Osteoporosis and Fractures in Postmenopausal Women Using Estrogen

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Background: Previous studies demonstrate that postmenopausal women who use estrogen are somewhat protected from bone loss and fractures compared with nonusers, but the extent to which estrogen users remain at risk for osteoporosis and fractures is uncertain.

Objective: To determine long-term probabilities for incident fractures among postmenopausal estrogen users.

Methods: We examined data from the Study of Osteoporotic Fractures, a prospective cohort study with 10 years of follow-up (1986-1999). This cohort includes 8816 women 65 years and older from community settings in 4 areas of the United States.

Main Outcome Measures: Hip, wrist, vertebral, and nonvertebral fractures.

Results: At baseline, using criteria developed by the World Health Organization, 40% of continuous estrogen users were osteopenic and 13% were osteoporotic at the hip or spine. Although women currently using estrogen lost less bone density than past users or those who never used estrogen, all user groups on average lost bone from the hip and calcaneus. During 10 years of observation, the adjusted probability of nonvertebral fractures was 19.6% for continuous estrogen users, similar to current partial users and lower than past users and those who never used estrogen (P<.05). These comparisons were similar for hip, wrist, and vertebral fractures.

Conclusions: Although estrogen use is associated with reduced prevalence of low bone density, less bone loss, and lower probabilities for fractures, osteoporosis and fractures are common in older women who used estrogen continuously since menopause. Estrogen users should be considered in strategies designed to detect, prevent, and treat osteoporosis.

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tive, a large randomized controlled prevention trial of combined estrogen use for 5 years, indicated reduced risk for all fractures (hazard ratio, 0.69 [adjusted 95% confidence interval, 0.63-0.92]). One arm of another trial conducted on nonosteoporotic women in early menopause indicated a protective effect for nonvertebral fractures (relative risk, 0.29 [95% confidence interval, 0.10-0.90]). Several trials, however, have not provided strong evidence of benefit.

These studies demonstrate that estrogen users are somewhat protected from bone loss and fractures compared with nonusers, but they do not, however, describe to what extent estrogen users remain at risk for osteoporosis and fractures. Although the protective effect of estrogen is important, women who choose to receive estrogen supplementation may still be at substantial risk, especially later in life when most fractures occur.

We have previously shown that women who use estrogen have a lower risk of fractures and lose less bone than those who had never used estrogen (never users). The purpose of the present study is to expand on previous work and determine long-term probabilities for fractures among postmenopausal estrogen users, particularly those who have used estrogen continuously since menopause. To address our research question, we examined data collected prospectively over 10 years in different estrogen user groups in the Study of Osteoporotic Fractures (SOF) cohort.

METHODS

SUBJECTS

Ambulatory, community-dwelling women 65 years and older were recruited from 1986 to 1988 in Portland, Ore; Minneapolis, Minn; Baltimore, Md; and the Monongahela Valley, Pa, from population-based lists. The study group consisted of 9704 white women; black women (because of their low incidence of hip fractures) and white women who had undergone bilateral hip replacement or had an earlier hip fracture were excluded. The appropriate committees on human research approved the study, and all the women provided written informed consent.

INTERVIEWS AND EXAMINATIONS

We obtained data for this study from questionnaires and examinations performed at multiple SOF visits from 1986 to 1998 (Figure 1). Methods for collecting baseline descriptive variables have been previously described. Type of menopause (surgical or natural), alcohol use in the previous year, and current and past cigarette smoking were obtained by a questionnaire reviewed with the participant by a trained interviewer. Total calcium intake was assessed by a food frequency questionnaire and by interview using standardized food models to estimate portions and included supplemental sources. A modified Paffenbarger questionnaire was used to assess sports and recreation activity for the previous year. History of osteoporosis was ascertained by asking women if a physician had ever told them whether they had osteoporosis or a spine fracture. History of fracture after age 50 years and prior to entry to the study was based on self-report. Women were asked whether they were currently using sedatives, anxiolytics, and corticosteroids and if they had ever used thyroid supplements. Cognitive function was assessed using the Modified Mini-Mental State Examination. Age was determined at baseline, and weight was obtained at each visit by balance beam scale.

Figure 1. Measurement of variables; data were collected serially over a mean 9.8 years of follow-up. BMD indicates bone mineral density.

Participants were categorized according to their oral estrogen use based on their responses to interviewer-administered questionnaires obtained at each SOF visit. Participants were asked to bring all medications to the clinic for verification of use, preparation, and dosage at visits 1 and 4. Also, pictures of tablets were presented to participants to assist them in the recollection of previously prescribed hormone preparations. Duration of use was based on their recall of previous use. Use of progestins was not specifically considered in this study because previous analyses showed no difference in fracture rates among unopposed compared with combination users, and there were few combination users in SOF. Only a very small number of participants used nonoral forms of estrogen, and they were not included.

Current users were those who reported using estrogen at the time of an interview. Those who used estrogen without interruption from the onset of their surgical or natural menopause until their SOF visit were considered continuous estrogen users. Age at menopause was defined as age of last menstrual period or age at hysterectomy with bilateral oophorectomy. Women who reported that they had a hysterectomy without bilateral oophorectomy, those who were unsure of their last period or oophorectomy status, or those with missing values were assigned a menopause age equal to the mean of the other women in the study (49 years) and included in the analysis. Estrogen users who had taken estrogen for at least 1 year but not continuously since menopause were considered partial users, and those who had never used estrogen for at least 1 year were considered never users. Partial users were further categorized based on current or past use (ie, partial users who were using estrogen at the time of the assessment were considered current partial users). Estrogen use status was assessed repeatedly at intervals of 2 to 3 years at follow-up visits.

Bone mineral density (calculated as grams per centimeters squared) of the total hip was measured using dual energy x-ray absorptiometry (QDR 1000; Hologic, Waltham, Mass) at the second and fourth SOF visits. Mean time between measurements was 3.6 years. We measured calcaneal bone mineral density using single-photon absorptiometry (OsteoAnalyzers; Siemens-Osteon, Wahiawa, Hawaii) at the first visit, and single x-ray absorptiometry at the fourth visit for a mean follow-up time of 3.8 years. Spine bone mineral density was measured once by dual x-ray absorptiometry at the second SOF visit. Details of these measurement methods have been previously published.
ASCERTAINMENT OF FRACTURES

Study participants were contacted by postcard or telephone every 4 months to inquire about incident fractures. All incident, nontraumatic, nonvertebral fractures were recorded and radiographically confirmed as they occurred for the entire SOF cohort over a mean 9.8 years of observation until June 1999. Details about methods of identifying new fractures during follow-up in SOF have been previously published.23 Incident vertebral fractures were determined by radiographic morphometric criteria24 over a period of 3.7 years.

STATISTICAL ANALYSIS

Frequencies and means were determined for baseline characteristics of each estrogen user group and compared by \( \chi^2 \) and least-square means tests using never users as the reference group. Frequencies of women identified as osteopenic and osteoporotic were determined using criteria developed by a consensus group of the World Health Organization (WHO) (bone density 2.5 SDs or more below the young healthy population mean defines osteoporosis; bone density between 1 and 2.5 SDs below the mean defines osteopenia).27

Multiple linear regression was used to compare rates of bone loss. Two multivariable models were developed to test differences between groups. One model included age and weight only, and another fully adjusted model included 14 variables known to influence bone density and fracture outcomes (age, weight, physical activity, body mass index, calcium use, hysterectomy status, general health status, thiazide use, mental state examination, alcohol use, smoking status, history of falls, sedative use, and thyroid supplement use).25,26,27 For each comparison, results were similar for both models, and we included only the age- and weight-adjusted models in this report to graph probability of fracture over time. All analyses were conducted twice, once including women with a self-reported diagnosis of osteoporosis prior to entry to SOF and once excluding them.

We used stratified Cox proportional hazard regression adjusted for age and weight to determine the probabilities of fracture in each of the estrogen user groups. Because estrogen use varied over time from baseline, we censored follow-up time in the analysis when estrogen use status changed. Otherwise, follow-up time was measured from baseline through first fracture or last contact. To adjust for differences between age and weight in the 4 groups, we equalized the means of these variables and then fit a Cox proportional hazard model stratified by estrogen use group. We used SAS software for all analyses (SAS Institute Inc, Cary, NC).

A total of 8816 women who underwent baseline examinations in the SOF had estrogen use variables for this analysis. Of these women, 373 used estrogen continuously from the onset of surgical or natural menopause until their baseline visit for a mean duration of 24.4 years (Table 1). A total of 2466 women used estrogen partially between the time of menopause until baseline, and

<table>
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<th>Characteristic</th>
<th>Continuous (n = 373)</th>
<th>Current Partial (n = 926)</th>
<th>Past (n = 1540)</th>
<th>Never (n = 5977)</th>
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<td>11.4</td>
<td>7.7</td>
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<td>Previous diagnosis of osteoporosis, %</td>
<td>13</td>
<td>29*</td>
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<td>Fracture after age 50 y, %</td>
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<td>70.9*</td>
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<td>22*</td>
<td>18*</td>
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<td>77*</td>
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<td>33*</td>
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<td>24*</td>
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*Bone density measurements were obtained at visit 2.
†Defined by World Health Organization criteria: bone density 2.5 or more SDs below the young healthy population mean defines osteoporosis; between 1 and 2.5 SDs below the mean defines osteopenia.
926 of them were using estrogen at the time of the baseline visit. A total of 5977 women never used estrogen for at least 1 year. Twice the proportion of current partial estrogen users (29%) reported that a physician had previously diagnosed them as having osteoporosis prior to enrollment in SOF compared with the other user groups. Approximately one third of all subjects reported at baseline that they had previously had a fracture after age 50 years, including 30% of the group using estrogen continuously since menopause.

Estrogen user groups differ by several baseline characteristics. Continuous and partial users are younger and weigh less than never users (P < .05). A higher proportion of continuous (38%) and partial users (22% current and 18% past users) have a history of surgical menopause compared with never users (8%; P < .05). Groups also vary by their alcohol use, smoking status, levels of physical activity, calcium intake, mental state examination, and use of sedatives and/or anxiolytics, corticosteroids, and thyroid medications as indicated in Table 1.

BONE DENSITY

Although fewer estrogen users have low bone density at baseline compared with never users, a substantial percentage of women in all estrogen user groups lost bone density at both the total hip and calcaneus. Asterisks indicate values significantly different from those of never users from multiple linear regression models adjusted for age and weight (P < .05).

Figure 2. Mean bone density loss by estrogen user group. Women in all estrogen user groups lost bone density at both the total hip and calcaneus. Asterisks indicate values significantly different from those of never users for both the hip and calcaneus. Continuous and current partial users were substantially less than those of nonusers for both the hip and calcaneus. Rates for past users are similar to those of never users. Rates of bone loss at both sites for all groups, as well as comparisons between groups, are similar when excluding women with a previous diagnosis of osteoporosis and when using the fully adjusted model.

INCIDENT FRACTURES

The probability of any nonvertebral fracture for continuous estrogen users over 10 years of observation is 19.6% after adjustment for age and weight using Cox proportional hazard models (Table 2). This rate is similar for current partial users (22.4%), but lower than past (29.6%) and never (30.9%) users (P < .001) (Figure 3). The rate for past users is not significantly lower than never users at 10 years.

Continuous and current partial users continue to be at risk for hip (10-year rates: 2.8% for continuous and 2.8% for current partial users) and wrist fractures (10-year rates: 3.3% for continuous and 3.5% for current partial users), albeit at lower rates than never users (P < .01) (Figure 4 and Figure 5). Wrist and hip fracture probabilities for past users are similar to never users.

When the same analysis is performed excluding women who reported at baseline that they previously had been told that they had osteoporosis, the probabilities for
fracture decrease slightly for all groups at all sites. Differences between groups remain the same.

The probability of an incident vertebral fracture (over 3.7 years of observation) was 2.5% among continuous users and 4.0% among never users. Differences between past and never users remained the same.

To determine if the continuous users who fractured are different from those who did not, we compared their baseline characteristics. Estrogen users who sustained fractures are slightly older (70.2 vs 69.2 years; \( P = .03 \)), are more likely to have smoked cigarettes (55.3% vs 41.5%; \( P = .04 \)) and more likely to take sedative or anxiolytic medications (48.7% vs 35.9%; \( P = .05 \)) than those who did not fracture. They did not differ on any of the other baseline characteristics.

Our analysis of estrogen users in the SOF cohort found that among older women using estrogen since menopause, a substantial proportion met diagnostic criteria for osteopenia or osteoporosis; most lost bone density; and they had 10-year fracture rates of 19.6% for nonvertebral, 2.8% for hip, and 3.3% for wrist fractures. These outcomes for continuous estrogen users have not been previously reported. How the determinants of osteoporosis in estrogen users, or its prevention and treatment, differ from similar processes in women not using estrogen is not known.

In our study, 80% of women experienced bone loss while receiving estrogen therapy. The group experiencing the least bone loss (current partial users) included women who had started estrogen more recently than the continuous users. Other studies indicate that the protective effect of estrogen persists for 10 years or more for women in the early postmenopausal period\(^{28} \) and for at least 2 to 3 years in older women.\(^{30-34} \) A separate evaluation of hip scans from SOF indicated that estrogen not only influences bone density but also seems to increase mechanical strength of the proximal femur by improving its geometric properties.\(^{35} \) The nature of bone loss in older women using estrogen deserves additional study.

Our results are consistent with our previous findings that women who use estrogen have a lower risk of fractures than never or past users, particularly if initiated early after menopause.\(^{9,36} \) However, about 1 in 5 women experienced a fracture in 10 years, indicating that a substantial health burden of osteoporosis persists among women using estrogen. When considering the self-selection and lifestyle biases that probably lead to an overestimation of the beneficial effects of estrogen in observational studies,\(^{37-41} \) the unbiased effects of estrogen may be even more modest.

The bone loss and frequency of osteopenia, osteoporosis, and fractures we observed in estrogen users indicate that, to some extent, skeletal fragility develops in women using estrogen. However, other causes of fractures that are not estrogen dependent, such as falls, become more frequent with age and may become more important than the estrogen effect. The information available in our study does not permit a comparison of these effects. Nevertheless, our conclusion that fractures are common in estrogen users emphasizes the need for additional study of the mechanisms of fracture.

Some clinical guidelines imply that estrogen users do not require any assessments of skeletal health,\(^{42} \) and clinicians and patients may feel that estrogen users are adequately protected from fractures. The findings of this study indicate that estrogen users remain at risk, and perhaps they should be considered in screening and treatment guidelines. The National Osteoporosis Foundation recommendations include the need for ongoing bone density assessments in estrogen users.\(^{43} \) Although the usefulness of this approach has not been tested, identifying low bone density in estrogen users could prove beneficial. For instance, other preventive measures could be instituted such as improving calcium and vitamin D nutrition, exercise, and modifying other risk factors. Other therapies, such as bisphosphonates, may also be indicated. Use of estrogen combined with other therapies is being explored. Controlled trials of the effectiveness of all these strategies in reducing fractures are needed.

This study has several limitations. Randomized controlled trials of older women with bone density and fracture end points would provide a more accurate estimate of the risk of osteoporosis in estrogen users. Despite our attempts to control for likely confounders, bias introduced by other unmeasured variables could be important.
in observational studies because estrogen users differ from nonusers in many ways. The advantage of this study, however, is that reliable prospective bone density and fracture outcomes have been collected on women with a wide range of estrogen use history, including a group of women with a mean of 24.4 years of continuous estrogen use. The cohort can be considered representative of similar community-dwelling women. Randomized controlled trials of estrogen replacement in postmenopausal women, even large trials, will not address the issue adequately unless they are of very long duration.

Another limitation of the present analysis is that estrogen use was determined by patient report and is subject to inaccuracy. We were not able to determine adherence, and our measures are not reliable enough to stratify effects by dosage or duration of use. We attempted to minimize this bias by strictly defining our continuous estrogen group as those who had been receiving estrogen since surgical or natural menopause. This approach should be less prone to error than using exact years of use as the basis of categorization. Because subjects were repeatedly questioned about continuing use every 2 to 3 years during the study, use estimates should be reliable. We did not investigate users of nonoral estrogen because previous analyses found that there were few in SOF, and their inclusion did not influence our results. Our estimates of the effects of partial estrogen use must be considered preliminary. Although the rates of bone loss and probabilities of fracture in these groups are substantial, the relative effects of current compared with past use must be defined more carefully in specifically designed studies.

In summary, we found that prolonged postmenopausal estrogen use provided incomplete protection against bone loss and osteoporotic fractures. Osteoporosis and fractures were common in women who had used estrogen since menopause, and clinicians cannot assume that women using estrogen are fully protected from fractures. Efforts should be directed at identifying those at continued risk while using estrogen and at developing and testing the effectiveness of new management options for women who have osteoporosis and are at high risk of fractures despite long-term use of estrogen.

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