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ARTICLE

Breast Cancer Incidence in the Randomized PEARL Trial of Lasofoxifene in Postmenopausal Osteoporotic Women

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Background Currently available selective estrogen receptor modulators reduce the risk of breast cancer, but they are not widely used. In the Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial, lasofoxifene was shown to reduce the risk of estrogen receptor–positive (ER+) breast cancer, nonvertebral and vertebral fractures, coronary artery disease, and stroke, but the effects on total breast cancer (invasive and ductal carcinoma in situ, ER+ and estrogen receptor–negative [ER−]) and ER+ invasive breast cancer are unknown.

Methods Postmenopausal women (n = 8556) aged 59–80 years with low bone density and normal mammograms were randomly assigned to two doses of lasofoxifene (0.25 and 0.5 mg) or placebo. The primary endpoints of the PEARL trial were incidence of ER+ breast cancer and nonvertebral fractures at 5 years. A nested case–control study of 49 incident breast cancer case patients and 156 unaffected control subjects from the PEARL trial was performed to evaluate treatment effects on risk of total and ER+ invasive breast cancer by baseline serum estradiol and sex hormone–binding globulin levels using logistic regression models. Cox proportional hazards models were used to evaluate risk of total breast cancer and ER+ invasive breast cancer using intention-to-treat analysis. All statistical tests were two-sided.

Results Breast cancer was confirmed in 49 women. Compared with placebo, 0.5 mg of lasofoxifene statistically significantly reduced the risk of total breast cancer by 79% (hazard ratio = 0.21; 95% confidence interval [CI] = 0.08 to 0.55) and ER+ invasive breast cancer by 83% (hazard ratio = 0.17; 95% CI = 0.05 to 0.57). The effects of 0.5 mg of lasofoxifene on total breast cancer were similar regardless of Gail score, whereas the effects were markedly stronger for women with baseline estradiol levels greater than the median (odds ratio = 0.11; 95% CI = 0.02 to 0.51) vs those with levels less than the median (odds ratio = 0.78; 95% CI = 0.16 to 3.79; $P_{interaction}$ = .04).

Conclusion A 0.5-mg dose of lasofoxifene appears to reduce the risks of both total and ER+ invasive breast cancer in postmenopausal women with osteoporosis.

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Nearly 200 000 new cases of invasive breast cancer are diagnosed in the United States annually, 45 500 in the United Kingdom, and more than one million worldwide. More than 40 000 American women, nearly 12 000 in the United Kingdom, and a half million worldwide die of breast cancer annually (1–3). The use of effective therapies to prevent breast cancer is low among postmenopausal women with high breast cancer risk (4), perhaps because of unacceptable side effects or lack of perceived benefit of the therapy on overall health. New agents without serious side effects, which reduce the occurrence of breast cancer and provide additional benefits such as reduction in clinical fractures and other chronic diseases, are needed.

Laboratory evidence has shown that the selective estrogen receptor modulator (SERM) tamoxifen, acting as an antiestrogen, prevents the development of estrogen-dependent breast tumors in rodents (5). Tamoxifen also reduces the risk of new contralateral breast cancer in women previously treated for breast cancer (6). Four randomized placebo-controlled trials of tamoxifen for prevention of breast cancer in healthy women have reported a reduction in total cholesterol and incidence of breast cancer (7–10). However, in study populations of pre- and postmenopausal women, tamoxifen had no effect on fractures or coronary events and statistically significantly increased the incidence of venous thromboembolism, cataracts, and gynecological events, including endometrial atypia, polyps, and cancer. Meta-analyses showed that tamoxifen increased the incidence of stroke (11,12). In 1998, tamoxifen was approved by the United States Food and Drug Administration for breast cancer risk reduction in pre- and postmenopausal healthy women at high risk for breast cancer.

In placebo-controlled trials, raloxifene, a second-generation SERM developed for the prevention and treatment of osteoporosis, was shown to reduce the incidence of vertebral fractures and breast cancer with improved gynecological safety relative to tamoxifen but with no statistically significant reduction in nonvertebral fractures (13,14). The placebo-controlled Raloxifene Use for The Heart (RUTH) trial, designed to evaluate the effects of raloxifene on the heart in postmenopausal women at increased coronary risk, showed a risk reduction for breast cancer but failed to show any statistically significant reduction in coronary events (15). Following these trials, the Study of Tamoxifen and Raloxifene trial directly compared tamoxifen with raloxifene in postmenopausal women and showed similar breast cancer risk reduction for both agents but with raloxifene having a statistically significantly lower incidence of endometrial cancer, venous thromboembolism, and cataracts than tamoxifen (16). Raloxifene was approved by the US Food and Drug Administration for use in postmenopausal osteoporotic women for osteoporosis prevention and treatment and for breast cancer risk reduction in women with osteoporosis or for those at high risk for invasive breast cancer.

Lasofoxifene, a potent third-generation SERM, was developed because of its potentially attractive pharmacological profile as an agent for risk reduction of fractures, breast cancer, and heart disease in postmenopausal women at increased risk of osteoporotic fractures. Preclinical laboratory evidence showed that lasofoxifene reduced bone loss and cholesterol, prevented experimental breast cancers, and did not cause endometrial hyperplasia (17–19). Early clinical studies confirmed its potency relative to raloxifene in reducing bone loss and serum cholesterol, whereas neither agent increased the risk for endometrial hyperplasia (20).

The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial was therefore undertaken to evaluate the safety and efficacy of lasofoxifene on the incidence of vertebral fractures at 3 years and nonvertebral fractures and ER+ breast cancer including ductal carcinoma in situ (DCIS) at 5 years in osteoporotic postmenopausal women. Safety endpoints included major coronary artery disease and stroke. The primary trial results on the effects of lasofoxifene on estrogen receptor–positive (ER+) breast cancer, including noninvasive tumors, have been described elsewhere (21). The objectives of this study were to examine the effects of lasofoxifene on all incident breast cancers and ER+ invasive breast cancer in the PEARL trial and to determine the consistency of effects across baseline characteristics influencing cancer risk, including age, body mass index, Gail score, and levels of serum sex hormones.

Methods

Study Design

The PEARL trial (NCT00141323) was a double-blind, placebo-controlled, randomized trial designed to evaluate the effects of two doses of lasofoxifene (0.25 and 0.5 mg) on the incidence nonvertebral fractures and all ER+ breast cancer during 5 years of follow-up. Details of the study design and methods have been described previously (21). The protocol was reviewed and approved by institutional review boards for each study site, and all women provided written informed consent.

CONTEXTS AND CAVEATS

Prior knowledge

The selective estrogen receptor modulator (SERM) lasofoxifene was shown to be associated with reductions in risk of estrogen receptor–positive (ER+) breast cancer, but the effects on total breast cancer and ER+ invasive breast cancer are unknown.

Study design

The randomized placebo-controlled Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene trial examined the incidence of ER+ breast cancer and nonvertebral fractures at 5 years in 8556 women with low bone density and normal mammograms. The work reported here analyzed the effects of lasofoxifene in this population on all incident breast cancers and ER+ invasive breast cancer overall and across baseline characteristics influencing cancer risk, including age, body mass index, Gail score, and levels of serum sex hormones.

Contribution

Compared with placebo, 0.5 mg of lasofoxifene statistically significantly reduced the risk of total breast cancer and ER+ invasive breast cancer in postmenopausal women with osteoporosis. Women with higher baseline estradiol levels were statistically significantly more likely to benefit from lasofoxifene.

Implications

SERMs such as lasofoxifene can reduce the risk of breast cancer without serious side effects and provide additional benefits such as reduction in clinical fractures and other chronic diseases, particularly in postmenopausal women with osteoporosis or higher estradiol levels.

Limitations

The small number of incident breast cancer cases limited the statistical power to detect statistically significant treatment interactions. There are currently no data on follow-up beyond 5 years for benefits or for safety, on the optimal duration of SERM therapy, or on direct comparisons between lasofoxifene and other SERMs.

From the Editors

Participants

Postmenopausal women aged 59–80 years with osteoporosis (femoral neck and/or lumbar spine bone density T score ≤ 2.5), a life expectancy of at least 5 years, and good or excellent self-rated health status were recruited from 113 centers in 32 countries beginning in September 2001. Eligibility included a mammogram within the previous 6 months showing no evidence or suspicion of breast cancer and a normal gynecological examination, including the PAP test. Women with a cancer diagnosis in the previous 5 years (except for basal cell skin carcinoma) or a previous history of breast cancer or DCIS (except lobular carcinoma in situ if treated by local excision) were excluded. Women taking bone active medications, including oral or transdermal estrogen, raloxifene, or tibolone in the previous 3 months; or bisphosphonates, parathyroid hormone, or sodium fluoride within the previous 2 years; or oral corticosteroids within the previous year, were not eligible.

Eligible women completed two screening visits and were randomly assigned to a 6- to 8-week single-blind placebo and calcium–vitamin D run-in period with at least 75% compliance in taking the

supplements. After random assignment, women made clinic visits at 3 and 6 months of follow-up and every 6 months thereafter for a total of 5 years of follow-up regardless of their adherence to study medication. Mammograms were required at each annual visit.

Study Medication, Random Assignment, and Blinding

Using a permuted block algorithm with block size of 6, eligible women were randomly assigned to treatment groups in a 1:1:1 ratio of 0.25 mg lasofoxifene, 0.5 mg lasofoxifene, or placebo. Random assignment occurred using either an interactive telephone system, where local technology permitted, or a sequential list. Placebo pills were similar to active pills in size, color, smell, taste, and appearance and were packaged identically. Calcium (1000 mg) and vitamin D (400–800 IU) were supplied to all participants using local commercial sources. Participants were asked to refrain from taking their own calcium and vitamin D supplements. Participants, clinic staff, and site principal investigators were masked to treatment assignment throughout the active treatment phase of the trial except when required in emergent situations for participant safety; only 11 participants were unblinded for this purpose, but the remaining participants continued to be blinded at the conclusion of the trial.

Ascertainment of Breast Cancer

In addition to annual mammographic screening, all participants were instructed to conduct monthly breast self-examinations, and clinical breast examinations were conducted at annual visits. When a breast cancer diagnosis occurred, data were obtained on tumor invasion status, grade, nodal status, receptor status, and size. Histological evaluation of breast biopsies occurred locally, and if the biopsy confirmed breast cancer, DCIS, lobular carcinoma in situ, or hyperplasia, a biopsy sample was submitted to a central breast pathologist (D. C. Allred) for independent assessment of the histopathological and tumor marker classifications. HER2 was classified on the basis of immunohistochemistry using the Dako Hercep Test (Dako North America, Inc, Carpinteria, CA). An independent Breast Cancer Endpoint Adjudication Committee (T. Powles, D. C. Allred, P. Goss, and C. K. Osborne) blinded to treatment assignment, reviewed the data submitted and determined the final classification of all breast cancer endpoints. The primary endpoint ER+ breast cancer included ER+ invasive breast cancer and ER+ DCIS. The work reported here focused on ER+ invasive breast cancer. Total breast cancer included all invasive breast cancer and DCIS regardless of ER status.

Breast density was determined using computer proprietary image analysis software (Synarc, Inc, Lyon, France) and computer-assisted methods; density was measured as the ratio of the dense tissue area to the total area of the breast image. It was centrally assessed from digital images of baseline and 1-, 2-, and 3-year follow-up mammograms in a subgroup of 1236 participants from 24 centers by radiologists (Synarc, Inc, San Francisco, CA) who were blinded to treatment assignment and the visit order of the digitized images.

Estradiol and Sex Hormone–Binding Globulin Measurements

A nested case–control study in a subset of PEARL participants was conducted to determine whether baseline levels of serum estradiol or sex hormone–binding globulin (SHBG) could modify treatment effects on incident invasive breast cancer. All case patients of incident breast cancer in PEARL were selected (n = 49 with incident tumors and available serum samples), and approximately three control subjects per case patient (n = 156) were selected at random from participants in PEARL who did not develop breast cancer. Laboratory assays for serum estradiol and SHBG were conducted by Esoterix Endocrinology (Calabasas Hills, CA) on baseline fasting serum specimens that had been stored frozen at −20°C for 59–82 months. Estradiol measurements were made using two-dimensional liquid chromatography with mass spectrometry detection after liquid–liquid extraction (lower limit of quantification = 0.1 ng/dL). The intra-assay coefficients of variation ranged from 1.80% to 3.43%, and the interassay coefficients of variation ranged from 3.33% to 4.86%. SHBG was measured using immunoradiometric assay (lower limit of quantification = 10 nmol/L). The intra-assay coefficients of variation ranged from 2.3% to 4.7%, and the interassay precision was 6.8%.

Statistical Methods

With 2500 participants per treatment group, the PEARL trial had 90% statistical power to detect a 70% reduction in the time to first ER+ breast cancer with a two-sided α level of statistical significance of .025. Three breast cancer events, one in each treatment arm, which were adjudicated as preexisting were excluded from the analysis. Primary analyses used time-to-event methods, according to the intent-to-treat principle. Women contributed follow-up time for this analysis until the time of breast cancer diagnosis or the date of their last mammogram. Breast cancer rates were calculated as number of events per 1000 person-years. Each dose of lasofoxifene was compared with placebo using Cox proportional hazards models, with assumptions of proportionality confirmed by review of the log–log survival plots. Treatment effects were estimated as hazard ratios (HR) and 95% confidence intervals (CI) derived from these models. The Hochberg procedure was used to control for multiplicity (22). Statistical tests of the differences were based on corresponding unstratified log-rank tests. Type 1 error was split between the two primary endpoints at 5 years (nonvertebral fractures and ER+ breast cancer). Potential differential effects across categories of important risk factors for breast cancer, including age (<67 years vs ≥67 years), body mass index (<25 kg/m^2 vs ≥25 kg/m^2), and Gail score (<1.66 vs ≥1.66) were tested individually with the use of a Wald χ^2 test for interaction between the risk factor and treatment assignment after including both as main effects. All reported *P* values were two-sided and, along with the confidence interval, were not adjusted for multiplicity.

For the nested case–control study evaluating intervention effects according to baseline serum estradiol and SHBG measurements, odds ratios (OR) for lasofoxifene treatment were estimated from logistic regression models among women with values above and below the median for each hormone analyte. A two-degree of freedom interaction *P* value was calculated for cross-product terms of categorical treatment group (three levels) by continuous serum hormone level. Estradiol and SHBG main effect odds ratios were calculated from logistic regression models, using the dichotomous biomarker levels (≥0.35 ng/dL vs <0.35 ng/dL for estradiol; ≥110 nmol/mL vs <110 nmol/mL for SHBG) to predict incident breast cancer.

Results

Of the 8556 participants who enrolled in PEARL, 2852 were randomly assigned to each of the three treatment groups. At least one follow-up mammogram was received from 2740 (96.1%) women taking placebo, 2729 (95.7%) women taking 0.25 mg lasofoxifene, and 2745 (96.2%) women taking 0.5 lasofoxifene (Figure 1). Baseline characteristics were evenly distributed across the groups (Table 1). The mean age of participants was 67 years, 74% of women were white, 18% were Asian, and representation of other race or ethnicity groups was 5% or less. Average body mass index was 25 kg/m^2, 10% of women had a prior breast biopsy, and 45.2% of women had a Gail score greater than 1.66%. The average 5-year risk of breast cancer as estimated by the Gail score was approximately 1.70%.

In the PEARL trial, 77% of women completed the closeout visit at 5 years, and 62% of women in the lasofoxifene groups were taking study medication at 5 years, compared with 64% of women in the placebo group. Time-to-event analyses were based on 96% of randomly assigned women. A total of 49 incident breast cancer events (ER+ and estrogen receptor–negative [ER−], invasive or noninvasive) occurred, and all were confirmed (Table 2 and Figure 2, A). Lasofoxifene at 0.5 mg statistically significantly reduced the incidence of all breast cancers by 79% (HR = 0.21; 95% CI = 0.08 to 0.55). Only five breast cancer events occurred in this dose group compared with 24 in the placebo group. Rates of breast cancer were statistically significantly reduced for ER+ invasive breast cancer (HR = 0.17; 95% CI = 0.05 to 0.57) (Table 2 and Figure 2, B). Treatment effects for the 0.5-mg dose in relation to invasive ER+ breast cancer did not differ statistically significantly by baseline age, body mass index, or Gail score (Figure 3). Hazard ratios for 0.5 mg lasofoxifene were markedly reduced in all strata (HR = 0.12, 95% CI = 0.02 to 0.98 for women with Gail scores <1.66; HR = 0.20, 95% CI = 0.04 to 0.93 for women with Gail scores = 1.66 or higher). Women with Gail scores of 1.66 or higher are the usual group targeted for breast cancer prevention with SERMs (Figure 3).

Hazard ratios for the 0.25-mg lasofoxifene dose were below 1.0 for all categories of breast cancer, all reductions were of lesser magnitude than for the higher dose, and none was statistically significantly different from placebo (data not shown). There were no statistically significant differences for either lasofoxifene treatment group compared with placebo for ER− breast cancer (12 events total) or for DCIS (10 events total).

Tumor characteristics for incident breast cancers did not appear to differ markedly among treatment groups, and the differences were not statistically significant for the number of positive nodes, tumor size, or HER2 status (Table 3). Tumor grade varied statistically significantly among the treatment groups, with seven

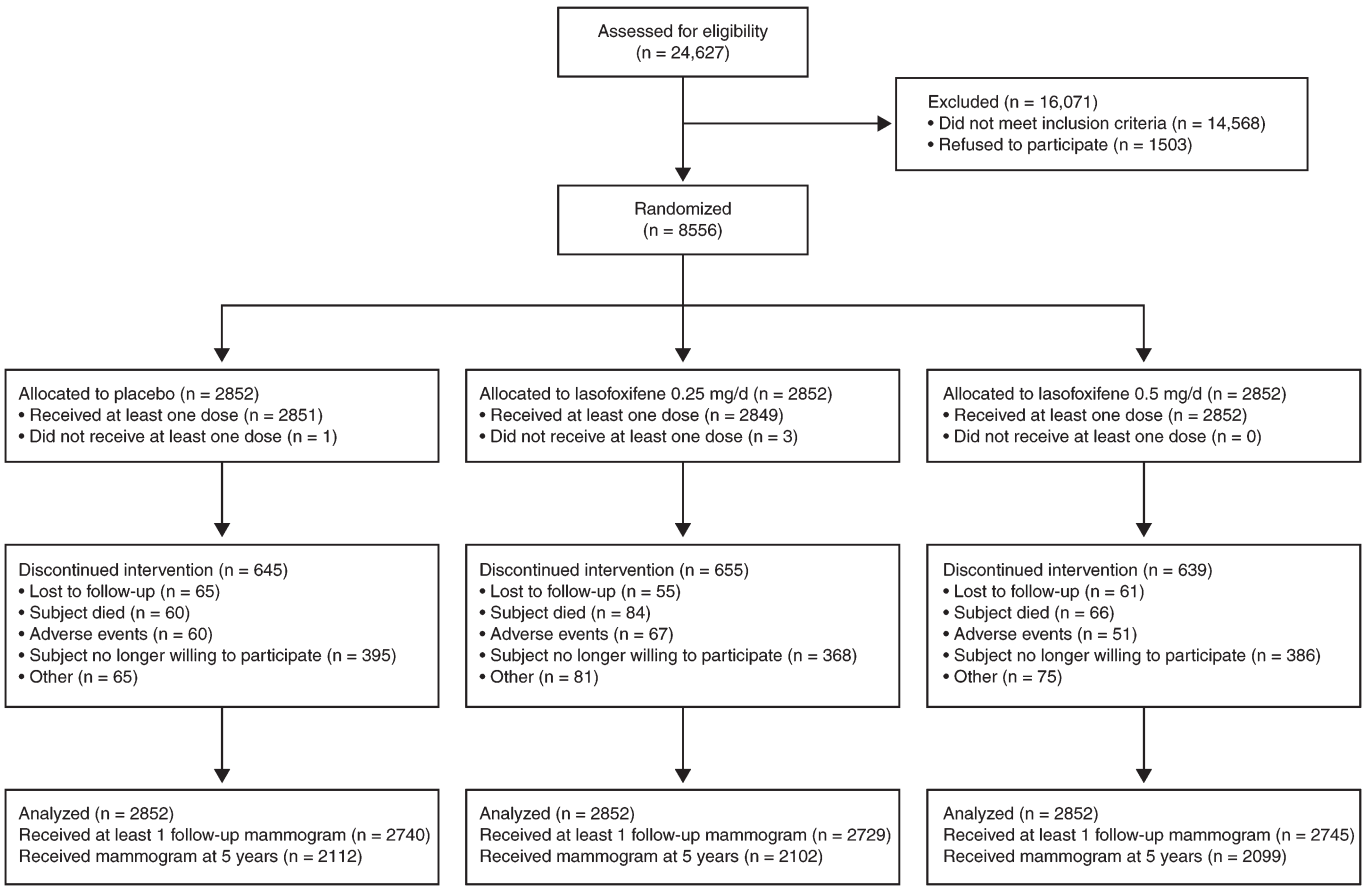

Figure 1. Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene trial flow diagram showing design, enrollment, and outcomes. Postmenopausal women aged 59–80 years with osteoporosis (femoral neck and/or lumbar spine bone density T score $\leq$ 2.5), a life expectancy of at least 5 years, and good or excellent self-rated health status were recruited for the study.

Table 1. Selected baseline characteristics by treatment group among all randomly assigned Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial participants*

Characteristic	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Mean age, y (SD)	67.5 (5.2)	67.5 (5.2)	67.3 (5.2)
Race, n (%)			
White	2118 (74.3)	2111 (74.0)	2108 (73.9)
Black	27 (0.9)	26 (0.9)	29 (1.0)
Asian	521 (18.3)	530 (18.6)	519 (18.2)
Hispanic	141 (4.9)	138 (4.8)	144 (5.0)
Other	45 (1.6)	47 (1.6)	52 (1.8)
Body mass index, kg/m^2, mean (SD)	25.4 (3.8)	25.2 (3.8)	25.4 (3.7)
Current smoker, n (%)	190 (6.7)	186 (6.5)	179 (6.3)
Alcohol use, n (%)	605 (21.2)	596 (20.9)	557 (19.5)
Hysterectomy, n (%)	543 (19.0)	554 (19.4)	550 (19.3)
Mean age at menarche, y (SD)	13.8 (1.8)	13.9 (1.8)	13.8 (1.8)
Mean age at menopause, y (SD)	47.8 (5.6)	47.9 (5.5)	47.7 (5.4)
Nulliparity, n (%)	313 (11.1)	315 (11.2)	297 (10.6)
Age at first live birth, y, mean (SD)	24.0 (4.8)	24.0 (4.7)	23.8 (4.7)
Family history of breast cancer, n (%)	234 (8.2)	253 (8.9)	246 (8.6)
Prior breast biopsy, n (%)	287 (10.1)	282 (9.9)	298 (10.5)
Prior use of estrogen, n (%)	162 (5.7)	179 (6.3)	161 (5.6)
Prior use of estrogen plus progestin, n (%)	181 (6.4)	195 (6.8)	193 (6.8)
Mean Gail score: 5-year risk of invasive breast cancer, % (SD)	1.69 (0.59)	1.71 (0.66)	1.68 (0.63)

* PEARL trial. A total of 2852 women were randomly assigned to each arm. Eligible participants were postmenopausal women aged 59–80 years with osteoporosis, with a life expectancy of at least 5 years and good or excellent self-rated health status. Those excluded were women with a cancer diagnosis in the past 5 years (except for basal cell skin carcinoma) or a previous history of breast cancer or ductal carcinoma in situ (except lobular carcinoma in situ if treated by local excision); women taking bone active medications, including oral or transdermal estrogen, raloxifene, or tibolone in the past 3 months, or bisphosphonates, parathyroid hormone, or sodium fluoride within the previous 2 years, or oral corticosteroids within the past year.

grade 3 tumors in the 0.25-mg group and none in the 0.5-mg group compared with two in the placebo group ($P = .02$).

Women with baseline estradiol levels less than 0.35 ng/dL (the median estradiol value in the substudy) were statistically significantly less likely to develop any incident breast cancer or invasive ER+ breast cancer compared with women with higher values (Table 4). In the placebo group alone, the odds ratio for low estradiol was 0.14 (95% CI = 0.04 to 0.54) for invasive ER+ breast cancer. The odds ratio for 0.5 mg lasofoxifene suggested larger reductions in risk of breast cancer for women with higher estradiol levels (for total breast cancer: OR = 0.11; 95% CI = 0.02 to 0.51) compared with women with lower estradiol levels (OR = 0.78; 95%

Table 2. Incident breast cancer events by lasofoxifene treatment group at 5 years of follow-up*

Breast cancer type	Placebo (N = 2740)	Lasofoxifene	
		0.25 mg (N = 2729)	0.5 mg (N = 2745)
All breast cancer			
No. with events (IR/1000 SY)	24 (1.97)	20 (1.64)	5 (0.41)
HR (95% CI)		0.82 (0.45 to 1.49)	0.21 (0.08 to 0.55)
P		.51	.001
ER+ invasive breast cancer			
No. with events (IR/1000 SY)	18 (1.48)	9 (0.74)	3 (0.25)
HR (95% CI)		0.50 (0.22 to 1.11)	0.17 (0.05 to 0.57)
P		.08	.001
ER− breast cancer			
No. with events (IR/1000 SY)	3 (0.25)	8 (0.66)	1 (0.08)
HR (95% CI)		2.55 (0.67 to 9.65)	0.35 (0.04 to 3.34)
P		.16	.40
DCIS			
No. with events (IR/1000 SY)	4 (0.33)	4 (0.33)	2 (0.16)
HR (95% CI)		1.00 (0.25 to 3.99)	0.50 (0.09 to 2.73)
P		.99	.41

* CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HR = hazard ratio; IR = incidence rate; SY = subject-years. Hazard ratio and confidence interval based on a Cox proportional hazards model with treatment as a covariate; *P* values (two-sided) are based on the log-rank statistic.

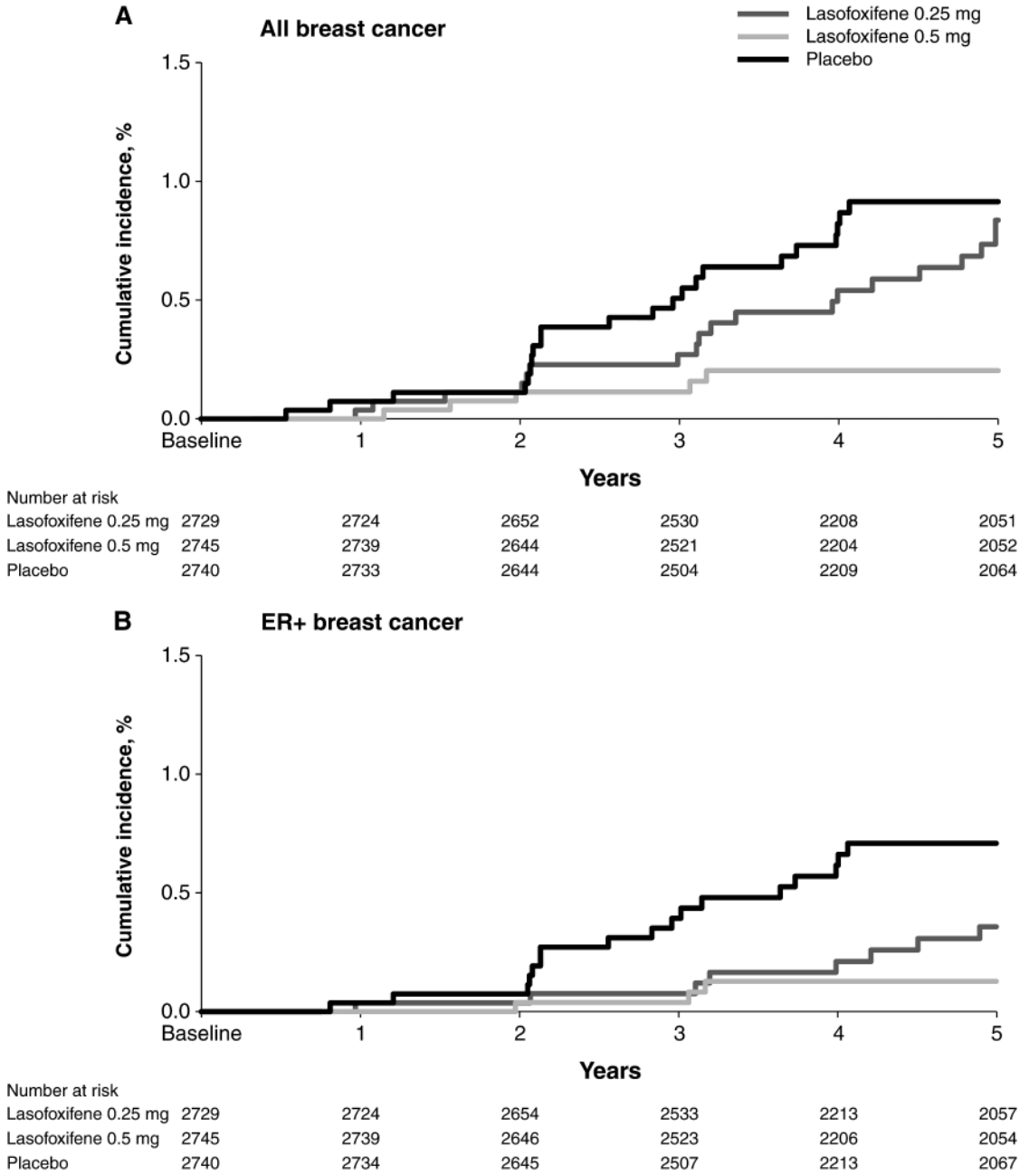

Figure 2. Cumulative incidence of breast cancer. **A)** All breast cancer. **B)** Estrogen receptor–positive (ER+) invasive breast cancer. Hazard ratio and confidence interval for these incidence curves are given in Table 2. Cumulative incidence is based on Kaplan–Meier estimation.

CI = 0.16 to 3.79). The interaction between estradiol level and lasofoxifene treatment was statistically significant (P = .04) for total breast cancer but not for invasive ER+ breast cancer (P = .16) (Table 4). Similar results were obtained when the interaction was tested using case-only methods (Cochran–Armitage test P =. 04 [approximate] and P = .05 [exact]). SHBG levels were not statistically significantly related to incident breast cancer or ER+ breast cancer and did not modify the lasofoxifene treatment effects.

Breast density measured at 3 years appeared to be slightly lower in the lasofoxifene treatment groups compared with placebo, but the differences were not statistically significant (data not shown).

Discussion

In this detailed analysis of breast cancer outcomes in the PEARL trial, there was a statistically significant (79%) reduction in all breast cancers (including noninvasive DCIS) and a statistically significant (83%) reduction in invasive ER+ breast cancers at 5 years with the 0.5-mg dose of lasofoxifene. The effects of 0.5-mg dose on total breast cancer were similar regardless of Gail score, whereas in the nested case–control study, the effects were markedly stronger for women with baseline estradiol levels above the median vs those with levels below

Risk factor	$P_{interaction}$	N	Placebo n (IR/1000 SY)	0.5 mg Lasofoxifene n (IR/1000 SY)	HR (95% CI)
BMI, kg/m²	.99				
<25		2614	6 (1.05)	1 (0.17)	0.17 (0.02 to 1.39)
≥25		2872	12 (1.87)	2 (0.31)	0.17 (0.04 to 0.75)
Gail score	.70				
<1.66		3001	8 (1.21)	1 (0.15)	0.12 (0.02 to 0.98)
≥1.66		2485	10 (1.80)	2 (0.37)	0.20 (0.04 to 0.93)
Age, y	.56				
<67		2683	9 (1.51)	1 (0.16)	0.11 (0.01 to 0.85)
≥67		2803	9 (1.45)	2 (0.33)	0.23 (0.05 to 1.06)

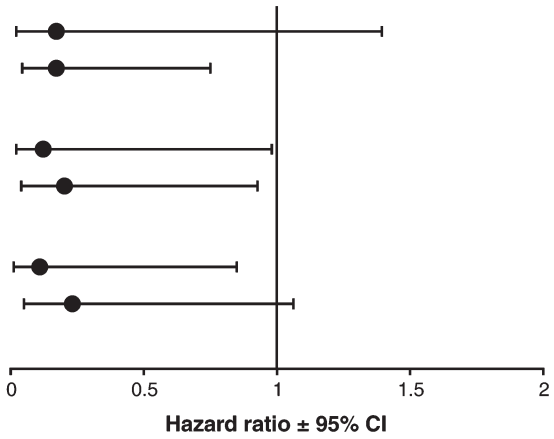

Figure 3. Hazard ratios for estrogen receptor–positive invasive breast cancer according to selected baseline characteristics. Hazard ratio (HR) and confidence interval (CI) based on a Cox proportional hazards model with treatment as a covariate. The *P* for interaction was based on a Cox proportional hazards model with a Wald χ^2 test for the interaction of treatment (0.5 mg lasofoxifene vs placebo) with categorical age, Gail score, and body mass index (BMI) tested in separate models. N = total subjects; n = number of events; IR = incidence rate; SY = subject-years.

the median. In the PEARL trial overall, the 0.5-mg dose of lasofoxifene showed statistically significant reductions compared with placebo in the incidence of vertebral fractures (42%), nonvertebral fractures (24%), and ER+ breast cancer (81%), including invasive and noninvasive (21). Furthermore, statistically significant reductions in major coronary events (32%) and stroke (36%) were observed with 0.5 mg lasofoxifene compared with placebo—effects not observed in previous trials with tamoxifen or raloxifene (11,12,15).

Safety evaluations with 0.5 mg lasofoxifene demonstrated an increased incidence of venous thromboembolism, leg cramps, and vasomotor symptoms. There was an increase in benign endometrial thickening, but no increase in endometrial hyperplasia, atypia, or cancer. There was no statistically significant increase in all-cause mortality through 5 years of follow-up for patients taking 0.5 mg lasofoxifene vs placebo, but there was an observed increased risk of all-cause mortality in the 0.25-mg lasofoxifene group that did not relate to any specific cause.

Table 3. Tumor histology and characteristics for incident breast cancers in the Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene trial*

Tumor characteristic	Placebo (N = 24)	Lasofoxifene		*P*†
		0.25 mg (N = 20)	0.5 mg (N = 5)	
Tumor grade, n (%)				.02
1	11 (45.8)	3 (15.0)	1 (20.0)	
2	5 (20.8)	5 (25.0)	1 (20.0)	
3	2 (8.3)	7 (35.0)	0 (0.0)	
Not reported	2 (8.3)	1 (5.0)	1 (20.0)	
N/A (all DCIS case patients)	4 (16.7)	4 (20.0)	2 (40.0)	
Positive nodes, n (%)				.93
0	14 (58.3)	11 (55.0)	2 (40.0)	
1–3	3 (12.5)	2 (10.0)	1 (20.0)	
≥4	2 (8.3)	1 (5.0)	0 (0.0)	
Not reported	5 (20.8)	6 (30.0)	2 (40.0)	
Tumor size, n (%)				.19
<1.0	1 (4.2)	1 (5.0)	1 (20.0)	
1.1–2.0	2 (8.3)	4 (20.0)	1 (20.0)	
2.1–3.0	1 (4.2)	1 (5.0)	1 (20.0)	
≥3.1	18 (75.0)	10 (50.0)	2 (40.0)	
Not reported	2 (8.3)	4 (20.0)	0 (0.0)	
HER2 status, n				.19
Positive	3	6	2	
Negative	19	10	3	
Not reported	2	4	0	

* Lymph node status is reported for all patients including ductal carcinoma in situ (DCIS) patients. Those with "no result" (n = 13) include all of the DCIS case patients (n = 10), plus three of the invasive case patients. N/A = not applicable.

† *P* values based on Cochran–Mantel–Haenszel row mean score test for treatments excluding "Not reported" cells. All tests were two-sided.

Table 4. Odds ratios for lasofoxifene according to baseline levels of estradiol and SHBG*

			Lasofoxifene				
		Placebo	0.25 mg		0.5 mg		
Baseline level	Main effect OR† for hormone level and breast cancer (95% CI)	No. with events/ control subjects	No. with events/ control subjects	OR† (95% CI)	No. with events/control subjects	OR† (95% CI)	$P_{interaction}$‡
All breast cancer							
Estradiol, ng/dL							
0.35	1.00 (referent)	20/20	12/29	0.41 (0.17 to 1.03)	2/19	0.11 (0.02 to 0.51)	.04
<0.35	0.32 (0.16 to 0.65)	4/29	6/25	1.74 (0.44 to 6.87)	3/28	0.78 (0.16 to 3.79)	
SHBG, nmol/L							
≥110	1.00 (referent)	12/21	10/31	0.56 (0.21 to 1.54)	0/30	N/A	.47
<110	1.31(0.68 to 2.51)	12/30	9/26	0.87 (0.31 to 2.38)	5/18	0.69 (0.21 to 2.30)	
ER+ invasive							
Estradiol, ng/dL							
≥0.35	1.00 (referent)	15/20	6/29	0.28 (0.09 to 0.83)	1/19	0.07 (0.01 to 0.58)	.16
<0.35	0.30 (0.13 to 0.72)	3/29	3/25	1.16 (0.21 to 6.27)	2/28	0.69 (0.11 to 4.45)	
SHBG, nmol/mL							
≥110	1.00 (referent)	9/21	5/31	0.38 (0.11 to 1.28)	0/30	N/A	.48
<110	1.27 (0.58 to 2.77)	9/30	4/26	0.51 (0.14 to 1.86)	3/18	0.56 (0.13 to 2.32)	

* Number of case patients differs from Table 2 because of insufficient specimens for the biomarker analyses for some case patients. Seven subjects had sufficient specimen for the sex hormone–binding globulin (SHBG) assay, but not for the estradiol assay. OR = odds ratio; N/A = not applicable .

† The main effect odds ratios for estradiol and SHBG are derived from logistic regression models predicting breast cancer with an indicator variable for the dichotomous hormone levels. Odds ratios for lasofoxifene treatment (0.25 and 0.5 mg) were estimated from logistic regression models among women with values above and below the median for each hormone analyte.

‡ All statistical tests were two-sided. The *P* value for interaction was estimated with a 2 degree of freedom χ^2 test for the interaction of treatment and continuous baseline estradiol or SHBG.

The magnitude of these risk reductions for breast cancer was similar to those previously reported for tamoxifen and raloxifene (13,23). There was no observed effect on the incidence of noninvasive breast cancers or ER− breast cancers; however, the trial was not designed to have sufficient statistical power to detect differences in these less common tumors. Lesser effects were seen with 0.25 mg lasofoxifene, making the PEARL trial unique among the SERM trials for demonstrating a dose–response relationship with lasofoxifene across a number of important clinical endpoints.

Overall, women in the PEARL trial were at lower risk for breast cancer than other women of similar age, perhaps because they entered with documented osteoporosis and came from internationally diverse populations, including countries with very low–reported breast cancer rates. We therefore examined effects of lasofoxifene among women at higher and lower risk for breast cancer as defined by Gail score and, separately, by serum estradiol and SHBG levels. Lasofoxifene was equally effective in reducing risk of ER+ invasive breast cancer among women with high and low Gail scores. This finding is consistent with the RUTH trial, in which raloxifene reduced the risk of breast cancer in women at high risk for coronary disease regardless of Gail score (24). In contrast, we observed a statistically significant interaction between baseline estradiol levels and lasofoxifene treatment. The 0.5 mg lasofoxifene dose reduced the incidence of breast cancer in women with estradiol levels above 0.35 ng/dL but had a lesser effect in women with lower serum estradiol levels. In addition, all breast cancer and ER+ invasive breast cancer were less likely to occur in subjects with low estradiol compared with subjects with higher levels. These findings are in agreement with a meta-analysis of nine prospective studies showing a twofold increased risk for breast cancer among postmenopausal women in the highest quintile of estradiol compared with the lowest quintile (25).

Similar to lasofoxifene in this trial, raloxifene reduced the risk for breast cancer to a statistically significantly greater extent for women with higher levels of estradiol than for those with low or undetectable levels (26). Alternatively, Beattie et al. (27) found no interaction between baseline estradiol level and effect of tamoxifen on risk of invasive breast cancer among women at high breast cancer risk. Estradiol levels have not been used in clinical practice to target women with SERM therapy for prevention of breast cancer because of the high cost of estradiol assays and lack of a validated cut point for recommending treatment. If lasofoxifene proves to be more effective for reducing breast cancer in postmenopausal women with higher estradiol levels through replication of the PEARL trial results, determining the best cut point for targeting therapy with an affordable standardized estradiol assay would be clinically important.

The PEARL trial had several limitations. The main limitation was the small number of incident breast cancer cases, which restricted the power to detect statistically significant treatment interactions. Another limitation was that although over the 5-year follow-up period, the percent risk reduction for breast cancer was clinically and statistically significant, the absolute number of prevented cancers was small, and there are no data on follow-up beyond 5 years for benefits or for safety. However, evidence from other breast cancer prevention trials using tamoxifen indicates that the risk reduction effect of SERMs continues long after the treatment period, whereas the safety concerns are confined for the most

part to the treatment period (9,28). It is likely that these long-term effects would be similar for all SERMs and should be taken into consideration when calculating the overall treatment benefit for these treatments. Other limitations include no information about the optimal duration of therapy for SERM treatments with multiple beneficial outcomes, although we do have a clear indication from the PEARL trial of the minimal dose for benefit. Furthermore, whereas lasofoxifene has demonstrated a pattern similar to oral bisphosphonates in efficacy against fractures and reductions in stroke and major coronary events similar to statins, we do not presently have data for direct comparisons between lasofoxifene and these other therapies approved for use in postmenopausal women. However, the magnitude of risk reduction of breast cancer seen with 0.5 mg lasofoxifene and the consistency of the results across endpoints make it likely that lasofoxifene is at least as effective as other SERMs.

The results of this study indicate that a 0.5-mg dose of lasofoxifene has clinical value for breast cancer prevention strategies in postmenopausal women with osteoporosis. Tamoxifen and raloxifene have been shown to reduce the incidence of ER+ breast cancer in postmenopausal women, and raloxifene also reduces the incidence of radiographic vertebral fractures but not hip or other clinical fractures. However, tamoxifen for breast cancer risk reduction has not been widely used principally because of the increased risk of endometrial cancer and other gynecological safety concerns in pre- and postmenopausal women. Although raloxifene did not increase endometrial cancer risk, it has been used less frequently than expected probably because the spectrum of benefit has been considered insufficient to justify use in healthy women. In particular, the inferior fracture efficacy compared with bisphosphonates (ie, the failure to show a benefit for nonvertebral fractures), and the absence of any statistically significant reduction in stroke or coronary heart disease, which have high incidence in this older population of postmenopausal women, may have deterred the use of raloxifene. Data from 2-year clinical trials directly comparing lasofoxifene with raloxifene have shown statistically significantly greater increases in bone mineral density, greater decreases in low-density lipoprotein cholesterol, and marked improvement in signs and symptoms of vulvovaginal atrophy for lasofoxifene-treated women and are consistent with the differences in clinical outcomes for the two agents (18). The spectrum of activity for lasofoxifene, including the clinically and statistically significant reductions of nonvertebral fractures, stroke, and serious heart events, makes it an attractive option, particularly for use in postmenopausal women with osteoporosis or higher estradiol levels.

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