Is surgical menopause associated with an increased risk of fracture in elderly U. S. women?

by

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

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ABSTRACT

Objective

The public health impact of osteoporotic fractures is significant. It has been estimated that, in 1995, there were $13.8 billion in direct medical expenditures related to osteoporotic fractures in the U.S., 75% for the treatment of women. Important risk factors for osteoporosis include increasing age, low weight, low bone mineral density, estrogen deficiency (postmenopausal status), and Caucasian race. No prospective study has evaluated the impact of surgical menopause on fracture risk. The objective of this study was to determine whether or not women who experience surgical menopause have a higher risk of postmenopausal osteoporotic fracture than women who experience natural menopause.

Methods

A secondary analysis of 20 years of data from the Study of Osteoporotic Fractures (SOF), an on-going, multi-center, prospective study of risk factors for fracture in 9704 community-dwelling, Caucasian women 65 years of age or older, was performed. Women who had undergone bilateral hip replacement or who were unable to walk without help were excluded.

For this study, the cohort was subdivided into four distinct menopausal groups: surgical menopause resulting from premenopausal bilateral oophorectomy (n=1157), natural menopause without previous oophorectomy or hysterectomy (n=5459), natural menopause with a history of oophorectomy or hysterectomy (n=1288), and premenopausal hysterectomy without history of simultaneous bilateral oophorectomy (n=1679). The primary outcome was nontraumatic, nonvertebral fracture. Fractures

were reported by the study participants during the course of observation and verified by review of x-ray reports.

Descriptive statistics were performed and multivariable Cox proportional hazards regression models were used to estimate the relative risk of hip, wrist, and any nonvertebral fracture for surgical compared to natural menopause. Because oral estrogen use has been shown to decrease the risk of fracture and surgical menopause is often an indication for oral estrogen use, the models were stratified by never and current use of oral estrogen.

Results

Women who experienced surgical menopause were younger in mean age at menopause and baseline, weighed more, had higher total hip bone mineral density, and were more likely to be current users of oral estrogen. Multivariable analyses revealed that, among women who had never used oral estrogen, there was a 1.2 fold increased risk of nonvertebral fracture for surgical compared to natural menopause (RR 1.23, 95% CI 1.04-1.45). Surgical menopause was not associated with an increased risk of wrist (RR 1.19, 95% CI 0.87-1.64) or hip fracture (RR 0.87, 95% CI 0.63-1.28).

Conclusion

Surgical menopause does not increase the risk of hip or wrist fracture. This is an important finding as hip fracture contributes the greatest risk of mortality and accounts for the greatest health resource utilization of all osteoporotic fractures. Among women who never used oral estrogen and experienced surgical menopause, there was a small increased risk of nonvertebral fractures. The clinical implication of this observation is uncertain given the small magnitude of risk.

BACKGROUND

Osteoporosis

Definition and public health burden

Osteoporosis is a systemic disease of the bone characterized by low bone density and increased bone fragility.[1, 2] It is currently estimated that 10 million Americans aged 50 and older have osteoporosis of the hip when defined by low bone density criteria. The majority of these (78% or 7.8 million) are women.[3] The public health impact of osteoporosis is substantial. For the year 1995, it was estimated that there were $13.8 billion in direct medical expenditures related to osteoporotic fractures in the U.S., 75% for the treatment of women.[4] In the U.S., of all types of osteoporotic fractures, hip fractures account for the largest portion of health resource utilization including 57% of hospitalizations, 2.1 million inpatient days, 77% of nursing home stays, and 23.5 million nursing home days.[4]

Fractures resulting from osteoporosis are associated with increased mortality. Of all fracture types, hip fracture is associated with the highest risk of mortality. Studies have demonstrated a 2- to 3-fold increased risk of mortality in women after hip fracture compared to women of the same age without fracture.[5, 6] In addition, mortality is increased approximately 1.2- to 1.7-fold after vertebral fracture[5, 7] and 1.9-fold after other major fractures (pelvis, distal femur, proximal tibia or humerus, and multiple rib).[5] In women age 60 or greater, life expectancy is significantly decreased after fracture, particularly after hip fracture. For hip fracture, the years of potential life lost range from 0.4 for women 80 or older to 11.2 years for women age 60-64. For vertebral and other

major fractures, the years of potential life lost range from 0.4 for women 80 or older to 1.9 years for women age 60-64.[5]

Diagnosis

Osteoporosis is diagnosed by the assessment of bone mineral density or by the occurrence of a fragility fracture. Fragility fractures, such as vertebral compression fractures, are those that occur under conditions that normally would not result in fracture. Bone mineral density is the mass of bone measured in a specific anatomic location, such as the femoral neck, divided by the area measured and is noted in grams/cm^2. For any given site of measurement of bone mineral density, osteopenia or low bone mass is defined as >1 standard deviation (SD) but <2.5 SD below the young adult mean. Osteoporosis is defined as $\geq$ 2.5 SD below the young adult mean.[2] The gold standard measure of bone mineral density is dual-energy x-ray absorptiometry (DXA), although there are other methods for the assessment of bone mineral density including single photon absorptiometry or single-energy x-ray absorptiometry (SPA or SXA) and quantitative ultrasound.[2] Bone mineral density measurements of the hip are the most highly predictive of subsequent hip fracture.[8] A one standard deviation decrease in bone mass at the femoral neck is associated with a 60% increased risk of nonvertebral fracture[9] and a 260% increased risk of hip fracture.[10] However, measurements at other sites (spine, calcaneous, or wrist) are also predictive of hip and nonvertebral fracture risk.[9,10]

Risk factors

Factors associated with increased hip fracture risk in postmenopausal women have been extensively studied in a large, prospective, U.S. cohort, the Study of Osteoporotic Fractures (SOF). These include family history of maternal hip fracture, personal history

of fracture (either premenopausal or after age 50), increasing age, low weight, low body mass index, high height at age 25 (per each 6 cm increase), weight loss since age 25, current smoking, no or excessive alcohol use, poor self-reported health status, current use of anticonvulsants or long-acting benzodiazepines, current caffeine intake (per 190 mg/day increase), history of hyperthyroidism or diabetes, four or fewer hours spent on feet per day, inability to rise from a chair without using one's arms, resting pulse rate > 80 beats per minute, poorer depth perception and low-frequency contrast sensitivity, history of falls, and nulliparity.[11-13] Factors associated with a decreased risk of hip fracture include weight gain since age 25 (per 20% increase), greater weight and body mass index, and walking regularly for exercise.[11]

Caucasian women have a higher prevalence of osteoporosis of the hip than women of other races or ethnicity. The age-adjusted prevalence of osteoporosis of the hip in postmenopausal White women in the U.S. is 17% compared to 14% for Mexican American women, 12% for Japanese women, and 6% for Black women.[3] At age 50 years, White women have a 40% lifetime risk of experiencing a hip, wrist, or vertebral fracture and a 17% lifetime risk of hip fracture.[2]

Effects of early menopause on bone mineral density and fracture

Peak bone mineral density is most likely achieved by the third decade of life.[14] Most women experience a rapid rate of decline in bone mineral density after menopause.[15] This decline probably continues, albeit at a slower rate, into old age.[16] Several studies have demonstrated a positive association of age at menopause with bone mineral density.[17, 18] In the Rancho Bernardo cohort of postmenopausal women, women who had menopause before age 48 had lower mean bone density at all sites compared to women

with a later menopause. In multiple regression analysis, early menopause was a significant predictor of reduced bone mineral density at the wrist, hip, and spine.[17]

A large cross-sectional study of women age 50-80 years in the Netherlands found that early menopause compared to later menopause (age < 45 years vs. age ≥ 45) was associated with increased risks of osteoporosis of the lumbar spine (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.2-1.8) and of fracture (all fractures as a group, OR 1.5, 95% CI 1.2-1.8).[18] In the SOF cohort, early menopause (age <45) was not associated with an increased risk of hip fracture.[11]

Hysterectomy and Oophorectomy

Definitions

Hysterectomy (surgical removal of the uterus) prior to natural menopause may hasten the onset of menopause.[19] If both ovaries are removed (bilateral oophorectomy) prior to natural menopause, a surgical menopause is induced. Menopause occurs because the ovaries are the primary source of estrogen in the female and surgical removal results in a precipitous drop in circulating estrogen levels.[19] Without estrogen therapy, menopausal symptoms may ensue and bone mineral density may begin the more rapid decline that is observed with the onset of natural menopause.[19]

Prevalence

Among women of reproductive age in the United States (U.S.), hysterectomy is the second most frequently performed surgical procedure after cesarean section. In the U.S., uterine fibroids, benign smooth muscle neoplasms, are the most common indication for hysterectomy.[20] It is estimated that approximately 20 million U.S. women have had a hysterectomy.[20] There are approximately 600,000 hysterectomies performed annually in

the U.S, about half of which include bilateral oophorectomy.[20] The percentage of concomitant bilateral oophorectomies has doubled since 1965.[20] Between 1994 and 1999, approximately one third (40%) of women aged 15-44 years who underwent a hysterectomy also had bilateral oophorectomy.[20]

Benefits of oophorectomy

Prevention of ovarian cancer is the primary reason for removal of the ovaries at the time of hysterectomy for benign gynecologic conditions, except in cases of endometriosis in which simultaneous hysterectomy and bilateral oophorectomy are considered definitive treatment.[19] "Prophylactic oophorectomy" refers to the removal of normal ovaries for the potential benefit of preventing long-term morbidity and mortality.[21] Although prophylactic oophorectomy may be performed as an isolated procedure in women at high risk for ovarian malignancy, it is commonly performed at the time of hysterectomy or other pelvic surgery in women with average risk for ovarian malignancy.

The lifetime risk of ovarian cancer among women in the U.S. is 1 in 58 (1.7%).[22] In comparison, the lifetime risk of breast cancer is 1 in 8 (12.5%).[22] Although the risk of developing breast cancer is higher than ovarian cancer, the rate of survival for breast cancer is two-fold greater than with ovarian cancer. During the time period 1995-2000, the relative 5-year survival rate was 88% for breast cancer compared to 44% for ovarian cancer.[23] In 2005, ovarian cancer was the 4th leading cause of cancer death in U.S. females, second only to breast cancer in death from cancers of the female reproductive tract.[24]

Unlike breast cancer, there is no effective screening tool for ovarian cancer.[22] Over half of ovarian cancer cases are diagnosed at Stage III or IV, i.e. after the cancer has

metastasized.[25] One retrospective cohort study performed in Athens identified 520 cases of ovarian cancer in 5262 women who had previously undergone hysterectomy.[26] The authors estimated that 49 (9.4%) cases would have been prevented if prophylactic bilateral oophorectomy had been performed in women undergoing hysterectomy at age 40 or above. In a national survey of 12,316 ovarian cancer cases in the United States, previous hysterectomy with ovarian conservation was reported by 18.2% of patients; 57.4% of the hysterectomies were performed after the age of 40.[27] If prophylactic oophorectomy had been performed for all women age 40 or greater, an estimated 1286 ovarian cancer cases could have been prevented.

Based on these data and their clinical experience in the care of patients with ovarian cancer, the authors of the textbook *Clinical Gynecologic Oncology* stated that they believe a prophylactic oophorectomy should be offered to all perimenopausal patients (40-50 years of age) undergoing pelvic surgery.[22] The American College of Obstetrics and Gynecology does not provide an age-specific recommendation for when prophylactic oophorectomy should be offered. The College instead states that the decision to perform prophylactic oophorectomy should be highly individualized and take into account several patient factors and choices in addition to age.[21]

Effects of bilateral oophorectomy on bone mineral density and fracture risk

One question that remains unanswered is how premenopausal bilateral oophorectomy affects subsequent fracture risk. This question has not been evaluated in a prospective cohort study. Existing prospective studies have assessed the effect of premenopausal bilateral oophorectomy on bone mineral density. A study of postmenopausal women enrolled in the Rancho Bernardo Cohort found that, when participants were stratified by

estrogen therapy use, bone mineral density (BMD) did not differ by hysterectomy or oophorectomy status. Estrogen therapy users had higher BMD at the hip than nonusers. In this cohort, early menopause (before age 48) and fewer reproductive years were significantly associated with lower BMD at the spine and hip and this relationship was not explained by estrogen use.[17, 28]

Four cohort studies have evaluated the risk of fracture after bilateral oophorectomy, only one of which specifically evaluated premenopausal oophorectomy. Two of the four cohort studies evaluated the effect of postmenopausal oophorectomy on fracture risk and presented conflicting results.[29, 30] One demonstrated an increased risk of fracture associated with postmenopausal bilateral oophorectomy,[30] the other did not.[29] In the Study of Osteoporotic Fractures, after 4.1 years of follow-up, bilateral oophorectomy was not observed to be a significant predictor of hip fracture.[11] In this analysis, bilateral oophorectomy was not stratified as occurring pre- or postmenopausally or by age at menopause.

The fourth study, a retrospective analysis of 463 women who underwent premenopausal bilateral oophorectomy between 1950 and 1979 in Olmstead County, Minnesota, found a modest increased risk of distal forearm (age-standardized mortality ratio [SMR] 1.4, 95% CI 1.0-2.0) and vertebral fractures (SMR 1.9, 95% CI 1.3-2.8), but not of hip fracture (SMR 1.1, 95% CI 0.6-1.9) when compared to age-standardized rates in the community. There was also a nonsignificant trend to increased risk of fracture with earlier onset (per 10-year decrease in age) of estrogen deficiency.[31]

STUDY RATIONALE

Given that hysterectomy with bilateral oophorectomy is such a common procedure in the United States and is often performed in premenopausal women, it is important to understand the impact of premenopausal bilateral oophorectomy on fracture risk. Such information is necessary in order to provide an accurate risk:benefit assessment to women who plan to undergo hysterectomy for benign gynecologic conditions. Since estrogen deficiency is associated with a loss in bone mineral density, it is especially important to assess the effect of surgical menopause on fracture risk in women who elect not to use estrogen therapy after bilateral oophorectomy.

Attitudes of women toward hormone therapy have become less favorable since the results of the Women's Health Initiative (WHI) became public,[32, 33] and many studies have reported a decline in prescriptions for hormone therapy and a decline in hormone therapy use.[34, 35] The WHI is a randomized clinical trial of the use of estrogen versus placebo for the primary prevention of multiple outcomes including osteoporotic fracture and cardiovascular disease.[36] The WHI demonstrated, among women with prior hysterectomy, a lack of overall protective effect of oral estrogen (Premarin®, conjugated equine estrogens) compared to placebo for cardiovascular disease and an increased risk of stroke. Oral estrogen therapy, however, was associated with a decreased risk of hip fracture.[37]

The WHI enrolled older postmenopausal women (mean age 63 at entry) and, therefore, the results may not apply to younger women contemplating premenopausal oophorectomies. However, given the current climate regarding hormone therapy use, it is

possible that women who undergo hysterectomy and bilateral oophorectomy in the coming years will be less likely to use oral estrogen therapy.

STUDY OBJECTIVES

The primary objective of this study is to determine whether or not surgical menopause, i.e. the removal of both ovaries prior to natural menopause, is associated with an increased risk of nontraumatic, nonvertebral, postmenopausal osteoporotic fracture.

The secondary objectives are to evaluate the roles estrogen use and age at menopause play in the relationship between surgical menopause and fracture.

HYPOTHESES

1) Women who undergo surgical menopause are at increased risk for nontraumatic, nonvertebral, postmenopausal fractures.
2) Oral estrogen use modifies the relationship between surgical menopause and fracture resulting in a decreased risk of fracture in women who use oral estrogen compared to those who do not.
3) The age at onset of menopause modifies the relationship between surgical menopause and fracture such that the earlier the age at onset of menopause, the greater the risk of fracture.
4) *Bone mineral density is a mediator of the relationship between surgical* menopause and fracture.

METHODS

Study Population

The Study of Osteoporotic Fractures is a multi-center prospective study of risk factors for fracture in 9704 community dwelling Caucasian women 65 years of age or older enrolled into the cohort from 1986 to 1988. Women were recruited from population-based listings of age-eligible women in four regions of the United States: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley near Pittsburgh, Pennsylvania. Women were excluded who had undergone bilateral hip replacement or who were unable to walk without help. All women provided written informed consent, and the study was approved by the Institutional Review Boards at each site.

This study involves a secondary analysis of the Study of Osteoporotic Fractures data accumulated through December 2004. As of October 1, 2004, the retention rate for the cohort was 91.3%. The present analysis was restricted to the 9583 women who at baseline self-reported whether or not they had had a hysterectomy and/or oophorectomy.

Determination of Menopause Type

The primary exposure for this analysis was type of menopause. The exposure status was determined by self-report. Validation of the exposure was not performed for this study but has been performed in other cohorts and found to be accurately reported.[38, 39] The participants were asked to provide their age at the time of their last natural menstrual period and their age at time of hysterectomy and removal of each ovary if applicable. To confirm hysterectomy status, the women were asked whether they still had menses after their hysterectomy.

"Surgical" menopause was defined as the removal of both ovaries with or without hysterectomy prior to the cessation of menses. "Natural" menopause was defined as the age-related cessation of menses. The natural menopause group included only women who had no history of hysterectomy or oophorectomy. Women who experienced natural menopause but had a hysterectomy and/or oophorectomy after menopause were categorized separately due to conflicting literature regarding the effect of postmenopausal oophorectomy on fracture risk.[29, 30] This group, which will subsequently be referred to as the "natural + surgery" group, also included women who reported having one ovary removed before the onset of natural menopause. Women who underwent premenopausal hysterectomy without simultaneous bilateral oophorectomy were also categorized separately from the natural menopause group as it has it has been suggested that hysterectomy with unilateral oophorectomy may result in impaired function of the remaining ovary[40] and that hysterectomy may be associated with earlier onset of menopause.[19] This group, which will be identified as the "hysterectomy" group, included women with no ovaries removed, one ovary removed, uncertainty regarding ovarian status, or bilateral oophorectomy performed at a later date.

Women who underwent hysterectomy without bilateral oophorectomy prior to menopause were considered to have an unknown age at menopause. There were also 77 women who experienced natural menopause but could not recall the age. Women who could not confirm whether their hysterectomy occurred before or after menstrual cessation (n=1), who did not know if they had had a hysterectomy (n=18), or who did not provide any information regarding menopause (n=102) were excluded (n=121).

Participant Characteristics

Information was collected from all participants at baseline by questionnaire, review of medication bottles, food intake diaries, and physical exam. Based on previous SOF analyses and/or biologic plausibility, characteristics of primary interest included history of maternal hip fracture, personal history of hip or any fracture after the age of 50, age at the time of study enrollment and at menopause, height at age 25, weight, smoking status, alcohol use, self-reported health status (excellent/good, fair, poor/very poor), current use of thiazides, anticonvulsants, and steroids, use of long-acting benzodiazepines in the last 12 months, dietary and supplemental intake of calcium, history of hyperthyroidism or diabetes, physical activity (walks for exercise), amount of time spent on feet per day ($\leq$4 vs. >4 hours), history of falls in the last 12 months, parity, history of pregnancy (yes or no), and breastfeeding history.[11, 12, 41]

Alcohol use, smoking status, parity, and breastfeeding history were examined as continuous and categorical variables. Alcohol intake was assessed as number of drinks/week in the last 30 days or as heavy ($\geq$14 drinks/week), light to moderate (1-14 drinks/week), and none.[41] Smoking status was assessed as current, past, or never and as pack-year history.[41] Parity was assessed in absolute number of live births and as a dichotomous variable ($\geq$1 live birth vs. none).[12] Breastfeeding history was evaluated as a dichotomous variable (yes/no) and in number of children breastfed. Participants were asked about history (current, past, never) and duration (years) of oral estrogen and estrogen patch use, and history (yes/no) and duration (years) of oral contraceptive use.

Baseline measurements included bone mineral density of the distal radius and calcaneous by single photon absorptiometry, height (by stadiometer), weight, depth

perception (using the Howard-Dohlman device), contrast sensitivity, ability to stand from a chair five times without using ones arms, and resting pulse.[11] At the second visit, between 1988 and 1990, bone mineral density measurements of the proximal femur by dual energy x-ray absorptiometry (DXA) (QDR 100, Hologic, Waltham, MA) were first performed for 8074 women (those surviving at that time) and then serially approximately every 2 years.

Identification of Fractures

Study participants were contacted by mail or telephone every four months to identify the occurrence of fractures. The follow up for fracture is 99% complete. Incident fractures were verified by review of the radiology report for each given fracture. The primary fractures of interest for this study were incident nontraumatic, nonvertebral fractures. This included 3668 women with any incident nontraumatic, nonvertebral, 1093 women with incident hip fractures, and 889 women with incident wrist fractures. The group of any nontraumatic, nonvertebral fracture is comprehensive and included hip and wrist fractures as well as any other nontraumatic, nonvertebral fractures such as rib, toe, and facial fractures. Fractures that occurred as a result of major trauma, e.g. motor vehicle accidents, were excluded.

Statistical Analyses

General linear models for continuous variables and Pearson chi-square tests for categorical variables were used to assess differences in baseline characteristics between the menopause groups. Comparisons between the surgical and natural menopause groups, the natural and natural + surgery groups, and surgical and hysterectomy groups were performed by Student's t-tests, chi-square, and Fisher's exact tests. No adjustments

for multiple comparisons were made as it was hypothesized prior to analysis that the surgical and natural menopause groups would differ, but the natural and natural + surgery as well as the surgical and hysterectomy groups would be similar.

Cox proportional hazards regression models were used to estimate incidence rate ratios as the measure of relative risk (RR) of fracture and the 95% confidence intervals (CI). Time to fracture was defined as the time from baseline to the first hip, wrist, or nonvertebral fracture. Women who did not have a fracture or died prior to fracture were censored at the time of death or at the time of their last available follow-up questionnaire. For hip fracture analyses, all women with a history of hip fracture after age 50 but prior to study enrollment were excluded. Two methods were used to determine whether oral estrogen use at baseline (current, past, never) and age at menopause (in five-year age groups ranging from <40 to ≥ 55) were effect modifiers. First, interaction terms (menopause type by estrogen use status, menopause type by age at menopause) were added to age and weight adjusted models. Second, Breslow-Day tests for homogeneity of odds ratios were performed.

Stratified fracture models were developed with estrogen use status as a time dependent covariate. For models of never users of oral estrogen, women who were never users of estrogen at baseline were censored at the time they reported estrogen use. For models of current users of estrogen, women who were current users of estrogen at baseline were censored at the time they reported discontinuation of estrogen use. Data regarding current use of oral estrogen were gathered at each clinic visit, approximately every two years. Imputational SAS arrays, which employed the last value carried forward method, were used to account for missing estrogen data at a given visit.

Sensitivity analyses for the stratified models were then performed. The multivariable models developed for never users of estrogen were applied to the full cohort and interaction terms for menopause type by oral estrogen use were added. The results from the full cohort model were then compared to those from the stratified models.

Menopause age was tested as a categorical and continuous variable in multivariable models that included only women with known age at menopause. It was not significant in any of the models and therefore was not further retained in any model.

Age and weight were included in all fracture models because they have been demonstrated to be powerful predictors of fracture.[42, 43] Potential confounding variables were assessed individually in age and weight adjusted models for each fracture type. Variables not significant in age and weight adjusted models were not used for model building. Variables significant in age and weight adjusted models were entered in a forward stepwise manner to build multivariable models for each fracture type. A best subsets approach was used for model building to avoid multicollinearity. In addition, covariates included in the models were examined for correlation. The p-value was ≤ 0.10 to enter a model and <0.05 to remain in the model. The final multivariable models selected represent the most parsimonious models developed for never users of estrogen.

Total hip BMD was added to multivariable models of fracture after the most parsimonious model without BMD had been developed. After adding total hip BMD to these models, all variables with p-values of ≥ 0.05 were removed, leaving the most parsimonious models after adjustment for total hip BMD.

All p-values were based on two-sided tests of significance and a p-value of <0.05 was considered significant. Statistical analyses were performed with SAS software, version

6.12 (SAS Institute Inc, Cary, NC). The proportional hazards assumption was tested for the primary exposure variable (menopause type) and was not violated.

RESULTS

Baseline Measures

The characteristics of the 9583 women for whom menopausal type could be determined are listed in Table 1. Overall, women who underwent surgical menopause were younger in age at baseline and at menopause than women in the natural menopause groups (p=0.0001). The mean age at baseline was 70.8 (±4.9 SD) for surgical and 71.7 (±5.4 SD) for natural menopause. The mean age at surgical menopause was 44.3 (±7.4 SD) and for natural menopause was 48.9 (±4.9 SD). This difference is more clearly illustrated by categorization of the women into age groups (Figures 1, 2). Women who had surgical menopause were more likely to be in the younger age groups both for age at baseline (Figure 1) and for age at menopause (Figure 2) than women who had natural menopause (p=0.001).

Women in the surgical menopause group differed significantly from the natural menopause group on many baseline measures. Women in the surgical menopause group gave birth to fewer children (2.4 vs. 2.7), breastfed fewer children (1.1 vs. 1.3), weighed more (67.8 vs. 66.7 kg), had higher BMI (26.7 vs. 26.3 kg/m^2), had greater weight change since age 25 (+11.4 vs. +10.5 kg), had a higher pack-year history of smoking (12.5 vs. 10.7), were less likely to report excellent or good health status (81% vs. 85%), and had higher bone mineral density of the hip (0.776 vs. 0.746 g/cm^2), wrist (0.373 vs. 0.356 g/cm^2), calcaneous (0.414 vs. 0.398 g/cm^2). They also varied in measures of depth perception and contrast sensitivity. Women in the surgical menopause group had a

higher mean weekly calcium intake from supplements (2942 vs. 2640 mg) and were more likely to be current users of oral estrogen (30% vs. 7%) and thiazides (30% vs. 24%) and to have used long-acting benzodiazepines in the last 12 months (11% vs. 8%). They also differed in mean duration of oral estrogen use (7.1 vs. 1.8 years).

As compared to the natural + surgery group, women in the natural menopause group were younger at baseline (71.7 vs. 72.5) and older at menopause (48.9 vs. 47.9). Women in the natural menopause group had a higher mean number of years of education (12.7 vs. 12.5) and number of alcoholic drinks per week in the past 30 days (1.9 vs. 1.6), a shorter mean duration of oral estrogen (1.8 vs. 4.7 years) and oral contraceptive use (4.8 vs. 4.9 years), a higher mean measure of contrast sensitivity (73.2 vs. 70.8), and a lower mean bone mineral density of the hip (0.746 vs. 0.761), distal radius (0.356 vs. 0.363) and calcaneous (0.398 vs. 0.405). They were less likely to have been pregnant (83% vs. 85%) or to have breastfed (56% vs. 60%), to have a history of falls in the last 12 months (29% vs. 33%), to ever have used oral estrogen (32% vs. 50%), or to use their arms to stand from a chair (4% vs. 5%). They were more likely to report heavy or light to moderate alcohol intake in the last month (56% vs. 51%) and to report excellent or good health (85% vs. 81%).

Women in the surgical menopause group were younger at baseline than those in the hysterectomy group (70.8 vs. 71.3). They were less likely to have been pregnant (83% vs. 87%), have one or more live births (79% vs. 85%), or to have breastfed (54% vs. 62%) and gave birth to (1.4 vs. 1.7) and breastfed fewer children (1.3 vs. 1.6). They were more likely to be current or past smokers (42% vs. 37%) and had a higher mean pack-year history of smoking (12.5 vs. 9.5). They were also more likely to be current or past

users of oral estrogen (62% vs. 52%) and had a longer mean duration of oral estrogen use (7.1 vs. 5.8 years).

Differences between never and ever users of oral estrogen

Within the SOF cohort, women who reported never using oral estrogen prior to baseline were compared to ever users of oral estrogen on all measures (Table 2). Women who had never used oral estrogen were older at baseline, had a younger mean age at menopause, and fewer years of education. They were less likely than ever users to have been pregnant or to have had 1 or more live births. As suggested by Table 1, never users of oral estrogen were less likely to have had gynecologic surgery or surgical menopause. Never users differed significantly from ever users of oral estrogen on all physical measures and in all but one lifestyle measure. They were less likely than ever users to report a history of maternal hip fracture, falls in the last 12 months, and a history of hyperthyroidism, but more likely to have had a bone fracture after age 50 and to have a history of diabetes. Never users were less likely than ever users to have taken oral contraceptives, oral steroids, and long-acting benzodiazepines.

Differences between the surgical and natural menopause groups among never users of oral estrogen

Since there were so many significant differences between the never and ever users of oral estrogen and because the proportion of women who used oral estrogens was so disparate between the surgical and natural menopause groups, descriptive analyses of the baseline characteristics were repeated for women who denied ever using oral estrogen at baseline and experienced surgical or natural menopause (Table 3). Among never users of estrogen, women who experienced surgical menopause had a lower mean age at

menopause, fewer number of live births, weighed more and had higher body mass index, had lower optical distance scores, breast fed fewer children, had fewer years of education, and a higher pack-year history of smoking. The surgical menopause group was more likely to be younger than age 45 at the time of menopause, to be current users of thiazide diuretics, and to have no alcohol intake in the last month. They were less likely to have ever taken oral contraceptives, to have breastfed, to take walks for exercise and to report excellent or good health status.

Outcome Measures

During a mean follow-up of 13 years, 3668 nontraumatic, nonvertebral fractures were identified of which there were 1093 hip and 889 wrist fractures. Women with surgical menopause had fewer incident wrist (8% vs. 10%, p=0.06), hip (9% vs. 12%, p=0.001), and nonvertebral fractures (38% vs. 42%, p=0.02) than those with natural menopause (Figure 3). Ever users of oral estrogen had a smaller proportion of incident nonvertebral fractures than never users (40% vs. 43%, p=0.01), including fewer wrist fractures (9% vs. 10%, p=0.01), but they did not differ significantly in the proportion of incident hip fractures (11% vs. 12%). Among never users of oral estrogen, there were no differences between the surgical and natural menopause groups in the proportion of incident fractures.

As suggested by bivariate analyses, the unadjusted incidence rates per 100,000 person-years of hip (705 vs. 983), wrist (639 vs. 793), and any nonvertebral fracture (3637 vs. 4165) were lower in the surgical menopause group than the natural menopause group (Figure 4). However, after age standardization to the 2000 U.S. census, women in the surgical menopause group appeared to have a higher incidence of wrist and

nonvertebral fracture and a lower incidence of hip fracture (Figure 5). These incident rates were then examined in Cox proportional hazards regression models to quantify their relation to menopause type after adjustment for potential confounders. Table 4 demonstrates the unadjusted and age-adjusted relative risks for hip, wrist, and nonvertebral fracture.

In unadjusted Cox models, lower risks of hip (RR 0.72, 95% CI 0.58-0.88), wrist (RR 0.81, 95% CI 0.65-1.01), and nonvertebral fractures (RR 0.87, 95% CI 0.79-0.97) were observed for surgical compared to natural menopause. After adjustment for age, only the risk of hip fracture remained significantly lower among those who had surgical menopause (RR 0.79, 95% CI 0.64-0.98). The natural + surgery group did not differ significantly from the natural menopause group and the results for the group of women who had hysterectomy without bilateral oophorectomy were similar to those who had surgical menopause.

There were significant interactions between menopause type and oral estrogen use at baseline in all age and weight adjusted fracture models, but no significant interactions between menopause type and age at menopause. The Breslow-Day test revealed that the fracture risk was heterogeneous across the estrogen use groups but not across menopausal age. Stratified models were thus developed for current and never users of estrogen for each fracture type.

Hip fracture

Multivariable models of hip fracture among never users of oral estrogen revealed no difference in the risk of hip fracture between the surgical and natural menopause groups (RR 0.87, 95% CI 0.63-1.21). The results were similar for the hysterectomy group (RR

0.81, 95% CI 0.63-1.05). The addition of total hip BMD to the model did not affect the results for the surgical menopause group, but rendered a statistically significant lower risk of hip fracture for the hysterectomy group (RR 0.67, 95% CI 0.49-0.91). The natural + surgery group did not differ from the natural menopause group in either model (Table 5).

Among current users of oral estrogen, surgical menopause was associated with a decreased risk of hip fracture (RR 0.38, 95% 0.16-0.90). Addition of total hip BMD to the model changed the statistical significance of this finding but not the direction of the relationship (RR 0.48, 95% 0.19-1.21). The other menopausal groups did not differ significantly from the natural menopause group (Table 6).

In the full cohort model of hip fracture with interaction terms for oral estrogen use and menopause type, the relative risks for current and never users of estrogen were almost identical to those of the stratified models (Table 7).

Wrist fracture

Multivariable models of wrist fracture among never users of oral estrogen revealed no significant increased risk of wrist fracture in the surgical menopause (RR 1.19, 95% CI 0.87-1.64), hysterectomy (RR 1.24, 95% CI 0.98-1.57) and natural + surgery (RR 0.98, 95% CI 0.73-1.32) groups compared to the natural menopause group. Addition of total hip BMD to these models did not change the results (Table 5).

Among current users of estrogen, the risks of wrist fracture were not increased in the surgical menopause (RR 0.44, 95% CI 0.18-1.11), hysterectomy (RR 0.69, 95% CI 0.32-1.52) and natural + surgery (HR 1.24, 95% CI 0.59-2.62) groups compared to the natural

menopause group. Addition of total hip BMD to these models did not change the results (Table 6).

In the full cohort model of wrist fracture with interaction terms for oral estrogen use and menopause type, the relative risks for current and never users of estrogen were similar to those of the stratified models (Table 7).

Any nonvertebral fracture

Multivariable models of any nonvertebral fracture among never users of oral estrogen revealed a significant but modestly increased risk of any nonvertebral fracture in the surgical menopause (RR 1.23, 95% CI 1.04-1.45) group compared to the natural menopause group, but no increased risk in the hysterectomy (RR 1.09, 95% CI 0.96-1.24) or natural + surgery (RR 1.11, 95% CI 0.97-1.28) groups. Addition of total hip BMD to these models did not change the results (Table 5).

Among current users of estrogen, there was a modestly decreased risk of any nonvertebral fracture for the surgical menopause (RR 0.72, 95% CI 0.51-1.01) group compared to the natural menopause group. The natural + surgery (RR 1.10, 95% CI 0.78-1.54) and hysterectomy groups (RR 0.87, 95% CI 0.63-1.20) did not differ significantly in risk from the natural menopause group in multivariable models. Addition of total hip BMD to these models did not change the results other than to render less significant the decreased risk in the surgical menopause group ($p= 0.06$ to $p=0.09$, Table 6).

In the full cohort model of any nonvertebral fracture with interaction terms for oral estrogen use and menopause type, the hazard ratios for current and never users of estrogen were similar to those of the stratified models (Table 7).

DISCUSSION

Comparison to Existing Literature

In this cohort of postmenopausal Caucasian women, there was no evidence of an increased risk of hip fracture in women who underwent surgical menopause. There was, however, a modest increased risk (23%) of any nontraumatic, nonvertebral fracture and a modest but not significantly increased (19%) risk of wrist fracture among women who underwent surgical menopause and never used oral estrogen. The risks for hip and wrist fracture mirror those found in the retrospective cohort study of women in Olmstead County, Minnesota. In that cohort, women with premenopausal bilateral oophorectomy had no increased risk of hip fracture compared to women in their community but did have a modest, but not significantly increased risk of distal forearm fracture.[31] That study also demonstrated a nonsignificant trend to increased risk of fracture with earlier onset (per 10-year decrease in age) of estrogen deficiency. However, in our analyses, age at onset of menopause, whether analyzed as a continuous or categorical variable, was not associated with an increased risk of fracture in multivariable models even among women who never used oral estrogen.

In models of current estrogen users, surgical menopause was not associated with an increased risk of hip, wrist, or any nonvertebral fracture. In women who experienced surgical menopause and did not use oral estrogen, the increased risk of any nonvertebral fracture was small and of uncertain clinical significance. The current literature suggests that hip fractures are associated with the most morbidity and mortality and the greatest public health burden of any fracture type,[4, 5] and hip fracture risk was not increased in this cohort. The reason that hip fracture risk would not be increased, whereas composite

nonvertebral fracture risk would be increased, is unclear. It could relate to variability in risk factors for different types of fracture and to different structural functions of those specific sites. Structurally, the hip bears a greater physical load than the wrist and other fracture sites, such as the arm, face and rib, and this may be somewhat protective.

Independent variables that remained significant predictors of fracture in multivariable models differed for hip, wrist, and any nonvertebral fracture, suggesting different factors contribute more significantly to fracture risk at different sites. It could be that women who have surgical menopause differ from women who have natural menopause in ways unrelated to estrogen deficiency that may affect their fracture risk. Among those who never used oral estrogen, bone mineral density measures were not significantly different between the surgical and natural menopause group and total hip BMD did not mediate the relationship between menopause and fracture in multivariable models. These findings support the theory that some other unexplained factors account for the differences in fracture risk among the different fracture groups.

In our study, women with surgical menopause differed significantly from women with natural menopause in key measures related to lifestyle and health. Differences between women with surgical and natural menopause have also been identified in other cohort studies. In the Women's Health Initiative Observational study of the 89,914 women for whom hysterectomy and oophorectomy status were available, 41% reported having a hysterectomy and 50% of those had bilateral oophorectomy. Women who had reported hysterectomy and/or oophorectomy compared to those who had not were more likely to be hypertensive, to ever have been diagnosed with diabetes or peripheral arterial disease, to use high cholesterol requiring pills or aspirin, to never have smoked, and to

have a family history of early myocardial infarction. They also had a higher mean body mass index, waist circumference, and systolic and diastolic blood pressures. Their overall incidence of fatal and nonfatal cardiovascular disease was significantly higher.[44] These data highlight the importance of multivariable adjustment in models evaluating the relationship between menopause type and the risk of fracture.

One of the limitations of this study is that we are unable to determine how premenopausal women who plan to undergo gynecologic surgery differ from those who do not. For example, there may be physiologic or genetic differences that predispose women to conditions for which gynecologic surgery is performed that also influence the micro-architectural structure of bone and subsequent fracture risk. Ongoing prospective studies of perimenopausal women may help further our knowledge regarding important differences between women who undergo surgical and natural menopause.[45] In addition, studies of decision-making in women at low risk for ovarian cancer may also provide greater insight as to how women choose between medical and surgical therapy for benign gynecologic conditions and could provide valuable information to the development of patient-focused, computerized, clinical decision-making tools for oophorectomy at the time of hysterectomy.[46]

In the SOF cohort, those who remained never users of oral estrogen throughout the study differed from ever users in almost all of the covariates examined. Differences between ever and never users of hormone therapy were assessed for two reasons. First and foremost, oral estrogen has been demonstrated to decrease the risk of fracture[37, 47] Second, many studies have suggested that women who use hormones differ from those

who do not in important measures of health and that women who undergo hysterectomy prior to menopause are more likely to use hormone therapy.[48-50]

A cross-sectional, population-based study of 495 postmenopausal, U.S. women aged 50-74 found that younger age, higher education and income levels, white ethnicity, and marital status were significantly associated with use of hormone therapy after stratification by hysterectomy status.[49] In addition, women who had undergone hysterectomy were more likely to use hormone therapy than those who had not. A prospective, population-based, cohort study in Gothenburg, Sweden of 1201 women found that, compared to never users, ever users of estrogen had lower systolic and diastolic blood pressures, lower body mass index, more years of education, and were more likely to be physically active during leisure time and to have high or medium socioeconomic status.[48] Finally, a prospective study of women in Walnut Creek, California, found that mortality in estrogen users was lower than in nonusers for all categories of cause of death except for cancer.[50] These data support the concept of the "healthy user." In our study, stratification of fracture models by estrogen use status was performed to limit the introduction of bias from this potential healthy user effect and to account for the role that estrogen plays both as a potential confounder and an effect modifier.

The mean age (48.9) and median age (49) at natural menopause in this cohort are lower than that generally cited in textbooks (mean 50.7, median 51.3).[19] However, they are consistent with other cohort studies. In the Rancho Bernardo cohort, the mean age for natural menopause was 48.2.[17] In a retrospective cohort analysis of the effects of postmenopausal oophorectomy on fracture risk among women in Olmstead County,

Minnesota, the median age of natural menopause was 50.[30] These cohorts also reported a lower mean age (46.8)[17] or median age (43.8)[31] at surgical compared to natural menopause, which is consistent with our findings (44.3).

Bias and Limitations

It is possible that recall may affect the ability of women to accurately report their menopausal status or the age at which they underwent hysterectomy, oophorectomy, or menopause. Although exposure information was collected upon entry into the study, menopause for most women would have occurred ≥20 years prior to enrollment as the mean age at enrollment was 71.7 and the mean age at menopause was 47.9. In one study of the reliability of reported age at menopause, there was no evidence of systematic age misclassification between women who underwent natural menopause or hysterectomy prior to menopause.[51] In this study, self-reported age at menopause was not compared with medical records. In the First National Health and Nutrition Examination Survey (NHANES I), women aged 25-74 who underwent hysterectomy reported a mean age of menopause about 1 year younger than that documented on hospital charts.[52] Comparisons of self-reported menopause age with medical records have found that 50-76% of women recall the age of natural menopause within 1 year of the actual date.[53]

Differences between menstrually defined menopausal status and self-reported menopausal status have also been assessed. Among women participating in the Melbourne Women's Midlife Health Project, there was no significant difference in self-ratings of menopausal status between women with and without a hysterectomy.[54] It has been demonstrated that subjective reports of surgeries, such as hysterectomies, agree well with medical records. However, recall of details of the surgeries may be less accurate.[39]

In the Rancho Bernardo cohort of women aged 60-89 years of age, the oophorectomy status of a subsample of women who had undergone hysterectomy was validated against medical records.[38] Of 86 women who had undergone hysterectomy, only 2.3% of women with bilateral oophorectomy and 15.1% of women with ovarian conservation did not know their correct oophorectomy status.

These data suggest that that systematic misclassification of menopausal status is unlikely. To limit exposure misclassification in this analysis, only participants who were able to provide complete data regarding bilateral oophorectomy were included in the surgical menopause group. Women who were unclear about their oophorectomy status were categorized in the group of women who had hysterectomy without oophorectomy or with unilateral oophorectomy. In addition, only women who had no pre- or postmenopausal history of oophorectomy and hysterectomy were included in the natural menopause group. Any misclassification of menopause type should attenuate the observed association. The classification of women reporting hysterectomy with bilateral oophorectomy as a separate group from women reporting hysterectomy without bilateral oophorectomy has also been employed by the Nurses' Health Study and the Women's Health Initiative.[44, 55]

Outcome misclassification is unlikely in this study as fracture reports were adjudicated without knowledge of exposure status. This study included a thorough assessment of nonvertebral fracture risk after surgical menopause, however, vertebral (spine) fractures were not examined for the following reasons. First, the majority of vertebral fractures are not clinically recognized and there is still some controversy regarding the best radiographic method for determining the presence of a vertebral

fracture. Second, the evaluation of the effect of surgical menopause on the risk of vertebral fracture requires a different method of statistical analysis than that chosen for clinically recognized nonvertebral fractures.

Because women could not enroll in SOF unless they were at least 65 years of age, there is the potential for survivor bias. In addition, the women in this cohort are volunteers, whose health may differ from those who do not volunteer and therefore the participants may not be truly representative of the communities from which they were identified. It is important to note, however, that women who had surgical menopause did not differ significantly at baseline from women who had natural menopause in the primary outcome measure – fracture. They also did not differ in many other important risk factors including measures of physical ability, falls, and maternal history of hip fracture. Covariates that differed significantly at baseline between the surgical and natural menopause groups, such as age at baseline, age at menopause, weight, and bone mineral density were evaluated in multivariable models for potential confounding effects.

As this is a study of primarily Caucasian women, it is not generalizable to women of other races. However, Caucasian women have a higher risk of fracture than other races or ethnicities and they account for the greatest amount of health resource utilization related to osteoporotic fracture.

Implications for Counseling of Women Undergoing Hysterectomy

Many studies in the U.S. and Europe have documented changes in women's and physicians' attitudes to estrogen therapy and have demonstrated a decline in hormone therapy use and prescribing since the results of the Women's Health Initiative were published.[32-35] However, the Women's Health Initiative enrolled older postmenopausal

women and the results of this study may not apply to younger women contemplating premenopausal oophorectomies. Nevertheless, the results of the WHI have complicated the counseling process physicians enter with their premenopausal patients prior to performing a hysterectomy. It is possible that fewer women in the coming years will choose to use oral estrogen therapy after surgical menopause. One reassuring finding from this prospective analysis is that hip fracture risk is not increased in women who decline oral estrogen therapy. This is important clinically as hip fractures account for the highest morbidity and mortality of all osteoporotic fractures.

The clinical significance of the modestly increased risk of any nontraumatic, nonvertebral fracture associated with surgical menopause among never users of oral estrogen in this cohort is unclear given the small magnitude of the risk estimate. For example, in this cohort, the age-standardized incidence rate of nonvertebral fracture among the natural menopause group was 4995 fractures per 100,000 person-years, or 5 per 100 person-years. A 1.2 fold increase, as demonstrated in this study, would result in an incidence rate of 6 nonvertebral fractures per 100 person-years or 1 additional fracture per 100 person-years of observation, a difference that may be difficult for a patient to comprehend when assessing her own risk of fracture attributable to surgical menopause. In addition, this small increased risk would only apply in the scenario in which the patient chooses not to use oral estrogen. Patients must weigh this risk against the risk of ovarian cancer which, over a lifetime, is approximately 1.7%. It is also important to note that, while there is no good screening test for ovarian cancer, there is for osteoporosis. Moreover, there is effective treatment for osteoporosis and the prevention of osteoporotic fracture.[8, 37]

This study is the first to prospectively assess the risk of fracture associated with surgical menopause. It is unlikely that this risk will ever be assessed in a randomized clinical trial for ethical reasons; therefore, the best risk estimates available to physicians and patients will be those provided by this analysis. Our risk estimates are similar to those reported by a good-quality, retrospective cohort study,[31] giving credence to their use in the clinical setting. One unanswered question that remains is whether or not the risk of vertebral fracture is increased after surgical menopause. Vertebral fracture risk was not evaluated in this study but could be addressed in future analyses.

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FIGURES

Figure 1. Distribution of age at baseline by menopause type

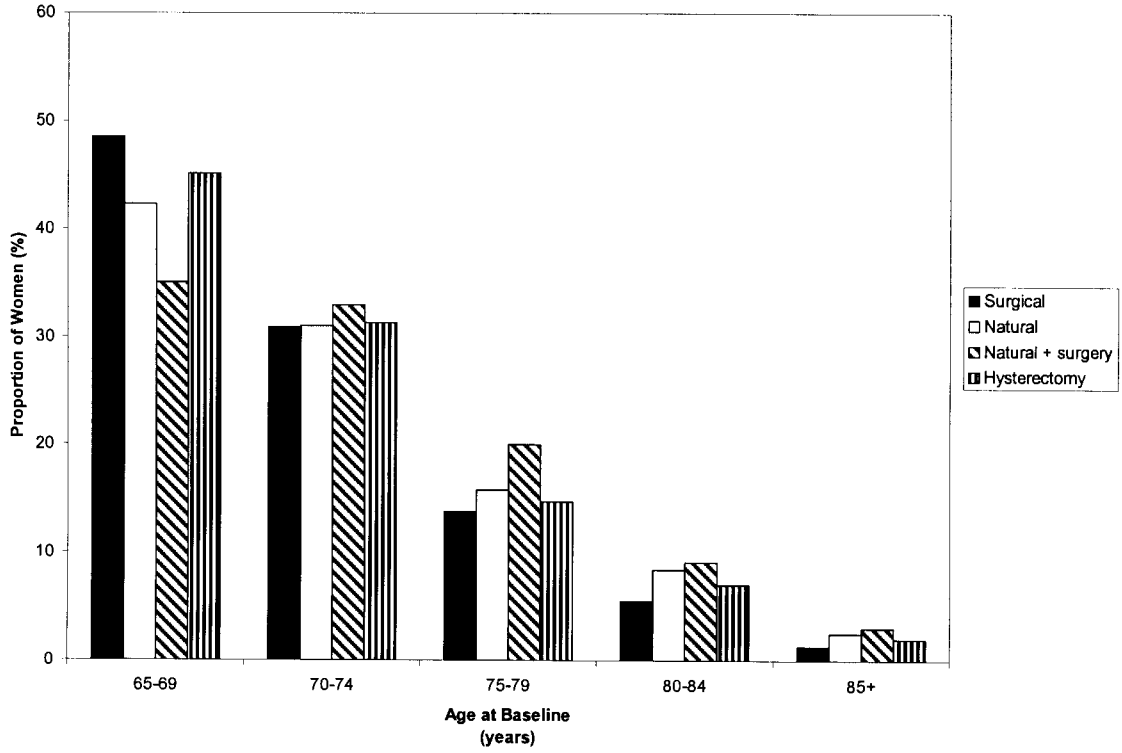


Figure 2. Distribution of age at menopause by menopause type

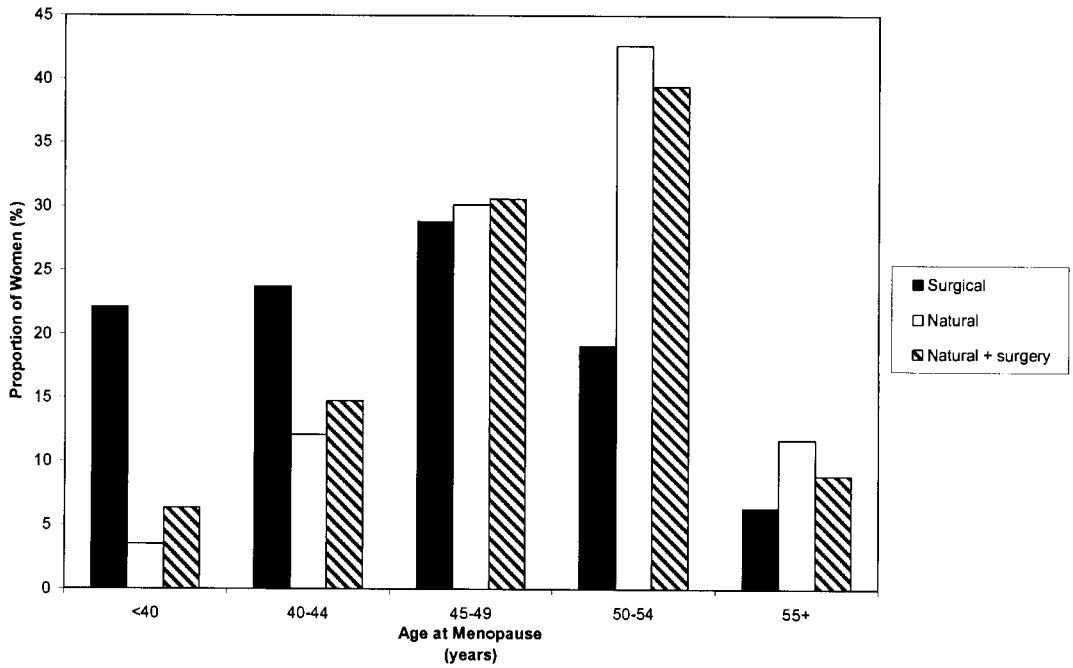
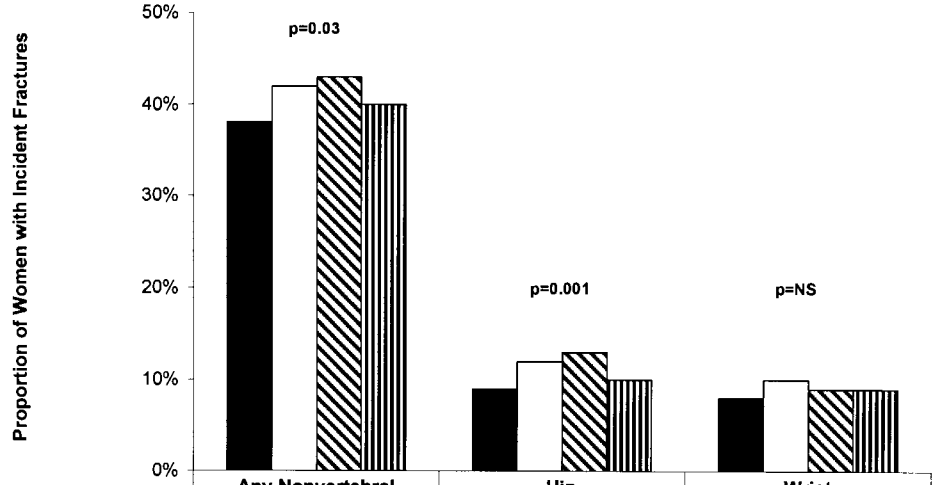


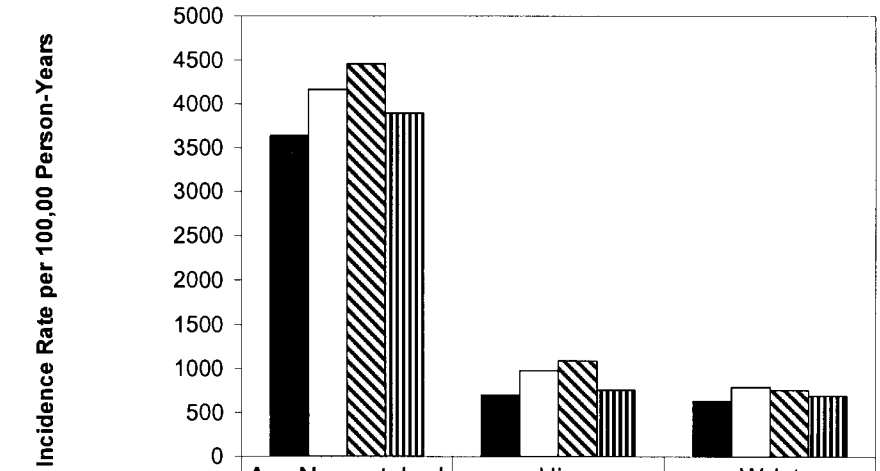
Figure 3. Proportion of incident fractures by menopause type*



	Any Nonvertebral	Hip	Wrist
■ Surgical	38%	9%	8%
□ Natural	42%	12%	10%
▨ Natural + Surgery	43%	13%	9%
▥ Hysterectomy	40%	10%	9%

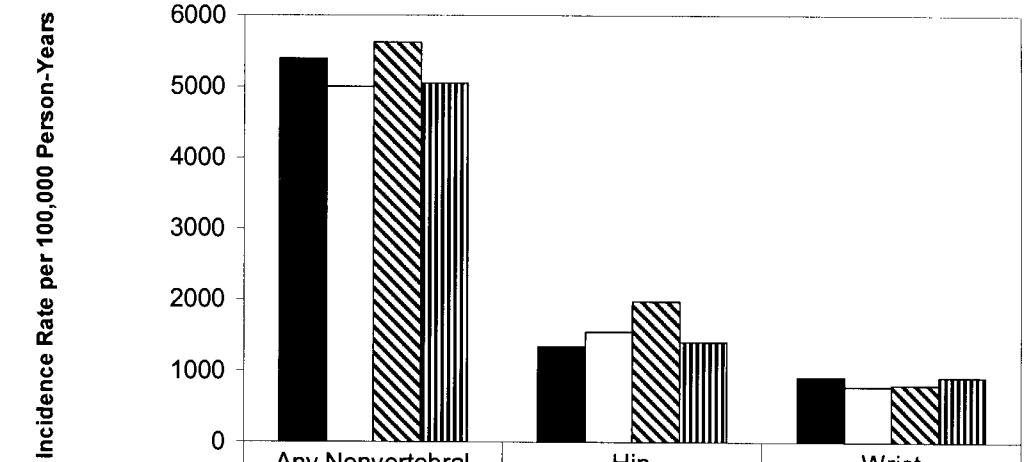
*p-values derived from chi-square test for comparison across all menopause types for each group of fractures

Figure 4. Unadjusted incidence rates of fracture



	Any Nonvertebral	Hip	Wrist
■ Surgical	3637	705	639
□ Natural	4165	983	793
▨ Natural + Surgery	4460	1095	759
▥ Hysterectomy	3891	761	693

Figure 5. Age-standardized incidence rates of fracture



	Any Nonvertebral	Hip	Wrist
■ Surgical	5394	1343	923
□ Natural	4995	1553	789
▨ Natural + Surgery	5625	1981	812
▥ Hysterectomy	5047	1415	916

TABLES

Table 1. Baseline characteristics by menopause type

Characteristics	Menopause Type mean (SD) or n (%) Surgical	Natural	Natural + surgery	Hysterectomy	Surgical vs. Natural	Natural vs. Natural + surgery	Surgical vs. Hysterectomy	Overall
	N=1157	N=5459	N=1288	N=1679	p	p	p	p
Demographic Characteristics								
Age (baseline, years)	70.8 (4.9)	71.7 (5.4)	72.5 (5.5)	71.3 (5.2)	<0.001	<0.001	0.009	<0.001
Age group (baseline, years)					0.001	0.001	0.155	0.001
65-69	561 (48.5%)	2311 (42.3%)	451 (35.0%)	757 (45.1%)				
70-74	358 (30.9%)	1692 (31.0%)	424 (32.9%)	525 (31.3%)				
75-79	160 (13.8%)	861 (15.8%)	257 (20.0%)	246 (14.7%)				
80-84	63 (5.5%)	457 (8.4%)	117 (9.1%)	117 (7.0%)				
85+	15 (1.3%)	138 (2.5%)	39 (3.0%)	34 (2.0%)				
Age at menopause (years)	44.3 (7.4)	48.9 (4.9)	47.9 (5.5)	N/A	<0.001	<0.001	N/A	<0.001
Age group (menopause, years)					0.001	0.001	N/A	0.001
<40	256 (22.1%)	187 (3.5%)	81 (6.3%)	N/A				
40-44	274 (23.7%)	651 (12.1%)	191 (14.8%)	N/A				
45-49	333 (28.8%)	1617 (30.1%)	394 (30.6%)	N/A				
50-54	221 (19.1%)	2292 (42.6%)	507 (39.4%)	N/A				
≥55	73 (6.3%)	631 (11.7%)	115 (8.9%)	N/A				
Education (years)	12.2 (2.7)	12.7 (2.8)	12.5 (2.8)	12.3 (2.8)	<0.001	0.039	0.475	<0.001
Reproductive history								
Ever pregnant	960 (83%)	4509 (83%)	1099 (85%)	1467 (87%)	0.690	0.020	0.001	0.001
Had ≥1 live birth	912 (79%)	4308 (80%)	1046 (81%)	1433 (85%)	0.262	0.514	0.001	0.001
Parity	2.4 (1.4)	2.7 (1.6)	2.6 (1.6)	2.8 (1.7)	<0.001	0.098	<0.001	<0.001
Ever breastfed	624 (54%)	3076 (56%)	771 (60%)	1041 (62%)	0.143	0.023	0.001	0.001
Number of children breastfed	1.1 (1.3)	1.3 (1.6)	1.4 (1.6)	1.4 (1.6)	<0.001	0.242	<0.001	<0.001

(continued)

Table 1. Baseline characteristics by menopause type

Characteristics	Menopause Type mean (SD) or n (%) Surgical	Natural	Natural + surgery	Hysterectomy	Surgical vs. Natural	Natural vs. Natural + surgery	Surgical vs. Hysterectomy	Overall
	N=1157	N=5459	N=1288	N=1679	p	p	p	p
Dietary/Lifestyle Factors								
Calcium intake (mg/week)								
supplement	2942 (4131.7)	2640 (4243.1)	2778 (4017.2)	2862 (4362.2)	0.029	0.298	0.624	0.072
food	4926 (2908.8)	4990 (2941.7)	5017 (2944.4)	5081 (3170.9)	0.506	0.773	0.174	0.563
Caffeine intake (g/day)	0.16 (0.14)	0.17 (0.14)	0.16 (0.14)	0.15 (0.14)	0.063	0.171	0.454	0.008
Smoking					0.426	0.144	0.006	0.016
Current	130 (11%)	575 (11%)	116 (9%)	136 (8%)				
Past	357 (31%)	1604 (29%)	364 (28%)	492 (29%)				
Never	669 (58%)	3260 (60%)	801 (63%)	1048 (63%)				
Pack-years	12.5 (21.8)	10.7 (19.9)	10.1 (19.7)	9.5 (18.7)	0.007	0.341	<0.001	0.001
Alcohol intake in last month (number of drinks)					0.051	0.003	0.949	0.003
Heavy (>14/week)	46 (4%)	225 (4%)	45 (3%)	63 (4%)				
Light-mod (1-14/week)	562 (49%)	2857 (52%)	615 (48%)	814 (48%)				
None	549 (47%)	2377 (44%)	628 (49%)	802 (48%)				
Drinks/week past 30 days	1.7 (3.7)	1.9 (3.9)	1.6 (3.5)	1.6 (3.6)	0.068	0.009	0.816	0.008
Walks for exercise	558 (48%)	2758 (51%)	654 (51%)	835 (50)	0.153	0.879	0.431	0.501
≤ 4hrs on feet/day	111 (10%)	523 (10%)	135 (10%)	166 (10)	0.999	0.331	0.784	0.796

(continued)

Table 1. Baseline characteristics by menopause type

Characteristics	Menopause Type mean (SD) or n (%) Surgical	Natural	Natural + surgery	Hysterectomy	Surgical vs. Natural	Natural vs. Natural + surgery	Surgical vs. Hysterectomy	Overall
	N=1157	N=5459	N=1288	N=1679	p	p	p	p
Medical History								
Self-reported health status					0.001	0.002	0.244	0.001
Excellent/Good	931 (81%)	4646 (85%)	1045 (81%)	1361 (81%)				
Fair	211 (18%)	740 (14%)	220 (17%)	284 (17%)				
Very poor/Poor	15 (1%)	73 (1%)	23 (2%)	34 (2%)				
Maternal history of hip fracture	115 (10%)	586 (11%)	133 (10%)	154 (9%)	0.425	0.669	0.493	0.310
History of falls (in last 12 months)	347 (30%)	1579 (29%)	418 (33%)	518 (31%)	0.461	0.012	0.649	0.066
Any bone fracture after age 50	409 (35%)	2047 (38%)	471 (37%)	598 (36%)	0.151	0.565	0.805	0.361
Hip fracture after age 50	21 (2%)	112 (2%)	25 (2%)	24 (1%)	0.601	0.797	0.428	0.446
Hyperthyroidism (ever)	113 (10%)	474 (9%)	128 (10%)	161 (10)	0.239	0.155	0.875	0.346
Diabetes					0.051	0.064	0.996	0.044
Yes, no insulin	77 (7%)	285 (5%)	86 (7%)	112 (7%)				
Yes, uses insulin	17 (1%)	54 (1%)	17 (1%)	24 (1%)				

(continued)

Table 1. Baseline characteristics by menopause type

Characteristics	Menopause Type mean (SD) or n (%) Surgical	Natural	Natural + surgery	Hysterectomy	Surgical vs. Natural	Natural vs. Natural + surgery	Surgical vs. Hysterectomy	Overall
	N=1157	N=5459	N=1288	N=1679	p	p	p	p
Medications								
Estrogen use, oral (baseline)					0.001	0.001	0.001	0.001
Current	345 (30%)	351 (7%)	259 (21%)	362 (22%)				
Past	366 (32%)	1357 (25%)	371 (29%)	496 (30%)				
Never	433 (38%)	3683 (68%)	634 (50%)	793 (48%)				
Duration of use (years)	7.1 (9.8)	1.8 (4.5)	4.7 (7.8)	5.8 (9.7)	<0.001	<0.001	<0.001	<0.001
Estrogen use, patch (baseline)								
Current	1	7	2	1				
Ever	2	9	2	1				
Oral contraceptive use					0.179	0.344	0.169	0.010
Ever	39 (3%)	231 (4%)	47 (4%)	42 (3%)				
Duration of use (years)	4.3 (5.3)	4.8 (4.9)	4.9 (5.1)	3.5 (3.8)	0.611	0.862	0.438	0.438
Thiazide use					0.001	0.001	0.273	0.001
Current	348 (30%)	1289 (24%)	370 (29%)	471 (28)				
Past	114 (10%)	476 (9%)	108 (8%)	153 (9)				
Never	679 (60%)	3638 (67%)	798 (63%)	1041 (63)				
Duration of use (years)	10.0 (7.9)	9.8 (8.6)	10.1 (8.9)	10.6 (9.3)	0.616	0.551	0.308	0.301
Steroid use					0.909	0.755	0.627	0.887
Current	21 (2%)	111 (2%)	22 (2%)	34 (2)				
Past	108 (10%)	515 (10%)	121 (9%)	173 (11)				
Never	998 (88%)	4750 (88%)	1123 (89%)	1427 (87)				
Benzodiazepine use in last 12 months (long-acting)	130 (11%)	455 (8%)	110 (9%)	180 (11)	0.001	0.826	0.640	0.001
Anticonvulsant use								
Current (still)	13	56	17	22	0.600	0.980	0.465	0.911
Ever	22 (2%)	86 (2%)	26 (2%)	32 (2%)	0.424	0.258	0.994	0.588

(continued)

Table 2. Cohort characteristics by history of oral estrogen use at baseline*

Characteristics	Estrogen use status at baseline* mean (SD), n (%) Never users of oral estrogen	Ever users of oral estrogen	Never vs. Ever Users
	N=5616	N=3952	p
Demographic Characteristics			
Age (baseline, years)	72.4 (5.7)	70.6 (4.6)	<0.001
Age group (baseline, years)			0.001
65-69	2116 (37.7%)	1950 (49.3%)	
70-74	1716 (30.6%)	1286 (32.5%)	
75-79	1016 (18.1%)	500 (12.7%)	
80-84	583 (10.4%)	176 (4.5%)	
85+	185 (3.3%)	40 (1.0%)	
Age at menopause (years)	47.8 (5.7)	48.1 (5.8)	0.011
Age group (menopause, years)			0.253
<40	346 (7.3%)	208 (6.8%)	
40-44	711 (14.9%)	415 (13.5%)	
45-49	1421 (29.9%)	905 (29.6%)	
50-54	1798 (37.8%)	1200 (39.2%)	
≥55	481 (10.1%)	335 (10.9%)	
Education (years)	12.3 (2.9)	12.9 (2.7)	<0.001
Reproductive history			
Ever pregnant	4639 (82.7%)	3374 (85.4%)	0.001
Had ≥1 live birth	4514 (80.4%)	3242 (82.1%)	0.042
Parity	2.7 (1.6)	2.6 (1.6)	0.055
Ever breastfed	3204 (57.1%)	2290 (58.0%)	0.390
Number of children breastfed	1.3 (1.6)	1.3 (1.5)	0.548
Menopause type			0.001
Surgical	433 (7.8%)	711 (18.2%)	
Natural	3683 (66.4%)	1708 (43.7%)	
Natural + Surgery	634 (11.4%)	630 (16.1%)	
Hysterectomy	793 (14.3%)	858 (22.0%)	
Dietary/Lifestyle Factors			
Calcium intake (mg/week)			
supplement	2217 (3977)	3494 (4465)	<0.001
food	4887 (2993)	5152 (2947)	<0.001
Caffeine intake (g/day)	0.17 (0.14)	0.16 (0.14)	0.010
Smoking			0.001
Current	535 (9.6%)	418 (10.6%)	
Past	1526 (27.3%)	1296(32.9%)	
Never	3534 (63.1%)	2229 (56.5%)	
Pack-years	10.1 (19.8)	11.5 (20.2)	0.001
Alcohol intake in last month (number			0.001
Heavy (>14/week)	201 (3.6%)	176 (4.5%)	
Light-mod (1-14/week)	2613 (46.5%)	2230 (56.4%)	
None	2802 (49.9%)	1546 (39.1%)	
Drinks/week past 30 days	1.6 (3.7)	2.0 (3.8)	<0.001
Walks for exercise	2617 (46.6%)	2180 (55.2%)	0.001
≤ 4hrs on feet/day	564 (10.1%)	372 (9.4%)	0.311

(continued)

Table 2. Cohort characteristics by history of oral estrogen use at baseline*

Characteristics	Estrogen use status at baseline* mean (SD), n (%)		
	Never users of oral estrogen	Ever users of oral estrogen	Never vs. Ever Users
	N=5616	N=3952	p
Medical History			
Self-reported health status			0.116
Excellent/Good	4637 (82.6%)	3326 (84.2%)	
Fair	887 (15.8%)	570 (14.4%)	
Very poor/Poor	92 (1.6%)	56 (1.4%)	
Maternal history of hip fracture	516 (9.2%)	458 (11.6%)	0.001
History of falls (in last 12 months)	1644 (29.3%)	1230 (31.2%)	0.048
Any bone fracture after age 50	2148 (38.4%)	1386 (35.3%)	0.002
Hip fracture after age 50	115 (2.1%)	69 (1.8%)	0.295
Hyperthyroidism (ever)	479 (8.5%)	400 (10.1%)	0.008
Diabetes			0.001
Yes, no insulin	403 (7.2%)	155 (3.9%)	
Yes, uses insulin	72 (1.3%)	40 (1.0%)	
Medications			
Estrogen use, patch (baseline)			
Current	4	7	
Ever	4	10	
Oral contraceptive use			0.001
Ever	142 (2.5%)	210 (5.3%)	
Duration of use (years)	4.3 (5.3)	4.7 (4.5)	0.512
Thiazide use			0.061
Current	1490 (26.7%)	992 (25.4%)	
Past	467 (8.4%)	376 (9.6%)	
Never	3615 (64.9%)	2533 (64.9%)	
Duration of use (years)	9.9 (8.9)	10.1 (8.5)	0.499
Steroid use			0.001
Current	109 (2.0%)	81 (2.1%)	
Past	430 (7.7%)	489 (12.7%)	
Never	5010 (90.3%)	3283 (85.2%)	
Benzodiazepine use last 12 months (long-acting)	449 (8.0%)	427 (10.9%)	0.001
Anticonvulsant use			
Current (still)	63 (1.1%)	46 (1.2%)	0.537
Ever	92 (1.6%)	72 (1.8%)	0.497
Physical measures			
Uses arms to stand from chair	267 (4.8%)	129 (3.3%)	0.001
Height in cm (baseline)	158.6 (6.0)	159.7 (6.0)	<0.001
Height in cm (age 25)	162.4 (5.9)	162.8 (6.0)	0.001
BMI (kg/m^2)	26.8 (4.8)	26.1 (4.4)	<0.001
Weight baseline (kg)	67.5 (12.8)	66.5 (12.0)	<0.001
Weight gain since age 25 (kg)	11.1 (11.5)	10.5 (10.5)	0.007
Resting pulse rate	70 (10.2)	68 (9.9)	<0.001
Depth perception†	2.4 (2.8)	2.1 (2.4)	<0.001
Contrast sensitivity‡	69.5 (34.7)	78.9 (36.1)	<0.001
Total hip BMD, visit 2 (g/cm^2)	0.743 (0.129)	0.776 (0.132)	<0.001
BMD distal (g/cm^2)	0.351 (0.083)	0.377 (0.086)	<0.001
BMD os calcis (g/cm^2)	0.393 (0.095)	0.419 (0.093)	<0.001

*Baseline estrogen use data were missing for 136 women.

†Standard deviation of 4 Howard-Dohlman Optical Distance scores

‡Overall contrast sensitivity score for low spatial freqency (both eyes)

Table 3. Baseline characteristics of women with no history of oral estrogen use

Characteristics	Menopause Type mean (SD), n (%) Surgical	Natural	Surgical vs. Natural
	N=433	N=3683	p
Demographic Characteristics			
Age (baseline, years)	72.2 (5.6)	72.3 (5.7)	0.568
Age group (baseline, years)			0.608
65-69	166 (38.3%)	1433 (38.9%)	
70-74	144 (33.3%)	1104 (30.0%)	
75-79	66 (15.2%)	646 (17.5%)	
80-84	44 (10.2%)	378 (10.3%)	
85+	13 (3.0%)	122 (3.3%)	
Age at menopause (years)	42.5 (7.6)	48.6 (4.9)	<0.001
Age group (menopause, years)			0.001
<40	131 (30.2%)	143 (3.9%)	
40-44	120 (27.7%)	470 (12.9%)	
45-49	102 (23.6%)	1110 (30.6%)	
50-54	61 (14.1%)	1494 (41.2%)	
≥55	19 (4.4%)	414 (11.4%)	
Education (years)	11.8 (2.9)	12.5 (2.8)	<0.001
Reproductive history			
Ever pregnant	347 (80%)	3018 (82%)	0.396
Had ≥1 live birth	334 (77%)	2951 (80%)	0.162
Parity	2.5 (1.5)	2.7 (1.6)	0.006
Ever breastfed	221 (51%)	2077 (56%)	0.036
Number of children breastfed	1.0 (1.3)	1.3 (1.6)	<0.001
Dietary/Lifestyle Factors			
Calcium intake (mg/week)			
supplement	2383 (4253)	2205 (4049)	0.397
food	4790 (3093)	4903 (2952)	0.454
Caffeine intake (g/day)	0.17 (0.14)	0.17 (0.14)	0.986
Smoking			0.305
Current	39 (9%)	364 (10%)	
Past	131 (30%)	987(27%)	
Never	262 (61%)	2319 (63%)	
Pack-years	12.2 (22.8)	9.9 (19.3)	0.049
Alcohol intake in last month (number of drinks)			0.002
Heavy (>14/week)	15 (3.5%)	134 (3.6%)	
Light-mod (1-14/week)	174 (40.2%)	1805 (49.0%)	
None	244 (56.3%)	1744 (47.4%)	
Drinks/week past 30 days	1.4 (3.7)	1.7 (3.8)	0.110
Walks for exercise	183 (42%)	1748 (47%)	0.040
≤ 4hrs on feet/day	38 (9%)	366 (10%)	0.438

(continued)

Table 3. Baseline characteristics of women with no history of oral estrogen use

Characteristics	Menopause Type mean (SD), n (%) Surgical	Natural	Surgical vs. Natural
	N=433	N=3683	p
Medical History			
Self-reported health status			0.018
Excellent/Good	344 (79%)	3119 (85%)	
Fair	81 (19%)	510 (14%)	
Very poor/Poor	8 (2%)	54 (1%)	
Maternal history of hip fracture	45 (10%)	348 (9%)	0.527
History of falls (in last 12 months)	119 (28%)	1052 (29%)	0.645
Any bone fracture after age 50	174 (40%)	1392 (38%)	0.374
Hip fracture after age 50	5 (1%)	83 (2%)	0.160
Hyperthyroidism (ever)	38 (9%)	305 (8%)	0.725
Diabetes			0.163
Yes, no insulin	36 (8%)	228 (6%)	
Yes, uses insulin	3 (1%)	43 (1%)	
Medications			
Estrogen use, patch (baseline)			
Current	0	3	
Ever	0	3	
Oral contraceptive use			0.001
Ever	3 (0.7%)	117 (3.2%)	
Duration of use (years)	0.3 (0.6)	4.4 (5.1)	<0.001
Thiazide use			0.007
Current	134 (31.3%)	899 (24.6%)	
Past	38 (8.9%)	308 (8.4%)	
Never	256 (59.8%)	2450 (67.0%)	
Duration of use (years)	9.7 (8.2)	9.8 (8.8)	0.916
Steroid use			0.149
Current	5 (1.2%)	76 (2.1%)	
Past	25 (5.9%)	286 (7.8%)	
Never	394 (92.9%)	3282 (90.1%)	
Benzodiazepine use last 12 months (long-acting)	37 (8.6%)	279 (7.6%)	0.457
Anticonvulsant use			
Current (still)	4 (1.4%)	34 (0.9%)	1.000
Ever	6 (1.4%)	51 (1.4%)	0.999
Physical measures			
Uses arms to stand from chair	23 (5%)	155 (4%)	0.286
Height in cm (baseline)	158.4 (6.3)	158.7 (6.0)	0.355
Height in cm (age 25)	162.2 (6.3)	162.5 (5.9)	0.249
BMI (kg/m^2)	27.4 (5.4)	26.6 (4.7)	0.004
Weight baseline (kg)	68.9 (14.5)	67.1 (12.6)	0.014
Weight gain since age 25 (kg)	11.8 (12.8)	10.8 (11.5)	0.127
Resting pulse rate	70 (9.7)	70 (10.2)	0.935
Depth perception†	2.1 (2.2)	2.4 (2.9)	0.003
Contrast sensitivity‡	71.3 (35.0)	70 (34.8)	0.460
Total hip BMD, visit 2 (g/cm^2)	0.742 (0.135)	0.742 (0.127)	0.967
BMD distal (g/cm^2)	0.345 (0.085)	0.352 (0.082)	0.110
BMD os calcis (g/cm^2)	0.385 (0.100)	0.394 (0.094)	0.067

†Standard deviation of 4 Howard-Dohlman Optical Distance scores

‡Overall contrast sensitivity score for low spatial freqency (both eyes)

Table 4. Estimated relative risks of fracture by menopause type compared to natural menopause

	Menopause Type Hazard Ratio (95% CI)					
Fracture Type	**Surgical**	p	**Natural + surgery**	p	**Hysterectomy**	p
Hip						
Unadjusted	0.72 (0.58-0.88)	0.002	1.13 (0.95-1.34)	0.171	0.77 (0.65-0.92)	0.003
Age adjusted	0.79 (0.64-0.98)	0.028	1.06 (0.90-1.26)	0.498	0.81 (0.68-0.96)	0.014
Wrist						
Unadjusted	0.81 (0.65-1.01)	0.056	0.96 (0.78-1.17)	0.668	0.87 (0.73-1.05)	0.151
Age adjusted	0.82 (0.66-1.03)	0.085	0.94 (0.77-1.15)	0.576	0.88 (0.74-1.06)	0.188
Any nonvertebral						
Unadjusted	0.87 (0.79-0.97)	0.012	1.07 (0.97-1.18)	0.155	0.93 (0.85-1.02)	0.135
Age adjusted	0.91 (0.82-1.02)	0.096	1.05 (0.95-1.15)	0.358	0.95 (0.87-1.04)	0.308

Table 5. Estimated relative risks of fracture compared to natural menopause in never users of oral estrogen

	Menopause Type Hazard Ratio (95% CI)					
Fracture Type	**Surgical**	p	**Natural + surgery**	p	**Hysterectomy**	p
Hip						
Unadjusted	0.91 (0.66-1.24)	0.543	1.16 (0.91-1.48)	0.232	0.86 (0.67-1.09)	0.210
Age + Weight	0.92 (0.67-1.26)	0.588	1.07 (0.84-1.37)	0.593	0.87 (0.68-1.10)	0.247
Multivariable[1]	0.87 (0.63-1.21)	0.414	1.02 (0.79-1.33)	0.862	0.81 (0.63-1.05)	0.117
Multivariable+Hip BMD[2]	0.89 (0.61-1.28)	0.511	1.10 (0.83-1.46)	0.504	0.67 (0.49-0.91)	0.011
Wrist						
Unadjusted	1.16 (0.84-1.59)	0.361	0.98 (0.73-1.31)	0.894	1.21 (0.95-1.53)	0.117
Age + Weight	1.17 (0.85-1.61)	0.327	0.98 (0.73-1.31)	0.877	1.22 (0.96-1.54)	0.103
Multivariable[3]	1.19 (0.87-1.64)	0.278	0.98 (0.73-1.32)	0.906	1.24 (0.98-1.57)	0.075
Multivariable+Hip BMD[4]	1.18 (0.83-1.66)	0.362	0.98 (0.72-1.35)	0.914	1.26 (0.98-1.64)	0.076
Any Nontraumatic, Non-vertebral Fracture						
Unadjusted	1.17 (0.99-1.37)	0.060	1.12 (0.98-1.28)	0.105	1.09 (0.96-1.23)	0.184
Age + Weight	1.19 (1.01-1.40)	0.034	1.09 (0.95-1.25)	0.213	1.10 (0.97-1.24)	0.150
Multivariable[5]	1.23 (1.04-1.45)	0.015	1.11 (0.97-1.28)	0.143	1.09 (0.96-1.24)	0.181
Multivariable+Hip BMD[6]	1.23 (1.03-1.47)	0.025	1.07 (0.92-1.24)	0.390	1.05 (0.91-1.21)	0.528

[1] age, weight, depth perception, personal history of fracture, pulse, number breastfed, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, self reported health status

[2] age, weight, depth perception, personal history of fracture, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, total hip BMD

[3] age, weight,personal history of fracture, height at age 25

[4] age, weight, personal history of fracture, total hip BMD

[5] age, weight, contrast sensitivity, calcium intake (supplement), benzodiazepine use, ≤4 hours on feet/day, height at age 25, resting pulse, diabetes history, personal history of fracture, smoking status

[6] age, weight, contrast sensitivity, calcium intake (supplement), height at age 25, ≤4 hours on feet/day, resting pulse, diabetes history, personal history of fracture, total hip BMD

Table 6. Estimated relative risks of fracture compared to natural menopause in current users of oral estrogen

	Menopause type Hazard Ratio (95% CI)					
Fracture Type	**Surgical**	p	**Natural + surgery**	p	**Hysterectomy**	p
Hip						
Unadjusted	0.39 (0.17-0.87)	0.021	1.14 (0.60-2.18)	0.688	0.89 (0.48-1.65)	0.708
Age + Weight	0.39 (0.18-0.88)	0.023	0.92 (0.48-1.78)	0.812	0.83 (0.45-1.55)	0.560
Multivariable[1]	0.38 (0.16-0.90)	0.029	1.01 (0.51-2.00)	0.986	1.01 (0.53-1.93)	0.981
Multivariable+Hip BMD[2]	0.48 (0.19-1.21)	0.120	1.28 (0.62-2.65)	0.509	1.38 (0.68-2.80)	0.380
Wrist						
Unadjusted	0.43 (0.17-1.06)	0.067	1.27 (0.61-2.63)	0.522	0.66 (0.30-1.42)	0.287
Age + Weight	0.42 (0.17-1.04)	0.060	1.15 (0.55-2.42)	0.710	0.63 (0.29-1.38)	0.248
Multivariable[3]	0.44 (0.18-1.11)	0.081	1.24 (0.59-2.62)	0.578	0.69 (0.32-1.52)	0.362
Multivariable+Hip BMD[4]	0.38 (0.13-1.08)	0.069	1.30 (0.60-2.84)	0.510	0.64 (0.27-1.54)	0.319
Any Nontraumatic, Non-vertebral Fracture						
Unadjusted	0.60 (0.43-0.84)	0.003	1.03 (0.75-1.41)	0.879	0.72 (0.53-0.98)	0.039
Age + Weight	0.63 (0.45-0.88)	0.006	1.01 (0.73-1.39)	0.971	0.72 (0.53-0.99)	0.041
Multivariable[5]	0.72 (0.51-1.01)	0.057	1.10 (0.78-1.54)	0.594	0.87 (0.63-1.20)	0.397
Multivariable+Hip BMD[6]	0.73 (0.50-1.05)	0.091	1.31 (0.91-1.87)	0.146	0.95 (0.67-1.36)	0.796

[1] age, weight, depth perception, personal history of fracture, pulse, number breastfed, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, self reported health status

[2] age, weight, depth perception, personal history of fracture, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, total hip BMD

[3] age, weight,personal history of fracture, height at age 25

[4] age, weight, personal history of fracture, total hip BMD

[5] age, weight, contrast sensitivity, calcium intake (supplement), benzodiazepine use, ≤4 hours on feet/day, height at age 25, resting pulse, diabetes history, personal history of fracture, smoking status

[6] age, weight, contrast sensitivity, calcium intake (supplement), height at age 25, ≤4 hours on feet/day, resting pulse, diabetes history, personal history of fracture, total hip BMD

Table 7. Estimated relative risks of fracture by baseline oral estrogen use compared to natural menopause

Multivariable Models with Estrogen Interaction Terms
Hazard Ratio (95% CI)

Fracture Type	Surgical	p	Natural + surgery	p	Hysterectomy	p
Hip[1]						
Current	0.39 (0.21-0.73)	0.003	1.12 (0.71-1.78)	0.628	0.78 (0.48-1.26)	0.313
Past	1.01 (0.71-1.44)	0.956	1.15 (0.83-1.60)	0.403	0.81 (0.58-1.12)	0.201
Never	0.90 (0.65-1.23)	0.500	1.05 (0.82-1.35)	0.709	0.82 (0.64-1.05)	0.115
Wrist[3]						
Current	0.58 (0.30-1.13)	0.108	1.30 (0.73-2.31)	0.369	0.74 (0.40-1.35)	0.320
Past	0.94 (0.65-1.37)	0.760	1.01 (0.70-1.45)	0.975	0.75 (0.52-1.08)	0.123
Never	1.16 (0.85-1.58)	0.361	0.98 (0.73-1.30)	0.866	1.20 (0.95-1.52)	0.124
Any nonvertebral[5]						
Current	0.76 (0.58-1.00)	0.046	1.18 (0.90-1.53)	0.225	0.83 (0.64-1.08)	0.163
Past	0.91 (0.75-1.11)	0.362	1.03 (0.85-1.24)	0.783	0.96 (0.81-1.15)	0.649
Never	1.21 (1.03-1.42)	0.019	1.09 (0.95-1.24)	0.237	1.11 (0.98-1.25)	0.106

Multivariable Models with Estrogen Interaction Terms + total hip BMD*
Hazard Ratio (95% CI)

Fracture Type	Surgical	p	Natural + surgery	p	Hysterectomy	p
Hip[2]						
Current	0.36 (0.18-0.73)	0.005	1.10 (0.67-1.79)	0.714	0.91 (0.55-1.51)	0.711
Past	1.00 (0.68-1.47)	0.985	1.08 (0.75-1.56)	0.672	0.78 (0.55-1.11)	0.164
Never	0.89 (0.62-1.26)	0.497	1.12 (0.85-1.47)	0.433	0.67 (0.49-0.90)	0.009
Wrist[4]						
Current	0.46 (0.21-0.99)	0.047	1.38 (0.76-2.49)	0.294	0.72 (0.38-1.38)	0.324
Past	0.97 (0.65-1.47)	0.912	1.08 (0.73-1.59)	0.707	0.74 (0.49-1.10)	0.138
Never	1.16 (0.82-1.62)	0.403	0.98 (0.72-1.33)	0.874	1.21 (0.94-1.56)	0.138
Any nonvertebral[6]						
Current	0.76 (0.57-1.02)	0.065	1.32 (1.00-1.74)	0.053	0.92 (0.70-1.22)	0.571
Past	0.91 (0.74-1.13)	0.407	1.00 (0.81-1.22)	0.968	0.94 (0.78-1.13)	0.518
Never	1.21 (1.02-1.44)	0.031	1.05 (0.90-1.22)	0.533	1.07 (0.93-1.23)	0.331

[1] age, weight, depth perception, personal history of fracture, pulse, number breastfed, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, self reported health status

[2] age, weight, depth perception, personal history of fracture, calcium intake (supplement), pack-year smoking, maternal hip fracture, alcohol intake, total hip BMD

[3] age, weight,personal history of fracture, height at age 25

[4] age, weight, personal history of fracture, total hip BMD

[5] age, weight, contrast sensitivity, calcium intake (supplement), benzodiazepine use, ≤4 hours on feet/day, height at age 25, resting pulse, diabetes history, personal history of fracture, smoking status

[6] age, weight, contrast sensitivity, calcium intake (supplement), height at age 25, ≤4 hours on feet/day, resting pulse, diabetes history, personal history of fracture, total hip BMD