

EDITORIALS



Risk–Benefit Profiles of Raloxifene for Women

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During the past decade, considerable scientific, clinical, and public interest in the benefits and risks of postmenopausal estrogen therapy has focused attention on selective estrogen-receptor modulators (SERMs). These act as estrogen agonists in some tissues and antagonists in others because of specific actions on at least two distinct estrogen receptors, the proportions of which differ across tissues. As such, SERMs have held the promise of conferring benefits similar to those associated with estrogen therapy, including a reduced risk of osteoporosis, while simultaneously reducing estrogen-related risks (e.g., invasive breast cancer). The once widely held belief that estrogen therapy was cardioprotective¹ also generated hope that a SERM might prevent coronary heart disease (CHD).

The Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project provided evidence in 1998 that a SERM, tamoxifen, could reduce breast cancer risk in a cohort of 13,388 women at increased risk for breast cancer.² Tamoxifen significantly reduced the risk of invasive breast cancer and, in particular, tumors with positive estrogen-receptor status (relative risk reductions, 49 percent and 69 percent, respectively). Tamoxifen also reduced the risk of fractures, though not significantly. However, it was associated with significantly increased risks of endometrial cancer, stroke, pulmonary emboli, deep-vein thrombosis, and cataracts, primarily in women 50 years of age or older.²

Additional support for the benefits of SERMs arose from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which studied 7705 postmenopausal women with osteoporosis.³ In this placebo-controlled trial, raloxifene increased bone density in the spine and femoral neck and significantly reduced the risk of vertebral — but

not hip — fractures, without increasing the risk of endometrial hyperplasia or cancer.³ Like tamoxifen, raloxifene significantly decreased the risk of invasive breast cancer (relative risk reduction on the basis of a small number of cases, 76 percent)⁴ but increased the risk of venous thromboembolism.^{3,4}

In this issue of the *Journal*, Barrett-Connor et al. report results of the placebo-controlled Raloxifene Use for the Heart (RUTH) trial.⁵ Initially designed to assess the effect of raloxifene (60 mg per day) on coronary events, the trial enrolled 10,101 postmenopausal women who had CHD or multiple risk factors for CHD. When the MORE trial results became known, invasive breast cancer was added to the RUTH trial as a second primary outcome.⁵ During a follow-up period of a median of 5.6 years, rates of the primary outcome of the incidence of coronary events (death from coronary causes, nonfatal myocardial infarction, and hospitalization for an acute coronary syndrome) did not differ between groups. However, as compared with placebo, raloxifene significantly reduced the risk of invasive breast cancer and, in particular, breast cancers with positive estrogen-receptor status (relative risk reductions, 44 percent and 55 percent, respectively). Raloxifene also reduced the risk of clinical vertebral fractures (relative risk reduction, 35 percent) but not of nonvertebral fractures.⁵ However, raloxifene increased the relative risks of venous thromboembolism (44 percent) and fatal stroke (49 percent). Other adverse events more common with raloxifene than with placebo included hot flashes, leg cramps, peripheral edema (all consistent with the MORE trial^{3,4}), and gallbladder disease.

Given the negative clinical trials of estrogen therapy and CHD in women with^{1,6} and without^{7,8} established CHD, it is not surprising that

raloxifene was not associated with a reduced risk of coronary events. As previously reported,^{9,10} however, raloxifene lowered the levels of low-density lipoprotein cholesterol and increased the levels of high-density lipoprotein cholesterol.⁶ These results reaffirm that, as demonstrated with postmenopausal estrogen therapy,^{1,6-8} favorable changes in these lipid levels cannot be assumed to translate into reduced coronary risk.

An important question raised by the RUTH trial is how to balance the substantial relative reductions in the risks of invasive breast cancer and clinical vertebral fractures with the increases in the risks of venous thromboembolism and fatal stroke. The Women's Health Initiative trial used a "global index" that included CHD, stroke, pulmonary embolism, invasive breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death from other causes to conclude that the risks of therapy with estrogen plus progestin outweighed the benefits,⁷ whereas risks and benefits were balanced for unopposed estrogen therapy⁸ in postmenopausal women who overall were not at high risk for CHD, breast cancer, or osteoporosis. Neither deep-vein thrombosis nor vertebral fractures were included in these calculations. When the same global index was applied to the participants in the MORE trial (selected on the basis of osteoporosis), results suggested a favorable risk-benefit safety profile for raloxifene, even though the risk of hip fractures was not significantly reduced.¹¹

The current report from the RUTH trial⁵ does not incorporate a global index, but attention to the absolute reductions and increases in individual end points provides perspective on the risk-benefit balance. The rate of invasive breast cancer in the placebo group was 2.7 per 1000 women per year; the 44 percent reduction translates to 1.2 fewer cancers per 1000 women treated with raloxifene per year. The rate of clinical vertebral fractures was 3.7 per 1000 women per year; the absolute reduction was 1.3 fractures per 1000 women per year. These benefits came at a cost of 1.2 more cases of venous thromboembolism and 0.7 excess fatal stroke per 1000 women treated per year. Thus, for women represented by the RUTH cohort of women with or at increased risk for CHD, the moderate benefits of raloxifene for breast cancer prophylaxis do not seem to justify the risks.

By comparison, in the Breast Cancer Prevention

Trial of women selected on the basis of breast cancer risk, participants assigned to placebo had 6.8 invasive breast cancers per 1000 women per year; the 49 percent risk reduction conferred by tamoxifen translated to 3.3 cancers per 1000 women per year.² In the recent Study of Tamoxifen and Raloxifene trial involving women at high risk for breast cancer, there was no placebo group, but the similar rates of invasive breast cancer between women assigned to raloxifene (4.4 per 1000) and those assigned to tamoxifen (4.3 per 1000) were interpreted as evidence that raloxifene is as effective as tamoxifen in reducing this risk.¹² The absolute rate of venous thromboembolism was significantly lower among women assigned to raloxifene (2.6 per 1000) than among those assigned to tamoxifen (3.7 per 1000)¹² (the rate in the raloxifene group was lower than that in the RUTH trial, in which the absolute rate was 3.9 per 1000 women per year⁵). These results underscore that both absolute benefits and absolute risks will vary depending on the risk profiles of women receiving treatment (i.e., those at high risk for breast cancer as compared with those at high risk for a coronary event).

The logical question is, What level of breast cancer risk would justify the use of raloxifene for the prevention of breast cancer for a given person, if one takes into account the competing risks and patient preferences? Complicating the answer is our inability to predict these risks with high accuracy on an individual basis.

The consistency of the relative risk reduction for invasive breast cancer observed with raloxifene in the RUTH trial with that observed with tamoxifen in the Breast Cancer Prevention Trial,² and the recent finding of similar risk reductions with raloxifene and tamoxifen,¹² indicates that one might reasonably apply these relative risk reductions to expected rates in other groups of women to determine absolute risk reductions anticipated with raloxifene. To use the placebo groups in the Women's Health Initiative trial (breast-cancer rates, 3.3 per 1000 women per year¹³ and 3.4 per 1000 women per year¹⁴) as a representative sample of postmenopausal women who are at "average" risk would lead one to expect absolute reductions with the use of raloxifene on the order of 1.7 cases of invasive breast cancer per 1000 women treated, underscoring the small expected benefits in women not selected on the basis of a high risk of breast cancer.

The report by Barrett-Connor and colleagues highlights the need to consider the risk of breast cancer as well as other risks and coexisting conditions in determining whether and when raloxifene or another SERM is warranted for an individual woman. For now, there is no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns.

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Diagnosing Hemolytic Disease of the Fetus — Time to Put the Needles Away?

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The RhD (Rh₀[D]) antigen is considered the most immunogenic of the antigens found on the surface of the human red cell. In 1941, Levine, Katzin, and Burham¹ showed that antibodies to the RhD antigen in pregnant women caused hemolysis and anemia in their offspring. Originally called erythroblastosis fetalis secondary to the finding of a large number of immature red cells in the neonatal circulation, today this condition is known as hemolytic disease of the fetus and newborn.

When RhD-positive fetal cells enter the maternal circulation as a result of pregnancy-related events such as miscarriage or delivery, anti-D antibody can be formed. The administration of RhD immune globulin in these instances is effective

in preventing the formation of anti-D antibody in more than 99 percent of cases. However, in rare cases, because of the inadvertent omission of the administration of immune globulin or improper dosing, the patient becomes sensitized to the RhD antigen. Although the fetus that causes this alloimmunization is usually unaffected, transplacental passage of maternal anti-D antibodies in a subsequent pregnancy allows for their attachment to RhD-positive fetal red cells, resulting in the sequestration and destruction of these cells in the fetal spleen. Without treatment, this condition may lead to progressive anemia, excessive fluid collection in extracellular spaces (hydrops fetalis), and eventually fetal death. In milder cases, neo-