Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual patient data


CRD summary
This review concluded that incidence of invasive oestrogen receptor-positive breast cancer was reduced by selective oestrogen receptor modulators during treatment and for at least five years after completion. Despite some limitations, the analyses contained a large group of participants with longer follow-up and the conclusion is likely to be reliable.

Authors' objectives
To assess the effectiveness of selective oestrogen receptor modulators on breast cancer incidence.

Searching
PubMed database was searched. Search terms were reported but search dates were not.

Study selection
Randomised controlled trials were eligible if they compared selective oestrogen receptor modulators with placebo or another drug in women without breast cancer. Studies had to have at least two years follow-up. Primary endpoint was incidence of breast cancer (including ductal carcinoma in situ) during 10 years of follow-up. Secondary endpoints were incidence of breast cancer in years zero to five and years five to ten, and all invasive oestrogen receptor-positive or oestrogen receptor-negative cancers, and ductal carcinoma in situ. Other pre-defined secondary endpoints were reported in the review.

Some trials recruited women at high risk of breast cancer and others were in normal risk post-menopausal women. Four trials compared tamoxifen 20mg with placebo, two trials compared raloxifene with placebo and one trial compared raloxifene with tamoxifen. One trial compared two different doses of lasofoxifene with placebo. Finally, one trial compared arzoxifene with placebo. Treatment duration lasted from four to eight years.

The authors did not state how many reviewers carried out study selection.

Assessment of study quality
The authors did not report any validation or checking of the data used in the analyses.

Data extraction
Individual participant data (IPD) for all participants were sought from trial investigators. Data were collected to calculate log hazard ratios, odds ratios and 95% confidence intervals. Data were analysed on an intention-to-treat basis.

Methods of synthesis
Pooled hazard ratios, odds ratios and 95% confidence intervals were calculated using fixed-effect models (inverse variance method) and also random-effects when there was an evidence of heterogeneity. A log hazard ratio for raloxifene versus placebo was calculated by subtracting the ratio for the direct comparison between raloxifene and tamoxifen from that for the direct comparison between tamoxifen and placebo in the other trials. Statistical heterogeneity was assessed by the Q statistic and I².

Results of the review
Nine trials were included (83,399 participants, 306,617 women-years of follow-up) in the individual participant data review. Median follow-up was 65 months.

Pooled individual participant data analysis showed a 38% (HR 0.62, 95% CI 0.56 to 0.69) reduction in breast cancer (including ductal carcinoma in situ) incidence with selective oestrogen receptor modulators. The authors calculated that to prevent one breast cancer event, 42 women would need to be treated in the first 10 years of follow-up. The
reduction in breast cancer incidence was greater in the first five years of follow-up than in years five to ten (HR 0.58, 95% CI 0.51 to 0.66; versus HR 0.75, 95% CI 0.61 to 0.93). No heterogeneity was observed between time periods. The analyses also showed statistically significant reductions in incidence of oestrogen receptor-positive breast cancer (HR 0.49, 95% CI 0.42 to 0.57; with heterogeneity); ductal carcinoma in situ (HR 0.69, 95% CI 0.53 to 0.90; with heterogeneity); and in incidence of all fractures (OR 0.85, 95% CI 0.80 to 0.89). Thromboembolic events were significantly increased with all selective oestrogen receptor modulators (OR 1.73, 95% CI 1.47 to 2.05).

There was no evidence that selective oestrogen receptor modulators increased the risk of overall mortality or other cancer apart from endometrial cancer which was higher in the selective oestrogen receptor modulators group in the first five years of follow-up (HR 1.56, 95% CI 1.13 to 2.14).

Authors’ conclusions
For all selective oestrogen receptor modulators, incidence of invasive oestrogen receptor-positive breast cancer was reduced both during treatment and for at least five years after completion. Similar to other preventive interventions, careful consideration of risks and benefits was needed to identify women who were most likely to benefit from these drugs.

CRD commentary
The review question and inclusion criteria were clear. The authors searched only one database and it was unclear whether language restrictions were applied, so it was possible that relevant trials may have been overlooked. The authors did not state whether study selection was conducted in duplicate, or whether the accuracy and integrity of the data used in the individual patient data analyses were checked. Therefore, error and bias could not be ruled out. Appropriate methods were used to pool data, but reporting of heterogeneity was sparse.

Despite concerns regarding conduct and/or reporting of the review, the analyses contained a large number of participants with longer follow-up, and the authors’ conservative conclusions were likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that similar to other preventative interventions, careful consideration of potential benefits and harms during the decision making process was needed to identify women most likely to benefit.

Research: The authors stated that further studies were needed for longer follow-up (greater than 10 years) to establish whether there was a reduction in deaths from breast cancer. Due to the promising preventive effect of lasofoxifene, further studies on lasofoxifene should be prioritised for prevention research. Finally, a comparison of aromatase inhibitors with selective oestrogen receptor modulators might be needed when long-term data for aromatase inhibitors are available.

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