Authors' objectives
To assess the efficacy of tamoxifen and raloxifene for preventing breast cancer in women without established disease.

Searching
MEDLINE, CINAHL, Current Contents, the Cochrane Library, HealthSTAR and the reference lists of key articles were searched for studies published in the English language between 1966 and August 2000. The MeSH search terms were 'breast neoplasms/prevention and control', 'chemoprevention', 'clinical trials', 'tamoxifen' and 'raloxifene'. Experts in the field were contacted for additional references (to January 2001).

Study selection
Study designs of evaluations included in the review
Open-label, single- or double-blind randomised trials with a placebo group were eligible if they reported breast cancer outcomes. The raloxifene study was a multicentre double-blind trial. Two of the tamoxifen trials were conducted in multiple centres, while the third was a single-centre study. The use of blinding was not reported for the tamoxifen trials.

Specific interventions included in the review
Comparisons of tamoxifen or raloxifene with a placebo for women without established breast cancer. The tamoxifen trials used a dose of 20 mg/day for a minimum of 5 years. There was no specific trial of raloxifene for the prevention of breast cancer, but a secondary analysis on breast cancer outcomes following raloxifene for osteoporosis was included. In this study, participants received 60 or 120 mg raloxifene or placebo daily for 40 months. The authors did not specify the inclusion and exclusion criteria used. Hormone therapy was prohibited in two of the included trials, while hormone replacement therapy was permitted in one included trial.

Participants included in the review
Two tamoxifen trials included women at increased risk of breast cancer. One of these trials included women if they were aged over 60 years, had a history of lobular carcinoma in situ or had a 5-year breast cancer risk of at least 1.66% (using Gail and associates’ risk assessment scale). The other trial included women aged 30 to 70 years who had a first-degree relative with breast cancer. The third tamoxifen trial included women aged 35 to 70 years undergoing hysterectomy for reasons other than breast cancer. Women with a history of thromboembolism were excluded from all trials of tamoxifen.

Postmenopausal women with osteoporosis were eligible for the raloxifene trial. Breast cancer risk was not evaluated prior to trial entry and no other information about the eligibility criteria was provided.

Outcomes assessed in the review
The primary outcome was breast cancer incidence. The secondary outcomes included mortality, incidence of vascular events and other adverse effects. The outcomes were measured using hospital records, registry data and self-report questionnaires.

How were decisions on the relevance of primary studies made?
The four primary authors applied standardised evidence-based evaluation methods to assess the relevance of the primary studies. The evaluation methods and the total number of studies identified were not described.

Assessment of study quality
The studies were reviewed using structured checklists and guidelines from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative's Steering Committee on Clinical Practice Guidelines. The checklist covered randomisation, study design and the number of research sites. The criteria used to assess validity were not fully reported. The four primary authors applied standardised evidence-based methods to assess the validity of the primary studies. The evaluation criteria were not described fully. It is unclear whether the reviewers were blinded to the outcomes when assessing study design and whether the assessments were made independently.

**Data extraction**

The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The primary findings from each study were described. The description included the number of participants, incidence of breast cancer, incidence of adverse effects, treatment duration, and length of follow-up. The data were not pooled quantitatively.

**Methods of synthesis**

**How were the studies combined?**

The authors described the major outcomes of each study, tabulated some data, and provided a narrative synthesis. A table summarising the overall recommendations and level of evidence was also provided. Publication bias was not assessed.

**How were differences between studies investigated?**

The authors do not state how differences between the studies were assessed. The differences were described in the narrative.

**Results of the review**

Four randomised trials were included, three of tamoxifen and one of raloxifene. There was a total of 28,972 women without breast cancer at baseline: 21,267 in the three studies of tamoxifen and 7,705 in the one trial of raloxifene.

The tamoxifen trials had varying results. In the National Surgical Adjuvant Breast and Bowel Project P-1 study, women at increased risk of breast cancer received tamoxifen or placebo for 5 years. Tamoxifen prevented breast cancer in all subgroups, including those with a history of lobular carcinoma in situ, those with a history of atypical hyperplasia, those with increased 5-year breast cancer risk, and all age groups. The risk of invasive breast cancer was reduced by 49% ($p<0.00001$) and the risk of noninvasive cancer was reduced by 50% ($p<0.002$). Serious adverse effects such as endometrial cancer (relative risk, RR 2.5, 95% confidence interval, CI: 1.4, 4.97), pulmonary embolism (RR 3, 95% CI: 1.2, 9.3) and new cataracts (RR 1.1, 95% CI: 1.01, 1.3) were more common in women receiving tamoxifen ($p<0.05$). There was no significant difference in the risk of stroke or deep vein thrombosis.

In the Italian Tamoxifen Prevention Study, women undergoing hysterectomy for reasons other than cancer received 5 years of tamoxifen or placebo. There was no difference in breast cancer incidence, although the subgroup analysis suggested that there was reduced breast cancer in women receiving hormone replacement therapy and tamoxifen ($p=0.02$). Thromboembolic events were more common among those receiving tamoxifen ($p=0.0053$).

In the Royal Marsden Hospital Tamoxifen Randomised Chemoprevention Trial, women received 8 years of tamoxifen or placebo. There was no difference in breast cancer incidence (RR 0.94, 95% CI: 0.7, 1.7) or adverse effects.

In the Multiple Outcomes of Raloxifene Evaluation trial, women received raloxifene or placebo. Raloxifene reduced the risk of oestrogen receptor-positive breast tumours by 90% (RR 0.1, 95% CI: 0.04, 0.24), but not the risk of oestrogen receptor-negative tumours (RR 0.88, 95% CI: 0.26, 3.0). Venous thromboembolic disease was more common in the raloxifene group (RR 3.1, 95% CI: 1.5, 6.2), as were hot flashes, influenza-like symptoms, leg cramps, endometrial cavity fluid, new or worsening diabetes, and peripheral oedema. The risk of endometrial cancer was not affected (RR 0.8, 95% CI: 0.2, 2.7). There was a reduction in the risk of vertebral fractures.
Authors' conclusions
There was fair evidence to recommend against the use of tamoxifen in women at low or normal risk of breast cancer. Women at high risk of breast cancer should receive counselling about the risks and benefits of tamoxifen for cancer prevention. There was no evidence to suggest that raloxifene should be used as chemoprevention for breast cancer outside of clinical trial settings.

CRD commentary
This review aimed to assist women and physicians making decisions about chemoprevention for breast cancer. The authors used well-defined questions, standard search techniques for published literature, and established validity assessment criteria. Five databases were searched and some efforts were made to identify unpublished literature. The findings should be interpreted with caution. There were three large studies of tamoxifen but these included different population groups, making comparisons difficult. For instance, in some studies hormone replacement therapy was prohibited, while in others it was allowed. Some studies included only older women, while others included a larger age range. The treatment duration and sample size of these studies was also heterogeneous. All of the studies reported an increase in vascular events, suggesting that any preventative benefits of tamoxifen must be carefully weighed against adverse effects.

Evidence about the effect of raloxifene was especially limited. Only a secondary analysis of women treated for osteoporosis was identified. This trial was not designed specifically to examine breast cancer, and there is no information about the statistical power of the study for assessing secondary breast cancer outcomes. There was no comparison of raloxifene and tamoxifen, so the relative efficacy of these treatments remains unclear.

In summary, although this review was well designed and implemented, it does not greatly enhance our knowledge about chemoprevention for breast cancer. The existing evidence about raloxifene is extremely weak and the potential benefits of tamoxifen must be weighed against increased vascular events.

Implications of the review for practice and research
Practice: The authors state that there is little evidence that tamoxifen can be used to prevent breast cancer in women at low or normal risk. Given the increase in vascular events, clinicians should discuss the possible benefits and risks of tamoxifen chemoprevention with women at high risk and make judgements for individual cases. Raloxifene should not be used as chemoprevention in clinical practice.

Research: The authors did not state any implications for research.

Reviewer's statement: Although three large trials of tamoxifen were identified, these used heterogeneous populations and different treatment durations. More research is needed to quantify the benefits and risks of tamoxifen for different subgroups of women. Research into raloxifene is limited. More trials are needed in this area.

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