancer prevention

Patient or population: women with above-average risk of developing breast cancer

Settings: prevention

Intervention: tamoxifen

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tamoxifen				
Overall breast cancer incidence Follow-up: 6–16 years	**72 per 1000**	**49 per 1000 **** (44 to 54)	**RR 0.68** (0.62 to 0.76)	22,832 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Severe toxicity Follow-up: 6–16 years	**35 per 1000**	**46 per 1000** (39 to 51)	**RR 1.28** (1.12 to 1.47)	20,361 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—

*The basis for the **assumed risk** (control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Number needed to treat: 43

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for inconsistency.

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Summary of findings 2. Aromatase inhibitors versus placebo

Aromatase inhibitors compared with placebo for primary breast cancer prevention

Patient or population: women with above-average risk of developing breast cancer

Settings: prevention

Intervention: aromatase inhibitors (anastrozole and exemestane)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Aromatase inhibitors				
Overall breast cancer incidence Follow-up 3–5 years	**31 per 1000**	**14 per 1000 **** (11 to 19)	**RR 0.47** (0.35 to 0.63)	8424 (2 RCTs)	⊕⊕⊕⊕ **High**	—
Severe toxicity Follow-up: 3–5 years	**214 per 1000**	**253 per 1000** (233 to 274)	**RR 1.18** (1.09 to 1.28)	8352 (2 RCTs)	⊕⊕⊕⊕ **High**	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Number needed to treat: 59

CI: confidence interval; **RCT**: randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

Summary of findings 3. Aromatase inhibitors versus tamoxifen (indirect comparison)[a]

Aromatase inhibitors compared with tamoxifen for primary breast cancer prevention (based on network meta-analysis findings)

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Patient or population: women with above-average risk of developing breast cancer

Settings: prevention

Intervention: aromatase inhibitors

Comparison: tamoxifen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tamoxifen	Aromatase inhibitors				
Overall breast cancer incidence Follow-up: 3–16 years	**49 per 1000**	**33 per 1000 **** (23 to 48)	**RR 0.67** (0.46 to 0.98)	31,256 (5 RCTs)	⊕⊕⊝⊝ **Low**[b]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Number needed to treat: 62

CI: confidence interval; **RCTs**: randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The findings are from indirect comparison (network meta-analysis) of two RCTs comparing aromatase inhibitors with placebo and three RCTs comparing tamoxifen with placebo.
[b]Downgraded two levels for partial lack of transitivity and inconsistency.

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BACKGROUND

Description of the condition

In women, breast cancer is the first tumor type by incidence, and the second cause of death by cancer (Torre 2015). The social burden of breast cancer in terms of mortality, morbidity, psychological stress, and economic cost is huge: accordingly, many efforts are being made to effectively and safely prevent this disease (De la Cruz 2014; Lebovic 2010).

Thus far, the vast majority of favorable results in terms of reducing the disease burden have been yielded by means of secondary prevention programs, which are based on the early detection of breast cancer (primarily by screening mammography) (Fuller 2015; Onega 2014), an approach that has been the subject of some criticism (Pace 2014; Stout 2014).

Several approaches have been advocated for primary prevention (any intervention that can decrease disease incidence, i.e. the occurrence of new cases of breast cancer), with the types of intervention depending upon the risk level of the target population. The lifetime risk of developing breast cancer (as per internationally established guidelines, such as those from the National Institute for health and Care Excellence (NICE 2017)), can be calculated by means of dedicated risk assessment tools (e.g. the Gail model; Gail 2015) based on a set of risk factors such as age, race, age at the time of first menstrual period, age at the time of first live birth of a child, and number of first-degree relatives with breast cancer). Family history of breast/ovarian cancer is used to assess personal risk of developing breast cancer, and some women have greater than 30% lifetime risk based on family history. Those at high risk (greater than 30%) may be offered screening breast magnetic resonance imaging, in addition to mammography.

Women at highest risk are those who carry germline pathogenic mutations in BRCA1 (personal risks estimated as 57%, 95% confidence Interval (CI) 47% to 66%, as per NICE 2017) or BRCA2 (personal risk 49%, 95% CI 40% to 57%). These women may consider risk-reducing surgery with bilateral mastectomies, which reduce the risk of developing breast cancer by up to 90%. As these women are at high risk of developing ovarian cancer (10% to 60% risk), risk-reducing bilateral salpingo-oophorectomy is strongly recommended, and, when performed around age 40 years, reduces the risk of developing breast cancer by 50% (Lostumbo 2010; Tuttle 2010), although this belief has been the focus of controversies (Heemskerk-Gerritsen 2015; Kotsopoulos 2016).

Primary prevention has also been suggested for women considered to be at above-average risk of breast cancer (lifetime risk between 17% and 30%, as per NICE 2017).

For women with an above-average risk, pharmacological prevention (also known as risk-reducing medication, chemoprevention, or preventive therapy) has been proposed to reduce the risk of breast cancer (Advani 2014; Colditz 2014; Sestak 2015). Of note, the compounds used for chemoprevention are not to be confused with cytotoxic chemotherapeutic agents, which are effective for adjuvant therapy, but have no role in prevention of breast cancer. Many chemoprevention compounds have been tested in clinical trials, and have shown risk-reducing properties against a variety of tumors (including breast cancer). Currently, some of these compounds (e.g. tamoxifen and raloxifene, which are approved for the treatment of early and advanced breast cancer) are recommended for breast cancer primary prevention in clinical practice (Carlson 2009; Chlebowski 2002; Colditz 2014; Stubert 2014).

Finally, lifestyle changes (e.g. physical exercise, healthy diet, and smoking/alcohol cessation; Gonçalves 2014; Rossi 2014) are recommended independently of the risk level, also in light of their positive effects on the risk of other illnesses.

Description of the intervention

Cancer prevention agents (CPAs) are a broad group of compounds sharing an anticancer activity, proven experimentally or clinically (or both), against one or more tumor types (Landis-Piwowar 2014; Serrano 2015). With regards to breast cancer pharmacological prevention (Chlebowski 2014; Cuzick 2011; Den Hollander 2013; Gabriel 2012), the CPA class most tested is that of selective estrogen receptor modulators (SERMs) (Cuzick 2013; Lazzeroni 2013; Visvanathan 2013), due to the hormone dependence of the majority of breast cancers (Williams 2014). Other CPAs have been investigated, such as other antiestrogen drugs (e.g. aromatase inhibitors; Behan 2015; Litton 2012; Olin 2014),; micronutrients (e.g. vitamins; Giammanco 2015; Lazzeroni 2011); and drugs already approved for the treatment of different diseases (e.g. antiosteoporosis agents; Chlebowski 2012; Liu 2012), anticholesterol agents (e.g. Ahern 2014; Santa-Maria 2013), non-steroidal anti-inflammatory drugs (NSAIDs) (Bosetti 2012; Jacobo-Herrera 2014; Thorat 2013), and antidiabetes agents (Gandini 2014; Stine 2014), for which experimental and (although not always conclusive) epidemiological evidence suggests anticancer activity. Of note, both SERMs and aromatase inhibitors are currently approved for breast cancer treatment both in the adjuvant setting (i.e. postoperatively in women with early disease) and in advanced/metastatic setting.

Overall, CPAs are a group of compounds that differ, often radically, from the chemical and pharmacological viewpoint. There are different CPA classes (e.g. SERMs, aromatase inhibitors, vitamins, NSAIDs, etc.), each one with different anticancer mechanisms, that are sometimes not fully elucidated. The SERMs and aromatase inhibitors, whose activity against breast cancer has been clearly demonstrated in women with both early and metastatic disease (Freedman 2015; Schiavon 2013), act by interfering with the estrogen receptor pathway, which is known to play a key role in breast carcinogenesis.

SERMs act on the estrogen receptor, behaving as both agonists (i.e. by stimulating receptor activity) and antagonists (i.e. by inhibiting receptor activity), depending on the target tissue. For instance, one of the most widely investigated SERMs, tamoxifen, acts as an agonist in bone and uterine tissues, while it acts as an antagonist in breast tissue. Overall, this tissue specificity determines most of the beneficial effects (e.g. antibreast cancer activity) as well as toxic effects (e.g. endometrial cancer-promoting activity) (Nazarali 2014). In contrast, the more-recently developed SERMs (e.g. raloxifene, lasofoxifene) act as agonists mainly in bone tissue, and antagonists in both breast and uterine tissues (Mirkin 2015). As their mechanism of action implies an interaction with the estrogen receptor, SERMs activity is much higher (about 10-fold) against tumors expressing the estrogen receptor or progesterone receptor (so-called hormone-positive breast cancer) (or both), and is not effective in tumors that do not express these receptors

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(estrogen receptor-negative and progesterone receptor-negative breast cancer).

Aromatase inhibitors (e.g. anastrozole, letrozole, exemestane) inhibit estrogen synthesis and are only active in postmenopausal women, when the main source of estrogen is the peripheral tissues (whereas the main source of estrogen is the ovaries in premenopausal women). In the peripheral tissues, androgens are converted into estrogens by the aromatase enzyme, which is the target of aromatase inhibitors. Therefore, aromatase inhibitors are used exclusively in postmenopausal women for either the prevention of primary breast cancer (women who never had a primary breast cancer, but who are at an above-average risk of developing it), or as adjuvant therapy for prevention of breast cancer recurrence, or for control of metastatic hormone-positive breast cancer (Campagnoli 2013; Chumsri 2015).

For other CPAs, the evidence in the field of breast cancer management is much less extensive. NSAIDs (such as aspirin), which have an established role in colorectal cancer primary prevention (Rothwell 2012; Sostres 2014), block the cyclo-oxygenase pathway, which is involved in tumor development. For micronutrients (such as vitamin D), a wealth of experimental and epidemiological evidence has been gathered that supports their anticancer potential (Feldman 2014), although their efficacy has yet to be clearly demonstrated in clinical trials. For antiosteoporosis agents, anticholesterol agents, and antidiabetes agents, the anticancer mechanism has only been partially elucidated, and some epidemiological evidence has suggested a potential anticancer effect in primary prevention (Gronich 2013). Finally, for other potential CPAs, only some preclinical evidence of anticancer activity has been reported (Romagnolo 2014; Wang 2015), without any epidemiological data being available on cancer risk reduction.

How the intervention might work

The rationale for using CPAs is to reduce the risk of breast cancer development (and thus to reduce breast cancer incidence, that is, the occurrence of new cases of this disease). The performance of the CPA depends upon two main aspects.

The first aspect is the risk level of the target population. In fact, the absolute risk reduction (ARR = EER – CER, where EER is experimental event rate and CER is control event rate) is higher as the disease risk increases, although the relative risk reduction (RRR = [EER – CER]/CER) is constant across risk levels. An important corollary is that it can be very difficult to demonstrate the efficacy of any type of prevention strategy in a low-risk population due to the low incidence of the disease, which would require a huge number of participants to be enrolled in order to yield adequate statistical power. Therefore, in order to prove the efficacy of a given CPA, trials usually enroll women at an above-average risk of breast cancer.

The second aspect is CPA-related toxicity. Since CPAs are administered to averagely healthy women, they should be characterized by a low (or very low) occurrence of adverse effects. The lower the toxicity rate (i.e. the higher the acceptability), the broader the population that might benefit from the preventive effect of a given CPA. If the CPA had no toxicity, it could be recommended to all women, independently of their risk of developing breast cancer. Since this 'ideal' type of CPA does not yet exist, chemoprevention is currently recommended only to women at an above-average risk of breast cancer. Risk assessment tools (such as the Gail score) have been devised to identify such a target population (Cummings 2009; Gail 2015; Howell 2014; Layeequr 2009), in which the risk of toxic effects associated with CPAs must be overwhelmed by the benefit in terms of breast cancer prevention.

The risk of toxicity associated with CPAs is the main cause of the relatively low rate of uptake of risk-reducing agents in breast cancer (Crew 2015; Smith 2016). However, other aspects have been suggested to impact on the uptake of CPAs, such as the impact of others' experience on beliefs about the CPA, the CPA perceived as a 'cancer drug', and daily reminder of cancer risk (Donnelly 2014).

Why it is important to do this review

Chemoprevention for breast cancer is a debated topic (Euhus 2015; Ropka 2010; Serrano 2015; Wuttke 2015). International guidelines such as the American Society of Clinical Oncology (ASCO) (Visvanathan 2013), the National Comprehensive Cancer Network (NCCN) (Gradishar 2015), the US Preventive Services Task Force (Moyer 2013), and the National Institute for Health and Care Excellence (NICE) (NICE 2017) guidelines, recommend offering some CPAs (i.e. tamoxifen and aromatase inhibitors) for women at an above-average risk of breast cancer (Alés-Martínez 2015).

Randomized controlled trials (RCTs) and meta-analyses of single CPAs (or a class of CPAs) support the efficacy of chemoprevention in women at higher than average risk for developing primary (no previous breast cancer) breast cancer (Cuzick 2013; Nelson 2013; Vogel 2015). However, the uptake of CPAs is low, for reasons including the low, but non-negligible rate of adverse effects associated with CPAs (Crew 2015; Holmberg 2015; Nichols 2014). Therefore, the balance between their benefits and harms is still debated.

For this review, we systematically assessed the RCT-based evidence for CPAs as potentially useful against primary breast cancer. This provides women, physicians, healthcare agencies, and policy-makers with objective information to make evidence-based decisions regarding the use of CPAs as a breast cancer risk-reducing strategy.

OBJECTIVES

To assess the efficacy and acceptability of single-agent CPAs for the prevention of primary breast cancer, in unaffected women, at an above-average risk of developing breast cancer.

Using a network meta-analysis, to rank single CPAs, based on their efficacy and acceptability (an endpoint that is defined as the inverse of CPA-related toxicity).

METHODS

Criteria for considering studies for this review

Types of studies

RCTs examining the performance of any CPA in women at an above-average risk of sporadic primary breast carcinoma.

We applied no language restrictions. We included RCTs in which allocation to treatment was not adequately concealed (or the concealment was unclear); however, we considered trial methodological quality in both the analysis and discussion. In

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the light of the preventive nature of the treatment (risk-reducing therapy), we expected that most trials would compare a given CPA with placebo (or observation). We excluded quasi-RCTs (i.e. trials in which treatment allocation depended upon predictable methods, such as date of birth or alternation).

Types of participants

Women with no personal history of breast cancer, but with above-average risk of developing breast cancer (i.e. with a lifetime risk greater than 17% but lower than 30%) represented the target population.

We excluded trials where all participants were women at high risk (i.e. with a lifetime risk greater than 30%) since robust evidence exists for the use of CPAs (e.g. tamoxifen and aromatase inhibitors) in this group (Advani 2014; Freedman 2015; Gradishar 2015; Tuttle 2010; Yeo 2014). In contrast, the use of CPAs for women at above-average risk of developing breast cancer is still controversial. We included trials of women at above-average risk (between 10% and 17%) and high risk (greater than 30%), provided the majority of participants were likely to be at above-average risk of breast cancer.

Types of interventions

- Intervention: any CPA with proven anticancer properties based on experimental or clinical evidence (epidemiological, i.e. observational, or trial-based) (or both) gathered for breast cancer or any other type of cancer.
  - Selective estrogen receptor modulators (SERMs): tamoxifen, raloxifene, lasofoxifene.
  - Aromatase inhibitors: anastrozole, letrozole, exemestane.
  - Vitamin D, aspirin, metformin, statins (pravastatin, simvastatin), bisphosphonate (zoledronate, alendronate).
- Comparator: placebo (or observation) or any other CPA.

Types of outcome measures

We utilized study-level data for the following outcomes.

Primary outcomes

We assessed each CPA in terms of:

- Overall breast cancer incidence (in situ and invasive carcinoma); and
- Severe toxicity (i.e. grade 3 and 4 toxicities according to the National Cancer Institute (NCI) Common Toxicity Criteria or equivalent) .

Secondary outcomes

We assessed each CPA in terms of:

- Invasive breast cancer incidence (excluding in situ carcinoma, as opposed to the primary outcome which included both in situ and invasive carcinomas); and
- Overall toxicity (any grade toxicity).

Search methods for identification of studies

Electronic searches

We searched the following databases on 17 August 2018.

- 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 on the Group's website. We extracted and considered for inclusion in the review, trials with the key words "breast cancer, breast carcinoma, chemoprevention, preventive therapy, primary prevention, risk, randomized controlled trial, tamoxifen, raloxifene, lasofoxifene, selective estrogen receptor modulator, SERM, aromatase inhibitor, anastrozole, letrozole, exemestane, vitamin D, aspirin, metformin, statin, pravastatin, simvastatin, bisphosphonate, zoledronate, alendronate".
- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1).
- MEDLINE (via OvidSP; Appendix 2). Results of this search were limited to specific years (i.e. 2012 to August 2018) due to the currency of the CBCG's Specialised Register.
- Embase (via OvidSP; Appendix 3). Results of this search were limited to specific years (i.e. 2014 to August 2018) due to the currency of Embase records in CENTRAL.
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal for all prospectively registered and ongoing trials (www.apps.who.int/trialsearch/Default.aspx; Appendix 4).
- ClinicalTrials.gov (www.clinicaltrials.gov; Appendix 5).

We applied no language restrictions for any of the searches.

Searching other resources

Bibliographic searching

We tried to identify additional studies from reference lists of identified relevant studies or reviews. We obtained a copy of the full article for each reference reporting a potentially eligible study.

Data collection and analysis

Selection of studies

We used the search strategy to identify titles and abstracts of relevant studies. Two review authors (SM, SP) independently screened these titles and abstracts, and they discarded non-relevant or duplicate publications. For studies where the classification of risk was unclear, these were discussed with the third author (AG). We screened studies and reviews that might have included information on potentially relevant studies. We retrieved the full text of potentially relevant publications in order to fully assess study eligibility. We applied no language restrictions. For articles written in languages other than Italian, English, French, and Spanish (the languages the authors know), we were prepared to organize translations. Any disagreement was resolved by iteration, discussion, and consensus with the third review author (AG).

Data extraction and management

Two review authors (SM, SP) independently extracted data using dedicated data extraction forms (i.e.in-house MS-Excel spreadsheets that were previously developed and used by the authors for other systematic reviews).

According to the population, intervention, comparison, outcomes, study design (PICOS) list, we extracted the following descriptive data for each study.

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- Population: mean age; menopausal status; breast cancer risk.
- Intervention: CPA; dosage; administration route; duration of administration.
- Comparison: as above (unless placebo or no treatment).
- Study design: inclusion criteria; primary endpoint; duration of follow-up; number of participants; date of publication; number of centers; sequence generation; allocation concealment; blinding of outcome assessors; attrition; selective outcome reporting.

Most (if not all) of these data could also be used as potential effect modifiers to investigate both between-study heterogeneity and inconsistency (and thus, to verify the key assumption of transitivity for network meta-analysis, see below for more details).

Additionally, we extracted outcome data (risk ratios (RR) for both treatment efficacy and treatment toxicity) from each study.

We (or others) were prepared to translate studies reported in non-English language journals before assessment. Where more than one publication of one study existed, we used the publication with the most complete and updated data in the analysis; however, if relevant outcomes were only published in earlier versions, we used these data as well. Any disagreement was resolved by iteration, discussion, and consensus with the third review author (AG).

Assessment of risk of bias in included studies

Two review authors (SM, SP) independently assessed the risk of bias in included studies using Cochrane's 'Risk of bias' assessment tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The tool is composed of seven domains: 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 outcome reporting (reporting bias), and other sources of bias (e.g. per-protocol analysis instead of intention-to-treat analysis). Based on the results obtained with this tool, we classified the included studies into one of the following categories: low, high, or unclear risk of bias. Any disagreement was resolved by iteration, discussion, and consensus with the third review author (AG).

Measures of treatment effect

Only dichotomous outcomes were expected, that is, efficacy (ratio of disease incidence in the intervention and comparator arms) and toxicity (ratio of disease rate in the intervention and comparator arms). Therefore, we expressed results as RRs with their 95% CIs. As for efficacy, an RR greater than 1.0 favors the intervention (as compared to comparator); when toxicity is considered, an RR greater than 1.0 favors the comparator.

Direct comparisons of treatment effects (CPA versus placebo/ observation or other CPA)

We first carried out a standard pair-wise meta-analysis of results from studies comparing the same interventions using a fixed-effect model; a random-effects model (and a non-iterative method of moments estimator as per DerSimonian 1986) can be used in case of between-study heterogeneity (I^2 statistic greater than 50%), but the limited number of studies available made the estimation of between-study heterogeneity unreliable. Therefore, the fixed-effect model was always used.

Assessment of heterogeneity within treatment comparisons

We evaluated between-study heterogeneity within each treatment comparison using the I^2 statistic (Higgins 2003). In the presence of statistical (I^2 statistic greater than 50%) or clinical heterogeneity, or both, we investigated the potential sources of heterogeneity (provided that necessary data were available; see below for more details).

Indirect and mixed comparisons of treatment effects

Network meta-analysis is the proposed method to summarize information from a network of studies addressing the same question, but testing different interventions (Caldwell 2014; Cipriani 2013; Salanti 2008; Salanti 2011).

This method allows for indirect treatment comparisons (i.e. comparisons not previously addressed directly), and improves estimate precision for comparisons with few data (as it combines both direct and indirect evidence). Moreover, network meta-analysis enables investigators to rank treatments based on both efficacy and safety (a measure inversely proportional to toxicity). The aim of adopting this sophisticated statistical method was to compare the two main drug classes used in breast cancer risk reduction (that is, SERMs and aromatase inhibitors) because no studies have ever directly compared these two drug classes.

Assessment of transitivity across treatment comparisons

We evaluated the main assumption underlying network meta-analysis, which is called transitivity. If one has information about comparisons AB and AC, then network meta-analysis can derive information regarding the BC comparison based on the transitivity equation AB – AC = BC (Higgins 2012; Veroniki 2013; White 2012). We expect that the transitivity assumption will hold assuming that:

- the common treatment (i.e. placebo or observation), used to compare different CPAs indirectly, is similar when it appears in different studies;
- all pair-wise comparisons do not differ substantially with respect to the distribution of effect modifiers (e.g. the design and study characteristics of a given CPA versus placebo studies are similar to those of studies comparing placebo to another CPA); and
- participants, could in principle, be randomized to any of the treatments being compared in the network.

We first evaluated the assumption of transitivity by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons. To this aim, we took into consideration the following potential effect modifiers (if data were available): menopausal status, mean age, breast cancer risk score (mean), drug schedule (dose, frequency, duration of treatment), risk of bias category, duration of follow-up, number of participants, and date of publication.

Assessment of statistical inconsistency

Lack of transitivity can manifest as inconsistency between direct and indirect estimates (loop inconsistency) or between estimates deriving from different study designs (design inconsistency) (Higgins 2012). Statistical methods can be employed to evaluate consistency in a network. We used the following methods (based on the type of studies and network that will result after the identification of the eligible studies).

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- Loop-specific approach: when at least three treatments are compared to each other in a network forming a closed path, indirect evidence can be contrasted to direct evidence and their difference defines the so-called inconsistency factor. To determine whether the inconsistency factor is different from zero, the Bucher method can be used (looking at the 95% CI and a loop-specific z-test) (Bucher 1997). This analysis can be extended to all closed loops, assuming a loop-specific heterogeneity. This approach can identify loops with large inconsistency factors, but cannot determine the consistency of the whole network. Therefore, caution must be used while interpreting the findings derived from this method. Moreover, since loop inconsistency cannot occur in a multi-arm trial (i.e. a trial with more than two arms), this method cannot be applied when multi-arm trials are present: thus, a different method must be adopted to unveil inconsistency (see 'design-by-treatment interaction model' below).
- Design-by-treatment interaction model: this has been proposed as a more comprehensive method to identify inconsistency (Higgins 2012), which encompasses both loop and design inconsistencies, and can be applied in the presence of both two-arm and multi-arm studies. While the above-mentioned loop inconsistency approach aims at assessing whether direct and indirect evidence are consistent with each other, design inconsistency addresses the issue of whether a particular study design is associated with different effect sizes for a given treatment comparison (it can be envisaged as a multivariable meta-regression where design is a study-level covariate). As an example, this approach tests whether the relative effectiveness of treatment A versus B is different when estimated in studies with different designs, such as AB and ABC. Importantly, the design-by-treatment interaction model provides a global test for network inconsistency.

In case of significant inconsistency, its possible sources can be investigated by using multivariable random-effects meta-regression. In particular, the distribution of prespecified clinical and methodological features (used as study-level covariates) that might represent potential sources of inconsistency can be investigated, such as menopausal status, mean age, breast cancer risk score (mean), drug schedule (dose, frequency, duration of treatment), risk of bias category, duration of follow-up, number of participants, and date of publication.

Unit of analysis issues

There were no unit of analysis issues in the included studies (all studies adopted a simple parallel-group design). Should we find such issues in updates of this review, we will deal with them as recommended by Cochrane guidelines (Higgins 2011).

Dealing with missing data

We performed an intention-to-treat analysis and recorded numbers lost to follow-up and withdrawals (attrition rates). In the review update, should we find missing data in studies, we will contact the investigators of these studies in order to obtain those data.

Assessment of heterogeneity

We quantified between-study heterogeneity within each direct comparison using the I^2 statistic (Higgins 2003). In particular, we considered heterogeneity to be high for I^2 values greater than 50%. Potential sources of heterogeneity (study-level effect modifiers) such as menopausal status, mean age, breast cancer risk score (mean), drug schedule (dose, frequency, duration of treatment), risk of bias category, duration of follow-up, number of participants, and date of publication could not be investigated due to the paucity of studies available. This analysis will be taken into consideration in the future should new data be available.

In order to fully describe heterogeneity in network meta-analysis, we described both the magnitude of heterogeneity within treatment comparisons and the magnitude of the heterogeneity variance assumed common across treatment comparisons. In relation to the common heterogeneity variance across treatment comparisons (also known as Tau^2), biostatisticians suggest referring to empirical distributions of heterogeneity values typically found in meta-analyses (in particular, they consider heterogeneity to be high for a Tau^2 value larger than the 75th quartile: Rhodes 2015; Salanti 2014; Turner 2012). Given that the interpretation of this variance is not straightforward, biostatisticians suggest presenting network meta-analysis summary effects together with their predictive intervals (i.e. an interval where the estimate of a potential future study is expected to be) in order to facilitate the understanding of the results in the light of the heterogeneity magnitude (Chaimani 2013), and we followed this guidance when conducting this review.

Assessment of reporting biases

In this review, we were unable to assess small-study effects (which includes publication bias) by using funnel plots because there were fewer than 10 studies (Higgins 2011). However, in review updates, we will assess funnel plot asymmetry by means of visual inspection and formally testing by means of Egger's test should we find a sufficient number of studies.

Data synthesis

We presented results for both treatment efficacy and toxicity as risk ratios (RRs) and their 95% confidence intervals (CIs). For standard pair-wise meta-analysis (using the fixed-effect model), we used Review Manager 5 software (Review Manager 2014).

We conducted a network meta-analysis using the Stata software 11.2/SE (StataCorp 2009); in particular, we used the mvmeta routine (Chaimani 2013; White 2011), that fits the multivariate random-effects meta-analysis model (using restricted maximum likelihood) as suggested by White 2011. We presented results from the network meta-analysis as summary effect sizes (RRs) along with their 95% CIs and predictive intervals. We assumed a common heterogeneity variance, that is, a single heterogeneity variance for the entire network, pertaining to every one of the direct comparisons (this assumption simplifies the analysis and allows for heterogeneity to be incorporated for direct comparisons with only one trial available).

We used the GRADE approach to assess the certainty of the evidence (Guyatt 2011). Briefly, certainty of evidence is graded into four levels: high, moderate, low, and very low certainty. Evidence from RCTs is considered high certainty; however, the certainty can be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: risk of bias, inconsistency (unexplained heterogeneity, inconsistency of results), indirectness (indirect population, intervention, control, outcomes), and imprecision (wide CIs, CIs crossing the null value

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(i.e. the results are compatible with both favorable and harmful effects)).

'Summary of findings' table

We included 'Summary of findings' tables (including the number needed to treat, that is, the number of women to be administered the risk reducing medication in order to avoid one case of breast cancer, which is calculated as 1/absolute risk reduction). The baseline risk was considered the mean event rate in the non-treatment (placebo or observation) arms of the included studies.

Subgroup analysis and investigation of heterogeneity

Neither subgroup analysis nor meta-regression were feasible, as data were not permissive (i.e. too few studies were available). Should new studies be available in the future, we will between-study heterogeneity by means of the following.

- Subgroup analysis: using the following grouping variables:
  - menopausal status (pre- versus postmenopause); and
  - estrogen receptor status (positive versus negative).
- Meta-regression: to assess an association between duration of both follow-up and treatment, and treatment efficacy.

Sensitivity analysis

We did not perform sensitivity analysis. However, should additional studies be available in the future, we will evaluate the robustness of the results by excluding studies with high risk of bias, studies not having breast cancer incidence as their primary endpoint, or studies using observation (no treatment) as a comparator.

RESULTS

Description of studies

Results of the search

The literature search led to the identification of 2717 records (see PRISMA flowchart: Figure 1). After the exclusion of duplicates, we screened the title and abstracts of 2381 records, which led to the identification of 41 potentially eligible records. We excluded 35 records after full-text review. The six remaining records corresponded to six studies that fulfilled the inclusion criteria and thus, were included in the qualitative (six studies) and quantitative (five studies) analyses.

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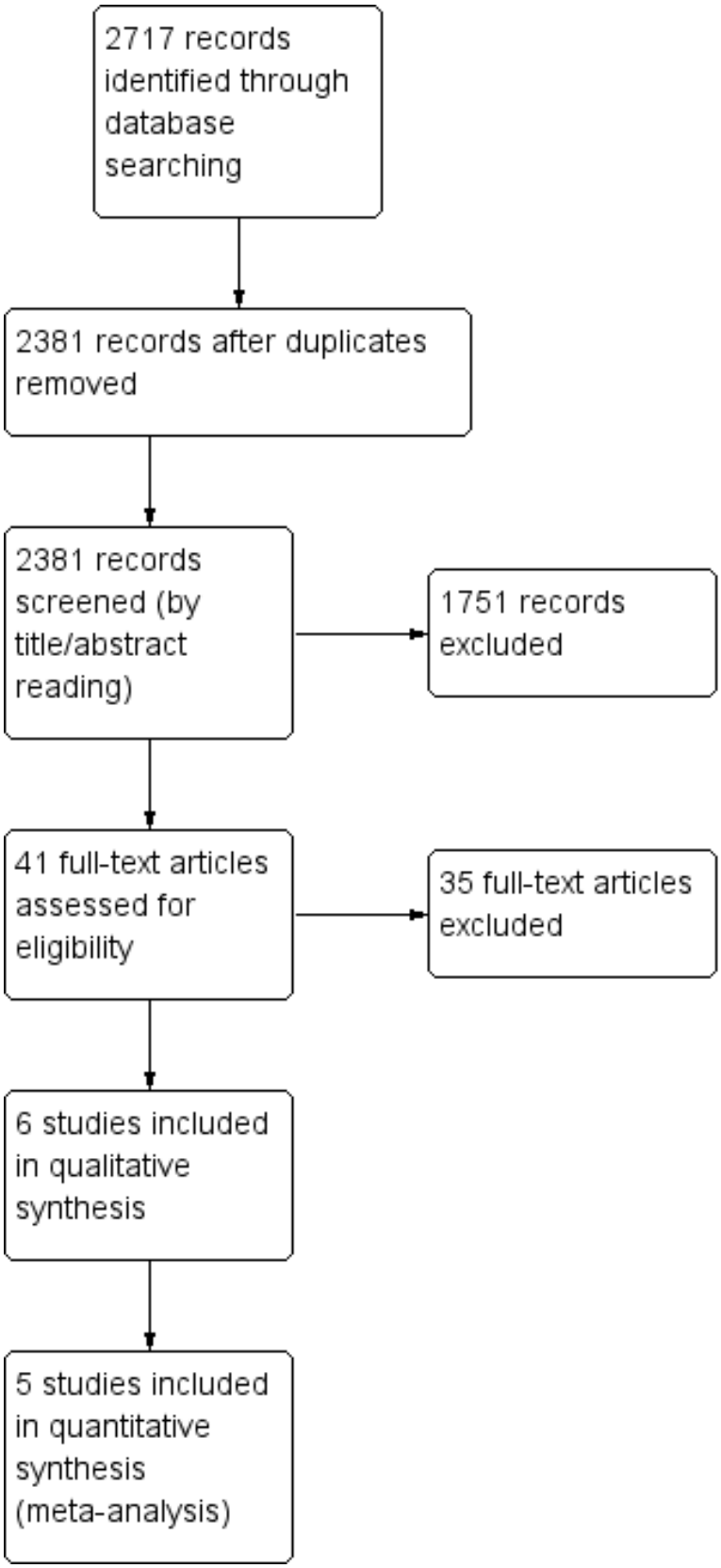
Figure 1. Study flow diagram.



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Included studies

The six included studies were published between 2005 and 2015 (Cuzick 2014; Cuzick 2015; Fisher 2005; Goss 2011; Powles 2007; Vogel 2010; see Characteristics of included studies table).

Overall, 50,927 women were enrolled with the mean number of women enrolled per study being 8491 (range 2494 to 19,490). Participants were:

- postmenopausal women at higher risk of breast cancer (Cuzick 2014; Goss 2011; Vogel 2010);
- women deemed to be at an increased risk of developing breast cancer based on a family history of breast cancer or abnormal benign breast disease (Cuzick 2015);
- women either 60 years of age or older or between 35 and 59 years of age with a five-year predicted risk for breast cancer of at least 1.66% (Fisher 2005); or
- women with a family history of breast cancer (Powles 2007).

The six studies (all designed as two-arm RCTs) investigated four agents: two SERMs (i.e. tamoxifen: Cuzick 2015; Fisher 2005; Powles 2007; Vogel 2010, and raloxifene: Vogel 2010), and two aromatase inhibitors (i.e. anastrozole: Cuzick 2014, and exemestane: Goss 2011). Five studies compared the risk-reducing medication with placebo (Cuzick 2014; Cuzick 2015; Fisher 2005; Goss 2011; Powles 2007), whereas one compared the efficacy of two SERMs (tamoxifen and raloxifene; Vogel 2010).

Excluded studies

We excluded 35 studies after evaluating the corresponding full-text articles. The two main reasons for exclusion were data duplication and an inadequate definition of the population risk of breast cancer (for further details, see Characteristics of excluded studies table).

Risk of bias in included studies

Overall, the risk of bias was low as the quality of all included studies was high (see Figure 2). In particular, there was no high risk of bias, and two studies had an unclear risk of bias. The risk of performance bias was unclear in two studies because they were unblinded (Fisher 2005; Vogel 2010). In one study, the risk of attrition bias was unclear due to loss to follow-up (1.3% of the originally randomized population) (Vogel 2010).

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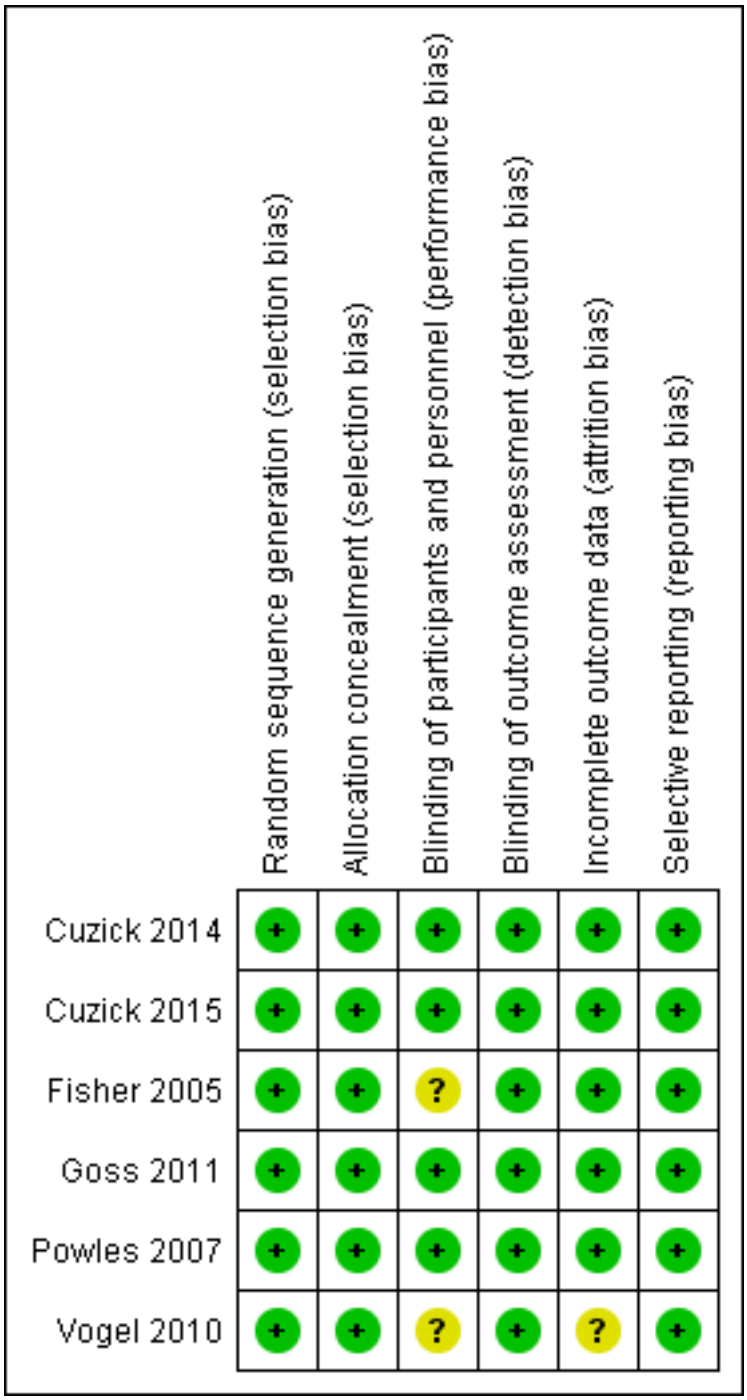
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The risk of selection bias was low in all six studies, both in terms of random sequence generation and allocation concealment.

Blinding

The risk of performance bias was generally low, although two studies designed as double blind were unblinded some time after the enrolment was ended (Fisher 2005; Vogel 2010). The impact of this unblinding on findings was unclear, since the results before and after unblinding appeared similar.

The risk of detection bias was low in all studies as all outcomes were considered to be objective outcome measures.

Incomplete outcome data

The risk of attrition bias was low in five out of six studies. In one study, 19,490 women out of the originally randomized 19,747 women participated in the study and the main reason for the attrition was loss at follow-up (i.e. data were available for 98.7% of initially randomized participants) (Vogel 2010). It is unclear if this

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loss may have caused any bias when these number of women lost at follow-up were evenly distributed between the two study arms.

Selective reporting

The risk of reporting bis was low in all included studies because all studies reported the outcomes as specified in the methods section of the trial publications.

Other potential sources of bias

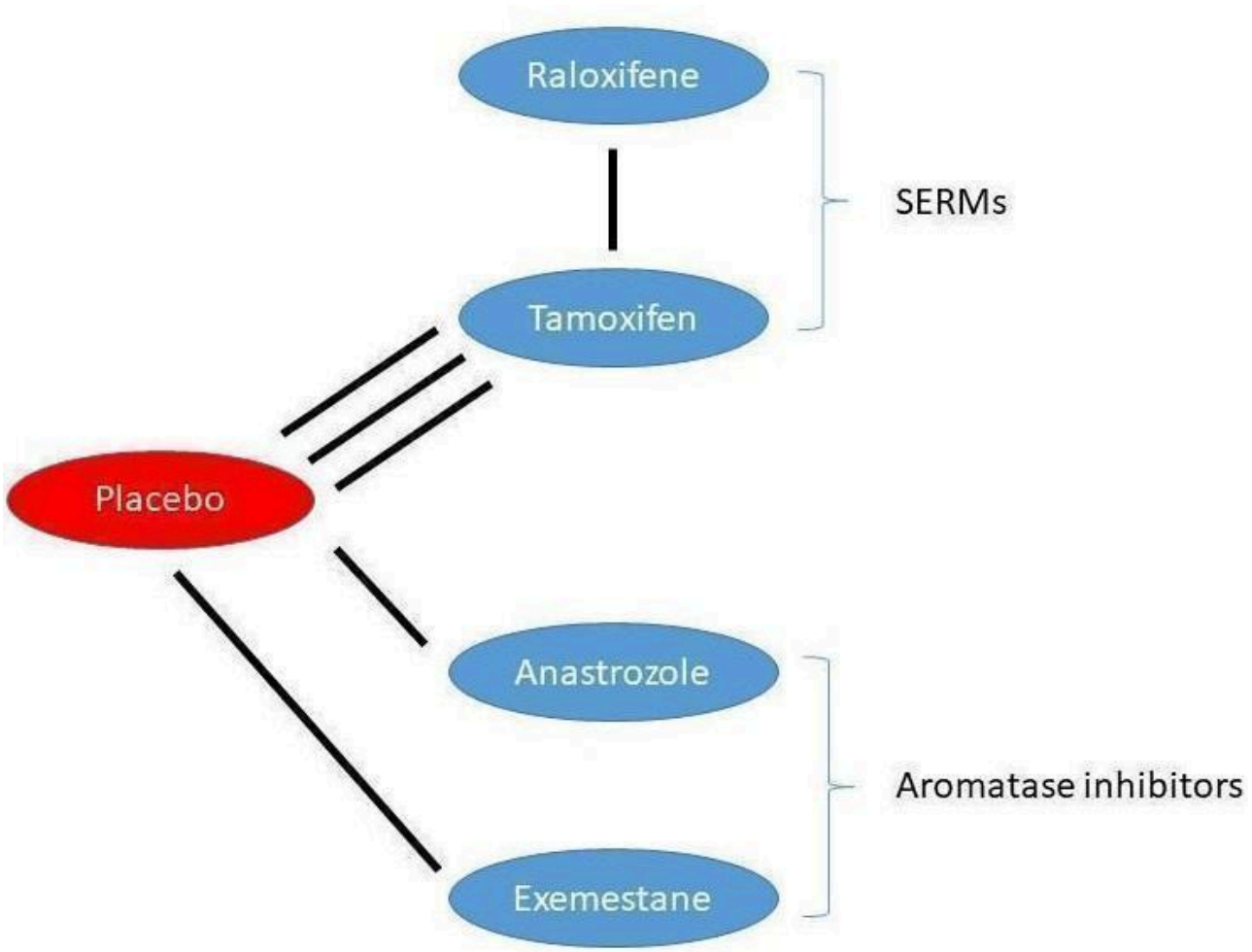
There were no other types of bias detected.

Effects of interventions

See: **Summary of findings for the main comparison** Tamoxifen versus placebo; **Summary of findings 2** Aromatase inhibitors versus placebo; **Summary of findings 3** Aromatase inhibitors versus tamoxifen (indirect comparison)[a]

For each of the four outcomes, data were available for the following comparisons: tamoxifen versus placebo (three studies), anastrozole versus placebo (one study), exemestane versus placebo (one study), and tamoxifen versus raloxifene (one study). Besides comparisons of single risk-reducing medications (i.e. tamoxifen, raloxifene, anastrozole, and exemestane), we also assessed the efficacy and toxicity of aromatase inhibitors (anastrozole and exemestane) as a single drug class. See Figure 3.

Figure 3. Network plot: the figure represents the available direct comparisons among breast cancer risk-reducing agents. Each study is represented by a black line. SERM: selective estrogen receptor modulator.



Due to the stringent inclusion criteria (especially in terms of risk of breast cancer), the included studies were highly homogeneous in terms of the type of population. The only difference across the population was the menopausal status of enrolled women. Tamoxifen can be administered both in pre- and postmenopausal women, whereas aromatase inhibitors are given to postmenopausal women. Accordingly, studies testing tamoxifen enrolled both pre- and postmenopausal women, and studies investigating aromatase inhibitors only enrolled postmenopausal women. This difference was taken into consideration when performing meta-analyses and interpreting the findings.

Due to the low number of studies available, we used the fixed-effect model for standard pair-wise meta-analysis, due to the intrinsic

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limit in the quantification of the between-study heterogeneity measure (Tau^2). Moreover, the scarcity of studies did not allow us to investigate the presence of publication bias by formally testing funnel plot asymmetry or to use meta-regression to investigate sources of between-study heterogeneity.

Since the two aromatase inhibitors (anastrozole and exemestane) share the same mechanism of action and were associated with very similar efficacy findings, we decided to pool their results. This choice should also favor more robust results of the network meta-analysis, where the evidence on tamoxifen was supported by three studies, while the evidence regarding the two aromatase inhibitors was supported by one study for each aromatase inhibitor.

See Summary of findings for the main comparison and Summary of findings 2.

Primary outcomes

Overall breast cancer incidence

Tamoxifen versus placebo

Based on data from three studies involving 22,832 women, we found that the use of tamoxifen probably reduced the risk of breast cancer (invasive and in situ carcinoma) by 32% compared to placebo (RR 0.68, 95% CI 0.62 to 0.76; Analysis 1.1; Cuzick 2015; Fisher 2005; Powles 2007). The certainty of evidence was moderate due to remarkable inconsistency (I^2 = 62%). We could not identify the source of such between-study heterogeneity. In particular, meta-regression suggested that neither a woman's age nor duration of follow-up had an impact on the outcome, although the limited number of available studies warranted caution when interpreting these findings.

Aromatase inhibitors versus placebo

In two studies, anastrozole and exemestane reduced the risk of breast cancer when compared to placebo (anastrozole: RR 0.48, 95% CI 0.33 to 0.69; Cuzick 2014; exemestane: RR 0.45, 95% CI 0.27 to 0.77; Goss 2011). Pooling the data from the two studies involving 8424 women, we found that the use of aromatase inhibitors reduced the risk of breast cancer by 53% compared to placebo (RR 0.47, 95% CI 0.35 to 0.63; Analysis 2.1). The certainty of the evidence was high.

Tamoxifen versus raloxifene

In the one study, involving 19,490 women, that compared two SERMs, raloxifene performed worse than tamoxifen in terms of breast cancer incidence reduction (RR 1.25, 95% CI 1.09 to 1.43; moderate-certainty evidence; Analysis 3.1; Vogel 2010).

Severe toxicity

Tamoxifen versus placebo

Two out of three studies comparing tamoxifen to placebo provided data on grade 3 to 4 adverse events (Cuzick 2015; Fisher 2005). Based on data from two studies involving 20,361 women, tamoxifen probably increased the risk of severe toxicity compared to placebo (RR 1.28, 95% CI 1.12 to 1.47; Analysis 1.2). The certainty of the evidence was moderate due to inconsistency (I^2 = 72%). We could not identify the source of such between-study heterogeneity.

In particular, women taking tamoxifen experienced a higher incidence of both endometrial carcinoma and thromboembolism in all studies (Table 1). Pooling the data from all three studies, tamoxifen significantly increased the risk of both endometrial cancer (RR 2.26, 95% CI 1.52 to 3.38; I^2 = 44%; high-certainty evidence) and thromboembolism (RR 2.10, 95% CI 1.14 to 3.89; no heterogeneity; high-certainty evidence). In contrast, in one of the two studies reporting bone fracture (Fisher 2005; Powles 2007), women in the tamoxifen arm showed a lower rate of bone fractures compared to women in the placebo arm (0.2% with tamoxifen versus 0.3% with placebo; RR 0.67, 95% CI 0.51 to 0.92; Fisher 2005).

Aromatase inhibitors versus placebo

In single studies, both anastrozole and exemestane increased the rate of severe toxicity when compared to placebo (anastrozole: RR 1.14, 95% CI 1.02 to 1.28; Cuzick 2014; exemestane: RR 1.22, 95% CI 1.10 to 1.36; Goss 2011). Pooling the data from the two studies involving 8352 women, aromatase inhibitors increased the risk of severe toxicity by 18% compared to placebo (RR 1.18, 95% CI 1.09 to 1.28; Analysis 2.2; high-certainty evidence).

These differences in adverse events were sustained particularly for endocrine (e.g. hot flashes), gastrointestinal (e.g. diarrhea), and musculoskeletal (e.g. arthralgia) adverse events. No significant difference in bone fracture incidence was observed between women in the treatment arms (ranging from 9% to 6.7% in the two studies) compared to those in the placebo arms (ranging from 8% to 6.4% in the two studies). Moreover, single studies suggested that this class of CPAs do not increase the risk of either endometrial cancer or thromboembolism (Table 2).

Tamoxifen versus raloxifene

In the one study comparing two SERMs involving 19,490 women, raloxifene performed better than tamoxifen in terms of grade 3 to 4 adverse events (RR 0.87, 95% CI 0.80 to 0.95; Analysis 3.2; Vogel 2010). Of note, this difference was mainly due to a higher incidence of both endometrial cancer (RR 1.76, 95% CI 1.15 to 2.71) and thromboembolism (RR 1.31, 95% CI 1.06 to 1.63) in women taking tamoxifen (Table 3).

Secondary outcomes

Invasive breast cancer incidence

Tamoxifen versus placebo

Based on data from three studies involving 22,832 women, tamoxifen probably reduced the risk of invasive breast carcinoma by 31% compared to placebo (RR 0.69, 95% CI 0.61 to 0.77; Analysis 1.3; Cuzick 2015; Fisher 2005; Powles 2007). The certainty of evidence was moderate due to remarkable inconsistency (I^2 = 53%). We could not identify the source of such between-study heterogeneity. In particular, meta-regression suggested that neither a woman's age nor duration of follow-up had an impact on the outcome, although the limited number of available studies warrants caution when interpreting these findings.

Aromatase inhibitors versus placebo

Based on single studies, both anastrozole and exemestane reduced the risk of breast cancer when compared to placebo (anastrozole: RR 0.51, 95% CI 0.33 to 0.77; Cuzick 2014; exemestane: RR 0.34, 95% CI 0.17 to 0.68; Goss 2011). Pooling the data from the two studies involving 8424 women, aromatase inhibitors reduced the risk of breast cancer by 55% compared to placebo (RR 0.45, 95% CI 0.32 to 0.64; Analysis 2.3; high-certainty evidence).

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Tamoxifen versus raloxifene

In the one study comparing two SERMs involving 19,490 women, raloxifene performed worse than tamoxifen in terms of breast cancer incidence reduction (RR 1.25, 95% CI 1.06 to 1.48; moderate-certainty evidence; Analysis 3.3; Vogel 2010).

Overall toxicity

Tamoxifen versus placebo

Only one out of three studies comparing tamoxifen to placebo reported data on adverse events of any grade (Powles 2007). In this study, where the authors reported the total number of events (including multiple events for the same participant) and not the number of participants experiencing at least one adverse event, tamoxifen was associated with an 18% increase of overall toxicity compared to placebo (3675 events with tamoxifen versus 3120 events with placebo). In particular, women taking tamoxifen experienced a higher incidence of endometrial carcinoma, thromboembolism, vasomotor symptoms (e.g. hot flashes), and cataract occurrence (Table 1). Of note, there was a higher risk of cataract with tamoxifen compared to both placebo (Powles 2007) and raloxifene (Vogel 2010).

Aromatase inhibitors versus placebo

In the one study comparing anastrozole to placebo, the overall toxicity rate was equal in the anastrozole (89%) and placebo groups (89%) (RR 1.00, 95% CI 0.98 to 1.03; Cuzick 2014). There was a slight increase in overall toxicity in the one study comparing exemestane (88%) to placebo (85%) (RR 1.04, 95% CI 1.01 to 1.06; Goss 2011), a difference mainly due to endocrine (e.g. hot flashes), gastrointestinal (e.g. diarrhea), and musculoskeletal (e.g. arthralgia) adverse events (Table 2).

When combining the data from the two aromatase inhibitors studies involving 8352 women, aromatase inhibitors increased the risk of overall toxicity by 2% compared to placebo with high between-study heterogeneity (RR 1.02, 95% CI 1.00 to 1.04; $I^2 = 72\%$; Analysis 2.4; very low-certainty evidence).

Tamoxifen versus raloxifene

The one study comparing two SERMs reported no data on overall toxicity (Vogel 2010).

Network meta-analysis (indirect comparisons)

An indirect comparison of treatment effects allowed us to compare two drug classes (i.e. SERMs and aromatase inhibitors), although no study ever directly compared these two types of agents. Of note, statistical inconsistency of the network could not be assessed due to the shape of the network itself (star-shaped network, which made it technically impossible to assess either loop or design inconsistency). The transitivity assumption was met in terms of trial design (placebo as the common control arm; study populations were similar in terms of breast cancer risk). However, the evidence generated by this type of meta-analysis was downgraded as participants could not have been randomized to any of the two drug classes due to the restriction of aromatase inhibitors to postmenopausal women (as opposed to SERMs, which can be administered also to premenopausal women).

In terms of efficacy, network meta-analysis showed that aromatase inhibitors may have reduced the risk of overall breast cancer (invasive and in situ) incidence compared to tamoxifen (RR 0.67, 95% CI 0.46 to 0.98). However, due to the above-mentioned partial lack of transitivity and considering the non-negligible between-study heterogeneity (95% prediction interval 0.27 to 1.68), the certainty of evidence was downgraded to low. See Summary of findings 3.

The lack of model convergence (likely due to the low event incidence combined with the availability of only two studies per drug class) did not allow us to analyze toxicity data.

DISCUSSION

Summary of main results

Our analysis supported the view that CPAs (tamoxifen, anastrozole, and exemestane, three drugs currently approved for the treatment of women with early or metastatic breast cancer) significantly reduced the incidence of breast cancer in unaffected women at above average to high risk of developing breast cancer, as summarized in Summary of findings for the main comparison (tamoxifen versus placebo) and Summary of findings 2 (aromatase inhibitors versus placebo). Interestingly, this reduction in incidence was found for both invasive breast carcinoma and for a combined endpoint assessing in situ disease (ductal carcinoma in situ) and invasive breast carcinoma.

Our findings confirm the results of individual studies, strengthening the evidence that CPAs reduce the risk of developing both invasive and in situ breast cancer. Moreover, using the network meta-analysis methodology (which allows indirect comparisons even in the absence of studies directly comparing two treatments), we found evidence suggesting that aromatase inhibitors are more effective than tamoxifen as CPAs (Summary of findings 3). Aromatase inhibitors further reduced the risk of disease by one third compared to tamoxifen, although the certainty of evidence was low due to indirectness of the assessment and inconsistency.

When compared to placebo, CPAs were associated with an increased risk of some adverse events. In particular, tamoxifen was associated with a significant increase of endometrial cancer and thromboembolism when compared to placebo. For the comparison between aromatase inhibitors and placebo, the data did not allow us to draw definitive conclusions because the two available RCTs used different drugs and reported toxicity in a different manner; however, the findings of single trials suggested that this class of CPAs was not associated with increased risk of either endometrial cancer or thromboembolism.

Finally, the new-generation SERM agent (raloxifene) showed a better toxicity profile compared to first-in-class tamoxifen because of the reduced incidence of endometrial cancer and thromboembolism; however, this advantage was counterbalanced by an inferior therapeutic effect (although this evidence was based on a single trial involving postmenopausal women only). Unfortunately, available data did not enable us to investigate the difference in toxicity between SERMs and aromatase inhibitors by means of indirect comparison (network meta-analysis). Of note, data on SERMs were on average more mature (with one study reaching a median follow-up of 16 years; Cuzick 2015) than those available for aromatase inhibitors (median follow-up approximately between three and five years). Therefore, any long-term adverse effects of aromatase inhibitors in the primary

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prevention setting (e.g. on bone health) may require much longer follow-up in order to be identified (and their extent quantified) and thus, to be comparable with findings with SERMs.

Overall completeness and applicability of evidence

The available evidence only partially addresses the objectives of this review. In fact, although we can state that investigated CPAs reduced the risk of breast cancer in the target population (women without a personal history of breast cancer but with an above-average risk of breast cancer), there is partial lack of toxicity data for a complete comparison between different drugs. In fact, not all studies reported separately the information on severe toxicity (grading of toxicity), which allowed us to perform direct comparisons including only some of the available studies and did not enable us to perform indirect comparisons using a network meta-analysis. Moreover, the drug comparison in terms of efficacy was limited to one RCT directly comparing two SERMs (tamoxifen versus raloxifene) and an indirect comparative analysis between SERMs and aromatase inhibitors (through network meta-analysis).

Therefore, present data support the efficacy of CPAs to reduce the risk of developing breast cancer. Guidelines such as NICE 2017 (UK) and eviQ (Australia) do recommend discussing the option of CPAs with women at both high risk and above-average risk of developing breast cancer. However, research has shown uptake is low with concerns regarding toxicity of therapy. Data are needed to fully address the issues in this field of preventive medicine, with special regard to the balance between benefit and adverse events.

Quality of the evidence

Current evidence hinges upon six studies enrolling overall 50,950 women. All studies were well conducted, with the risk of bias being low. For the tamoxifen versus placebo comparison, the certainty of evidence for both efficacy and toxicity was moderate with the reason for downgrading being between-study inconsistency.

For the aromatase inhibitors versus placebo comparison, the certainty of evidence was high for both efficacy and toxicity.

Finally, the certainty of the evidence supporting the superiority of aromatase inhibitors over SERMs was low due to limitations in the network meta-analysis, as there was inconsistency and partial lack of transitivity assumption (which is intrinsic for any indirect comparison such as that carried out in this case by means of network meta-analysis).

Potential biases in the review process

The authors believe there were no potential biases in the review process.

Agreements and disagreements with other studies or reviews

In one individual participant-data meta-analysis of RCTs testing SERMs as breast cancer risk-reducing medications, the investigators reported findings that are largely in agreement with ours in terms of both efficacy and toxicity (Cuzick 2013).

In another systematic review and meta-analysis dedicated to the role of CPAs against breast cancer (Mocellin 2015), the authors considered a different population, that is, any woman independent of the baseline risk of breast cancer: this led to the inclusion of more studies and more types of CPAs as compared to the present work. However, there were similar findings in terms of efficacy of CPAs included in the present review (tamoxifen, exemestane, and anastrozole).

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence supports the use of cancer prevention agents (CPAs) such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors in terms of efficacy. There is less serious toxicity with raloxifene compared to tamoxifen for postmenopausal women. Aromatase inhibitors do not have the serious potential toxicity of endometrial cancer or deep-vein thrombosis. Long-term data on toxicities from unaffected women taking tamoxifen are available while the follow-up data for unaffected women taking aromatase inhibitors are short. Aromatase inhibitors appear to be more effective at reducing the incidence of breast cancer for above-average and high-risk women. More data about the severity of less-serious adverse effects such as hot flashes, arthralgias, and bone fractures would assist in determining the balance of benefit and harm. This supports recommendations in existing guidelines (NICE 2017).

Implications for research

CPAs reduce the risk of breast cancer in this patient population (compared to placebo). They may cause toxicity which is mostly reversible on cessation of therapy, but uptake of CPAs is low. Therefore, we believe that three main lines of research are needed in this field of medicine.

- The direct comparison of different CPAs to identify the CPA with the best efficacy and lowest toxicity; in fact, although network meta-analysis suggested that aromatase inhibitors perform better than tamoxifen in terms of efficacy, no such (indirect) comparison was feasible for toxicity, which requires direct comparison in randomized and blinded clinical trials.
- Research into drug acceptability and toxicity (i.e. the toxicity issue in the field of cancer prevention), which appears to be the main barrier to the routine implementation of this class of compounds (Crew 2015).
- Investigation regarding the reasons (so called 'barriers') why women often refuse to take drugs aimed at reducing disease occurrence and the ways these obstacles can be overcome.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cuzick 2014

Methods	Multicenter, international, 2-arm double-blind RCT Role of anastrozole in preventing primary breast cancer Accrual time: February 2003 to January 2012 Mean follow-up: 5 years
Participants	3864 women in total 1920 women in anastrozole group 1944 women in placebo group Mean age (years): 59.5 Eligibility criteria: postmenopausal women at higher risk of breast cancer. In particular, women were deemed to be postmenopausal when they were ages ≥ 60 years; had had a bilateral oophorectomy; were ages < 60 years, but had a uterus and had had amenorrhea for ≥ 12 months; or were ages < 60 years, had no uterus, and had a concentration of follicle stimulating hormone > 30 IU/L. Entry criteria were designed to include women ages 45–60 years who had a relative risk of breast cancer that was at least 2 times higher than in the general population, those ages 60–70 years who had a risk that was ≥ 1.5 times higher, and those ages 40–44 years who had a risk that was 4 times higher. To be eligible, women had to meet ≥ 1 of the criteria.

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Cuzick 2014 *(Continued)*

	Exclusion criteria: premenopausal status; any previous diagnosis of breast cancer (except for estrogen receptor-positive ductal carcinoma in situ diagnosed < 6 months previously and treated by mastectomy); any invasive cancer in the previous 5 years (except for non-melanoma skin cancer or cervical cancer); present or previous use of SERMs for > 6 months (unless as part of IBIS-I and treatment was completed ≥ 5 years before study entry); intention to continue hormone replacement therapy; prophylactic mastectomy; evidence of severe osteoporosis (T score < –4 or > 2 vertebral fractures); life expectancy < 10 years; psychologically unfit women or women with history of gluten or lactose intolerance.
Interventions	Group 1: anastrozole 1 mg/day for 5 years Group 2: placebo for 5 years
Outcomes	Primary outcome: breast cancer (invasive and in situ) incidence Secondary outcomes: estrogen receptor-positive breast cancer, breast cancer mortality, other cancers, cardiovascular disease, fractures, adverse events, and deaths not due to breast cancer
Notes	Trial acronym: IBIS-II

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible women were randomly assigned (1:1) by central computer allocation to either anastrozole or matching placebo. Randomisation was stratified by country and was done with randomly chosen randomisation blocks (size six, eight, or ten) to maintain balance."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible women were randomly assigned (1:1) by central computer allocation to either anastrozole or matching placebo. Randomisation was stratified by country and was done with randomly chosen randomisation blocks (size six, eight, or ten) to maintain balance."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All IBIS-II personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician had access to unblinded data."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All IBIS-II personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician had access to unblinded data."
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 non-eligible participants out of 3864 participants (0.33%), which should not have led to any attrition bias.
Selective reporting (reporting bias)	Low risk	No deviations from protocol (ISRCTN31488319).

Cuzick 2015

Methods	Multicenter, international, 2-arm double-blind RCT Role of tamoxifen in preventing primary breast cancer Recruitment: April 1992 to March 2001

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Cuzick 2015 *(Continued)*

	Median follow-up: 16 years
Participants	7154 women in total 3579 women in tamoxifen group 3575 women in placebo group Mean age (years): 49.9 Multicenter international trial (UK leading) Eligibility criteria: deemed at an increased risk of developing breast cancer based on a family history of breast cancer or abnormal benign breast disease; risk factors for breast cancer indicating at least a 2-fold increased risk for the disease in women ages 45–70 years, whereas this risk needed to be higher than 2-fold for women < 45 years of age. Women were defined as postmenopausal if they had 12 consecutive months of amenorrhea or had an oophorectomy. Menopausal hormone therapy use was allowed during the trial. Exclusion criteria: history of any invasive cancer (excluding skin cancer), DVT, pulmonary embolism, or who wanted to become pregnant
Interventions	Group 1: tamoxifen 20 mg/day for 5 years Group 2: placebo for 5 years
Outcomes	Primary endpoint: occurrence of any type of breast cancer (including ductal carcinoma in situ) Secondary endpoints: occurrence of invasive estrogen receptor-positive breast cancer, all-cause mortality, and adverse events
Notes	Trial acronym: IBIS-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced block randomization done centrally by the IBIS study group (with no external input) by telephone or fax.
Allocation concealment (selection bias)	Low risk	Balanced block randomization done centrally by the IBIS study group (with no external input) by telephone or fax.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All IBIS-I personnel, participants, and clinicians were masked to treatment allocation and only the IBIS-I trial statistician had access to unmasked data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7169 women were initially enrolled into the trial and randomly assigned to the 2 treatment groups. 15 (0.21%) women were subsequently found to be ineligible because of previous breast cancer diagnosis (9 of those assigned to placebo and 6 assigned to tamoxifen), leaving 7154 women in the trial. Therefore, attrition bias appeared unlikely.
Selective reporting (reporting bias)	Low risk	No deviations from protocol (ISRCTN91879928).

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Fisher 2005

Methods	2-arm RCT (designed as double blind and then was unblinded in 1998 when first results were reported and participants subsequently chose whether to remain on their allocated treatment or cross-over) Role of tamoxifen in preventing primary breast cancer Recruitment: 1992–1997 Mean follow-up: 74 months (6.16 years)
Participants	13,388 women in total 6681 women in tamoxifen group 6707 women in placebo group Multicenter, USA Eligibility criteria: either ages ≥ 60 years or ages 35–59 years with a 5-year predicted risk for breast cancer of ≥ 1.66%; or history of LCIS or atypical hyperplasia. Within 180 days before randomization, women had to have undergone a mammogram that was determined to be negative for breast cancer. Exclusion criteria: received estrogen or progesterone replacement therapy, oral contraceptives, or androgens within 3 months of randomization; history of DVT or pulmonary embolism. Mean age (years): 90% between 40 and 60: • 35–39 years: placebo: 186 (2.8%), tamoxifen: 160 (2.4%) • 40–49 years: placebo: 2414 (36.5%), tamoxifen: 2429 (36.8%) • 50–59 years: placebo: 2022 (30.6%). tamoxifen: 2037 (30.9%) • 60–69 years: placebo: 1592 (24.1%), tamoxifen: 1577 (23.9%) • > 70 years: placebo: 396 (6.0%), tamoxifen: 394 (6.0%)
Interventions	Group 1: tamoxifen 20 mg/day for 5 years Group 2: placebo for 5 years
Outcomes	Primary outcome: breast cancer (invasive and in situ) incidence Secondary outcomes: adverse effects
Notes	Trial acronym: NSABP-P1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization of participants was performed centrally in a double-blind fashion by the NSABP Biostatistical Center.
Allocation concealment (selection bias)	Low risk	Details unreported, but this bias was unlikely to have occurred.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was unblinded in 1998 when first results were reported and participants subsequently chose whether to remain on their allocated treatment or cross-over. It was unclear whether or not this unblinding could have had any impact on final results. Quote: "Despite the potential bias caused by the unblinding of the P-1 trial, the magnitudes of all beneficial and undesirable treatment effects of tamoxifen

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Fisher 2005 *(Continued)*

		were similar to those initially reported, with notable reductions in breast cancer and increased risks of thromboembolic events and endometrial cancer."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details unreported, but this bias was unlikely to have occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13,388 randomized, 180 without follow-up (1.34%), which made attrition bias unlikely.
Selective reporting (reporting bias)	Low risk	No deviations from protocol (protocol available in previous publication PMID 9747868; Fisher 1998).

Goss 2011

Methods	Multicenter, international, 2-arm, double-blind RCT Role of exemestane in preventing primary breast cancer Recruitment: September 2004 to March 2010 Median follow-up: 35 months (3.12 years)
Participants	4560 women in total 2285 women in exemestane group 2275 women in placebo group Eligibility criteria: women ages ≥ 35 years; postmenopausal (ages > 50 years with no spontaneous menses for ≥ 12 months; or ≤ 50 years either with no spontaneous menses (amenorrheic) within 12 months of randomization (e.g. spontaneous or secondary to hysterectomy) and a follicle-stimulating hormone level within the postmenopausal range or with prior bilateral oophorectomy)). In addition, women had ≥ 1 of the following risk factors: ages ≥ 60 years; Gail risk score > 1.66%; prior atypical ductal or lobular hyperplasia or LCIS on breast biopsy or prior ductal carcinoma in situ treated with mastectomy. Exclusion criteria: premenopausal, had prior invasive breast cancer or prior ductal carcinoma in situ treated with lumpectomy; known carriers of the BRCA1 or BRCA2 gene; or history of other malignancies. Median age (years): 62.5
Interventions	Group 1: exemestane 25 mg/day (event-driven duration: treatment was continued until event or maximum 5 years) Group 2: placebo
Outcomes	Primary outcome: incidence of invasive breast cancer Secondary endpoints: combined incidence of invasive and non-invasive (ductal carcinoma in situ) breast cancer; incidence of receptor-negative invasive breast cancer; incidence of combined atypical ductal hyperplasia, atypical lobular hyperplasia, and LCIS; number of clinical breast biopsies; clinical fractures; adverse cardiovascular events, including myocardial infarction or coronary heart disease that resulted in death; overall incidence of other cancers; adverse-effect profile and safety; and health-related and menopause-specific quality of life
Notes	Trial acronym: NCIC CTG MAP.3

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Goss 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dynamic minimization algorithm-based randomization.
Allocation concealment (selection bias)	Low risk	Details unreported, but this bias was unlikely to have occurred.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details unreported, but this bias was unlikely to have occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomization, 15 women (6 taking exemestane and 9 taking placebo) were considered to be ineligible to continue with the study (0.33%), but are included in the primary intention-to-treat analysis as randomly assigned. It is unlikely this led to any bias.
Selective reporting (reporting bias)	Low risk	No deviations from protocol (NCT00083174).

Powles 2007

Methods	Single-center, 2-arm, double-blind RCT Role of tamoxifen in preventing primary breast cancer Recruitment: October 1986 to April 1996 Median follow-up: 13 years and 2 months
Participants	2494 women in total 1238 women in tamoxifen group 1233 women in placebo group Eligibility criteria: ≥ 1 first-degree relative who was < 50 years when diagnosed with breast cancer, 1 first-degree relative with bilateral breast cancer, or 1 first-degree relative with breast cancer who was diagnosed at any age plus at least 1 other affected first- or second-degree relative with breast cancer. Women with a history of a benign breast biopsy who had a first-degree relative with breast cancer were also eligible. Exclusion criteria: history of any cancer, DVT, or pulmonary embolism; risk of pregnancy; or who using oral contraceptives. Median age (years): 47
Interventions	Group 1: tamoxifen 20 mg/day for 8 years Group 2: placebo for 8 years

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Powles 2007 *(Continued)*

Outcomes	Primary outcome: breast cancer (invasive and in situ) incidence Secondary outcome: estrogen receptor-positive breast cancer
Notes	11 women in this study were reassigned to a treatment group in error.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As per protocol (ISRCTN07027313).
Allocation concealment (selection bias)	Low risk	Details unreported, but this bias was unlikely to have occurred.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, clinicians, and data-processing staff have remained blinded to the treatment options throughout follow-up."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2494 women enrolled, 23 women resulting non-eligible (0.92%), which made attrition bias unlikely.
Selective reporting (reporting bias)	Low risk	No deviations from protocol (ISRCTN07027313).

Vogel 2010

Methods	Multicenter, 2-arm RCT in USA (mainly) and Canada (this trial was designed as double-blind, but in April 2006 it was unblinded). Role of tamoxifen vs raloxifene in preventing primary breast cancer Recruitment: July 1999 to November 2004 Median follow-up: 81 months (6.75 years)
Participants	19,490 women in total 9736 women in tamoxifen group 9754 women in raloxifene group Eligibility criteria: postmenopausal women, ages ≥ 35 years, with 5-year predicted breast cancer risk ≥ 1.66% were eligible for STAR. Risk determination based on Gail model, as modified and applied in the Breast Cancer Prevention Trial (BCPT P-1). Participants also met the following criteria: not taking either tamoxifen or raloxifene, hormone therapy, oral contraceptives, or androgens for ≥ 3 months before randomization; not currently taking warfarin or cholestyramine; no history of stroke, transient ischemic attack, pulmonary embolism, or DVT; no atrial fibrillation, uncontrolled diabetes, or uncontrolled hypertension; no psychiatric condition that would interfere with adherence; performance status that would not restrict normal activity; and no history of previous malignancy except basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or LCIS of the breast.

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Vogel 2010 *(Continued)*

	Age (years): • ≤ 49: tamoxifen: 884 (9.1%); raloxifene: 878 (9.0%) • 50–59: tamoxifen: 4856 (49.9%); raloxifene: 4855 (49.8%) • 60–69: tamoxifen: 3137 (32.2%); raloxifene: 3174 (32.5%) • ≥ 70: tamoxifen: 859 (8.8%); raloxifene: 847 (8.7%)
Interventions	Group 1: tamoxifen 20 mg/day Group 2: raloxifene 60 mg/day
Outcomes	Primary endpoint: invasive breast cancer Secondary endpoints: endometrial cancer, in situ breast cancer, cardiovascular disease, stroke, pulmonary embolism, DVT, transient ischemic attack, osteoporotic fracture, cataracts, death, and quality of life; data on all other invasive cancers were collected prospectively.
Notes	Data were from the update of the original trial (Vogel 2006), which was initially scheduled to last until December 2005; the trial was unblinded in April 2006. Trial acronym: STAR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was accomplished using a biased-coin minimization algorithm."
Allocation concealment (selection bias)	Low risk	The reported biased-coin minimization algorithm should have guaranteed correct allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This trial (which started enrolling in 1999 and finished the enrolment in 2004) was designed and conducted as a double-blind study. However, in April 2006, the trial was unblinded: it was unclear whether this unblinding affected the results, which were based on a cutoff date of 31 March 2009.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Details unreported, but this bias was unlikely to have occurred.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the originally randomized 19,747 women, 19,490 participated in the STAR follow-up described here." Comment: due to loss to follow-up (i.e. data were available for 98.7% of initially randomized participants: it was unclear if this loss may have caused any bias, also considering that these lost participants were evenly distributed between the 2 study arms).
Selective reporting (reporting bias)	Low risk	All outcomes planned to be investigated were reported.

DVT: deep-vein thrombosis; IBIS: International Breast Cancer Intervention Study; LCIS: lobular carcinoma in situ; NSABP-P: National Surgical Adjuvant Breast and Bowel Project, Prevention; RCT: randomized controlled trial; SERM: selective estrogen receptor modulator; STAR: Study of Tamoxifen And Raloxifene.

Characteristics of excluded studies *[ordered by study ID]*

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Study	Reason for exclusion
ALLHAT 2002	Investigated the protective effect of pravastatin. Breast cancer risk of men and women with risk factors for coronary heart disease was undefined. Main outcome: coronary heart disease (trial acronym: ALLHAT).
Archer 2009	RCT investigating protective effect of bazedoxifene. Breast cancer risk of osteoporotic post-menopausal women was undefined. Main outcome: osteoporosis.
Avenell 2012	RCT investigating protective effect of raloxifene. Breast cancer risk of postmenopausal women was undefined (trial acronym: RECORD).
Barrett-Connor 2006	RCT investigating protective effect of raloxifene. Breast cancer risk of postmenopausal women was undefined (trial acronym: RUTH).
Bolland 2011	RCT investigating protective effect of calcium and vitamin D. Breast cancer risk of postmenopausal women was undefined (trial acronym: WHI)
Chlebowski 2008	Duplicate of Prentice 2013.
Cook 2013	RCT investigating the protective effect of aspirin. Breast cancer risk of healthy women ages ≥ 45 years was undefined. Main outcome: cardiovascular diseases (trial acronym: WHS).
Cummings 2008	RCT investigating the protective effect of tibolone. Postmenopausal women were selected based on bone mineral density and not on breast cancer risk. Main outcome: bone fracture.
Cuzick 2002	First report of Cuzick 2002, which was used in this review as the source of data from that trial.
DeCensi 2009	RCT investigating the protective effect of tamoxifen and fenretinide. Most of the population of pre-menopausal women had breast cancer (77%).
DeCensi 2013	RCT investigating the protective effect of tamoxifen. Postmenopausal women were taking hormone replacement therapy by design (trial acronym: HOT).
Downs 1998	RCT investigating the protective effect of lovastatin. Breast cancer risk of men and women without cardiovascular disease was undefined. Main outcome: cardiovascular diseases (trial acronym: AFCAPS/TexCAPS).
Erdmann 2014	RCT investigating the protective effect of pioglitazone. Breast cancer risk of men and women with diabetes was undefined. Main outcome: diabetes and cardiovascular diseases (trial acronym: PROactive).
Fisher 1998	First report of Fisher 2005, which was used in this review as the source of data from that trial.
Grady 2008	Duplicate of Barrett-Connor 2006.
Hercberg 2004	RCT investigating the protective effect of vitamin C, vitamin A, and vitamin E. Breast cancer risk of men and women was undefined. Main outcome: cardiovascular diseases and cancer (trials acronym: SUVIMAX).
Home 2009	Duplicate of Home 2010.
Home 2010	RCT investigating the protective effect of rosiglitazone, glibenclamide, and metformin. Breast cancer risk of men and women with diabetes was undefined. Main outcome: diabetes and cardiovascular diseases (trials acronym: ADOPT and RECORD).
HPSCG 2002	RCT investigating the protective effect of simvastatin. Breast cancer risk of men and women at high risk of cardiovascular diseases was undefined. Main outcome: cardiovascular diseases.

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Study	Reason for exclusion
Hue 2014	RCTs investigating the protective effect of alendronate and zoledronate. Breast cancer risk of postmenopausal women was undefined. Main outcome: bone fracture (trials acronym: FIT and HORIZON-PTF).
LaCroix 2010	RCT investigating the protective effect of lasofoxifene. Breast cancer risk of postmenopausal women with osteoporosis was undefined. Main outcomes: bone fracture and cancer incidence (trial acronym: PEARL).
Lappe 2007	RCT investigating the protective effect of calcium and vitamin D. Breast cancer risk of healthy postmenopausal women was undefined. Main outcome: bone fracture.
Lee 1999	RCT investigating the protective effect of vitamin A. Breast cancer risk of healthy women ages ≥ 45 years was undefined. Main outcomes: cardiovascular diseases and cancer (trial acronym: WHS).
Lee 2005	RCT investigating the protective effect of vitamin E. Breast cancer risk of healthy women ages ≥ 45 years was undefined. Main outcomes: cardiovascular diseases and cancer (trial acronym: WHS).
LIPID 1998	RCT investigating the protective effect of pravastatin. Breast cancer risk of men and women with cardiovascular disease was undefined. Main outcome: cardiovascular diseases (trial acronym: LIPID)
López 2016	RCT investigating the protective effect of 2 regimens of letrozole. Primary endpoint was suppression in serum estradiol levels at the end of letrozole intervention. Secondary endpoints included changes in serum estrone, testosterone, C-telopeptide (marker of bone resorption), lipid profile, and quality of life following treatment.
Martino 2004	RCT investigating the protective effect of raloxifene. Breast cancer risk of postmenopausal women with osteoporosis was undefined. Main outcome: bone fracture (trial acronym: MORE-CORE).
Powles 2012	RCT investigating the protective effect of arzoxifene. Breast cancer risk of postmenopausal women with osteoporosis was undefined. Main outcome: bone fracture.
Prentice 2013	RCT investigating the protective effect of calcium and vitamin D. Breast cancer risk of postmenopausal women was undefined (trial acronym: WHI).
Sacks 1996	RCT investigating the protective effect of pravastatin. Breast cancer risk of men and women with myocardial infarction was undefined. Main outcome: cardiovascular disease.
Shepherd 2002	RCT investigating the protective effect of pravastatin. Breast cancer risk of men and women ages ≥ 70 years at high risk of cardiovascular disease was undefined. Main outcome: cardiovascular disease (trial acronym: PROSPER).
Strandberg 2004	RCT investigating the protective effect of simvastatin. Breast cancer risk of men and women at high risk of cardiovascular disease was undefined. Main outcome: cardiovascular disease.
Trivedi 2003	RCT investigating the protective effect of vitamin D. Breast cancer risk of healthy men and women ages ≥ 65 years was undefined. Main outcome: bone fracture.
Veronesi 2007	RCT investigating the protective effect of tamoxifen. Breast cancer risk of healthy women who underwent hysterectomy was undefined.
Vogel 2006	First report of Vogel 2010, which was used in this review as the source of data from that trial (trial acronym: STAR).

ADOPT: A Diabetes Outcome Progression Trial; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; FIT: Fracture Intervention Trial; HOT: Hypertension Optimal

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Treatment Study; HORIZON-PTF: Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; LIPID: Long-Term Intervention with Pravastatin in Ischaemic Disease; MORE-CORE: Multiple Outcomes of Raloxifene Evaluation-Continuing Outcomes Relevant to Evista; PEARL: Postmenopausal Evaluation and Risk-reduction With Lasofoxifene; PROactive: Prospective Pioglitazone Clinical Trial In Macrovascular Events; PROSPER: Prospective Study Of Pravastatin In The Elderly At Risk; RCT: randomized controlled trial; RECORD: Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes; RUTH: Raloxifene Use for The Heart; STAR: Study of Tamoxifen And Raloxifene; SUVIMAX: Supplémentation en Vitamines et Minéraux Antioxydants; WHI: Women's Health Initiative; WHS: Women's Health Study.

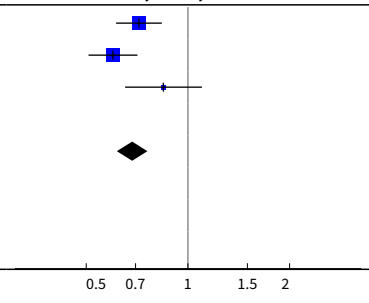
DATA AND ANALYSES

Comparison 1. Tamoxifen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall breast cancer incidence	3	22832	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.62, 0.76]
2 Severe toxicity	2	20361	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.12, 1.47]
3 Invasive breast cancer incidence	3	22832	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.61, 0.77]

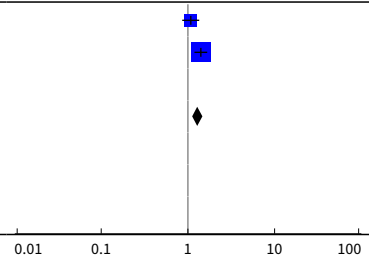
Analysis 1.1. Comparison 1 Tamoxifen versus placebo, Outcome 1 Overall breast cancer incidence.

Study or subgroup	Tamoxifen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cuzick 2015	251/3579	350/3575		42.86%	0.72[0.61,0.84]
Fisher 2005	212/6597	354/6610		43.28%	0.6[0.51,0.71]
Powles 2007	96/1238	113/1233		13.86%	0.85[0.65,1.1]
Total (95% CI)	**11414**	**11418**		**100%**	**0.68[0.62,0.76]**
Total events: 559 (Tamoxifen), 817 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.27, df=2(P=0.07); I^2=62.07%					
Test for overall effect: Z=7.16(P<0.0001)					



Analysis 1.2. Comparison 1 Tamoxifen versus placebo, Outcome 2 Severe toxicity.

Study or subgroup	Tamoxifen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cuzick 2015	151/3579	140/3575		38.6%	1.08[0.86,1.35]
Fisher 2005	314/6597	223/6610		61.4%	1.41[1.19,1.67]
Total (95% CI)	**10176**	**10185**		**100%**	**1.28[1.12,1.47]**
Total events: 465 (Tamoxifen), 363 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.54, df=1(P=0.06); I^2=71.71%					
Test for overall effect: Z=3.62(P=0)					



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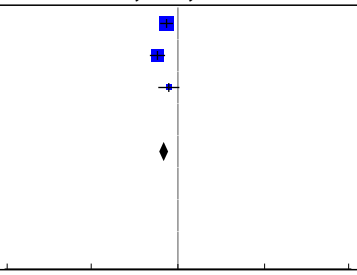
Analysis 1.3. Comparison 1 Tamoxifen versus placebo, Outcome 3 Invasive breast cancer incidence.

Study or subgroup	Tamoxifen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cuzick 2015	214/3579	289/3575		44.96%	0.74[0.62,0.88]
Fisher 2005	145/6597	250/6610		38.83%	0.58[0.47,0.71]
Powles 2007	82/1238	104/1233		16.2%	0.79[0.59,1.04]
Total (95% CI)	**11414**	**11418**		**100%**	**0.69[0.61,0.77]**
Total events: 441 (Tamoxifen), 643 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.25, df=2(P=0.12); I^2=52.97%					
Test for overall effect: Z=6.28(P<0.0001)					



Comparison 2. Aromatase inhibitors (AI) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall breast cancer incidence	2	8424	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.35, 0.63]
1.1 Anastrozole vs placebo	1	3864	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.33, 0.69]
1.2 Exemestane vs placebo	1	4560	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.27, 0.77]
2 Severe toxicity	2	8352	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.09, 1.28]
2.1 Anastrozole vs placebo	1	3864	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.02, 1.28]
2.2 Exemestane vs placebo	1	4488	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.10, 1.36]
3 Invasive breast cancer incidence	2	8424	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.32, 0.64]
3.1 Anastrozole vs placebo	1	3864	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.33, 0.77]
3.2 Exemestane vs placebo	1	4560	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.17, 0.68]
4 Overall toxicity	2	8352	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [1.00, 1.04]
4.1 Anastrozole vs placebo	1	3864	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.98, 1.03]
4.2 Exemestane vs placebo	1	4488	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [1.01, 1.06]

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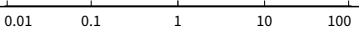
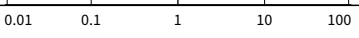
Analysis 2.1. Comparison 2 Aromatase inhibitors (AI) versus placebo, Outcome 1 Overall breast cancer incidence.

Study or subgroup	Aromatase inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Anastrozole vs placebo					
Cuzick 2014	40/1920	85/1944		65.7%	0.48[0.33,0.69]
Subtotal (95% CI)	**1920**	**1944**		**65.7%**	**0.48[0.33,0.69]**
Total events: 40 (Aromatase inhibitor), 85 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.92(P<0.0001)					
2.1.2 Exemestane vs placebo					
Goss 2011	20/2285	44/2275		34.3%	0.45[0.27,0.77]
Subtotal (95% CI)	**2285**	**2275**		**34.3%**	**0.45[0.27,0.77]**
Total events: 20 (Aromatase inhibitor), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.96(P=0)					
Total (95% CI)	**4205**	**4219**		**100%**	**0.47[0.35,0.63]**
Total events: 60 (Aromatase inhibitor), 129 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=4.91(P<0.0001)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



Analysis 2.2. Comparison 2 Aromatase inhibitors (AI) versus placebo, Outcome 2 Severe toxicity.

Study or subgroup	Aromatase inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Anastrozole vs placebo					
Cuzick 2014	485/1920	431/1944		47.88%	1.14[1.02,1.28]
Subtotal (95% CI)	**1920**	**1944**		**47.88%**	**1.14[1.02,1.28]**
Total events: 485 (Aromatase inhibitor), 431 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.26(P=0.02)					
2.2.2 Exemestane vs placebo					
Goss 2011	568/2240	467/2248		52.12%	1.22[1.1,1.36]
Subtotal (95% CI)	**2240**	**2248**		**52.12%**	**1.22[1.1,1.36]**
Total events: 568 (Aromatase inhibitor), 467 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=3.63(P=0)					
Total (95% CI)	**4160**	**4192**		**100%**	**1.18[1.09,1.28]**
Total events: 1053 (Aromatase inhibitor), 898 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=4.19(P<0.0001)					
Test for subgroup differences: Chi^2=0.75, df=1 (P=0.39), I^2=0%					



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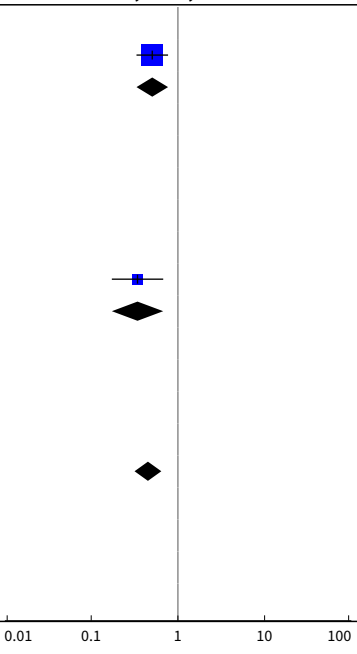
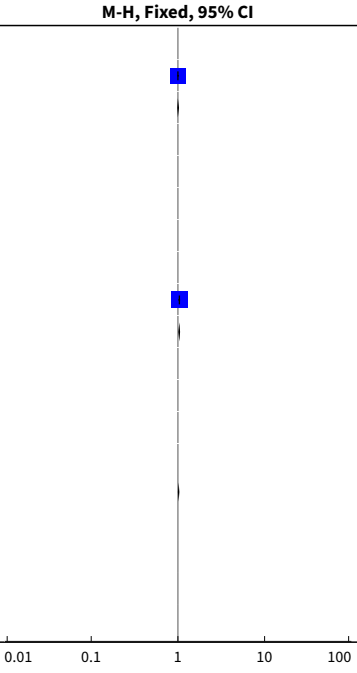
Analysis 2.3. Comparison 2 Aromatase inhibitors (AI) versus placebo, Outcome 3 Invasive breast cancer incidence.

Study or subgroup	Aromatase inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Anastrozole vs placebo					
Cuzick 2014	32/1920	64/1944		66.48%	0.51[0.33,0.77]
Subtotal (95% CI)	**1920**	**1944**		**66.48%**	**0.51[0.33,0.77]**
Total events: 32 (Aromatase inhibitor), 64 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.18(P=0)					
2.3.2 Exemestane vs placebo					
Goss 2011	11/2285	32/2275		33.52%	0.34[0.17,0.68]
Subtotal (95% CI)	**2285**	**2275**		**33.52%**	**0.34[0.17,0.68]**
Total events: 11 (Aromatase inhibitor), 32 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.08(P=0)					
Total (95% CI)	**4205**	**4219**		**100%**	**0.45[0.32,0.64]**
Total events: 43 (Aromatase inhibitor), 96 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=4.38(P<0.0001)					
Test for subgroup differences: Chi^2=0.92, df=1 (P=0.34), I^2=0%					



Analysis 2.4. Comparison 2 Aromatase inhibitors (AI) versus placebo, Outcome 4 Overall toxicity.

Study or subgroup	Aromatase inhibitor n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Anastrozole vs placebo					
Cuzick 2014	1709/1920	1723/1944		47.43%	1[0.98,1.03]
Subtotal (95% CI)	**1920**	**1944**		**47.43%**	**1[0.98,1.03]**
Total events: 1709 (Aromatase inhibitor), 1723 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
2.4.2 Exemestane vs placebo					
Goss 2011	1963/2240	1901/2248		52.57%	1.04[1.01,1.06]
Subtotal (95% CI)	**2240**	**2248**		**52.57%**	**1.04[1.01,1.06]**
Total events: 1963 (Aromatase inhibitor), 1901 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.97(P=0)					
Total (95% CI)	**4160**	**4192**		**100%**	**1.02[1,1.04]**
Total events: 3672 (Aromatase inhibitor), 3624 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.63, df=1(P=0.06); I^2=72.49%					
Test for overall effect: Z=2.51(P=0.01)					
Test for subgroup differences: Chi^2=3.59, df=1 (P=0.06), I^2=72.15%					



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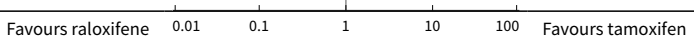
Comparison 3. Tamoxifen versus raloxifene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall breast cancer incidence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Severe toxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Invasive breast cancer incidence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

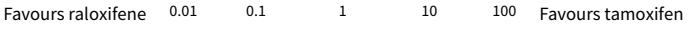
Analysis 3.1. Comparison 3 Tamoxifen versus raloxifene, Outcome 1 Overall breast cancer incidence.

Study or subgroup	Raloxifene n/N	Tamoxifen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vogel 2010	447/9754	358/9736	+	0%	1.25[1.09,1.43]



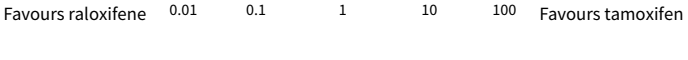
Analysis 3.2. Comparison 3 Tamoxifen versus raloxifene, Outcome 2 Severe toxicity.

Study or subgroup	Raloxifene n/N	Tamoxifen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vogel 2010	975/9754	1115/9736	+	0%	0.87[0.8,0.95]



Analysis 3.3. Comparison 3 Tamoxifen versus raloxifene, Outcome 3 Invasive breast cancer incidence.

Study or subgroup	Raloxifene n/N	Tamoxifen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vogel 2010	310/9754	247/9736	+	0%	1.25[1.06,1.48]



ADDITIONAL TABLES

Table 1. Adverse events: tamoxifen versus placebo

Fisher 2005

Adverse event	Tamoxifen[a]	Placebo[a]	RR (95% CI)
Endometrial cancer	2.24	0.68	3.28 (1.87 to 6.03)[b]

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Table 1. Adverse events: tamoxifen versus placebo *(Continued)*

Myocardial infarction	2.79	2.70	1.03 (0.79 to 1.36)
Stroke	1.75	1.23	1.42 (0.97 to 2.08)
Thromboembolism	0.69	0.32	2.15 (1.08 to 4.51)[b]
Bone fractures	1.97	2.88	0.68 (0.51 to 0.92)[b]
Total deaths	3.08	2.80	1.10 (0.85 to 1.43)
Powles 2007			
Adverse event	**Tamoxifen[a]**	**Placebo[a]**	**RR (95% CI)**
Endometrial cancer	10.50	4.05	2.59 (0.86 to 9.30)
Myocardial infarction	8.07	9.73	0.83 (0.32 to 2.10)
Stroke	5.65	7.29	0.77 (0.24 to 2.34)
Thromboembolism	6.46	2.43	2.65 (0.63 to 15.5)
Bone fracture	15.34	17.84	0.86 (0.44 to 1.67)
Cataract	7.26	0.81	8.96 (1.24 to 393)[b]
Hot flashes	483.04	319.54	1.51 (1.29 to 1.76)[b]
Arthritis	54.12	46.23	1.17 (0.80 to 1.71)
Constipation/diarrhea	33.92	36.49	0.93 (0.59 to 1.45)
Total deaths	43.62	43.79	0.99 (0.66 to 1.49)
Cuzick 2015			
Adverse event	**Tamoxifen[a]**	**Placebo[a]**	**RR (95% CI)**
Endometrial cancer	8.10	5.59	1.45 (0.79 to 2.71)
Non-breast cancer	98.07	88.11	1.12 (0.94 to 1.31)
Cardiac deaths	3.35	3.91	0.85 (0.36 to 1.99)
Cerebrovascular deaths	2.79	3.35	0.83 (0.32 to 2.10)
Thromboembolic deaths	1.12	0.84	1.33 (0.22 to 9.09)
Total deaths	50.85	46.43	1.09 (0.88 to 1.36)

[a]Rates per 1000 participants of adverse events reported in three RCTs comparing tamoxifen with placebo.
[b]Statistically significant difference.
CI: confidence interval; RR: risk ratio.

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Table 2. Adverse events: aromatase inhibitors versus placebo

Goss 2011			
Adverse event	**Exemestane[a]**	**Placebo[a]**	**RR (95% CI)**
Non-breast cancer	19.19	16.90	1.13 (0.71 to 1.81)
Cardiovascular events	47.32	49.3	0.96 (0.72 to 1.27)
Bone fracture	66.51	63.61	1.04 (0.82 to 1.33)
Hot flashes (grade 3–4)	29.91	19.12	1.56 (1.04 to 2.36)[b]
Arthritis (grade 3–4)	14.28	7.56	1.89 (1.01 to 3.63)[b]
Diarrhea (grade 3–4)	4.01	0.44	9.03 (1.24 to 395)[b]
Any (grade 3–4)	253.57	207.74	1.22 (1.06 to 1.40)[b]
Cuzick 2014			
Adverse event	**Anastrozole[a]**	**Placebo[a]**	**RR (95% CI)**
Endometrial cancer	1.56	2.57	0.61 (0.09 to 3.12)
Non-breast cancer	20.83	36.01	0.58 (0.38 to 0.87)[b]
Other cardiovascular[c]	5.73	7.71	0.74 (0.31 to 1.73)
Thromboembolism	9.89	8.74	1.13 (0.59 to 2.17)
Bone fractures	85.41	76.64	1.11 (0.90 to 1.38)
Cataract	46.87	48.86	0.96 (0.72 to 1.27)
Hot flashes	567.71	494.34	1.15 (1.08 to 1.22)[b]
Arthritis	506.25	459.87	1.10 (1.03 to 1.18)[b]
Total deaths	9.37	8.74	1.07 (0.52 to 2.22)

[a]Rates per 1000 participants of adverse events reported in two randomized controlled trials comparing two aromatase inhibitors (exemestane and anastrozole) with placebo.
[b]Statistically significant difference.
[c]Myocardial infarction, heart failure or cerebrovascular accident.
CI: confidence interval; RR: risk ratio.

Table 3. Adverse events: tamoxifen versus raloxifene

Vogel 2010			
Adverse event	**Tamoxifen[a]**	**Raloxifene[a]**	**RR (95% CI)**
Endometrial cancer	2.25	1.23	1.76 (1.15 to 2.71)[b]

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Table 3. Adverse events: tamoxifen versus raloxifene *(Continued)*

Cardiovascular deaths	4.31	4.30	1.00 (0.64 to 1.57)
Thromboembolism	3.30	2.47	1.31 (1.06 to 1.63)[b]
Cataracts	14.58	11.69	1.22 (1.10 to 1.37)[b]
Total deaths	3.81	3.22	1.17 (0.96 to 1.42)

[a]Rates per 1000 participants of adverse events reported in an RCT comparing Tamoxifen with Raloxifene.
[b]Statistically significant difference.
CI: confidence interval; RR: risk ratio.

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near cancer*
#3 breast near neoplasm*
#4 breast near carcinoma*
#5 breast near tumour*
#6 breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Anticarcinogenic Agents] explode all trees
#9 MeSH descriptor: [Chemoprevention] explode all trees
#10 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
#11 Selective Estrogen Receptor Modulator* or SERM
#12 MeSH descriptor: [Tamoxifen] explode all trees
#13 MeSH descriptor: [Raloxifene] explode all trees
#14 (tamoxifen or raloxifene or lasofoxifene)
#15 MeSH descriptor: [Aromatase Inhibitors] explode all trees
#16 aromatase inhibitor*
#17 exemestane or letrozole or anastrozole or arimidex or femara
#18 MeSH descriptor: [Vitamin D] explode all trees
#19 vitamin D
#20 MeSH descriptor: [Aspirin] explode all trees
#21 acetylsalicylic acid or aspirin
#22 MeSH descriptor: [Metformin] explode all trees
#23 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#24 MeSH descriptor: [Simvastatin] explode all trees
#25 MeSH descriptor: [Pravastatin] explode all trees
#26 MeSH descriptor: [Lovastatin] explode all trees
#27 statin or tenivastatin or simvastatin or rosuvastatin or pravastatin or pitavastatin or mevinolin or glenvastatin or fluindostatin or dalvastatin or crilvastatin or compactin or cerivastatin or bervastatin or atorvastatin
#28 MeSH descriptor: [Diphosphonates] explode all trees
#29 biphosphonate* or diphosphonate* or diphosphanate*
#30 MeSH descriptor: [Etidronic Acid] explode all trees
#31 MeSH descriptor: [Clodronic Acid] explode all trees
#32 MeSH descriptor: [Alendronate] explode all trees
#33 etidronate* or clodronate* or pamidronate* or alendronate* or risedronate* or tiludronate* or ibandronate* or zoledronate* or incadronate* or olpadronate* or neridronate*
#34 MeSH descriptor: [RANK Ligand] explode all trees
#35 RANK ligand inhibitor
#36 denosumab
#37 prolia
#38 Xgeva

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#39 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 MeSH descriptor: [Chemoprevention] explode all trees
#41 chemoprevent* or chemoprophyla*
#42 prevent* or prophyla*
#43 MeSH descriptor: [Risk Reduction Behavior] explode all trees
#44 "risk reduc*"
#45 risk near reduc*
#46 #40 or $41 or #42 or #43 or #44 or #45
#47 #7 and #39 and #46

Appendix 2. MEDLINE (via OvidSP)

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/
10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	(breast adj6 cancer$).tw.
14	(breast adj6 neoplasm$).tw.
15	(breast adj6 carcinoma$).tw.
16	(breast adj6 tumo?r$).tw.
17	or/12-16
18	exp Anticarcinogenic Agents/
19	exp Selective Estrogen Receptor Modulators/
20	selective estrogen receptor modulator.tw.
21	exp Tamoxifen/
22	exp Raloxifene/

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(Continued)

23	(Tamoxifen or Raloxifene or lasofoxifene).tw.
24	exp Aromatase Inhibitors/
25	aromatase inhibitor*.tw.
26	(exemestane or anastrozole or arimidex or femara or aromasin).tw.
27	exp Vitamin D/
28	vitamin D.tw.
29	exp Aspirin/
30	(aspirin or acetylsalicylic acid).tw.
31	exp Metformin/
32	metformin.tw.
33	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
34	((Hydroxymethylglutaryl-CoA or hydroxymethylglutaryl coenzyme a) and reductase inhibitor).tw.
35	exp Simvastatin/
36	exp Pravastatin/
37	(statin or simvastatin or tenivastatin or rosuvastatin or pravastatin or mevinolin or glenvastatin or fluindostatin or dalvastatin or crilvastatin or compactin or cerivastatin or bervastatin or atorvastatin).tw.
38	exp Diphosphonates/
39	(biphosphonate$ or bisphosphanate$ or diphosphonate$ or diphosphanate$).tw.
40	exp Etidronic Acid/
41	exp Clodronic Acid/
42	exp Alendronate/
43	(etidronate$ or clodronate$ or pamidronate$ or alendronate or risedronate$ or tiludronate$ or ibandronate$ or zoledronate$ or incadronate$ or olpadronate$ or neridronate$).tw.
44	RANK Ligand/
45	(RANK ligand or denosumab or prolia or Xgeva).tw.
46	or/18-45
47	11 and 17 and 46
48	Animals/ not Humans/
49	47 not 48

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(Continued)

50	exp chemoprevention/
51	(chemoprevent$ or chemoprophyla$).tw.
52	(prevent$ or prophyla$).tw.
53	exp Risk Reduction Behavior/
54	risk reduc$.tw.
55	(risk adj6 reduc$).tw.
56	or/51-55
57	49 and 56

Appendix 3. Embase (via OvidSP)

1	Randomized controlled trial/
2	Controlled clinical study/
3	Random$.ti,ab.
4	randomization/
5	intermethod comparison/
6	placebo.ti,ab.
7	(compare or compared or comparison).ti.
8	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9	(open adj label).ti,ab.
10	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11	double blind procedure/
12	parallel group$1.ti,ab.
13	(crossover or cross over).ti,ab.
14	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15	(assigned or allocated).ti,ab.
16	(controlled adj7 (study or design or trial)).ti,ab.

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(Continued)

17	(volunteer or volunteers).ti,ab.
18	human experiment/
19	trial.ti.
20	or/1-19
21	exp breast/
22	exp breast disease/
23	(21 or 22) and exp neoplasm/
24	exp breast tumor/
25	exp breast cancer/
26	exp breast carcinoma/
27	(breast$ adj5 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).ti,ab.
28	23 or 24 or 25 or 26 or 27
29	exp tamoxifen/
30	exp raloxifene/
31	exp lasofoxifene/
32	exp selective estrogen receptor modulator/
33	exp aromatase inhibitors/
34	exp exemestane/
35	exp letrozole/
36	exp anastrazole/
37	exp arimidex/
38	exp femara/
39	exp aromasin/
40	(Tamoxifen or Raloxifene or lasofoxifene).tw.
41	(selective estrogen receptor modulator or SERM).tw.
42	(aromatase inhibitors or exemestane or letrozole or anastrazole or arimidex or femara or aromasin).tw.
43	exp vitamin D/
44	exp acetylsalicylic acid/

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(Continued)

45	exp Metformin/
46	(vitamin d or acetylsalicylic acid or aspirin or metformin).tw.
47	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
48	exp tenivastatin/
49	exp simvastatin/
50	exp rosuvastatin/
51	exp pravastatin/
52	exp pitavastatin/
53	exp mevinolin/
54	exp glenvastatin/
55	exp fluindostatin/
56	exp dalvastatin/
57	exp crilvastatin/
58	exp compactin/
59	exp cerivastatin/
60	exp bervastatin/
61	exp atorvastatin/
62	(hydroxymethylglutaryl coenzyme a reductase inhibitor or statin or tenivastatin or simvastatin or rosuvastatin or pravastatin or pitavastatin or mevinolin or glenvastatin or fluindostatin or dalvastatin or crilvastatin or compactin or cerivastatin or bervastatin or atorvastatin).tw.
63	exp bisphosphonic acid derivative/
64	exp etidronic acid/
65	exp clodronic acid/
66	exp pamidronic acid/
67	exp alendronic acid/
68	exp risedronic acid/
69	exp tiludronic acid/
70	exp ibandronic acid/
71	exp zoledronic acid/

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(Continued)

72	exp incadronic acid/
73	exp olpadronic acid/
74	(bisphosph?nate* or biphosph?nate* or diphosph?nate* or etidron* or clodron* or pamidron* or alendron* or risedron* or tiludron* or ibandron* or zoledron* or incadron* or olpadron* or rank ligand or (rank and ligand) or denosumab or xgeva or prolia).tw.
75	or/29-74
76	exp chemoprophylaxis/
77	(chemoprevent$ or chemoprophyla$).tw.
78	exp risk reduction/
79	(prevent$ or prophyla$).tw.
80	risk reduc$.tw.
81	(risk adj6 reduc$).tw.
82	exp prevention/
83	or/76-82
84	20 and 28 and 75 and 83
85	1 or 2
86	limit 85 to yr="1902 - 2015"
87	84 not (84 and 86)

Appendix 4. WHO ICTRP

Basic searches:

1. breast cancer AND chemoprevention

2. breast cancer AND anticarcinogenic agent

3. breast cancer AND primary prevention

4. breast cancer AND cancer prevention

5. breast cancer AND carcinopreventive agent

6. breast cancer AND pharmacological prevention

7. breast cancer AND risk reducing agent

Advanced searches:

1. Title: 1. prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

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Intervention: tamoxifen OR raloxifene OR lasofoxifene OR selective estrogen receptor modulator OR SERM OR vitamin D OR aspirin OR acetylsalicylic acid OR metformin

Recruitment status: ALL

2. Title: prevention OR preventing OR preventive

Condition: breast cancer OR breast neoplasm

Intervention: aromatase inhibitors OR exemestane OR letrozole OR anastrazole OR arimidex OR femara OR aromasin

Recruitment status: ALL

3. Title: 1. prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

Intervention: CoA reductase inhibitor OR statin

Recruitment status: ALL

4. Title: 1. prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

Intervention: Denosumab OR Prolia OR Xgeva OR RANK ligand

Recruitment status: ALL

5. Title: 1. prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

Intervention: Bisphosphonates OR Diphosphonates OR Zoledronate OR clodronate OR Alendronate OR Ibandronate OR Pamidronate OR Risedronate OR Tiludronate OR Incadronate OR Olpadronate OR Neridronate

Recruitment status: ALL

Appendix 5. Clinicaltrials.gov

Basic searches:

1. breast cancer AND chemoprevention

2. breast cancer AND anticarcinogenic agent

3. breast cancer AND risk reducing agent

Advanced searches:

1. Search terms: prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

Intervention: tamoxifen OR raloxifene OR lasofoxifene OR selective estrogen receptor modulator OR SERM OR vitamin D or aspirin OR acetylsalicylic acid OR metformin

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

2. Search terms: prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

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Intervention: aromatase inhibitors OR exemestane OR letrozole OR anastrazole OR arimidex OR femara OR aromasin OR coenzyme a reductase inhibitor OR statin

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

3. Search terms: prevention OR prophylaxis OR prophylactic OR risk reducing OR risk reduction

Condition: breast cancer OR breast neoplasm

Intervention: Bisphosphonates OR Diphosphonates OR Denosumab OR Prolia OR Xgeva OR "RANK ligand"

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

4. Condition: breast cancer OR breast neoplasm

Intervention: Zoledronate OR "Zoledronic acid" OR clodronate OR "Clodronic acid" OR "Etidronic acid" OR Alendronate OR Ibandronate OR Pamidronate OR Risedronate OR Tiludronate OR Incadronate Olpadronate OR Neridronate

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

CONTRIBUTIONS OF AUTHORS

Draft the protocol: SM, AG, SP.

Study selection: SM, AG, SP.

Extract data from studies: SM, SP.

Enter data into Review Manager 5: SM, SP.

Carry-out the analysis: SM.

Interpret the analysis: SM.

Draft the final review: SM, AG, SP.

Disagreement resolution: SM, AG, SP (by iteration, discussion, and consensus).

Update the review: SM, SP.

DECLARATIONS OF INTEREST

SM: none.
AG: no competing interest associated with funding of travel to attend a national and international educational meeting or to provide expertise regarding Cancer Genetic counselling in Australia.
SP: none.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We slightly amended the description of the primary and secondary outcomes in the protocol to align with all other sections of the review. That is, we amended: (a) 'efficacy: relative risk of incidence breast cancer (in situ and invasive carcinoma)' to 'overall breast cancer incidence', (b) 'toxicity: relative risk of severe adverse effects (i.e. grade 3 and 4 toxicities)' to 'severe toxicity (i.e. grade 3 and 4 toxicities), (c) 'efficacy: invasive breast cancer only' to 'invasive breast cancer incidence (excluding in situ carcinoma)' and (d) 'toxicity: overall toxicity (any grade toxicity)' to 'overall toxicity (any grade toxicity)'.

INDEX TERMS

Medical Subject Headings (MeSH)

Aromatase Inhibitors [*therapeutic use]; Breast Neoplasms [*drug therapy]; Network Meta-Analysis; Randomized Controlled Trials as Topic; Selective Estrogen Receptor Modulators [*therapeutic use]

MeSH check words

Female; Humans

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