

Bone Mineral Density Loss in Relation to the Final Menstrual Period in a Multiethnic Cohort: Results From the Study of Women's Health Across the Nation (SWAN)

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ABSTRACT

The objective of this study was to describe the time of onset and offset of bone mineral density (BMD) loss relative to the date of the final menstrual period (FMP); the rate and amount of BMD decline during the 5 years before and the 5 years after the FMP; and the independent associations between age at FMP, body mass index (BMI), and race/ethnicity with rates of BMD loss during this time interval. The sample included 242 African American, 384 white, 117 Chinese, and 119 Japanese women, pre- or early perimenopausal at baseline, who had experienced their FMP and for whom an FMP date could be determined. Loess-smoothed curves showed that BMD loss began 1 year before the FMP and decelerated (but did not cease) 2 years after the FMP, at both the lumbar spine (LS) and femoral neck (FN) sites. Piecewise, linear, mixed-effects regression models demonstrated that during the 10-year observation period, at each bone site, the rates and cumulative amounts of bone loss were greatest from 1 year before through 2 years after the FMP, termed the transmenopause. Postmenopausal loss rates, those occurring between 2 and 5 years after the FMP, were less than those observed during transmenopause. Cumulative, 10-year LS BMD loss was 10.6%; 7.38% was lost during the transmenopause. Cumulative FN loss was 9.1%; 5.8% was lost during the transmenopause. Greater BMI and African American heritage were related to slower loss rates, whereas the opposite was true of Japanese and Chinese ancestry. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: MENOPAUSE; PERIMENOPAUSE; BONE MINERAL DENSITY; ETHNIC DIFFERENCES; LONGITUDINAL COHORT

Introduction

Bone loss begins before the cessation of menses. Dual-energy X-ray absorptiometry (DXA) detects unequivocal decline in bone mineral density during late perimenopause, when women have experienced between 3 and 11 months of amenorrhea, whereas little, if any, loss is seen during early perimenopause, when menstrual cycles are irregular but there has not yet been a gap of at least 3 months between periods.^(1–3) Menstrually defined menopause transition (MT) categories, which classify stages of the menopause according to menstrual irregularity or number of months of amenorrhea, are imprecise predictors of when the final menstrual period (FMP) will occur. Women who are in early or late perimenopause may be more or less proximal

to their FMP, and rates of bone mineral density (BMD) loss may therefore differ within menstrually defined stages. Similarly, the time at which bone loss decelerates after the FMP cannot be discriminated using menstrually classified MT stages.

A more precise description of onset and offset of bone loss can be obtained by modeling BMD change in relation to the FMP date. Using this approach, two longitudinal studies of white women found BMD loss accelerated about 2 years before the FMP and slowed, but did not cease, about 2 years after it.^(4,5) However, sample sizes in these investigations were modest and neither included minority women, which is an important consideration because ethnic-specific patterns of bone loss during the MT could contribute to the known ethnic variation in fracture rates.^(6–9)

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Additional Supporting Information may be found in the online version of this article.

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This analysis examines rates of BMD change in relation to the observed date of the FMP, in contrast to menopause transition stages, in a multiethnic cohort of African American, white, Chinese, and Japanese midlife women. The objectives of this study were to: 1) describe the timing of the onset and offset of accelerated BMD loss in relation to FMP date; 2) quantify the rate and amount of BMD decline at the lumbar spine (LS) and femoral neck (FN) during the 5 years before and after the FMP; and 3) assess whether body mass index, ethnic/racial origin, or age at FMP influenced the rate of BMD loss.

Materials and Methods

Study sample

The Study of Women's Health Across the Nation (SWAN) is a multisite, community-based, longitudinal cohort study of the MT.⁽¹⁰⁾ Eligibility criteria were: age between 42 and 52 years, intact uterus and at least one intact ovary, not currently using hormone therapy, at least one menstrual period in the 3 months before screening, and self-identification as a member of one of five eligible ethnic groups. Participants were enrolled at seven sites in the US: Boston, MA; Chicago, IL; Detroit, MI; Pittsburgh, PA; Los Angeles, CA; Newark, NJ; and Oakland, CA (N = 3302). All sites enrolled whites. Boston, Chicago, Detroit, and Pittsburgh enrolled African Americans, and the remaining three sites enrolled Japanese, Hispanic, and Chinese women, respectively. The Chicago and Newark sites did not measure BMD, leaving a potential of 2413 participants for the SWAN bone-density cohort. Of these, 2335 were enrolled in the bone cohort at baseline. The current analysis includes data from baseline to follow-up visit 10; only bone cohort participants who had a determinable natural (not surgical) FMP date were eligible. Hormone therapy use and other pharmacological agents that affect bone (ie, tamoxifen, raloxifene, GnRH agonists, corticosteroids, or osteoporosis treatments) were exclusions, applied at baseline. The inception cohort size was 862. Data from women who initiated bone-active medicine were censored at the time of first use. See Supplemental Fig. S1 for a flow diagram of the sample derivation. Participants gave written informed consent and sites obtained institutional review board approval.

Outcomes

LS and FN BMD (g/cm^2) were measured annually using Hologic instruments (Hologic, Inc., Waltham, MA, USA). Three sites used Hologic 4500A models throughout. Two sites upgraded from 2000 to 4500A models at follow-up visit 8. These sites scanned 40 women on both their old and new machines to develop cross-calibration regression equations. A standard quality-control program, conducted in collaboration with Synarc, Inc. (Newark, CA, USA), included daily phantom measurements, 6-month cross-calibration with a circulating anthropomorphic spine standard, local site review of all scans, central review of scans that met problem-flagging criteria, and central review of a 5% random sample of scans. Short-term in vivo measurement variability was $0.014 \text{ g}/\text{cm}^2$ (1.4%) for the LS and $0.016 \text{ g}/\text{cm}^2$ (2.2%) for the FN.

Primary predictor

The primary exposure, the number of months before or after the FMP that the BMD was taken, was computed using the month and year of the FMP and the month and year of each annual BMD assessment. FMP date was determined by annual, standardized interview. FMP date was defined as the last menstrual bleeding date reported during the visit immediately before the first visit when the participant was classified as postmenopausal (had 12 months of amenorrhea).

Other predictors

Age (years), self-defined race/ethnicity (African American, white, Chinese, Japanese), menstrual bleeding patterns, hormone therapy use (yes/no, time-varying), use of any medication that affects bone density (yes/no, time-varying) were obtained using annual, standardized interviews. Menopause transition stages (time-varying, based on reported annual bleeding patterns) were defined as: premenopausal (regular menses, no change from individual's pattern), early perimenopausal (menses within the last 3 months but less predictable than individual's pattern), late perimenopausal (at least 3 months but less than 12 consecutive months of amenorrhea), and postmenopausal (12 or more months without menses). Weight (kilograms, time-varying) and height (meters) were assessed annually, using calibrated scales and stadiometers. Body mass index (BMI, $[\text{weight in kilograms}/(\text{height in meters})^2]$) was calculated annually.

Data analysis

Characteristics of bone cohort participants included and excluded from analysis were compared using *t* tests (continuous variables) and chi-squared tests (categorical variables). To analyze change in BMD in relation to FMP date, we used a staged approach, consisting of 1) nonparametric, loess-based selection of the functional form of the BMD trajectory in relation to FMP date, 2) piecewise linear regression to determine knot placement for the parametric BMD trajectory, and 3) piecewise linear regression with fixed knots to estimate BMD decline rates during each phase of the trajectory. First, the loess method was used on repeated annual LS or FN measurements; each participant's BMD was normalized to her baseline.⁽¹¹⁾

In steps 2 and 3, we used mixed effects regression to fit piecewise linear models to repeated measurements of baseline-normalized LS or FN BMD (in separate models) as functions of time before or after FMP, using linear splines with fixed knots at FMP minus 1 year and FMP plus 2 years. To account for within-woman correlation between repeated observations, we included random effects for the intercept and 3 slopes (allowing the intercept and slopes to vary from woman to woman). In step 2, we tested model adequacy and appropriateness of knot locations by running null models with only random effects and no fixed effects. The fraction of within-woman variance in BMD explained by the three-segment, piecewise-linear, null model was 84.2% for LS BMD and 71.7% for FN BMD. We evaluated knot selection by examining the change in the explained proportion of within-woman variance (pseudo

R-square) when the knots were varied around FMP minus 1 year and FMP plus 2 years. The amount of explained variance was unambiguously lessened by knot movement (in 6-month intervals) away from FMP minus 1 year. However, the explained fraction was unaltered by subtracting or adding 6 months to the knot at FMP plus 2 years. We therefore chose FMP plus 2 years for the knot placement because it represented the midpoint (indicating gradual deceleration, in contrast to the fairly rapid acceleration at FMP minus 1 year). The explained fraction of within-woman variance also did not change when we used raw (unnormalized) or log-transformed BMD instead of baseline-normalized BMD. We present baseline-normalized BMD for ease of interpretation: The regression slopes are equivalent to percentage changes in BMD from baseline. Because we adjusted the models for baseline BMD, individual differences in starting BMD do not influence estimated percentages.

In the third step, we added age at FMP, race/ethnicity, and baseline BMI to the mixed-effects piecewise models, as fixed effects on the intercept and three slopes, to assess how each influenced the rate of BMD decline during each segment of the longitudinal, piecewise model. The BMD trajectories were divided into three linear segments in relation to FMP date (time 0): years -5 to -1 relative to the FMP, termed pretransmenopause; years -1 to $+2$ relative to the FMP, termed transmenopause; and years $+2$ to $+5$ after the FMP, termed postmenopause. We also modeled the effect of change in BMI since baseline on BMD values at follow-up. Models were adjusted for baseline BMD and clinical site. The effects of each predictor on the slopes for each segment were combined to obtain total effects on BMD decline during the 10-year period. Results are expressed as means and 95% confidence intervals (CI); 95% CIs that exclude 1 are considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The analytic sample consisted of 242 African American, 384 white, 117 Chinese, and 119 Japanese women. At baseline, mean value of age was 46.7 years (standard deviation [SD] 2.6 years), mean age at FMP was 51.6 (SD 2.4 years), and average body mass index was 27.4 kg/m^2 (SD 7 kg/m^2). The baseline percentages of premenopausal and early perimenopausal women were 58% and 41%, respectively; 16% were current smokers. These characteristics were similar to those of the SWAN bone cohort participants who were not included (data not shown). In the analysis sample, the mean number of BMDs per woman was 9 and the median was 10 (of a maximum possible 10).

Figures 1 and 2 illustrate the longitudinal loess plots of mean LS and FN BMD as a function of number of months before or after the FMP (based on the date each BMD was obtained and the FMP date). At both bone sites, there appeared to be no decline in BMD before 1 year before the FMP, bone loss began 1 year before the FMP, and decelerated, but did not cease, 2 years after the FMP. The loess plots also showed that trajectories were essentially linear within each of these three time intervals. To construct piecewise regressions, we therefore divided the BMD trajectories

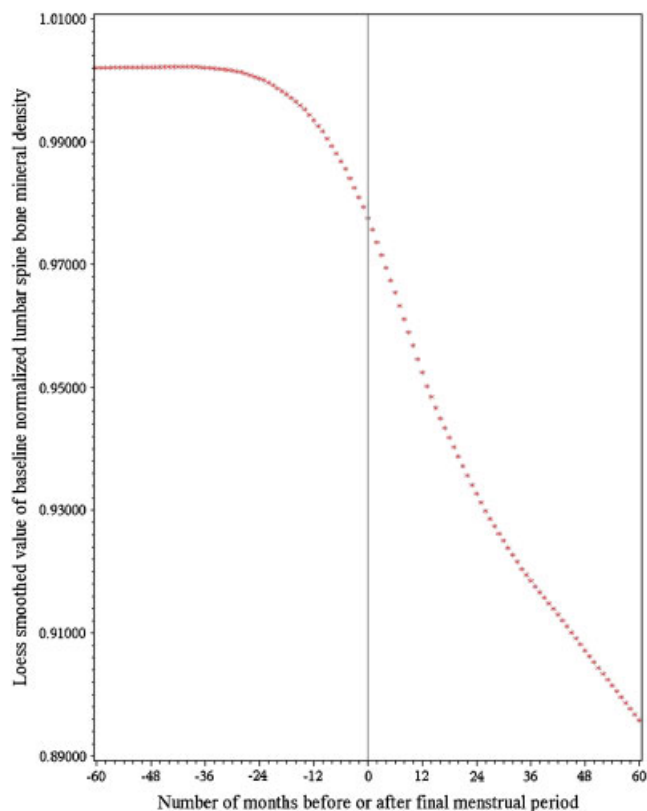


Fig. 1. The longitudinal trajectory of baseline-normalized lumbar spine bone mineral density (BMD) values in relation to the amount of time before (negative numbers) or after (positive numbers) the final menstrual period (FMP [time zero]). This loess plot illustrates no measurable decline in lumbar spine BMD during the interval between 5 years and 1 year before the FMP, BMD loss starting 1 year before the FMP that continued for 2 years after the FMP, and a deceleration, but not cessation, of BMD loss 2 years after the FMP.

into three linear segments in relation to FMP date. The first segment consisted of the period from 5 years before the FMP to 1 year before the FMP, termed pretransmenopause. The second segment spanned the interval from 1 year before the FMP through 2 years after the FMP, termed transmenopause. The final segment started 2 years after the FMP and ended 5 years after the FMP, termed postmenopause. (See Materials and Methods for tests of adequacy of breakpoint [knot] selections.)

Table 1 summarizes the results of the piecewise linear models that quantified LS BMD loss in each of the three segments, ie, pretransmenopause, transmenopause, and postmenopause. White women with average baseline LS BMD of 1.066 gm/cm^2 , average baseline BMI of 27.1 kg/m^2 , and average age at FMP of 51.6 years are the reference sample. The slopes shown for the white referent (row 1) are absolute slopes, reflecting the average rate of change in BMD during each segment. White transmenopausal change in LS BMD was -2.46% per year and postmenopausal change was -1.04% annually; summed 10-year change was -10.6% .

Also shown in Table 1 are the associations of BMI (per kg/m^2), race/ethnicity, and age at FMP with slopes in each of the segments. The figures shown in rows 2 to 6 are relative slopes; when added to the slope values of the white referent, the figures in rows 2 to 6 of the table yield the average slopes in women who

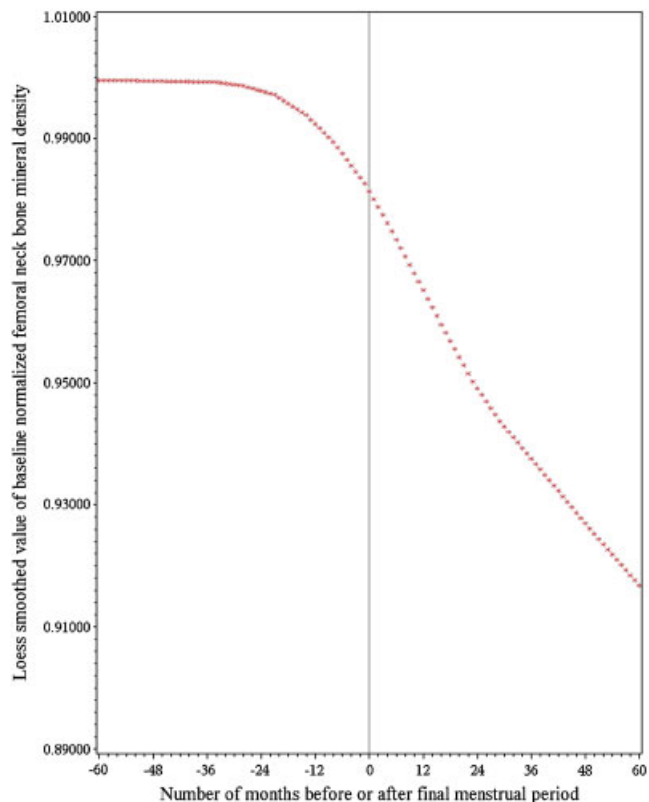


Fig. 2. The longitudinal trajectory of baseline-normalized femoral neck bone mineral density (BMD) values relative to time before or after the FMP (FMP [time zero]). The span between 5 years and 1 year before the FMP was characterized by no measurable drop in BMD. This loess plot illustrates no measurable decline in femoral neck BMD during the interval between 5 years and 1 year before the FMP, BMD loss starting 1 year before the FMP that continued for 2 years after the FMP, and a deceleration, but not cessation, of BMD loss 2 years after the FMP.

have that alternate characteristic. For example, higher BMI was associated with less bone loss in all segments of the curve, indicated by positive coefficients in pretransmenopause, transmenopause, and postmenopause (+0.008%, +0.063%, +0.018%, respectively, per BMI unit). These positive coefficients do not indicate that women with greater BMI gained bone. Rather, they show that average rates of bone loss (given in row 1 of Table 1) were lessened by these amounts in women with a BMI one unit higher than the sample average. Whites with BMI values one standard deviation (7.5 kg/m²) above average would still lose bone—a 10-year total of 8.50%—but a statistically smaller amount than the sample average 10-year loss of 10.6%. Being African American was associated with less transmenopausal spinal BMD loss (2.19% per year) and a 10-year BMD change of -9.6%, borderline statistically significantly lower than the Caucasian 10-year rate. During the pretransmenopausal segment, Chinese women lost LS BMD at a faster rate than White and Chinese 10-year LS BMD loss was 12.6%.

Results for FN BMD are presented in Table 2. White women with sample-average BMI, age at FMP, and baseline FN BMD (0.832 gm/cm²) lost 1.76% annually during the transmenopausal interval. They lost 1.15% of FN BMD annually during the postmenopausal segment. Total 10-year FN loss was 9.1%. Higher BMI was related to less BMD loss but only during the transmenopausal interval. The transmenopausal annual FN FMD loss rate was 1.42% in African Americans, 2.13% in Japanese, and 2.17% in Chinese women. Compared with whites, 10-year FN BMD loss was greater in Asians and less in African Americans.

Later age at FMP was related to greater loss of both bone sites during the transmenopause but had no effect on the 10-year cumulative loss (Tables 1 and 2). Not shown in the tables, women whose BMI changed during the 10-year period had an ending LS BMD that was higher by 0.10% per increasing BMI unit (95% CI

Table 1. Annual Rates of Change of Lumbar Spine (LS) Bone Mineral Density (BMD) in Relation to the Date of the Final Menstrual Period (FMP) and the Influence of Body Mass Index (BMI), Race, and Age at the FMP on LS BMD Before, During, and After the FMP^a

	Annual BMD slopes during each time interval before and after the FMP (95% confidence interval)			
	Pretransmenopause 5 years to 1 year before FMP	Transmenopause 1 year before to 2 years after FMP	Postmenopause 2 to 5 years after FMP	Cumulative BMD change ^b (95% confidence interval)
White referent ^c	-0.02% (-0.08%, +0.05%)	-2.46% (-2.61%, -2.31%)	-1.06% (-1.21%, -0.91%)	-10.6% (-11.2%, -10.0%)
Baseline BMI (per kg/m ²) ^d	+0.008% (+0.001%, +0.015%)	+0.063% (+0.046, +0.080%)	+0.018% (+0.001%, +0.035%)	+0.28% (+0.21%, +0.34%)
Race				
Japanese	+0.01% (-0.12%, +0.14%)	+0.20% (-0.12%, +0.52%)	-0.04% (-0.35%, +0.28%)	+0.5% (-0.7%, +1.8%)
Chinese	-0.14% (-0.27%, -0.01%)	-0.23% (-0.54%, +0.08%)	-0.22% (-0.51%, +0.06%)	-2.0% (-3.1%, -0.7%)
African American	-0.07% (-0.18%, +0.04%)	+0.27% (+0.02%, +0.52%)	+0.13% (-0.11%, +0.37%)	+0.9% (-0.1%, +1.9%)
Increasing age at FMP (years)	+0.002% (-0.020%, +0.016%)	-0.050% (-0.091%, -0.009%)	+0.040% (+0.002%, +0.079%)	-0.04% (-0.19%, +0.12%)

^aIn addition to the variables listed, the model is also adjusted for baseline BMD and clinical site. Slope referent values are for white women of average age at FMP (51.7 years), average baseline BMD (1.066 gms/cm² at the lumbar spine), and average BMI at baseline (27.1 kg/m²).

^bCumulative change during the 10-year period spanning 5 years before to 5 years after the final menstrual period.

^cStatistically significant associations are shown in bold italic typeface; significance test of nonzero slopes for white referent; significance test of difference between slopes in white referent and slopes in the other specified groups.

^dSlopes for BMI, race, and age at FMP, when added to the white slope referent values, give the slope in women who have each of these characteristics.

Table 2. Annual Rates of Change of Femoral Neck (FN) Bone Mineral Density (BMD) in Relation to the Date of the Final Menstrual Period (FMP) and the Influence of Body Mass Index (BMI), Race and Age at the FMP on FN BMD Before, During, and After the FMP^a

	Annual BMD slopes during each time interval before and after the FMP (95% confidence interval)			
	Pretransmenopause 5 years to 1 year before FMP	Transmenopause 1 year before to 2 years after FMP	Postmenopause 2 to 5 years after FMP	Cumulative BMD change ^b (95% confidence interval)
White referent ^c	-0.06% (-0.13%, +0.01%)	-1.76% (-1.92%, -1.61%)	-1.12% (-1.32%, -1.04%)	-9.1% (-9.7%, -8.5%)
Baseline BMI (per kg/m ²) ^d	+0.001% (-0.008%, +0.010%)	+0.025% (+0.006%, +0.044%)	+0.001% (-0.015%, +0.017%)	+0.08% (+0.01%, +0.16%)
Race				
Japanese	-0.05% (-0.20%, +0.11%)	-0.37% (-0.70%, -0.04%)	-0.12% (-0.41%, +0.17%)	-1.7% (-2.9%, -0.38%)
Chinese	-0.06% (-0.22%, +0.09%)	-0.41% (-0.73%, -0.09%)	+0.11% (-0.15%, +0.37%)	-1.2% (-2.4%, +0.0%)
African American	-0.02% (-0.14%, +0.11%)	+0.34% (+0.08%, +0.61%)	+0.03% (-0.19%, +0.26%)	+1.1% (+0.1%, +2.1%)
Increasing age at FMP (years)	+0.013% (-0.008%, +0.035%)	-0.055% (-0.098%, -0.013%)	+0.000% (-0.035%, +0.035%)	-0.11% (-0.27%, +0.05%)

^aIn addition to the variables listed, the model is also adjusted for baseline femoral neck BMD and clinical site. Slope referent values are for white women of average age at FMP (51.7 years), average baseline BMD (0.832 gms/cm² at the femoral neck), and average BMI at baseline (27.1 kg/m²).

^bCumulative change during the 10-year period spanning 5 years before to 5 years after the final menstrual period.

^cStatistically significant associations are shown in bold italic typeface; significance test of nonzero slopes for white referent; significance test of difference between slopes in white referent and slopes in the other specified groups.

^dSlopes for BMI, race, and age at FMP, when added to the white slope referent values, give the slope in women who have each of these characteristics.

0.06% to 0.14%) and FN BMD that was higher by 0.35% per unit increase in BMI (95% CI 0.30% to 0.40%).

It is not possible to know the FMP date prospectively. Menstrually defined menopause transition categories, based on bleeding patterns, are therefore used in an attempt to stage the transition. The inference is that the later the transition stage, the

closer to the FMP. To assess the usefulness of stages based on bleeding patterns (ie, premenopause, early perimenopause, late perimenopause, and postmenopause) in gauging where women are in the bone-loss trajectory, we mapped the menstrually based stages onto each yearly interval before and after the FMP (Table 3). During the year before the FMP, when bone loss

Table 3. Number of Observations Made in Each 12-Month Period Before and After the Final Menstrual Period (FMP) and the Relation Between Time to or from FMP and Menstrually Defined Menopause Transition Stages

No. of months before (negative sign) or after (positive sign) FMP ^b	No. of observations	Crude lumbar spine BMD ^c	Crude femoral neck BMD ^c	Menstrually defined menopause transition stages ^a			
				Premenopausal <i>n</i> (%)	Early perimenopausal <i>n</i> (%)	Late perimenopausal <i>n</i> (%)	Postmenopausal <i>n</i> (%)
-60 to -49	485	1.07	0.83	178 (36.8)	304 (62.8)	2 (0.4)	0 (0.0)
-48 to -37	563	1.07	0.83	155 (27.6)	396 (70.5)	11 (1.9)	0 (0.0)
-36 to -25	618	1.07	0.83	116 (18.8)	481 (77.8)	21 (3.4)	0 (0.0)
-24 to -13	697	1.07	0.83	64 (9.2)	552 (79.7)	77 (11.1)	0 (0.0)
-12 to FMP	742	1.05	0.82	32 (4.3)	503 (68.0)	205 (27.7)	0 (0.0)
FMP to +12	871	1.03	0.82	8 (0.9)	266 (30.5)	535 (61.4)	62 (7.1)
13 to 24	703	1.00	0.79	0 (0.0)	0 (0.0)	0 (0.0)	703 (100)
25 to 36	602	0.99	0.78	0 (0.0)	0 (0.0)	0 (0.0)	602 (100)
37 to 48	456	0.97	0.77	0 (0.0)	0 (0.0)	0 (0.0)	456 (100)
49 to 60	372	0.97	0.77	0 (0.0)	0 (0.0)	0 (0.0)	372 (100)

^aMenstrually defined menopause stages are based on self-reported bleeding patterns obtained by annual interview. Menopause transition stage categories are: premenopausal, characterized by regular menses; early perimenopausal, defined as menses within the last 3 months but less predictable compared with participant's prior pattern; late perimenopausal, defined as having had at least 3 months, but less than 12 consecutive months, of amenorrhea; and postmenopausal, characterized by having experienced 12 or more months without menses.

^bThe number of months either before or after the FMP that each on-study BMD was obtained. In this article, based on patterns of BMD loss in relation to the FMP, the following terminology is used: The time interval between 5 years and 1 year before the FMP is called pretransmenopause. The interval spanning 1 year before to 2 years after the FMP is termed the transmenopause. The interval between 2 and 5 years after the FMP is called the postmenopause. These FMP-based categories are distinct from the menstrually based menopause transition category definitions given in footnote *a*.

^cCrude mean values of lumbar spine or femoral neck BMD in each 1-year interval before or after the FMP.

accelerated, 68% of participants who were observed were still classified as early perimenopausal based on bleeding patterns. Even in the year after the FMP, 30% of observations were in women still classified as early perimenopausal according to bleeding patterns. In the year immediately preceding the FMP, only 30% of BMD observations were in women classified as late perimenopausal. In the year immediately after the FMP, 62% of observations were in women classified as late perimenopausal. Table 3 also provides the crude mean BMD values during each yearly time interval before and after the FMP. The patterns of crude mean bone loss correspond closely to the loess plots (Figs. 1 and 2) and to the piecewise regression models (Tables 1 and 2).

Discussion

In the time span consisting of 5 years before and 5 years after the FMP, change in BMD was divisible into three linear phases. Bone loss was not evident during the pretransmenopause, except in Chinese women, who had a small annual decline. At both the LS and FN, BMD loss began 1 year before the FMP and slowed 2 years after it, and this transmenopausal loss was greater at the LS than the FN. Postmenopausal loss rates, defined here as starting 2 years after the FMP, were of similar magnitude at each bone site and were less than transmenopausal rates of loss. Cumulative, 10-year LS BMD loss was 10.6%; 7.38% was lost during the transmenopause. Cumulative, 10-year FN loss was 9.1%; 5.8% was lost during the transmenopause. Base-case estimates of bone loss rates were based on whites with sample-average characteristics. Greater BMI and African American heritage were related to slower loss rates, whereas the opposite was true of Japanese and Chinese ancestry.

The trajectory of menopause-related bone change is best captured by anchoring it to the FMP, as was done a decade ago in an 8-year longitudinal study of 75 initially premenopausal white women, in which an exponential curve was used to characterize BMD loss relative to FMP date.⁽⁴⁾ In that study, LS and FN bone loss accelerated 2 years before the FMP. Loss continued for 3 to 4 years after the FMP at the LS and for about 1.5 years after the FMP at the FN. These estimated times of onset and offset of transmenopausal loss ostensibly differ from SWAN's, but the former study did not report parametric testing of the acceleration and deceleration points. Because of differences in statistical modeling used in the former and the current study, it is not feasible to compare their estimates of transmenopausal bone loss. However, in the former study, cumulative BMD losses in the period spanning 4 years before and 4 years after the FMP were 10% at the spine and 9.5% at the hip, similar to SWAN's 10-year cumulative losses. Using a combination of splines and piecewise linear models in a longitudinal sample of 183 white women, the Michigan Bone Health and Metabolism Study (MBHMS) found that spine BMD loss accelerated 2 years before and continued for the 2 years after the FMP, whereas the FN BMD acceleration began about 2 to 3 years before the FMP and lasted for 2 years after it.⁽⁵⁾ Differences in estimated acceleration and deceleration times between MBHMS and SWAN may be in part because of the

smaller sample size in the former study and to the challenge of estimating velocity changes when these are gradual. In the MBHMS, spine and hip losses during the interval spanning 1 year before through 2 years after the FMP were 8.3% and 4.7%, respectively, concordant with SWAN's estimates of 7.3% and 5.3% during the same interval at the same bone sites. Dissimilarities in estimated timing of transmenopausal acceleration and deceleration are less important than similarities among these three analyses, each of which demonstrate a period of rapid bone loss in the few years before and after the FMP, more pronounced at the LS than at the FN.

Transmenopausal BMD loss was greater at the LS than at the FN, concordant with the higher proportion of trabecular bone at the former compared with the latter site.^(12,13) Riggs, Khosla, and Melton originally proposed that accelerated, early postmenopausal bone loss affected trabecular bone to a greater degree than it affected cortical bone and that the subsequent, slower rate of BMD loss was similar in both bone compartments.⁽¹⁴⁾ The initial, accelerated phase was ascribed to the loss of a tonic estrogen effect on bone turnover; the slower phase to estrogen-deficiency-caused secondary hyperparathyroidism. Newer, CT-based studies still find a menopausal acceleration of trabecular bone loss (more pronounced at the lumbar spine than at the distal tibia or radius) but newly report that trabecular loss begins in women during their 20s, whereas tibial and radial cortical bone losses do not differ from no loss until the MT.⁽¹⁵⁾ We did not observe bone loss before the transmenopause, likely because of the lesser sensitivity of DXA compared with CT. The MT (and concomitant change in estradiol and other factors) appears to play a major role in onset of cortical bone loss and the amplification of trabecular bone loss in midlife women.^(16,17)

Body mass, racial/ethnic origin, and age at FMP were each associated with bone loss rates, but their effects were manifest during different segments of the bone loss curves and differed at the LS and FN sites. Higher baseline BMI was related to slower rates of LS bone loss during all phases, whereas at the FN it was associated with slower loss during the transmenopause. Nonetheless, when cumulated over 10 years, higher BMI predicted slower bone loss rates at both bone sites, in accord with most,^(1,3,5,18) but not all,⁽¹⁾ longitudinal studies of the MT. Unlike SWAN's initial longitudinal findings, we found BMI-independent, racial/ethnic variation in cumulative 10-year bone loss, mainly because of differences in the rates of transmenopausal bone loss. The discordance between SWAN's first longitudinal report and the current one is likely because of a doubling of the follow-up time and also to our use of the FMP-date-based primary predictor. Racial/ethnic differences in cumulative, 10-year bone loss were small, on the order of 1% to 2%. This absolute difference in amount of bone loss is unlikely to explain racial/ethnic variations in fracture rates.⁽⁶⁻⁹⁾ However, it is intriguing that the racial/ethnic variations in bone loss rates were almost entirely confined to the transmenopausal segment, which may have long-term impact on structural integrity (discussed below). Finally, the effect of increasing age at FMP on bone loss rate, also isolated to the transmenopause, was quite small and is not likely to be of clinical or biological significance.

Mapping the menstrually defined MT stages onto the number of years before or after the FMP (Table 3) pointed out that

menopause transition stages were not useful clinical signals of the onset of transmenopausal BMD loss. In the year before the FMP, 70% of women were classified as early perimenopausal and only 30% of women were in late perimenopause. This result appears counter to earlier reports that found minimal BMD loss during early perimenopause and a dramatic increase in BMD in late perimenopause—but careful scrutiny will demonstrate that the findings are indeed compatible and provide complementary information.^(1–3) In the current study, 60% to 80% of the BMD measures that were made in the years spanning 5 years to 1 year before the FMP (when no BMD loss occurred) were in early perimenopausal women; therefore, when one computes average BMD loss among all women classified as early perimenopausal, it is predominantly influenced by this 4-year period of no loss. The time span during which women were in late perimenopause was shorter, mainly 1 year before and 1 year after the FMP, consistent with the higher rates of BMD loss computed for this stage when menstrually based classifications are used. But only 28% of women had reached late perimenopause when rapid BMD loss began, demonstrating that late perimenopause is not a clinically sensitive indicator that substantive BMD loss is starting. Finally, it may seem counterintuitive that 30% of participants were classified as early perimenopausal the year after their FMP occurred. However, the FMP date can only be known in retrospect; these are women who have “more abrupt” natural menopause—ie, who transition directly from irregular menses to no menses without having had a menstrual gap of at least 3 months.

Does accelerated BMD loss during the transmenopause have clinical implications? On average, the absolute quantity of BMD lost during the 3-year transmenopausal phase, 7.4% at the LS and 5.3% at the FN, is unlikely to result in a BMD value sufficiently low to meet even the most conservative treatment recommendations. For example, a white woman with a baseline FN BMD at the 5th percentile for SWAN whites, 0.69 g/cm² (a *T*-score –1.4), would have a femoral neck BMD of ~0.64 g/cm² 2 years after the FMP (a *T*-score of –1.8). But absolute decline in BMD may be less critical than the rapid bone turnover that it signals. Rapid turnover may damage skeletal structural integrity, through loss of trabecular elements, diminished trabecular connectivity, weakened trabeculae, and erosion of the endosteal cortex.⁽¹⁹⁾ During the MT, histomorphometry and 3D micro CT demonstrate declines in trabecular number, enlargement of trabecular spacing, and conversion of trabecular plates to rods, in direct correspondence with increases in activation frequency.^(19,20) Concern about irreparable architectural damage to bone has led some to advocate for short-term antiresorptive therapy during the MT in an attempt to prevent such damage.⁽²¹⁾ Although we concur that the major import of transmenopausal accelerated bone loss may be its threat to microarchitecture, we do not believe that the currently available data are sufficient to recommend treatment. Rather, further characterization of this phenomenon is essential.

Strengths of this analysis include its large sample size, number of FMPs observed, ability to compare patterns of bone loss directly among women from four racial/ethnic groups, and multiple longitudinal measurements. The analysis method, linking patterns of bone loss to the FMP, newly points out the incapacity of menstrually defined MT stages to signal the onset

of transmenopausal BMD loss. Study limitations include some uncertainty in the timing of the acceleration and deceleration of BMD loss, especially the latter, which was much less distinct. Ten-year loss rates were computed to militate against this uncertainty in knot placement. Because SWAN enrolled women who were in their mid-40s, we cannot capture the period of time earlier than 5 years before the FMP; additional follow-up will permit us to extend observations beyond 5 years post-FMP. Non-white sample sizes were large enough to detect racial/ethnic differences in BMD trajectories but not large enough for us to test for interactions within race. Two sites changed Hologic bone densitometer models; however, in vivo cross-calibration protocols were done.

In conclusion, this analysis confirms that there is a period of rapid BMD loss that brackets the FMP and commences about 1 year before it and newly reports that transmenopausal BMD loss is independently influenced by ethnicity and body mass. Future work should determine whether rapid transmenopausal bone loss permanently damages bone microarchitecture or bone strength. Clinically useful signals that presage the onset of transmenopausal BMD loss also require elucidation.

Disclosures

All the authors state that they have no conflicts of interest.

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