

NEWS Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® program of The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive the complete program by joining the Society (www.menopause.org). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

Progesterone may increase breast cancer risk less than progestin

Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Intl J Cancer* 2004 (e-publ in advance).

Oral progestin, the synthetic form of progesterone, significantly increases the breast cancer risk associated with postmenopausal hormone therapy, but micronized oral progesterone does not increase the risk, according to data from the E3N study, a subset of the European Prospective Investigation into Cancer and Nutrition study. The E3N is a prospective cohort study conducted in France. Investigators enrolled 54,548 postmenopausal women (mean age, 52.8 years) who had not used estrogen-containing therapy for at least 1 year. During the study, women completed questionnaires every 2 years regarding use of postmenopausal hormone therapy.

Mean duration of follow-up was 5.8 years. More than half of the women (n = 29,420) used postmenopausal hormone therapy during the study, either estrogen

therapy alone (ET) or estrogen plus progesterone (EPT). The mean duration of ET/EPT use was 2.8 years. Most women used transdermal estradiol, administered in either a gel or patch formulation. All progesterones used were oral formulations.

Overall, ET/EPT users had a significantly increased relative risk (RR) for breast cancer of 1.2 (95% CI, 1.1-1.4) compared with nonusers. Individually, EPT users had a significantly increased RR of 1.3 (95% CI, 1.1-1.5), but ET alone did not increase the risk (RR, 1.1; 95% CI, 0.8-1.6). However, the difference between ET and EPT was not significant.

When comparing types of progesterones contained in EPT, the RR for progestins was 1.4 (95% CI, 1.2-1.7) and 0.9 (95% CI, 0.7-1.2) for micronized progesterone, a statistically significant between-group difference ($P < 0.001$). Progestins significantly increased the breast cancer risk when added to either transdermal, percutaneous, or oral estrogen formulations, even for relatively short-term use. When used for less than 2 years, the RRs were 1.6 (95% CI, 1.3-2.0) for those receiving progestin plus transdermal/percutaneous estrogen and 1.2 (95% CI, 0.8-1.7) for those receiving progestin plus oral estrogen. When used for 2 to 4 years, the RRs were 1.4 (95% CI, 1.0-1.8) for progestin plus transdermal/percutaneous estrogen and 1.6 (95% CI, 1.2-3.2) for oral EPT.

Comment. This report from an ongoing French cohort study involved multiple statistical manipulations. The major conclusion is this: the risk of breast cancer is slightly increased with a postmenopausal hormone therapy regimen consisting largely of transdermal estradiol combined with synthetic progestins but not when combined with progesterone. Furthermore, this increased risk appears quickly, even with short-term use.

There are several points that raise

concern. The hormone users have many differences compared with nonusers, especially in characteristics that influence the risk of breast cancer. The users were more likely to be younger, to have had an earlier menarche and later menopause, to be parous, to have more benign breast disease, to be better educated, and to have used oral contraceptives and progestational agents before menopause. The authors state that statistical adjustments were made for these variables; however, the relative risks and confidence intervals before and after adjustment are identical. How is it possible for these risk factors to be more common in the user group and not to have an impact on the numbers after adjustment?

The statistical power of the study was concentrated in synthetic progestins users (268 cases vs 55 cases among micronized progesterone users). Because the reported differences are not large, a shift of a few cases (affected by the various risk factors noted above) could change the conclusions.

The rapid appearance of an increased breast cancer risk raises the following question: do the statistical results reflect a slight increase in risk or an impact on preexisting tumors? As this remains an unanswered question, it is not appropriate for the authors to say that the carcinogenic effect of estrogen plus progestin in continuous administration was proved by the Women's Health Initiative trial. The force of the authors' discussion is further diluted by repeated references to the Million Women Study, a study that has been soundly dissected and criticized for multiple flaws.

Because of these concerns, I wouldn't base my advice or prescription choices on these results.

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Raloxifene provides breast cancer benefits for at least 8 years

Martino S, Cauley JA, Barrett-Connor B, et al, for the CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004;96:1751-61.

Postmenopausal women with osteoporosis who are treated with raloxifene receive the added benefit of reduced invasive breast cancer risks, a benefit that continues for longer than 4 years of use, according to the randomized, double-blind, placebo-controlled Continuing Outcomes Relevant to Evista (CORE) trial, an extension of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. In the 4-year MORE trial, raloxifene reduced the breast cancer incidence by 72%. In the CORE trial, 5,213 women from the MORE trial (N = 6,511) who did not have breast cancer were continued for another 4 years on their regimens of raloxifene (60 mg/day) or placebo, as randomly assigned in the MORE trial. The end point was invasive breast cancer incidence.

At study end, raloxifene recipients had significantly reduced incidences of breast cancer (hazard ratio [HR], 0.41; 95% CI, 0.24-0.71) and estrogen receptor (ER)-positive breast cancer (HR, 0.35; 95% CI, 0.18-0.66) when compared with placebo recipients. During the 8 years combining both trials, the overall incidences of breast cancer and ER-positive breast cancer were significantly reduced by 66% (HR, 0.34; 95% CI, 0.18-0.66) and 76% (HR, 0.24; 95% CI, 0.15-0.40), respectively, compared with placebo recipients. Increased risks for thromboembolism were more than two-fold higher for raloxifene than placebo during CORE (HR, 2.17; 95% CI, 0.83-5.70). Significantly increased thromboembolism risks were also observed during MORE. No new adverse events were noted during CORE.

Comment. This paper raises many important issues worthy of comment. In women

picked for an osteoporosis study, not because of any personal history of breast cancer or for being at risk for breast cancer, 8 years of raloxifene therapy significantly reduced their invasive breast cancer risk.

Much has been rumored about drug resistance with tamoxifen, another selective estrogen-receptor modulator, and concerns that tamoxifen may actually increase breast cancer risk with prolonged use. In reality, the 5-year limitation on tamoxifen therapy is based on these two factors: (1) no additional benefits are seen after 5 years, and (2) there are ongoing, but small, risks of deep vein thrombosis and endometrial carcinomas with tamoxifen.

It is reassuring that raloxifene through 8 years of use shows no diminution of its ability to reduce breast cancer in these osteoporotic women. However, this does not mean that all women at risk for breast cancer (and not in need of bone pharmacotherapy) should be offered raloxifene. That answer will have to await results from the Study of Tamoxifen and Raloxifene (STAR) trial in which women at high risk for breast cancer are being compared head-to-head. Remember, MORE and CORE participants were not picked for being at high risk for breast cancer.

Interestingly, we had believed that women with osteoporosis were at lower risk for breast cancer. However, in the MORE/CORE placebo group, there was an incidence of 5.4 cases per 1,000 women-years, which is higher than the Surveillance, Epidemiology, and End Points (SEER) database rates of 4.4 and 4.5 cases per 1,000 women-years for women aged 65 to 74 and 75 and over, respectively.

In summary, data from the CORE trial and 8-year combined data from the MORE and CORE trials suggest that the reduced incidence of invasive breast cancer in women receiving raloxifene may continue beyond 5 years.

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Comment. This article describes breast cancer incidences from the combined MORE and CORE trials. The 72% reduction in the raloxifene group is both compelling and of great interest. The impact appears to be entirely on the ER-positive cancers. There was no effect on ER-negative cancers. This would suggest that it is the woman's estrogen level that causes the difference in tumors that have receptors capable of responding. The study subjects are women who are presumably at lower risk of getting breast cancer, as all of them have low bone density, which has been associated with a lower risk of breast cancer. With the addition of the MORE subjects, the rate was 1.4 cases per 1,000 women per year in the raloxifene group as opposed to 4.2 cases per 1,000 women per year in the placebo group.

This article should be read together with the Missmer article [Missmer *J Natl Cancer Inst* 2004] from the Nurses' Health Study that measured actual levels of these hormones and found a clear relationship of endogenous estrogen with breast cancer incidence. The higher quartile of endogenous estrogen levels was associated with a 3.3 relative risk of breast cancer. This was also only true for ER-positive breast cancers with no relationship to ER-negative cancers. Neither progesterone nor androgen levels reached statistical significance.

Taking both articles together, they add to the cumulative literature that estrogen levels play a major role in breast cancer. Whether this is a permissive role or causative one is not clear. Raloxifene, which blocks estrogen at the receptor level, may be as good as or better than tamoxifen in preventing breast cancer. The STAR trial is currently comparing Evista against tamoxifen in breast cancer prevention.

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