Serum Estradiol Level and Risk of Breast Cancer During Treatment With Raloxifene

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Prospective studies have found that the risk of breast cancer rises with increases in endogenous estradiol levels.\(^1\text{-}\text{4}\) The selective estrogen receptor modulators tamoxifen and raloxifene block the effects of endogenous estrogen in the breast\(^5\text{-}\text{6}\) and reduce the risk of breast cancer.\(^7\text{-}\text{9}\) Therefore, the effects of selective estrogen receptor modulators might depend on endogenous levels of estrogen. In a previous analysis of raloxifene effects in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, Lippman and colleagues\(^10\) observed that characteristics that might reflect high lifetime exposure to estrogen, such as high bone mineral density, were associated with an increased risk of breast cancer and somewhat greater reduction in cancer risk with raloxifene. They also reported that raloxifene reduced breast cancer significantly in women whether their estradiol levels were above or below the upper tertile, but the study did not analyze the full range of estradiol levels.

We postulated that the risk of breast cancer and the effect of raloxifene on risk of breast cancer would depend on serum concentrations of estradiol. Specifically, we hypothesized that women with a low estradiol level may have a lower breast cancer risk and that women with a high estradiol level may have a higher breast cancer risk. In a previous analysis of raloxifene effects in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, Lippman and colleagues\(^10\) observed that characteristics that might reflect high lifetime exposure to estrogen, such as high bone mineral density, were associated with an increased risk of breast cancer and somewhat greater reduction in cancer risk with raloxifene. They also reported that raloxifene reduced breast cancer significantly in women whether their estradiol levels were above or below the upper tertile, but the study did not analyze the full range of estradiol levels.

We postulated that the risk of breast cancer and the effect of raloxifene on risk of breast cancer would depend on serum concentrations of estradiol. Specifically, we hypothesized that women

**Context** As endogenous estradiol increases, risk of breast cancer increases. Raloxifene competes with endogenous estrogen for binding to estrogen receptors in breast tissue. A woman's estradiol level may alter the effects of raloxifene on breast cancer and other outcomes.

**Objective** To test the hypothesis that raloxifene reduces breast cancer risk more in women with relatively high estradiol levels than in women with very low estradiol levels.

**Design** Analysis of the Multiple Outcomes of Raloxifene Evaluation, a randomized, double-blind, placebo-controlled trial conducted from 1994 to 1999.

**Setting** One hundred eighty community settings and medical practices in 25 countries including the United States.

**Participants** A total of 7290 postmenopausal women aged 80 years or younger with osteoporosis who had baseline serum estradiol concentrations measured by a central laboratory using a sensitive assay. Women with a history of breast cancer or estrogen use were excluded.

**Intervention** Participants were randomly assigned to receive 60 mg/d or 120 mg/d of raloxifene (n=4843) or matching placebo (n=2447) for 4 years.

**Main Outcome Measure** New cases of histopathologically confirmed breast cancer in the treatment and placebo groups, stratified by estradiol levels.

**Results** In the placebo group, women with estradiol levels greater than 10 pmol/L (2.7 pg/mL) had a 6.8-fold higher rate of breast cancer (3.0% per 4 years; 95% confidence interval [CI], 1.8%-4.1%) than that of women with undetectable estradiol levels (0.6% per 4 years; 95% CI, 0%-1.1%; \(P=.005\) for trend). Women with estradiol levels greater than 10 pmol/L in the raloxifene group had a rate of breast cancer that was 76% (95% CI, 53%-88%) lower than that of women with estradiol levels greater than 10 pmol/L in the placebo group (absolute rate reduction, 2.2% [95% CI, 1.0%-3.5%; number needed to treat=45]). In contrast, women with undetectable estradiol levels had similar breast cancer risk whether or not they were treated with raloxifene (risk difference, \(-0.1\%\); 95% CI, \(-0.8\% to 0.6\%\); \(P=.02\) for the interaction). In this cohort, treating women with estradiol levels greater than 10 pmol/L with raloxifene for 4 years would have avoided 47% of breast cancer cases.

**Conclusions** Measurement of estradiol level by sensitive assay in postmenopausal women identifies those at high risk of breast cancer who may benefit most from raloxifene. If confirmed, this suggests that measuring estradiol and treating women with high estradiol levels could substantially reduce the rate of breast cancer among postmenopausal women.

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with undetectable serum concentrations of estradiol would have a very low breast cancer risk that would not be further reduced by raloxifene and that women with high estradiol levels would have a high risk of breast cancer that would be substantially reduced by raloxifene. Raloxifene also reduces the risk of vertebral fractures and increases the risk of venous thromboembolism (VTE).9,11,12 and we postulated that these effects might also depend on estradiol level. We tested these hypotheses using data from the MORE trial.9,11

**METHODS**

The MORE trial, a multicenter, randomized, double-blind, placebo-controlled trial designed to test the primary hypothesis that raloxifene would reduce the risk of vertebral fracture in postmenopausal women with osteoporosis,9,12 monitored participants for the occurrence of breast cancer. We enrolled 7705 postmenopausal women with osteoporosis who were aged 80 years or younger.9 Women with a history of breast cancer were excluded. Eligible women were randomly assigned to receive 60 mg/d or 120 mg/d of raloxifene or placebo.

**Ascertainment of Breast Cancer**

All participants had mammography at baseline and annually after the first year.9 Participants who declined a mammogram could undergo breast ultrasonography instead. Diagnosis of breast cancer was confirmed by reports of histopathology and estrogen receptor status was determined from medical records. Investigators performing these assessments were blinded to treatment assignment.

**Estradiol Measurements**

To confirm that participants were postmenopausal, serum was obtained at baseline after at least a 6-hour fast and shipped the same day to the laboratory where estradiol was measured. We limited our analysis to the 7290 participants who had estradiol levels assayed by SciCor (Covance) Central Laboratory Services (Indianapolis, Ind). Estradiol concentration was determined using a double-antibody procedure. The serum sample was preincubated with antiestriadiol antisemur. Sodium iodide I 125-labeled estradiol, which competes with estradiol for binding sites, was then incubated with the sample for a fixed time. Bound and free estradiol was separated by the polyethylene glycol–accelerated double-antibody method, and the antibody-bound fraction was precipitated and counted, and the concentration of estradiol in the sample was read from a calibration curve. The intra-assay coefficient of variation is 6.5% (SD, 2.1 pmol/L [0.6 pg/mL]) at an estradiol concentration of 33 pmol/L (9.0 pg/mL).

Serum estradiol concentrations were initially reported by the laboratory as less than 5 pmol/L (1.4 pg/mL) or exact value at least 5 pmol/L. To analyze levels less than 5 pmol/L, we obtained the exact values from Covance Laboratories for the 24 cases with breast cancer whose values had been reported as less than 5 pmol/L.

From women who did not develop breast cancer, we randomly selected 222 women as a comparison group (3 times the number of cases). Of these, 112 women had estradiol levels of less than 5 pmol/L. We obtained exact estradiol levels for these women also.

**Data Analysis**

The primary outcome of the analyses was rate of breast cancer. Both dosages of raloxifene produced similar reductions in risk of breast cancer, so the 2 treatment groups were pooled.9,11 All comparisons were by intention-to-treat analyses.

The prospectively defined analysis grouped estradiol levels as 0 pmol/L (undetectable in comparison to the curve limit for the assay), more than 0 to less than 5 pmol/L, 5 to 10 pmol/L (2.7 pg/mL), and more than 10 pmol/L. The risk difference was defined as the difference between breast cancer rates in the placebo and raloxifene groups within each of the 4 groups stratified by estradiol level. Its reciprocal is the estimated number needed to treat for 4 years to prevent 1 case of breast cancer.

To estimate the absolute rates of breast cancer in all women in the trial who had very low estradiol levels, we assumed that the distributions of undetectable and low estradiol (>0 to <5 pmol/L) in the breast cancer cases and 222 participants without breast cancer were similar to the entire cohort. The 95% confidence intervals (CIs) for the estimated rates were calculated using the delta method, which accounts for uncertainty in the number of women in each group, as estimated from the sample of women with and without breast cancer.9,11 We used logistic regression models to test for an interaction between estradiol category and the effect of raloxifene on risk of breast cancer.

Vertebral fractures, VTEs, and hot flashes were assessed as previously described.9,11 We compared the rates in women assigned to placebo and raloxifene stratified by serum estradiol concentrations that were less than 5 pmol/L, 5 to 10 pmol/L, and more than 10 pmol/L (exact values <5 pmol/L were not available for these women).

**RESULTS**

A total of 7290 (95%) of the 7705 women enrolled in MORE had baseline measurement of estradiol performed by the central laboratory, of whom 2447 were assigned to placebo and 4843 to raloxifene, 60 mg/d or 120 mg/d. Mean age was 66.5 years, and 97% were white (TABLE 1). All 4 years of follow-up were completed by 1760 (72%) who were assigned to placebo and 3532 (73%) who were assigned to raloxifene. Of women who completed the trial, 5025 (95%) in both groups took at least 80% of the study medication.

During 4 years, 74 cases of breast cancer were confirmed, of which 59 were invasive; 44 were estrogen receptor–positive, and 13 were estrogen receptor–negative; receptor status was not available for 17. Among the women in this analysis, women randomized to raloxifene had a 70% (odds ratio, 0.3; 95% CI, 0.2-0.5) lower risk of invasive breast cancer and an 80% (odds ratio, 0.2; 95% CI, 0.1-0.4) lower risk of estrogen receptor–positive cancer compared with...
women randomized to placebo. These reductions are similar to the 72% reduction in invasive cancer and 84% reduction in estrogen receptor–positive cancer after 4 years in the entire trial.11

A total of 24 women with breast cancer had an estradiol level of less than 5 pmol/L. Of these, 15 had undetectable estradiol levels and 9 had estradiol levels between 0 and 5 pmol/L. Of the 222 women without breast cancer selected for comparison, 112 had levels less than 5 pmol/L. Of these, 75 had levels that were more than 0 but less than 5 pmol/L. Age, weight, and family history of breast cancer were similar in women in the sample of the cohort for whom exact estradiol values were available and in the remainder of participants (P > .30).

**Estradiol Level and Breast Cancer Rates in the Placebo Group**

The risk of breast cancer in the placebo group increased from 0.6% per 4 years (95% CI, 0%-1.1%) in women with undetectable estradiol levels to 3.0% (95% CI, 1.8%-4.1%) in those with levels of more than 10 pmol/L (P = .005 for trend; Table 2 and Figure). The risk of breast cancer in women with estradiol levels of more than 10 pmol/L was 6.8 times higher (95% CI, 2.2-21.0) than in women with undetectable estradiol. A similar association was observed between estradiol level and both invasive breast cancer and estrogen receptor–positive cancer (P = .003 for both).

**Estradiol Level and Effect of Raloxifene**

The raloxifene group had low rates of breast cancer at all levels of estradiol (Table 2 and Figure). Women with the highest serum concentrations of estradiol had the greatest reductions in absolute risk of breast cancer compared with women with similar levels in the placebo group. Among those with estradiol levels of more than 10 pmol/L who were randomized to raloxifene, breast cancer risk was reduced by 76% (95% CI, 53%-88%) but had no significant effect in those with undetectable levels (P = .02 for interaction between estradiol level and breast cancer reduction with raloxifene). This relationship remained in analyses of invasive cancer (79%; 95% CI, 55%-90%) and estrogen receptor–positive cancer (81%;

### Table 1. Characteristics of 7290 Participants in the MORE Trial With Baseline Measurements of Estradiol

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Raloxifene†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2447</td>
<td>4843</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>66.6</td>
<td>66.4</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>2356 (96.7)</td>
<td>4688 (96.6)</td>
</tr>
<tr>
<td>Mean weight, kg</td>
<td>63.9</td>
<td>64.0</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>25.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>412 (17.1)</td>
<td>831 (17.4)</td>
</tr>
<tr>
<td>Alcoholic drinks/wk, No. (%)</td>
<td>409 (16.7)</td>
<td>836 (17.3)</td>
</tr>
<tr>
<td>Family history of breast cancer, No. (%)</td>
<td>301 (12.6)</td>
<td>605 (12.8)</td>
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</tbody>
</table>

*More indicates multiple outcomes of raloxifene evaluation.
†P > .05 for all comparisons.

### Table 2. Number, Rate, and Difference in Rate of Breast Cancer Cases Between Placebo and Raloxifene Groups (n = 1290) by Baseline Concentration of Estradiol*

<table>
<thead>
<tr>
<th>Baseline Serum Estradiol Concentration, pmol/L</th>
<th>Placebo (n = 716)</th>
<th>Raloxifene (n = 1710)</th>
<th>Placebo (n = 511)</th>
<th>Raloxifene (n = 717)</th>
<th>Placebo (n = 341)</th>
<th>Raloxifene (n = 645)</th>
<th>Placebo (n = 879)</th>
<th>Raloxifene (n = 1771)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
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<tr>
<td>Cases, No. (%)</td>
<td>4 (0.6)</td>
<td>11 (0.6)</td>
<td>6 (1.2)</td>
<td>3 (0.4)</td>
<td>6 (1.8)</td>
<td>5 (0.8)</td>
<td>26 (3.0)</td>
<td>13 (0.7)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>-0.1 (-0.8 to 0.6)</td>
<td>0.8 (-0.4 to 1.9)</td>
<td>1.0 (-0.8 to 2.8)</td>
<td>2.3 (1.0 to 3.5)</td>
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<tr>
<td>RR (95% CI)§</td>
<td>1.5 (0.4 to 5.3)</td>
<td>0.3 (0.1 to 1.3)</td>
<td>0.3 (0.1 to 1.4)</td>
<td>0.2 (0.1 to 0.5)</td>
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<tr>
<td>Invasive breast cancer</td>
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<tr>
<td>Cases, No. (%)</td>
<td>2 (0.3)</td>
<td>6 (0.4)</td>
<td>6 (1.2)</td>
<td>2 (0.3)</td>
<td>6 (1.8)</td>
<td>4 (0.6)</td>
<td>23 (2.6)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>-0.1 (-0.6 to 0.4)</td>
<td>0.9 (-0.2 to 2.0)</td>
<td>1.2 (-0.6 to 2.9)</td>
<td>2.0 (0.9 to 3.2)</td>
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<tr>
<td>RR (95% CI)§</td>
<td>1.6 (0.3 to 8.5)</td>
<td>0.2 (0.03 to 1.0)</td>
<td>0.2 (0.1 to 1.1)</td>
<td>0.2 (0.1 to 0.5)</td>
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<tr>
<td>Estrogen receptor–positive breast cancer</td>
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<tr>
<td>Cases, No. (%)</td>
<td>0 (0)</td>
<td>4 (0.2)</td>
<td>6 (1.2)</td>
<td>1 (0.1)</td>
<td>5 (1.8)</td>
<td>0 (0)</td>
<td>20 (2.3)</td>
<td>8 (0.5)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>-0.2 (-0.5 to 0)</td>
<td>1.1 (0.0 to 2.1)</td>
<td>1.8 (0.0 to 3.0)</td>
<td>1.8 (0.7 to 2.9)</td>
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<tr>
<td>RR (95% CI)§</td>
<td>4.4 (0.2 to 84.3)</td>
<td>0.1 (0.01 to 0.6)</td>
<td>0.05 (0.003 to 0.9)</td>
<td>0.2 (0.1 to 0.4)</td>
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</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†Zero represents undetectable levels of estradiol.
‡Estimated number of women in the 2 lowest estradiol groups, based on proportions assessed in samples with and without breast cancer (136 women with estradiol <5 pmol/L).
§For placebo, 28 had undetectable estradiol and 20 had estradiol of 0-<5 pmol/L. For raloxifene, 62 had undetectable estradiol and 26 had estradiol of 0-<5 pmol/L.
¶Adjusted for age, bone mineral density, body mass index, and prevalent vertebral fracture.
‖Adjusted RRs are reported because parametric modeling was not possible with 0 cases in the placebo group.
¶¶Correction of 0.5 added to every cell with 0 cases to permit an estimate of RR.
95% CI, 59%-91%) and for the 60-
mg/d and 120-mg/d dosages of raloxi-
fene. The associations between estra-
diol level and risk of breast cancer as
well as the interactions between estradiol level and reduction in breast cancer risk with treatment remained sig-
ificant (P ≤0.03) after adjustment for
weight or body mass index, femoral
neck bone mineral density, and pres-
ence or absence of vertebral fractures.

The number needed to treat for 4
years to prevent 1 case of breast can-
cer varied from 45 among women with
estriol concentrations of more than
10 pmol/L to 100 and 125, respect-
ively, for women with estradiol levels
of 5 to 10 pmol/L and more than 0 to
less than 5 pmol/L. The numbers
needed to treat for invasive cancer were
48, 91, and 111, respectively.

**Estradiol Level and
Other Effects of Raloxifene**

Among the women in this analysis, ralo-
oxifene decreased risk of vertebral frac-
ture by 40%. The reduction in risk was
similar for all levels of estradiol
(TABLE 3). The increased risk of VTEs
with raloxifene (2.1; 95% CI, 1.4-3.3)
and increased occurrence of hot flashes
were also similar in estradiol groups
(Table 3).

**COMMENT**

As in previous studies, estradiol levels were strongly associated with risk of breast cancer in postmeno-
pausal women in the placebo group; the
36% of women with estradiol levels of
more than 10 pmol/L had a 3% 4-year
risk of breast cancer. Among women with
estriol levels of 10 pmol/L or
less, raloxifene reduced the risk of
breast cancer by 76%, and 45 women
needed to be treated for 4 years to avoid
1 case of breast cancer. Additionally,
62% of breast cancer cases occurred in
this group, so treating only those with
the highest estradiol would have re-
duced the overall rate of breast cancer by about 47%. In contrast, raloxifene
did not decrease the already low risk
of breast cancer in women with unde-
tectable estradiol levels. This is consis-
tent with the belief that raloxifene re-
duces breast cancer risk by blocking the
effect of estradiol on the breast. Since
tamoxifen may act by a similar mecha-
nism, the interaction between endog-
ogenous estradiol and the effect of tamoxi-
fen on breast cancer risk deserves
study.

Treatment with raloxifene reduced the
risk of vertebral fractures and in-
creased the risk of VTE and hot flashes
to a similar degree, regardless of estra-
diol level. Although women with un-
detectable levels of estradiol did not ap-
tear to benefit from a reduction in risk
of breast cancer with raloxifene, women
with undetectable estradiol levels have
an increased risk of vertebral frac-
tures, so they might derive greater
benefit from raloxifene’s reduction in
vertebral fracture risk.

This study has limitations. Women
with osteoporosis tend to have a lower
risk of breast cancer and lower levels
of estradiol than other women. Therefore, the proportion of women
with undetectable estradiol levels may
be higher and the proportion with lev-
els of more than 10 pmol/L is likely to
be lower in this cohort than in the gen-
eral population. The effect of ralo-
xifene on risk of breast cancer was a sec-
ondary aim of MORE, and raloxifene
is not approved by the US Food and
Drug Administration for labeling for
prevention of breast cancer. Our re-
sults are based on 4 years of treatment
with raloxifene. The effects of long-
term treatment with raloxifene are being
studied in a continuation of the MORE
trial. Finally, we sampled only a por-
tion of women without breast cancer to
obtain exact estradiol levels. How-
ever, this random sample’s character-
istics did not differ significantly from
the entire cohort from which it was
drawn.

Lippman et al previously reported
that women enrolled in the MORE trial
who had estradiol levels of at least 12
pmol/L and those with levels less than

<table>
<thead>
<tr>
<th>Baseline Serum Estradiol Concentration, pmol/L</th>
<th>Placebo (n = 1227)</th>
<th>Raloxifene (n = 2427)</th>
<th>Placebo (n = 341)</th>
<th>Raloxifene (n = 645)</th>
<th>Placebo (n = 879)</th>
<th>Raloxifene (n = 1771)</th>
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<tbody>
<tr>
<td>Venous thromboembolism</td>
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<tr>
<td>Cases, No. (%)</td>
<td>13 (1.1)</td>
<td>41 (1.7)</td>
<td>1 (0.3)</td>
<td>10 (1.6)</td>
<td>10 (1.1)</td>
<td>39 (2.2)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>−0.6 (−1.1 to 0.2)</td>
<td>−1.3 (−2.6 to 0.1)</td>
<td>−1.1 (−2.1 to −0.0002)</td>
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<tr>
<td>RR (95% CI)</td>
<td>1.6 (0.9 to 3.0)</td>
<td>5.4 (0.9 to 33.7)</td>
<td>2.0 (1.0 to 3.9)</td>
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<tr>
<td>New vertebral fracture</td>
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<tr>
<td>Cases, No. (%)</td>
<td>137 (12.7)</td>
<td>187 (8.6)</td>
<td>32 (10.7)</td>
<td>37 (6.5)</td>
<td>102 (13.0)</td>
<td>109 (7.1)</td>
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<tr>
<td>Risk difference (95% CI)</td>
<td>4.1 (1.7 to 6.4)</td>
<td>4.2 (−0.1 to 8.5)</td>
<td>5.9 (3.1 to 8.6)</td>
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<tr>
<td>RR (95% CI)</td>
<td>0.7 (0.5 to 0.8)</td>
<td>0.6 (0.4 to 1.0)</td>
<td>0.5 (0.4 to 0.7)</td>
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<tr>
<td>Hot flashes</td>
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<tr>
<td>Cases, No. (%)</td>
<td>71 (5.8)</td>
<td>264 (10.9)</td>
<td>28 (8.2)</td>
<td>78 (12.1)</td>
<td>74 (8.4)</td>
<td>214 (12.1)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>−5.1 (−7.5 to −2.8)</td>
<td>−3.9 (−8.0 to 0.2)</td>
<td>−3.7 (−6.1 to −1.2)</td>
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<tr>
<td>RR (95% CI)</td>
<td>2.0 (1.5 to 2.6)</td>
<td>1.5 (1.0 to 2.4)</td>
<td>1.5 (1.1 to 2.0)</td>
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</table>

*RR indicates relative risk; CI, confidence interval.

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12 pmol/L had similar and significant reductions in risk of breast cancer (79% and 64%, respectively) during treatment with raloxifene. However, that study did not analyze the full range of estradiol values, did not have exact values of estradiol below 5 pmol/L, and included women with estradiol measurements by local laboratories.

Risk factors for breast cancer other than estradiol might be useful predictors of response to raloxifene. Only some of the risk factors used in the model of Gail et al. found that serum concentrations of estradiol in postmenopausal women remain relatively stable (r = 0.7) over 2 or 3 years. Estradiol levels below 5 pmol/L have been considered unreliable because the coefficient of variation (SD divided by mean value) is large when the mean value is low (<5 pmol/L). Our results suggest that differentiating undetectable values from extremely low values may have clinical utility despite this variability. Variability tends to dilute associations, so the true relationship between endogenous estradiol level and the effects of raloxifene may be stronger than we observed in this study.

Sensitive estradiol assays of the type used in this study are not yet widely available for clinical use. If sensitive measurements of estradiol are used to make treatment decisions regarding breast cancer risk, it will be important to standardize the methods and reporting of results.

We conclude that in the MORE trial, measurement of estradiol concentration in older postmenopausal women identified those at high risk of breast cancer who benefited most from reduction in risk of breast cancer with raloxifene treatment. If confirmed by other studies, measuring estradiol to determine breast cancer risk may help identify women likely to experience the greatest reduction in breast cancer risk from treatment with raloxifene.

**Author Contributions:** Dr Cummings, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

**Study concept and design:** Cummings, Acquisition of data: Cummings, Kenyon, Krueger.

**Analysis and interpretation of data:** Cummings, Duong, Cauley, Whitehead, Krueger.

**Drafting of the manuscript:** Cummings, Whitehead.

**Critical revision of the manuscript for important intellectual content:** Cummings, Duong, Kenyon, Cauley, Whitehead, Krueger.

**Statistical expertise:** Duong.

**Obtained funding:** Cummings.

**Administrative, technical, or material support:** Kenyon, Whitehead.

**Study supervision:** Cummings, Kenyon.

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**REFERENCES**


