Maturitas 114 (2018) 27–33

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

The risk of stroke after bilateral salpingo-oophorectomy at hysterectomy for benign diseases: A nationwide cohort study

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ARTICLE INFO

Keywords:
Hormonal therapy
Hysterectomy
Oophorectomy
Population surveillance
Stroke
Taiwan

ABSTRACT

Objective: To assess the risk of stroke (and subtypes of stroke) in women after elective bilateral salpingo-oophorectomy at hysterectomy for benign diseases.
Study design: We conducted a nationwide population-based, retrospective cohort study using claims data from Taiwan's National Health Insurance program between 1997 and 2013. Women aged 20 years or more who underwent bilateral salpingo-oophorectomy at hysterectomy for benign diseases (n = 1083) were compared with women who did not undergo bilateral salpingo-oophorectomy at hysterectomy for benign diseases (n = 3903). The follow-up period ranged from 10 to 16 years. Age-adjusted (or unadjusted) and multivariate Cox proportional hazards regression models were used to estimate the risk of stroke between the two groups.
Main outcome measures: A diagnosis of stroke (and subtypes of stroke).
Results: We did not find a significant association between bilateral salpingo-oophorectomy and the risk of incident stroke (or subtypes of stroke) over an average follow-up of 13 years. Among women aged 50 years or more who used estrogen therapy, the risk of developing stroke was 64% lower in those who had undergone bilateral salpingo-oophorectomy (hazard ratio, 0.36; 95% confidence interval, 0.16–0.79) than in those who had undergone hysterectomy only.
Conclusion: This study suggests that the use of estrogen after bilateral salpingo-oophorectomy at hysterectomy for benign diseases reduces the risk of stroke in women aged 50 years or more.

1. Introduction

Elective bilateral salpingo-oophorectomy (BSO) is commonly performed on women who are undergoing hysterectomy for benign indications to avoid the future risk of ovarian cancer [1]. The BSO rate at benign hysterectomy was 39% in the United States and 15% in Taiwan [2,3]. Despite its high performing rates, it has been controversial whether the addition of a BSO to hysterectomy for benign indications increases the risk of stroke. The Swedish Cohort study showed a 47% increased the risk of stroke in women who had BSO at hysterectomy before age 50 years compared with those who had either BSO or hysterectomy [4]. In contrast, the Nurses' Health Study (NHS) and Women's Health Initiative (WHI) Study reported that BSO at hysterectomy was not associated with an increased risk of developing stroke [5,6]. However, the NHS study identified a 119% increased risk of developing stroke after BSO in women who never used estrogen therapy and younger than 50 years [5]. Moreover, no existing studies have investigated the effect of BSO on the risk of stroke in Asian women. Given the significantly higher risks of stroke in Asian than white [7], the generalizability of the above results to other racial and ethnic population remains uncertain [4–6]. More importantly, none of the studies above perform stratified analysis on stroke subtypes (ischemic or

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https://doi.org/10.1016/j.maturitas.2018.05.007
Received 14 March 2018; Received in revised form 9 May 2018; Accepted 14 May 2018
0378-5122/

hemorrhagic) and baseline comorbid conditions in their outcome measurements. Since there are important differences between the pathogenic mechanisms of ischemic and hemorrhagic strokes, outcome measurement using stroke subtypes may more accurately represent the risk of BSO on stroke [8]. In our previous investigation, we found that older women with baseline comorbid condition were more likely to undergo BSO at hysterectomy [3]. We anticipate that BSO may lead to a higher chance of developing stroke among older women with comorbid illness. The aim of this study was to perform a nationwide population-based covariate-adjusted analysis comparing the subsequent risk of developing stroke and stroke subtypes between women who underwent a BSO at hysterectomy for benign diseases and those who had hysterectomy only.

2. Methods

2.1. Study design and data source

We conducted a nationwide population-based, retrospective cohort study. Data on hysterectomy and oophorectomy were retrieved from the longitudinal health insurance database (LHID) of one million randomly selected beneficiaries, representing approximately 5% of all enrollees covered under the Taiwan's National Health Insurance (NHI) Program in 2005 [9]. The NHI is a single-payer insurance program with an enrollment rate of more than 99% of Taiwan's civilian residents in 2011. Being a reliable and consistent data source with rigorous validation of claim data on an annual basis [10–14], the LHID has been used in various biomedical research studies [3,15–17]. The accuracy of diagnosis of hypertension, diabetes mellitus, and stroke has been validated for this database [14,18]. For this study, we utilized the 1997–2013 NHI enrollment files, medical claims for inpatient admission and outpatient visit, prescription details, catastrophic illness registry, and hospital registry. One primary and up to four secondary codes (based on the International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM), were provided for disease diagnosis and surgical/diagnostic/therapeutic procedures for each inpatient admission claims, and three disease diagnosis codes (based on ICD-9-CM or A-code re-imbursement coding system) were provided for each outpatient visit claim. To ensure the confidentiality of enrollees, the administrative claims data of all beneficiaries were received as de-identified secondary data and managed by a double scrambling protocol to protect the privacy of all beneficiaries in the LHID database. The study conformed to STROBE guidelines for analyzing observational studies and was approved by the Institutional Review Board at MacKay Memorial Hospital, Taipei, Taiwan (No. 17MMHIS118).

2.2. Study population

For this study, we retrospectively identified all incident cases of benign hysterectomy from the inpatient admission claims over a 6-year period from January 1, 1998 and December 31, 2003 using the following ICD-9-CM procedure codes: subtotal abdominal hysterectomy (68.3), total abdominal hysterectomy (68.4), or vaginal hysterectomy (68.5) (n = 6349). The index admission was defined as the date of hysterectomy on the inpatient admission claims. The exclusion criteria were: (1) age less than 20 years (n = 8) to include only adult women; (2) ICD-9-CM diagnosis codes for primary/secondary malignant neoplasm of the female genitourinary organs (179–184) within the same inpatient admission claims (n = 282) to include only benign hysterectomy; (3) ICD-9-CM procedural codes for partial (65.2), unilateral (65.3), and bilateral oophorectomy (including the removal of remaining ovary) (65.5), unilateral (65.4) and bilateral salpingo-oophorectomy for the removal of remaining ovary (65.62, 65.64; prior or within the same inpatient admission claims), as well as an ICD-9-CM procedural codes (65.6) in prior inpatient admission claims to maintain homogeneity with respect to prognosis for this study (n = 856); (4) hysterectomy procedures performed in clinic setting (n = 17); (5) previous diagnosis of stroke before index admission (n = 41); and (6) missing information on independent variables of interests (n = 159). A total of 4986 women aged 20 years or older who underwent hysterectomy were identified during this period. Women with an ICD-9-CM procedure code for BSO (65.6) were classified into BSO-hysterectomy group (n = 1083), and the remaining into hysterectomy-only group (n = 3903).

2.3. Covariates

Women's residential urbanicity was defined according to Liu et al. [19]. Medical center, regional hospital, or district hospital was assigned by the Taiwan Joint Commission on Hospital Accreditation [20]. The status of pre-existing baseline medical comorbidity was based on at least 2 outpatient claims less than a year apart filed prior to index admission, including type 2 diabetes mellitus (DM) (ICD-9-CM code: 250 or A-code: A181), hypertension (HPT) (ICD-9-CM code: 401–405 or A-code: A260, A269), hyperlipidemia (HLP) (ICD-9-CM code: 272 or A-code: A182), coronary heart disease (CHD) (ICD-9-CM code: 410–414 or A-code: A270, A279), chronic rheumatic heart disease (CRHD) (ICD-9-CM code: 391, 393–398, or A-code: A251), and other types of heart disease (ICD-9-CM code: 420–429, or A-code: A281). The exposure status of hormone replacement therapy (HRT) was classified as never, past, or current use of estrogen replacement therapy (ERT), (combined or alternating) estrogen-progestin replacement therapy (EPRT), or progestin replacement therapy (PRT) in oral dosage form (capsules, oral suspension, tablets) or through injection. In accordance with Anatomic Therapeutic Chemical (ATC) classification system code, we identified all prescriptions for ERT (ATC codes: G03CA03, G03CA04, G03CA07, G03CA53, G03CA57, G03CB03), EPRT (ATC codes: G03FA01, G03FA02, G03FA04, G03FA10, G03FA11, G03FA12, G03FB01, G03FB06, G03FB09, G03HB01), and PRT (ATC codes: G03DA02, G03DA03, G03DA04, G03DC02). The cumulative duration of HRT exposure was defined as the sum of days for prescribing HRT to patients based on outpatient claim filed for ERT, EPRT, or PRT between 1997 and 2013.

2.4. Outcomes

Overall cumulative survival was defined as the index admission to the onset date of stroke, change in oophorectomy status, death, or administratively censored at the end of follow-up on December 31, 2013. The onset date was defined as the inpatient admission date due to the following outcome diseases based on ICD-9-CM diagnosis codes: any stroke (430–438), hemorrhagic stroke (430–432), and ischemic stroke (433–438). The change in oophorectomy status was defined as the inpatient admission for (partial) oophorectomy after index admission for women in the hysterectomy-only group. The date of death was defined by the death date in the registry of catastrophic illness, ending date of insurance coverage (as validated by Lien et al. [21]), or discharge reasons with death for all women without any inpatient or outpatient claims with at least 6 months of observation period after ending date of coverage to December 31, 2013. Each subject was followed up for a minimum of 10 years and a maximum of 16 years.

2.5. Statistical analysis

Mean (standard deviations [SD]), frequency (%), and 95% confidence interval (CI) were presented for continuous variable, categorical variable, and hazard ratios (HR), respectively. Significance levels for association between continuous and nominal variables were analyzed by the Student's *t*-test and Pearson's χ^2 (or Fisher exact) test, respectively. The incidence rate was calculated as the number of incident strokes per 1000 person-years. Age-adjusted (or unadjusted) and multivariate Cox proportional hazards regression models were performed