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Original Article

Estimation of the Prevalence of Low Bone Density in Canadian Women and Men Using a Population-Specific DXA Reference Standard: The Canadian Multicentre Osteoporosis Study (CaMos)

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Abstract. The Canadian Multicentre Osteoporosis Study (CaMos) is a prospective cohort study which will measure the incidence and prevalence of osteoporosis and fractures, and the effect of putative risk factors, in a random sample of 10 061 women and men aged $\geqslant 25$ years recruited in approximately equal numbers in nine centers across Canada. In this paper we report the results of studies to establish peak bone mass (PBM) which would be appropriate reference data for use in Canada. These reference data are used to estimate the prevalence of osteoporosis and osteopenia in Canadian women and men aged $\geqslant 50$ years. Participants were recruited via randomly selected household telephone listings. Bone mineral density (BMD) of the lumbar spine and femoral neck were measured by dual-energy X-ray absorptiometry using Hologic QDR 1000 or 2000 or Lunar DPX densitometers. BMD results for lumbar spine and femoral neck were converted to a Hologic base. BMD of the lumbar spine in 578 women and 467 men was constant to age 39 years giving a PBM of 1.042 ± 0.121 g/cm^2 for women and 1.058 ± 0.127 g/cm^2 for men. BMD at the femoral neck declined from age 29 years. The mean femoral neck BMD between 25 and 29 years was taken as PBM and was found to be 0.857 ± 0.125 g/cm^2 for women and 0.910 ± 0.125 g/cm^2 for men. Prevalence of osteoporosis, as defined by WHO criteria, in Canadian women aged $\geqslant 50$ years was 12.1% at the lumbar spine and 7.9% at the femoral neck with a combined prevalence of 15.8%. In men it was 2.9% at the lumbar spine and 4.8% at the femoral neck with a combined prevalence of 6.6%.

Keywords: BMD; Men; Osteopenia; Osteoporosis; Prevalence; Women

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Introduction

Osteoporosis has been defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to enhanced bone fragility and

increased fracture risk [1]. A panel convened by the World Health Organization (WHO) defined osteoporosis in terms of bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA). The panel suggested that osteoporosis is a BMD 2.5 SD (*T*-score $\leqslant -2.5$) or more below peak bone mass (PBM), which is itself defined as the average maximum bone mass achieved by young healthy sex- and race-matched adults [2]. Osteopenia, a reduction of bone mass with an increased risk of osteoporosis, is defined as a BMD between 1.0 and 2.5 SD below PBM (*T*-score between -1.0 and -2.5). Although these criteria were based on observations in postmenopausal Caucasian women they are now generally applied to other at-risk populations and are very frequently used to confirm a diagnosis of osteoporosis and to estimate fracture risk [3,4]. It follows, therefore, that the confidence with which at-risk individuals are identified depends on the reliability and precision with which the PBM reference standard and *T*-scores are determined and the applicability of that PBM to the population being assessed.

PBM has not been determined for Canadians nor have there been any population studies to estimate the prevalence of osteoporosis in Canadian men or women. The Canadian Multicentre Osteoporosis Study (CaMos) is a prospective cohort study which will measure the prevalence and incidence of osteoporosis and fractures, and the effect of putative risk factors, in a random sample of 10 061 women and men aged $\geqslant 25$ years recruited from nine centers across Canada. In this paper we report the results of studies using the CaMos cohort to establish PBM at various skeletal sites which would be appropriate for use in Canada. These reference data are used to estimate the prevalence of osteoporosis and osteopenia in Canadian women and men 50 years of age or older.

Subjects and Methods

A total of 10 061 (9423 + 638 from the pilot study) individuals aged 25 years and older were recruited via randomly selected household telephone listings, in approximately equal numbers from nine regions across Canada (St John's, Halifax, Quebec City, Kingston, Toronto, Hamilton, Saskatoon, Calgary and Vancouver). An introductory letter was sent to each household followed by a telephone call soliciting participation by a randomly selected household member aged $\geqslant 25$ years. The sample was stratified by age and sex. Selected household members who refused full participation were asked to provide answers to a one-page questionnaire on major risk factors for osteoporosis, including age, sex, race, fracture history, family history of osteoporosis and smoking status. Baseline data collection included an extensive interviewer-administered questionnaire including sociodemographic information, medical and fracture history, dietary intake, physical activity, tobacco smoking and secondary exposure, the Rand SF-36 Questionnaire and the Health Utilities Index [5]. A detailed description of the study, the response rates and the analysis of the characteristics of partial and full responders appear elsewhere [6]. Informed consent was obtained from each participating subject and the study received approval from the Institutional Review Boards of each of the participating institutions. In the study reported here all non-Caucasian CaMos participants were eliminated (423), as were all those who did not have DXA of lumbar spine and hip (1037) either because they refused the test or could not be tested because of severe deformity and/or previous surgery. This reduced the number of subjects for this study to 8601.

Bone Density Measurements

BMD of the lumbar spine (L1–L4) and femoral neck were measured by DXA using Hologic QDR 1000 or 2000 or Lunar DPX densitometers. Machine calibration was done daily. Daily and weekly quality assurance tests were performed as recommended by the DXA machine manufacturers. The densitometers at each of the nine participating centers were cross-calibrated at the start of the study and once each year thereafter by the same medical physicist using the same European Spine Phantom. While most were Hologic devices, two centers (St John's and Hamilton) used Lunar densitometers. BMD results for lumbar spine and femoral neck from all densitometers were converted to a Hologic base using the method of Genant et al. [7].

Statistical Analysis

All analyses were stratified on sex. PBM varies between individuals, and individuals may reach their maximum at different ages. Therefore, estimating the average PBM in a population via a cross-sectional survey is problematic. Because one cannot be sure that one is, in fact, measuring the BMD at its peak in each individual, any estimate is likely to be an underestimate of the true average. Nevertheless, longitudinal studies have shown that, in most individuals, bone mass at several skeletal sites increases from birth to reach a peak in the second or third decade of life [8–10]. Bones mass is then relatively stable for some time until age-dependent bone loss begins. On this basis, it is reasonable to assume that a cross-sectional average of young adult subjects in their second and third decade will provide a reasonable estimate of PBM.

We used two complementary methods to determine the best age range over which to estimate PBM. The first was a linear regression model selection technique to determine the largest age at which a linear regression for age versus mean BMD would prefer a model with a slope of zero rather than a model with a negative slope. Approximate Bayes factors, as calculated through the Bayesian Information Criterion (BIC) [11], were used to select the final model. While useful as an approximation, this method is likely to overestimate the age at which

mean BMD begins to decline, because of a low probability of detecting changes in slope in the first few years after decline begins. We therefore used change-point methods [12] to find the best cut-point where BMD begins to decline. In this method, a segmented linear regression model for mean BMD versus age was fit, where the slope of the before change-point regression line was constrained to be zero, and with no constraint for the after change-point slope. The change-point was successively moved from the minimum to maximum possible value (here 25 to 44 years of age) so that each age range was tested for the possibility of preceding the age at which decline begins. The 'best' change-point is that which maximizes the probability of obtaining the observed data. We used the Gibbs sampler [13] to estimate this model and to find the optimal change-point value. The mean of the BMD values for all subjects whose age falls before the best change-point was considered to be an estimate of the PBM in our sample.

To estimate this mean PBM value such that it best reflects the Canadian population, we needed to derive a weighted average of each center-specific BMD. Within each center, we assumed that the individual subject's BMD values are normally distributed with a center-specific mean. For the femoral neck, we used a center-specific within-center variance, but for the lumbar spine a single variance across all centers was used, as indicated by the data. The nine center-specific means were defined in our study to be the PBM for each center, and a weight was attached to each value according to the 1996 Canadian census figures for each of our nine centers. The nine PBM values were assumed to follow a Normal distribution with an overall mean representing the overall PBM in Canada, and with a variance parameter representing the spread of PBM between centers. The advantage of this random-effects hierarchical model is that it can serve to stabilize PBM estimates in centers with smaller numbers of subjects by 'borrowing strength' from the other centers via use of the overall PBM mean. In this way more stable estimates for the overall Canadian average are obtained [14].

All Bayesian analyses begin with eliciting a prior distribution over all unknown parameters (here over all means and variances) that summarize what is known about these parameters before the data are analyzed. The information in the data then updates the prior distribution to a posterior distribution through Bayes theorem. Here we used noninformative prior distributions, which allow approximately equal probability a priori to all values in the feasible range. Therefore the posterior distribution reflects the information in the data, with the prior distribution contributing only negligible information. All inferences are made via the posterior density. For example, the points between which 95% of the area under the curve of the posterior distribution lies form a 95% credible interval, which is the Bayesian analogue of the usual 95% confidence intervals. In practice, these calculations involve high-dimensional multiple integration, which we carried out using the software package called BUGS [15], which implements a Markov Chain Monte Carlo Gibbs sampler algorithm to approximate the high-dimensional integrals [13].

The prevalences of osteoporosis and osteopenia at each skeletal site were calculated using the WHO panel's definition of osteoporosis and osteopenia [2]. In each case the PBM used for calculating *T*-scores in women was that determined for the specific skeletal site in women. Because there is no consensus as to which reference standard should be used when measuring bone mass in men two *T*-scores were calculated, one using PBMs for the specific skeletal site for men and a second comparable set using the PBM for women. To compare Canadian results with those of NHANES III [16], prevalences were also calculated using the NHANES III reference standards.

Results

As illustrated in Table 1, BMD of the lumbar spine was constant between 25 and 39 years for both women and men. This was confirmed by change-point analysis, i.e., the slope of a line of BMD versus age is 0 for ages 25–39 years. Between 35–39 years and 40–44 years BMD of the lumbar spine in women declines by 2.6% while that in men declines by 4.7%. In contrast, the femoral neck BMD declines for all ages between 25–29 and 40–44 years. The rate of decline was 3.7% from 25–29 years to 35–39 years and 7.5% from 25–29 years to 40–45 years for women. For men the corresponding results were a 1.4% decline to age 35–39 years and 6.9% to age 40–45 years.

Based on these results the CaMos PBM of the lumbar spine for both women and men is defined as the mean BMD of the lumbar spine in those aged 25–39 years. The CaMos PBM for the femoral neck for both women and men is defined as the mean BMD at that skeletal site for the subjects aged 25–29 years. These results are summarized in Table 2. According to WHO criteria, therefore, in Canadians osteoporosis of the lumbar spine exists at BMD $\leqslant 0.740$ g/cm^2 in women and $\leqslant 0.741$ g/cm^2 in men. Osteopenia of the lumbar spine exists at BMD between 0.921 g/cm^2 and 0.740 g/cm^2 for women and 0.931 g/cm^2 and 0.741 g/cm^2 for men. For the femoral neck a BMD $\leqslant 0.545$ g/cm^2 for women and $\leqslant 0.598$ g/cm^2 for men defines osteoporosis whereas osteopenia is defined as a BMD between 0.732 g/cm^2 and 0.545 g/cm^2 for women and between 0.785 g/cm^2 and 0.598 g/cm^2 for men.

The BMD of the femoral neck as a function of age is shown in Table 3 for women and Table 4 for men. For comparison the results of NHANES III [17] are included. In both cohorts the BMD decreases with age from the earliest age measured, with an increase in the rate of decline at age 40–50 years which persists at least to age 80 years. The BMD of Canadians over age 50 years tends to be slightly greater than that of the NHANES III subjects but these differences are small, ranging from 2% to 9%, and are not significant.

Table 1. Mean bone mineral density (BMD) of lumbar spine (L1–L4) and femoral neck in Canadian women and men aged 25–44 years

	Age group (years)							
	25–29		30–34		35–39		40–44	
	BMD[a] (SD)	95% CI	BMD[a] (SD)	95% CI	BMD[a] (SD)	95% CI	BMD[a] (SD)	95% CI
Women	(n = 95)		(n = 161)		(n = 178)		(n =179)	
Lumbar spine	1.034 (0.126)	0.997, 1.075	1.034 (0.121)	1.008, 1.059	1.045 (0.123)	1.021, 1.069	1.018 (0.125)	0.997, 1.041
Femoral neck	0.857 (0.125)	0.816, 0.904	0.825 (0.102)	0.804, 0.847	0.823 (0.120)	0.795, 0.853	0.792 (0.114)	0.772, 0.812
Men	(n = 101)		(n = 129)		(n = 136)		(n = 101)	
Lumbar spine	1.053 (0.134)	1.021, 1.087	1.063 (0.131)	1.035, 1.091	1.056 (0.123)	1.029, 1.082	1.006 (0.135)	0.971, 1.040
Femoral neck	0.910 (0.125)	0.875, 0.945	0.897 (0.129)	0.869, 0.924	0.887 (0.098)	0.864, 0.910	0.847 (0.137)	0.812, 0.882

[a] In g/cm^2 standardized to Hologic values. Densitometers at the different CaMos centers were standardized using a single European Spine Phantom.

Table 2. Mean Canadian peak bone mass[a]

Skeletal site	Women			Men		
	n	BMD[b] (SD)	95% CI	n	BMD[b] (SD)	95% CI
Lumbar spine	432	1.042 (0.121)	1.024, 1.059	366	1.058 (0.127)	1.040, 1.077
Femoral neck	95	0.857 (0.125)	0.816, 0.904	101	0.910 (0.125)	0.875, 0.945

[a] The population used to determine peak bone mass (PBM) at the lumbar spine (L1–L4) was Caucasian women and men 25–39 years old. The Caucasian women and men used to determine PBM for the femoral neck were 25–29 years old.
[b] In g/cm^2 standardized to Hologic values. Densitometers at the different CaMos centers were standardized using a single European Spine Phantom.

Table 3. Mean BMD of the femoral neck in women as a function of age: CaMos and NHANES III data

Age (years)	CaMos		NHANES III[a]	
	n	BMD g/cm^2 ($\pm$ SD)	n	BMD g/cm^2 ($\pm$ SD)
20–29[b]	95	0.857 (0.125)	409	0.858 (0.120)
30–39	339	0.826 (0.109)	518	0.825 (0.120)
40–49	682	0.799 (0.116)	444	0.791 (0.125)
50–59	1284	0.759 (0.119)	450	0.737 (0.121)
60–69	1819	0.695 (0.110)	454	0.681 (0.119)
70–79	1351	0.661 (0.114)	556	0.619 (0.110)
80+	307	0.593 (0.104)	420	0.573 (0.108)

[a] Looker et al. [17].
[b] The CaMos sample is aged 25–29 years.

Table 4. Mean BMD of the femoral neck in men as a function of age: CaMos and NHANES III data

Age (years)	CaMos		NHANES III[a]	
	n	BMD g/cm^2 ($\pm$ SD)	n	BMD g/cm^2 ($\pm$ SD)
20–29[b]	101	0.910 (0.125)	382	0.934 (0.137)
30–39	264	0.892 (0.114)	416	0.887 (0.134)
40–49	376	0.832 (0.115)	409	0.839 (0.124)
50–59	569	0.811 (0.114)	393	0.813 (0.125)
60–69	674	0.811 (0.131)	477	0.788 (0.135)
70–79	513	0.773 (0.140)	445	0.754 (131)
80+	115	0.722 (0.129)	408	0.698 (0.140)

[a] Looker et al. [17].
[b] The CaMos sample is aged 25–29 years.

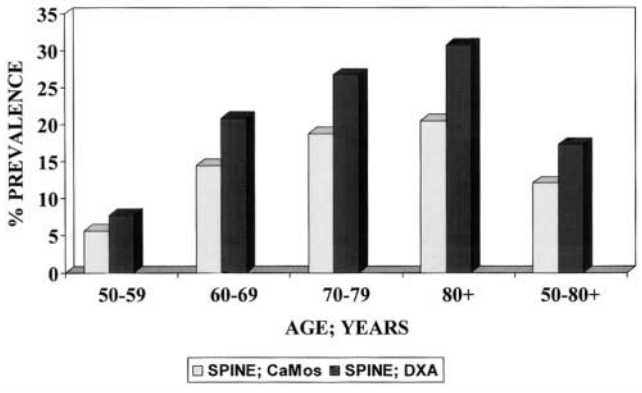

Fig. 1. The prevalence of osteoporosis of the lumbar spine as defined by WHO criteria, adjusted to the Canadian population, in women aged $\geqslant 50$ years calculated using peak bone mass (PBM) shown in Table 2 as reference standard.

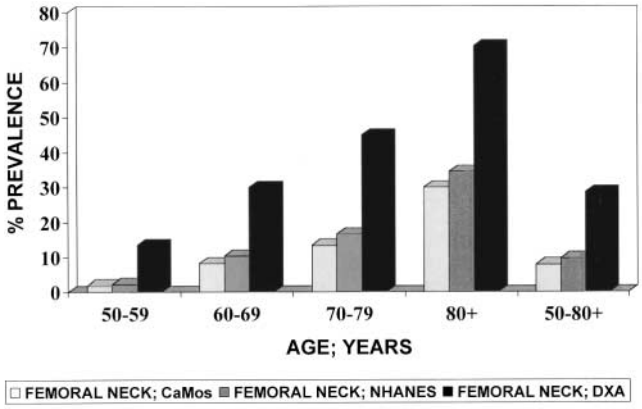

Fig. 2. The prevalence of osteoporosis of the femoral neck as defined by WHO criteria, adjusted to the Canadian population, in women aged $\geqslant 50$ years calculated using peak bone mass (PBM) shown in Table 2 as reference standard.

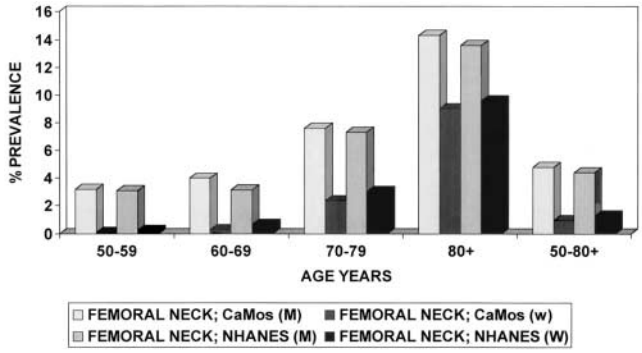

Fig. 3. The prevalence of osteoporosis of the femoral neck as defined by WHO criteria, adjusted to the Canadian population, in men aged $\geqslant 50$ years calculated using peak bone mass (PBM) shown in Table 2 as reference standard. (W) indicates that the PBM for women was used as the reference, (M) indicates that the PBM for men was used as the reference.

Table 5. Prevalence of osteopenia of the femoral neck in Canadian women and men aged $\geqslant 50$ years

	% Prevalence of osteopenia[a]	
	CaMos	NHANES III[b]
Women	45.9	50.0
Men (W)	26.7	47.0
Men (M)	39.1	33.0

The BMDs used as reference standards for the calculation of osteopenia are the peak bone mass (PBM) mean values shown in Tables 3 and 4. In men both the women's (W) and the men's (M) reference standards were used.

[a] Osteopenia, defined according to WHO criteria, is all BMD values between -1.0 and -2.5 SD below PBM.

[b] Looker et al. [16].

Estimates of the prevalence of osteoporosis at the lumbar spine and femoral neck in women and men 50 years and older were calculated according to WHO criteria. These results are shown in Figs 1–3. In each case the estimates made using CaMos, NHANES III (femoral neck only) and DXA manufacturer standards were compared. The estimates obtained using CaMos and NHANES III standards are very similar whereas use of the DXA manufacturer standards leads to estimates which are always larger. Table 5 shows the prevalence of osteopenia of the femoral neck in women and men older than 50 years compared with the results reported for a comparable US population [16]. As can be seen the estimates of the prevalence of osteopenia are very similar for the two populations.

Discussion

There is considerable evidence that as BMD decreases, risk of fracture increases [18–21], and although not a perfect predictor BMD, as measured by DXA, appears to be the single best, generally available, objective measure of fracture risk. Encouraged by published guidelines [3], including those of the Osteoporosis Society of Canada [4], it has become common practice to use the WHO criteria to aid in the diagnosis of osteopenia, osteoporosis and fracture risk. The validity of this practice is largely dependent upon the appropriateness and accuracy, with respect to the population in question, of the DXA standard used to determine *T*-scores. There is evidence that suggests that the best DXA reference standard (PBM) is one derived from the population being assessed. Manufacturer-provided reference ranges often lead to very different estimates of the prevalence of osteoporosis than those calculated from local reference populations [22]. One British study found that when WHO criteria were applied, 14.8% of a random sample of 702 women had osteoporosis using local reference data, compared with 5.8% using the manufacturer's data [23]. There is evidence to suggest that a single universal

reference standard may not be possible. Population-specific DXA standards have been established in Australia [24,25], Finland [26], UK [27] United States [16,24], and Sweden [28]. In each case the results are sufficiently different from each other to result in substantial differences in *T*-scores and therefore in estimates of osteoporosis and osteopenia prevalence.

In 1997 the International Committee for Standards in Bone Measurement recommended that the reference data for bone density of the proximal femur be those collected in the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) [17,29,30]. They also recommended that the units of measurement be the 'sBMD' expressed in mg/cm^2 rather than the manufacturer-specific BMD expressed in g/cm^2 and that the region of interest used for femur evaluation be the Total Femur rather than the Femoral Neck. This committee made no recommendations with respect to the reference standards for lumbar spine BMD measurements. In CaMos, which began almost 2 years before publication of the above recommendations, we established the Canadian reference data (PBM) for the lumbar spine and femoral neck for women and men using a randomly selected sample equally distributed in nine centers encompassing approximately 40% of the Canadian population. In NHANES III [17], the sex-specific mean BMD of the femoral neck in subjects age 20–29 years was taken as PBM and was used to generate *T*-scores for the calculation of osteoporosis and osteopenia prevalence. The NHANES III study did not confirm that BMD over that age range was in fact constant; however, there is evidence which suggests that at the femoral neck BMD begins to decrease after age 29 years [31]. We could not confirm the constancy of BMD at the femoral neck before age 25 years but we did show that at that skeletal site BMD declines from age 30 years in both women and men. For this reason femoral neck PBM in our data was defined as the mean BMD between 25 and 29 years. Further, we demonstrated that the average cross-sectional BMD of the lumbar spine was constant between ages 25 and 39 years but that there was a considerable decrease in BMD at this site with greater age. The mean BMD at this site in women and men between ages 25 and 39 years satisfies the definition of PBM and is therefore appropriate for use in the diagnosis of osteoporosis and osteopenia as defined by the WHO [2].

The reported NHANES III reference bone density and SD of the femoral neck are very similar to that found in this study (0.858 ± 0.120 vs 0.857 ± 0.125 g/cm^2 for NHANES III and CaMos respectively for women and 0.934 ± 0.137 vs 0.910 ± 0.125 g/cm^2 for men). Using the CaMos standard the prevalence of osteoporosis in Canadian women aged $\geqslant 50$ years is 7.93% whereas when the NHANES standard is used in the same population the prevalence is found to be 22% greater at 9.68%. This illustrates the remarkable sensitivity of *T*-score estimates to very small changes in PBM and SD. Looker et al. [16] estimated the prevalence of osteoporosis in US non-Hispanic white women $\geqslant 50$ years old using NHANES III reference standards and found it to be 18%. This is approximately double the prevalence we found in Canadian women independent of whether the CaMos or NHANES III reference standards are used. There are at least two factors that might contribute to this difference: the PBM is greater in US women compared with Canadians, and/or the BMD of US women $\geqslant 50$ years old is lower than that in corresponding Canadians. As we have seen in Table 3, the PBM is identical although the SD is slightly smaller for US (0.120) versus Canadian (0.125) women. Also, the BMD of US women tends to be smaller than that of Canadian women of the same age, the difference ranging from 2% at 60–69 years to 7.4% at 70–79 years (Table 3). These differences would tend to result in an estimate of osteoporosis that is greater for US women. Further, a review of the latest census data from Canada (1996) and the USA (1990) reveals that the age distribution of US women is shifted slightly such that a smaller proportion is in the 50–59 year age group (31.8% vs 35.7%), with a larger proportion in the 60–69 (31.1% vs 28.9%) and 70-79 (24.6 vs 22.8%) year age groups. The proportion of the population over age 50 years that is $\geqslant 80$ years is the same in both countries (12.5%). This shift to a somewhat older population in the US might explain to some extent the lower BMD among US women $\geqslant 50$ years. The prevalence of osteopenia, as defined by the WHO, of the femoral neck in Canadian women $\geqslant 50$ years old is 45.9% whether the CaMos or NHANES III reference standard is used and is very similar to what has been reported by NHANES III (50.0%) for the corresponding US population [16].

Another possible explanation for the difference in prevalence of osteoporosis between Canadian and US populations is that age-dependent bone loss begins earlier and/or occurs at a greater rate in women in the United States, at least at the femoral neck. If true it predicts that osteoporosis prevalence would be very similar in the two populations at 50–59 years but diverge, with the difference in prevalence becoming progressively larger with increasing age. This could not be tested, as we do not have the NHANES III data set. The important question, as yet unanswerable, is whether these differences reflect different fracture risks in the two populations.

Efforts to establish prevalence of low bone mass in men are complicated by the uncertainty as to which reference standard to use. If the WHO criteria for the definition of osteoporosis which were proposed for postmenopausal women were to be transposed for use in men it seems reasonable that the skeletal site-specific PBM for men be used. This would identify those men at increased risk to fracture if, as is generally believed, the relationship of bone mass to fracture risk is at least qualitatively the same in men as in women. The recent report by De Laet et al. [32] suggests that this relationship is the same in women and men, at least for hip fracture. On the other hand there are those who argue that fracture risk is a function of absolute bone mass and if a male standard were to be used it would

necessarily lead to the result that at any given bone mass fracture risk in men is greater than in women. For this reason, it is argued, the female reference standard should be used. There is some evidence that, on average, the BMD in men with fractures is greater than the BMD in a population of women with fractures [33–36]. This issue will only be resolved with prospective studies that clearly establish the relationship of fracture risk to BMD.

The main limitation of the data reported here is that they are cross-sectional and so may be subject to cohort effects. Another problem may arise from combining the populations from all nine geographic regions of the country to give a single 'Canadian' reference standard. The European Vertebral Osteoporosis Study (EVOS) found substantial differences in BMD between different populations [37]. The population of Canada participating in CaMos may be as diverse as that included in EVOS. It is therefore possible that CaMos participants constitute a heterogeneous population and that there may be a need for multiple reference standards for DXA in Canada.

In summary, a Canadian reference BMD for women and men has been established for the lumbar spine and femoral neck using a randomly selected population. Although the reference BMD for the femoral neck is very similar to that reported by NHANES for non-Hispanic Caucasian Americans, the prevalence of osteoporosis estimated using these new references is substantially less for Canadian women and men. The reason for this discrepancy is not known.

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