

Continuing Outcomes Relevant to Evista: Breast Cancer Incidence in Postmenopausal Osteoporotic Women in a Randomized Trial of Raloxifene

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For the CORE Investigators

Background: The randomized, double-blind Multiple Outcomes of Raloxifene Evaluation (MORE) trial found that 4 years of raloxifene therapy decreased the incidence of invasive breast cancer among postmenopausal women with osteoporosis by 72% compared with placebo. We conducted the Continuing Outcomes Relevant to Evista (CORE) trial to examine the effect of 4 additional years of raloxifene therapy on the incidence of invasive breast cancer in women in MORE who agreed to continue in CORE. **Methods:** Women who had been randomly assigned to receive raloxifene (either 60 or 120 mg/day) in MORE were assigned to receive raloxifene (60 mg/day) in CORE (n = 3510), and women who had been assigned to receive placebo in MORE continued on placebo in CORE (n = 1703). Breast cancer incidence was analyzed by a log-rank test, and a Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. **Results:** During the CORE trial, the 4-year incidences of invasive breast cancer and estrogen receptor (ER)-positive invasive breast cancer were reduced by 59% (HR = 0.41; 95% CI = 0.24 to 0.71) and 66% (HR = 0.34; 95% CI = 0.18 to 0.66), respectively, in the raloxifene group compared with the placebo group. There was no difference between the two groups in incidence of ER-negative invasive breast cancer during CORE (P = .86). Over the 8 years of both trials, the incidences of invasive breast cancer and ER-positive invasive breast cancer were reduced by 66% (HR = 0.34; 95% CI = 0.22 to 0.50) and 76% (HR = 0.24; 95% CI = 0.15 to 0.40), respectively, in the raloxifene group compared with the placebo group. During the CORE trial, the relative risk of thromboembolism in the raloxifene group compared with that in the placebo group was 2.17 (95% CI = 0.83 to 5.70). This increased risk, also observed in the MORE trial, persisted over the 8 years of both trials. **Conclusions:** The reduction in invasive breast cancer incidence continues beyond 4 years of raloxifene treatment in postmenopausal women with osteoporosis. No new safety concerns related to raloxifene therapy were identified during CORE. [J Natl Cancer Inst 2004;96:1751-61]

Selective estrogen receptor modulators (SERMs) are a group of nonsteroidal compounds that are chemically distinct from estradiol and act as estrogen agonists in some tissues, such as bone, and as estrogen antagonists in other tissues, such as breast, through specific, high-affinity binding to the estrogen receptor (ER). Because of their estrogen antagonist effects in the breast, SERMs have been and continue to be studied for their effects on breast cancer risk reduction. Tamoxifen, a triphenylethylene

SERM approved for the treatment of breast cancer, is the only agent approved in the United States to reduce the incidence of breast cancer in women at high risk for the disease (1).

Raloxifene (Evista) is a benzothiophene SERM that is chemically distinct from tamoxifen. Raloxifene increases bone mineral density in postmenopausal women (2), reduces the risk of vertebral fracture in postmenopausal women with osteoporosis (3), and is approved in the United States and several other countries for the prevention and treatment of postmenopausal osteoporosis (4). Results of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, in which the incidence of breast cancer was a predefined secondary outcome provided the first evidence of possible breast cancer risk reduction effects of raloxifene therapy. In that trial, the incidence of invasive breast cancer was reduced by 76% after 3 years (5) and by 72% after 4 years (6) among women treated with raloxifene compared with women treated with placebo.

The Continuing Outcomes Relevant to Evista (CORE) trial was designed to evaluate the efficacy of an additional 4 years of raloxifene therapy in preventing invasive breast cancer in women who participated in the MORE trial. Here we report the incidences of invasive breast cancer during the 4 years of the CORE trial and during the 8 years of the MORE and CORE trials.

METHODS

Study Design

CORE was a multicenter, double-blind, placebo-controlled clinical trial. The primary objective of the CORE trial was to investigate the effect of 4 additional years of raloxifene (at 60 mg/day) on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. The CORE trial was conducted in the subset of the MORE cohort that agreed to participate in

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what was an extension of the MORE trial, with a change in the primary endpoint from vertebral fracture incidence to invasive breast cancer incidence effective January 1, 1999. A secondary objective of the CORE trial was to examine the effect of raloxifene (at 60 mg/day) on the incidence of invasive ER-positive breast cancer. As specified in the CORE protocol, the observation period for the breast cancer-related objectives began on January 1, 1999, during the fourth year of the MORE trial, and continued through the additional 4 years of the CORE trial. January 1, 1999, was chosen as the start date because data collected before this date had been unblinded for the 3-year MORE analysis. The CORE trial consisted of five visits. During visit 1, the baseline visit, which took place 4.5–5 years after random assignment to a MORE treatment group, the women signed the informed consent document, received a clinical breast exam, and had a mammogram unless one had already been performed within the preceding 12 months. Visits 2, 3, 4, and 5 occurred during the double-blind treatment period and were scheduled annually, approximately at the anniversary date of their random assignment in the MORE trial. Mammograms were scheduled for visit 3 and visit 5.

Subjects

Of the 180 investigative sites that participated in the MORE trial, 130 sites in 24 countries agreed to participate in the CORE trial. All MORE trial participants at these 130 sites who were randomly assigned to receive raloxifene or placebo ($N = 6511$) were eligible for the CORE trial; the 4011 participants who chose to enroll in the CORE trial will subsequently be referred to as CORE enrollees (Fig. 1). Of the 2500 MORE trial participants who chose not to enroll in the CORE trial, 1217 women were still participating in the MORE trial as of January 1, 1999. Those 1217 women contributed data for the CORE primary breast cancer analysis from January 1, 1999, until their completion of the MORE trial. The remaining 1283 women had completed their participation in the MORE trial before January 1, 1999, and thus did not contribute data for any of the CORE trial analyses. Fifteen CORE enrollees were diagnosed with breast cancer before January 1, 1999, and were excluded from the CORE breast cancer and sensitivity analyses but were included in the safety analyses. Thus, the CORE primary breast cancer analysis dataset included 1217 women who were still participating in the MORE trial as of the January 1, 1999, start date for CORE, and 3996 CORE enrollees who had not been diagnosed with breast cancer as of January 1, 1999, for a total of 5213 women ($n = 3510$ on raloxifene and $n = 1703$ on placebo). Figure 1 shows the flow of participants from the MORE trial into the CORE trial.

The eligibility criteria for enrollment in the MORE trial have been described in detail (3,5). In brief, women were eligible for the MORE trial if they were 80 years old or younger, had osteoporosis, and were at least 2 years beyond menopause. Osteoporosis was defined as a lumbar spine or femoral neck bone mineral density T-score equal to or less than 2.5 according to the densitometer manufacturer's reference database or as the presence of a vertebral fracture on a radiograph.

MORE participants were encouraged to continue in the CORE trial even if they chose not to continue taking study medication. In addition, according to the CORE protocol, MORE participants were allowed to participate in the CORE

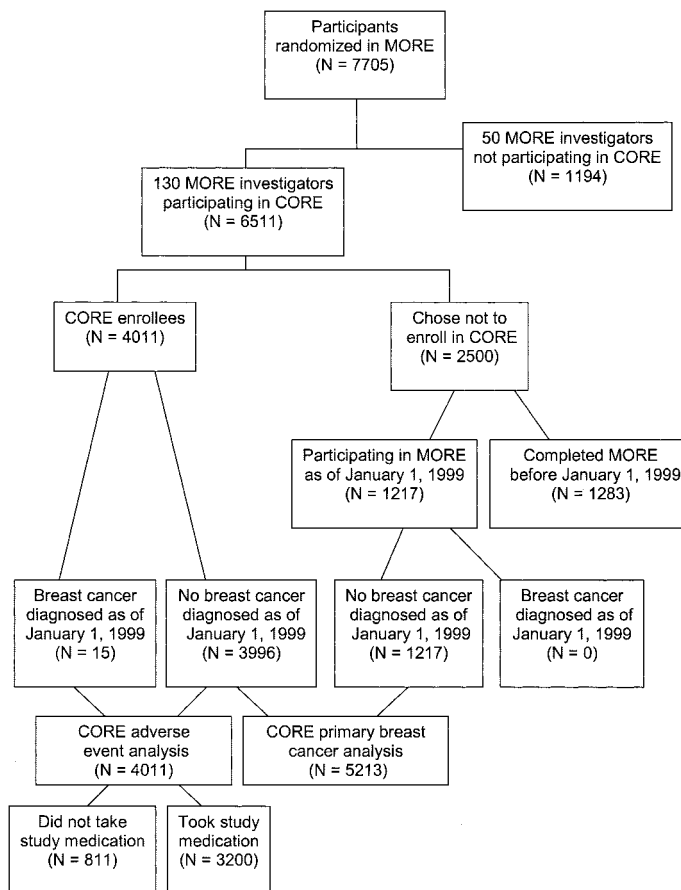


Fig. 1. Flow of participants from the MORE trial into the CORE trial.

trial but were not allowed to take study medication if they had a diagnosis of any malignancy considered to be estrogen dependent (including malignancies of the breast or uterus); had a history of venous thromboembolism; were undergoing treatment with cholestyramine, prescribed raloxifene, tamoxifen, systemic hormone therapy, or other reproductive-hormone products during the CORE trial; had such severe postmenopausal symptoms at visit 1 of CORE that estrogen therapy was required; or had a safety concern during the MORE trial that necessitated unblinding of their treatment assignment. Of the CORE enrollees, 811 women (20%) did not take study medication, either because they met one of the criteria listed above ($n = 435$) or because they chose not to ($n = 376$). For the 3200 women who resumed taking study medication during the CORE trial, compliance was assessed at each visit by dividing the difference between the number of tablets dispensed and the number of tablets remaining at each visit by the number of days on study. The participant was considered to be compliant if this calculation produced a value of 80% or greater as specified in the CORE protocol, on the basis of the observation that more than 90% of both raloxifene and placebo participants took at least 80% of the study medication during the first 3 years of the MORE trial (5).

Women who participated in the CORE trial had been eligible to enroll in the MORE trial because they had osteoporosis. Therefore, during the CORE trial, participants were allowed to take specific bone-active agents, including bisphosphonates, calcitonin, or fluoride, and all participants received daily supplements of calcium (500 mg) and vitamin D (400–600 IU). At

each CORE visit, participants were asked specifically if they had taken any hormones or SERMs.

The ethical review board for each investigative site approved the CORE trial protocol. All women provided written informed consent for participation in the CORE trial, in accordance with principles outlined in the Declaration of Helsinki. Women who participated in the MORE trial but chose not to participate in the CORE trial had previously provided written informed consent for their participation in MORE and contributed data for the CORE analyses only for the time of their participation in MORE.

Randomization and Treatment

CORE enrollees ($n = 4011$) were not rerandomized; instead, the randomization assignment from the MORE trial was carried forward to the CORE trial. All CORE enrollees and investigators remained blinded to treatment assignment from the beginning of the MORE trial to the end of the CORE trial. Whereas the MORE trial compared three treatment groups (raloxifene at 60 mg/day, raloxifene at 120 mg/day, and placebo), the CORE trial compared only raloxifene at 60 mg/day (Evista; Eli Lilly and Company, Indianapolis, IN) with placebo (tablets identical in appearance to raloxifene; Eli Lilly and Company). The study sponsor was Eli Lilly and Company, hereafter referred to as the study sponsor. The CORE trial protocol was designed by the study sponsor in consultation with the coordinating center at the University of California, San Francisco. The statistical analysis plan was written and executed by the study sponsor. We chose raloxifene at 60 mg/day as the only active treatment in the CORE trial because it is the dose that is approved for the prevention and treatment of osteoporosis (4) and because the 60 mg/day and the 120 mg/day dosage groups in the MORE trial had similar reductions in incidence of breast cancer (5,6). CORE enrollees continued in their original randomized treatment groups that were established in the MORE trial, i.e., those who were randomly assigned to receive raloxifene at either 60 mg/day or 120 mg/day in the MORE trial were assigned to receive raloxifene at 60 mg/day in the CORE trial and those who were randomly assigned to receive placebo in the MORE trial continued on placebo in the CORE trial. As a result, for the CORE enrollees, approximately twice as many women were assigned to the raloxifene group ($n = 2725$) as to the placebo group ($n = 1286$).

Breast Cancer Ascertainment

At visit 1 of CORE, CORE enrollees provided information about the risk factors that are included in the Gail breast cancer risk assessment model; we used that information to calculate their 5-year predicted risk of breast cancer as previously described (7). These factors included current age, age at menarche, age at first live birth, the number of breast biopsies, the presence of atypical hyperplasia in a biopsy sample, the number of first-degree relatives diagnosed with breast cancer, and race (white or black). All CORE enrollees were required to have had a bilateral mammogram within the year before they entered the CORE trial or at entry into the CORE trial and at 2 and 4 years after entry into the CORE trial. At each yearly visit, each woman was given a clinical breast exam and asked if she had received a diagnosis of breast cancer or had had a breast biopsy or breast surgery. We obtained the medical records of any woman with a known or

suspected diagnosis of breast cancer. According to the study protocol, study medications were stopped for these women, and the medical records were sent for adjudication by an independent review board that consisted of a radiologist (Valerie Jackson, MD, Indiana University, Indianapolis, IN), a surgical oncologist (S. Chace Lottich, MD, Center for Women's Health, Indianapolis, IN), and a medical oncologist (Kathy Miller, MD, Indiana University, Indianapolis, IN), none of whom were employed by the study sponsor. The board reviewed all available clinical data, including mammography films and reports, surgical records, and histopathology reports, and either rejected or confirmed the diagnosis of breast cancer, including its invasiveness and ER status, without knowledge of the woman's treatment assignment.

Determination of Adverse Events

Adverse events for 8 years could be collected only for the CORE enrollees ($n = 4011$). At each annual visit, CORE enrollees were given a questionnaire that asked whether they had experienced vaginal bleeding, endometrial hyperplasia, endometrial cancer, deep vein thrombosis, pulmonary embolism, or retinal vein thrombosis. They were also questioned about any other adverse events they had experienced and about their use of medications. The determination of whether an adverse event met the definition of a serious adverse event was made by the investigator. A serious adverse event was defined as death, a life-threatening experience, hospitalization, severe or permanent disability, cancer, or any other clinically significant event. According to the CORE protocol, we recorded adverse events that occurred among the CORE enrollees starting at visit 1 of CORE and ending at visit 5. We report adverse events that occurred among the CORE enrollees from visit 1 of CORE through visit 5, a total of 4 years, and from the time of randomization in MORE to the end of CORE, a total of 8 years.

Statistical Analyses

By using a log-rank test as the primary statistical analysis and by assuming an annual event rate for the placebo group of 0.334% based on MORE trial data and a relative risk of 0.34 for the raloxifene group versus the placebo group, this study had a 91% power to detect a statistically significant difference in the incidence of invasive breast cancer between the two groups for a sample size of 4000 women. Data were analyzed by the study sponsor according to a prospectively written statistical analysis plan. Analyses were performed using the intent-to-treat approach, with all participants allocated to assigned treatment regardless of whether she took study medication or other post-baseline factors. Unless otherwise stated, all hypotheses were tested at the 0.05 (two-sided) level of statistical significance. Baseline characteristics were compared by using a Student's *t* test for continuous data and a chi-square test for categorical parameters.

We used data from the primary breast cancer analysis dataset ($N = 5213$) for the primary CORE analysis, which compared the incidence of invasive breast cancer in women assigned to raloxifene ($n = 3510$) with that in women assigned to placebo ($n = 1703$). The incidence of the first invasive breast cancer was measured from January 1, 1999, and the statistical significance of the difference in incidence between treatment groups was assessed by using a log-rank test. We used a Cox proportional

hazards model to assess treatment effect and to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was found to be valid for these data when tested by addition of a time varying covariate to the model. Time from January 1, 1999, to the end of participation in CORE was calculated and used to compute the absolute incidence rate per 1000 woman-years. We used the same survival analysis approach to analyze the secondary endpoint, the incidence of ER-positive invasive breast cancer, and to examine the sensitivity of the results to the specified population. As prespecified by the statistical analysis plan, sensitivity analyses examined the incidence of invasive breast cancer for the 3996 CORE enrollees who did not have a breast cancer diagnosis as of the start of CORE trial and for the 3200 CORE enrollees who took study medication.

As part of the secondary analysis, we also examined the incidence of invasive breast cancer in the 7705 women who were enrolled in the MORE trial (hereafter referred to as MORE participants) from their randomization in the MORE trial until the end of their participation in the CORE trial or, for those who chose not to enroll in CORE, until the end of their participation in the MORE trial. Kaplan–Meier curves were generated for each treatment group to show the cumulative incidence of invasive breast cancer from MORE randomization to the end of CORE, and a log-rank test was used to determine the statistical significance of the difference in the survival curves for the two treatment groups. Treatment effects were assessed by hazard ratios and 95% CIs computed using the Cox proportional hazards model, and the absolute incidence rate per 1000 woman-years was computed based on the time from randomization in MORE to end of participation in CORE.

Adverse events that either first occurred or worsened in severity after enrollment in CORE were analyzed for the CORE enrollees from CORE visit 1 to CORE visit 5 (4 years total) and from randomization in MORE until the end of CORE (8 years total). All adverse events were reported to the sponsor without regard to possible causality or relationship to study drug. However, in this article, we report only the incidence of the specifically solicited adverse events (i.e., vaginal bleeding, endometrial hyperplasia, endometrial cancer, deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis) as well as the incidence of other adverse events with potential relevance to raloxifene or to SERMs in general (i.e., flushing or hot flushes,

leg cramps, and peripheral edema). We used Fisher's exact test to determine the statistical significance of differences in the incidence of adverse events reported for the two treatment groups.

One planned interim analysis was performed after all CORE enrollees had their mammogram and follow-up at 2 years after entry into CORE (visit 3). Because the results of that analysis revealed that the incidence of invasive breast cancer was not statistically significantly different between the treatment groups at the prespecified statistical significance level of .001, the data monitoring board recommended that the study continue as planned. For the final analysis, we tested the primary endpoint at the .0495 level of statistical significance to maintain an overall statistical significance level of .05 for the study.

RESULTS

Demographics, Baseline Characteristics, and Study Accrual

The women who comprised the CORE breast cancer primary analysis dataset and the CORE enrollees were subsets of the MORE cohort and, as expected, were similar to each other and to the MORE participants with respect to the MORE baseline characteristics shown in Table 1. In addition, there was no difference ($P > .05$) in any of the baseline characteristics shown in Table 1 between the placebo and raloxifene groups in any of the three populations (data not shown). For the CORE enrollees, there was no difference ($P = .10$) in mean weight change between treatment groups from visit 1 through visit 5 of the CORE trial or for the 8-year period of the MORE and CORE trials combined (data not shown).

The beginning of the CORE trial did not coincide exactly with the end of the MORE trial. The median time between the end of participation in the MORE trial and enrollment in the CORE trial was 10.6 months (range = 2.6 to 62 months) for both treatment groups. For approximately 95% of women assigned to raloxifene and 94% of women assigned to placebo, the interval between end of the MORE trial and their enrollment in the CORE trial was less than 2 years. The median time from randomization in MORE to end of participation in CORE was 7.9 years for each treatment group (range = 4.6 to 8.5 years). For the CORE enrollees, 17.7% of those assigned to placebo and

Table 1. Baseline characteristics at the beginning of MORE for all MORE participants, the CORE breast cancer primary analysis dataset, and CORE enrollees*

Characteristic	MORE participants (N = 7705)	CORE breast cancer primary analysis dataset (N = 5213)	CORE enrollees (N = 4011)
Mean age, y (SD)	66.5 (7.1)	66.2 (6.9)	65.8 (6.8)
Age \geq 60 y, No. (%)	6283 (81.5)	4233 (81.2)	3213 (80.1)
Mean height, cm (SD)	159 (6.6)	159 (6.6)	159 (6.6)
Mean weight, kg (SD)	63.8 (10.6)	63.9 (10.2)	63.8 (10.0)
Mean BMI, kg/m ² (SD)	25.2 (4.0)	25.3 (3.9)	25.2 (3.9)
White, No. (%)	7372 (95.7)	4979 (95.5)	3857 (96.2)
Current smoker, No. (%)	1274 (16.7)	832 (16.2)	634 (16.0)
Consumes \geq 4 alcoholic drinks/wk, No. (%)	1342 (17.4)	887 (17.0)	659 (16.4)
Mean time (y) since menopause, (SD)	18.7 (8.4)	18.4 (8.2)	17.9 (8.0)
Had family history of breast cancer, No. (%)	949 (12.6)	611 (12.0)	466 (11.9)
Had hysterectomy, No. (%)	1748 (22.7)	1113 (21.4)	818 (20.4)
Previous hormone therapy use, No. (%)	2235 (29.1)	1379 (26.5)	1024 (25.6)

*The CORE breast cancer primary analysis dataset and those enrolling in CORE are subsets of the MORE population and therefore cannot be statistically compared with the MORE participants. SD = standard deviation; BMI = body mass index.

18.4% of those assigned to raloxifene reported that they had taken a hormone or a SERM during the interval between their completion of the MORE trial and their enrollment in the CORE trial ($P = .63$).

Women could continue in the CORE trial even if they experienced an adverse event while in the MORE trial and, as a result of having had the adverse event, were no longer allowed to take study medication or chose not to take study medication in the CORE trial. Of the 4011 CORE enrollees, 80% (or 3200 women) resumed taking study medication; approximately 69% of those women were considered to be compliant (i.e., they took at least 80% of their study medication). There was no difference between the placebo and raloxifene treatment groups in the number of CORE enrollees who were compliant ($P > .05$).

At CORE baseline (visit 1), 99.3% of the CORE enrollees underwent mammography (Fig. 2). At visits 3 and 5 (which occurred at 6 and 8 years, respectively, after randomization in MORE), 98.1% and 98.3%, respectively, of those continuing in the CORE trial had a mammogram performed. Overall, 85.8% of the CORE enrollees (85.7% of those in the raloxifene group and 86.0% of those in the placebo group) completed the study. The most common reason given for study discontinuation was personal decision, which was cited by 7.9% of those in the raloxifene group and 6.4% those in the placebo group ($P > .05$).

Among the CORE enrollees, there was no difference in the mean (\pm standard deviation) 5-year predicted risk of breast cancer, as determined by the Gail model (7), between those in the raloxifene group and those in the placebo group ($1.94\% \pm$

1.0% versus $1.94\% \pm 0.9\%$; $P = .903$). Among the CORE enrollees, 52.9% of those in the placebo group versus 54.4% of those in the raloxifene group ($P = .37$) were considered at high risk for invasive breast cancer because their 5-year predicted risk of breast cancer was 1.67% or greater.

Breast Cancer Incidence During the CORE Trial

During the 4 years of the CORE trial, 61 cases of breast cancer (30 in the placebo group and 31 in the raloxifene group) were reported and confirmed by adjudication. Fourteen of these cases, eight in the placebo group and six in the raloxifene group, were previously reported by Cauley et al. (6). Of the 61 breast cancer cases, 52 cases (28 in the placebo group and 24 in the raloxifene group) were classified as invasive breast cancer (Table 2). Women in the raloxifene group had a 59% reduction in the incidence of invasive breast cancer compared with women in the placebo group (2.1 versus 5.2 cases per 1000 woman-years; HR = 0.41, 95% CI = 0.24 to 0.71). The ER status was determined for 46 of the 52 cases of invasive breast cancer; 36 cases (78%) were ER positive. Women in the raloxifene group had a 66% reduction in the incidence of invasive ER-positive breast cancers compared with women in the placebo group (1.3 versus 3.9 cases per 1000 woman-years; HR = 0.34, 95% CI = 0.18 to 0.66) (Table 2). By contrast, the incidence of invasive ER-negative breast cancer in women who received raloxifene was not statistically significantly different from that in women who received placebo (HR = 1.13, 95% CI = 0.29 to 4.35; $P = .86$) (Table 2). We were unable to classify the ER status for six cases (two cases in the raloxifene group and four cases in the placebo group) because of insufficient data. Nine noninvasive breast cancers were reported, seven in the raloxifene group and two in the placebo group (HR = 1.78, 95% CI = 0.37 to 8.61; $P = .47$) (Table 2). The overall incidence of breast cancer, regardless of invasiveness, was reduced by 50% in the raloxifene group compared with the placebo group (2.7 versus 5.5 cases per 1000 woman-years; HR = 0.50, 95% CI = 0.30 to 0.82) (Table 2).

Breast Cancer Incidence for 8 Years From Randomization in MORE to the End of CORE

For the 7705 MORE participants, the total number of reported breast cancers confirmed by adjudication from randomization in MORE to the end of their participation in either MORE or CORE was 121 (56 cancers in the raloxifene group and 65 cancers in the placebo group). During these 8 years, 40 invasive breast cancers were reported in the raloxifene group (1.4 cases per 1000 woman-years) and 58 invasive breast cancers were reported in the placebo group (4.2 cases per 1000 woman-years); thus, the raloxifene group had a 66% reduction in the incidence of invasive breast cancer compared with the placebo group (HR = 0.34, 95% CI = 0.22 to 0.50) (Fig. 3). ER status was determined for 88 cases, and 75% of these were ER positive. During these 8 years, the raloxifene group had a 76% reduction in the incidence of invasive ER-positive breast cancer compared with the placebo group (0.8 versus 3.2 cases per 1000 woman-years; HR = 0.24; 95% CI = 0.15 to 0.40) (Fig. 4). There was no difference in the incidence rates of invasive ER-negative breast cancer between the raloxifene group and the placebo group (0.53 versus 0.51 per 1000 woman-years; HR = 1.06; 95% CI = 0.43 to 2.59; $P = .90$) (Fig. 4). Insufficient data

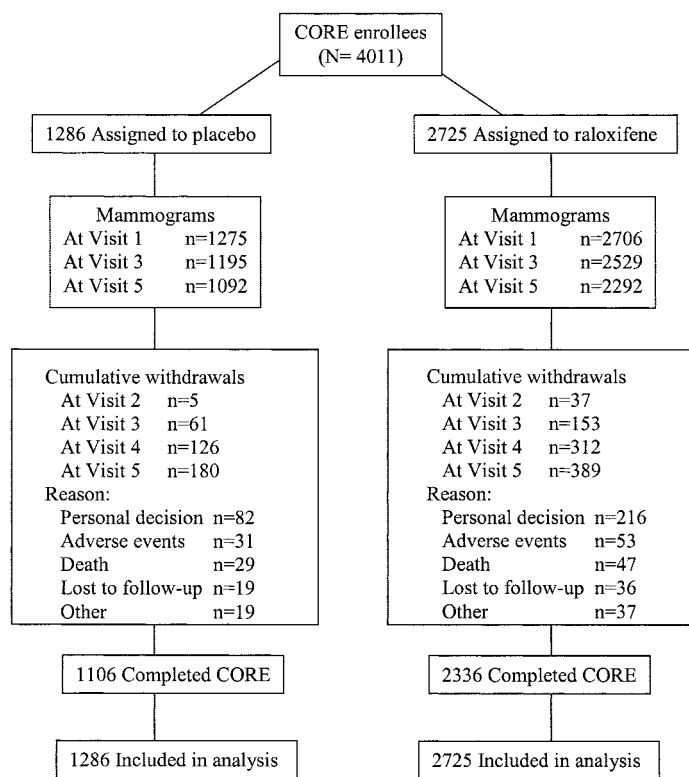


Fig. 2. Follow-up of CORE trial enrollees. Visit 1 was scheduled at time of enrollment in the CORE trial and generally occurred 4.5–5 years after randomization in the MORE trial. Visits 2, 3, 4, and 5 occurred approximately 5, 6, 7, and 8 years, respectively, after randomization in the MORE trial. The category “other” under “Reasons for withdrawal” included participant having moved, protocol entry criteria not having been met, and protocol variance.

Table 2. Incidence of breast cancer by treatment group and ER status for the primary CORE breast cancer analysis dataset*

Breast cancer type	Placebo group (N = 1703) 5435 woman-years		Raloxifene group† (N = 3510) 11 438 woman-years		HR§ (95% CI)	P
	% (No.)	Rate‡	% (No.)	Rate‡		
Invasive breast cancer	1.6 (28)	5.2	0.7 (24)	2.1	0.41 (0.24 to 0.71)	<.001
ER-positive	1.2 (21)	3.9	0.4 (15)	1.3	0.34 (0.18 to 0.66)	<.001
ER-negative	0.18 (3)	0.55	0.20 (7)	0.61	1.13 (0.29 to 4.35)	.86
ER status unknown	0.23 (4)	0.74	0.06 (2)	0.17	0.24 (0.04 to 1.30)	.071
Noninvasive breast cancer	0.1 (2)	0.37	0.2 (7)	0.61	1.78 (0.37 to 8.61)	.47
All breast cancer¶	1.8 (30)	5.5	0.9 (31)	2.7	0.50 (0.30 to 0.82)	.005

*CORE = Continuing Outcomes Relevant to Evista; CI = confidence interval; ER = estrogen.

†Dose of 60 mg of raloxifene per day.

‡Number of cases per 1000 woman-years.

§Based on Cox proportional hazards model.

||Assessed by the log-rank test (two-sided).

¶Includes invasive and noninvasive breast cancer.

were available to classify the ER status of 10 cases, three of which occurred in the raloxifene group. There was no statistically significant difference in the incidence of noninvasive breast cancers reported in the two treatment groups (16 cases for the raloxifene group versus 7 cases for the placebo group; HR = 1.12, 95% CI = 0.46 to 2.73; $P = .80$). During the 8 years of the MORE and CORE trials, the overall incidence of breast cancer, regardless of invasiveness, was reduced by 58% in the raloxifene group compared with the placebo group (HR = 0.42, 95% CI = 0.29 to 0.60; $P < .001$).

Breast Cancer Sensitivity Analyses

Fifteen of the CORE enrollees were diagnosed with breast cancer before January 1, 1999, the start date for CORE data

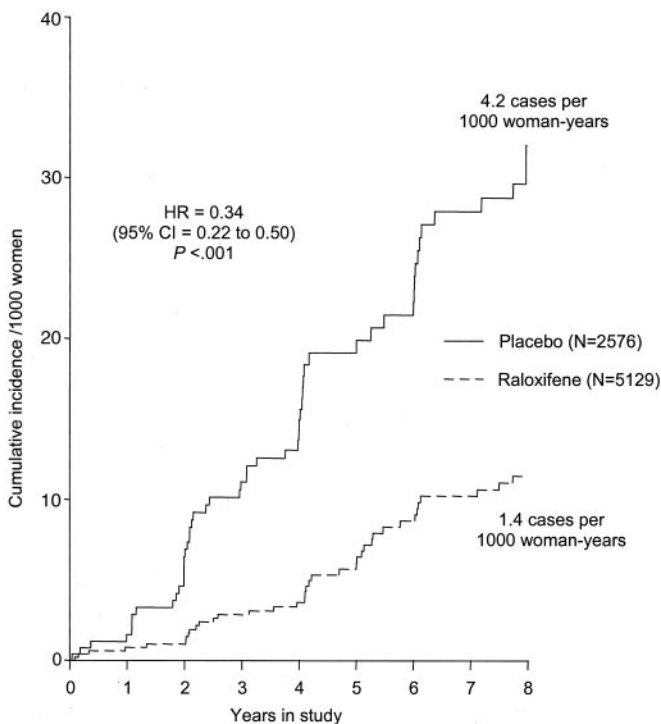


Fig. 3. Cumulative incidence of adjudicated invasive breast cancers per 1000 women over the 8 years from randomization in the MORE trial to the end of the CORE trial for the 7705 MORE participants. Statistical significance of the difference between treatment groups was assessed by a two-sided log-rank test.

collection, and therefore were not included in the sensitivity analysis. Among the 3996 CORE enrollees who did not have a breast cancer diagnosis at the start of CORE, those in the raloxifene group had a 58% reduction in the incidence of invasive breast cancer compared with those in the placebo group (1.9 versus 4.6 cases per 1000 woman-years; HR = 0.42, 95% CI = 0.23 to 0.75). Among the 3200 CORE enrollees who resumed taking study medication upon enrollment in the CORE trial, those in the raloxifene group had a 64% reduction in the incidence of invasive breast cancer compared with those in the placebo group (HR = 0.36; 95% CI = 0.17 to 0.74).

Adverse Events

During the 4 years of the CORE trial, 80% of the CORE enrollees reported an adverse event (79.9% of women in the

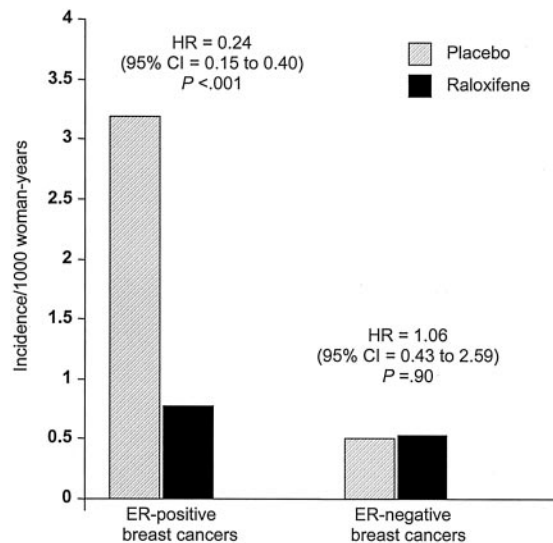


Fig. 4. Annual incidence rate per 1000 woman-years of follow-up for adjudicated invasive breast cancers over the 8 years from the time of randomization in the MORE trial to the end of the CORE trial for the 7705 MORE participants. The numbers of ER-positive invasive breast cancers in the placebo and raloxifene groups were 44 and 22, respectively; the numbers of ER-negative invasive breast cancers in the placebo and raloxifene groups were 7 and 15, respectively. Hazard ratios and 95% CIs for the raloxifene group relative to placebo are shown for ER-positive and ER-negative invasive breast cancers. Statistical significance of the difference between treatment groups was assessed by two-sided log-rank tests.

Table 3. Overview of adverse events reported during the CORE trial*

Adverse event†	CORE enrollees, % (No.)		P‡
	Placebo (N = 1286)	Raloxifene‡ (N = 2725)	
Deaths	2.3 (29)	1.7 (47)	.27
Serious adverse events	24.7 (317)	22.8 (622)	.22
All adverse events	80.0 (1029)	79.9 (2178)	.97
Discontinuations from the CORE trial due to an adverse event	2.4 (31)	1.9 (53)	.35

*Visit 1 in the CORE trial occurred approximately 4.5–5 years after women were randomly assigned to treatment groups in the MORE trial. CORE = Continuing Outcomes Relevant to Evista; MORE = Multiple Outcomes of Raloxifene Evaluation.

†Women may be counted in more than one category.

‡Dose of 60 mg of raloxifene per day.

§Based on Fisher's exact test (two-sided).

||Defined as an adverse event associated with death, a life-threatening experience, hospitalization, severe or permanent disability, cancer, or any other clinically significant event.

¶Adverse events that first occurred or worsened in severity after enrollment in CORE.

raloxifene group versus 80.0% of women in the placebo group, $P = .97$; Table 3). There were no statistically significant differences between the raloxifene group and the placebo group in the percentage of women who stopped taking study medication because of an adverse event (1.9% versus 2.4%; $P = .35$). There were no statistically significant differences between treatment groups in the percentage of women reporting a serious adverse event (24.7% for placebo versus 22.8% for raloxifene; $P = .22$) or in the number of deaths reported (29 deaths in the placebo group versus 47 deaths in the raloxifene group; $P = .27$) (Table 3). No deaths due to breast cancer were reported during the CORE trial. During the 8 years of the MORE and CORE trials, one death due to breast cancer was reported during the MORE trial in a woman assigned to the raloxifene group (6).

The reported incidences of vaginal bleeding, endometrial hyperplasia, and endometrial cancer were not statistically significantly different for the two treatment groups during the 4 years of the CORE trial or during the 8 years of the MORE and CORE trials ($P > .2$ for each event; Table 4). During the 4 years of the CORE trial, the incidences of hot flushes, leg cramps, and peripheral edema, adverse events that are known to be associated with raloxifene therapy, were not statistically significantly different between treatment groups ($P > .5$ for each event; Table 4). For the 8 years from randomization in the MORE trial to the end of the CORE trial, hot flushes and leg cramps, but not peripheral edema, were reported more often by women in the raloxifene group than by women in the placebo group ($P < .001$, $P = .008$, and $P = .24$, respectively; Table 4). During the 4 years of the CORE trial and during the 8 years of the MORE and CORE trials, there were no statistically significant differences in the incidence of ovarian cancer, breast symptoms (e.g., breast pain), pelvic prolapse, cataracts, stroke, or myocardial infarction between the raloxifene and placebo groups ($P > .1$ for each event; data not shown).

Thromboembolic disease is a serious adverse event associated with raloxifene therapy (6). Although women in the raloxifene group had a higher incidence of thromboembolic disease, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis, than women in the placebo group, those differences were not statistically significant, either during the 4 years of the CORE trial ($P = .15$) or during the 8 years of the MORE and CORE trials ($P = .094$) (Table 4). During the CORE trial, the relative risk of thromboembolism in the raloxifene group (2.9 events per 1000 woman-years) compared with those in the placebo group (1.3 events per 1000 woman-years) was 2.17 (95% CI = 0.83 to 5.70) for the CORE enrollees and 3.11 (95% CI = 0.92 to 10.44) for the 3200 CORE enrollees who resumed taking study medication during the CORE trial. During the 8 years of the MORE and CORE trials, the incidence rate for venous thromboembolic events was 2.2 and 1.3 events per 1000 woman-years for the raloxifene and placebo groups, respectively. During the CORE trial, no cases of pulmonary embo-

Table 4. Rates of adverse events among the CORE enrollees*

Adverse event	CORE enrollees, % (No.)					
	4 years beginning at visit 1 of the CORE trial			8 years beginning at randomization in the MORE trial		
	Placebo group (N = 1286)	Raloxifene group† (N = 2725)	P‡	Placebo group (N = 1286)	Raloxifene group§ (N = 2725)	P‡
Vaginal bleeding	0.20 (2)	0.19 (4)	>.99	1.36 (14)	1.25 (27)	.87
Endometrial hyperplasia	0.20 (2)	0.05 (1)	.24	0.29 (3)	0.37 (8)	>.99
Endometrial cancer	0.30 (3)	0.19 (4)	.69	0.39 (4)	0.32 (7)	.75
Thromboembolic disease	0.39 (5)	0.84 (23)	.15	1.01 (13)	1.72 (47)	.094
Deep vein thrombosis	0.39 (5)	0.62 (17)	.49	0.78 (10)	1.14 (31)	.32
Pulmonary embolism	0.00 (0)	0.33 (9)	.066	0.16 (2)	0.62 (17)	.048
Retinal vein thrombosis	0.00 (0)	0.07 (2)	>.99	0.16 (2)	0.22 (6)	>.99
Flushing (hot flushes)	0.86 (11)	1.10 (30)	.61	6.92 (89)	12.55 (342)	<.001
Leg cramps	3.11 (40)	3.56 (97)	.52	11.82 (152)	14.94 (407)	.008
Peripheral edema	2.41 (31)	2.50 (68)	.91	9.33 (120)	10.57 (288)	.24

*CORE = Continuing Outcomes of Relevant to Evista; MORE = Multiple Outcomes of Raloxifene Evaluation.

†Dose of 60 mg of raloxifene per day during the CORE trial.

‡Based on two-sided Fisher's exact test.

§Doses of 60 mg or 120 mg of raloxifene per day during the MORE trial and 60 mg of raloxifene per day during the CORE trial.

||Includes only women who had an intact uterus at baseline of the MORE trial. For 4 years beginning at visit 1 of CORE, $n = 1008$ and $n = 2138$ for the placebo and raloxifene groups, respectively. For 8 years beginning at randomization in MORE, $n = 1026$ and $n = 2167$ for the placebo and raloxifene groups, respectively.

lism were reported in the placebo group, compared with nine cases reported in the raloxifene group ($P = .066$). During the 8 years from randomization in MORE until the end of the CORE trial, two women assigned to placebo (0.16%) and 17 women assigned to raloxifene (0.62%) developed a pulmonary embolism ($P = .048$; Table 4). One death due to pulmonary embolism was reported in the raloxifene group during the 4 years of the CORE trial.

DISCUSSION

During the CORE trial, raloxifene statistically significantly reduced the 4-year incidence of invasive breast cancer and of invasive ER-positive breast cancer by 59% and 66%, respectively. The reduction in the incidence of invasive breast cancer observed among women in the raloxifene group during the 4 years of the MORE trial was also observed for the additional 4 years that they participated in the CORE trial. Thus, the reduction in invasive breast cancer incidence continued throughout the 8 years for women assigned to raloxifene, and the magnitude of the risk reduction during the second 4 years of raloxifene therapy was similar to that observed during the first 4 years of therapy (6). It is possible that some of the risk reduction observed during the second 4 years (i.e., during the CORE trial) could be a carryover effect from the first 4 years of therapy in the MORE trial. Although the CORE trial was not designed to examine this question, the consistent risk reduction over the 8 years as shown in Fig. 3 implies that at least some of the risk reduction comes from continuing therapy beyond 4 years. As previously reported for the MORE trial (5,6), and as we now also report for the CORE trial, the incidence of ER-negative invasive breast cancer in women who received raloxifene was similar to that in women who received placebo. The lack of an apparent effect of raloxifene on ER-negative invasive breast cancers provides additional support for the hypothesis that SERMs inhibit estrogen-induced proliferation by binding to ERs in the breast (8,9). We found that raloxifene had no apparent effect on noninvasive breast cancer during the CORE trial, consistent with previously reported results from the MORE trial (5,6). Thus, the reduction in incidence of breast cancer observed with raloxifene appears to be limited to ER-positive invasive breast cancer.

Tamoxifen has also been reported to reduce the risk of invasive breast cancer among women who are at high risk for breast cancer (10). The breast cancer prevention effects of tamoxifen have been studied in four clinical trials (11–14). Combined results from these four trials showed that, compared with placebo, tamoxifen at 20 mg/day reduced the incidence of invasive breast cancer by approximately 36% and the incidence of ER-positive invasive breast cancer by 48% in pre- and postmenopausal women at high risk of breast cancer (10). In the largest of these four prevention trials, the Breast Cancer Prevention Trial (P-1) conducted by the National Surgical Adjuvant Breast and Bowel Project (14), tamoxifen reduced the incidence of invasive breast cancer and of invasive ER-positive breast cancer by 49% and 69%, respectively, compared with placebo, after a median follow-up of 54.6 months. By contrast, tamoxifen did not reduce the risk of ER-negative breast cancer (10,13,14).

The P-1 trial also showed that tamoxifen reduced the risk of noninvasive breast cancer by 50% (14), a result that differs from our finding that raloxifene had no effect on noninvasive breast cancer incidence. There are several possible explanations for this

apparent difference between the effects of tamoxifen and raloxifene on the incidence of noninvasive breast cancer. These include the lack of a sufficient number of cases of noninvasive breast cancer reported in the MORE and CORE trials to detect a treatment difference, differences in the populations studied (pre- and postmenopausal women in the P-1 trial versus postmenopausal women with osteoporosis in the MORE and CORE trials), and differences in the biologic activities of raloxifene and tamoxifen. Results of the ongoing Study of Tamoxifen and Raloxifene (STAR) trial, which directly compares the effects of raloxifene and tamoxifen in postmenopausal women at high risk for breast cancer, may clarify the basis for this difference (15,16).

Tamoxifen is approved in the United States for the reduction in incidence of breast cancer in women at high risk (defined as being at least 35 years of age with a 5-year predicted risk of breast cancer of 1.67% or greater, as calculated by the Gail model) for the disease (1). The maximum duration recommended for this use of tamoxifen is 5 years, presumably based on the limited clinical trial experience with more than 5 years of use in the prevention setting and on breast cancer treatment data suggesting that continuation of tamoxifen therapy beyond 5 years in the adjuvant setting may not provide additional benefit (17). The data from the CORE trial and the 8-year data from the MORE and CORE trials suggest that the reduction in incidence of invasive breast cancer in women receiving raloxifene may continue beyond 5 years.

Women with osteoporosis or low bone mineral density are considered to be at a lower risk for breast cancer than women with high bone mineral density, possibly because bone mineral density directly reflects a woman's lifetime exposure to estrogen (18–20). Because the CORE enrollees had osteoporosis, one might have expected their breast cancer risk to be low. A 5-year predicted risk for invasive breast cancer of 1.67% or greater, as estimated by the Gail model (7), is commonly used to classify women as being at high risk for invasive breast cancer. At CORE baseline, the mean 5-year predicted risk for invasive breast cancer for the CORE enrollees was 1.94% for both the raloxifene and placebo groups; therefore, both groups would be considered to be at high risk for breast cancer. The breast cancer incidence rate for the placebo group in the CORE trial was 5.4 cases per 1000 woman-years. This incidence rate is slightly higher than the incidence rates of 4.4 and 4.5 cases per 1000 woman-years for women who are 65–74 years of age and those 75 years or older, respectively, reported by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (21). These data suggest that the CORE participants were not at a lower risk for breast cancer than the general population, despite having osteoporosis, and suggest that postmenopausal women with low bone mineral density or osteoporosis should not be assumed to be at a low risk of breast cancer.

Raloxifene was generally well tolerated during the 4 years of the CORE trial and during the 8 years from randomization in the MORE trial to the end of the CORE trial. During the CORE trial, women who received raloxifene reported no increase in breast symptoms, including breast pain, consistent with the observations from the MORE trial (6). During the 8 years of the MORE and CORE trials, raloxifene increased the risk for hot flashes and leg cramps compared with placebo; these increased risks were observed during the MORE trial (6) but not during the additional 4 years of therapy in CORE, suggesting that hot flashes and leg

cramps may be early events which do not persist with continued therapy. Alternatively, it is possible that we did not observe an increased risk of these adverse events during the CORE trial because of selection bias, i.e., women who experienced hot flushes and leg cramps during the MORE trial may have chosen not to continue in the CORE trial. During the CORE trial, raloxifene did not increase the incidence of vaginal bleeding, endometrial hyperplasia, or endometrial cancer compared with placebo, consistent with previous results from the MORE trial (5,6) and other raloxifene trials (22). By contrast, tamoxifen therapy has been associated with increased incidence of endometrial cancer (10,13,14). The observations that raloxifene does not increase the incidence of endometrial cancer and that tamoxifen is associated with an increased incidence of endometrial cancer may be clinically important.

Another clinically important question is whether a decrease in the incidence of invasive breast cancer translates into a survival benefit. During the CORE trial, there was no difference between the raloxifene and the placebo groups in the number of deaths from any cause, and no deaths due to breast cancer were reported. Because survival was not an endpoint of the CORE trial, these data should not be used to draw any conclusions about the possible survival benefits associated with raloxifene therapy.

Thromboembolic disease is a serious adverse event associated with raloxifene therapy (6), and raloxifene is contraindicated in women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis (4). The twofold increase in venous thromboembolic events observed for the raloxifene group in the CORE trial was similar to that reported for the MORE trial (23). The most life-threatening complication of thromboembolic disease is pulmonary embolism, which, although an uncommon event, occurred more frequently in the raloxifene group than the placebo group. During the CORE trial, nine cases of pulmonary embolism were reported, all in the raloxifene group. The increased risk for venous thromboembolism must be considered when raloxifene is used.

The CORE trial, when combined with the MORE trial, provides clinical trial data for approximately 8 years of exposure to raloxifene, the longest duration of clinical trial exposure for this drug. This long-term study of raloxifene effects was possible because the randomization assignment from the MORE trial was carried forward into the CORE trial and because CORE trial participants remained blinded to therapy assignment. Nevertheless, the CORE trial has several limitations. First, because both the MORE investigators and the MORE trial participants, in consultation with the investigator, could choose whether or not to continue in the CORE trial, selection bias could have been introduced. For example, less healthy and/or more symptomatic women may have chosen not to continue in the CORE trial. Second, because the beginning of the CORE trial did not coincide with the end of the MORE trial, there was a gap between the two trials, during which time women could have taken prescribed raloxifene, hormone therapy, or no therapy. Use or lack of use of raloxifene or hormone therapy during the gap could have confounded interpretation of the results for both the raloxifene and placebo groups. Third, approximately 20% of the women who enrolled in the CORE trial never resumed taking the study medication, which could have reduced the effects observed for breast cancer incidence and venous thromboembolism in the raloxifene group. However, the sensitivity analysis of the

3200 women who resumed taking study medication showed a similar reduction in invasive breast cancer risk and a similar increase in relative risk of thromboembolism. Fourth, because all CORE trial participants were postmenopausal women with osteoporosis (defined by low femoral neck or lumbar spine bone mineral density or a history of fracture), our results cannot be extrapolated to other populations, including premenopausal women, for whom raloxifene is not indicated. In addition, most of the women in our study were white, which may limit extrapolation of our results to other racial groups.

In summary, these data demonstrate that the incidence of ER-positive invasive breast cancer continues to be reduced through 8 years of raloxifene treatment in postmenopausal women with osteoporosis. No increase in the incidence of ER-negative breast cancer was observed. During 8 years of raloxifene therapy, there was no increase in endometrial cancer and, except for those that have been previously reported, no other safety concerns were noted. The effect of raloxifene on breast cancer incidence is currently being evaluated in postmenopausal women at high risk for heart disease in the Raloxifene Use for The Heart (RUTH) trial (24,25) and in postmenopausal women at high risk for breast cancer in the STAR trial (15,16).

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