Surgical Menopause and Frailty Risk in Community-Dwelling Older Women: Study of Osteoporotic Fractures

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Abstract

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OBJECTIVES: To determine whether women with surgical menopause have a higher risk of frailty than naturally menopausal women.

DESIGN: Prospective cohort study with up to 18 years of follow-up.

SETTING: Four U.S clinical centers.

PARTICIPANTS: Community-dwelling white women aged 65 and older (mean 71.2 ± 5.2) enrolled in the Study of Osteoporotic Fractures (N=7,699).

MEASUREMENTS: Surgical menopause was based on participant self-report of having undergone bilateral oophorectomy before menopause. The outcome was incident frailty, classified as robust, prefrail, frail, or death at 4 follow-up interviews, conducted 6 to 18 years after baseline. Information on baseline serum total testosterone concentrations was available for 541 participants.

RESULTS: At baseline, 12.6% reported surgical meno-pause. Over the follow-up period, 22.0% died, and 10.1% were classified as frail, 39.7% as prefrail, and 28.3% as robust. Surgically menopausal women had significantly lower total serum testosterone levels (13.2 ± 7.8 ng/dL) than naturally menopausal women (21.7 ± 14.8 ng/dL) (p=0.000), although they were not at greater risk of frailty (adjusted odds ratio (aOR)=0.94, 95% confidence interval (CI)=0.72–1.22), prefrailty (aOR=0.96, 95% CI=0.80–1.10), or death (aOR=1.17, 95% CI=0.97–1.42) after adjusting for age, body mass index, and number of instrumental activity of daily living impairments. There was no evidence that oral estrogen use modified these associations.

CONCLUSION: In postmenopausal women, surgical menopause was not associated with greater risk for frailty than natural menopause, even in the absence of estrogen therapy. Future prospective studies are needed to investigate hormonal mechanisms involved in development of frailty in older postmenopausal women.

Frailty is becoming increasingly recognized as an important complex syndrome that disproportionately affects older women and increases the risk of disability and mortality.[1,2] Testosterone levels decline progressively with age in women, and very low serum testosterone is a risk factor for frailty.[3] Bilateral oophorectomy also results in a dramatic decline in production of testosterone.[4] Although surgical menopause (premenopausal bilateral oophorectomy) is associated with greater risk of physical dysfunction, osteoporosis, and death,[5] whether it increases the long-term risk of frailty in older women is unknown.

Biological and epidemiological studies suggest that surgical menopause may increase frailty risk by decreasing serum testosterone levels. Despite the decline in ovarian production of estrogen during natural menopause, the ovaries continue to produce testosterone.[6] By contrast, surgical menopause results in a significant reduction in serum testosterone levels as a result of bilateral oophorectomy. Approximately 1 in 9 women aged 35 to 45 have undergone hysterectomy, with 40% undergoing concurrent bilateral oophorectomy,[6,7] resulting in abrupt onset of menopause and decline in serum testosterone and estradiol levels. This abrupt menopause and resulting low testosterone may pre-dispose women to

frailty. Surgically menopausal women have poorer physical performance than naturally menopausal women, regardless of estrogen replacement therapy use.[6,7] Furthermore, low testosterone is associated with greater risk of frailty in older men[8] and with poor physical functioning in older women, and therefore may contribute to the onset of frailty in this population.[9]

Using data from the Study of Osteoporotic Fractures (SOF), we explored whether older women with a history of surgical menopause would be at higher risk of developing frailty than women with natural menopause and whether adjustment for use of estrogen therapy would attenuate this association.

METHODS

Study Sample

The sample comprised of participants enrolled in the SOF,[10] a prospective study of 9,704 community-dwelling white women aged 65 and older recruited between 1986 and 1988 from 4 U.S geographical areas: Baltimore, Maryland; Minneapolis, Minnesota; the Monongahela Valley, Pennsylvania; and Portland, Oregon. Women who had undergone bilateral hip replacement or were unable to walk without assistance were excluded. Interviews and comprehensive clinical assessments were conducted approximately every 2 years from 1986 to 2008 (baseline through Visit 9). At baseline, 9,314 women self-reported their age at menopause; whether they had had 1 or both of their ovaries removed; and if so, at what age. Of these women, 7,699 had data on frailty status assessed at the Year 6 (conducted between 1992 and 1994), Year 8 (1995–96), Year 10 (1997–98), or Year 18 (2004–05) examination; 1,012 died before the first frailty assessment at Year 6. Thus, the present analysis included 7,699 women with data on menopause history, frailty, and vital status over the follow-up period (Figure 1).

Type of Menopause

At the baseline interview, women reported whether they had ever had a hysterectomy or oophorectomy (unilateral or bilateral), their age at this procedure, and age at menopause (defined as age of last menstrual period for natural menopause and age when bilateral oophorectomy was performed for surgical menopause). Participants were classified as having surgical menopause if both ovaries had been removed before menopause. Participants who had at least 1 ovary after reported age at menopause were classified as having natural menopause (reference group). For secondary analyses, we defined women who had undergone natural menopause as those who reported an age at menopause without previous hysterectomy or oophorectomy to prevent potential misclassification bias from inaccurate reporting of the date and type of surgery.

Frailty

SOF lacked key components of frailty at baseline, but given that the inclusion criteria required women to be relatively healthy, we assumed that no participants were frail at baseline. Frailty status was categorized at the Year 6, 8, 10, and 18 follow-up examinations. Frailty was based on the SOF frailty index, which is a variation on the Cardiovascular Health

Study (CHS) frailty index.[2] The SOF Frailty Index has been well validated as being comparable with the more complex CHS criteria[11–13] and performs similarly to the CHS index in predicting falls, incident functional limitations, fractures, and death.[2,14] The SOF index consisted of 3 components: intentional or unintentional weight loss of greater than 5% in the past year, inability to rise from a chair 5 consecutive times without using arms, and perceived low energy level based on an item from the Geriatric Depression Scale.[14] Participants who had at least 2 of these criteria were categorized as frail, those with 1 were considered prefrail, and those who met no criteria were defined as robust.

A single outcome variable was created that combined information from all 4 follow-up examinations when frailty status was assessed. First, we prioritized the outcome categories as follows: frailty, death, prefrail, and robust. A participant was considered to have an incident case of frailty at the first follow-up visit at which she met SOF criteria for frailty. For example, if a participant was classified as frail at any of these 4 visits, she was classified as frail. If a participant was not classified as frail at any of these 4 visits but was classified as prefrail at any of these visits, she was classified as prefrail in our outcome variable. If a woman died before Year 18 and was not classified as frail at any of the follow-up visits, she was classified as dead; this included women who were classified as prefrail at a follow-up visit and died before Year 18, under the assumption that they died before the visit at which they might have been classified as frail. Otherwise, women who were not classified as frail or prefrail at any of these visits and survived to Year 18 or were missing information on frailty status at follow-up visits but did not die (had frailty status assessed at Years 6 and 8 but not at subsequent visits) were classified as robust.

Covariables

Covariables included baseline age, years of education, smoking status, body mass index (BMI), and number of instrumental activity of daily living (IADLs, range 0–5) difficulties. Self-reported oral corticosteroid and estrogen use were categorized as never, past, and current. Number of chronic diseases was the sum of 4 diseases: coronary heart disease, diabetes mellitus, stroke, and chronic obstructive pulmonary disease (range 0–4). Usual walking speed (m/s) was calculated as an average of 2 timed walks at usual pace over a 6-m course.[15] Self-rated health was categorized as excellent, good, and fair or poor.

Blood Collection and Hormone Measurements

Blood was collected at the baseline examination from all participants after an overnight fast and immediately frozen to −20°C. Within 2 weeks, all samples were shipped to a central repository and stored in liquid nitrogen at −190°C until hormones were assayed. Testosterone assays were available on 541 women who were included in the breast cancer and fracture case-control substudies of SOF but who had not experienced either of these outcomes at the time of blood collection. (Serum testosterone levels were obtained before subjects were identified as cases or controls.) Methodology of testosterone measurements was similar between the 2 substudies for total testosterone but not free testosterone, so only total testosterone was analyzed. Serum concentrations of total testosterone (ng/dL) were measured using radioimmunoassay after extraction and aluminum oxide column chromatography with an interassay coefficient of variation of 6.1% to 13.4%[16,17] (Endocrine

Science, Calabasas Hill, CA; Corning Nichols Institute, San Juan Capistrano, CA). Overall, mean total testosterone levels did not significantly differ between the 2 substudies (Supplementary Table S1).

Statistical analysis

Characteristics of women who underwent surgical menopause were compared with those of women who underwent natural menopause using the Student t-test for continuous variables and chi-square test for categorical variables. Multinomial logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the association between surgical menopause and each level of frailty (prefrail, frail, death) (reference robust). This logistic regression framework[18] was used to combine incidence results across the multiple examinations. In secondary analyses, we evaluated the association between serum total testosterone levels and each level of frailty in our subsample. Given the positively skewed distribution of total testosterone levels, these data were normalized using natural logarithm transformation for analysis.

The multivariable model included age and BMI because they were considered clinically important covariates. Using an iterative process, potential confounders were identified and added to the multivariate model if they were independently associated with frailty status (p<. 05) and their addition to a model that included only the surgical menopause variable changed the estimate for that variable by 10% or more. Covariates used to define surgical menopause (e.g., age at menopause) were not included in multivariable models. We tested effect modification according to oral estrogen use by adding an interaction term between surgical menopause and estrogen use into the regression model. We also performed stratified analysis of never, past, and current oral estrogen users. All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Sample Characteristics

The mean age of the 7,699 participants was 71.2 ± 5.2;13.8% were using oral estrogen, and 12.6% reported surgical menopause. Surgically menopausal women were significantly younger at menopause than naturally menopausal women, were more likely to have taken estrogen and to have used it for a longer time, and had significantly lower serum total testosterone levels (13.2 ± 8.2 vs 21.7 ± 14.9 ng/dL; p<.01) (Table 1). Baseline characteristics of women excluded from the analyses (n=2,005) did not significantly differ from the analytical sample.

Surgical Menopause and Risk of Frailty

Average age at interview at which women were first classified as frail was 79.6. Approximately 10% of women became frail between Years 6 and 18, 39.7% became prefrail, and 28.3% were robust; 22% died before being classified as prefrail or frail. In multinomial logistic regression analyses, surgical menopause was not associated with risk of any level of frailty or death (frailty: adjusted OR (aORs)=0.94, 95% CI=0.72–1.22; prefrailty: aOR=0.96, 95% CI=0.80–1.10); death: aOR=1.17, 95% CI=0.97–1.42) (Table 2).

Stratified Analyses According to Oral Estrogen Use

There was no significant association between the interaction between estrogen use and surgical menopause and risk of frailty or death (prefrail, p=0.757 frail, p=0.834; death, p=0.930). Surgical menopause was not associated with frailty risk in women who never used oral estrogen or in current or past users (Supplementary Table S2).

Serum Total Testosterone and Frailty

Total testosterone levels were not associated with any frailty level (Supplementary Table S3). Because of the small sample size, we lacked power to compare effect modification in surgically and naturally menopausal women.

Sensitivity Analyses

Our results did not change when we redefined naturally menopausal women as those with intact uterus and ovaries (Supplementary Table S4), excluded women in the natural menopause group who underwent postmenopausal bilateral oophorectomy(n=362) (Supplementary Table S5), excluded women aged 85 and older, or adjusted for age at menopause and duration of estrogen use (data not shown).

DISCUSSION

In a large sample of postmenopausal Caucasian women followed for up to 18 years, those with surgically induced menopause were not at greater risk of developing frailty than naturally menopausal women. Contrary to our hypothesis, our findings suggest that low serum testosterone levels may not be a primary mechanism to explain the higher prevalence of frailty in older postmenopausal women. Furthermore, estrogen use did not modify this relationship. To our knowledge, this is the first population-based prospective cohort study to investigate this association in postmenopausal women and adds to studies of testosterone concentrations and frailty that have been conducted primarily in men.[8,19]

Women who had previously undergone bilateral oophorectomy had significantly lower serum testosterone levels. It was hypothesized that they would be at greater risk of frailty based on the role of androgens in maintaining muscle mass, bone health, and physical function[20,21] and findings that testosterone therapy significantly increased total lean body mass in oophorectomized women.[22] Future prospective studies are needed to replicate or refute our findings.

Naturally menopausal women with lower estrogen levels have been found in cross-sectional studies to have less muscle mass and strength,[23,24] suggesting a beneficial role of estrogen therapy, but we found no modification according to use of estrogen. Our results contradict a recent study that found that higher endogenous estradiol levels were associated with frailty in older women who had undergone natural menopause.[25] It is likely that SOF participants are not representative of current estrogen users because they were enrolled in the late 1980s, before safety concerns about hormone therapy were raised.[26]

Our results are consistent with previous SOF analyses that found no effect of bilateral oophorectomy before natural menopause[27] or postmenopausal bilateral oophorectomy[28] on

fracture risk, although the long-term health consequences of premenopausal bilateral oophorectomy may not result solely from hormonal changes after surgical menopause but could result from conditions (e.g., cancer, fibroids) that led to this surgery being performed.

Limitations of our study include the sample being primarily older white women without significant physical impairments. Thus, our results may have limited generalizability to other racial or ethnic groups or populations at high risk of disability. The proportion of the surgical menopause group was small (12.6%). We lacked medical records to confirm type of surgery and age at oophorectomy, although misclassification of surgical menopause was unlikely because of the significantly lower serum testosterone concentrations in these women and similar results when restricting the natural menopause group to women with intact ovaries and uterus. Our outcome variable combined data from 4 follow-up examinations to maximize power by using all available data on frailty, although we may have misclassified some participants as robust or prefrail because they were missing later follow-up visits at which they might have been classified as frail, potentially biasing our results toward the null. Covariates such as BMI and IADL impairment were measured at the baseline visit, long after surgical or natural menopause, making it possible that they were on the causal pathway rather than confounders. In addition, total testosterone was measured at a single time point and may not reflect commonly seen diurnal variations. A less sensitive radio-immunoassay was used instead of the gold standard technique of tandem mass spectrometry.[29]

Strengths of our study included its large, geographically diverse sample, use of the validated SOF frailty index,[14] and multinomial modeling to capture all levels of frailty and the competing risk of death concurrently. In conclusion, neither surgically induced menopause nor serum total testosterone concentration was associated with frailty in older women. These findings provide reassurance that long-term risk of frailty is not greater in surgically menopausal women, regardless of estrogen use. Nonetheless, given the low incidence of frailty in our sample and the current debate about prophylactic oophorectomy in women undergoing hysterectomy to prevent ovarian cancer,[30] more research is needed to better understand the association between surgical menopause and frailty and potential underlying hormonal mechanisms in older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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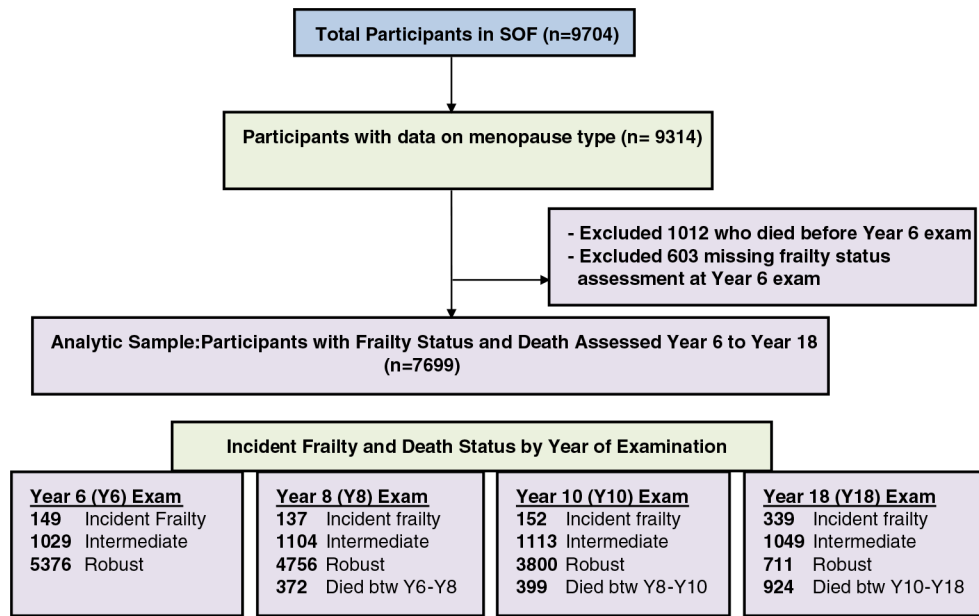
Figure 1.

Study of Osteoporotic Fractures participants: 7,699 women with data on exposure (surgical or natural menopause) and outcome (frailty status or death) constituted the analytical sample.

Table 1.

Baseline Characteristics of Study of Osteoporotic Fractures Participants (N = 7,699)

Characteristic	Natural Menopause, n = 6,731	Surgical Menopause, n = 968	P-Value[21]
Age, mean ± SD	71.3 ± 5.0	70.6 ± 4.7	0.000
Smoking status, n (%)			0.339
Nonsmoker	4131 (61.6)	575 (59.5)	
Former smoker	1,962 (29.3)	292 (30.2)	
Current smoker	614(9.2)	100 (10.3)	
Education, years, mean ± SD	12.8 ± 2.8	12.3 ± 2.7	0.000
Body mass index, kg/m^2, mean ± SD	26.4 ± 4.4	26.6 ± 4.7	0.242
Age at menopause, mean ± SD	48.7 ± 5.0	44.4 ± 7.4	0.000
Hysterectomy, n (%)	1,946 (29.0)	967 (99.9)	<.01
Number of chronic conditions, mean ± SD[32]	0.2 ± 0.5	0.3 ± 0.5	0.012
Number of instrumental activity of daily living impairments, mean ± SD	1.0 ± 2.1	1.3 ± 2.3	0.002
Walking speed, m/s, mean ± SD	1.0 ± 0.2	1.0 ± 0.2	0.513
Oral corticosteroid use, n (%)			0.913
Never	5,847 (88.3)	841 (89.7)	
Past	658 (9.9)	91 (9.6)	
Current	120 (1.8)	16(1.7)	
Oral estrogen use, n (%)			0.000
Never	4,012 (60.4)	350 (36.6)	
Past	1,840 (27.7)	311 (32.5)	
Current	792 (11.9)	295 (30.9)	
Total number of years taking oral estrogen, mean ± SD	7.7 ± 8.6	11.7 ± 10.6	0.000
Self-rated health, n (%)			0.000
Excellent	2,256 (33.5)	272 (28.1)	
Good	3,497 (52.0)	512 (52.9)	
Fair, poor, very poor	978 (14.5)	183 (18.9)	
Total testosterone, ng/dL, mean ± SD (n = 541)	21.7 ± 14.8	13.2 ± 7.8	0.000

[1] T-tests or chi-square tests for comparison of characteristics according to menopause type.

[2] Heart disease, stroke, chronic obstructive pulmonary disease, diabetes.

SD = standard deviation.

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Table 2.

Association Between Surgical Menopause and Incidence of Frailty (N = 7,699)

		Prefrail		Frail		Died	
				Odds Ratio (95% Confidence Interval)			
Exposure	Frail, n (%)	Adjusted Adjusted	Fully Adjusted[1]	Adjusted Adjusted	Fully Adjusted[1]	Adjusted Adjusted	Fully Adjusted[1]
Surgical menopause	90 (9)	1.02 (0.86–1.21)	0.96 (0.8–1.1)	1.00 (0.77–1.29)	0.94 (0.72–1.22)	1.20 (0.99–1.45)	1.17 (0.97–1.42)

[1] Adjusted for age, body mass index, and number of instrumental activity of daily living impairments.

Natural menopause (frail: n = 687, 10%) is the reference group.