Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Bone-Density Testing Interval and Transition to Osteoporosis in Older Women

Supplementary Appendix Table of Contents

Authors' Contributions: Jason Fine, John Preisser and Margaret Gourlay designed the analysis. Kristine Ensrud and other investigators in the Study of Osteoporotic Fractures Research Group gathered the data. John Preisser, Ryan May and Chenxi Li analyzed the data; Drs. Preisser, May, Li and Fine vouch for the data and the analysis. Margaret Gourlay wrote the first draft of the main manuscript, and John Preisser wrote the first draft of the Supplementary Appendix. The manuscript and Appendix were subsequently revised by all of the authors. No writing assistance was provided by any other person. Margaret Gourlay and Kristine Ensrud decided to publish the paper. There were no agreements concerning confidentiality of the data between the funding agencies and the authors or the institutions named in the credit lines.

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INTRODUCTION

Osteoporosis Screening Guidelines

The International Society of Clinical Densitometry[1] and some experts[2] have recommended using bone densitometer precision error and the corresponding least significant change in bone mineral density (BMD) to help determine a minimum interval for follow-up measurements. Using this rationale, the National Osteoporosis Foundation,[3] American College of Preventive Medicine[1,4] and American College of Obstetrics and Gynecology[1,5] recommend BMD screening not more frequently than every 2 years in most cases, and the North American Menopause Society states that for untreated postmenopausal women, repeat DXA testing is not useful until 2 to 5 years

have passed.[1,6] The American Association of Clinical Endocrinologists guidelines[1,7] state that until data are available, patients with normal baseline BMD T-scores (>= -1) should be tested every 3 to 5 years, and patients in an osteoporosis prevention program might have testing every 1 to 2 years until stable BMD is documented, then measurements every 2 to 3 years. The US Preventive Services Task Force (USPSTF) stated in 2011 that, "because of limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in BMD; however, longer intervals may be necessary to improve fracture risk prediction."[8] The Task Force noted that "evidence is lacking about optimal intervals for repeated screening."

Definitions of Osteoporosis

The World Health Organization (WHO) diagnostic criteria[9] define osteoporosis by BMD T-score ([BMD of participant – mean BMD of reference population]/SD of BMD of reference population). Application of the WHO criteria in our analysis is described in the Appendix Methods: World Health Organization BMD classifications.

The 2001 NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture."[10]

The 2004 Surgeon General's Report on Bone Health and Osteoporosis[11] defined osteoporosis as "low bone mass leading to structural fragility" and cited the WHO diagnostic criteria.

The 2010 National Osteoporosis Foundation Clinician's Guide[3] defines osteoporosis as, "characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength and an increase in the risk of fracture," then cites the WHO diagnostic criteria.

Our methods are consistent with the above definitions of osteoporosis that focus on low BMD that can be detected and treated to help prevent fracture. Accordingly, our analysis focuses on the estimated time to osteoporosis, with hip and clinical vertebral fractures treated as competing risks.

Past Relevant Studies

Lee and Zelen proposed a "threshold method" of determining a screening interval based on a fixed probability of being in a preclinical (asymptomatic with detectable disease) state at a given age.[12,13] They defined an "optimal" screening interval as the testing interval needed to identify a predetermined fraction of the expected number of cases in the population being screened. Such an approach might be reasonable for BMD screening because of the strong association between lower BMD and increased fracture risk.[14] Prior studies have suggested the rate of change in BMD measured by DXA is a predictor of subsequent fracture risk, independent of baseline BMD, albeit a weaker predictor compared with initial BMD.[15,16] As mentioned in the main text, a previous prospective analysis[17] of data from the Study of Osteoporotic Fractures suggested that repeating a BMD measurement up to 8 years later provided little additional value beyond the initial BMD for predicting incident fractures in elderly women. A 2009 longitudinal, Australian

population-based analysis (median follow-up 7.1 years) including 1008 women and 750 men aged 60 years and older at baseline estimated a 1.9 to 8.9-year time for women to develop either osteoporosis or incident fragility fracture, depending on age and BMD T-score.[18]

METHODS

Study Examinations and Selection of the Analytical Cohort

At each Study of Osteoporotic Fractures (SOF) study examination, participants completed detailed questionnaires and interviews about risk factors for osteoporosis and fracture, medical history, hormonal history, medications, lifestyle and fracture history. Dual energy x-ray absorptiometry (DXA, Hologic, Waltham, MA) bone mineral density (BMD) measurements at the hip were not available at the first examination, but were performed at multiple examinations beginning with the Year 2 examination between 1989 and 1990.

Of the original 9704 study participants, 8514 women had DXA hip BMD measurements at one or more examinations (Figure 1) and were potentially eligible for inclusion in the analytical cohort. Of these women, participants who had inadequate BMD data (17 women), had osteoporosis (defined by a BMD T-score of -2.50 or below at the total hip or femoral neck) at their first examination (2197 women), had a history of hip (69 women) or clinical vertebral (189 women) fracture or took calcitonin (2 women) before the Year 2 SOF examination,were excluded in succession. Women with only one BMD measurement at the femoral neck and total hip were retained in the competing risk analysis if they subsequently reported bisphosphonate or calcitonin use or incident hip or clinical vertebral fracture prior to loss to follow-up; otherwise they were excluded (1083 women). The 3557 women excluded from this analysis were, on average, similar to the 4957 women in the analytical cohort with respect to age (each 73.3 years, P=0.71), femoral neck T-scores (-1.75 vs. -1.74 respectively, P=0.47), and total hip T-scores (-1.52 vs. -1.51 respectively, P=0.97). Women with morphometric vertebral fractures (identified on the basis of baseline exam lateral spine radiograph findings alone) were not excluded or censored because patients with these clinically silent fractures would still be screened by clinicians.

Of the 4957 women in the analytical cohort at baseline, 3688 (74.6%) were aged 67 to 74 years, 4943 (99.7%) were white, 1758 (37.6%) had a BMI <25 (normal or underweight), 853 (17.2%) were current users of hormone therapy, and 1680 (34.1%) had a history of any fracture since age 50 years at the year 2 examination. Ninety percent of the women were followed for more than 3.5 years, 75% were followed for more than 5.5 years, 50% were followed for more than 7.9 years; 25% were followed for more than 12.3 years, and 10% were followed for more than 13.1 years. The average follow-up time was 8.2 years, with a minimum of 1.1 years and a maximum of 14.6 years. Among the 1255 women who were studied for transition from normal BMD to osteoporosis, the average follow-up time was 9.4 years, with a minimum of 1.5 years and a maximum of 14.6 years. Among the 4215 women studied for transition from osteopenia to osteoporosis, the average follow-up time was 8.1 years, with a minimum of 1.1 years and a maximum of 14.6 years. Of these women, 1214/4215 (28.8%) of women made the full transition to osteoporosis during the study period.

World Health Organization BMD classifications

The World Health Organization (WHO) diagnostic criteria for osteoporosis[9] were used to classify participants into four groups based on femoral neck and total hip BMD T-scores: osteoporosis, lowest T-score -2.5 or below; mild (lowest T-score between -1.01 and -1.49), moderate (lowest T-score between -1.50 and -1.99) and advanced (lowest T-score between -2.00 and -2.49) osteopenia; and normal BMD, lowest T-score -1.00 or above. Femoral neck and total hip T-scores were calculated using National Health and Nutrition Examination Study (NHANES) III BMD norms for non-Hispanic white women aged 20-29 years.[19] The primary definition of osteoporosis was T-score -2.5 or below at the femoral neck or total hip. Osteopenia was defined as femoral neck or total hip T-score (lowest value) between -1.01 and -2.49, including mild (T-score between -1.01 and -1.49), moderate (T-score between -1.50 and -1.99) and advanced (T-score between -2.00 and -2.49) osteopenia. Normal BMD was femoral neck and total hip T-score -1.00 or above. In addition, the following secondary definitions for osteoporosis, osteopenia and normal BMD were used in sensitivity analyses: osteoporosis was femoral neck T-score -2.5 or below; osteopenia was femoral neck T-score between -1.01 and -2.49; normal BMD was femoral neck T-score -1.00 or above.

Clinical Risk Factors for Fracture

Several clinical risk factors for fracture, including components from the FRAX fracture risk assessment tool,[20] were covariates in the time-to-event analyses, including age, BMI, baseline estrogen use status, any fracture after age 50 years, current smoking, ever use of oral glucocorticoids and self-reported rheumatoid arthritis (missing value was considered lack of disease). Parent with hip fracture is also a risk variable in the FRAX tool, but was not included as a covariate due to >10% missing data. We did not adjust for secondary causes of osteoporosis because analyses by the WHO suggested that "the impact of many secondary causes of fracture risk is mediated primarily through their effects on BMD."[21] Estrogen use status was considered a clinical risk factor rather than a treatment because the FDA has approved estrogen for osteoporosis prevention (not treatment)[22] and recommends the shortest possible duration of use, and because of evidence that the benefits of estrogen on BMD and fracture risk are transient.[23,24]

Ascertainment of Fractures

Participants were contacted every 4 months by postcard (or telephone follow-up for nonresponders) to ascertain incident fractures; more than 95% of these contacts were completed. Incident hip fractures were physician-adjudicated from review of radiology reports. Clinical spine fractures were also adjudicated, when reported, by review of radiology reports.

Statistical Analysis

Rationale for use of competing risk analyses

We employed competing risk analyses[25,26] to account for multiple competing events that could influence the estimated time to osteoporosis prior to fracture or initiation of osteoporosis

treatment. In osteoporosis screening, the event of interest is the probability of transitioning to osteoporosis prior to competing events (hip or clinical vertebral fracture, osteoporosis treatment). Competing risks analyses are explicitly constructed to estimate this probability, accounting for the potential dependence between osteoporosis and the competing events. The reason for focusing on this probability is that it defines the percentage of the screened population that might have reduced fracture risk from osteoporosis detection (screening) followed by treatment. In contrast, standard survival analysis methods would treat fracture prior to detection and treatment prior to detection as independent censoring events. Such methods are not appropriate for estimating the probability of osteoporosis prior to major fracture or treatment.

Estimation of interval BMD in participants with competing risks

As mentioned previously, incident hip fractures or clinical vertebral fractures or first reported use of an FDA-approved osteoporosis treatment agent (bisphosphonate, calcitonin, or raloxifene) prior to osteoporosis were managed as competing risks in the time-to-osteoporosis analysis. Compared to participants without a competing risk, participants who sustained fractures or were treated would be more likely to have osteoporosis at the time of the competing event. BMD measurements were only available during SOF study examinations. BMD values at the time of competing events between study examinations had to be imputed.

To impute BMD at the time of a competing event, we created linear mixed effects models to calculate rates of BMD loss using BMD measurements from SOF participants who had not yet developed osteoporosis, experienced a hip or clinical vertebral fracture or reported use of an osteoporosis treatment agent. These rates were stratified by T-score and used to impute peri-fracture BMD imputed at the known date of fracture, and peri-treatment BMD at the midpoint between the last study examination without treatment and first study examination when treatment was reported.

For the normal group, the time variable in the linear mixed effects model was time since baseline examination. The intercept was adjusted for age at baseline and treated as a random effect. The slope of time since baseline was also adjusted for age but was treated as a fixed effect, because the estimation algorithm didn't converge when using both random intercept and random slope.

The linear mixed effects model for the osteopenia group was the same as for the normal group except that both the intercept and the slope were adjusted for osteopenia stage, age, BMI, estrogen use, any fracture after 50, current smoking, ever use of oral glucocorticoids, and rheumatoid arthritis. Again, the slope was treated as a fixed effect because the estimation algorithm didn't converge when using both random intercept and random slope.

Analysis to estimate time to osteoporosis

The competing risk model for the cumulative incidence of transitions from normal BMD (femoral neck and total hip T-scores >= -1) to osteoporosis included T-score as a continuous variable and was adjusted only for age due to few observed events. The competing risk model for the cumulative incidence of transitions from osteopenia to osteoporosis was stratified into three T-score ranges (minimum T-score at femoral neck or total hip): mild (T-score -1.01 to -

1.49), moderate (T-score -1.50 to -1.99), advanced (T-score -2.00 to -2.49) osteopenia. Results were adjusted for the seven clinical risk factors for fracture: age, BMI, current estrogen use, any fracture after age 50 years, current smoking, ever use of oral glucocorticoids, self-reported rheumatoid arthritis. A final model was selected using backwards elimination to retain statistically significant ($P<0.05$) pairwise interactions while forcing all main effect covariates to remain in the final model. In addition to estimates for the entire cohort, time-to-osteoporosis was estimated for specific ages, BMI values, and according to category of estrogen use (past or never, current). For age and BMI, results were presented for relevant ranges of specific values, i.e. for age 67, then every 5 years from age 70, and for BMI thresholds for underweight (BMI <18.5), overweight (BMI >=25) and obese (BMI >=30).

As described by Lindsey and Ryan,[27] we used SAS PROC LIFEREG to fit parametric survival models to interval censored data, after coding the data as described in Hudgens, Li and Fine[28] for naïve parametric analyses of interval censored competing risks data. Here, the occurrence of hip or clinical vertebral fracture or use of an osteoporosis treatment agent (bisphosphonate, calcitonin, or raloxifene) prior to development of osteoporosis serves as the competing risk for osteoporosis. Among several statistical distributions that were examined, the log logistic distribution was chosen because it fit our data well (Figure A) and because its mathematical form permitted us to invert the cumulative incidence curve to easily obtain screening intervals estimates. Based on the log logistic model, the cumulative probability of osteoporosis by time t prior to hip or clinical vertebral fracture or osteoporosis treatment is given by

$$\Pr(\text{Osteoporosis by time } t) = 1\text{-}1/\left[1 + \alpha_i\, t^{\gamma}\right]$$

where $\gamma = 1/\sigma$ and $\alpha_i = \exp(-\mu_i/\sigma)$. σ and $\mu_i = \mu(x_i^T\beta)$ are the scale and (covariate-dependent) location parameters for which estimates were provided by SAS. This regression model corresponds to a parametric version of the cumulative incidence regression model described in Fine (2001),[29] which generalizes that in Fine and Gray (1999).[30] Regression parameter estimates of β are not reported.

Letting S= 1-Pr(Osteoporosis by time t) (e.g. S=0.90, or 10% transitioning), the estimated optimal screening interval based on inverting the cumulative incidence function (Peng and Fine, 2007)[31] is

$$t^* = [(1 - S)/(\alpha S)]^{\sigma}$$

Here, t* corresponds to a quantile from the cumulative incidence function for time to osteoporosis. The "delta method" was used to determine a large sample standard error for the natural logarithm of the solution, from which a 95% confidence interval for the optimal screening time is determined by exponentiation of the lower and upper confidence bounds for the log of t*. Calculations for the adjusted screening intervals (last column of Table 2) were carried out in a way similar to that of the unadjusted model, except that covariates were set to their sample mean values. Using the sample mean values for the covariates approximates the quantiles at the population level, after adjusting for the covariate effects.

We evaluated the adequacy of the chosen log logistic form of the parametric model for the cumulative incidence function using plots of its cumulative distribution function compared to nonparametric cumulative incidence curves (Figure A). As the exact transition time is not observed for any woman and hip/clinical vertebral fracture and treatment are competing risks for osteoporosis we could not use standard Kaplan-Meier curves, but rather we used nonparametric

maximum likelihood estimation applicable to interval censored data with competing risks (Hudgens, Satten, Longini, 2001).[32] Specifically, we plotted cumulative incidence curves for each of the four groups of women with osteopenia or normal BMD at baseline.

Sensitivity analysis: screening intervals for estimating time to osteoporosis based on alternative parametric models and an alternative definition of osteoporosis

Two sets of sensitivity analyses were performed for estimating screening intervals for the time to osteoporosis from normal or osteopenic baseline BMD status. First, we fit the parametric model based on the log logistic distribution using the secondary definition of osteoporosis based on BMD T-score at the femoral neck only as described in "World Health Organization BMD classifications" above. Second, in order to investigate the sensitivity of the estimates of the screening intervals based on the primary definition of osteoporosis to the selection of the parametric model that fits the data, we also computed the screening interval estimates based on the exponential, Weibull and log normal distributions and compared them with the estimates based on the log logistic distribution. This comparison is important, as some of the screening interval estimates exceed 15 years, the maximum follow-up time and the goodness-of-fit of the log logistic model cannot be assessed using the nonparametric estimates, which are limited to 15 years.

Analysis to estimate time to hip or clinical vertebral fracture

To better study women who experienced a fracture before transitioning to osteoporosis by WHO diagnostic criteria or initiating treatment for osteoporosis, we also calculated the time for 2% of women to sustain a hip or clinical vertebral fracture in competing risk analyses of data from the same study population stratified by the four T-score ranges. This analysis was similar to the osteoporosis analysis except we used hip or clinical vertebral fracture as the outcome and incident osteoporosis and first reported use of an osteoporosis treatment agent (bisphosphonate, calcitonin, or raloxifene) prior to hip or clinical vertebral fracture as competing risks. Participants were censored for death or drop-out using the approach in Hudgens et al (2011).[28] We chose the log logistic distribution to model the cumulative incidence of time to fracture prior to osteoporosis by WHO diagnostic criteria or treatment using the same statistical approach that was employed for the cumulative incidence of time to osteoporosis prior to fracture or treatment.

Sensitivity analysis: screening intervals for fracture based on other parametric models

In order to investigate the sensitivity of the estimates of the screening intervals for fracture to the selection of the parametric model that fits the data, we also computed the screening interval estimates based on the exponential, Weibull and log normal distributions and compared them with the estimates based on the log logistic distribution. As with osteoporosis, some of the screening interval estimates exceed 15 years and it is of interest to assess the sensitivity of these estimates to different modeling assumptions.

RESULTS

Estimated Interval BMD in Participants with Competing Risks

According to the results from the linear mixed effects models, only 2 treated participants were reclassified as having osteoporosis when we estimated BMD T-score at the mid-point of the interval between the last examination without treatment and the first examination where treatment was reported. The other treated participants and all participants with incident hip/clinical vertebral fracture remained non-osteoporotic as in their study examination immediately preceding the competing event.

Screening Interval Estimates

Screening interval lengths for 10% of women to transition to osteoporosis were reported in Table 2 of the main paper. Similar time interval estimates for any fixed percentage of women transitioning can be approximately determined from Figure A. Figure A also shows that the fitted parameter cumulative incidence curves, upon which screening interval estimation is based, closely approximate the respective nonparametric cumulative incidence curves for the period of follow-up observed in the study (< 15 years), providing evidence of goodness of fit for the log logistic model.

Sensitivity Analysis: Screening Intervals Redefined by Different Percent Transitions to Osteoporosis (T-score <= -2.50 at Femoral Neck or Total Hip)

For any selected percentage of women who transition to osteoporosis, results should not be extrapolated far from the range of observed data. The follow-up time in this study ranged from 1.1-14.6 years; hence, transition percentage thresholds corresponding to screening interval extrapolations shorter than 1 year, or longer than 15 years are considered unreliable. We used a 10% transition threshold in the main analyses. For the women with advanced osteopenia at baseline, a transition threshold less than 10% is not appropriate since it corresponds to an estimated screening interval that is shorter than 1 year. For women with mild osteopenia or normal BMD at baseline, a transition threshold greater than 10% cannot be recommended for use with data from this cohort since it corresponds to an estimated screening interval that is significantly longer than 15 years, the length of maximum follow-up in our study. For this reason, transition percentage thresholds in these ranges for the specified cohorts should be interpreted with caution.

As a sensitivity analysis, screening intervals were computed for 20% of women to transition from osteopenia to osteoporosis prior to initiation of osteoporosis treatment or incident hip or clinical vertebral fracture (Table A). As expected, the screening intervals were longer than those for 10% of women to transition to osteoporosis (Table 2).

Table B reports screening interval estimates for 1%, 2% and 5% of women to transition from normal BMD to osteoporosis. The interval estimate for 5% of women to transition to osteoporosis was 13.3 years.

Sensitivity Analysis: Screening Intervals for Osteoporosis Based on Other Parametric Models

The time intervals for 10% of participants to transition to osteoporosis (T-score <= -2.50 at Femoral Neck or Total Hip) based on the exponential, Weibull and log normal distributions are tabulated in Table C. Those time intervals are very close to the ones based on the log logistic distribution; the one exception is shown in Table C for women transitioning from normal BMD to osteoporosis, where the interval estimates based on the exponential distribution are substantially greater than the estimates based on the other distributions. These results are due to the poor fit of the exponential distribution for these data relative to the Weibull distribution, the former being a special case of the latter (Likelihood Ratio Test to reject the Exponential distribution was $p < 0.02$ for both unadjusted and adjusted models). On the other hand, the similarity of results for the log logistic, Weibull and log normal models implies that estimates of the screening intervals for osteoporosis are not sensitive to the selection of the parametric model that is used to fit the data.

Sensitivity Analysis: Screening Intervals for Osteoporosis Defined as T score <= -2.50 at Femoral Neck

A second sensitivity analysis was conducted using femoral neck BMD T-score only to define normal BMD, osteopenia, and osteoporosis. Tables D and E show results using this secondary definition of osteoporosis (femoral neck BMD T-score -2.50 or below by World Health Organization diagnostic criteria[9]).

Analysis to Estimate Time to Hip or Clinical Vertebral Fracture

Within each T-score range, these proportions of women made the full transition to hip or clinical vertebral fracture during the follow-up period: normal BMD, 8/1255 (0.64%); mild osteopenia, 17/1386 (1.23%); moderate osteopenia, 52/1478 (3.52%); advanced osteopenia, 46/1351 (3.40%). For all of the osteopenic T-score ranges taken together (T-score -1.01 to -2.49), 115/4215 (2.73%) of women made the full transition to hip or clinical vertebral fracture.

For women with osteopenia at baseline, T-score group, BMI, any fracture after age 50 years, and the interaction of age by self-reported rheumatoid arthritis were significant predictors in the final model (all $P < 0.03$). The other covariates---including age, current estrogen use, current smoking, ever use of oral glucocorticoids and self-reported rheumatoid arthritis---were not significant (all $P > 0.06$). The estimated times for 2% of women to transition to hip or clinical vertebral fracture according to baseline T-score range were tabulated in Table F. Calculations for the adjusted estimates (last column of Table F) were carried out in a way similar to that of the unadjusted model, except that covariates were set to their sample mean values.

Sensitivity Analysis: Screening Intervals for Fracture Based on Other Parametric Models

The time intervals for 2% of participants to transition to hip or clinical vertebral fracture based on the exponential, Weibull and log normal distributions are tabulated in Table G. Those time intervals are very close to the ones based on the log logistic distribution, which implies that the

estimates of the screening intervals for fracture are not sensitive to the selection of the parametric model that is used to fit the data.

References

1. Lewiecki E, Gordon C, Baim S, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 2008;43:1115-21.
2. Bonnick S, Johnston CJ, Kleerekoper M, et al. Importance of precision in bone density measurements. J Clin Densitom 2001;4:105-10.
3. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010.
4. Lim LS, Hoeksema LJ, Sherin K; ACPM Prevention Practice Committee. Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med. 2009;36:366-75.
5. American College of Obstetricians and Gynecologists (ACOG); 2004 Jan. 14 p. (ACOG practice bulletin; no. 50, reaffirmed 2008).
6. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause 2010:25-54.
7. AACE Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition with selected updates for 2003. Endocr Pract 2003;9:544-64.
8. Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med 2011;154:356-64.
9. World Health Organization. Assessment of osteoporotic fracture risk and its role in screening for postmenopausal osteoporosis. WHO Technical report series no. 843. Geneva: World Health Organization 1994.
10. NIH consensus development panel on osteoporosis prevention, diagnosis and therapy. Osteoporosis prevention, diagnosis and therapy. JAMA 2001;285:785-795.
11. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004.
12. Lee S, Zelen M. Scheduling periodic examinations for the early detection of disease: applications to breast cancer. J Am Stat Assoc 1998;93:1271-81.
13. Lee S, Huang H, Zelen M. Early detection of disease and scheduling of screening examinations. Stat Methods Med Res 2004;13:443-56.
14. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254-9.
15. Nguyen T, Center J, Eisman J. Femoral neck bone loss predicts fracture risk independent of baseline BMD. J Bone Miner Res 2005;20:1195-201.
16. Sornay-Rendu E, Munoz F, DuBoeuf F, Delmas P. Rate of forearm bone loss is associated with an increased risk of fracture independently of bone mass in postmenopausal women: the OFELY study. J Bone Miner Res 2005;20:1929-35.
17. Hillier T, Stone K, Bauer D, et al. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women. Arch Intern Med 2007;167:155-60.
18. Frost S, Nguyen N, Center J, Eisman J, Nguyen T. Timing of repeat BMD measurements: development of an absolute risk-based prognostic model. J Bone Miner Res 2009;24:1800-7.

19. Looker A, Wahner H, Dunn W, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8:468-89.
20. Kanis J, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clinical practice. Bone 2009;44:734-43.
21. Dawson-Hughes B. A revised clinician's guide to the prevention and treatment of osteoporosis. J Clin Endocrinol Metab 2008;93:2463-5.
22. US Food and Drug Administration. Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm, accessed July 16, 2011.
23. Greendale G, Espeland M, Slone S, Marcus R, Barrett-Connor E. Bone mass response to discontinuation of long-term hormone replacement therapy. Arch Intern Med 2002;162:665-72.
24. Cauley J, Seeley D, Ensrud K, Ettinger B, Black D, Cummings S. Estrogen replacement therapy and fractures in older women. Ann Intern Med 1995;122:9-16.
25. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res 2007;13:559-65.
26. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. Med Care 2010;48:S96-105.
27. Lindsey J, Ryan L. Tutorial in biostatistics: methods for interval-censored data. Stat Med 1998;17:219-38.
28. Hudgens M, Li C, Fine J, "Parametric Estimation of Cumulative Incidence Functions for Interval Censored Competing Risks Data" (December 2011). The University of North Carolina at Chapel Hill Department of Biostatistics Technical Report Series. Working Paper 23. http://biostats.bepress.com/uncbiostat/papers/art23.
29. Fine JP. Regression modeling of competing crude failure probabilities. Biostatistics 2001;2:85-97.
30. Fine J, Gray R. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999;94:496-509.
31. Peng L, Fine J. Nonparametric Quantile Inference with Competing-Risks Data. Biometrika 2007;94:735-44.
32. Hudgens MG, Satten GA, Longini IM, Jr. Nonparametric maximum likelihood estimation for competing risks survival data subject to interval censoring and truncation. Biometrics 2001;57:74-80.

Table A. Time intervals for 20% of participants to transition from osteopenia to osteoporosis (T-score <= -2.5 at femoral neck or total hip) according to baseline T-score score range

Baseline T-score range	**Time interval for 20% of participants to transition to osteoporosis**	
	Unadjusted years (95% CI)	Adjusted* years (95% CI)
Mild osteopenia (T-score -1.01 to -1.49)	-----	-----
Moderate osteopenia (T-score -1.50 to -1.99)	8.54 (7.75, 9.42)	8.52 (7.74, 9.38)
Advanced osteopenia (T-score -2.00 to -2.49)	1.80 (1.61, 2.00)	2.03 (1.82, 2.25)

*model adjusted for age, BMI, current estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis- besides baseline T-score group (n=4097 complete cases).

Time estimates for 20% of women with mild osteopenia to transition to osteoporosis should be interpreted with caution due to extrapolation beyond the maximum follow-up time of the study. Estimates greater than 15 years with 95% CIs excluding 15 years are not presented.

Table B. Time intervals for 1% to 5% of participants to transition from normal BMD to osteoporosis (T-score <= -2.5 at femoral neck or total hip)

Percent transitioning to osteoporosis	**Time interval in years for participants to transition to osteoporosis**
1%	7.39 (4.98, 10.96)
2%	9.50 (6.83, 13.22)
5%	13.33 (9.52, 18.67)

Based on log logistic model that includes only baseline BMD (n=1255). Evaluated for women with lowest possible baseline normal BMD.

Table C. Sensitivity analysis: screening intervals for osteoporosis based log logistic model vs. other parametric models

Baseline T-score range/ statistical model	**Time interval for 10% of participants to transition to osteoporosis**	
	Unadjusted years (95% CI)	Adjusted* years (95% CI)
Normal BMD (T-score >=-1.00)		
Log logistic	*17.4 (11.5,26.3)*	*16.8 (11.5,24.6)*
Exponential	*43.6 (18.2, 104)*	*44.6 (18.5, 108)*
Weibull	*17.2 (11.5, 25.8)*	*16.7 (11.5, 24.2)*
Log normal	*20.0 (11.8, 33.8)*	*18.9 (11.7, 30.3)*
Mild osteopenia (T-score -1.01 to -1.49)		
Log logistic	*16.5 (13.6,20.2)*	*17.3 (13.9, 21.5)*
Exponential	*18.9 (14.8, 24.2)*	*20.6 (15.6, 27.2)*
Weibull	*19.5 (15.0, 25.3)*	*20.6 (15.5, 27.3)*
Log normal	*15.3 (13.0, 17.9)*	*15.9 (13.4, 19.0)*
Moderate osteopenia (T-score -1.50 to -1.99)		
Log logistic	4.57 (4.11,5.09)	4.66 (4.19, 5.17)
Exponential	4.02 (3.59, 4.49)	3.99 (3.56, 4.47)
Weibull	3.89 (3.41, 4.43)	4.00 (3.52, 4.54)
Log normal	4.73 (4.28, 5.22)	4.79 (4.34, 5.29)
Advanced osteopenia (T-score -2.00 to -2.49)		
Log logistic	0.96 (0.83,1.11)	1.11 (0.96,1.27)
Exponential	0.88 (0.82, 0.94)	0.93 (0.87, 1.01)
Weibull	0.80 (0.68, 0.95)	0.94 (0.80, 1.11)
Log normal	0.96 (0.83, 1.11)	1.10 (0.96, 1.26)

*models adjusted for age, BMI, current estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis- besides baseline T-score group (n=4097 complete cases). For normal BMD group, adjusted for continuous BMD and age only (N=1255 complete cases).

Estimates greater than 15 years (italicized) have questionable reliability due to excessive extrapolation required for 10% to transition to osteoporosis.

Table D. Time intervals for 10% of participants to transition from osteopenia to osteoporosis (T-score <= -2.5 at femoral neck) according to baseline T-score range

Baseline T-score range	**Time interval for 10% of participants to transition to osteoporosis**	
	Unadjusted years (95% CI)	Adjusted* years (95% CI)
Normal BMD (T-score>=1.00)	-----	-----
Mild osteopenia (T-score -1.01 to -1.49)	-----	*18.7 (14.9, 23.4)*
Moderate osteopenia (T-score -1.50 to -1.99)	4.60 (4.09, 5.17)	4.71 (4.20, 5.29)
Advanced osteopenia (T-score -2.00 to -2.49)	0.89 (0.76, 1.05)	1.04 (0.89, 1.22)

*adjusted for age, BMI, current estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis- besides baseline T-score range (n=4209 complete cases).

Estimates greater than 15 years (italicized) have questionable reliability due to excessive extrapolation required for 10% to transition to osteoporosis as illustrated in Figure A. Estimates greater than 15 years with 95% CIs excluding 15 years are not presented. Estimated time intervals for 5% of women with normal BMD to transition to osteoporosis are: unadjusted 23.4 (10.5, 52), and adjusted 22.7 (12.2, 42).

Table E. Time intervals for 10% of participants to transition from osteopenia to osteoporosis (T-score <= -2.5 at femoral neck), by age, BMI and estrogen use

Baseline Covariate Value	**Adjusted time interval in years for 10% of participants to transition from osteopenia to osteoporosis***		
	Mild osteopenia (T-score -1.01 to -1.49)	Moderate osteopenia (T-score -1.50 to -1.99)	Advanced osteopenia (T-score -2.00 to -2.49)
Age			
67 yrs	----	5.48 (4.76, 6.32)	1.21 (1.01, 1.46)
70 yrs	-----	5.08 (4.50, 5.74)	1.13 (0.96, 1.33)
75 yrs	*17.8 (14.1, 22.4)*	4.49 (3.98, 5.06)	0.99 (0.85, 1.16)
80 yrs	*15.7 (12.2, 20.2)*	3.96 (3.39, 4.62)	0.88 (0.73, 1.05)
85 yrs	13.8 (10.4, 18.5)	3.49 (2.83, 4.31)	0.77 (0.62, 0.97)
BMI			
18.5	*20.8 (12.7, 33.9)*	3.65 (2.88, 4.61)	0.69 (0.55, 0.86)
25.0	*19.0 (14.8, 24.5)*	4.50 (4.00, 5.07)	0.97 (0.83, 1.13)
30.0	*17.8 (13.9, 22.7)*	5.29 (4.52, 6.19)	1.26 (1.05, 1.51)
Estrogen use			
Current	-----	6.90 (5.61, 8.48)	1.53 (1.22, 1.92)
Past or Never	*17.4 (13.9, 21.9)*	4.40 (3.90, 4.96)	0.97 (0.83, 1.14)

* estimated time to osteoporosis, adjusted for age, BMI, estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis . These values are based on a model that includes interactions of T-score group with BMI.

Estimates greater than 15 years (italicized) have questionable reliability due to excessive extrapolation required for 10% to transition to osteoporosis. Estimates greater than 15 years with 95% CIs excluding 15 years are not presented.

Table F. Time intervals for 2% of participants to transition to hip or clinical vertebral fracture according to baseline T-score range

Baseline T-score range	**Time interval for 2% of participants to transition to hip or clinical vertebral fracture**	
	Unadjusted years (95% CI)	Adjusted* years (95% CI)
Normal BMD (T-score >=-1.00)	*24.97 (6.98, 89.39)*	*24.97 (6.92, 90.10)*
Mild osteopenia (T-score -1.01 to -1.49)	14.49 (8.44, 24.88)	*15.36 (9.07, 25.99)*
Moderate osteopenia (T-score -1.50 to -1.99)	4.62 (3.27, 6.51)	5.54 (3.98, 7.73)
Advanced osteopenia (T-score -2.00 to -2.49)	4.75 (3.32, 6.79)	5.37 (3.80, 7.60)

* adjusted for age, BMI, current estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis (N=4097 complete cases). For normal BMD group, adjusted for continuous BMD and age only (N=1255 complete cases).

Estimates greater than 15 years (italicized) have questionable reliability due to excessive extrapolation required for 2% to transition to hip or clinical vertebral fracture.

Table G. Sensitivity analysis: screening intervals for transition to hip or clinical vertebral fracture based log logistic model vs. other parametric models

Baseline T-score range/ statistical model	**Time interval for 2% of participants to transition to hip or clinical vertebral fracture**	
	Unadjusted years (95% CI)	Adjusted* years (95% CI)
Normal BMD (T-score >=-1.00)		
Log logistic	*24.97 (6.98, 89.39)*	*24.97 (6.92, 90.10)*
Exponential	*24.49 (9.08, 66.10)*	*24.49 (9.07, 66.12)*
Weibull	*24.89 (6.98, 88.76)*	*24.88 (6.92, 89.47)*
Log normal	*27.83 (7.03, 110.14)*	*27.71 (6.98, 109.94)*
Mild osteopenia (T-score -1.01 to -1.49)		
Log logistic	14.49 (8.44, 24.88)	*15.36 (9.07, 25.99)*
Exponential	13.83 (8.60, 22.24)	*15.47 (9.44, 25.34)*
Weibull	14.54 (8.44, 25.04)	*15.40 (9.07, 26.15)*
Log normal	13.98 (8.46, 23.09)	*15.23 (9.26, 25.05)*
Moderate osteopenia (T-score -1.50 to -1.99)		
Log logistic	4.62 (3.27, 6.51)	5.54 (3.98, 7.73)
Exponential	5.00 (3.81, 6.56)	5.72 (4.25, 7.69)
Weibull	4.62 (3.28, 6.51)	5.56 (3.99, 7.75)
Log normal	4.56 (3.22, 6.46)	5.56 (3.97, 7.79)
Advanced osteopenia (T-score -2.00 to -2.49)		
Log logistic	4.75 (3.32, 6.79)	5.37 (3.80, 7.60)
Exponential	5.13 (3.84, 6.84)	5.60 (4.10, 7.64)
Weibull	4.76 (3.33, 6.81)	5.38 (3.81, 7.61)
Log normal	4.61 (3.21, 6.62)	5.28 (3.72, 7.49)

* adjusted for age, BMI, current estrogen use, any fracture after age 50 years, current smoking, oral glucocorticoid use, rheumatoid arthritis (N=4097 complete cases). For normal BMD group, adjusted for continuous BMD and age only (N=1255 complete cases).

Estimates greater than 15 years (italicized) have questionable reliability due to excessive extrapolation required for 2% to transition to hip/clinical vertebral fracture.

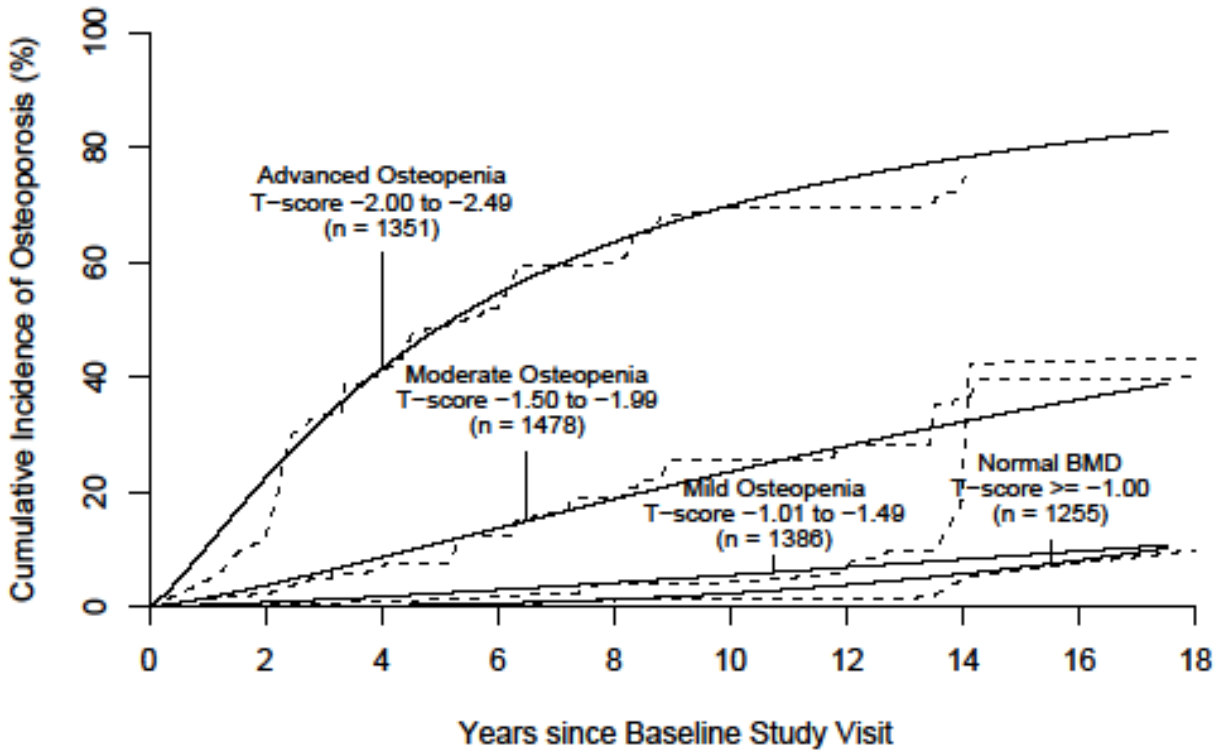

Figure A. Cumulative incidence of osteoporosis predicted by parametric model compared to nonparametric model.