A familial risk profile for osteoporosis

L.B. Henderson, MD^{1,2}, J.S. Adams, MD^{1,3}, D.R. Goldstein, PhD², G.D. Braunstein, MD^{1,3}, J.I. Rotter, MD^{1,2}, and M.T. Scheuner, MD, MPH^{1,2}

Purpose: To describe genetic epidemiologic aspects of osteoporosis. **Methods:** 69 patients with osteoporosis were interviewed regarding personal and family histories of osteoporosis and related fractures. Family history information was obtained on 421 first degree and 748 second degree relatives. **Results:** 45% of cases reported a family history of osteoporosis. Familial cases were characterized neither by an earlier age of diagnosis nor by a greater degree of phenotypic severity. Empiric risks for osteoporosis were highest for mothers, 33%, and were 19% for sisters. **Conclusion:** These results provide an initial genetic epidemiologic profile for osteoporosis and information useful for genetic counseling. *Genetics in Medicine*, 2000;2(4):222–225.

Key Words: genetic epidemiology, osteoporosis, family history, genetic counseling, empiric risk

Though a major public health concern, prevalence data for osteoporosis are imprecise as there exists an assortment of phenotypic and diagnostic assessment strategies. An estimated 16.8 million (54%) postmenopausal Caucasian women in the United States have low bone mineral density, and an additional 9.4 million (30%) are thought to have osteoporosis.¹ Osteoporosis is the underlying etiology for more than one million total fractures and 50,000 deaths per year, and it accounts for an estimated 10–14 billion dollars in annual health care expenditures.^{2–4}

Historically, osteoporosis has been described as a clinical syndrome characterized by skeletal deformation, pain, and fracture in susceptible individuals with decreased bone mineral density (BMD). Deformation often results from fractures of predominantly trabecular bone including, but not limited to, the femoral neck, distal radius, ribs, or vertebrae.^{5–7} Vertebral crush fractures often lead to a loss of height and an exaggeration of the thoracic kyphosis.⁸ The advent of dual energy x-ray absorptiometry (DEXA) has heralded the evolution of diagnostic criteria. The World Health Organization (WHO) criteria state that individuals whose BMD is between 1.0 and 2.5 standard deviations below an idealized young adult mean have osteopenia, and those whose BMD is 2.5 standard deviations or more below such a mean are now classified as having osteoporosis.^{9,10} z-Scores are the corresponding analogous values given to patients for each anatomic site studied. For instance, a patient given a right femoral neck z-score of –2.5 has BMD at

that site 2.5 standard deviations below the idealized young adult mean.

Among the metabolic risk factors known to contribute to the development of osteoporosis are estrogen deficiency, corticosteroid excess, hyperparathyroidism, hyperthyroidism, prolonged immobility, prolonged dietary calcium deficiency, hypercalciuric states, hypovitaminosis D, and low peak bone mass.^{4,11–17} Tobacco smoking and alcohol use are also known risk factors.^{15,16,18}

Evidence for a genetic contribution to the disorder derives from several types of investigations. Ethnic differences in frequency are recognized with Caucasian and Asian individuals at a significantly greater risk for the condition compared to their Hispanic and African American counterparts.^{19,20} The On-line Mendelian Inheritance in Man database²¹ records more than 70 genetic syndromes inherited in a mendelian fashion that feature osteoporosis.²² The presence of mendelian varieties of a condition suggests that at least a subset of the “garden variety” condition has genetic underpinnings. A greater correlation for BMD among family members exists when compared with controls.^{22,23} In a prospective study following white women of mean age 72 years, a maternal history of hip fracture doubled the risk of an initial hip fracture during a 4.1 year average follow-up period.²⁴ Both twin studies and population association studies have made more definitive the evidence of a genetic etiology for osteoporosis. Several twin studies have demonstrated a greater concordance rate of BMD among monozygotic twin pairs when compared with dizygotic twin pair counterparts.^{25–28} Furthermore, the heritability of the trait of peak bone mass, a trait that is inversely correlated with the likelihood for the development of osteoporosis, has been estimated to be as much as 90% in the lumbar spine and 70% at the femoral neck.^{22,23,25,29}

There is evidence for and against population associations between BMD and Vitamin D receptor polymorphisms. The BB genotype was found predictive of low BMD or fracture in several studies,^{30–33} but in other studies^{34–38} not only is this

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From the ¹Department of Internal Medicine, ²Division of Medical Genetics, and ³Division of Endocrinology and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California.

Leon Henderson, MD, Cedars-Sinai Medical Center, Medical Genetics, 8700 Beverly Boulevard, SSB 378, Los Angeles, CA 90048.

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genotype not predictive of low BMD, but also it fails to predict fracture. The Col1A1 Sp polymorphism may be an important marker for low bone mass and vertebral fracture,³⁹ and some families exist in which individuals with "idiopathic" osteoporosis are more likely to have specific mutations in the Col1A1 or Col1A2 gene.^{40,41}

Although a "positive family history" has been long touted as a factor contributing to the risk of the development of osteoporosis, and despite a vast array of literature suggesting that osteoporosis is a disorder with a major genetic influence and appreciable heritability, sufficiently refined empiric risk estimates for meaningful genetic counseling is, to our knowledge, lacking in the medical literature. Moreover, it is not known the degree to which familial cases differ from nonfamilial cases. Genetic epidemiologic data including empiric risk estimates may be used in conjunction with other clinical data to establish a risk profile to facilitate, in an asymptomatic individual, the development of appropriate preventive strategies and anticipatory care. In osteoporosis, such data may be used in concert with radiographic and clinical data to assess the need for therapies designed to favorably impact a consultant's BMD. Estrogen, calcium, and vitamin D supplementation has been used toward this clinical goal as has weight-bearing exercise, smoking cessation programs, and osteoclast-stabilizing pharmacologic agents.

Thus we sought to refine our knowledge of the genetic epidemiologic aspects of osteoporosis in the Caucasian population. Our aims were (1) to assess the differences between familial and nonfamilial cases, and (2) to estimate gender and relative-specific empiric risks for first and second degree family members.

MATERIALS AND METHODS

The study subjects were ascertained from two clinical endocrinology practices at Cedars-Sinai Medical Center. Institutional Review Board approval was obtained. Charts were reviewed in order to identify those with the diagnosis of osteoporosis as defined by reduced bone mineral density (ascertained by DEXA) or clinical criteria. All measurements were performed by DEXA on a QDR-2000 (Hologic, Inc., Waltham, MA) or a DPX-L densitometer (Lunar Corp., Madison, WI). Individuals with BMD greater than or equal to 2.5 standard deviations below an idealized young adult mean, by DEXA, were considered to have osteoporosis. Those with BMD between 1 and 2.5 SD below such a mean were also considered to have osteoporosis if they had a history of low trauma fracture or evidence of compromised bone tissue such as loss of height or an exaggerated thoracic kyphosis. All affected individuals had a documented history of osteoporosis in their clinical chart. Subjects were excluded if they had hyperparathyroidism,²⁵ hyperthyroidism,¹² used steroids for six months or longer,^{4,12} had abnormal 25-hydroxy vitamin D levels,¹⁰ or were unable to participate in the phone interview (12). The charts of each proband were reviewed in order to obtain relevant data from their most recent DEXA scan.

A standardized phone questionnaire was administered. Standard demographics, age of osteoporosis diagnosis, history of osteoporotic fractures, and family history regarding all first and second degree relatives were obtained from each subject. Family histories included age or age at death, cause of death, history of osteoporosis and related fractures, and the ages of diagnosis for these conditions. A family history of osteoporosis was considered when there was a report of at least one first degree relative with either a diagnosis of osteoporosis or a related fracture of the neck, back, rib, wrist, or hip at an age greater than or equal to 50.

Descriptive statistics were used to estimate empiric risks. The chi-square test of homogeneity for proportions and t-test for differences between means were used to assess statistical significance of differences between compared values.

RESULTS

Data were collected from 69 patients; 97% were Caucasian, and 83% were female. Their mean age was 62 years (range: 36–86), and their mean age of osteoporosis diagnosis was 57 years (range: 29–80) for females, and 62 years (49–81) for males. Mean z-scores at the lumbar spine were $-2.56 (\pm 1.08)$ for females and $-1.62 (\pm 2.00)$ for males. The mean z-scores at the right femoral neck were $-2.43 (\pm 0.91)$ for females and $-2.53 (\pm 1.48)$ for males. 20% of cases reported osteoporosis-related fractures. Family history data were obtained regarding 421 first degree relatives and 748 second degree relatives. The percentage of first degree relatives reported to have a diagnosis of osteoporosis was greater than the proportion of second degree relatives reported to have the diagnosis (8.0% vs. 3.7%, respectively, $P = 0.008$). Among all relatives, the first degree relatives did not differ significantly (at the $P = 0.05$ level) from the second degree relatives with respect to proportion female, mean age at osteoporosis diagnosis, and proportion with an osteoporosis-related fracture.

Forty-five percent of the probands reported a family history of osteoporosis. Overall, the 57 females and 12 males did not differ significantly with regard to their age, age at diagnosis of osteoporosis, percentage with osteoporosis related fracture, and percentage with a family history of osteoporosis (Table 1). The 31 familial cases were virtually identical to the 38 nonfamilial cases with respect to mean age, mean age of osteoporosis diagnosis, proportion of females, proportion with a history of an osteoporosis-related fracture, mean pedigree size, BMD at the lumbar spine, and BMD at the right femoral neck (Table 2).

Twenty-three mothers either had the diagnosis of osteoporosis or an osteoporosis-related fracture. Thus, the empiric risk for mothers was $23/69 \times 100\%$ or 33%. Likewise, as 4 of 69 fathers were affected, the empiric risk for fathers was 6%. Sisters and brothers had empiric risks of 19% and 3%, respectively. Grandmothers and aunts had a 6% risk, whereas grandfathers and uncles had a 1% risk. The female to male risk ratio ranged from 4.7 for siblings to 6.0 for both grandparents and avuncular relatives. The female to male risk ratio for parents was 5.5 (Table 3).

Table 1
Proband characteristics (n = 69)*

Parameter	Female (n = 57)	Male (n = 12)
Mean age (range)	62 (36,85)	66 (52,86)
Mean age at diagnosis (range)	57 (29,80)	62 (49,81)
Percent with fracture > 50 years old	20.0% (10/50)	33.3% (4/12)
Percent with family history of osteoporosis	47% (27/57)	33% (4/12)
Lumbar BMD z-score	-2.56 ($\pm$ 1.08)	-1.62 ($\pm$ 2.00)
Right femoral neck BMD z-score	-2.43 ($\pm$ 0.91)	-2.53 ($\pm$ 1.48)

*There are no significant differences at the $p = 0.05$ level.

Table 2
Familial versus nonfamilial cases*

Parameter	Familial Cases (n = 31)	Nonfamilial Cases (n = 38)
Mean age in years (range)	62 (37,81)	64 (36,86)
Mean age at diagnosis in years (range)	57 (32,77)	59 (29,81)
Percent female	87	79
Percent with fracture > 50 years old	25 (7/28)	20 (7/35)
Mean pedigree size (# relatives)	17.4	16.1
Lumbar BMD z-score	-2.24 ($\pm$ 1.48)	-2.54 ($\pm$ 1.18)
Right femoral neck BMD z-score	-2.27 ($\pm$ 1.04)	-2.60 ($\pm$ 1.32)
Mean age at fracture	59	63

*There are no significant differences at the $p = 0.05$ level.

Table 3
Empiric risk estimates for osteoporosis

Relative Type (No. Female/Male)	% Risk to Females (no.)	% Risk to Males (no.)
Parents (69/69)	33 (23)	6 (4)
Siblings (75/79)	19 (10)	3 (2)
Offspring (70/59)	0 (0)	0 (0)
Grandparents (138/138)	6 (8)	1 (2)
Aunts/uncles (232/240)	6 (15)	1 (3)

DISCUSSION

Forty-five percent of probands reported a family history of osteoporosis. There were no significant demographic or phenotypic differences between familial and nonfamilial cases. Although we did not verify family history reports, accuracy of family history reports for other common, chronic disorders is relatively high.^{42,43} Furthermore, self-reports of hip, wrist, and humerus, fractures are known to be reasonably accurate.⁴⁴

This included age, age at osteoporosis diagnosis, gender proportion, proportion with osteoporosis-related fracture, mean pedigree size, and BMD z-scores at both the lumbar and right

femoral neck regions. The observation that familial cases did not significantly differ from nonfamilial cases appears to violate a tenet of common disease genetics, as it is often claimed that in most common diseases with a genetic component, individuals with a positive family history tend to have more severe phenotype and earlier age of onset or diagnosis.

Overwhelming evidence such as that derived from twin and population studies exists verifying a genetic contribution to the etiology of osteoporosis. Our finding of a lack of differences between familial and nonfamilial osteoporosis cases might appear incongruous with this knowledge. However, there is precedence for this concept, as type I diabetes with and without family history is phenotypically similar and both have strong associations with HLA class II.⁴⁵

In our investigation, the group at greatest risk for osteoporosis were female relatives, with an empiric risk as high as 33% for mothers. This risk is not significantly different from the estimated population risk of approximately 30% for postmenopausal Caucasian women.¹ Both aunts and grandmothers had empiric risks of 6%. Since we would expect these women to have at least the population's risk, the risk estimates for second degree relatives may well be underestimates due to underreporting. In male relatives, a similar trend was observed with fathers having an empiric risk six times greater than uncles and grandfathers. In siblings and offspring, the empiric risks are likewise probable underestimates because of nonpenetrance in this disease of later onset. Relevant age-specific incidence data for osteoporosis are not available. This prohibits age-adjustment, which could provide more accurate empiric risk estimation for these younger relatives.

Our data suggest that for clinical risk assessment and prevention strategy planning, in general, the family history does not appear to substantially alter or impact the risk stratification of a consultand presenting with a family history of osteoporosis. However, this does not obviate the need for documenting reports of osteoporosis in the family, particularly since there are some rare single gene disorders that feature osteoporosis and the family history may reveal such a diagnosis. These results also suggest that identification of osteoporosis genes might be as amenable to population association studies as compared with family-based linkage analysis. Once osteoporosis genes are identified, population-based screening in high risk ethnic groups may be more appropriate than family-based screening.

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