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Baseline age and time to major fracture in younger postmenopausal women

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Abstract

Objective—To estimate the incidence of first hip or clinical vertebral fracture or major osteoporotic (hip, clinical vertebral, proximal humerus or wrist) fracture in postmenopausal women receiving their first bone mineral density (BMD) test before age 65.

Methods—We studied 4068 postmenopausal women aged 50 to 64 without hip or clinical vertebral fracture or antifracture treatment at baseline, participating in the Women's Health Initiative BMD cohort study. BMD tests were performed between October 1993 and April 2005, with fracture follow-up through 2012. The outcomes were the times for 1% of women to sustain a hip or clinical vertebral fracture, and for 3% to sustain a major osteoporotic fracture before

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initiating treatment, adjusting for clinical risk factors and accounting for competing risks. Women without and with osteoporosis on their first BMD test were analyzed separately.

Results—During a maximum 11.2 years of concurrent BMD and fracture follow-up, the adjusted estimated time for 1% of women to have a hip or clinical vertebral fracture was 12.8 years (95% CI, 8.0, 20.4) for aged 50 to 54 and 7.6 years (95% CI, 4.8 to 12.1) for aged 60 to 64 for those without baseline osteoporosis, and 3.0 years (95% CI, 1.3, 7.1) for all women aged 50 to 64 with baseline osteoporosis. Results were similar for major osteoporotic fracture.

Conclusion—Due to very low rates of major osteoporotic fracture, postmenopausal women age 50 and 64 without osteoporosis on a first BMD test are unlikely to benefit from frequent rescreening before age 65.

Keywords

bone density; fractures/bone; mass screening; osteoporosis/postmenopausal

Introduction

While routine bone mineral density (BMD) screening is universally recommended for women aged 65 years and older,[1-8] the optimal schedule for BMD screening in younger (aged 50 to 64) postmenopausal women is unknown. Four percent of US women aged 50-59 and 20% of women aged 60-69 were reported to have osteoporosis (very low BMD) in 1995,[9] and the overall prevalence of osteoporosis in women aged 50 and older decreased by 2006.[10] Because of these low prevalence rates, identification of osteoporosis in younger postmenopausal women is challenging. Clinical practice guidelines typically encourage BMD screening in postmenopausal women under age 65 according to their risk factors for fracture,[2, 3] but there is no agreement regarding which factors to choose from lists of up to 90 predictors. Unlike most clinical screening guidelines for chronic diseases, BMD screening guidelines do not specify a standard testing interval. Younger postmenopausal women without extra risk factors for BMD loss may question whether routine (repeated) BMD testing should be performed soon after the onset of menopause, or whether this test can safely be deferred.[11] Age-defined data are essential for younger postmenopausal women and their primary care providers to use in shared decision making regarding the timing of BMD tests.

For women over age 65, the estimated time-to-osteoporosis is a useful metric to decide a BMD screening interval because of known significant fracture rates in this age range of women.[12] In contrast, time-to-fracture estimates must inform the frequency of BMD screening in younger postmenopausal women because their fracture rates may be low despite transitory accelerated BMD loss immediately after the onset of menopause.[13] In women aged 50 to 54, the estimated 5-year risk is 0.2% for first spine fracture and 0.0% for first hip fracture, compared to 1.5% and 0.8% for the respective risks in women aged 65 to 69.[14] At the same time, a large study of postmenopausal women followed for up to 3 years after baseline peripheral (heel, forearm, or finger) BMD measures found that relative risks for fracture were similar in women aged 50 to 59 compared to older age groups.[15] To thoroughly examine the clinical utility of BMD screening in younger postmenopausal

women, those without and with osteoporosis must be studied, with adequate follow-up to estimate fracture incidence before age 65 (when routine BMD testing is recommended).

To characterize the incidence of hip or clinical vertebral fracture in younger postmenopausal women at any baseline BMD level, we conducted competing risk analyses of 4068 postmenopausal women aged 50 to 64 years without a history of hip or clinical vertebral fracture or treatment for osteoporosis, followed longitudinally for up to 11 years in the Women's Health Initiative bone density cohort. We hypothesized that younger postmenopausal women without osteoporosis (hip and lumbar spine T-scores >-2.50) at baseline would be unlikely to experience a hip or clinical vertebral fracture or other major osteoporotic fracture before age 65.

Methods

Study participants

We studied 4068 postmenopausal women aged 50 to 64 years at baseline participating in the Women's Health Initiative Observational Study (WHI-OS) or Clinical Trials (CT, Hormone Therapy, Calcium/vitamin D and Dietary Trials) placebo groups who had at least one DXA scan between October 1993 and April 2005 at the Tucson/Phoenix, Pittsburgh or Birmingham clinical centers. BMD was followed for a maximum of 11.2 years, and fracture was followed for a maximum of 18.6 years in the analytical cohort as a whole. Because the competing risk framework requires concurrent follow-up of the primary endpoint (hip or clinical vertebral fracture) and competing risks (including BMD measurements), the effective maximum length of follow-up for the analyses of time to fracture was 11.2 years. However, data from the full period of fracture follow-up (18.6 years) were tabulated in a separate analysis.

Women with any BMD T-score at baseline (including osteoporosis) were included in the competing risk analyses. Details of the study examinations and selection of the analytical cohort are described in the Supplemental Digital Content and Figure 1. The study protocol and consent forms for the WHI study were approved by the institutional review boards for all participating institutions. The analysis protocol was reviewed and approved by the Institutional Review Board of the University of North Carolina.

BMD classifications and definition of osteoporosis

Eligible participants had DXA BMD measurements at the femoral neck, total hip and lumbar spine at one or more study examinations. World Health Organization diagnostic criteria[16] for osteoporosis were used to classify participants by their baseline BMD T-scores ([BMD of participant – mean BMD of reference population]/SD of BMD of reference population) at the femoral neck, total hip or lumbar spine. T-scores were calculated using National Health and Nutrition Examination Study III BMD norms for non-Hispanic white women aged 20-29.[17, 18] Data from participants without (T score at femoral neck, total hip, and lumbar spine > -2.50) and with osteoporosis (lowest T-score <= -2.50) were analyzed separately. We emphasized BMD screening in this study because numerous randomized trials[19-22] have demonstrated the benefit of pharmacologic treatment in postmenopausal

women who have osteoporosis as defined by BMD criteria, and because the US Preventive Services Task Force[1, 23] has rigorously reviewed the magnitude of benefits, harms, and net benefit of the use of DXA BMD screening in postmenopausal women.

Outcomes

The primary outcome was the estimated time interval for 1% of participants in three age groups to transition from the baseline T-score categories to hip or clinical vertebral fracture before developing osteoporosis (for those without osteoporosis at baseline), before initiating treatment for osteoporosis, and prior to dying. The secondary outcome was the time for 3% of women in each age group to have a major osteoporotic fracture (includes hip, clinical spine, proximal humerus, or wrist fracture according to the World Health Organization definition[24]).

Fractures were verified by review of radiology, magnetic resonance imaging, or operative reports by centrally trained physician adjudicators at each of the BMD clinics participating in WHI. For fracture sites other than hip, local clinic physician-adjudicated fractures were used. Final adjudication of hip fractures was performed centrally by blinded WHI physician adjudicators. The agreement between central and local adjudication for hip fracture was 94%. Additional details regarding fracture adjudication are included in the Supplemental Digital Content.

Independent variables

Demographics and prevalence of risk factors for osteoporosis and fracture were tabulated. The regression models for occurrence of fracture for women without osteoporosis at baseline were adjusted for baseline age group (50-54, 55-59, 60-64), continuous T-score (centered at mean of lowest T-score at any site for each individual without osteoporosis at baseline), body mass index (BMI), race/ethnicity (black [referent] vs. non-black-non-white vs. white) and current hormone therapy use status at baseline. The regression model for women with osteoporosis at baseline was adjusted only for age (centered at mean age of women with baseline osteoporosis).

Medication use

Use of Food and Drug Administration–approved agents for the treatment of osteoporosis (bisphosphonates including alendronate, risedronate, pamidronate or zoledronate; calcitonin; raloxifene; parathyroid hormone) was assessed in the WHI Observational Study and WHI Extension Hormone Use Update medication follow-up surveys (see Supplemental Digital Content for survey questions). Osteoporosis treatment agents were prescribed by the participant's doctor(s), not by WHI study personnel. Participants were asked to report any use of the individual agents in the past year. The exact length of therapy was unknown.

Statistical analysis

Competing risk analyses were conducted to estimate the cumulative incidence functions for each age group for the time to the development of a hip or clinical vertebral fracture, and the corresponding intervals for 1% of participants to make the transition to fracture. The competing risks were development of osteoporosis (for women without osteoporosis at

baseline), initiation of a Food and Drug Administration–approved agent for the treatment of osteoporosis, and death. The time origin was the first study visit including BMD measurements at all three anatomical sites (femoral neck, total hip, lumbar spine), with follow-up continuing until the study examination preceding death or drop-out. Parametric regression models[25] were fit to the cumulative incidence of fracture using naïve maximum likelihood analysis. The 1% time intervals and associated confidence intervals were based on the competing risks quantile methodology,[26] as implemented for parametric models by Lee and Fine.[27] Similar competing risk models were constructed to estimate the time for 3% of women in each age group to have a major osteoporotic fracture. Technical details are provided in the Supplemental Digital Content.

The very small number of major fracture events precluded use of competing risk regression analysis to estimate time to fracture adjusting for additional clinical risk factors beyond those listed above. We instead used Fisher's exact test to compare the crude number of participants without and with osteoporosis at baseline who had a hip or clinical vertebral fracture after their baseline visit, cross-tabulated with key categorical risk factors described in the independent variables section. Because concurrent BMD and fracture follow-up was not required, we used the full amount of fracture follow-up data (over a maximum of 18.6 years) and included all hip and clinical vertebral fractures, whether or not they occurred before a competing risk. For this reason, the total number of fractures was greater in the Fisher's exact test analysis compared to the competing risk analyses.

All analyses were performed using Statistical Analysis Software (SAS) 9.3.[28]

Results

Characteristics of the analytical cohort

Baseline characteristics of the analytical cohort are shown in Table 1. Tabulations of osteoporosis according to three different definitions (Table A1 and Supplement Tables A2-A3) revealed that 51% (170/344) of the osteoporosis diagnoses were determined by the lumbar spine BMD measurement (lumbar spine T-score <=-2.50, femoral neck and total hip T-score >-2.50).

Estimated time to hip or clinical vertebral fracture

The following proportions of women (including those with osteoporosis at baseline) sustained a hip or clinical vertebral fracture before initiating osteoporosis treatment: aged 50 to 54 at baseline, 12/1069 (1.1%); aged 55 to 59 at baseline, 24/1391 (1.7%); aged 60 to 64 at baseline, 37/1608 (2.3%); all ages 73/4068 (1.8%).

Unadjusted (Fig. 2) and covariate-adjusted estimates of the cumulative incidence of first hip or clinical vertebral fracture as a function of testing interval length were similar. The adjusted estimated times for 1% of women without osteoporosis to transition to hip or clinical vertebral fracture decreased with increasing age (Table 2), ranging from 12.8 years (95% CI, 8.0, 20.4) for aged 50 to 54, to 11.7 years (95% CI, 6.9, 20.0) for aged 55 to 59, to 7.6 years (95% CI, 4.8, 12.1) for aged 60 to 64. For those with osteoporosis, the age-

adjusted time interval was 3.0 years (95% CI, 1.3, 7.1) for women aged 50 to 64 analyzed together.

The crude proportion (not accounting for competing risks) of participants that had at least one hip or clinical vertebral fracture by the end of follow-up was significantly higher for women with osteoporosis compared to women without osteoporosis at baseline in all subgroups of age, BMI, personal fracture history, parental history of hip fracture, smoking and hormone therapy use (Table 3). Tabulations of primary endpoint and competing risk events (Table A1) showed that treatment was the first event for 673 women (16.5% of the analytical cohort), i.e., 531 (13.1% of the analytical cohort) participants without osteoporosis at baseline were treated before they developed osteoporosis or had a hip or clinical vertebral fracture, and 142 (3.5% of the analytical cohort) women with baseline osteoporosis were treated before they had a hip or clinical vertebral fracture.

Estimated time to major osteoporotic fracture

These proportions of women (including those with osteoporosis at baseline) sustained a major osteoporotic fracture before initiating osteoporosis treatment: aged 50 to 54 at baseline, 38/1069 (3.6%); aged 55 to 59 at baseline, 71/1391 (5.1%); aged 60 to 64 at baseline, 93/1608 (5.8%); all ages, 202/4068 (5.0%).

The estimated times for 3% of women without baseline osteoporosis to have a major osteoporotic fracture (hip, clinical spine, proximal humerus, or wrist) ranged from 11.5 years (95% CI, 8.0, 16.7) for women aged 50 to 54, to 8.6 years (95% CI, 5.8, 12.8) for women aged 60 to 64 at baseline (Table 4).

For all women aged 50 to 64 with baseline osteoporosis analyzed together, the age-adjusted time for 3% to have a major osteoporotic fracture was 2.5 years (95% CI, 1.2, 5.3; event N 31/344, 9.0%). The proportions of women with baseline osteoporosis who had a major osteoporotic fracture before initiating treatment were: 3/40 (7.5%) for age 50 to 54; 10/106 (9.43%) for age 55 to 59; 18/198 (9.1%) for age 60 to 64. Within these groups, 3, 7 and 9 women respectively had a major osteoporotic fracture before age 65.

Discussion

This longitudinal study found that among postmenopausal women aged 50 to 64 without osteoporosis on their first BMD test, less than 1% experienced a hip or clinical vertebral fracture and less than 3% experienced a major osteoporotic fracture by 7 years. The analysis accounted for different clinical trajectories, i.e., incident osteoporosis, death or initiation of treatment before a first major osteoporotic fracture was modeled as a competing risk. Our results suggest that younger postmenopausal women without osteoporosis on their first BMD scan are unlikely to benefit from frequent rescreening before age 65. Adjustment for several clinical risk factors for fracture did not substantially alter these findings. Women with osteoporosis on their first BMD test (8.5% of cohort) had a significantly higher risk of fracture before age 65 compared to women without osteoporosis.

Empirical data on age-appropriate osteoporosis screening are important because of substantial underutilization of BMD testing in women aged 65 and older,[29] and inappropriate use in other postmenopausal women who do not meet screening criteria in published clinical practice guidelines.[30] In 2011, the National Physicians Alliance initiated a project titled “Promoting Good Stewardship in Clinical Practice” that aimed to develop a list of the top 5 activities in family medicine, internal medicine, and pediatrics where the quality of care could be improved.[31] This list included the recommendation, “don't use DEXA screening for osteoporosis in women under age 65 years or men under 70 years with no risk factors,” citing the lack of cost-effectiveness in these groups. While the project's focus on cost control was understandable, the BMD testing recommendations were not based on original studies testing this hypothesis. Our results substantiate that DXA BMD testing has a lower yield for younger postmenopausal women compared to women age 65 and older. However, because hip and spine fractures would be catastrophic for working adult women who are otherwise healthy, we do not interpret our results to mean that no postmenopausal women under age 65 should have a DXA test. Instead, the data suggest that before age 65, postmenopausal women would be unlikely to have a major fracture, but development of osteoporosis by BMD criteria remains important because it confers higher immediate risk of major fracture compared to greater BMD levels. Our results are generalizable to younger postmenopausal women with good general health who are candidates for BMD screening in a primary care practice. Our results should not be applied to patients with existing fragility fracture or secondary causes of osteoporosis who are seen in subspecialty clinics, or to patients who have taken anti-fracture treatment agents. Those individuals are no longer candidates for screening because they have higher baseline risk for subsequent fractures, and thereby different testing and treatment criteria.

Current clinical practice guidelines encourage the use of risk factors for fracture to select postmenopausal women under age 65 who are good candidates for DXA testing.[1, 2] Two analyses of large cohorts of postmenopausal women aged 50 to 64 at baseline suggest that simple fracture risk assessment tools (including one calculated from age and weight) perform as well as more complicated tools for this purpose.[32, 33] Our data can help inform a BMD testing interval for postmenopausal women who are screened before age 65. Using the more conservative time estimates for major osteoporotic fracture, clinicians might allow women aged 50 and 54 without osteoporosis on their first BMD test to wait 10 years for their next test. Similarly, women aged 60 to 64 without osteoporosis on their first BMD test might wait until after age 65 for their next test. Other approaches have been considered, e.g. Reid and Gamble's 2014 modeling study based on the doubling time for predicted hip fracture risk suggested that a BMD screening interval of 5 to 6 years may be appropriate for many intermediate-risk women aged 65 and older.[34] This 5-to-6-year interval might be interpreted as a conservative estimate for intermediate-risk younger postmenopausal women.

Women found to have osteoporosis in this age range are no longer candidates for a routine screening schedule. We included these women in the analysis because if they had osteoporosis but did not sustain a fracture until well after age 65, the value of any BMD screening before age 65 would be questioned. Instead, we found that all (3/3) of the women aged 50 to 54 and over half (16/28) of those aged 55 to 64 with baseline osteoporosis who had a major osteoporotic fracture during follow-up had the fracture before age 65. This

suggests that clinicians should promptly counsel younger postmenopausal women with osteoporosis regarding the benefits and harms of treatment, rather than assuming this discussion can be deferred. Although women with osteoporosis had a substantially higher risk of fracture, most of the hip and clinical vertebral fractures in the cohort as a whole occurred in women with baseline T-scores >-2.50 (i.e., 65 of 3724 [1.7%] women with baseline T-scores >-2.50 vs. 25 of 344 [7.3%] women with baseline T-scores <=-2.50 had a hip or clinical vertebral fracture). These results are consistent with other longitudinal studies of postmenopausal women,[35, 36] and they demonstrate that BMD testing cannot identify every individual who will have a future fragility fracture. Such findings emphasize the importance of further investigations of risk factor assessment and screening methods to identify poor bone quality that also contributes to increased fracture risk.

According to current clinical practice guidelines,[2, 5, 8] women with asymptomatic radiographic vertebral fractures should also receive osteoporosis treatment, regardless of BMD T-score level. Radiographic vertebral fracture data were not available in the WHI study, but a US population-based study reported very low vertebral fracture incidence rates for this age range of women (215-349 per 100,000 [0.35%] for women aged 50 to 64).[37] Considering that one-third or fewer of incident radiographically identified vertebral fractures are clinically diagnosed, clinicians may consider additional imaging (lateral thoracic and lumbar spine radiographs or densitometric vertebral fracture assessment imaging) in postmenopausal women with BMD T-scores between -1.5 and -2.4 who have height loss or other risk factors that may suggest prevalent radiographic vertebral fracture.[38]

The low incidence rates of hip or clinical vertebral fractures in our analysis are consistent with the 2008 Cochrane review of alendronate treatment that showed very low absolute risk reductions (ARR) for hip and clinical vertebral fractures in younger postmenopausal women. Women aged 50 to 54 treated with alendronate had 5-year ARR of 0.1% for first spine fracture and 0.0% for first hip fracture, with analogous figures of 0.5% and 0.1% for women aged 60 to 64, and 0.7% and 0.4% for women aged 65 to 69.[39] In contrast, the ARR for alendronate-treated women aged 90 and older was 11.1% for spine fracture and 2.1% for hip fracture. The very low treatment efficacy of alendronate in the younger women was likely due to their low baseline (untreated) fracture rates, so that treatments did not confer significant absolute fracture risk reduction. Because of these low fracture rates, BMD screening and treatment in younger postmenopausal women is likely to have less of an impact on the population burden of fracture compared to screening and treatment in women aged 65 and older. Careful selection of women for screening and treatment is especially important before age 65 because the risk of complications such as atypical femoral fractures[40] and osteonecrosis of the jaw[41] appears to rise with increasing duration of exposure to bisphosphonates. The 3% fracture threshold used in our analysis of major osteoporotic fractures was much lower than the 20% estimated fracture risk threshold for which treatment may be recommended according to the WHO FRAX fracture risk algorithm.[24] Thus, our time estimates for the major osteoporotic fracture endpoint should not be viewed as an estimated time until treatment initiation.

Our study had several limitations. Our time estimates were based only on transitions to major fracture; the full benefits and risks of screening and cost-effectiveness were not

considered. The analysis had inadequate power to study fracture risk in subgroups defined by individual risk factors. For example, a higher proportion of women with osteoporosis and current hormone therapy use at baseline had a hip or clinical vertebral fracture during follow-up compared to women with osteoporosis and without current hormone therapy use at baseline. This might have represented confounding by treatment indication or mere variability in an estimate based on very few fracture events. Over 97 percent of the original WHI participants were not eligible for this analysis because they were not part of the BMD cohort. However, our study population included 89.9% (4068/4527) of the WHI participants with technically adequate BMD measurements at one or more study examinations. Seventy-four percent of our sample comprised white women, and 15 percent comprised black women; because the prevalence of hip osteoporosis in white women is lower than the prevalence in African American women by NHANES estimates,[10] our calculated estimates of time to major fracture are likely to be a reasonable estimate for women of all races. Because of rare fracture events for the lowest-risk women, some of our time estimates were extrapolations with wide confidence intervals. Strengths of the analysis include the large size of the cohort and the long follow-up period involving repeated BMD testing, fracture ascertainment between study visits, inclusion of the lumbar spine site in the BMD measurements and inclusion of mortality as a competing risk.

Conclusions

In conclusion, postmenopausal women aged 50 to 64 without osteoporosis on their first BMD test were very unlikely to have a major osteoporotic fracture before age 65. Although less than 10% of our cohort had osteoporosis at baseline, the osteoporosis subgroup had a significantly higher immediate risk of major fracture. Screening frequency should be based on age and baseline T-score to maximize the clinical utility of BMD testing in this age range.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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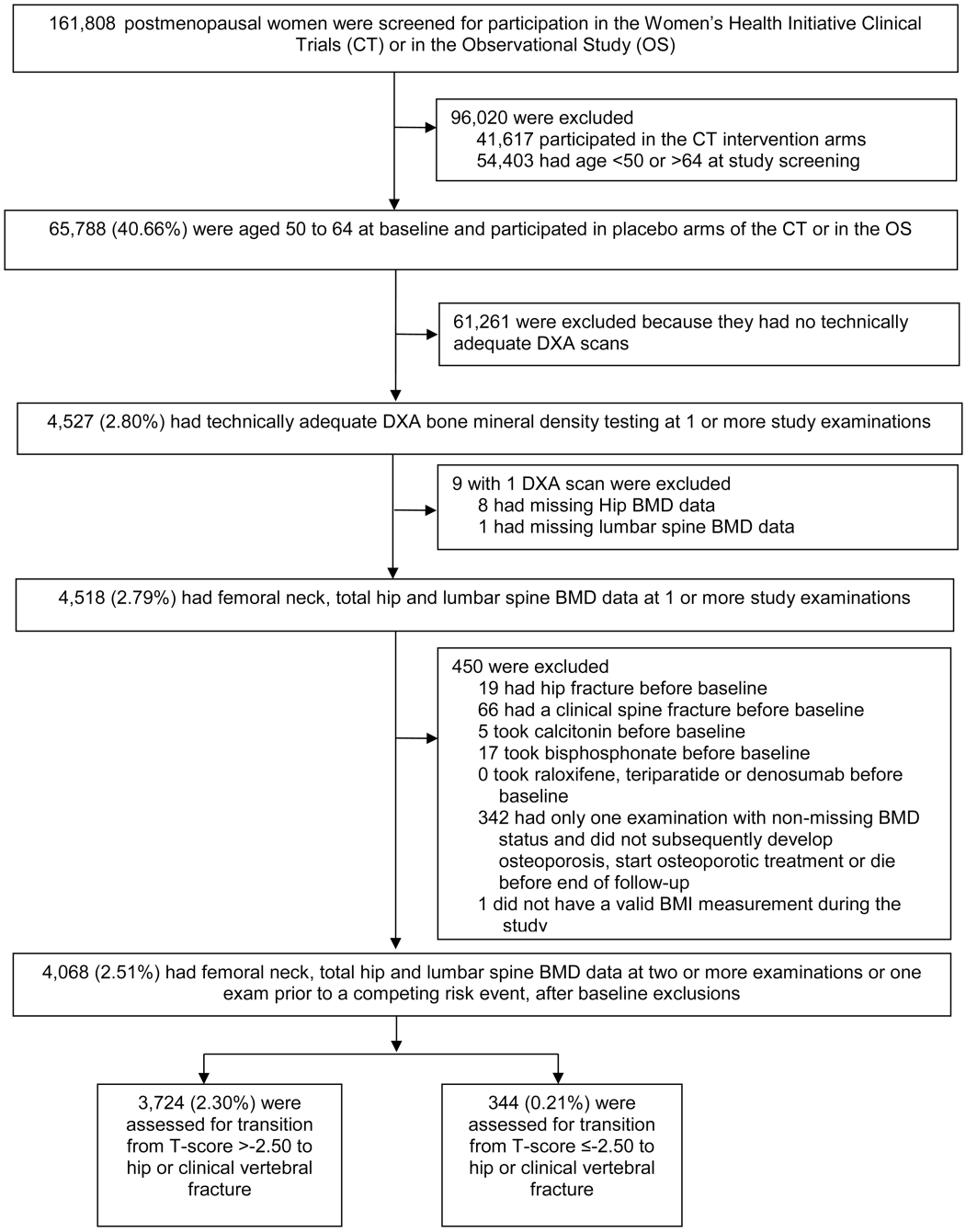

Figure 1. Study population for analyses of time to hip or clinical vertebral fracture

Of the 4527 women who had DXA bone mineral density (BMD) testing, 459 were excluded, including those who had a past hip or clinical vertebral fracture or osteoporosis treatment (bisphosphonate or calcitonin) at their first study examination, or who did not have BMD measurements at two or more examinations, or one BMD measurement and subsequent development of a competing risk. In the analytical cohort of 4068 women with adequate femoral neck, total hip, and lumbar spine BMD measurements prior to censoring, two

transitions were studied: T-score >-2.50 to first hip or clinical vertebral fracture (N=3724), and T-score <=-2.50 to first hip or clinical vertebral fracture (N=344).

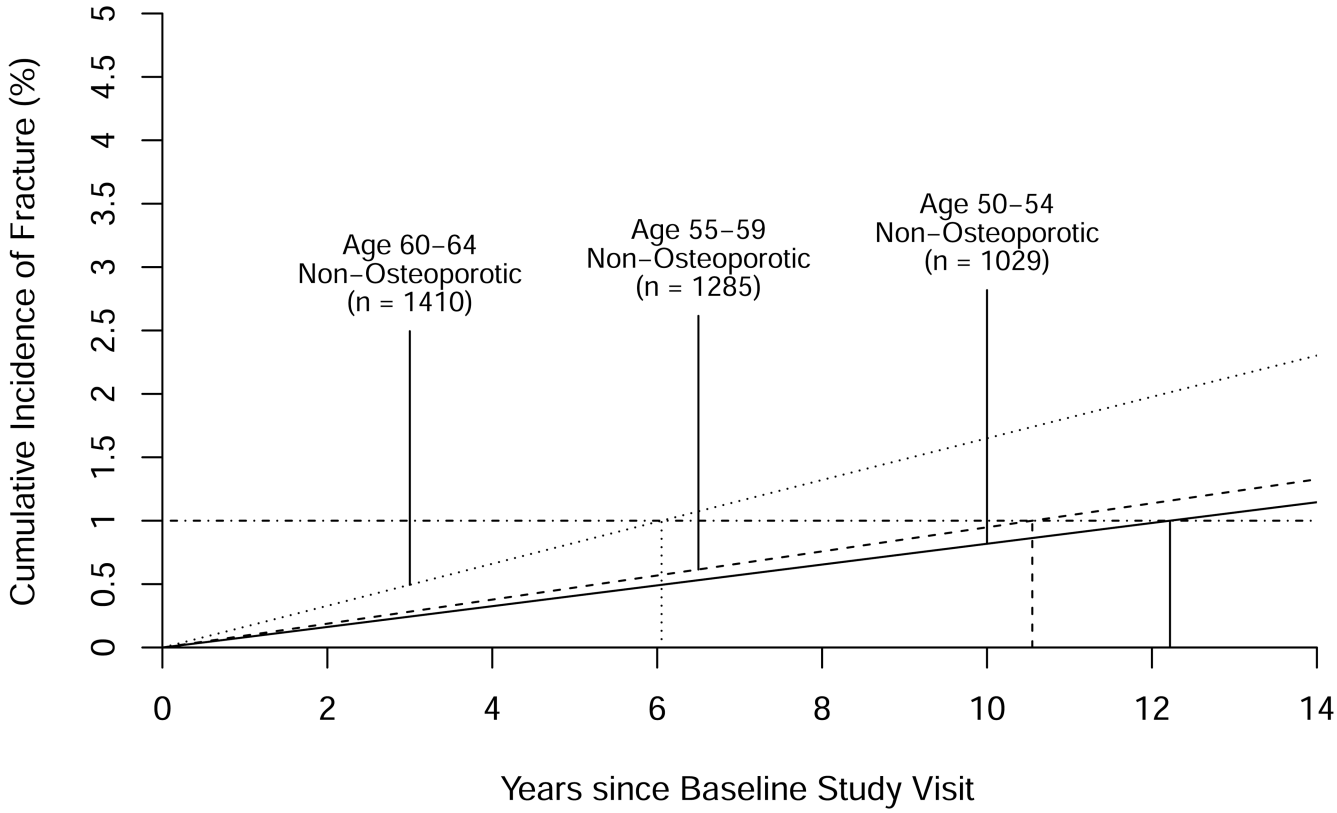

Figure 2. Unadjusted cumulative incidence of hip or clinical vertebral fracture according to baseline age range

The proportion of women who had transitioned to first hip or clinical vertebral fracture is plotted as a function of time. The cumulative incidence curves are estimated by parametric cumulative incidence models for known fracture dates. The dotted horizontal line shows where 1% of women have transitioned to first hip or clinical vertebral fracture; where this line intersects with each cumulative incidence curve, a vertical line to the x-axis marks the estimated time interval.

Table 1

Baseline characteristics and follow-up time of the women studied to determine time to major fracture

Characteristics at baseline	Number (%) or Mean (SD)		
	Baseline T-score >-2.50 (N=3724)[a]	Baseline T-score ≤-2.50 (n=344)[a]	All participants (n=4068)
Age			
50-54	1029 (27.6)	40 (11.6)	1069 (26.3)
55-59	1285 (34.5)	106 (30.8)	1391 (34.2)
60-64	1410 (37.9)	198 (57.6)	1608 (39.5)
BMI[b]			
<25	1202 (32.3)	215 (62.5)	1417 (34.8)
≥25	2522 (67.7)	129 (37.5)	2651 (65.2)
Race no./ total no. (%)			
White (non-Hispanic)	2729/3717 (73.4)	286/344 (83.1)	3015/4061 (74.2)
African American	587/3717 (15.8)	19/344 (5.5)	606/4061 (14.9)
Asian	16/3717 (0.4)	3/344 (0.9)	19/4061 (0.5)
Hispanic	307/3717 (8.3)	28/344 (8.1)	335/4061 (8.3)
Other	78/3717 (2.1)	8/344 (2.3)	86/4061 (2.1)
Years of education no./ total no. (%)			
Less than high school	260/3692 (7.0)	29/342 (8.5)	289/4034 (7.2)
High school/some college	2176/3692 (58.9)	195/342 (57.0)	2371/4034 (58.8)
College/some graduate school	641/3692 (17.4)	68/342 (19.9)	709/4034 (17.6)
Completed graduate school	615/3692 (16.7)	50/342 (14.6)	665/4034 (16.5)
Previous fracture after age 55 no./ total no. (%)			
Yes	193/2253 (8.57)	37/230 (15.5)	230/2491 (9.2)
No	2060/2253 (91.4)	201/230 (84.5)	2261/2491 (90.8)
Hormone therapy use no./ total no. (%)			
Yes	463/3641 (12.7)	52/332 (15.7)	515/3973 (13.0)
Past	1806/3641 (49.6)	95/332 (28.6)	1901/3973 (47.8)
Never	1372/3641 (37.7)	185/332 (55.7)	1557/3973 (39.2)
Current smoker no./ total no. (%)			
Current	244/3701 (6.6)	28/342 (8.2)	272/4043 (6.7)
Past	1413/3701 (38.2)	117/342 (34.2)	1530/4043 (37.8)
Never	2044/3701 (55.2)	197/342 (57.6)	2241/4043 (55.4)
Alcohol consumption (drinks per week) no./ total no. (%)			
0 drinks per week	579/3693 (15.7)	63/343 (18.4)	642/4036 (15.9)
<1 drinks per week	1259/3693 (34.1)	120/343 (35.0)	1379/4036 (34.2)

Characteristics at baseline	Number (%) or Mean (SD)		
	Baseline T-score >-2.50 (N=3724)[a]	Baseline T-score ≤-2.50 (n=344)[a]	All participants (n=4068)
1 to 6 drinks per week	784/3693 (21.2)	60/343 (17.5)	844/4036 (20.9)
≥7 drinks per week	275/3693 (7.5)	23/343 (6.7)	298/4036 (7.4)
Past drinker	796/3693 (21.6)	77/343 (22.4)	873/4036 (21.6)
History of parent with hip fracture			
Yes	825 (22.2)	101 (29.4)	926 (22.8)
No	2899 (77.8)	243 (70.6)	3142 (77.2)
Rheumatoid arthritis no./ total no. (%)			
Yes	155/3722 (4.2)	18/344 (5.23)	173/4066 (4.3)
No	3567/3722 (95.8)	326/344 (94.8)	3893/4066 (95.7)
Current oral glucocorticoid use			
Yes	96 (2.6)	14 (4.1)	110 (2.7)
No	3628 (97.4)	330 (95.9)	3958 (97.3)
Mean menopause duration (years)[c]	12.0 (7.7)	14.1 (7.3)	12.2 (7.7)
Bone Mineral Density T-score			
Femoral neck	-0.75 (0.98)	-2.27 (0.59)	-0.88 (1.04)
Total hip	-0.35 (1.02)	-2.04 (0.65)	-0.49 (1.10)
Lumbar spine	-0.23 (1.30)	-2.60 (0.88)	-0.43 (1.43)
Prevalence of osteoporosis			
Definition A1 (FN, THD, LS, white female norms)	-	344 (100)	344 (100)
Definition A2 (FN, THD, white female norms)	-	174 (50.6)	174 (50.6)
Definition A3 (FN, white female norms)	-	153 (44.5)	153 (44.5)
Total follow-up time (years)			
Mean	14.0 (3.8)	13.6 (4.1)	14.0 (3.9)
Minimum	0.06	1.7	0.06
Maximum	18.6	18.5	18.6

[a] Based on Definition A1 in Supplement (FN femoral neck, THD total hip, LS lumbar spine BMD, white young female norms)

[b] 108 subjects BMI were recorded after their first bone mineral density

[c] Based on 3012 responses and 292 responses

Table A1

Number of women who transitioned to osteoporosis, hip or clinical vertebral fracture, treatment with bisphosphonate/calcitonin/raloxifene/teriparatide, or death by end of follow-up, by age and baseline T-score[a]

Age at baseline	Baseline BMD T-score range	Number of participants in age/T-score group	N (percent of age/T-score group)[b]				
			Osteoporosis Definition A1	Hip fracture	Clinical vertebral fracture	Treatment	Death
50-54	> -1.50	798	1 (0.1)	2 (0.3)	6 (0.8)	46 (5.8)	47 (5.9)
			1 (0.1)	2 (0.3)	6 (0.8)	47 (5.9)	48 (6.0)
	-1.50 to -2.49	231	29 (12.6)	2 (0.9)	0 (0.0)	79 (34.2)	4 (1.7)
			31 (13.4)	2 (0.9)	0 (0.0)	91 (39.4)	9 (3.9)
	<= -2.50	40	-	2 (5.0)	0 (0.0)	21 (52.5)	0 (0.0)
			-	3 (7.5)	0 (0.0)	22 (55.0)	1 (2.5)
55-59	> -1.50	896	0 (0.0)	6 (0.7)	7 (0.8)	79 (8.8)	73 (8.2)
			0 (0.0)	7 (0.8)	7 (0.8)	80 (8.9)	78 (8.7)
	-1.50 to -2.49	389	40 (10.3)	3 (0.8)	2 (0.5)	101 (26.0)	28 (7.2)
			43 (11.1)	6 (1.5)	2 (0.5)	109 (28.0)	35 (9.0)
	<= -2.50	106	-	3 (2.8)	3 (2.8)	42 (39.6)	6 (5.7)
			-	4 (3.8)	3 (2.8)	42 (39.6)	12 (11.3)
60-64	> -1.50	860	1 (0.1)	7 (0.8)	7 (0.8)	85 (9.9)	91 (10.6)
			1 (0.1)	9 (1.1)	7 (0.8)	87 (10.1)	101 (11.7)
	-1.50 to -2.49	550	57 (10.4)	11 (2.0)	4 (0.7)	141 (25.6)	42 (7.6)
			63 (11.5)	13 (2.4)	6 (1.1)	156 (28.4)	60 (10.9)
	<= -2.50	198	-	4 (2.0)	4 (2.0)	79 (39.9)	15 (7.6)
			-	9 (4.6)	6 (3.0)	81 (40.9)	26 (13.1)
All		4068	128 (3.1)	40 (1.0)	33 (0.8)	673 (16.5)	306 (7.5) (7.55)
			139 (3.4)	55 (1.4)	37 (0.9)	715 (17.6)	370 (9.1)

[a] femoral neck or total hip or lumbar spine BMD T-score, using white young female norms

[b] The top number in each cell is the number of FIRST events (among osteoporosis, hip fracture, clinical vertebral fracture, treatment, death). The bottom number is the number of TOTAL events (total events overlap among columns). Tabulations exclude the 2 treated participants whose status was considered to be osteoporosis after imputation.

Table 2

Time for 1% of participants without osteoporosis at baseline to transition to hip or clinical vertebral fracture, according to age group

Baseline age ranges	Event N/ Group N (%)	Time for 1% of participants without osteoporosis to have a hip or clinical vertebral fracture	
		Unadjusted years (95% CI)	Adjusted years (95% CI)[a]
50 to 54	10/1029 (0.97)	*12.22 (7.70, 19.40)*	*12.79 (8.02, 20.40)*
55 to 59	18/1285 (1.40)	10.55 (6.22, 17.91)	*11.72 (6.87, 19.99)*
60 to 64	29/1410 (2.06)	6.05 (3.88, 9.45)	7.64 (4.82, 12.10)

[a] estimated time to hip or clinical vertebral fracture, based on competing risks regression, adjusted for age group, centered T-score, race/ethnicity, BMI, current hormone therapy use in the model.

Estimates greater than 11 years (italicized) have questionable reliability due to excessive extrapolation required for 1% to transition to hip or clinical vertebral fracture.

Table 3

Crude number of participants with hip or clinical vertebral fracture during the study period, according to baseline T-score (without or with osteoporosis) and clinical risk factors

Group	Number (%) of participants with a hip or clinical vertebral fracture		
	Baseline T-score >-2.50 (3724 women)	Baseline T-score <=-2.50 (344 women)	P value[b]
Baseline age (yrs)			
50 to 54	10/1029 (1.0%)	3/40 (7.5%)	0.01
55 to 59	21/1285 (1.6%)	7/106 (6.6%)	0.004
60 to 64	34/1410 (2.4%)	15/198 (7.6%)	<0.001
BMI			
<25	21/1202 (1.8%)	15/215 (7.0%)	<0.001
>=25	44/2522 (1.7%)	10/129 (7.8%)	<0.001
Race/ethnicity			
African-American	3/587 (0.5%)	1/19 (5.3%)	0.12
Other [a]	4/401 (1.0%)	3/39 (7.7%)	0.02
White	58/2736 (2.1%)	21/286 (7.3%)	<0.001
Any fracture after age 55			
Yes	9/193 (4.7%)	6/37 (16.2%)	0.02
No	41/2060 (2.0%)	12/201 (6.0%)	0.002
Parent fractured hip[c]			
Yes	18/825 (2.2%)	10/101 (9.9%)	<0.001
No	47/2899 (1.6%)	15/243 (6.2%)	<0.001
Current smoking			
Yes	7/244 (2.9%)	3/28 (10.7%)	<0.001
No	58/3457 (1.7%)	22/314 (7.0%)	<0.001
Oral glucocorticoids			
Current	4/96 (4.2%)	2/14 (14.3%)	0.16
Past or Never	61/3628 (1.7%)	23/330 (7.0%)	<0.001
Rheumatoid arthritis			
Yes	3/155 (1.9%)	0/18 (0.0%)	-----
No	62/3567 (1.7%)	25/326 (7.7%)	<0.001
Alcohol >=3 units daily			
Yes	1/27 (3.7%)	0/2 (0.0%)	-----
No	64/3697 (1.7%)	25/342 (7.3%)	<0.001
Hormone therapy use			
Current	7/463 (1.5%)	6/52 (11.5%)	<0.001
Past or Never	56/3178 (1.8%)	17/280 (6.1%)	<0.001

[a] Other includes all races not African-American or White

[b] P value for 2-sided Fisher exact test comparing the difference of two proportions, by baseline T-score. All hip and clinical vertebral fracture that occurred during follow-up were included. P value could not be calculated if one or more cells contained zeroes.

[c] For parent who fractured hip or spine, P=<0.001

Table 4

Time for 3% of participants without osteoporosis at baseline to transition to major osteoporotic fracture (hip, clinical spine, proximal humerus, wrist), according to age group

Baseline age ranges	Event N/ Group N (%)	Time for 3% of participants without osteoporosis to have a major osteoporotic fracture	
		Unadjusted years (95% CI)	Adjusted years (95% CI)[a]
50-54	34/1029 (3.30)	10.11 (7.14, 14.31)	*11.51 (7.95, 16.65)*
55-59	61/1285 (4.75)	7.25 (4.92, 10.69)	8.95 (5.96, 13.45)
60-64	73/1410 (5.18)	6.11 (4.24, 8.79)	8.60 (5.80, 12.76)

[a] estimated time to major osteoporotic fracture, based on competing risks regression, adjusted for age group, centered T-score, race/ethnicity, BMI, current hormone therapy use in the model.

Estimates greater than 11 years (italicized) have questionable reliability due to excessive extrapolation required for 3% to transition to fracture.