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Identification of women at risk for developing postmenopausal osteoporosis with vertebral fractures: role of history and single photon absorptiometry*

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Summary

Putative risk factors for the development of postmenopausal osteoporosis (PMO) with vertebral fractures were examined in a retrospective study of 663 postmenopausal white females aged 45–75 years (266 women with non-traumatic vertebral compression fractures (VF+), 134 non-fractured women from a general medicine clinic (controls) and 263 non-fractured women who were evaluated when they presented specifically for osteoporosis screening (VF–)). The VF+ women differed from control women in several respects. The VF+ group reported a higher prevalence of a positive family history of osteoporosis, and a higher prevalence of a history of medical or surgical conditions known to be independently associated with metabolic bone disease, had fewer children, were smaller (weight, height) and were slightly older. The two groups, VF+ and controls, did not differ with respect to cigarette smoking, alcohol consumption, exercise habits, menstrual or menopausal history, dietary intake of milk and cheese or in amount taking calcium supplements during pregnancy.

The VF+ group also differed in certain respects from the VF– group. The VF+ group were smaller (weight, height) and were older. The VF+ group had lower cortical bone mass (measured by single photon absorptiometry of the non-dominant forearm) than either the control or VF– groups. The latter two groups did not differ from each other with respect to this measurement.

These markers demonstrated limited sensitivity and specificity as estimated from a confirmatory data set, particularly for the historical and anthropometric variables. We conclude that an assessment of the risk of developing PMO with vertebral fractures cannot be based on the putative risk factors as measured in our study, but must be based on measurement of bone mass.

Key words: Osteoporosis; Fracture; Risk factor; Screening; Bone density

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Introduction

The magnitude of the community health problem posed by postmenopausal osteoporosis (PMO) has been amply documented in the medical and lay literature over the past several years. Since a proven effective therapy for osteoporosis has not yet been established, it seems prudent to seek out and implement an effective prophylactic program to minimize the prevalence of this disease in the community. Such a program, early (within 5–7 years of the menopause) and prolonged (minimum 5–10 years) administration of estrogen, has been clearly and repeatedly demonstrated to retard the rate of postmenopausal bone loss [1,2] and significantly reduce the incidence of osteoporotic fractures of the forearm [3], spine [4,5] and hips [3,6–8]. There is a reluctance on the part of physicians and the general public to implement this prophylactic program on a widespread basis without making some attempt to identify those women who are at greatest risk for the development of osteoporosis and therefore most likely to receive greatest benefit from prophylaxis.

There is usually a lag time of 10–15 years between the last menstrual period and the development of the first osteoporotic vertebral fracture. To gather data on women age 50 and follow them until age 65 in order to prospectively test our ability to accurately predict who will or will not develop osteoporosis with fracture would be a tremendous undertaking, and is unlikely to be performed in one institution. We therefore undertook a retrospective study in an attempt to document those presumed risk factors that were more prevalent in women with osteoporotic vertebral fractures when compared to a non-fractured population.

Methods and Materials

Subjects

All participants were white females aged 45–75 and who were at least one year postmenopausal at the time of evaluation. Three groups of subjects were analysed.

Screened subjects

These two groups consisted of women meeting the above criteria and presenting for possible inclusion into a clinical trial studying the efficacy of sodium fluoride on osteoporosis. Subjects were solicited by media announcements of the trial and by notifying referring physicians of the trial. All women were physician or self-referred to the Bone and Mineral Division of Henry Ford Hospital, because osteoporosis was suspected or there was concern about the risk of developing osteoporosis. All patients were interviewed and examined by a physician and/or research nurse. All patients were classified into the following two groups.

Vertebral fracture group (VF+) ($n = 366$)

The VF+ group included women with definite postmenopausal osteoporosis with one or more vertebral compression fractures that had occurred in the absence of

trauma or in response to only trivial trauma. Radiographic documentation of vertebral fractures was obtained for each subject using criteria we have previously reported [9].

Nonvertebral fracture group (VF–) (n = 263)

The VF– group included women without evidence of one or more vertebral compression fractures that had occurred in the absence of trauma or in response to only trivial trauma. The absence of fracture was confirmed by radiographic documentation.

Clinic subjects

Control group (C) (n = 134)

The control group included consecutive patients who attended the general internal medicine clinics at two satellite facilities of Henry Ford Hospital. They had never been physician or self-referred to the Bone and Mineral Division and all denied ever having sought medical attention or advice about osteoporosis. Seventy-seven of these women were interviewed by telephone by a research nurse within one week of their attendance at the general medical clinic. The remaining 57 women were interviewed by telephone the day prior to their appointment at the clinic. Weight and height measurements were abstracted from the patient's medical record for that clinic visit. Radiographic documentation of the presence or absence of vertebral fractures was not sought in any subject in Group C.

Questionnaire

Each patient completed a standardized, detailed questionnaire designed to document putative risk factors in the pathogenesis of osteoporosis and the extent and severity of involvement of osteoporosis. There were 21 categorical (yes/no) responses and 8 numerical responses. We attempted to make the interview process as uniform as possible by limiting the number of interviewers. Every attempt was made to have the subjects restrict their responses to their diet and life-style during most of their adult life and avoid reporting recent changes. In a similar vein, all interviewers stressed that questions on exercise concerned involvement in a regular exercise program and not exercise associated with the activities of daily living.

Calcium intake was calculated based on a food frequency questionnaire pertaining to usual weekly intake of milk and cheese (see Table 1), which provide approximately 60% of dietary calcium in the American diet [10]. (The remaining 40% is distributed among more than 40 different foods.) Each response category was graded as to approximate calcium intake by a dietician and a summary score was computed. Smoking status was coded as current, ex and never. Detailed information about quantity and duration were not available. Alcohol intake and exercise were coded into three categories corresponding to frequent, moderate and none.

A subject was recorded as having a history of medical illness associated with accelerated bone loss if she reported any of the following: hyperparathyroidism, en-

dogenous and exogenous hyperthyroidism, endogenous and exogenous hypercortisolism, nontropical sprue, gastrectomy or short-bowel syndrome.

Anthropometry

Height and weight were measured in indoor clothes, without shoes, on all subjects interviewed. Those questioned by telephone were asked their height and weight and this was verified by review of the medical records, which should be fairly accurate since the woman had just had a clinic visit. Stature was measured with a Harpenden stadiometer [11], except at the satellite clinics (Group C), where a conventional scale was used. Subjects were asked to stand erect, with eyes directed straight ahead, and the horizontal plate or bar was lowered onto the crown of the head. An index of body size was derived from weight/height, which is a general measure of body bulk for epidemiological studies in Western female populations [12].

Bone mass

Appendicular bone mass was assessed by single photon absorptiometry [13]. Using a Norland bone densitometer bone mineral content (BM, g/cm) and bone width (BW, cm) were measured in the non-dominant radius at standard proximal and distal sites as the mean of four repeat scans, but without correction for possible calibration error. Precision (2–4%) and accuracy (<3% error) are acceptable for cross-sectional epidemiological studies. Because of problems in locating the distal site accurately, and because there was no significant difference in BM between the two sites in the VF+ and VF– groups, only the proximal measurement was obtained in the C group. The ratio BM/BW partly corrects for differences in body size and represents an estimate of linear mass density. The deviation of BM/BW from mean value at skeletal maturity is an estimate of absolute bone loss, and the deviation from the mean for subjects of the same age is an estimate of relative bone loss. Age-specific reference values were determined by interpolation from decade-specific values determined on normal subjects in Wisconsin. These deviations were expressed as z scores by dividing by the age specific standard deviation.

Statistical analysis

The three groups VF+, VF– and C were compared for differences between baseline characteristics. Analysis of variance or the nonparametric Kruskal-Wallis test were used to compare continuous variables as appropriate. Categorical variables were examined using χ^2 tests for $r \times c$ contingency tables. If significance ($P < 0.05$) was observed, all pairwise comparisons were examined. The Bonferroni method of adjustment for multiple testing was used.

Multiple stepwise logistic regression (MLR) was used to find sets of variables which best predicted vertebral fractures when comparing the VF+ and control groups and when comparing the VF+ and VF– groups [14]. A forward stepwise al-

gorithm was used. This procedure was implemented on a randomly selected subpopulation consisting of approximately one half of the available patients. The model was then evaluated for possible use as a screening tool by applying it to the remaining half of the subjects.

The screening characteristics of the models were evaluated using receiver operating characteristic (ROC) curves [15]. These plot the sensitivity versus one minus the specificity for all reference or cutpoint values possible. The set of cutpoints were defined as the probabilities of fracture generated for each patient from the final logistic model. The areas under the curve are computed and compared between various models. The area can be interpreted as the average sensitivity over all possible values of the specificity. We had no a priori range of specificities of interest and so the entire area under the ROC curve is important.

A single cutpoint, for each logistic model, was evaluated to determine estimates of predictive values. The cutpoint was chosen by minimizing a weighted sum of misclassifications where the weights were the sample size of the classification group [16]. The minimization procedure was performed on the data used to generate the model. Assessment was then made using the confirmatory data set. A single stage screening, based on each model generated, was evaluated. A two-stage screen was also considered where the questionnaire-based model was used to identify patients for further screening with bone densitometry. All predictive values were computed assuming a prevalence of vertebral fractures of 5% in the population to be screened [5].

Multiple linear regression techniques were used to generate models predicting various bone mineral content measures. A stepwise algorithm was used with the inclusion/exclusion *P*-value set at 0.05. The entire set of data was used in this analysis.

Results

Table 1 summarizes the historical and anthropometric data on the three groups of women. The women with osteoporosis and vertebral compression fractures (VF+) were older than the other two groups and consequently more years had elapsed since their menopause. These women were lighter than both controls and VF− groups and smaller (weight/height) than the control group.

Menstrual and menopausal history were similar in the three groups. The VF− group had the highest percentage of women with a surgical menopause, the highest percentage receiving hormonal therapy and the greatest average duration of therapy. However, none of these results were statistically significant as compared to either VF+ or C groups.

With regard to reproductive history, the VF+ group had slightly fewer children than the control group but the prevalence of nulliparity was similar in the three groups. Differences in prevalence of lactation and lifetime duration of lactation could not be detected.

A greater percentage of women with osteoporosis and vertebral compression fractures (VF+) were current smokers than in the VF− and C groups but the results

Table 1
Patient characteristics (mean ± SD)

	Vertebral compression fracture (VF+) (n = 266)	Control group (C) (n = 134)	Nonvertebral fracture group (VF−) (n = 263)	Significance[a]
General				
age (years)	65.1 ± 6.5	63.3 ± 7.5	61.8 ± 7.2	1, 2
years post menopause	19.0 ± 8.2	16.0 ± 8.3	16.0 ± 9.8	1, 2
height (cm)	155.4 ± 8.3	155.4 ± 9.1	158.8 ± 7.5	2, 3
weight (kg)	61.6 ± 12.9	67.6 ± 15.7	64.6 ± 13.4	1, 2
weight/height	0.40 ± 0.08	0.44 ± 0.09	0.41 ± 0.08	1, 3
Menstrual and menopausal history				
menarche (years)	13 ± 2	13 ± 2	13 ± 1	
last menstrual period (age)	46.1 ± 6.8	47.3 ± 5.8	45.9 ± 7.2	
surgical menopause (%)	29.5	31.1	38.5	
hormonal therapy (%)	52.9	45.9	55.6	
duration (years)	2.3 ± 4.9	2.2 ± 4.6	2.9 ± 5.4	
Reproductive history				
Pregnancies to term	2.1 ± 1.6	2.8 ± 1.7	2.5 ± 1.7	1
nulliparity (%()	17.9	10.6	14.6	
breast fed (%)	41.2	51.5	42.4	
total lactation (months)	4.1 ± 8.3	6.2 ± 9.8	6.1 ± 10.7	
calcium supplements (%)	13.0	5.3	15.7	3
History				
family history of osteoporosis (%)	46.0	32.8	45.7	1, 3
history of medical illness associated with accelerated bone loss (%)	10.2	1.5	5.0	1
Diet and lifestyle				
Smoking status:				
% current	27.2	21.6	19.5	
% ex	23.4	27.6	22.7	
Alcoholic beverages:				
% frequent	16.0	16.9	15.5	
% occasionally	53.0	53.1	60.0	
Exercise:				
% daily	28.0	28.5	33.9	3
% infrequently	24.0	17.7	31.2	
Calcium intake (mg/day)	490 ± 259	441 ± 238	480 ± 242	
Diet history				
Milk by glass:				
daily	54.5	43.6	52.7	
once/week	8.2	15.8	16.1	
< once/week	11.9	8.3	11.7	

(*continued*)

Table 1 (*continued*)

	Vertebral compression fracture (VF+) (n = 266)	Control group (C) (n = 134)	Nonvertebral fracture group (VF–) (n = 263)	Significance[a]
Milk in cereal:				
daily	49.6	45.5	53.8	
once/week	17.1	21.6	18.4	
< once/week	11.4	8.2	9.4	
Cheese:				
daily	48.3	42.9	50.2	
once/week	32.2	43.6	36.2	
< once/week	13.4	12.8	11.5	

[a] Any entry in this column indicates that test for differences among the 3 groups was significant, $P < 0.05$. The pairwise comparisons, 1, VF+ vs. C, 2, VF+ vs. VF– and 3, VF– vs. C, are indicated if $P < 0.017$.

were not statistically significant. It is also the case that more women in the VF– group exercised than in the other two groups.

A positive family history of osteoporosis was very common in the subjects evaluated in this study. While this history was more prevalent in those groups seeking consultation for osteoporosis (VF+, VF–), nearly one-third of women in the control group, who had specifically denied ever seeking medical attention for osteopo-

Table 2

Bone densitometry (means ± SD)

Variable	Vertebral compression fracture (VF+) (n = 266)	Control (C) (n = 134)	Nonvertebral fracture group (VF–) (n = 263)	Significance[a]
Proximal				
bone mineral content	0.63 ± 0.13	0.73 ± 0.13	0.73 ± 0.13	1, 2
bone mineral/bone width	0.52 ± 0.09	0.59 ± 0.09	0.59 ± 0.10	1, 2
adjusted bone mineral	−1.60 ± 1.25	−0.80 ± 1.12	−1.04 ± 1.32	1, 2
absolute bone mineral	−4.87 ± 1.93	−3.64 ± 1.86	−3.66 ± 2.04	1, 2
Distal				
bone mineral content	0.63 ± 0.15	–	0.73 ± 0.15	2
bone mineral/bone width	0.37 ± 0.07	–	0.43 ± 0.09	2
adjusted bone mineral	−1.82 ± 1.45	–	−1.15 ± 1.59	2
absolute bone mineral	−5.05 ± 2.15	–	−3.61 ± 2.13	2

[a] Any entry in this column indicates that test for differences among the 3 groups was significant, $P < 0.05$. The pairwise comparisons, 1, VF+ vs. C, 2, VF+ vs. VF–, and 3, VF– vs. C, are indicated if $P < 0.017$.

rosis or its prevention, had a positive family history of osteoporosis.

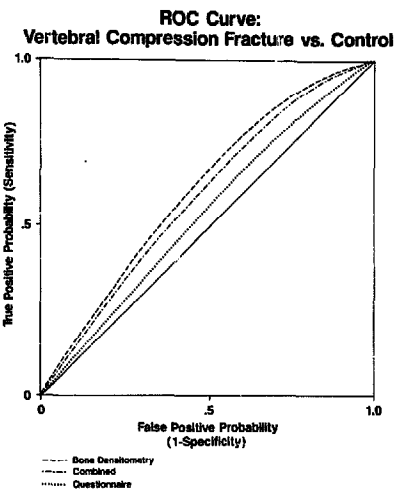
Bone mineral content measured by SPA was significantly lower in the VF+ group than the other two groups. There was no difference in bone mineral content between the two control groups (Table 2).

Since the method of entry into the study was different for both groups without vertebral fractures (VF– and C) and statistically significant differences could be demonstrated between these two groups, subsequent analysis was made comparing VF+ to C and VF+ to VF–. No analyses were performed considering VF– and C as a single control group.

Three models were developed using MLR analysis to identify the set of variables predicting the presence of vertebral fractures comparing the VF+ to control group. The models were based on the questionnaire data, the bone densitometry results and the combined data respectively. The models are summarized in Table 3.

The characteristics of the ROC curves (Fig. 1A,B) resulting from these models were compared by examining the areas under the curves (Table 5). The model based on the ratio of bone mineral content to bone width (bone densitometry model) had a slightly higher area although the difference was not statistically significant. The model based on the combined data was intermediate in area.

Figure 1A



The optimal cutpoints, defined by minimizing weighted false classifications, resulted in poor screening characteristics (Table 6). In all cases the sensitivity and specificity were low. The positive predictive value, which measures the conditional probability of having a vertebral fracture, given that the test indicates this, is only slightly elevated beyond the 5% a priori probability of having a vertebral fracture. The analogous conditional probability for not having a vertebral fracture, negative predictive value, is also only slightly elevated above the a priori probability of 95%.

Similar results hold for the comparison of the VF+ to VF− groups (Table 4). The model based on the bone densitometry results has a larger area under the ROC curve than either the model generated by the questionnaire data or the model generated by the combined data ($P < 0.01$) (Table 5). This is also indicated by the consideration of the optimal screening parameters. The estimates of both predictive probabilities are higher for the bone densitometry based model (Table 6).

Again all three models have poor screening characteristics. The sensitivities and

Figure 1B

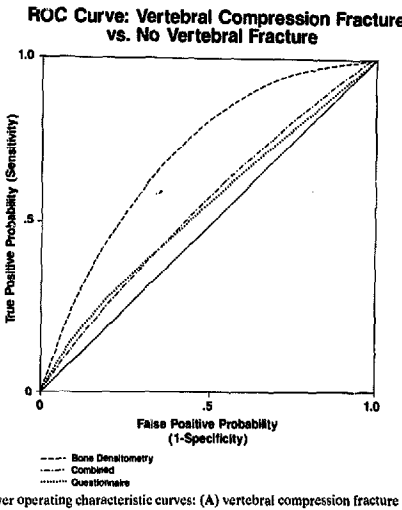


Fig. 1. Receiver operating characteristic curves: (A) vertebral compression fracture vs. control; (B) vertebral compression fracture vs. no vertebral fracture. Sources: (--------) bone densitometry; (·····) questionnaire; (-·-·-·-·-) combined.

Table 3

Logistic regression model: vertebral compression fracture vs. control

	Coefficient	SD	*P*
Questionnaire data			
constant	−1.695	1.411	–
total lactation (months)	−0.046	0.023	0.034
family history of osteoporosis	1.155	0.402	0.003
years post menopause	0.073	0.027	0.004
weight	−0.056	0.017	0.001
Model, $P < 0.001$ ($n = 150$)			
Bone densitometry data			
constant	−7.119	1.525	–
bone mineral/bone width	−10.269	2.625	0.001
Model, $P < 0.001$ ($n = 146$)			
Combined data			
constant	−10.661	2.062	–
bone mineral/bone width	−9.437	2.782	0.001
weight	−0.062	0.020	0.001
Model, $P < 0.001$ ($n = 144$)			

specificities are low and the screen results in too many misclassified patients to be of practical use (Table 6).

Discussion

In 1983 the Council on Scientific Affairs of the American Medical Association recognized the role of estrogen replacement therapy (ERT) in the prevention of postmenopausal osteoporosis. They concluded that "the election of estrogen replacement for this purpose in the *normal* menopausal patient can be based only on an assessment of the relative risks and benefits applicable to the individual patient" [17]. However, no information was provided as to how these risks and benefits might be assessed.

In 1984 the NIH consensus Conference on Osteoporosis reached a similar conclusion about the benefit of estrogen in preventing osteoporosis [18]. This conference concluded that osteoporosis is more common in underweight women, that cigarette smoking may be a predictor, and that calcium deficiency has been implicated in the pathogenesis of osteoporosis. The possible role of exercise, heredity and other dietary factors (alcohol, vitamin A and C, magnesium and protein) were recognized by this conference as being "less firmly established." At the follow-up Research Development conference on osteoporosis sponsored by the NIH in 1987, the

Table 4

Logistic regression model: vertebral compression fracture vs. no vertebral compression fracture

	Coefficient	SD	P
Questionnaire data			
constant	8.663	2.242	–
breast fed	−0.595	0.298	0.044
surgical menopause	−0.779	0.304	0.010
age at menarche	0.333	0.104	0.001
age	0.057	0.022	0.008
smoking status:			
ex smoker	0.644	0.373	0.001
current smoker	1.507	0.388	
Model, $P < 0.001$ ($n \approx 230$)			
Bone densitometry data			
constant	−2.968	0.838	–
bone mineral/bone width	−4.971	1.466	0.001
Model, $P < 0.001$ ($n = 215$)			
Combined data			
constant	2.277	2.251	–
age at menarche	0.334	0.116	0.003
surgical menopause	−0.919	0.337	0.005
smoking status:			
ex smoker	0.538	0.417	0.001
current smoker	1.542	0.440	
bone mineral/bone width	−4.030	1.642	0.012
breast fed	−0.646	0.328	0.047
Model, $P < 0.001$ ($n = 195$)			

Table 5

Screening characteristics[a]

Model:	VF+ vs. C				VF− vs. C			
	n		ROC		*n*		ROC	
Source	C	VF+	area	SE	VF−	VF+	area	SE
Quest	28	80	0.55	0.070	88	106	0.51	0.042
BD	28	80	0.62	0.064	88	106	0.72	0.037
BD + Quest	28	80	0.61	0.065	88	106	0.54	0.041

ROC, receiver operating characteristics; Quest, questionnaire; BD, bone densitometry; VF+, vertebral compression fracture; VF−, no vertebral compression fracture; C, control.

[a] Patients used to compute these statistics were not included in the set used to identify the model.

Table 6
Screening characteristics for optimal screen

Model	sens	spec	$P+$	$P-$
VF+ vs. C ($n = 80, n = 28$)				
bone densitometry	54 ± 5.6	61 ± 9.2	6.8 ± 1.6	96.2 ± 0.7
	(43, 65)	(42, 79)	(3.6, 10.0)	(94.8, 97.6)
questionnaire	56 ± 5.5	54 ± 9.4	6.0 ± 1.3	95.9 ± 0.8
	(45, 67)	(36, 72)	(3.5, 8.5)	(94.2, 97.6)
bone dens & ques	64 ± 5.4	57 ± 9.4	7.3 ± 1.6	96.8 ± 0.7
	(53, 75)	(39, 75)	(4.2, 10.3)	(95.4, 98.1)
two-stage	36 ± 5.4	79 ± 7.7	8.3 ± 3.0	95.9 ± 0.5
	(25, 47)	(64, 94)	(2.4, 14.2)	(94.9, 96.9)
VF+ vs. VF− ($n = 106, n = 88$)				
bone densitometry	48 ± 4.9	78 ± 4.4	10.3 ± 2.1	96.6 ± 0.4
	(38, 58)	(69, 87)	(6.2, 14.4)	(95.9, 97.3)
questionnaire	63 ± 4.7	39 ± 5.2	5.2 ± 0.6	95.2 ± 0.8
	(54, 72)	(29, 49)	(4.1, 6.2)	(93.6, 96.9)
bone dens & ques	44 ± 4.8	58 ± 5.3	5.2 ± 0.8	95.2 ± 0.6
	(35, 53)	(48, 68)	(3.6, 6.8)	(94.0, 96.3)
two-stage	32 ± 4.5	82 ± 4.1	8.6 ± 2.1	95.8 ± 0.3
	(23, 41)	(74, 90)	(4.4, 12.7)	(95.2, 96.5)

sens, sensitivity; spec, specificity; $P+$, positive predictive value; $P-$, negative predictive value. Mean ± SE with 95% confidence interval reported.

results of which were recently reported [19], stated little progress had been made in identifying historical risk factors for the development of PMO. In particular the risk attributed to alcohol, smoking and low dietary calcium was considered not well established.

We were unable to confirm that several putative diet and life style characteristics help predict who will or will not develop PMO with vertebral fractures. A low dietary calcium intake during childhood and adolescence results in a lower peak adult bone mass and an increased prevalence of osteoporotic fractures [20] but the role of dietary calcium once peak adult bone mass has been established has recently been questioned [21]. Furthermore, the prevalence of a low dietary calcium intake in peri- and postmenopausal women in the United States is so high [22] that it is not surprising that the discriminant value of this characteristic is low.

Our control group was recruited from general medical clinics where the incidence of tobacco- and alcohol-related illnesses may be high and this group may not be representative of the use of these substances in the general community. However, the prevalence of both tobacco and alcohol use in our control population is very similar to that reported by the National Center for Health Statistics for 1987 [23], the most recent year for which such information is available. We are unaware of any similar data with respect to participation in regular exercise, which is difficult to quantitate.

The VF− and VF+ groups are not representative of the general population. These groups together, however, are representative of those most likely to be

screened for possible high risk of osteoporosis.

Both the AMA and NIH reports recognized that osteoporosis is less frequent in blacks and in obese women and more frequent in women with a premature menopause. Several medical and surgical conditions (e.g., hyperparathyroidism, endogenous and exogenous hyperthyroidism, endogenous and exogenous hypercortisolism, nontropical sprue, gastrectomy and short-bowel syndrome) are known to be independently associated with metabolic bone disease, including osteoporosis. Women who, at the time of their menopause, provide a past or current history of one or more of these conditions should also be regarded as being at increased risk for the development of PMO with vertebral fractures.

If one excluded from an osteoporosis screening program black or obese women (because their risk is low) or women with premature menopause or one of the above mentioned medical or surgical conditions (because their risk is high) one is still left with the vast majority of white (and possibly Asian) women who enter the menopause between age 45 and 55 years enjoying good health. As long as the prevailing medical practice is to restrict estrogen prophylaxis against osteoporosis to those otherwise healthy women felt to be at risk of its development, it is imperative to establish some mechanism for assessing that risk.

Spinal radiographs were not obtained in our control population raising the possibility of misclassification. However, the correct classification of the VF- group was verified by X-ray making it unlikely that potential misclassification of the control group influenced the negative results of this study since the VF+ versus C and VF+ versus VF- results were similar.

Ideally, determination of risk should be based on prospective studies performed on a randomly selected group of white women. Retrospective cross-sectional studies, such as the one we report here, do represent a compromise and their interpretation is subject to the many limitations of such studies. Nonetheless, it is apparent

Table 7

Comparison of areas under ROC curve

Source	Method	Area
Present study	SPA (forearms (control))	63 ± 6
	SPA (forearms (VF-))	71 ± 4
Ref. 27	SPA (forearm)	65 ± 3[a]
	DPA (spine)	78 ± 2[a]
Ref. 28	SPA	73 ± 3
	DPA	71 ± 5
	QCT	77 ± 4
	TBC	78 ± 4
Ref. 29	SPA	84 ± 2
	DPA	86 ± 3
	TBC	90 ± 2

SPA, single photon absorptiometry; DPA, dual photon absorptiometry; QCT, quantitative computed tomography; TBC, total body calcium by neutron activation.

[a] We estimated standard errors based on data given in paper.

from our data that, while differences can be demonstrated between the groups of women we studied by both uni- and multiple variate analysis, these differences are small and of questionable biological significance. They also lack the necessary sensitivity and specificity to answer the clinical question we have addressed, i.e., can one identify the woman most likely to develop a fracture and therefore to derive benefit from ERT for prophylaxis against PMO?

Our study can be criticized for the crude nature of the instruments we have used. However, clinical history, simple anthropometry and measurement of radial bone mineral density (BMD) by single photon absorptiometry remain the cheapest, most convenient and widely available methods and therefore are most suited to a community-wide screening program. Furthermore, despite the availability of more rigorous methods, dietary histories and SPA provide reasonably good measurements. For example, in a review of dietary assessment methods, Block concludes that diet histories reflect "some reasonably stable marker which is similarly revealed by different methods . . . and which bears some relationship to clinical criteria" [24]. Even when dietary calcium intake has changed, as is often the case in postmenopausal women [25], dietary histories are fairly reliable [26]. The bone density results obtained by SPA, as seen in Table 7 are similar to those reported for the more expensive and time-consuming methods of dual photon absorptiometry, quantitative computed tomography and total body calcium by neutron activation analysis [27–29].

Table 8

Predictive models for bone mineral content

	Coefficient	SE	*P*
Bone width/bone mass			
constant	0.6704	0.1066	0.001
age	−0.0068	0.0006	0.001
height	0.0019	0.0005	0.001
weight/height	0.1092	0.0450	0.015
reproductive years	0.0014	0.0006	0.015
hormone duration	0.0017	0.0008	0.026
history of illness	−0.0708	0.0159	0.001
Model, $P < 0.001$, $R = 0.61$, $R^2 = 0.37$, $n = 417$			
Age-adjusted bone mineral content			
constant	−6.446	1.297	0.001
height	0.023	0.008	0.003
weight	0.012	0.004	0.004
nulliparity[a]	−0.375	0.157	0.017
reproductive years	0.027	0.008	0.001
history of illness[a]	−0.722	0.223	0.001
Model, $P < 0.001$, $R = 0.34$, $R^2 = 0.12$, $n = 435$			

[a] Nulliparity (1 = no, 2 = yes); history of illness (1 = no, 2 = yes).

The putative historical risk factors and anthropometry are more likely to be determinants of bone mass rather than independent determinants of the risk of sustaining an osteoporotic vertebral fracture and this is borne out by the ROC curves we have generated. In fact, 37% of the variance in bone mass can be accounted for by components of the questionnaire (Table 8). When age is removed from this consideration, only 12% of the variance of the age-adjusted z score for bone mass can be accounted for by components of the questionnaire (Table 8). A major determinant of bone mass not directly addressed by our study is that attributable to genetic factors (e.g., parental maternal bone mass). Our data strongly support the argument that an assessment of risk of developing PMO with vertebral fractures cannot be made without some measurement of bone mass. This is particularly evident from Tables 1 and 2 which demonstrate differences in the historical and anthropometric data in the two control groups (VF– and C) but no difference whatever in their cortical bone mass.

This retrospective analysis also cannot, in the strictest sense, permit an assessment of the risk of developing PMO with vertebral fractures. More correctly, it is an assessment of the sensitivity and specificity of the methods with respect to the diagnosis of such fractures — a diagnosis that should only be established by spine radiographs. Nonetheless, it seems logical to conclude that the limited differences documented between these well defined groups are likely to be even more limited in the healthy, younger perimenopausal population without fractures.

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