GYNECOLOGY

Increased risk of osteoporosis with hysterectomy: A longitudinal follow-up study using a national sample cohort

Hyo Geun Choi, MD, PhD; Yoon Jung Jung, MD; Suk Woo Lee, MD, PhD

BACKGROUND: Premenopausal hysterectomy is associated with a decreased ovarian reserve, follicular atresia, and subsequently reduced long-term estrogen secretion. Therefore, women who undergo hysterectomy will experience greater gradual bone mineral loss than women with an intact uterus and have an increased risk of osteoporosis.

OBJECTIVE: This study aimed to evaluate the association between hysterectomy without/with bilateral oophorectomy and the occurrence of osteoporosis using a national sample cohort from South Korea.

STUDY DESIGN: Using the national cohort study from the Korean National Health Insurance Service, we extracted data for patients who had undergone hysterectomy (n=9082) and for a 1:4 matched control group (n=36,328) and then analyzed the occurrence of osteoporosis. The patients were matched according to age, sex, income, region of residence, and medical history. A Cox proportional hazards model was used to analyze the hazard ratios and 95% confidence intervals. Subgroup analyses were performed based on age and bilateral oophorectomy status. The age of the participants was defined as the age at the time of hysterectomy.

RESULTS: The adjusted hazard ratio for osteoporosis was 1.45 (95% confidence interval, 1.37–1.53, $P<.001$) in the hysterectomy group. The adjusted hazard ratios for osteoporosis in the different age subgroups of this group were 1.84 (95% confidence interval, 1.61–2.10) for ages 40–44 years, 1.52 (95% confidence interval, 1.39–1.66) for ages 45–49 years, 1.44 (95% confidence interval, 1.28–1.62) for ages 50–54 years, 1.61 (95% confidence interval, 1.33–1.96, all $P<.001$) for ages 55–59 years, and 1.08 (95% confidence interval, 0.95–1.23, $P=.223$) for ages ≥60 years. The adjusted hazard ratios for osteoporosis according to hysterectomy/oophorectomy status were 1.43 (95% confidence interval, 1.34–1.51) in the hysterectomy without bilateral oophorectomy group and 1.57 (95% confidence interval, 1.37–1.79) in the hysterectomy with bilateral oophorectomy group.

CONCLUSION: The occurrence of osteoporosis was increased in patients who had undergone hysterectomy compared with that in matched control subjects regardless of bilateral oophorectomy status.

Key words: cohort studies, hysterectomy, Korea, osteoporosis

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.[1] According to a nationwide-based study of the Korean population, the prevalence of osteoporosis in Korea is 38% in females aged 50 years and older.[2] One of the most important risk factors for bone loss in middle-aged women is a deficiency of sex-steroid hormones, namely, estrogen and testosterone, due to a decreased ovarian reserve.[3,4] Premature menopause and bilateral oophorectomy (BO) are also risk factors for osteoporosis.[5–7]

Hysterectomy is one of most commonly implemented major gynecologic procedures performed in premenopausal women for leiomyoma, heavy menstrual bleeding, dysmenorrhea, chronic pelvic pain, endometriosis, uterine prolapse, and gynecologic cancer.[8] In Korea, the annual hysterectomy rate for gynecologic benign disease is 1.52/1000 women aged ≥16 years.[9] Although most hysterectomies that are performed for benign gynecologic disease include ovarian conservation, premenopausal hysterectomy has a negative effect on ovarian function due to reductions in ovarian blood flow and follicular atresia; however, the data are conflicting.[10–12]

One hypothesis is that premenopausal hysterectomy is associated with a decreased ovarian reserve, follicular atresia, and subsequently, reduced long-term estrogen secretion and that women who undergo hysterectomy experience greater gradual bone mineral loss than women with an intact uterus and have a greater risk of osteoporosis. However, few investigations of the association between hysterectomy and osteoporosis have been reported, and most previous studies had small sample sizes and short follow-up periods; therefore, the reported results are not generalizable.[13,14] Although a population-based study of the relationship between hysterectomy and osteoporotic fracture has been conducted, we have been unable to find a large-scale study addressing the effect of hysterectomy on bone mineral density (BMD).[15]

The aim of this study was to investigate the risk of osteoporosis in women who have undergone hysterectomy in South Korea using a nationwide, population-based dataset obtained from the Korean National Health Insurance Service (NHIS).

Materials and Methods

Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The requirement for written

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AJOG at a Glance

Why was the study conducted?

To investigate the risk of osteoporosis in women who have undergone hysterectomy compared with women with an intact uterus in South Korea, using a nationwide, population-based dataset obtained from the Korean National Health Insurance Service.

Key findings

The overall adjusted hazard ratio for osteoporosis was significantly greater in the hysterectomy group than in the control group. Women older than 40 years of age who underwent hysterectomy had a greater incidence of osteoporosis in group of ages younger than 60 years than women with intact uterus. The adjusted hazard ratio for osteoporosis according to hysterectomy/oophorectomy status was significantly greater in both the hysterectomy without bilateral oophorectomy group and the hysterectomy with bilateral oophorectomy group than in the control group.

What does this add to what is known?

There were no previous studies showing that hysterectomy increases the incidence of osteoporosis. We showed a new conclusion that hysterectomy increases the incidence of osteoporosis through a nationwide population-based cohort study.

informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service—National Patient Sample. The Korean NHIS selects samples directly from the database of the entire population to prevent nonsampling errors. Approximately 2% of the samples (1 million) were selected from the entire Korean population (50 million). The selected data can be classified at 1476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. The appropriateness of the sample was verified in a previous study.[16] The National Health Insurance Sharing Service provides the details of the methods used to perform these procedures (http://nhiss.nhis.or.kr/). This cohort database included (1) personal information, (2) health insurance claim codes (procedures and prescriptions), (3) *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) diagnostic codes, (4) death records from the Korean National Statistical Office (using the Korean Standard Classification of disease), (5) socioeconomic data (residence and income), and (6) medical examination data for each participant from 2002 to 2013.

All Korean citizens are recognized by a 13-digit resident registration number from birth to death. Therefore, exact population statistics can be determined using this database. All Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. All medical treatments in Korea are tracked without exception using the Korean Health Insurance Review and Assessment Service system. In Korea, notice of death to an administrative entity is legally required before a funeral can be held. Causes and dates of death are recorded by medical doctors on death certificates.

Participant selection

Of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who underwent hysterectomy without/with BO, which were defined by the Korean Classification of Operations and Major Procedures in the Korean Inpatient Register as follows: (1) hysterectomy (operation codes R4143, R4144, R4145, R4146, R4154, R4155, R4183, R4202, R4203, R4221, R4223, R4482, R4507-R4510, R5001, and R5002) categorized as yes or no; (2) oophorectomy performed concurrently with hysterectomy (operation codes R4427 and R4428); and (3) bilateral oophorectomy once or unilateral oophorectomy twice (operation codes R4330-R4332 and R4423-R4426). The hysterectomy without BO group included patients with an operation code for hysterectomy alone or hysterectomy with concurrent surgery-preserving ovarian parenchyma. The hysterectomy with BO group included patients with either an operation code for oophorectomy performed concurrently with hysterectomy or an operation code for both hysterectomy and BO once or unilateral oophorectomy twice.

Osteoporosis was defined using the ICD-10 codes M80 (Osteoporosis with pathological fracture), M81 (Osteoporosis without pathological fracture), and M82 (Osteoporosis in diseases classified elsewhere) from 2002 through 2013. Among the patients diagnosed with osteoporosis, we selected those who were treated for osteoporosis $\geq$2 times or had been diagnosed with osteoporosis by dual-energy X-ray absorptiometry (DEXA) or computed tomography (claim codes: E7001-E7004). Because the Korean NHIS defined a T-score ≤ -2.5 at the lumbar spine or femoral neck based on BMD by DEXA for a diagnosis of osteoporosis, all participants underwent a DEXA.

The hysterectomy participants were matched 1:4 with participants (control group) from 2002 through 2013 who had never undergone hysterectomy. The control group participants were selected from the original population (n=1,125,691). The participants were matched for age, group, sex, income group, region of residence, and medical history (hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression).

To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random-number generator and then selected from top to bottom. The assumption was that the matched control participants were evaluated at the same time as each matched hysterectomy participant (index date). Therefore, individuals in the control group who died before the index date were excluded. In both the hysterectomy and control groups, those participants with histories of osteoporosis before the index date were excluded. In the hysterectomy group, 1185 participants were excluded due to a previous diagnosis of osteoporosis. None of the participants were excluded due to lack of matching. We excluded participants younger than 40 years old (n=1126) because the prevalence of osteoporosis was low in this age group. Finally, 1:4 matching resulted in the inclusion of 9082 hysterectomy participants and 36,328 control participants. The participants were not matched for ischemic heart disease, stroke, or depression history because matching based on these characteristics increased the drop-out rate for hysterectomy subjects due to a lack of control participants (Figure). The participants were followed up for a maximum of 12 years.

Variables

The participants were classified into age groups of 5-year intervals (40—44, 45—49, 50—54, etc, up to 70+ years), yielding a total of 7 age groups. The age of the participants was defined as age at the time of hysterectomy. The income groups initially comprised 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] to class 5 [highest income]). Region of residence initially comprised 16 areas representing administrative districts. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi,

TABLE 1
General characteristics of the participants

	Total participants		
Characteristic	Hysterectomy (n, %)	Control (n, %)	*P* value
Age, y			1.000
40—44	2609 (28.7)	10,436 (28.7)	
45—49	3580 (39.4)	14,320 (39.4)	
50—54	1589 (17.5)	6356 (17.5)	
55—59	472 (5.2)	1888 (5.2)	
60—64	317 (3.5)	1268 (3.5)	
65—69	271 (3.0)	1084 (3.0)	
70—74	142 (1.6)	568 (1.6)	
75—79	75 (0.8)	300 (0.8)	
80+	27 (0.3)	108 (0.3)	
Income			1.000
1 (lowest)	1386 (15.3)	5544 (15.3)	
2	1464 (16.1)	5856 (16.1)	
3	1614 (17.8)	6456 (17.8)	
4	1913 (21.1)	7652 (21.1)	
5 (highest)	2705 (29.8)	10,820 (29.8)	
Region of residence			1.000
Urban	4466 (49.2)	17,864 (49.2)	
Rural	4616 (50.8)	18,464 (50.8)	
Hypertension			1.000
Yes	2874 (31.6)	11,496 (31.6)	
No	6208 (68.4)	24,832 (68.4)	
Diabetes			1.000
Yes	1273 (14.0)	5092 (14.0)	
No	7809 (86.0)	31,236 (86.0)	
Dyslipidemia			1.000
Yes	2675 (29.5)	10,700 (29.5)	
No	6407 (70.5)	25,628 (70.5)	
Ischemic heart disease[a]			.029
Yes	376 (4.1)	1327 (3.7)	
No	8706 (95.9)	35,001 (96.3)	
Stroke			.211
Yes	534 (5.9)	2013 (5.5)	
No	8548 (94.1)	34,315 (94.5)	
Depression[a]			.008
Yes	1034 (11.4)	3787 (10.4)	
No	8048 (88.6)	32,541 (89.6)	

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.
(continued)

TABLE 1
General characteristics of the participants *(continued)*

Characteristic	Total participants		
	Hysterectomy (n, %)	Control (n, %)	*P* value
Osteoporosis[a]			<.001
Yes	1765 (19.4)	5168 (14.2)	
No	7317 (80.6)	31,160 (85.8)	

Statistical analyses performed by χ^2 test. Significance at $P<.05$.

[a] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The medical histories of the participants were evaluated using ICD-10 codes. To reduce error in the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assigned to those participants treated ≥2 times. Ischemic heart disease (I24 and I25) and stroke (I60-I66) were assigned if the participant had been treated ≥1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F33 (recurrent depressive disorder) and was assigned if the participant had been treated by a psychiatrist ≥2 times.

Statistical analyses

The χ^2 test was used to compare general characteristics between the hysterectomy and control groups. To analyze the hazard ratios (HRs) for osteoporosis under hysterectomy, Cox proportional hazard models were used. Crude (simple) and adjusted (age, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression) models were used, and 95% confidence intervals (CIs) were calculated.

We analyzed the characteristics of women undergoing hysterectomy without/with BO stratified according to age (40−44 years, 45−49 years, 50−54 years, 55−59 years and ages ≥60 years); the results are shown in Supplemental Tables 1 and 2.

Two-tailed analyses were conducted, and *P* values less than .05 were considered statistically significant. The analyses were performed using SPSS v. 21.0 (IBM Corp, Armonk, NY).

Results

The mean follow-up period for osteoporosis risk assessment was 63.0 months (standard deviation=41.0 months) in the hysterectomy group and 66.9 months (standard deviation=40.7 months) in the control group.

The general characteristics (age, income, region of residence, hypertension, diabetes, and dyslipidemia) of the participants did not differ significantly between the 2 groups due to the matching procedure (P=1.000). The rate of osteoporosis was greater in the hysterectomy group (19.4% [1765/9082]) than in the control group (14.2% [5168/36,328], $P<.001$, Table 1). The same pattern was observed when analyzing the hysterectomy without BO group and the hysterectomy with BO group separately (Supplemental Tables 1 and 2).

The adjusted HR for osteoporosis in the hysterectomy group was 1.45 (95% CI, 1.37−1.53, $P<.001$, Table 2). The adjusted model included age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression.

In the analyses by age subgroup, the adjusted HRs for osteoporosis in the hysterectomy group were 1.84 (95% CI, 1.61−2.10, $P<.001$) for ages 40−44 years, 1.52 (95% CI, 1.39−1.66, $P<.001$) for ages 45−49 years, 1.44 (95% CI, 1.28−1.62, $P<.001$) for ages 50−54 years, 1.61 (95% CI, 1.33−1.96, $P<.001$) for ages 55−59 years, and 1.08 (95% CI, 0.95−1.23, P=.223) for ages ≥60 years ($P<.001$, Table 3). These differences were observed when analyzing the hysterectomy without BO group and the hysterectomy with BO group separately (Supplemental Tables 3 and 4).

In the subgroup analysis according to hysterectomy/oophorectomy status, the adjusted HRs for osteoporosis were 1.43 (95% CI, 1.34−1.51) in the hysterectomy without BO group and 1.57 (95% CI, 1.37−1.79) in the hysterectomy with BO group (both $P<.001$, Table 4).

Comment

In the present nationwide cohort study, we found that undergoing hysterectomy is associated with an increased risk of osteoporosis later in life regardless of BO status. Sex-steroid hormones such as estrogen and androgen have major roles in regulating bone metabolism in adulthood and sex-steroid hormone deficiency during menopause leads to an

TABLE 2
Crude and adjusted HRs (95% CIs) for osteoporosis in women with hysterectomy with/without bilateral oophorectomy for osteoporosis

Group	Hazard ratio (95% CI)			
	Crude	*P* value	Adjusted[a]	*P* value
Hysterectomy[b]	1.45 (1.37−1.53)	< .001	1.45 (1.37−1.53)	<.001
Control	1.00		1.00	

CI, confidence interval; *HR*, hazard ratio.

Statistical analyses by Cox proportional hazard regression model. Significance at $P<.05$.

[a] Adjusted model for age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression; [b] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

TABLE 3
Crude and adjusted HRs (95% CIs) for osteoporosis in subgroups of women who underwent hysterectomy with/without bilateral oophorectomy according to age

	HR (95% CI)			
Subgroup	Crude	*P* value	Adjusted[a]	*P* value
Age 40–44 y old (n=13,045)				
Hysterectomy[b]	1.83 (1.61–2.10)	<.001	1.84 (1.61–2.10)	<.001
Control	1.00		1.00	
Age 45–49 y old (n=17,900)				
Hysterectomy[b]	1.52 (1.39–1.67)	<.001	1.52 (1.39–1.66)	<.001
Control	1.00		1.00	
Age 50–54 y old (n=7945)				
Hysterectomy[b]	1.44 (1.28–1.62)	<.001	1.44 (1.28–1.62)	<.001
Control	1.00		1.00	
Age 55–59 y old (n=2360)				
Hysterectomy[b]	1.61 (1.33–1.95)	<.001	1.61 (1.33–1.96)	<.001
Control	1.00		1.00	
Age ≥60 y old (n=4160)				
Hysterectomy	1.08 (0.95–1.22)	.243	1.08 (0.95–1.23)	.223
Control	1.00		1.00	

CI, confidence interval; *HR*, hazard ratio.

Statistical analyses by Cox proportional hazard regression model. Significance at $P<.05$.

[a] Adjusted model for age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression; [b] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

increased rate of bone turnover and bone resorption and accelerates bone loss.[17,18]

Although most hysterectomies performed for gynecologically benign conditions involve ovarian conservation, occasionally, some clinicians prefer prophylactic BO with hysterectomy to prevent the future development of cancer, such as hereditary cancer, in conserved ovaries.[19-21] BO in premenopausal women leads to a sudden deprivation of sex-steroid hormones and is known to accelerate bone mineral loss, thus increasing the risks of osteoporosis and osteoporotic fracture.[22-24]

TABLE 4
Crude and adjusted HRs (95% CIs) for osteoporosis in women who underwent hysterectomy in subgroups of surgery type

	HR (95% CI)			
Subgroup	Crude	*P* value	Adjusted[a]	*P* value
Hysterectomy without bilateral oophorectomy (n=39,790)				
Hysterectomy[b] (n=7958)	1.42 (1.34–1.51)	<.001	1.43 (1.34–1.51)	<.001
Control (n=31,832)	1.00		1.00	
Hysterectomy with bilateral oophorectomy (n=5620)				
Hysterectomy[b] (n=1124)	1.60 (1.40–1.83)	<.001	1.57 (1.37–1.79)	<.001
Control (n=4496)	1.00		1.00	

CI, confidence interval; *HR*, hazard ratio.

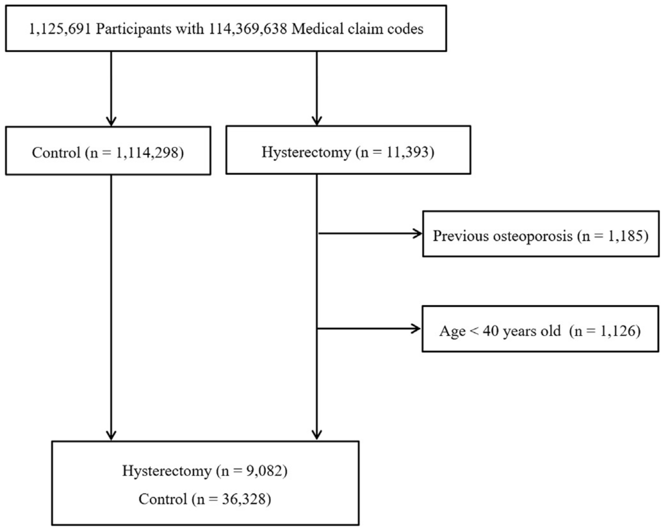
Statistical analyses by Cox proportional hazard regression model. Significance at $P<.05$.

[a] Adjusted model for age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression; [b] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

Theoretically, hysterectomy with ovarian conservation has no adverse effects on ovarian function.[25] However, previous longitudinal studies have shown that hysterectomy is associated with an acceleration in ovarian reserve decrease and earlier menopause. In a 5-year follow-up study, Moorman et al[26] reported that women undergoing hysterectomy were at an increased risk for ovarian failure compared with women with an intact uterus (HR, 1.92; 95% CI, 1.29–2.86). Trabuco et al[11] reported that women undergoing hysterectomy had a greater percent decrease in an ovarian reserve marker, namely, anti-Müllerian hormone, after 1 year than did women with an intact uterus. The mechanism of

FIGURE
A schematic illustration of the participant selection process



Among a total of 1,125,691 participants, 9082 hysterectomy participants were matched with 36,328 control participants for age, group, sex, income group, region of residence, and medical history.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

reduced ovarian function after hysterectomy is not clear, and several hypotheses have been proposed. One hypothesis is that removal of the uterus compromises blood flow to the ovaries after transection of the utero-ovarian ligament, which contains the uterine and ovarian arteries, and results in reduced hormone production.[27] A second hypothesis is that the uterus has paracrine or endocrine effects on ovarian function.[28] A third hypothesis is that because the uterus has an inhibitory influence on pituitary follicle-stimulating hormone secretion and, consequently, an effect on follicular atresia, the removal of the uterus allows follicle-stimulating hormone levels to rise and accelerates follicular depletion.[29]

Studies investigating the effects of hysterectomy with ovarian conservation on BMD and the risks of osteoporosis and osteoporotic fracture in treated women compared with women with an intact uterus were introduced in the 1990s.[13,14,25] Early studies showed that premenopausal hysterectomy had no deleterious effect on BMD. However, these studies had small sample sizes of fewer than 100 women who had undergone hysterectomy and employed cross-sectional designs. Subsequently, several studies were performed to clarify the association between hysterectomy and osteoporosis.

A study of BMD and bone turnover that compared a group of women who had undergone hysterectomy with ovarian conservation with a group having no history of hysterectomy showed that the former had lower levels of a bone turnover marker and a greater BMD of the lumbar spine and femoral neck than the latter. The authors concluded that the uterus may play a role in modulating bone metabolism that is independent of estrogen and hypothesized that hysterectomy is associated with increased total body fat and extragonadal sex hormone production in adipose tissue compared with the levels in the presence of an intact uterus.[30,31] In a population-based observational study, hysterectomy did not increase the long-term risk of osteoporotic fracture (HR, 1.09; 95% CI, 0.98−1.22).[15]

In contrast to previous studies, our study showed that women who underwent hysterectomy at any age had a greater incidence of osteoporosis. We were unable to find a study on the negative effect of hysterectomy on bone mass in the recent literature. We conclude that if a deficiency in sex-steroid hormones plays a predominant role in bone loss, then an early decrease in sex hormone levels in women who have undergone hysterectomy may cause earlier bone loss in these women than in women with intact uteri and thereby increase the risk of osteoporosis.

The HR of osteoporosis was significantly greater in women who undergone hysterectomy with BO in subgroup of aged 40−44 years than in any other subgroup. The risk of osteoporosis in both the hysterectomy without/with BO groups was increased compared with that of the control group for women aged 50−54 and 55−59 years but not those older than 60 years of age. The mean age of menopause in Korean women is 49.3 years.[32] Androgen is known as one of the hormones involved in maintaining bone mass and preventing osteoporosis, and it is converted into endogenous estrogen. Postmenopausal ovaries produce significant amounts of androgen for many years. This observation indicates that sex-steroid hormones produced by the ovaries function in maintaining bone mass for some period after menopause and that hysterectomy before 60 years of age may reduce androgen production and increase the risk of osteoporosis.[33] BO before 45 years is a well-established risk factor for osteoporosis, and BO during menopausal transition and postmenopause is associated with increased risks of osteoporosis and osteoporotic fracture.[23,34,35]

The present study has some limitations. First, although the control group was matched for medical histories of several conditions and demographic factors, some possible confounders were not considered, including family history of osteoporosis, obesity, alcohol intake, smoking, and other medical diseases that affect bone mass. The smoking and heavy-alcohol drinking rates of Korean middle-aged women were reported to be 3.3% and 4.1%, respectively, in the Korean National Health and Nutrition Examination Survey.[36,37] We considered it very likely that the control group selected by the randomization process had smoking and drinking rates similar to those of the women who underwent hysterectomy. Because obesity is closely related to hypertension, diabetes, and hyperlipidemia, we considered hypertension, diabetes, and hyperlipidemia rather than obesity in the Cox proportional hazard regression. We believe that these conditions can serve as proxies for obesity when analyzing confounding factors of osteoporosis. Second, it is well known that hormone-replacement therapy (HRT) has a positive effect on bone metabolism. HRT helps slow the rate of bone loss and increases BMD at all skeletal sites in early and late postmenopausal women.[18] Because of the lack of information on HRT in the national health registry, these data could not be retrieved from the Korean nationwide medical records. However, the percentage of long-term users of HRT among Korean women is only approximately 4.5% because of concerns regarding cancer and cardiovascular disease.[38] In addition, it was difficult to consider hormone therapy in the present study because many sex-hormone preparations, including natural/synthetic hormones and oral contraceptives, can be purchased without prescription as over-the-counter drugs. The control group was generated using a random selection process, and the likelihood of considerably different HRT use between the hysterectomy and control groups is low. Third, we used health insurance claim data and assigned osteoporosis based on the number of visits for osteoporosis treatment, which may not accurately reflect the actual incidence of osteoporosis among the patients. The use of ICD codes from extensive claim code data may lead to the possibility of misdiagnosis.

Several strengths exist in this study. First, based on an analysis of a nationwide population-based cohort, our study is the first to evaluate the risk of osteoporosis in women who undergo hysterectomy. Second, the control group was selected from an inventory of the population of South Korea and matched with the hysterectomy group not only for basic characteristics, including age, sex, income, and region of residence, but also for medical history. This detailed matching may provide valid evidence for the effect of hysterectomy on bone health.

Conclusion

Our study shows that hysterectomy is associated with an increased risk of osteoporosis at any age regardless of BO status. ■

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SUPPLEMENTAL TABLE 1
General characteristics of participants with hysterectomy without bilateral oophorectomy and control participants

Characteristic	Total participants Hysterectomy (n, %)	Control (n, %)	*P* value
Age, y			1.000
40—44	2393 (30.1)	9572 (30.1)	
45—49	3254 (40.9)	13,016 (40.9)	
50—54	1317 (16.5)	5268 (16.5)	
55—59	353 (4.4)	1412 (4.4)	
60—64	229 (2.9)	916 (2.9)	
65—69	218 (2.7)	872 (2.7)	
70—74	113 (1.4)	452 (1.4)	
75—79	57 (0.7)	228 (0.7)	
80+	24 (0.3)	96 (0.3)	
Income			1.000
1 (lowest)	1212 (15.2)	4848 (15.2)	
2	1291 (16.2)	5164 (16.2)	
3	1420 (17.8)	5680 (17.8)	
4	1682 (21.1)	6728 (21.1)	
5 (highest)	2353 (29.6)	9412 (29.6)	
Region of residence			1.000
Urban	3933 (49.4)	15,732 (49.4)	
Rural	4025 (50.6)	16,100 (50.6)	
Hypertension			1.000
Yes	2483 (31.2)	9932 (31.2)	
No	5475 (68.8)	21,900 (68.8)	
Diabetes			1.000
Yes	1075 (13.5)	4300 (13.5)	
No	6883 (86.5)	27,532 (86.5)	
Dyslipidemia			1.000
Yes	2303 (28.9)	9212 (28.9)	
No	5655 (71.1)	22,620 (71.1)	
Ischemic heart disease[a]			.002
Yes	337 (4.2)	1117 (3.5)	
No	7621 (95.8)	30,715 (96.5)	
Stroke[a]			.028
Yes	468 (5.9)	1674 (5.3)	
No	7490 (94.1)	30,158 (94.7)	
Depression[a]			.004
Yes	900 (11.3)	3250 (10.2)	
No	7,058 (88.7)	28,582 (98.8)	

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTAL TABLE 1

General characteristics of participants with hysterectomy without bilateral oophorectomy and control participants *(continued)*

Characteristic	Total participants		
	Hysterectomy (n, %)	Control (n, %)	*P* value
Osteoporosis[a]			< .001
Yes	1474 (18.5)	4374 (13.7)	
No	6484 (81.5)	27,458 (86.3)	

Statistical analyses by χ^2 test. Significance at $P<.05$.

[a] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 2

General characteristics of participants with hysterectomy with bilateral oophorectomy and control participants

Characteristic	Total participants		
	Hysterectomy (n, %)	Control (n, %)	*P* value
Age, y			1.000
40—44	216 (19.2)	864 (19.2)	
45—49	326 (29.0)	1304 (29.0)	
50—54	272 (24.2)	1088 (24.2)	
55—59	119 (10.6)	476 (10.6)	
60—64	88 (7.8)	352 (7.8)	
65—69	53 (4.7)	212 (4.7)	
70—74	29 (2.6)	116 (2.6)	
75—79	18 (1.6)	72 (1.6)	
80+	3 (0.3)	12 (0.3)	
Income			1.000
1 (lowest)	174 (15.5)	696 (15.5)	
2	173 (15.4)	692 (15.4)	
3	194 (17.3)	776 (17.3)	
4	231 (20.6)	924 (20.6)	
5 (highest)	352 (31.3)	1408 (31.3)	
Region of residence			1.000
Urban	533 (47.4)	2132 (47.4)	
Rural	591 (52.6)	2364 (52.6)	
Hypertension			1.000
Yes	391 (34.8)	1564 (34.8)	
No	733 (65.2)	2932 (65.2)	

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 2

General characteristics of participants with hysterectomy with bilateral oophorectomy and control participants *(continued)*

Characteristic	Total participants Hysterectomy (n, %)	Control (n, %)	*P* value
Diabetes			1.000
Yes	198 (17.6)	792 (17.6)	
No	926 (82.4)	3704 (82.4)	
Dyslipidemia			1.000
Yes	372 (33.1)	1488 (33.1)	
No	752 (66.9)	3008 (66.9)	
Ischemic heart disease			.080
Yes	39 (3.5)	210 (4.7)	
No	1085 (96.5)	4286 (95.3)	
Stroke			.053
Yes	66 (5.9)	339 (7.5)	
No	1058 (94.1)	4157 (92.5)	
Depression			.984
Yes	134 (11.9)	537 (11.9)	
No	990 (88.1)	3959 (88.1)	
Osteoporosis[a]			< .001
Yes	291 (25.9)	794 (17.7)	
No	833 (74.1)	3702 (82.3)	

Statistical analyses by χ^2 test. Significance at $P<.05$.

[a] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 3

Crude and adjusted HRs (95% CIs) for osteoporosis in different age subgroups of women who underwent hysterectomy without bilateral oophorectomy

Subgroup	Hazard ratio (95% CI) Crude	*P* value	Adjusted[a]	*P* value
Age 40–44 y (n=11,965)				
Hysterectomy[b]	1.67 (1.45–1.93)	<.001	1.65 (1.43–1.91)	<.001
Control	1.00		1.00	
Age 45–49 y (n=16,270)				
Hysterectomy[b]	1.51 (1.37–1.66)	<.001	1.49 (1.36–1.64)	<.001
Control	1.00		1.00	
Age 50–54 y (n=6585)				
Hysterectomy[b]	1.40 (1.23–1.60)	<.001	1.40 (1.23–1.59)	<.001
Control	1.00		1.00	
Age 55–59 y (n=1765)				
Hysterectomy[b]	1.54 (1.23–1.93)	<.001	1.54 (1.23–1.93)	<.001
Control	1.00		1.00	
Age ≥60 y (n=3205)				
Hysterectomy	1.12 (0.97–1.29)	.126	1.12 (0.97–1.29)	.120
Control	1.00		1.00	

CI, confidence interval; *HR*, hazard ratio.

Statistical analyses by Cox proportional hazard regression model. Significance at $P<.05$.

[a] Adjusted model for age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression; [b] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 4

Crude and adjusted HRs (95% CIs) for osteoporosis in different age subgroups of women who underwent hysterectomy with bilateral oophorectomy

Subgroup	Hazard ratio (95% CI) Crude	*P* value	Adjusted[a]	*P* value
Age 40—44 years (n = 1080)				
Hysterectomy[b]	3.39 (2.39—4.81)	<.001	3.35 (2.35—4.78)	<.001
Control	1.00		1.00	
Age 45—49 years (n = 1630)				
Hysterectomy[b]	1.62 (1.24—2.11)	<.001	1.61 (1.23—2.11)	.001
Control	1.00		1.00	
Age 50—54 years (n = 1360)				
Hysterectomy[b]	1.60 (1.22—2.11)	.001	1.58 (1.20—2.09)	.001
Control	1.00		1.00	
Age 55—59 years (n = 595)				
Hysterectomy[b]	1.83 (1.25—2.68)	.002	1.84 (1.26—2.71)	.002
Control	1.00		1.00	
Age ≥ 60 years (n = 955)				
Hysterectomy	0.95 (0.72—1.27)	.736	0.96 (0.72—1.27)	.752
Control	1.00		1.00	

CI, confidence interval; *HR*, hazard ratio.

Statistical analyses by Cox proportional hazard regression model. Significance at $P<.05$.

[a] Adjusted model for age, income, region of residence, and histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and depression; [b] $P<.05$.

Choi et al. Increased the risk of osteoporosis with hysterectomy: a longitudinal follow-up study using a national sample cohort. Am J Obstet Gynecol 2019.