**The Effect of Raloxifene on Risk of Breast Cancer in Postmenopausal Women**

**Context** Raloxifene hydrochloride is a selective estrogen receptor modulator that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting.

**Objective** To determine whether women taking raloxifene have a lower risk of invasive breast cancer.

**Design and Setting** The Multiple Outcomes of Raloxifene Evaluation (MORE), a multicenter, randomized, double-blind trial, in which women taking raloxifene or placebo were followed up for a median of 40 months (SD, 3 years), from 1994 through 1998, at 180 clinical centers composed of community settings and medical practices in 25 countries, mainly in the United States and Europe.

**Participants** A total of 7500 postmenopausal women, younger than 81 (mean age, 66.5) years, with osteoporosis. Women who had a history of breast cancer or who were taking estrogen were excluded.

**Intervention** Raloxifene, 60 mg, 2 tablets daily; or raloxifene, 60 mg, 1 tablet daily and 1 placebo tablet; or 2 placebo tablets.

**Main Outcome Measures** New cases of breast cancer, confirmed by histopathology. Deep vein thrombosis or pulmonary embolism were determined by chart review.

**Results** Thirteen cases of breast cancer were confirmed among the 5000 women assigned to raloxifene vs 26 among the 2500 women assigned to placebo (relative risk [RR], 0.25; 95% confidence interval [CI], 0.13-0.49; Chi-Square = 19.5, P<.001). To prevent 1 case of breast cancer, 128 women would need to be treated. Raloxifene increased the risk of venous thromboembolic disease (RR, 3.0; 95% CI, 1.5-6.1), but did not increase the risk of endometrial cancer (RR, 0.8; 95% CI, 0.2-2.7).

**Conclusion** Among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 75% during 3 years of treatment with raloxifene.

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**Notes: (1) The numbers in the abstract have been "rounded" to make calculations easier. (2) The data from the 2 regimens were combined in the abstract. Thus, twice as many women received raloxifene as placebo.**

1 Show how the authors calculated the "128 would need to be treated"

2 Reproduce the CI accompanying the RR of 0.25.

3 Would you expect a test-based CI to give close to the same CI? Compute it and comment on how close it is.

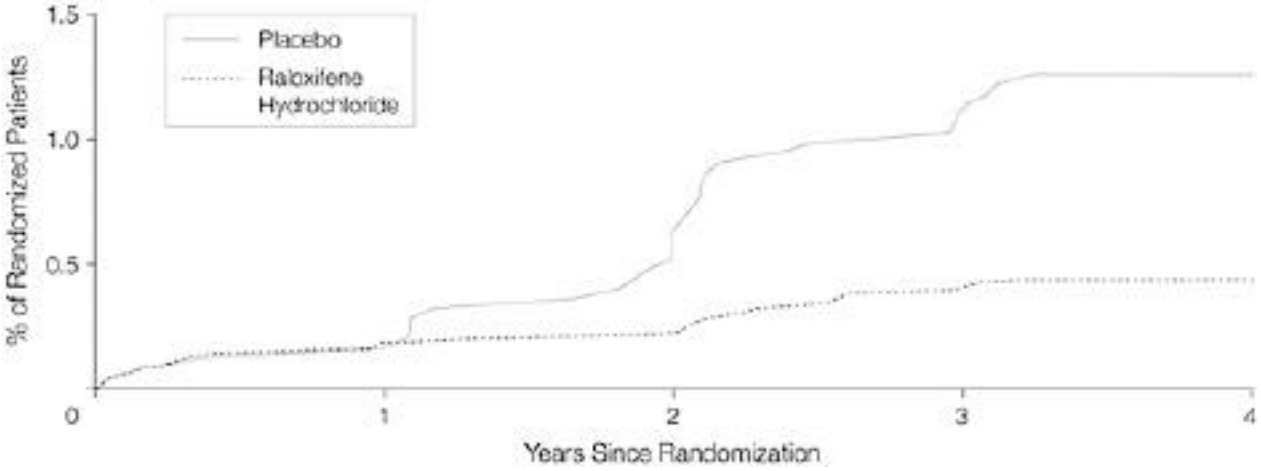
4 If half of the 7500 women had been allocated to receive raloxifene and half to receive placebo, and if the cancer rates had been the same, would the CI have been narrower, wider or the same width? Explain.

It is important to set the reduction in breast cancer against the increase in thromboembolic disease. Interestingly, the abstract does not to report the numbers of such cases, only the RR of 6 and the CI.

5 From the information provided in the abstract, determine -- analytically or by trial and error -- how many cases of thromboembolic disease must there have been [Hint: log 1.5 = 0.4 ; ln 3 = 1.1 ; ln 6.1 = 1.8 ; and use 2 as an approximation to 1.96]

In Table 2 of the paper, the authors report 15,000 and 7,500 women years of follow-up in the two groups.

6 Does using these rather than the "person" denominators in the abstract change the CI's? Why/why not?




*"Figure 2 The cumulative incidence of breast cancer among subjects in the placebo group and those in the combined raloxifene group are represented as a percentage of all patients randomized to either group. Statistical significance of the difference between the groups was tested by a log-rank test (P<0.001).*

7 Show how to carry out the logrank test manually for these data.

8 Suggest a way to reduce the numbers of calculations.

*"Participants were followed up every 6 months. Mammography screenings were optional after the first year but were mandatory after 2 years and after 3 years of treatment. Participants who declined mammography screening could have a breast ultrasonography instead. At every visit, participants were also asked if they had been diagnosed as having breast cancer, had an abnormal mammogram or breast sonogram result or a breast biopsy specimen, or had had surgery since the previous visit. If breast cancer was suspected, records of procedures were obtained."[Methods]*

9 Sketch the hazard curve for the placebo group.