Hysterectomy does not increase the risk of hemorrhagic or ischemic stroke over a mean follow-up of 6 years: A longitudinal national cohort study

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ABSTRACT

Objectives: This study sought to evaluate the association between hysterectomy and the occurrence of stroke in a Korean national cohort.
Study design: Data from 2002 to 2013 were collected for individuals in the Korean National Health Insurance Service-National Cohort. We extracted data for patients who had undergone a hysterectomy (N = 11,280) and a 1:4 matched control group (N = 45,120) and then analyzed the occurrence of stroke. The patients were matched according to age, sex, income, region of residence, and medical history.
Main outcome measures: Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model. Subgroup analyses were based on age (those under and those over 45 years of age) and type of hysterectomy (with or without bilateral oophorectomy).
Results: No significant difference in risk of hemorrhagic stroke (adjusted HR = 0.91, p = 0.592) or ischemic stroke (adjusted HR = 0.85, p = 0.188) was found between women with and without hysterectomy. No significant differences were found in the subgroup analyses according to age or type of hysterectomy for hemorrhagic and ischemic stroke.
Conclusion: Over a mean follow-up of 6 years, hysterectomy is not associated with an increased risk of either ischemic or hemorrhagic stroke at any age after adjusting for CVD risk factors including, hypertension, diabetes mellitus, and dyslipidemia, regardless of bilateral oophorectomy.

1. Introduction

Hysterectomy is one of the most common major gynecologic surgeries performed in women worldwide. The indications of hysterectomy are leiomyoma, menorrhagia, dysmenorrhea, endometriosis, chronic pelvic pain, pelvic organ prolapse, and gynecologic malignancy [1]. Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels and include coronary artery diseases, stroke, and other heart diseases [2]. In the obstetric and gynecologic field, there are several conditions with an increased risk of CVD, including preeclampsia, gestational hypertension, gestational diabetes mellitus (DM), polycystic ovarian syndrome, and premature menopause [3,4].

Stroke is a medical condition in which poor blood flow to the brain results in cell death. Stroke can be classified into two main types: ischemic stroke, which results from an obstruction within a blood vessel that supplies blood to the brain, and hemorrhagic stroke, which results

from weakened blood vessel ruptures [5]. Stroke continues to be one of the leading causes of disability and death among women and has a negative impact on their lives. The main risk factors for stroke are high blood pressure, smoking, obesity, high blood cholesterol, and DM [6]. Deficiency in endogenous sex steroid hormones is also a risk factor for stroke. Women have a lower risk of stroke during middle age, whereas the menopausal transition is a time when many women develop CVD risk factors, and during the 10 years after menopause, the risk of stroke roughly doubles in women [7,8]. Although bilateral salpingo-oophorectomy (BSO) decreases the risk of ovarian cancer, CVD risks and overall mortality may be increased after BSO [9,10].

Because previous studies have reported that endogenous sex steroid hormone levels were reduced after hysterectomy with ovarian conservation compared to intact uterus, concerns have been raised about the long-term health consequences after hysterectomy [11,12]. Several previous studies have analyzed the association between hysterectomy
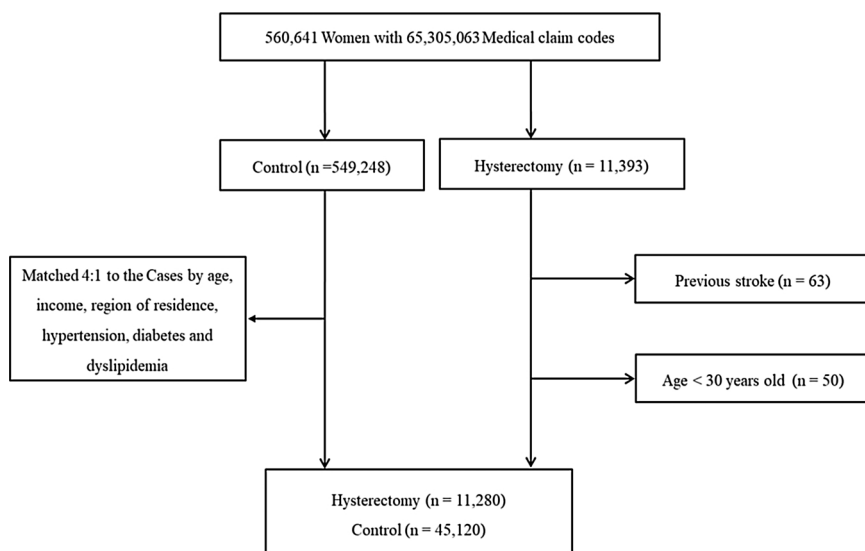
Fig. 1. A schematic illustration of the participant selection process using the Korean National Health Insurance Service-National Sample Cohort. Out of a total of 560,641 participants, 11,280 hysterectomy participants were matched with 45,120 control participants in terms of age, income, region of residence, and the past medical history.

and stroke, but these studies showed conflicting results [13–17]. It is important to reassess the correlation between hysterectomy and the risk of stroke with a large-scale population-based study.

The aim of this study was to investigate the risk of stroke in women who underwent hysterectomy in South Korea using a nationwide, population-based dataset obtained from the Korean National Health Insurance Service (NHIS) (Fig. 1).

2. Materials and methods

2.1. Study population and data collection

The ethics committee of Hallym University approved the use of these data (2014-I148). Written 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 (HIRA-NPS). The Korean NHIS selects samples directly from the database of the entire population to prevent nonsampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). These selected data can be classified according to 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. After data selection, the appropriateness of the sample was verified by a statistician who compared the data from the entire Korean population to the sample data. The details of the methods used to perform these procedures have been provided by the National Health Insurance Sharing Service (http://nhiss.nhis.or.kr/). The cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office, (using the Korean Standard Classification of disease), (v) socioeconomic data (residence and income), and (vi) medical examination data for each participant over a period ranging from 2002 to 2013.

Because all Korean citizens are recognized by a 13-digit resident registration number from birth to death, exact population statistics can be determined using this database. It is mandatory for all Koreans 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. Moreover, all medical treatments in Korea can be tracked without

exception using the Health Insurance Review &Assessment (HIRA) 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.

2.2. Participant selection

Out of 560,641 cases with 65,305,063 medical claim codes, we included participants who underwent hysterectomy and oophorectomy, which were defined by the Korean Classification of Operations and Major Procedures in the Korean Inpatient Register as follows: (i) hysterectomy (operation codes R4143, R4144, R4145, R4146, R4154, R4155, R4183, R4202, R4203, R4221, R4223, R4482, from R4507 to R4510, R5001, and R5002) categorized as yes or no; (ii) oopherectomy performed concurrent with the hysterectomy (operation codes R4427, R4428); (iii) bilateral oophorectomy once or unilateral oophorectomy twice (operation codes from R4330 to R4332 and from R4423 to R4426). The hysterectomy only group was defined as the participants with an operation code for hysterectomy alone or hysterectomy with ovarian conservative surgery. The hysterectomy with bilateral oophorectomy group was defined as the participants with either an operation code for oophorectomy performed concurrent with the hysterectomy or an operation code for both hysterectomy and bilateral oophorectomy once or unilateral oophorectomy twice.

The history of admission for hemorrhagic stroke (I60: subarachnoid hemorrhage, I61: intracerebral hemorrhage, and I62: other nontraumatic intracranial hemorrhage) and ischemic stroke (I63: cerebral infarction) was identified using ICD-10 codes. We selected the participants who were treated ≥1 time. These methods were used in other studies that evaluated the incidence of stroke in Korea [18,19].

The hysterectomy participants were matched 1:4 with participants (control group) who never underwent a hysterectomy between 2002 and 2013. The control participants were selected from the mother population (N = 549,248) and were matched for age, income, region of residence, and the past medical history (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. It was assumed that the matched control participants were evaluated at the same time as each matched hysterectomy participant (index date). Therefore, the control participants who died before the index date were excluded. In both the hysterectomy and control groups, the participants who had a history of hemorrhagic or ischemic stroke before the index date were excluded. In the hysterectomy group, 63 participants were