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Original Article

Fractures Before Menopause: A Red Flag for Physicians

W. D. Hosmer[1,2], H. K. Genant[3] and W. S. Browner[1,2]

[1]General Internal Medicine Section, Veterans Affairs Medical Center, San Francisco & Department of Medicine, University of California, San Francisco; [2]Department of Epidemiology and Biostatistics; and [3]Department of Radiology, University of California, San Francisco, California, USA

Abstract. There is substantial interest in the early identification of women at risk for osteoporotic fractures, so that preventive measures may be instituted early. We examined whether women with a history of fractures before menopause were at an increased risk of fractures after menopause. We obtained information about any lifetime fractures of the hip, arm, spine, wrist, leg, ankle, foot and finger from 9086 ambulatory white women ages 65 years and older participating in the Study of Osteoporotic Fractures. We also measured bone mineral density and recorded history of falls, maternal fracture history, drug use, diet, functional status, and other characteristics commonly associated with osteoporotic fractures. We used proportional hazards models to estimate the effects of fractures that occurred before menopause on the risk of fractures after menopause, in particular those that occurred during the 12 years of study follow-up. The risk of fractures of all types during the study period was greater among women with a premenopausal fracture of any type compared with women without a premenopausal fracture (hazard ratio (HR), 1.33; 95% confidence interval (CI), 1.14–1.56; $p<0.001$). Adjustment for possible confounders, including bone mineral density, had only a modest effect (HR, 1.25; 95% CI, 1.03–1.50; $p<0.02$). An increased risk of fracture among women with a premenopausal fracture was also seen after stratification by estrogen use, propensity to fall and maternal fracture history. Premenopausal fractures are therefore a risk factor for subsequent fractures independent of other risk factors for osteoporotic fractures, such as bone mineral density. A fracture history, including fractures before menopause, should be obtained when making decisions about preventive treatments.

Keywords: Osteoporotic fracture; Premenopausal fractures; Postmenopausal fractures; Risk factors

Introduction

Identifying characteristics that predict which patients are at risk for osteoporotic fractures can assist physicians in making decisions about beginning preventive measures in middle-aged and elderly patients. Previous studies have reported a 1.5- to 7-fold increase in the risk of future fracture among patients with previous fractures [1–7]. This risk may be even greater among patients with a low bone mineral density [8,9], especially in the years following the initial fracture [2]. Most studies, however, have not evaluated the importance of fractures before menopause as a risk factor for fractures after menopause. Those that did examine this relation were limited by power, the types of fractures examined, the amount of follow-up time, and the ability to adjust for confounding variables [2,10,11].

If women at an increased risk for future fractures can be identified before menopause, preventive measures can begin earlier. The purpose of this study was to examine the relation between fractures before and after menopause in elderly white women.

Correspondence and offprint requests to: Warren S. Browner, California Pacific Medical Center, 2340 Clay Street, San Francisco, CA 94115, USA. Tel: +1 (415) 600 1400. Fax: +1 (415) 885 8686. e-mail: warren@cooper.cpmc.org

Subjects and Methods

Study Subjects

Between September 1986 and October 1988, a total of 9704 ambulatory white women who were at least 65 years of age were recruited for the Study of Osteoporotic Fractures (SOF) from population-based listings in Baltimore, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley, PA [1,12]. The cohort was followed for 12 years with clinic follow-up visits every 2 years. Between visits, participants were contacted approximately every 4 months by postcard or telephone to inquire about new fractures. The cumulative rate of postcard return was 99%.

Measurements

Age at menopause was recorded on the baseline questionnaire as each subject's recall of her age at her last natural menstrual period. This menopause age was used to define premenopausal versus postmenopausal fractures. We excluded 618 women who had a reported menopause age greater than 2 SD from the mean (>59 years or <39 years), leaving 9086 patients. The 1780 women with an uncertain or missing menopause age were assigned the median age of menopause (49 years).

For the current study, we included fractures that occurred from age 25 years to 100 years. All fractures that occurred after enrollment were confirmed with a radiographic review by a physician investigator [13]. Women answered questions on the baseline questionnaire about the occurrence of selected fractures (hip, wrist, arm leg, ankle or foot, vertebral, and finger fractures) and the circumstances of these fractures before enrollment in the study. Only fractures that occurred after a fall from standing height or less were included.

Height and weight were measured at baseline; body mass index (kg/m^2) was estimated. Current alcohol use (drinks/week), estimated lifetime caffeine intake (mg), number of falls in the previous year, pack-years of cigarette smoking, current calcium intake from food and supplements (mg/week), weight gain from age 25 years to baseline, current perceived health status (excellent/good vs fair/poor/very poor), maternal fracture history (yes/no any fracture during lifetime), and use of estrogen, thiazide diuretics, non-thiazide diuretics, corticosteroids, thyroid hormone and anticonvulsant medications (current, never, ever used) were obtained by questionnaire. We assessed self-reported physical activity at ages 30 years, 50 years and the year before enrollment by counting the total times of activity per year (ages 30 and 50 years) or by determining the average kilocalories burned per week while exercising (year before enrollment). Cognitive function (as a modified Mini-Mental State Exam with a 0 to 26 scale), time needed to rise five times from a sitting position, walking speed and overall functional status (the number of six common tasks, walking, climbing stairs, preparing meals, housework and shopping that the participants could not perform unassisted) were measured. At enrollment, women had bone mineral density measured at the calcaneus and the proximal and distal forearm using single photon absorptiometry (Osteo-Analyzer, Siemens-Osteon, Wahaiwa, HI). Two years later, 7786 participants who returned for a second clinic visit had measurements made of bone mineral density of the hip (total hip, femoral neck) and spine using dual-energy X-ray absorptiometry (QDR 1000, Hologic, Waltham, MA).

Statistical Analysis

The baseline characteristics of subjects with and without a premenopausal fracture were compared with *t*-tests and chi-square tests. The association between premenopausal fracture and postmenopausal fracture (as the hazard ratio (HR) with 95% confidence intervals (CI)) was determined without adjustment, after adjusting for bone mineral density, and after adjusting for confounding variables. This assocation was examined separately for fractures between menopause and SOF enrollment, and for fractures after SOF enrollment. Survival curves were generated based on time to fracture after the study began. For some analyses, calcaneus bone mineral density was divided into age-adjusted quartiles by assigning participants to quartiles of subjects in the same 5-year age group (65–70, 71–75, 76–80 and 81+ years).

Multivariate proportional hazards models were built in a stepwise fashion by examining the univariate relations between potential confounding variables and postmenopausal fracture. Variables with a statistically significant relation ($p<0.10$) were included in multivariate models, and all other variables were excluded. This process was continued until the final model contained only varaiables that were associated with the outcome at $p<0.10$. Since 2200 women were missing data about maternal fracture history, we repeated our analyses without maternal fracture history; hazard ratios for the other variables in the model were not changed substantially. The final multivariate model was then stratified by quartiles of age-adjusted calcaneal bone mineral density, current estrogen use, number of falls (0, 1, 2+) or maternal fracture history to examine the consistency of the relations between premenopausal and postmenopausal fractures, and to examine the associations between specific premenopausal and postmenopausal fractures. A p value <0.05 was considered statistically significant. All analyses were done using STATA 5.0 (Stata Corporation, College Station, TX).

Results

Of the 9086 participants, 454 (5.0%) reported fractures before menopause. Women with a premenopausal fracture had slightly lower calceneal and total hip bone mineral density, and were more likely to be taking

Table 1. Baseline characteristics of the 9086 participants in the Study of Osteoporotic Fractures, stratified by reported fracture before menopause

Variables	No premenopausal fracture (n = 8632)	Premenopausal fracture (n = 454)	p value
Age at study baseline (years)	72.3 ± 5.3	71.9 ± 5.1	0.1
Self-reported health (rated as fair/poor/very poor)	16	22	0.03
Cognitive function (Mini Mental State Exam)	24.7 ± 1.7	24.8 ± 1.5	0.2
Functional status (1–6 scale)	1.2 ± 1.3	1.5 ± 1.4	0.01
Number of falls in year before enrollment			0.001
1	19	23	
2+	9	17	
Alcohol (current drinks/week)	1.9 ± 4.0	2.1 ± 4.1	0.2
Current smoker	9.7	9.8	0.99
Lifetime caffeine intake (g)	4100 ± 2500	3800 ± 2400	0.01
Calcium intake (mg/week)	10 600 ± 5400	10 500 ± 5200	0.71
Maternal fracture	30	38	0.004
Weight gain from age 25 years (kg)	10.7 ± 11.0	11.8 ± 11.5	0.05
Body mass index (kg/m^2)	26.5 ± 4.6	26.9 ± 4.8	0.04
Exercise			
At age 50 years (no. of times/year)	122 ± 148	135 ± 154	0.08
At enrollment (kcal/week)	1602 ± 1673	1650 ± 1494	0.57
Medication use			
Estrogen	14	17	0.006
Thiazide diuretics	27	34	0.004
Corticosteroids	2	2	0.08
Thyroid hormone	12	12	0.5
Anticonvulsants	1	3	0.001
Bone mineral density (g/cm^2)			
Calcaneus	0.41 ± 0.09	0.39 ± 0.09	0.01
Total hip[a]	0.76 ± 0.13	0.74 ± 0.13	0.01

Values are percent, or mean ± SD.
[a] Measured at the second follow up visit (n = 7786).

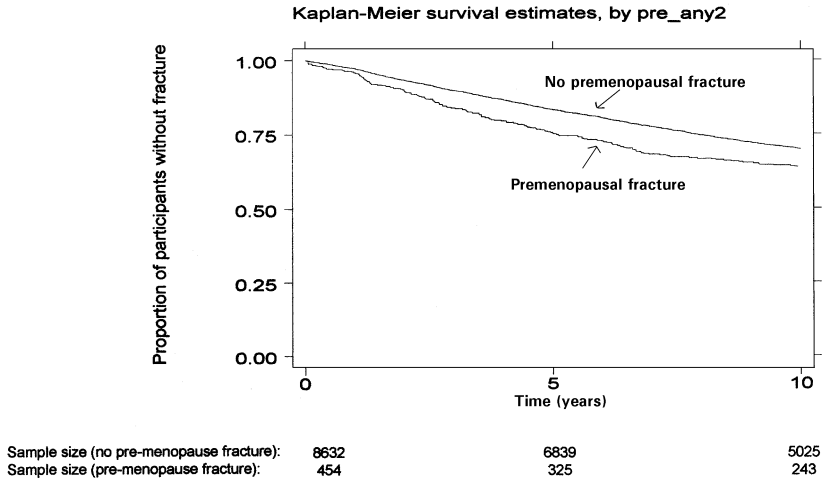

Fig. 1. The number of fractures occurring during the study period in 9086 women, stratified by those with and those without a premenopausal fracture.

estrogen, thiazides and anticonvulsant medications at enrollment than women without a premenopausal fracture (Table 1). They also had more self-reported falls in the year before enrollment, were more likely to report poor health, had worse functional status, and were more likely to have a history of maternal fracture (Table 1).

Women with a premenopausal fracture were about 35% more likely to have a fracture during the SOF study period than women without a premenopausal fracture (47.7 fractures per 1000 person-years vs 35.1 fractures per 1000 person-years, p=0.001). The difference in risk between those with and without a premenopausal fracture was apparent soon after the study period began (Fig. 1). An increased risk for women with premenopausal fractures was also seen in analyses that stratified by quartiles of calcaneal bone mineral density (Fig. 2).

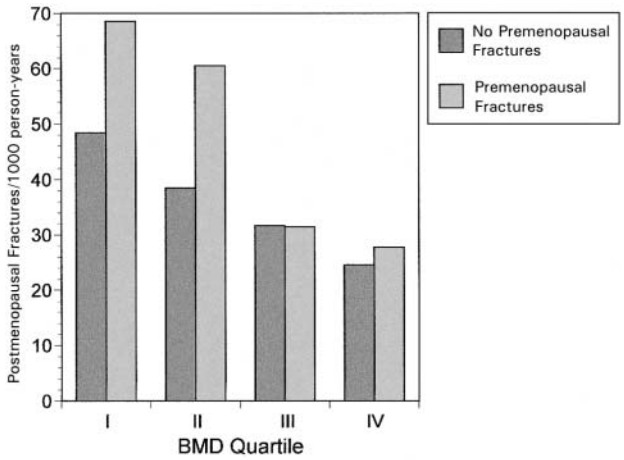

Fig. 2. Occurrence of fracture during the study period by history of fracture before menpause among 9086 women, stratified by age-adjusted quartile (from lowest (I) to highest (IV)) of calcaneus bone mineral density at enrollment.

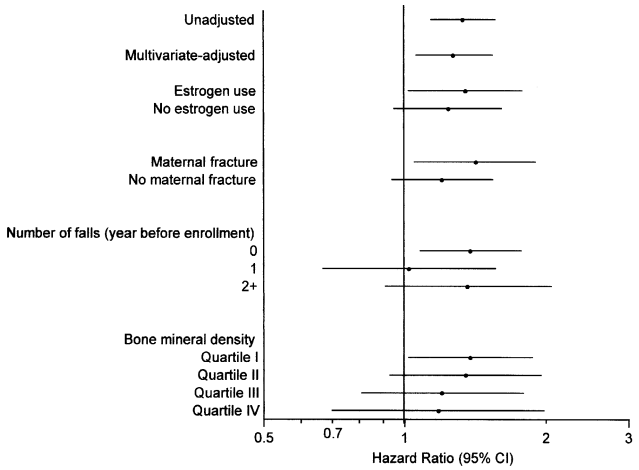

Fig. 3. Hazard ratios for premenopausal fracture as a risk factor for fracture during the study period. Multivariate models were stratified by variables listed above and adjusted for age at baseline, calcaneus bne mineral density, use of steroids and anticonvulsant medication, body mass index, number of falls and maternal fracture history. No evidence for heterogeneity in risk was fond among subgroups ($p>0.05$ for all interactions).

In analyses that adjusted for age, use of steroids and anticonvulsant medications, body mass index, number of falls and maternal fracture history, women with premenopausal fracture had a significantly greater risk of fracture during the study than women without a premenopausal fracture (HR, 1.25; 95% CI, 1.03–1.50; $p=0.01$). An increased risk associated with premenopausal fractures remained in analyses that were stratified by calcaneal bone mineral density, estrogen use, number of falls or maternal fracture history (Fig. 3). Analyses that used different measurements of bone mineral density (proximal or distal forearm, total hip, spine or femoral neck) gave similar results.

Fractures Between Menopause and SOF Enrollment

We also analyzed the association between premenopausal fractures and fractures between menopause and the start of the SOF study; these fractures were ascertained by self-report on the baseline questionnaire. Women with a premenopausal fracture were about 60% more likely to have a fracture between menopause and entry into the SOF cohort than women without a premenopausal fracture (16.0 fractures per 1000 person-years vs 10.0 fractures per 1000 person-years, $p<0.001$). In analyses that adjusted for calcaneal bone mineral density, use of steroids and anticonvulsant medications, body mass index, number of falls and maternal fracture history, women with premenopausal fracture had a significantly greater risk of fracture between menopause and the SOF study then women without a premenopausal fracture (HR, 1.6; 95% CI, 1.3–2.0; $p<0.001$).

Specific Type of Fractures

The final multivariate model, including fractures during the study period, included 333 women who reported at least one premenopausal fracture (ankle or foot (n = 132), wrist (n = 102), leg (n = 26), finger (n = 21) and other (n = 23), and 2011 women who reported at least one fracture during the study period (Table 2). Premenopausal wrist fracture increased the risk for the same type of fracture after menopause (Table 2). A

Table 2. Association between the most common premenopausal fractures and subsequent fractures during the study period in 9086 women

Premenopausal fracture	Postmenopausal fracture				
	Any (n = 2001)	Wrist (n = 424)	Ankle/foot (n = 384)	Hip (n = 376)	Humerus (n = 261)
Any (n = 333)	1.3 (1.1–1.5)	1.4 (0.9–2.0)	1.2 (0.8–1.8)	0.7 (0.4–1.3)	0.9 (0.5–1.7)
Ankle (n = 132)	1.2 (0.9–1.6)	0.5 (0.2–1.3)	1.0 (0.5–2.1)	0.8 (0.3–1.7)	0.3 (0.1–1.4)
Wrist (n = 102)	1.3 (0.9–1.8)	2.2 (1.3–3.7)	1.1 (0.5–2.3)	0.5 (0.2–1.4)	1.1 (0.4–2.6)
Leg (n = 26)	1.0 (0.5–1.9)	1.7 (0.5–5.3)	0.6 (0.1–4.2)	1.4 (0.4–5.7)	0.9 (0.1–6.2)
Finger (n = 21)	2.2 (1.2–4.1)	2.3 (0.7–7.0)	No fractures	3.0 (1.0–9.4)	2.7 (0.7–10.8)

Values are hazard ratio (95% confidence interval).
Adjusted for calcaneus bone mineral density, age at study baseline, use of steroids and anticonvulsant medications, body mass index, number of falls and maternal fracture history.

premenopausal finger fracture was the only type of fracture that was a risk factor for future hip fracture.

The numbers of premenopausal hip fractures ($n = 7$), as well as of other premenopausal fractures (rib, spine, humerus and shoulder), were too small to examine the relations between these fractures and postmenopausal fractures.

Discussion

We found that a fracture before menopause was a strong predictor of a fracture after menopause, such that women with a fracture before menopause had about a 30% greater rate of postmenopausal fracture. Adjustment for differences in age, bone mineral density, the propensity to fall, estrogen and other medication use, maternal fracture history and general functional ability did not explain this association. We restricted most of our analysis to fractures that occurred after women were enrolled in the SOF study, because all these fractures were confirmed by a study physician and were therefore more accurate than self-reported fractures [13].

Previous studies have found that past fractures are associated with an increased risk of future fracture [1–7,10]. Most of these studies, however, focused on predictors of hip fracture in postmenopausal women. Owen et al. [3] found that fractures of the distal radius were associated with a 1.3-fold increased risk of subsequent hip fracture, but only among women who were more than 70 years old at the time of the radius fracture. Lauritzen et al. [2] followed women aged 20–99 years for up to 9 years and found that a radius fracture doubled the risk of subsequent hip fracture among women aged 60–79 years. The relative risks at other ages were not statistically significant [2]. Another study reported that previous fractures of the trochanter, forearm or spine were risk factors for future fractures, especially soon after menopause [10]. None of these studies adjusted for bone mineral density.

The analysis of postmenopausal fractures that occurred before the study showed a stronger association between premenopausal and postmenopausal fractures than for fractures that occurred after the study began. This may reflect a true biologic association or, alternatively, women who recalled premenopausal fractures may also have been more likely to recall fractures between menopause and SOF enrollment.

This study is limited because the premenopausal fractures were determined by recall. However, recall of past fractures is fairly accurate, at between 80% and 100% [14,15]. We previously found that the false-positive rate ranged from 5% for upper arm and shoulder fracture to 20% for hand or finger fracture [13]. The lower accuracy of self-reported fractures in our study mimics the situation in clinical practice, in which a physician does not always have access to accurate records of previous fractures. Also, since only seven hip fractures occurred before menopause, we did not have the power to examine the relation between these fractures and the risk of future fractures. Finally, the subjects in this study were community-dwelling white women, so our results may not be applicable to men, to women who live in nursing homes, or possibly to women of other races.

In conclusion, we found that a premenopausal fracture is a risk factor for subsequent fracture after menopause, independent of bne mineral density. The increased risk is less than that from a 1 SD decrease in bone mineral density, but similar to a maternal history of fracture or a history of two or more falls in the previous year. This information may be helpful in the decision whether to measure bone mineral density or to institute preventive care for osteoporosis.

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