Identification and Fracture Outcomes of Undiagnosed Low Bone Mineral Density in Postmenopausal Women

Results From the National Osteoporosis Risk Assessment

Ethel S. Siris, MD

Paul D. Miller, MD

Elizabeth Barrett-Connor, MD

Kenneth G. Faulkner, PhD

Lois E. Wehren, MD

Thomas A. Abbott, PhD

Marc L. Berger, MD

Arthur C. Santora, MD

Louis M. Sherwood, MD

O STEOPOROTIC FRACTURES are an important cause of disability.[1] Hip fracture is associated with a 20% excess mortality in the year following fracture.[2] The cost of managing fractures is substantial: approximately $13.8 billion dollars were spent in the United States in 1995 alone[3]; estimates of current costs would almost certainly be larger. The size of the population aged 50 years or older will increase markedly during the next several decades, driven by the aging of the baby boomers and by increasing longevity. Thus, the direct as well as indirect costs of fractures are expected to increase correspondingly, both in the United States and worldwide.[4]

Low bone mineral density (BMD) is the single best predictor of fracture risk in asymptomatic postmenopausal women.[5,6] Dual-energy x-ray absorptiometry (DXA) of the hip and spine is

Context Large segments of the population at risk for osteoporosis and fracture have not been evaluated, and the usefulness of peripheral measurements for short-term prediction of fracture risk is uncertain.

Objectives To describe the occurrence of low bone mineral density (BMD) in postmenopausal women, its risk factors, and fracture incidence during short-term follow-up.

Design The National Osteoporosis Risk Assessment, a longitudinal observational study initiated September 1997 to March 1999, with approximately 12 months of subsequent follow-up.

Setting and Participants A total of 200160 ambulatory postmenopausal women aged 50 years or older with no previous osteoporosis diagnosis, derived from 4236 primary care practices in 34 states.

Main Outcome Measures Baseline BMD T scores, obtained from peripheral bone densitometry performed at the heel, finger, or forearm; risk factors for low BMD, derived from questionnaire responses; and clinical fracture rates at 12-month follow-up.

Results Using World Health Organization criteria, 39.6% had osteopenia (T score of –1 to –2.49) and 7.2% had osteoporosis (T score ≤–2.5). Age, personal or family history of fracture, Asian or Hispanic heritage, smoking, and cortisone use were associated with significantly increased likelihood of osteoporosis; higher body mass index, African American heritage, estrogen or diuretic use, exercise, and alcohol consumption significantly decreased the likelihood. Among the 163979 participants with follow-up information, osteoporosis was associated with a fracture rate approximately 4 times that of normal BMD (rate ratio, 4.03; 95% confidence interval [CI], 3.59-4.53) and osteopenia was associated with a 1.8-fold higher rate (95% CI, 1.49-2.18).

Conclusions Almost half of this population had previously undetected low BMD, including 7% with osteoporosis. Peripheral BMD results were highly predictive of fracture risk. Given the economic and social costs of osteoporotic fractures, strategies to identify and manage osteoporosis in the primary care setting need to be established and implemented.

JAMA. 2001;286:2815-2822   www.jama.com

currently the "gold standard" for measurement of BMD.[7] Central DXA equipment is large, expensive, and not universally available. Testing costs are not consistently covered by insurance companies, especially for women younger than 65 years. The availability of lower-cost, small, portable technologies that

Author Affiliations: Columbia University College of Physicians and Surgeons, New York, NY (Dr Siris); Colorado Center for Bone Research, Lakewood (Dr Miller); University of California, San Diego, La Jolla (Dr Barrett-Connor); Synarc, Portland, Ore (Dr Faulkner); University of Maryland, Baltimore (Dr Wehren); and Merck & Co Inc, West Point, Pa (Drs Wehren, Abbott, Berger, Santora, and Sherwood).
Corresponding Author and Reprints: Ethel S. Siris, MD, Toni Stabile Osteoporosis Center, Columbia Presbyterian Medical Center, 180 Fort Washington Ave, New York, NY 10032-3784 (e-mail: es27@columbia.edu).

test peripheral skeletal sites has improved access to testing.[8] Bone mineral density at appendicular skeletal sites, including the distal radius, phalanx, and calcaneus, correlates reasonably well ($r \approx 0.6$) with density in the axial skeleton (hip and spine); the correlation is similar to that between hip and spinal measurements.[9]

More importantly, peripheral BMD measurement can be used to assess fracture risk at both peripheral and central sites[10,11] and performs as well as central BMD, with the exception of assessment of hip fracture risk, which is best predicted by hip BMD measurement.[12] Unfortunately, despite the availability of densitometry, osteoporosis often remains undiagnosed until a fracture occurs, and reluctance exists among physicians to rely on results of peripheral BMD testing for management decisions. Early identification of women at increased risk of fracture because of osteoporosis presents an opportunity for intervention to decrease fracture risk.

The National Osteoporosis Risk Assessment (NORA) is a longitudinal observational study of osteoporosis among postmenopausal women in primary care practices in the United States. An objective of the study is to increase awareness and understanding of osteoporosis among women and their physicians. To address these issues, NORA has measured BMD in and is collecting information longitudinally from more than 200 000 postmenopausal women across the United States. Initial goals of the study include assessment of the association between potential risk factors and low BMD and assessment of the association of BMD and other risk factors with short-term fracture incidence.[13] In this article, we report the prevalence of low appendicular BMD within the NORA cohort, its association with risk factors for osteoporosis, and its relation to fracture incidence during 1 year of follow-up.

METHODS
Patient Population

A detailed description of the entire study design has been published.[13] Enrollment in the primary care arm was conducted in the 34 states in which more than 80% of women older than 50 years reside, based on US census data. Physicians were recruited for participation on the basis of caring for large numbers of postmenopausal women and not having in-office BMD testing equipment. Approximately 17% of invited physicians agreed to consider participation; of these, 75% to 80% participated.

Each office provided randomly selected names of up to 300 eligible women, of whom 40 to 100 accepted the invitation to participate. Overall, about 30% of women who were invited to participate did so. There were no general health or preexisting medical condition exclusions, although women had to be ambulatory and able to visit their physician offices. Women who were currently being treated with a bisphosphonate, calcitonin, or raloxifene were ineligible for participation (current estrogen use was not an exclusion criterion), as were women who were participants in any clinical trial related to osteoporosis. Postmenopausal women (defined as having no menstrual period, bleeding, or spotting during the 6 months prior to enrollment) who were at least 50 years old, had not had a previous diagnosis of osteoporosis, and had not had a BMD measurement within the preceding 12 months were eligible to participate in the study and comprise the population for this report. These women were recruited from the practices of 4236 primary care physicians and were enrolled between September 1997 and March 1999. Written informed consent was obtained from each participant. Participants received no payment. Both the study protocol and consent documents were approved by the national Essex Institutional Review Board.

Questionnaires

Each participant completed a core questionnaire that included general demographic information as well as questions about personal and family history of fracture, lifestyle behaviors, and medication use. At approximately 12 months after enrollment, each participant received a follow-up questionnaire that included questions about new fractures.

BMD Measurement

In the physician's office, each participant had peripheral BMD measurement at no cost during a scheduled NORA visit. Each participant had 1 of the following BMD measurements: forearm, using peripheral DXA (pDEXA; Norland, Fort Atkinson, Wis); finger, using pDXA (Accu-DEXA, Schick, Long Island City, NY); or heel, using either single x-ray absorptiometry (SXA) (Osteoanalyzer, Siemens-Osteon, Wahiawa, Hawaii) or ultrasonography (Sahara, Hologic, Bedford, Mass). All instruments were calibrated daily and before use in each new location using the manufacturer's internal standard. All testing was conducted by licensed technicians who had completed training by the manufacturer of the equipment they were using and by the International Society for Clinical Densitometry. Quality assurance throughout the project was maintained by staff of the quality assurance center at Synarc, Portland, Ore, who monitored each technician's scans according to a rigorous formal protocol.[14]

Definition of Low BMD

World Health Organization (WHO) criteria for low BMD, which were based on BMD measurements at the forearm, were applied for this analysis.[15] T scores were calculated from the manufacturers' healthy, white young adult reference databases using the standard formula as follows: T score = BMD of participant − mean BMD of reference population/SD of BMD of reference population. A T score of 0 means that the measured BMD is equivalent to the mean peak BMD of a population of healthy premenopausal white women aged 20 to 29 years, as reported by the equipment manufacturers. A T score of −1 represents a BMD measurement 1 SD below this mean, and

each SD decline in T score is associated with an approximate doubling of relative risk of fracture.[11] T scores between 1 and 2.5 SDs below the average for the reference population were classified as osteopenia. Measurements 2.5 SDs or more below the young adult mean were classified as osteoporosis.

Definitions of Risk Factors

Potential risk factors for osteoporosis used in these analyses were identified from the medical literature and included age, racial/ethnic background, height, weight, age at menopause, postmenopausal estrogen use, maternal history of osteoporosis, personal and family history of fracture, cigarette smoking, exercise, use of calcium supplements, use of thyroid hormone, cortisone, or diuretic medication, and caffeine and alcohol consumption. If a woman was uncertain of her current height, she was asked to have someone measure it. Past use and current regular use of postmenopausal estrogen and current regular use of calcium supplements, thyroid hormone, cortisone, or diuretics were questioned. Use of progestational agents was not queried, so "estrogen use" reflects use of both unopposed estrogen and estrogen plus progesterone. Exercise was defined as engaging in any variety of physical activities for the purpose of exercise. Cigarette smoking, consumption of caffeinated beverages or alcoholic beverages, and amounts of their use were queried. Previous osteoporotic fractures (for the participant and her close female relatives) were limited to clinically diagnosed fractures of the hip, rib, wrist, or spine that occurred after age 45 years. Body mass index (BMI) was calculated from the reported height and weight; quartiles of BMI were used in logistic regression analysis.

Data Analysis

Analyses were performed using SAS Version 6.12 software (SAS Institute, Inc, Cary, NC). With the exception of race, each risk factor was divided at the median for estimation of its bivariable association with low bone mass, using χ^2 tests of significance. The odds ratio

(OR) of low bone mass was then estimated in a multivariable logistic regression model, and ORs and 95% confidence intervals (95% CIs) are presented. All potential risk factors, whether or not they demonstrated significant associations with BMD in bivariable analysis, were included in an initial model, and backward stepwise elimination was used to arrive at the final model. For continuous variables, missing data were omitted; for categorical variables, a separate category of "missing" was entered into analyses. Goodness of fit was evaluated using the Hosmer-Lemeshow statistic. In these analyses, BMD was modeled as T score above or below the cutoff value for osteoporosis (ie, 2.5 SDs below the young adult mean value).

Incident fractures (wrist/forearm, rib, spine, hip, and other) were identified from responses to questionnaires mailed approximately 12 months after enrollment. Reported new fractures were compared with fractures that had been reported at baseline. If the sites were identical, the fracture was considered to be preexisting and was not included in the analysis. If a participant reported 4 or more new fractures, these data were also excluded from analysis. Overall fracture rates were calculated per person, not by total number of fractures (ie, if a participant reported 2 new fractures, they were counted as 1 fracture event), weighted for time of follow-up. Risk ratios, unadjusted and adjusted for age, BMD site/device, race/ethnicity, prior fracture, and estrogen use, were based on Cox proportional hazards models. No time-dependent variables or interaction terms were included. Proportional hazards assumptions were tested and met within the models by plotting log-log survivor functions.

RESULTS

Baseline information was available for 200 160 women (**TABLE 1**); 163 979 participants (81.9%) provided follow-up information. The mean (SD) age was 64.5 (9.3) years (range, 50-104 years). Although most participants (89.7%) were white, the study population also

Table 1. Demographics and Risk Factor Profiles of Participants (N = 200 160) at Baseline

Characteristics	No. (%)
Age group, y	
50-59	70 984 (35.5)
60-69	67 300 (33.6)
70-79	48 645 (24.3)
≥80	13 161 (6.6)
Missing/unknown	70 (0.0)
Race/ethnicity	
African American	7784 (3.9)
White	179 471 (89.7)
Asian	1912 (1.0)
Hispanic	6973 (3.5)
Native American	1708 (0.9)
Other/missing	2312 (1.2)
Education	
High school or less	117 062 (58.5)
At least some college	81 702 (40.8)
Missing/unknown	1396 (0.7)
Self-rated health status	
Excellent	22 827 (11.4)
Very good	64 440 (32.2)
Good	76 810 (38.4)
Fair/poor	33 847 (16.9)
Missing/unknown	2236 (1.1)
Years since menopause	
0-9	42 846 (21.4)
10-19	51 131 (25.5)
20-29	52 554 (26.3)
≥30	30 266 (15.1)
Missing/unknown	23 363 (11.7)
Geographic region	
North	43 332 (21.6)
Central	52 668 (26.3)
West	35 113 (17.5)
South	69 047 (34.5)
Body mass index, kg/m²	
<23	40 118 (20.0)
23.01-25.99	46 836 (23.4)
26-29.99	50 114 (25.0)
≥30	55 972 (28.0)
Missing/unknown	7120 (3.6)
History of fracture after age 45 y	
Any fracture	22 096 (11.0)
Hip	2808 (1.4)
Rib	7372 (3.7)
Wrist	12 319 (6.2)
Spine	2424
Maternal history of osteoporosis	23 477 (11.7)
Maternal history of fracture	44 379 (22.2)
Medication use	
Thyroid hormone	35 946 (18.0)
Cortisone	4617 (2.3)
Diuretics	34 126 (17.0)
Estrogen use	
Never	68 528 (34.2)
Past	36 421 (18.2)
Current	90 166 (45.0)
Missing/unknown	5045 (2.5)
Cigarette smoking	
Never	105 872 (52.9)
Past	69 973 (35.0)
Current	21 417 (10.7)
Missing/unknown	2898 (1.4)
Regular exercise, times/wk	
0-2	99 447 (49.7)
≥3	97 220 (48.6)
Missing/unknown	3493 (1.7)
Alcohol use, drinks/wk	
None	144 990 (72.4)
<7	34 140 (17.1)
7-13	10 319 (5.2)
≥14	5098 (2.5)
Missing/unknown	5613 (2.8)

included 7784 African American, 6973 Hispanic, 1912 Asian, and 1708 Native American women. Current health status was reported as good, very good, or excellent by 82.0%. At baseline, more than 22 000 women (11.0%) reported having at least 1 fracture after age 45 years. Wrist fractures were the most common, reported by 12 319 women (6.2%); 2808 women (1.4%) reported a hip fracture. A maternal history of a diagnosis of osteoporosis was reported by 11.7%, although 22.2% reported that their mothers had experienced at least 1 fracture after age 45 years and 24.0% reported that another close female relative had done so. Current or past use of estrogen was reported by 63.2% and current or past cigarette smoking by 45.7%; 72.4% denied any recent alcohol consumption.

TABLE 2 shows the distribution of T scores, overall and separately for each technology/site. Heel SXA was used to test 107 897 women, distal forearm pDXA for 67 566 women, finger pDXA for 15 011 women, and heel ultrasonography for 9686 women. Of those tested with SXA at the heel, 44.4% were identified as having osteopenia and an additional 4.9% had osteoporosis; the corresponding percentages for pDXA at the forearm were 35.3% and 10.2%; for pDXA at the finger, 27.8% and 13.5%; and for ultrasonography at the heel, 34.1% and 3.4%. Overall, 39.6% of women tested had osteopenia and another 7.2% had osteoporosis.

The ORs and 95% CIs for the final multivariable logistic regression model, with T score of –2.5 or lower as the dependent variable, are shown in TABLE 3. The effect of advancing age was independent of all other factors, with odds of osteoporosis increasing from 1.79 (95% CI, 1.56-2.06) for women aged 55 to 59 years to 22.56 (95% CI, 19.82-25.67) for women aged 80 years or older. Number of years since menopause was associated with significantly greater odds of osteoporosis, independent of age, only among women with more than 30 years since menopause. Poor self-rated health, personal history of fracture at the hip, wrist, spine, or rib, maternal history of osteoporosis, and maternal history of fracture after age 45 years were each associated with a significantly increased likelihood of osteoporosis. Compared with white women, the odds of osteoporosis were increased for Asian women (OR, 1.56) and Hispanic women (OR, 1.31) and decreased for African American women (OR, 0.55). Native Americans were similar to whites (OR, 0.97). Both current and former smokers were more likely to have T scores consistent with osteoporosis (OR, 1.58 and 1.14, respectively), as were current users of cortisone (OR, 1.63).

Increasing BMI was associated with decreased odds of osteoporosis (OR, 0.16 for BMI $\geq$30 kg/m^2 compared with BMI <23 kg/m^2). Both former and cur-

rent use of postmenopausal estrogen were associated with decreased odds of osteoporosis (OR, 0.77 and 0.27, respectively), with current estrogen use demonstrating a stronger association. Current diuretic use and current exercise were associated with decreased odds of osteoporosis (OR, 0.81 and 0.86). Consumption of 1 to 6 alcoholic beverages per week decreased the odds of osteoporosis (OR, 0.85). Higher levels of alcohol consumption were also associated with a lower likelihood of osteoporosis than no use of alcohol (OR, 0.76 for 7-13 drinks per week and 0.62 for $\geq$14 drinks per week).

Because the unadjusted probability of having a T score of –2.5 or lower ranged from 3.4% to 13.5% according to which site was measured and which device was used (Table 2), we controlled for measurement site and device in the multivariable analysis (Table 3). The analysis shows that in comparison to heel SXA, individuals measured with ultrasonography at the heel had somewhat decreased odds of osteoporosis (OR, 0.79), while those measured with DXA at the forearm or finger had increased odds (OR, 2.86 and 4.82, respectively).

The median interval of follow-up was 406 days (99% range, 313-784 days). When responders to follow-up (n=163 979) were compared with nonresponders, the nonresponders were older, less well educated, in poorer general health, less likely to be white, less

Table 2. Distributions of Bone Mineral Density (BMD) Among Participants

		Technology			
	Total	Heel Single-Energy X-Ray Absorptiometry	Forearm Peripheral Dual-Energy X-Ray Absorptiometry	Finger Peripheral Dual-Energy X-Ray Absorptiometry	Heel Ultrasonography
BMD, mg/cm^2					
No.	200 160	107 897	67 566	15 011	9686
Mean (SD)		361.31 (83.93)	308.1 (65.43)	479.69 (87.45)	517.83 (129.71)
Median		360.9	308	481	509.55
T score					
Mean (SD)		–0.974 (0.93)	–0.835 (1.30)	–0.628 (1.00)	–0.564 (1.16)
Median		–0.98	–0.84	–0.6	–0.64
Category, %					
$\geq$–0.99	53.2	50.7	54.5	58.7	62.5
–1.00 to –2.49	39.6	44.4	35.3	27.8	34.1
$\leq$–2.50	7.2	4.9	10.2	13.5	3.4

likely to have used estrogen, more likely to be current smokers, and less likely to exercise regularly than women who responded to follow-up questionnaires. Because of the very large sample size, all differences between responders and nonresponders were statistically significant ($P<.001$).

Fracture rates according to the T-score categories of normal BMD, osteopenia, and osteoporosis are shown in TABLE 4. Overall, osteoporosis was associated with a 4-fold higher rate of fracture than normal BMD. Women with osteopenia experienced a 1.8-fold higher rate of fracture. Osteoporosis was associated with a higher rate of fracture than osteopenia: rate ratios (osteoporosis vs osteopenia) for individual sites ranged from 1.86 (for forearm fracture) to 3.30 (for hip fracture). Fracture rates in osteopenic women were intermediate between the normal BMD and osteoporotic groups.

In a Cox proportional hazards model (TABLE 5), osteopenia was associated with 1.73 times the risk of fracture and osteoporosis with 2.74 times the risk of incident fracture within 1 year. Independent predictors of fracture were similar to those predictive of osteoporosis. Increasing age (relative hazard [RH], 1.32 for women aged ≥80 years), years since menopause (RH, 1.18 for women with 10-19 years since menopause; 1.51 for women with ≥30 years since menopause), higher education (RH, 1.26), fair or poor self-rated health status (RH, 1.79), personal history of fracture (ranging from 1.72 for hip fracture to 2.14 for spinal fracture), maternal history of fracture (RH, 1.27), current cortisone use (RH, 1.57), and former (RH, 1.09) and current (RH, 1.14) cigarette smoking were associated with increased risk of wrist, spine, rib, or hip fracture in the 12 months after BMD testing. Current estrogen use (RH, 0.82), low alcohol use (RH, 0.85 for 1-6 drinks per week), Asian race (RH, 0.41), and African American race (RH, 0.54) were the only covariates associated with significantly decreased risk of fracture.

COMMENT

NORA is the largest study of postmenopausal osteoporosis conducted in the United States. In this cohort, almost half of the 200160 participants without known osteoporosis had low BMD, including about 7% who had osteoporosis, as defined by WHO criteria. These results are consistent with the 50% to 68% estimated national prevalence of low hip BMD observed among women aged 50 years or older, based on the representative but much smaller Third National Health and Nutrition Examination Survey (NHANES III) cohort of only 3175 women.[16]

The large sample size allowed us to confirm the independent importance of multiple risk factors for low BMD. Age was the most important risk factor for predicting low BMD, even after controlling for years since menopause and other covariates, including prior fracture and BMI.

This cohort included more than 18000 minority women, making this by far the largest study of osteoporosis among racial/ethnic minority women. The low frequency of osteoporosis among African American women and the increased frequency among Asian women in this study are consistent with other reports.[16-18] Although low BMD was significantly less prevalent among African Americans, 32% of African American women had osteopenia and 4% had osteoporosis, suggesting that their absolute risk of fracture may be substantial, although less than that of women of other racial/ethnic groups. Future follow-up of NORA participants will allow us to address the association between BMD and fracture risk by BMD and ethnic group.

The data from this very large, diverse population confirm the associations of low weight, maternal history of osteoporosis or fracture, personal history of fracture, cigarette smoking, lack of exercise, use of glucocorticoid medication, and nonuse of estrogen with low BMD that were previously reported in smaller studies.[19-21] The BMD-protective factors included higher BMI, African American heritage, estrogen

Table 3. Multivariable Logistic Regression Model of Statistically Significant Correlates of T Score ≤−2.5

Risk Factors	Odds Ratio (95% Confidence Interval)
Age group, y	
50-54	1.00 (Referent)
55-59	1.79 (1.56-2.06)
60-64	3.84 (3.37-4.37)
65-69	5.94 (5.24-6.74)
70-74	9.54 (8.42-10.81)
75-79	14.34 (12.64-16.26)
≥80	22.56 (19.82-25.67)
Years since menopause	
≤5	1.00 (Referent)
6-10	0.79 (0.70-0.89)
11-15	0.83 (0.76-0.91)
16-20	0.96 (0.89-1.03)
21-25	1.01 (0.95-1.08)
26-30	1.02 (0.95-1.09)
31-35	1.10 (1.03-1.19)
36-40	1.14 (1.05-1.24)
≥41	1.24 (1.14-1.35)
College education or higher	0.91 (0.87-0.94)
Self-rated health status	
Excellent	1.00 (Referent)
Very good	1.04 (0.97-1.13)
Good	1.23 (1.14-1.33)
Fair/poor	1.62 (1.50-1.76)
Fracture history	
Hip	1.96 (1.75-2.20)
Wrist	1.90 (1.77-2.03)
Spine	1.34 (1.17-1.54)
Rib	1.43 (1.32-1.56)
Maternal history of osteoporosis	1.08 (1.01-1.17)
Maternal history of fracture	1.16 (1.11-1.22)
Race/ethnicity	
White	1.00 (Referent)
African American	0.55 (0.48-0.62)
Native American	0.97 (0.82-1.14)
Hispanic	1.31 (1.19-1.44)
Asian	1.56 (1.32-1.85)
Body mass index, kg/m²	
<23	1.00 (Referent)
23.01-25.99	0.46 (0.44-0.48)
26.00-29.99	0.27 (0.26-0.28)
≥30	0.16 (0.15-0.17)
Current medication use	
Cortisone	1.63 (1.47-1.81)
Diuretics	0.81 (0.76-0.85)
Estrogen use	
Former	0.77 (0.73-0.80)
Current	0.27 (0.25-0.28)
Cigarette smoking	
Former	1.14 (1.10-1.19)
Current	1.58 (1.48-1.68)
Regular exercise	0.86 (0.82-0.89)
Alcohol use, drinks/wk	
None	1.00 (Referent)
1-6	0.85 (0.80-0.90)
7-13	0.76 (0.69-0.83)
≥14	0.62 (0.54-0.71)
Technology	
Heel single-energy x-ray absorptiometry	1.00 (Referent)
Forearm peripheral dual-energy x-ray absorptiometry	2.86 (2.75-2.99)
Finger peripheral dual-energy x-ray absorptiometry	4.86 (4.56-5.18)
Heel ultrasonography	0.79 (0.70-0.90)

Table 4. Fracture Rates per 100 Person-Years of Follow-up According to T Score

	Fracture Rate (SE)			Fracture Rate Ratio (95% Confidence Interval)		
Fracture Type	T>−1.0 (Normal)	−1.0>T>−2.5 (Osteopenic)	T≤−2.5 (Osteoporotic)	Osteoporotic vs Normal	Osteoporotic vs Osteopenic	Osteopenic vs Normal
Any osteoporotic fracture	0.86 (0.024)	1.55 (0.044)	3.47 (0.160)	4.03 (3.59-4.53)	2.24 (2.01-2.50)	1.80 (1.49-2.18)
Hip	0.10 (0.009)	0.27 (0.019)	0.89 (0.082)	8.90 (6.84-11.57)	3.30 (2.63-4.14)	2.70 (2.14-3.40)
Spine	0.09 (0.009)	0.17 (0.014)	0.45 (0.058)	5.00 (3.63-6.88)	2.65 (1.95-3.60)	1.89 (1.46-2.44)
Rib	0.23 (0.014)	0.43 (0.023)	0.88 (0.081)	3.83 (3.07-4.78)	2.05 (1.66-2.53)	1.87 (1.59-2.20)
Wrist	0.22 (0.014)	0.61 (0.028)	1.17 (0.094)	5.32 (4.34-6.51)	1.92 (1.60-2.30)	2.77 (2.37-3.23)
Forearm	0.09 (0.009)	0.14 (0.013)	0.26 (0.044)	2.89 (1.96-4.26)	1.86 (1.26-2.73)	1.56 (1.19-2.05)

Table 5. Relative Hazard for New Fracture According to Baseline T Score, Adjusted for Covariates

Risk Factors	Relative Hazard (95% Confidence Interval)
Baseline T score	
>−1.0	1.00 (Referent)
−1.0 to −2.5	1.73 (1.57-1.91)
≤−2.5	2.74 (2.40-3.13)
Age, y	
50-59	1.00 (Referent)
60-69	0.90 (0.80-1.03)
70-79	1.05 (0.91-1.21)
≥80	1.32 (1.10-1.59)
Years since menopause	
<10	1.00 (Referent)
10-19	1.18 (1.01-1.38)
20-29	1.31 (1.12-1.54)
≥30	1.51 (1.26-1.81)
College education or higher	1.26 (1.16-1.38)
Self-rated health status	
Excellent	1.00 (Referent)
Very good	1.03 (0.88-1.20)
Good	1.13 (0.96-1.31)
Fair/poor	1.79 (1.52-2.11)
Fracture history	
Hip	1.72 (1.38-2.15)
Wrist	1.79 (1.56-2.06)
Spine	2.14 (1.72-2.67)
Rib	2.04 (1.76-2.37)
Maternal history of fracture	1.27 (1.16-1.40)
Race/ethnicity	
White	1.00 (Referent)
African American	0.54 (0.41-0.72)
Native American	0.89 (0.59-1.34)
Hispanic	0.91 (0.72-1.15)
Asian	0.41 (0.21-1.79)
Current cortisone use	1.57 (1.29-1.90)
Estrogen use	
Former	1.00 (0.90-1.11)
Current	0.82 (0.74-0.91)
Cigarette smoking	
Former	1.09 (1.00-1.19)
Current	1.14 (1.00-1.30)
Alcohol use, drinks/wk	
None	1.00 (Referent)
1-6	0.85 (0.75-0.96)
7-13	0.90 (0.74-1.09)
≥14	1.00 (0.78-1.30)

use, diuretic use, and exercise. Women who reported any alcohol consumption, regardless of amount, were less likely to have osteoporosis than were women who abstained, consistent with previous studies.[22] The determinants of low BMD at peripheral skeletal sites observed here are similar to those published for hip and spine.[6,20-22]

Different devices and sites yielded different estimates of low BMD and osteoporosis prevalence, such that a lower percentage of women tested with SXA at the heel were identified as having osteoporosis compared with measurement with pDXA measured at the forearm. Phalangeal measurements yielded the highest proportion of women identified with osteoporosis; heel ultrasonographic measurements yielded the lowest. Whether the source of these differences is biological, technological, or dependent on manufacturers' reference populations remains to be determined. Because the T score is calculated from the mean BMD and SD of that BMD in a young, healthy reference population database for each device, different young, healthy reference populations from different manufacturers may lead to different T scores, even in the same patient, when using different equipment.[9]

The 11% prevalence (n=22096) at baseline of fractures of the wrist, rib, hip, and spine since age 45 years among women in the NORA cohort is disturbing. These fractures are most likely to be a clinical consequence of osteoporosis, yet the diagnosis of osteoporosis had not been made, nor had appropriate treatment been implemented. This finding is consistent with several recently published reports, in which only 1 in 5 patients who had been seen with a minimal trauma fracture of the hip, wrist, spine, or shoulder had received treat-

ment for osteoporosis within the next year; the likelihood of treatment decreased with increasing age at time of fracture.[23-25] These results demonstrate an urgent need to educate health care professionals and patients that fracture in postmenopausal women implies osteoporosis unless proven otherwise.

This urgency is underscored by the fracture experience of NORA participants during the year after BMD testing. Low peripheral BMD clearly identifies women at risk of fracture. Women in NORA who were found to be osteoporotic at any peripheral site were at markedly increased risk of fracturing within 12 months of the finding. Similar results were reported in the Study of Osteoporotic Fractures (SOF).[7] In SOF, peripheral measurements at the heel or distal radius predicted fracture as well as femoral measurements. The association of low BMD and fracture is strongest for sites generally considered at risk in osteoporosis (wrist, forearm, rib, spine, and hip), but is apparent for fractures at other sites as well. In a longer follow-up of the SOF cohort, Seeley et al[10] found low BMD at the radius or calcaneus to be associated with fractures at all sites except the ankle, elbow, finger, and face.

In NORA, women with T scores of −2.5 or lower on any of the devices were more likely to have fractures than women whose T scores ranged from −1.0 to −2.49; in turn, these osteopenic women were more likely to sustain a fracture than women whose BMD was normal. Although each woman was tested with only a single device, all peripheral sites measured in NORA showed similar predictive ability for

overall fracture risk after accounting for age differences in the subgroups, as demonstrated by receiver operating characteristics curves.[26] In white women with BMD measured at heel SXA and forearm pDXA, who constitute 83% of that NORA cohort, the observed areas under the curve for hip fracture were 0.749 and 0.773, respectively.[27] These findings are comparable with those reported by Cummings et al[12] (0.75-0.78) for prediction of hip fracture in older women using measurements at hip sites, as well as observations in other populations.[28-31]

Differences in fracture incidence according to racial/ethnic group were observed in NORA. Although the prevalence of osteoporosis was higher among Asian and Hispanic women than among whites, the likelihood of fracture was no different for Hispanics and was lower for Asians. The results for Asian women are consistent with other reports[32-34]; lower incidence of hip fracture has also been observed in Hispanic women.[34,35] In general, other studies have not controlled for BMD or BMI, and adjustment for these factors has been shown to greatly reduce differences in fracture risk between white and Asian women.[36]

Despite the advantages of large size and broad geographic and ethnic participation, the NORA study has several limitations. The women who participated in NORA are a large but not nationally representative sample of women aged 50 years or older because women who had been diagnosed as having osteoporosis, were under treatment for osteoporosis, or had recent BMD testing were ineligible for participation. Thus, the true occurrence of osteoporosis was underestimated. However, the women who agreed to participate in NORA may have done so because they were worried about osteoporosis, leading to an overestimate. In NORA, all information about medical history, family history, risk factors, and fracture was collected by self-report, without corroboration from medical records or other sources. Questions that require remote recall may have been answered with some lack of

precision, which would tend to underestimate associations. This is not likely to differentially affect participants according to measured BMD or fracture incidence. Further, self-report of fractures has been observed to be generally reliable.[37-40] Because the majority of the spine fractures are asymptomatic or at least unrecognized,[41] NORA cannot address the value of risk factors or peripheral BMD to predict nonclinical spine fractures. Over the long term, both clinical and subclinical vertebral fractures are associated with increased morbidity and mortality.[42]

This report reaffirms the existence of a large population of women expected to live well into the 21st century who are at risk for future fracture. It also affirms the immediacy of risk posed by the finding of low BMD at peripheral skeletal sites; the risk of fracture is not a decade or more in the future but, rather, exists at the time of the diagnosis. No single measurement (peripheral or central) identifies all women with low BMD,[43] nor does any measurement necessarily identify individuals who will experience fracture; nevertheless, these data demonstrate the practical clinical value of information derived from single-site peripheral measurements in postmenopausal women. Given the economic and social costs of osteoporotic fractures, strategies to identify and manage osteoporosis in the primary care setting need to be established and implemented.

REFERENCES

1. Greendale GA, Barrett-Connor E, Ingles S, Haile R. Late physical and functional effects of osteoporotic fracture in women: the Rancho Bernardo study. *J Am Geriatr Soc.* 1995;43:955-961.
2. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporos Int.* 1998;8(suppl 4):S1-S88.
3. Ray NF, Chan JK, Thamer M, Melton LJ. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res.* 1997;12:24-35.
4. Johnell O. The socioeconomic burden of fractures: today and in the 21st century. *Am J Med.* 1997; 103(2A):20S-26S.
5. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res.* 1994;9:1137-1141.
6. Lips P. Epidemiology and predictors of fractures associated with osteoporosis. *Am J Med.* 1997;103(2A): 3S-11S.
7. Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W. Axial and appendicular bone density predict fractures in older women. *J Bone Miner Res.* 1992;7:633-638.
8. Miller PD, Bonnick SL, Johnston CC, et al. The challenges of peripheral bone density testing: which patients need additional central density skeletal measurements? *J Clin Densitom.* 1998;1:211-217.
9. Grampp S, Genant HK, Mathur A, et al. Comparisons of noninvasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. *J Bone Miner Res.* 1997;12: 697-711.
10. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associ-

ated with low appendicular bone mass in elderly women? *Ann Intern Med.* 1991;115:837-842.

11. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ.* 1996;312:1254-1259.

12. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet.* 1993;341:72-75.

13. Siris E, Miller P, Barrett-Connor E, Abbott T, Sherwood L, Berger M. Design of NORA, the National Osteoporosis Risk Assessment Program: a longitudinal US registry of postmenopausal women. *Osteoporos Int.* 1998;8(suppl 1):S62-S69.

14. Fasano G, Gaither K, Siris E, et al. The impact of quality assurance on bone densitometry in the National Osteoporosis Risk Assessment [abstract]. *Bone.* 1998;23(suppl):S590.

15. World Health Organization. *Assessment of Fracture Risk and Application to Screening for Postmenopausal Osteoporosis.* Geneva, Switzerland: World Health Organization; 1994.

16. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int.* 1998;8:468-489.

17. Davis JW, Novotny R, Ross PD, Wasnich RD. The peak bone mass of Hawaiian, Filipino, Japanese, and white women living in Hawaii. *Calcif Tissue Int.* 1994;55:249-252.

18. Pollitzer WS, Anderson JJ. Ethnic and genetic differences in bone mass: a review with a hereditary vs environmental perspective. *Am J Clin Nutr.* 1989;50:1244-1259.

19. Burger H, de Laet CE, van Daele PL, et al. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. *Am J Epidemiol.* 1998;147:871-879.

20. Kroger H, Tuppurainen M, Honkanen R, Alhava E, Saarikoski S. Bone mineral density and risk factors for osteoporosis: a population-based study of 1600 perimenopausal women. *Calcif Tissue Int.* 1994;55:1-7.

21. Nguyen TV, Kelly PJ, Sambrook PN, Gilbert C, Pocock NA, Eisman JA. Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention. *J Bone Miner Res.* 1994;9:1339-1346.

22. Holbrook TL, Barrett-Connor E. A prospective study of alcohol consumption and bone mineral density. *BMJ.* 1993;306:1506-1509.

23. Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fractures. *CMAJ.* 2000;163:819-822.

24. Kamel HK, Hussain MS, Tariq S, Perry HM, Morley JE. Failure to diagnose and treat osteoporosis in elderly patients hospitalized with hip fracture. *Am J Med.* 2000;109:326-328.

25. Freedman KB, Kaplan FS, Bilker WB, Strom BL, Lowe RA. Treatment of osteoporosis: are physicians missing an opportunity? *J Bone Joint Surg Am.* 2000;82:1063-1070.

26. Miller P, Abbott T, Wehren L, et al. Fracture risk assessment across peripheral sites: results from the NORA study. Presented at: International Society for Clinical Densitometry Annual Scientific Meeting; March 14-17, 2001; Dallas, Tex.

27. Miller P, Siris E, Abbott T, et al. Prediction of fracture risk in postmenopausal Caucasian women with peripheral bone densitometry: evidence from National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res.* 2001;16:S193.

28. Garnero P, Dargent-Molina P, Hans D, et al. Do markers of bone resorption add to bone mineral density and ultrasonographic heel measurement for the prediction of hip fracture in elderly women? the EPIDOS prospective study. *Osteoporos Int.* 1998;8:563-569.

29. Pothuaud L, Lespessailles E, Harba R, et al. Fractal analysis of trabecular bone texture on radiographs: discriminant value in postmenopausal osteoporosis. *Osteoporos Int.* 1998;8:618-625.

30. Schott AM, Weill-Engerer S, Hans D, Duboeuf F, Delmas PD, Meunier PJ. Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray absorptiometry and independently of bone mineral density. *J Bone Miner Res.* 1995;10:243-249.

31. Turner CH, Peacock M, Timmerman L, Neal JM, Johnston CC. Calcaneal ultrasonic measurements discriminate hip fracture independently of bone mass. *Osteoporos Int.* 1995;5:130-135.

32. Ross PD, Norimatsu H, Davis JW, et al. A comparison of hip fracture incidence among native Japanese, Japanese Americans, and American Caucasians. *Am J Epidemiol.* 1991;133:801-809.

33. Anderson JJ, Pollitzer WS. Ethnic and genetic differences in susceptibility to osteoporotic fractures. *Adv Nutr Res.* 1994;9:129-149.

34. Silverman SL, Madison RE. Decreased incidence of hip fracture in Hispanics, Asians, and blacks: California hospital discharge data. *Am J Public Health.* 1988;78:1482-1483.

35. Bauer RL. Ethnic differences in hip fracture: a reduced incidence in Mexican Americans. *Am J Epidemiol.* 1988;127:145-149.

36. Ross PD, He Y, Yates AJ, et al. Body size accounts for most differences in bone density between Asian and Caucasian women. *Calcif Tissue Int.* 1996;59:339-343.

37. Honkanen K, Honkanen R, Heikkinen L, Kroger H, Saarikoski S. Validity of self-reports of fractures in perimenopausal women. *Am J Epidemiol.* 1999;150:511-516.

38. Ismail AA, O'Neill TW, Cockerill W, et al. Validity of self-report of fractures: results from a prospective study in men and women across Europe. *Osteoporos Int.* 2000;11:248-254.

39. Nevitt MC, Cummings SR, Browner WS, et al. The accuracy of self-report of fractures in elderly women: evidence from a prospective study. *Am J Epidemiol.* 1992;135:490-499.

40. Bergmann MM, Byers T, Freedman DS, Mokdad A. Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. *Am J Epidemiol.* 1998;147:969-977.

41. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ. The incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res.* 1992;7:221-227.

42. Ensrud KE, Thompson DE, Cauley JA, et al. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. *J Am Geriatr Soc.* 2000;48:241-249.

43. Davis JW, Ross PD, Wasnich RD. Evidence for both generalized and regional low bone mass among elderly women. *J Bone Miner Res.* 1994;9:305-309.