Commentary

Prevention of breast cancer using selective oestrogen receptor modulators (SERMs)

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Abstract

Placebo controlled trials in over 25,000 women showed that tamoxifen reduced breast cancer risk by about 40% and osteoporotic fracture risk by about 32%. Similarly placebo controlled trials in nearly 18,000 women showed that raloxifene reduced breast cancer risk by 44-72% and osteoporotic fractures risk by 30-50%. A direct comparison of tamoxifen with raloxifene showed similar risk reduction for breast cancer and osteoporotic fractures with less toxicity for raloxifene.

The results of two very large clinical trials evaluating the selective oestrogen receptor modulator (SERM) raloxifene for prevention of breast cancer have been published in the past few weeks and consolidate our position on the use of these agents in the prevention of breast cancer.

The first, by Vogel and colleagues [1], reports the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P2 trial, which directly compares the breast cancer risk reduction potential of tamoxifen and raloxifene. The second, by Barrett-Connor and colleagues [2], reports the results of the Raloxifene Use for the Heart (RUTH) trial, which compares raloxifene with placebo in women at high risk of ischaemic heart disease or cardiac events. Breast cancer incidence was a co-primary outcome in this trial. These trials follow 20 years of clinical research involving nearly 40,000 women using SERMs to prevent breast cancer.

The first SERM to be evaluated was tamoxifen, which was tested in four placebo controlled trials started between 1986 and 1992. Over 25,000 healthy women at high risk of breast cancer were randomised to tamoxifen or placebo for at least five years. A meta-analysis of these trials in 1993 showed that tamoxifen reduced breast cancer risk by about 40%, as well as resulted in a significant reduction in osteoporotic fractures and serum cholesterol. However, there was significant toxicity, especially a clinically significant increase in gynaecological problems, including the need for hysterectomy, uterine fibroids, endometrial atypia, polyps, and cancer [3]. The largest of these tamoxifen trials was the NSABP P1 trial, which randomised 13,388 pre- and postmenopausal women with an estimated breast cancer risk of >1.66% over 5 years estimated by the Gail Risk algorithm [4]. The breast cancer incidence at about 4 years of follow-up showed a very significant 44% reduction in breast cancer risk [5]. This provided the basis for approval of tamoxifen by the Food and Drugs Administration (FDA) for breast cancer risk reduction in the USA in 1998.

In 1994 another SERM, raloxifene, was evaluated as an anti-osteoporotic agent in a clinical trial, the Multiple Outcomes Relevant to Evista (MORE) trial. Subjects in this study were randomised into three arms, two doses of raloxifene versus placebo, aimed at determining the effect on the risk of fracture in 7,700 postmenopausal women with osteoporosis. At 36 months there was a significant reduction in the risk of vertebral fractures for both doses of raloxifene (relative risk (RR) 0.7, 95% confidence interval (CI) 0.5 to 0.8 for 60 mg/day dose; RR 0.5, 95% CI 0.4 to 0.7 for 120 mg/day dose) but no effect on non-vertebral fracture risk (RR 0.9, 95% CI 0.8 to 1.1) [6]. In this trial breast cancer incidence was a secondary outcome, and was reduced by 72% at 4 years [7]. With an extension of this trial for a further 4 years with breast cancer as the primary outcome in the Continuing Outcomes Relevant to Evista (CORE) trial, analysis at 8 years confirmed a 66% risk reduction for breast cancer [8]. These results have now been recently confirmed in another raloxifene placebo controlled trial, the RUTH trial. This trial randomised 10,101 postmenopausal women at high risk of cardiac events to raloxifene 60 mg/day or placebo. After a median follow up of 5.6 years there was no effect on the incidence of heart events but there was a significantly

CI = confidence interval; FDA = Food and Drugs Administration; NSABP = National Surgical Adjuvant Breast and Bowel Project; RUTH = Raloxifene Use for the Heart; SERM = selective oestrogen receptor modulator.

reduced risk of invasive breast cancer (RR 0.56, 95% CI 0.38 to 0.83) and clinical vertebral fractures (RR 0.65, 95% CI 0.47 to 0.89) [2]. In these trials there was evidence of an increase in thromboembolism but no evidence of an increase in endometrial polyps, atypia or carcinoma.

The results of the raloxifene placebo controlled trials together with the approval by the FDA of tamoxifen for breast cancer risk reduction led the NSABP to their P2 trial, which was designed as a head to head comparison of tamoxifen versus raloxifene. This started in 1999 and randomised a total of 19,747 postmenopausal women with a Gail risk >1.66% to raloxifene 60 mg/day or tamoxifen 20 mg/day. The overall mean Gail score for these women was 4.03 ± 2.17% [1].

The results showed an almost identical incidence of invasive breast cancer for tamoxifen and raloxifene (RR 1.02, 95% CI 0.82 to 1.28), indicating that both are equally effective at reducing breast cancer risk. However, for non-invasive breast cancer the incidence is higher for women on raloxifene than tamoxifen, indicating a possible lesser risk reduction benefit for this condition. The toxicity data from this trial confirmed the previous results of low uterine toxicity for raloxifene, with a significant reduction in the incidence of endometrial hyperplasia, atypia and the requirement for hysterectomy. The incidence of endometrial cancer was less for raloxifene than tamoxifen (RR 0.62, 95% CI 0.35 to 1.08), in keeping with the previous indirect comparisons from placebo controlled trials showing no increase in endometrial cancer risk with raloxifene. With regard to other toxicities, there were significantly less thromboembolic events and cataracts with raloxifene than tamoxifen. There was no difference in the incidence of ischemic heart disease, stroke, osteoporotic fractures, other cancers or death.

Overall, the results of these trials show that raloxifene and tamoxifen are equally effective at reducing the risk of invasive breast cancer by about 40% and osteoporotic vertebral fractures by about 35%. However, the toxicity of tamoxifen, particularly the gynaecological problems, limit its clinical use for prevention in healthy women. The P2 trial confirms that raloxifene is less toxic than tamoxifen and, therefore, an attractive alternative as a risk reduction agent for breast cancer and vertebral fractures in postmenopausal women.

Which healthy women should be considered for breast cancer risk reduction? The Gail model is complex and not generally perceived by women as model for risk assessment, especially outside the USA. The predominant risk factors that are recognised as important are a family history of any first degree relatives and/or a premalignant biopsy (atypia or lobular carcinoma *in situ*). Generally, women also recognise osteoporosis as a potential problem and, therefore, an increased risk of vertebral fracture because of a previous fracture, low bone mineral density and/or a family history of osteoporosis would indicate an added benefit for use of raloxifene for risk reduction of breast cancer.Some sort of algorithm or global index is needed so that women and their doctors can make sensible decisions about the use of SERMs for breast cancer and osteoporotic fracture risk reduction. This means that the clinical trials must deal with the statistical issues concerning multiple outcomes. The design of treatment trials with one primary outcome balanced against toxicity is not appropriate for agents like SERMs in a prevention setting where multiple benefits may ensue and need to be considered against long term toxicity in healthy women. It is also important that regulatory authorities have mechanisms to evaluate these multiple outcomes.

So, where do we go from here? New SERMs are in the pipeline. Arzoxifene and lasofoxifene are both being evaluated for multiple outcome benefits, including breast cancer risk reduction in large clinical trials in healthy women. These will hopefully build on the success of the clinical trials already undertaken with tamoxifen and raloxifene. There is no doubt that SERMs have the potential to prevent breast cancer and the results from the recent trials with raloxifene offer us encouragement to achieve this goal.

Conclusion

The SERMs tamoxifen and raloxifene have similar risk reduction activity for breast cancer and osteoporotic fractures. Raloxifene has less toxicity, particularly on the uterus, making it a more attractive option than tamoxifen for use as a breast cancer risk reduction agent in healthy women.

Competing interests

TJP has received honoraria for his role as a lecturer and advisor to Eli Lilly and Pfizer.

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