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CLINICAL TRIAL

Risk factors for breast cancer in older women: the relative contribution of bone mineral density and other established risk factors

Jane A. Cauley · Jingli Song · Sherie A. Dowsett · John L. Mershon · Steven R. Cummings

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Abstract
Aim To determine the contribution of bone mineral density (BMD) to breast cancer risk relative to other established breast cancer risk factors in postmenopausal women with osteoporosis.
Methods Data for this analysis comprised those collected from women randomized to placebo in the MORE and CORE trials (N = 2,576). Risk factors measured at baseline included age, family history of breast cancer, estradiol level, body mass index, prior hormone therapy, BMD and vertebral fracture status. Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs).
Results Over a total of 13,698 woman-years of follow-up, 65 incident breast cancers occurred. In univariate analyses, older age and family history of breast cancer were the strongest predictors of breast cancer risk, associated with a 2.4- and 2.6-fold increase in breast cancer incidence. A higher estradiol level was associated with a 1.9-fold increase in breast cancer incidence. The association between femoral neck BMD and breast cancer incidence was only significant after adjustment for age (P = 0.03). The final multivariable model included age, family history, estradiol, BMD, and the BMD-estradiol interaction since the effect of BMD on breast cancer varied by estradiol level (interaction P-value, 0.04); in those with a lower estradiol level, a higher BMD was associated with a 2.6-fold increased in breast cancer.
Conclusion Overall, BMD is a relatively weak predictor of breast cancer risk in these postmenopausal women with osteoporosis, after taking into consideration age, family history and endogenous estradiol level.

Keywords Breast cancer · Bone mineral density · Osteoporosis · Age · Risk factors · Postmenopausal

J. A. Cauley (✉)
Department of Epidemiology, University of Pittsburgh, 130 DeSoto Street, Crabtree Hall A524, Pittsburgh, PA 15261, USA
e-mail: jcauley@edc.pitt.edu

J. Song · S. A. Dowsett · J. L. Mershon
Eli Lilly and Company, Indianapolis, IN, USA

S. R. Cummings
San Francisco Coordinating Center, CPMC, San Francisco, CA, USA

Introduction

Breast cancer is the most common cancer in women, accounting for one-third of all new cancers [1]. Risk for breast cancer increases with age, with 78% of all breast cancers occurring in women of more than 50 years of age, and 86% of breast cancer deaths occurring in this age group [2].

Postmenopausal women at higher risk for breast cancer generally have a greater lifetime estrogen exposure, as assessed through surrogate indicators of estrogen exposure including age at menopause, body mass index (BMI), estradiol level, and use of hormone therapy [3–6]. While useful in assessing risk in younger women, these traditional risk factors do not necessarily discriminate between older women at higher and lower breast cancer risk. It is important to identify specific risk factors for breast cancer, and their relative importance,

in older women to identify those women at greater risk for developing the disease and to devise prevention strategies targeted to this growing population.

In older postmenopausal women, the risk of breast cancer increases with increasing levels of endogenous estradiol; the collaborative reanalysis of nine prospective studies showed that women with the highest serum estradiol had a 2-fold increased risk of breast cancer compared to women with the lowest estradiol [5]. These results were, however, based on a single blood draw. Efforts have generally focused on using measures of bone density as an indicator of lifetime cumulative exposure to estrogen since estrogen receptors are present in bone and greater exposure to estrogen increases bone mineral density (BMD). We and others have found that women with higher BMD have an increased risk of breast cancer compared to women with lower BMD [7–10]. However, other studies have found this link to be weak [11–13]. The importance of BMD relative to other recognized breast cancer risk factors has not been established.

The aim of the current study was to examine the relationship between BMD and breast cancer risk and to determine the contribution of BMD to breast cancer risk relative to that of other established breast cancer risk factors. While a higher BMD is potentially a marker of increased breast cancer risk, BMD decreases with age and yet breast cancer risk increases with age. We thus also explored this relationship between BMD, age and breast cancer risk.

These analyses were conducted using placebo data from the Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista® (CORE) trials. MORE was an osteoporosis treatment trial designed to assess the effect of raloxifene on BMD and vertebral fracture risk, with breast cancer as a secondary safety endpoint. Of those 7,705 women participating in MORE, 4,011 went on to participate in a follow-up study, the CORE trial, designed to assess the effect of an additional 4 years of raloxifene compared with placebo on invasive breast cancer incidence. These trials together provide data from more than 2,500 women assigned placebo and followed for up to 8 years.

Materials and methods

Data for this analysis comprised those collected from women assigned to placebo in the MORE and CORE trials (N = 2,576). Of these women, 1,290 participated only in the 4-year MORE trial, and 1,286 participated in the 8-years of MORE plus CORE.

Study design and participants

The designs of both the MORE and CORE trials have been described elsewhere [14, 15]. For each trial, the study protocol was approved by the ethical review board at each investigative site, and all women gave written informed consent for participation in MORE and CORE separately.

The MORE trial was a 4-year international double-blind multi-center placebo-controlled clinical trial designed to determine the effect of raloxifene on BMD and the risk of vertebral fracture in women with osteoporosis. Eligibility criteria for enrollment in the MORE trial have been previously published [14]. Briefly, women were ≤80 years of age, were at least 2 years postmenopausal, and had documented osteoporosis as defined by a lumbar spine or femoral neck BMD T-score of ≤–2.5, and/or the presence of radiographically apparent vertebral fracture. Women with a history of breast cancer, invasive endometrial cancer, or a history of stroke or venous thromboembolism during the preceding 10 years were excluded. Participants were discontinued from the MORE trial if they developed cancer of the breast, uterus or other malignancies considered to be estrogen-dependent, or experienced a venous thromboembolic event. These women were not followed further, unless they chose to participate in CORE, for which they were still eligible.

The CORE trial was a 4 year follow-up study to MORE, in which 4,011 women chose to participate. The primary objective of CORE was to determine the effect of an additional 4 years of raloxifene therapy on breast cancer incidence. Those women assigned to placebo in MORE were also assigned to placebo in CORE. The beginning of the CORE trial did not coincide with the end of the MORE trial, and the median time between the end of participation in MORE and enrollment in CORE was 10.6 months for the placebo group. The average time from randomization in MORE to end of participation in CORE was 7.8 years.

Breast cancer risk factor assessment

Femoral neck and lumbar spine BMD were measured at baseline of the MORE trial by dual-energy X-ray absorptiometry. Pre-existing vertebral fractures were identified on lateral spine radiographs at baseline using a semi-quantitative scale for each vertebra [16, 17]. Serum estradiol was measured at MORE baseline by a central laboratory, using a double-antibody procedure [18]. Estradiol levels less than 5 pmol/l were below the limit of accurate quantification.

Information on a family history of breast cancer (first degree female relative), prior estrogen therapy, years since menopause, alcohol and cigarette use and history of hysterectomy was obtained by questionnaire. Weight, measured in light indoor clothing, and height, measured by wall mounted stadiometer, were used to calculate the body mass index (BMI: wt[kg]/ht[cm]^2).

Breast cancer ascertainment

In the MORE trial, mammograms were required at baseline, and at years 2, 3, and 4, and were optional at year 1. In the CORE trial, mammograms were required within 1 year of entering the trial, and at 2 years and 4 years. At each visit of MORE (bi-annually) and CORE (annually), women received a clinical breast examination and were asked if they had been diagnosed with breast cancer or had had a breast biopsy or breast surgery that had occurred since their last visit. If breast cancer was suspected, study medication was stopped and all available information, e.g., mammography report, histopathology reports and surgical records, was sent for adjudication by an independent oncology review board.

Statistical analysis

Characteristics at entry into MORE were compared between those who developed incident breast cancer during the MORE or CORE trial (cases) and those who did not (controls) using a χ^2 test for categorical variables and a paired *t*-test for continuous variables.

Baseline variables with a previously-established association with breast cancer risk (age, family history of breast cancer, estradiol level, BMI, BMD and presence/absence of vertebral fracture) and any further baseline characteristics exhibiting significant differences between cases and controls were evaluated for their predictive effect on breast cancer using time-to-event analyses. Continuous variables were dichotomized using the median value as the cut off, except for estradiol levels. Estradiol levels were categorized as ≤10 and >10 pmol/l for all analyses since in the MORE trial, estradiol levels greater than 10 were associated with greatest risk for breast cancer [18]. Incidence rates and 95% confidence intervals (CIs) as well as the 5-year predicted absolute risks of breast cancer were calculated for each risk group using a non-parametric method [19]. A Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% CI for each risk factor. Subsequently, a multivariate model was fitted using the Cox proportional hazards regression model with factors statistically significant at $P < 0.10$ in the univariate model. Pairwise interactions were added individually to the multivariate model; if the interaction was significant ($P < 0.10$), the interaction term was included in the final multivariate model.

Since age is common risk factor for low BMD and breast cancer, we explored the relationship between breast cancer incidence, age and femoral neck BMD; breast cancer incidence rates were calculated in subgroups defined by median age (≤66.9 year vs. >66.9 years) and median femoral neck BMD (≤0.62 g/cm^2 vs. >0.62 g/cm^2). A Cox proportional hazards regression model was fitted with age, femoral neck BMD and their interaction to estimate the HRs and 95% CIs.

Results

In those women assigned to placebo (mean age, 66.6 ± 7.1 years) and participating in only the MORE trial (N = 1,290) or both the MORE and CORE trials (N = 1,286), 65 incident breast cancers (58 of which were invasive) were confirmed over a total of 13,698 woman-year of follow-up. The incidence of all breast cancers was 4.75 cases per 1,000 woman-years.

Women with breast cancer were older, and were more likely to have a higher estradiol level, or a family history of breast cancer ($P < 0.05$) (Table 1). The mean femoral neck BMD was higher in cases than controls, but the difference was marginally significant ($P = 0.05$). There was no difference between cases and controls for pre-existing vertebral fracture, mean lumbar spine BMD, mean years since menopause, current smoking or alcohol use, prior hormone therapy or history of hysterectomy.

In the univariate analyses, a higher age (>66.9 years), a higher estradiol level (>10 pmol/l) and a family history of breast cancer were associated with a significant 1.9–2.6-fold greater incidence of breast cancer (Table 2). The association between a higher femoral neck BMD (>0.62 g/cm^2) and breast cancer incidence was marginally significant (HR 1.60, 95% CI 0.96–2.64; $P = 0.07$). After adjustment for age, a higher femoral neck BMD was associated with a 1.8-fold increase in breast cancer incidence (95% CI 1.06–2.91; $P = 0.03$). When femoral neck BMD was considered as a continuous variable, the incidence of breast cancer was increased 1.3-fold per 1 standard deviation increase in femoral neck BMD with adjustment of age (HR 1.31, 95% CI 1.03–1.67; $P = 0.03$). A higher lumbar spine BMD (>0.8 g/cm^2) was not associated with a significant increase in breast cancer incidence

Table 1 MORE trial baseline characteristics of women assigned placebo who did not (controls) and who did (cases) develop breast cancer during their participation in the MORE or CORE trial

		Controls (N = 2,511)	Cases (N = 65)	P-value*
Mean age ± SD (years)		66.6 ± 7.1	68.6 ± 5.9	0.007
Age (years), N (%)	≤66.9	1,267 (50.5)	21 (32.3)	
	>66.9	1,244 (49.5)	44 (67.7)	0.004
Mean BMI ± SD (kg/m^2)		25.2 ± 4.0	25.9 ± 4.2	0.18
BMI (kg/m^2), N (%)	≤24.8	1,258 (50.1)	30 (46.2)	
	>24.8	1,252 (49.9)	35 (53.9)	0.53
Mean femoral neck BMD ± SD (g/cm^2)		0.62 ± 0.08	0.64 ± 0.07	0.05
Femoral Neck BMD (g/cm^2), N (%)	≤0.62	1,259 (50.4)	24 (36.9)	
	>0.62	1,239 (49.6)	41 (63.1)	0.03
Mean lumbar spine BMD ± SD (g/cm^2)		0.81 ± 0.14	0.83 ± 0.15	0.25
Lumbar Spine BMD (g/cm^2), N (%)	≤0.80	1,245 (49.9)	35(53.9)	
	>0.80	1,250 (50.1)	30(46.2)	0.53
Pre-existing vertebral fracture, N (%)	No	1,582 (63.3)	47 (72.3)	
	Yes	918 (36.7)	18 (27.7)	0.14
Mean years postmenopausal ± SD		18.9 ± 8.5	19.9 ± 7.8	0.33
Family history of breast cancer, N (%)	No	2,150 (87.9)	46 (74.2)	
	Yes	297 (12.1)	16 (25.8)	0.001
Current smoker, N (%)	No	2,073 (83.6)	51 (81.0)	
	Yes	408 (16.4)	12 (19.0)	0.58
Alcohol use[a], N (%)	No	2,081 (83.0)	51 (78.5)	
	Yes	426 (17.0)	14 (21.5)	0.34
Prior hormone therapy, N (%)	No	1,790 (71.4)	43 (66.2)	
	Yes	716 (28.6)	22 (33.8)	0.35
Prior hysterectomy, N (%)	No	1,947 (77.5)	51 (78.5)	
	Yes	564 (22.5)	14 (21.5)	0.86
Estradiol level (pmol/l), N (%)	≤10	1,537 (64.4)	30 (49.2)	
	>10	849 (35.6)	31 (50.8)	0.01

* χ^2 test for categorical variables and the paired t-test for continuous variables

[a] Alcohol use defined as ≥ 4 alcohol drinks per week

nor was pre-existing vertebral fracture. Incidence rates for breast cancer ranged from 2.9 to 10.0 per 1,000 woman-years, depending upon covariate subgroup.

The final multivariate model was fitted with age, family history, estradiol, femoral neck BMD and the estradiol–femoral neck BMD interaction. In this model, a higher age was associated with a 2.4-fold greater risk of breast cancer, while family history was associated with a 2.8-fold greater risk (Table 3). Since the interaction was evident between estradiol level and femoral neck BMD in the model (P = 0.04), HRs are presented for high versus low BMD by estradiol level

Table 2 Hazard ratio (HR) and 95% confidence interval (CI) for incident breast cancer by covariate based on univariate models. The absolute risk for breast cancer is also tabulated

All continuous covariates were dichotomized at the median, except for estradiol level

		HR (95% CI)	P-value	Incidence rate (95% CI), per 1,000 woman-years	Predicted 5-year risk (%)
Age (years)	≤66.9	1.00		2.9 (1.7–4.1)	1.4
	>66.9	2.40 (1.42–4.03)	0.001	6.8 (4.8–8.8)	3.3
Estradiol level (pmol/l)	≤10	1.00		3.6 (2.3–4.8)	1.8
	>10	1.91 (1.16, 3.16)	0.01	6.9 (4.5–9.4)	3.4
Family history of breast cancer	No	1.00		3.9 (2.8–5.0)	1.9
	Yes	2.57 (1.46–4.54)	0.001	10.0 (5.1–15.0)	4.9
Femoral neck BMD (g/cm^2)	≤0.62	1.00		3.6 (2.2–5.1)	1.8
	>0.62	1.60 (0.96–2.64)	0.07	5.8 (4.0–7.6)	2.9
Lumbar spine BMD (g/cm^2)	≤0.80	1.00		5.2 (3.5–6.9)	2.6
	>0.80	0.82 (0.50–1.33)	0.41	4.3 (2.8–5.9)	2.1
Vertebral fracture	Yes	1.00		5.3 (3.8–6.8)	2.6
	No	1.34 (0.78–2.31)	0.29	3.8 (2.1–5.6)	1.9
BMI (kg/m^2)	≤24.8	1.00		4.4 (2.8–5.9)	2.2
	>24.8	1.11 (0.68–1.81)	0.68	5.1 (3.4–6.8)	2.5

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for incident breast cancer by covariate based on the mulitvariate model

			HR (95% CI)	*P*-value
Age (years)		≤66.9	1.00	
		>66.9	2.39 (1.38–4.16)	0.002
Family history of breast cancer		No	1.00	
		Yes	2.83 (1.58–5.05)	<0.001
Subset with estradiol ≤10 pmol/l:	Femoral neck BMD (g/cm^2)	≤0.62	1.00	
		>0.62	2.59 (1.18–5.66)	0.02
Subset with estradiol >10 pmol/l:	Femoral neck BMD (g/cm^2)	≤0.62	1.00	
		>0.62	0.85 (0.40–1.79)	0.67

Continuous covariates were dichotomized at the median, except for estradiol level. The final multivariate model included age, family history, estradiol level, femoral neck bone mineral density (BMD), and the estradiol–femoral neck BMD interaction (interaction *P*-value, 0.04)

(≤10, >10 pmol/l). In women with lower estradiol level, a higher femoral neck BMD was associated with a 2.6-fold greater risk of breast cancer; with higher estradiol level, femoral neck BMD was not predictive of breast cancer risk (Table 3).

Since there was a significant interaction between estradiol level and femoral neck BMD observed in the final multivariate model, we calculated breast cancer incidence rates in subgroups defined by estradiol level (≤10 pmol/l vs. >10 pmol/l) and femoral neck BMD (≤0.62 g/cm^2 vs. >0.62 g/cm^2) (Fig. 1). In women with lower estradiol level, the breast cancer incidence rates in women with a higher and lower femoral neck BMD were 2.1 and 5.1 per 1,000 woman-years, respectively. In women with higher estradiol level, the incidence rates were 7.3 and 6.7 per 1,000 woman-years, respectively.

Breast cancer incidence rates were also compared between subgroups defined by both age and femoral neck BMD. Irrespective of femoral neck BMD, the incidence of breast cancer was significantly higher in older versus younger women (Fig. 2); in those women with lower BMD, the incidence of breast cancer was 2.8-fold greater in the older versus younger women (HR 2.77, 95% CI 1.10–6.99) while in women with higher BMD, the incidence of breast cancer was 2.5-fold greater in the older versus younger women (HR 2.46, 95% CI 1.30–4.64). Irrespective of age, the incidence of breast cancer was higher in those with higher versus lower femoral neck BMD, but these differences were not significant ($P > 0.1$). Older women with a higher BMD were at 4.7-fold greater incidence of breast cancer than younger women with a lower BMD (HR 4.70, 95% CI 1.93–11.42). No interaction was evident between age and femoral neck BMD when both covariates were dichotomized ($P = 0.83$).

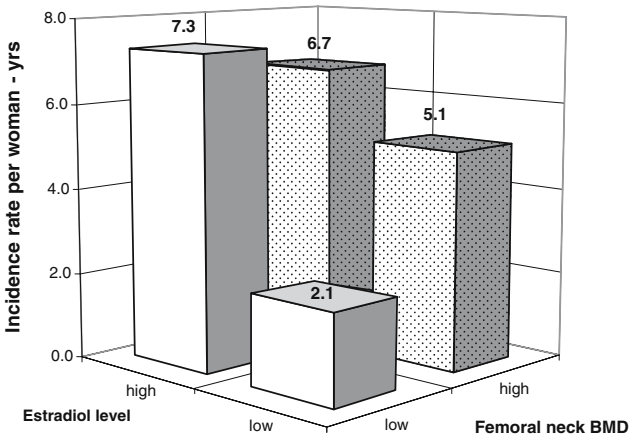

Fig. 1 Incidence rates for breast cancer according to baseline estradiol level (≤10 pmol/l vs. >10 pmol/l) and femoral neck bone mineral density (BMD) (≤0.62 g/cm^2 vs. >0.62 g/cm^2). An interaction was evident between estradiol level and femoral neck BMD ($P = 0.04$ in final multivariate model)

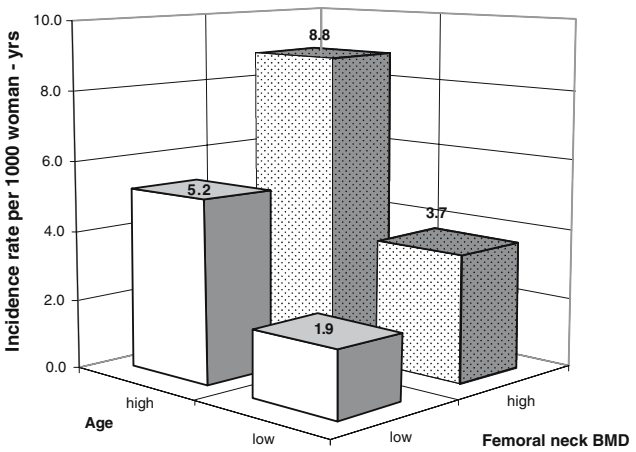

Fig. 2 Incidence rate of breast cancer according to baseline age (≤66.9 years vs. >66.9 years) and femoral neck bone mineral density (BMD) (≤0.62 g/cm^2 vs. >0.62 g/cm^2). No interaction was evident between age and BMD ($P = 0.83$)

Discussion

In this population of postmenopausal women with osteoporosis, established risk factors for breast cancer were confirmed. Without adjustment, a family history of breast cancer was associated with a 2.6-fold increase in breast cancer incidence, age >67 years versus <67 years with a 2.4-fold increase in breast cancer incidence, and estradiol level >10 pmol/l versus ≤10 pmol/l with a 1.9-fold increase in breast cancer incidence. Neither BMI nor prior hormone therapy were risk factors for breast cancer.

In this population of postmenopausal women with osteoporosis, the effect of femoral neck BMD on breast cancer incidence was marginal overall, and neither lumbar spine BMD nor previous vertebral fracture were associated with an increased incidence of breast cancer. These results suggest that severity of osteoporosis, as determined by BMD or the presence/absence of preexisting vertebral fracture, is a relatively weak predictor of breast cancer risk. The significant interaction that was evident between BMD and estradiol level suggests that any effect of BMD on breast cancer risk is not independent of circulating estrogens.

Previous studies have explored a possible association between BMD and breast cancer risk, and results have not been consistent. A higher BMD was associated with a greater risk of breast cancer in the Study of Osteoporotic Fractures [7, 20] and the Dubbo Osteoporosis Epidemiology [8], Epidemiologie de l'Osteoporose (EPIDOS) [9], and Framingham [10] studies; in the NHANES follow up [21], Fracture Intervention Trial (FIT) [12], and Rotterdam [13] studies, the association between BMD and breast cancer risk was weak or the results inconclusive. Most recently, a large (N = 15,254) case-control study of women in the San Francisco mammography registry concluded that BMD was not a strong risk factor for breast cancer [11]. The majority of these prior studies have been carried out in older women, similar to the age of the women in the current study. A more recent report failed to observe an association between BMD and breast cancer in younger perimenopausal women, with an average age of 48 years and minimal exposure to exogenous hormones [22].

In the present study, the effect of BMD on breast cancer risk was influenced by estradiol level, and this relationship between BMD, estradiol level and breast cancer risk appears complex. A greater risk of breast cancer with higher versus lower BMD was only seen in women with lower estradiol levels (≤10 pmol/l). This suggests that other factors, unidentified in this study, correlate with BMD and influence breast cancer incidence only when the overriding effect of high estradiol levels (>10 pmol/l) is removed. One possibility may be an effect of testosterone, which has been associated with an increased risk of breast cancer independent of estradiol [23, 24]. Testosterone has been shown in some studies to have a favorable effect on BMD [25]. Alternatively, women with low estradiol, but higher BMD are responding to the low estradiol levels in an exaggerated manner. This could possibly arise from an estrogen receptor (ER) gene mutation resulting in activation at lower than normal levels of estradiol, or through modification of the ER. One example of such an ER mutation, in the ERα isoform, has been described by Fuqua et al. [26]. This ER mutation was associated with increased proliferation of breast cancer cells, and was found in a high percentage of patients with hyperplastic breast tissue. If such a mutation was present in both the bone and breast tissue, very low levels of estradiol could preserve BMD and still increase the risk of breast cancer.

We also explored this three-way relationship between BMD, age and breast cancer risk, since while higher BMD may be a marker of increased breast cancer risk, BMD decreases with age and breast cancer risk increases. Irrespective of BMD group, higher age was associated with a greater incidence of breast cancer. Conversely, in both age groups, a higher BMD was associated with a non-significant increase in breast cancer incidence. Those women who were older and with higher BMD were at a 4.7-fold greater risk for breast cancer than younger women with low BMD. The apparent paradox seems to be explained by age being a stronger risk factor than BMD.

The Gail Model [27, 28] is the most commonly used tool to estimate invasive breast cancer risk; using this model, the 5-year predicted risk is calculated based on the presence/absence of select breast cancer risk factors. Women at ''high risk'' are generally defined as those with a 5-year predicted risk of invasive breast cancer of >1.66%. In the present study, although we examined all and not just invasive breast cancers, we found that the ''high risk'' group, based on age, estradiol or family history, had a 5-year predicted risk of breast cancer twice this high risk cut-off used in the Gail Model. This may reflect the underlying high risk of breast cancer in this elderly population.

Our analysis is one of the first analyses of the relative importance of key risk factors for breast cancer in older women that includes circulating estrogen levels as well as a marker of a woman's cumulative exposure to estrogen, BMD. We examined the risk of breast cancer over a relatively long follow-up of up to 8 years. There are, however, several limitations. All of the

women in MORE and CORE had low BMD and were older (mean age, 67 years), and our results may not be generalizable to other populations. Analysis was based on only 65 breast cancer cases which may have resulted in low statistical power to detect significant effects of BMD on breast cancer risk. We did not differentiate breast cancers based on their invasiveness (invasive or non invasive) or ER receptor status (ER-positive, ER-negative or ER status unknown) but the majority of the breast cancers were invasive (89%) and ER positive (69%).

Conclusion

Findings from this study suggest that, overall, BMD is a relatively weak predictor of breast cancer risk in these postmenopausal women with osteoporosis after taking into consideration age, family history and endogenous estradiol values.

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