Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer

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CRD summary
This review concluded that tamoxifen, raloxifene and tibolone reduced the risk for primary breast cancer in middle aged women without pre-existing breast cancer, but these drugs increased the risk of some adverse events. Given the potential for missed studies and each pooled result being based on only up to four studies, the results should be viewed with some caution.

Authors' objectives
To evaluate the benefits and harms of tamoxifen, raloxifene and tibolone when used to reduce the risk for primary breast cancer.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched for English-language studies from inception to January 2009; the search strategy was reported in the original report (see Other Publications of Related Interest). Bibliographies of included studies and clinical trials registries were searched and a Web of Science citation search was conducted. Trialists were contacted to obtain unpublished data.

Study selection
Randomised controlled trials (RCTs) with at least 100 women without pre-existing breast cancer and a minimum of three months follow-up and which compared tamoxifen, raloxifene or tibolone to each other or placebo were eligible for the assessment of efficacy. The outcomes of interest were the incidence of breast cancer and adverse events. Controlled observational studies were also included for the assessment of adverse events. Where reported, the age of participants ranged from 30 to 85 years. Most women were white. Between 0% and 52% were post-hysterectomy. The women in the tamoxifen trials were generally younger than those in trials of the other drugs. The dose of tamoxifen was 20mg/day, raloxifene ranged from 60mg/day to 150mg/day and tibolone 0.3mg/day to 2.5 mg/day. Follow-up ranged from three months to 13.2 years. Most studies were conducted in the United States.

One reviewer selected studies and the selection was checked by a second; discrepancies were resolved by group consensus.

Assessment of study quality
Studies were classified as good, fair or poor quality based on the US Preventative Services Task Force criteria (Quality: randomisation, blinding, baseline comparability, loss to follow-up, use of valid measures, definitions of intervention, outcomes considered and use of an intention-to-treat analysis. Applicability: population, intervention, comparator, outcomes, timing of measures and setting) by two independent reviewers; discrepancies were resolved by group consensus.

Data extraction
The risk ratio (RR) and 95% confidence intervals (CI) were extracted, or calculated from reported incidences, for breast cancer, mortality, fracture and adverse events. Event rates per 1,000 women-years were also extracted or calculated. One reviewer extracted data and a second checked for accuracy.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using a random-effects model. Results for tamoxifen and raloxifene were analysed separately. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Subgroup analyses were conducted to investigate the impact of age, family history, hormone replacement therapy, menopausal status and body mass index. Stratified analysis was conducted to compare active and post-treatment phases. Combined event rates were obtained using a random effects Poisson model of placebo event rates, raw data of the incidence of events and...
Results of the review
Fifty eight articles met the inclusion criteria. Eight trials assessed effectiveness (n=70,280, range 2,471 to 19,747) and 29 assessed adverse events (n=1,826,860, range 101 to 423,813). Most studies were fair to good in terms of quality, but several of the trials that reported on adverse events were classified as poor for applicability. The meta-analysis concentrated on a sub-set of studies.

Effectiveness: The incidence of invasive breast cancer was reduced in middle aged and older women with tamoxifen (RR 0.70, 95% CI 0.59 to 0.82; four trials), raloxifene (RR 0.44, 95% CI 0.27 to 0.71; two trials) and tibolone (RR 0.32, 95% CI 0.13 to 0.80; one trial) when compared to placebo. For tamoxifen and raloxifene the reduction was primarily in the incidence of receptor-positive invasive breast cancer. When compared directly, there was little difference in any outcome between tamoxifen and raloxifene (one study). There was no difference between any of the drugs and placebo in terms of all-cause mortality or, where reported, breast cancer mortality. Tamoxifen, raloxifene and tibolone all reduced at least some types of fracture (four studies); there was no difference between tamoxifen and raloxifene (one study). The results for several subgroup analyses were reported.

Adverse events: Incidence of thromboembolic events was increased with tamoxifen (RR 1.93, 95% CI 1.41 to 2.64; four trials) and raloxifene (RR 1.60, 95% CI 1.15 to 2.23; two trials) when compared to placebo; the risk returned to normal after discontinuation of tamoxifen (two trials). Tamoxifen increased the incidence of endometrial cancer (RR 2.13, 95% CI 1.36 to 3.32; three trials), but raloxifene did not. Tibolone increased the risk of stroke (RR 2.19, 95% CI 1.14 to 4.23; one RCT). Further results regarding cardiovascular events, bleeding, surgical procedures and more minor side effects (such as hot flushes) were reported, as were results for several subgroup analyses.

Authors’ conclusions
Three medications reduced the risk for primary breast cancer in middle aged women without pre-existing breast cancer, but tamoxifen and raloxifene increased the risk for thromboembolic events, tamoxifen increased the risk of endometrial cancer, and tibolone increased the risk of stroke.

CRD commentary
The authors addressed a clear review question supported by appropriate inclusion criteria. Several relevant sources were searched and attempts were made to obtain unpublished data. Only English-language studies were sought, therefore, relevant studies may have been missed. Study selection was conducted by two reviewers, but not independently, therefore, selection bias and missed studies could not be ruled out. Data extraction and quality assessment were conducted in duplicate, which reduced the potential for error and bias during data extraction. The criteria used to categorise studies as good, fair or poor quality were not reported in the paper; reference to the previous report or a methodological paper was necessary. The review of adverse events seemed to concentrate on the results of a small proportion of the studies identified.

The conclusion that tibolone increased the risk of stroke was based on a single study in women over the age of 60 and the generalisability of this result to younger women was uncertain. Given the potential for missed studies and each pooled result being based on only up to four studies, the results should be viewed with some caution, particularly for adverse events.

Implications of the review for practice and research
Practice: The authors advised clinicians to ensure that women understood their individual risks for breast cancer before applying the results of the review.

Research: The authors identified a number of evidence gaps and stated that follow-up of women enrolled in current trials would provide data on longer-term outcomes. Further evaluation of tibolone was considered necessary, particularly with regards to safety outcomes. Other recommendations included the evaluation of emerging medications once available and controlled trials of lifestyle modification interventions.

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