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Hysterectomy is associated with higher risk of coronary artery disease

A nationwide retrospective cohort study in Taiwan

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Abstract

Hysterectomy is a common procedure for benign pathologies of the uterus. Reduced production of estrogen following hysterectomy has been reported. Yet the association between hysterectomy and coronary artery disease (CAD) risk remains controversial. The aim of this study was to investigate the effect of hysterectomy on the risk of CAD; calculations were adjusted for traditional risk factors.

This study used a 1 million patient cohort of the Taiwan National Health Insurance database and included a total of 7331 women who received hysterectomy from 2000 to 2013. We randomly selected a control group composed of 29,324 women without hysterectomy by 1:4 matching the age (exact year) with the hysterectomy group.

The mean (standard deviation) age was 43.5 ± 4.0 in the hysterectomy and 43.6 ± 4.0 in the control group. A total of 1986 CAD cases developed in both groups during a median follow-up of 7 years. Significant differences were observed in CAD incidence in the hysterectomy versus control group (9.82 vs. 7.17/1000 person-years, $P < .001$, adjusted hazard ratio = 1.31 [95% confidence interval: 1.18–1.45]).

We found a significant association between hysterectomy and CAD, even after adjustment for baseline CAD risk factors.

Abbreviations: BSO = bilateral salpingo-oophorectomy, CAD = coronary artery disease, CI = confidence interval, HR = hazard ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

Keywords: cardiovascular disease, coronary heart disease, hysterectomy, nationwide cohort, retrospective

1. Introduction

Hysterectomy is the most common gynecologic surgery in the United States as well as in Taiwan.[1,2] The indications for hysterectomy include uterine myoma, endometriosis, uterine prolapse, and genital cancers.[1,2] The prevalence of hysterectomy is 5.1 to 5.8 per 1000 women in the United States and 2.68 to 3.03 per 1000 women in Taiwan.[1–3]

Hysterectomy was reported to be associated with increased incidence of obesity, hypertension, and hyperlipidemia, which are cardiovascular risk factors.[4–6] Nevertheless, small sample size and lack of generalizability were noted in these studies and limited their value.[4–6] Moreover, these studies applied different risk factors in cardiovascular disease. Most studies did not mention preexisting cardiovascular risk factors before hysterectomy. Thus the conclusion from these studies may lead to conflicting results.

Bilateral salpingo-oophorectomy (BSO) is performed with >50% of hysterectomies because it tends to decrease ovarian cancer risk.[7,8] Because BSO can decrease endogenous sex hormone levels, which in turn may increase the risk of cardiovascular disease,[8–10] the American College of Obstetrics and Gynecology suggests ovarian preservation can be done in premenopausal women who receive hysterectomy without genetic risk for ovarian cancer.[11] However, the ovarian sparing hysterectomy also reduces endogenous hormone,[12] therefore long-term health consequences following hysterectomy are unknown. Conflicting associations between hysterectomy and the risk of coronary artery disease (CAD) have been observed.[7,9,13–16]

The objective of this analysis was to evaluate a sample, consisting of 1 million insurees recorded in the Taiwan National Health Insurance (NHI) Database, to demonstrate the effect of hysterectomy, performed to treat benign gynecologic diseases, on the risk of CAD after accounting for traditional risk factors.

2. Methods

2.1. Data source

The Taiwan NHI program is a government-run system launched on March 1, 1995. It covers more than 99% of the entire

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population and has contracted with 93% of the medical institutions in Taiwan. The NHI Research database (NHIRD) is an electronic database, which consists of registration files and original claims data collected from the NHI program (details are available at: http://nhird.nhri.org.tw/en/index.htm). All data are de-identified by encrypted identification numbers for beneficiaries and medical facilities. We used a data subset containing 1 million people randomly selected from the insured persons in the NHIRD in 2000 to investigate the possible association between hysterectomy and CAD. The complete medical records of each insuree from 1996 to 2013 are available by referencing the scrambled identifier of that insuree in the NHIRD. Disease diagnoses were identified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). A disease diagnosis without valid clinical findings may be considered as a medical fraud by NHI with a penalty of 100-fold of the payment claimed by the treating physician or hospital. This study was approved by the International Review Board, China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115). All research was performed in accordance with relevant guidelines/regulations.[17,18]

2.2. Study subjects

We identified 12,763 women who received hysterectomy between 2000 and 2013. The date of hysterectomy was considered as the index date. We included women aged between 30 and 50 years. Those with a diagnosis of cancer or CAD before hysterectomy or within 1 year after hysterectomy were excluded, as well as those with a diagnosis of CAD (ICD-9 code: 410–414), those who were deceased, and those who had withdrawn from the insurance program before hysterectomy. The control group was randomly selected and included women who had never received hysterectomy and were matched with the date of hysterectomy and age (exact year) based on a 1:4 of case to control ratio. A total of 7331 women who received hysterectomy and 29,324 women who never received hysterectomy were included in this study (Fig. 1). All patients were followed up from the index date to the first occurrence of one of the following: CAD, death, withdrawal from the NHI program, or the last day of 2013. Baseline comorbidities before the index date, including atrial fibrillation (ICD-9 code: 427.31), hypertension (ICD-9 code: 401–405), diabetes (ICD-9 code: 250), and chronic kidney disease (ICD-9 code: 585–586, 588.8–588.9), were also considered in this study.

Figure 1. Patient population from the National Health Insurance Research database enrolled for analysis.

Table 1

Baseline characteristics in women with normal delivery and comparison group among hysterectomy patients.

	Hysterectomy (n = 7331)	Comparison group (n = 29,324)	*P*
Age, y			
Mean (SD)	43.5 (4.0)	43.6 (4.0)	.9512
Follow-up duration, y			
Mean (SD)	7.0 (4.1)	7.1 (4.1)	.1063
Comorbidity, n (%)			
Atrial fibrillation	7 (0.1)	23 (0.1)	.6479
Hypertension	803 (11.0)	2288 (7.8)	<.0001
Diabetes	453 (6.2)	1368 (4.7)	<.0001
CKD	50 (0.7)	159 (0.5)	.155

CKD = chronic kidney disease, SD = standard deviation.

2.3. Statistical analysis

The differences in baseline characteristics between hysterectomy and control groups were examined by chi-squared tests for categorical variables and Wilcoxon rank-sum test for continuous variables. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) and interactions between hysterectomy and age, and between hysterectomy and comorbidities were calculated by Cox regressions. Log-rank testing was used to evaluate the difference between hysterectomy and comparison groups. All statistical analyses were performed by using SAS version 9.4 (SAS Institute Inc., Carey, NC). A 2-tailed *P* value below .05 was considered to be significant.

3. Results

The mean (standard deviation) ages were similar for the hysterectomy and control groups (Table 1; 43.5 ± 4.0 vs. 43.6 ± 4.0, respectively). Women with hysterectomy had higher percentages of hypertension and diabetes than women in the control group had (11.0% vs. 7.8% and 6.2% vs. 4.7%, respectively). The median follow-up time was 7 years.

Women with hysterectomy had higher risk of CAD than women in the control group had (Table 2; adjusted HR = 1.31, 95% CI = 1.18–1.45). No significant interaction between hysterectomy and age was observed ($P = .2087$; data not shown). The CAD-free rates in the hysterectomy and control groups are shown in Fig. 2. The incidence of CAD in the hysterectomy group was higher than that in the control group (log-rank $P < .0001$).

Significant interactions between comorbidities and hysterectomy were observed (Fig. 3; $P < .0001$ for both hypertension and diabetes). In an analysis stratified by comorbidity status, a significantly higher risk of CAD was observed in women with hysterectomy than in the control group among subjects without hypertension (HR = 1.37 with 95% CI = 1.22–1.53) or diabetes (HR = 1.34 with 95% CI = 1.20–1.49).

4. Discussion

The present population cohort study, which consisted of 7331 hysterectomy cases and 29,324 matched controls with a median follow-up time of 7 years, showed that hysterectomy was associated with elevated risk of CAD.

A previous cohort study demonstrated that young women (<50 years) with hysterectomy had an increased risk of cardiovascular disease.[9] A Finnish population study suggested that the risk factor was hysterectomy rather than the surgery

Table 2

Risk of coronary artery disease in women with hysterectomy compared with the comparison group.

	N	Event	Person-years	Incidence per 1000 person-years	HR (95% CI)	
					Crude	Adjusted*
Comparison group	29,324	1484	207,095	7.17	1 (reference)	1 (reference)
Hysterectomy	7331	502	51,144	9.82	1.37 (1.24, 1.52)	1.31 (1.18, 1.45)

CI = confidence interval, HR = hazard ratio.

* Model was adjusted for age, sex, and comorbidities listed in Table 1.

itself.[19] However, in these studies traditional cardiovascular risk factors[9] and age[19] were not accounted for in the multivariate analysis. A Swedish cohort study showed that hysterectomy was associated with an increased risk of myocardial infarction (MI) in women after menopause; however, the calculations were not appropriately adjusted for the risk factors of MI.[13] Another study demonstrated that hysterectomy was not associated with an increased risk of mortality from cardiovascular diseases, but this study reported only mortality as the endpoint.[14]

Postmenopausal women between 50 and 79 years of age with hysterectomy exhibited an elevated effect[7] or no effect[20] on cardiovascular risk factor profile and incidence in Women's Health Initiative studies. Furthermore, a higher risk of stroke following hysterectomy was reported in women younger than 36 years than in women who were >50 years.[15] Our cohort did not include women who were older than 50 years and that is a limitation of this study.

The risk of CAD and stroke after hysterectomy has been reported on the basis of information from the same NHRI database.[16] Yeh et al reported that women who received hysterectomy before the age of 45 years carried an elevated risk of stroke and a typical risk of CAD. However, their study differed from the present study in data collection years (2000–2013 vs. 1997–2009) and age stratification groups (30–50 years vs. <45, 45–54, 55–64, and >65 years).

The pathophysiology between hysterectomy and increased CAD risk remains unknown. One of the hypotheses is that hysterectomy may reduce ovarian blood flow from ovarian ligaments, leading to premature ovarian failure. The resulting reduced hormone status may accelerate atherosclerosis.

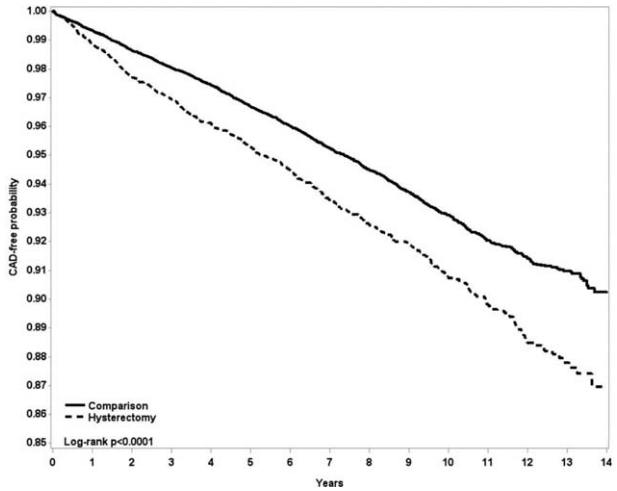

Figure 2. Kaplan–Meier curves of free from coronary artery disease in women receiving hysterectomy (dashed line) compared with age and comorbidity-matched controls (solid line).

Recently, it has become popular in gynecology to perform prophylactic salpingectomy with hysterectomy to prevent ovarian cancer.[21,22] However, the consequences for ovarian function have remained controversial; some studies have shown decreased ovarian function[23] whereas others have shown unchanged ovarian function.[24,25] Cardiovascular risk was increased with ovarian preservation in patients with hysterectomy.[15] Furthermore, stroke occurred more frequently in these patients than in controls (without hysterectomy or oophorectomy) in women younger than 30 years. However, stroke and congestive heart failure were significantly less common in patients older than 50 years than in controls.[15]

Biological age is a classical cardiovascular risk factor[26] and age at the time of surgery is another important risk factor for CAD that may be overlooked.[19] An advantage of our nationwide study cohort was that the surgical date was identified by the ICD code of the surgery; therefore, the biological age and age at the time of surgery were the same and could be easily used for matching and adjustment.

The average age of menopause in Taiwan is 49.5 years.[27] Although menopausal status is not available in Taiwan's National Registry, the age in our study cohort was <50 years with a mean age of 44 years, suggesting that all included women were premenopausal.

A notable strength of our study was the inclusion of age- and comorbidity-matched controls. A notable limitation of our study was that we did not check whether each hysterectomy was associated with BSO status. According to the rules of Taiwanese health insurance, the Diagnosis-Related Group (DRG) imposes a ceiling on all fees. In Taiwan, a gynecologic surgeon may not apply for a concurrent BSO fee from Taiwanese insurance, because the upper limit of the DRG fee must not be exceeded. Thus, we cannot confirm patients' BSO statuses. Furthermore, although we have controlled most of the cardiovascular risk factors, some confounding factors cannot be retrieved from the

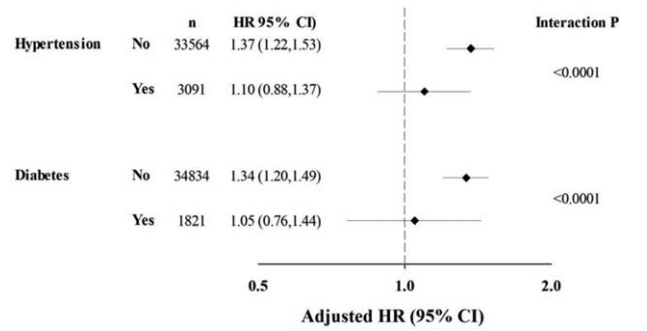

Figure 3. Hazard ratio of coronary artery disease stratified according to underlying status of hypertension and diabetes. The *P* values are for interaction association.

registry, such as body mass index, obesity, smoking habit, and menopausal age. However, the smoking population of Taiwanese women is generally low at 2% to 5%.[28]

5. Conclusion

Hysterectomy with benign gynecologic indication is the second most common surgery in women.[15] Based on this study, women who received hysterectomy for benign disease may have higher risk of CAD. Before hysterectomy, doctors should explain the CAD risk and arrange preventive measures.

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