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Prior Hysterectomy and Oophorectomy and Incident Venous Thrombosis Risk among Postmenopausal Women: a Population-based, Case-control Study

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Abstract

Objective—Hysterectomy and bilateral salpingo-oophorectomy (BSO) are associated with changes in endogenous hormone levels, yet the risk of venous thrombosis (VT) associated with hysterectomy and BSO is incompletely characterized. This study evaluated the risk of incident VT among postmenopausal women associated with combined prior hysterectomy/oophorectomy status and current use of hormone therapy (HT).

Methods—In a case-control study, we identified incident VT cases (n=1,623) among postmenopausal Group Health Cooperative enrollees without reproductive cancer, defining their “index date” as their VT diagnosis date (1995-2010). Matched controls had not experienced a

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prior VT (n=4,480). Multiple logistic regression models estimated adjusted relative risks for VT associated with combinations of prior hysterectomy/oophorectomy status and HT use at the index date.

Results—Compared with women with an intact uterus who were not using HT, there was no suggestion of greater VT risk in women with prior hysterectomy without BSO, whether they were (adjusted odds ratio (aOR)=0.80 [95% confidence interval (CI): 0.57, 1.12]) or were not using HT (aOR=1.09 [95% CI: 0.89, 1.35]). Women with prior hysterectomy and BSO who were using HT were not at a greater VT risk (OR=1.00 [95% CI: 0.78, 1.27]), but there was evidence of a 25% greater risk associated with prior hysterectomy with BSO and no current HT use (OR=1.25 [95% CI: 1.05, 1.49]).

Conclusions—Collectively, these and prior data do not suggest a substantial impact of hysterectomy, with or without BSO, on the risk of VT among postmenopausal women.

Keywords

cardiovascular diseases; hormones; hysterectomy; ovariectomy; thrombosis; women

Introduction

In more than 50% of all hysterectomies in the United States, bilateral salpingo-oophorectomy (BSO) is completed concurrently¹. Among premenopausal women, removal of the ovaries is associated with decreases in ovarian androgen and estrogen levels that persist into postmenopause². Hysterectomy-alone is associated with smaller reductions in hormone levels²⁻⁴ which are thought to result from reduced ovarian blood supply and subsequently impaired ovarian function⁵. The hormonal decreases associated with hysterectomy with and without concurrent BSO have been hypothesized to increase thrombotic event risk. Furthermore, the association of early natural menopause with cardiovascular disease (CVD)⁶ and venous thrombosis (VT) risk^{7, 8} has led to the hypothesis that hysterectomy and BSO prior to natural menopause may increase the risk of venous and arterial thrombosis compared with hysterectomy-alone.

Hysterectomy with and without BSO have been inconsistently associated with the risk of arterial thrombotic events⁹⁻¹² and few studies have evaluated their associations with the risk of VT^{7, 10, 13}. Due to differences in reference groups between studies and small numbers of VT cases with a prior BSO in some studies, the association between hysterectomy with and without BSO and the risk of VT remains incompletely characterized^{7, 10, 13}. In this population-based, case-control study in postmenopausal women, we evaluated the relative risks of incident VT associated with combined prior hysterectomy/oophorectomy status and current use of HT. Also, among women with a prior hysterectomy we evaluated the risk of VT associated with BSO compared with hysterectomy-alone, on average and separately by natural menopausal status at the time of hysterectomy, by age at hysterectomy, and by current HT use at the event date.

Methods

Our setting was the Heart and Vascular Health (HVH) study, a population-based, case-control study set in Group Health Cooperative (GHC), an integrated health care system in Washington State. The HVH study's original aims evaluated risk factors for CVD, including myocardial infarction, stroke, atrial fibrillation, and VT¹⁴⁻¹⁷. The study was approved by the GHC Human Subjects Review Committee.

Cases and controls

Cases—All first VT events occurring among postmenopausal GHC members 18-89 years of age were identified between 1995 and 2010. Potential events, which included deep vein thrombosis (DVT) and pulmonary embolism (PE) events, were identified using *International Classification of Diseases, Ninth Revision (ICD-9)* hospital discharge and urgent care clinic diagnosis codes and *ICD-10* death record codes (Supplemental Digital Content Table 1). Receipt of a prescription for low molecular weight heparin was used to identify potential non-hospitalized cases of DVT. Review of the inpatient and outpatient medical records was performed by trained medical record abstractors, who validated all potential VT events identified during screening using criteria described in previous publications¹⁸. VT cases had no previous VT event before their “index date”, which was defined as the date of diagnosis.

Controls—Controls were postmenopausal women selected at random from among GHC members, with their index date defined as a randomly chosen date within the calendar year for which they were a control. Controls had no history of VT before their index date and were frequency-matched to myocardial infarction cases, the largest case group in the original HVH study design, on age (by decade), hypertension, and calendar year of the index date.

Prior reproductive cancer exclusion—We excluded cases and controls with ovarian, endometrial, cervical, vaginal, vulvar, and other/unspecified female genital cancers prior to the index date (n=321 of 7,418; 4.3%) in an effort to restrict our population to women who underwent hysterectomy/oophorectomy for benign conditions.

Measures

HVH study data were abstracted from medical records, laboratory and pharmacy data, and from a telephone interview with consenting, surviving individuals. GHC medical records contain documentation of all inpatient and outpatient care received at GHC facilities or non-GHC care reimbursed by GHC. Women averaged 23 years of documented follow-up between the first GHC visit and the index date.

Menopausal, hysterectomy, and oophorectomy status—Based on information in the GHC medical record, women were considered to be postmenopausal following the cessation of menses, receipt of BSO, the onset of menopausal symptoms in women who had a hysterectomy without BSO, or at 55 years of age. Hysterectomy and oophorectomy status, surgical dates, and the number of ovaries removed were determined by review of

GHC medical records. Hysterectomy/oophorectomy performed prior to GHC enrollment (53% of eligible hysterectomies) were recorded if noted in the medical record. We identified the source of hysterectomy information (patient-reported, physician's note, operative pathology report, or unknown) and whether hysterectomy occurred during natural pre/perimenopause, postmenopause, or whether a concurrent oophorectomy induced a transition into postmenopause.

Hormone therapy—Current HT use at the index date, assuming 80% compliance, was determined using computerized pharmacy records from GHC that included prescription fill dates, quantity of medication prescribed, and dosing instructions. In this population, 92% of women who participated in a telephone survey reported that they filled all or almost all prescriptions at a GHC pharmacy.

Reproductive cancer—For women with an index date on or after January 1, 1999, cancer information was abstracted from GHC medical records. For women with an index date between January 1, 1995 and December 31, 1998, cancer diagnosis data was collected from the Surveillance, Epidemiology, and End Results Program¹⁹.

Covariates—Demographic and health characteristics prior to the index date were collected via review of the GHC medical record. Race, education, and smoking were self-reported during the telephone interview and augmented with data from the medical record. Body mass index (BMI) was determined using height and weight information contained in the medical record and was augmented with information reported during the telephone interview. From the medical record we collected information regarding cardiovascular risk factors, including hypertension status, history of CVD, history of diabetes mellitus and the most recent total cholesterol level prior to the index date. Data were missing for BMI in 1.1%, race in 0.6%, education in 25.8%, smoking in 0.3%, physical activity in 5.9%, and total cholesterol level in 5.1% of women.

Statistical analyses

Data management—We classified a woman's hysterectomy and oophorectomy status at the index date into 3 categories: no hysterectomy or oophorectomy, hysterectomy without the removal of any ovaries (hysterectomy-alone), and hysterectomy with BSO. From among 7,097 potentially eligible women, we excluded women with an unknown hysterectomy or oophorectomy status (n=396, 5.6%), an oophorectomy without a hysterectomy (n=106, 1.5%), a hysterectomy with the removal of 1 ovary (n=273, 3.8%) or an unknown number of ovaries removed (n=12, 0.17%), a hysterectomy with an unknown date of hysterectomy (n=119, 1.7%), or a hysterectomy and BSO performed on different dates (n=119, 1.7%).

Women were excluded from analyses if the type of HT used at the index date was not as expected based on hysterectomy status: current estrogen plus progestogen therapy (EPT) use with prior hysterectomy (n=16, 0.23%), current estrogen-alone therapy (ET) use without prior hysterectomy (n=79, 1.1%), or current progestogen (P)-alone use (n=47, 0.66%). After these exclusions, 6,103 women remained eligible for analyses.

Analyses among all women—Multiple logistic regression was used to estimate relative risks by comparing 5 mutually exclusive groups of women defined by their prior hysterectomy/BSO status and current HT use to a single reference group of women whose uterus was intact and who were not currently using HT. Groups compared with this reference category were: 1) no prior hysterectomy and current EPT use; 2) prior hysterectomy-alone and no current HT use; 3) prior hysterectomy-alone and current ET use; 4) prior hysterectomy with BSO and no current HT use; and 5) prior hysterectomy with BSO and current ET use. Relative risks were adjusted for case-control design variables (age at the index date [linear], treated hypertension [yes vs. no], grouped index year [categorical]) and for variables judged *a priori* to possibly be associated with both the exposure and outcome: race (White vs. non-White), BMI (linear), education (greater than high school education vs. high school or less), tobacco smoking status (current vs. former/never), and prevalent CVD (any vs. none). We estimated adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Missing data for BMI, race, education, and smoking status were imputed using a chained equations approach²⁰ in Stata 13.1²¹ with 10 imputed datasets. Case-control status (categorical), combined hysterectomy/oophorectomy and HT use (categorical), age (linear), age in decade (categorical), hypertension (yes vs. no), index year (categorical), and decade of birth (linear) were included as predictors in the imputation model. A likelihood ratio test was used to test for multiplicative statistical interaction between hysterectomy-BSO status and HT use at the index date.

Analyses among women with a prior hysterectomy—In analyses limited to women with a prior hysterectomy, we directly evaluated the risk of VT associated with prior hysterectomy with BSO compared with prior hysterectomy without BSO. In addition to adjustment variables included in primary analyses, we adjusted for current HT use (any vs. none), since all HT used by women with a prior hysterectomy was consistently ET. We used logistic regression to evaluate the relative risk of VT associated with hysterectomy with BSO among subgroups of women separately by menopausal status at the time of hysterectomy (naturally pre/perimenopausal vs. postmenopausal), age category at the time of hysterectomy (<45 years, 45-54 years, 55 years), and HT use at the index date. Separate likelihood ratio tests were used to evaluate whether relative risks associated with BSO differed by categories of each of these variables.

Results

Between January 1, 1995 and December 31, 2010, we identified 1,623 postmenopausal women with incident VT and 4,480 eligible controls (N=6,103). Fifty-two percent (n=848) of the VT events included a PE with or without a diagnosed DVT. On average, eligible women were 70 years of age at the index date (Table 1). Compared with controls, cases had a higher mean BMI and a larger proportion had a history of CVD. Among women with a prior hysterectomy, the average interval between the hysterectomy and the index date was 25 years (standard deviation=12.4; range=0-62.4 years). Characteristics of controls by hysterectomy and oophorectomy status and current use of HT at the index date are presented online in Supplemental Digital Content Table 2.

Women who had undergone a prior hysterectomy but not BSO, whether or not they currently were using HT, were not at an increased risk of VT relative to women with an intact uterus who were not currently using HT (Table 2). Women with prior hysterectomy with BSO but no current HT use were at a 25% greater risk of VT than women with no prior hysterectomy and no current HT use (OR=1.25 [95% CI: 1.05, 1.49]), whereas there was no corresponding elevation in risk among women with prior hysterectomy with BSO who were currently using HT.

Among women with a prior hysterectomy, receipt of BSO may be associated with but a modestly greater risk of VT (OR=1.16 [95% CI: 0.94, 1.43]) (Table 3). We found no evidence that the size of this association differed by menopausal status (P=0.5), age at hysterectomy (P=0.6), or by current HT use at the index date (P=0.7).

Discussion

In this population-based, case-control study, we evaluated the risk of VT associated with a history of hysterectomy/oophorectomy, also classifying women by current HT use at the index date. Among women not currently using HT, we estimated a 25% greater risk of VT associated with prior hysterectomy with BSO compared with no prior hysterectomy or BSO. There was no greater risk of VT associated with prior hysterectomy-alone, with or without current HT use, or with a prior hysterectomy with BSO and current HT use, compared with no prior hysterectomy and no current HT use.

Our study, which included a larger population of VT cases with prior hysterectomy with BSO (n=334) and of VT cases with prior hysterectomy-alone (n=195) than prior studies^{7, 13}, categorized women jointly by their prior hysterectomy/oophorectomy status and current use of HT. Some women initiate HT following a hysterectomy or oophorectomy, and the use of HT among women with and without a prior hysterectomy has been previously associated with greater VT risk²²⁻²⁵. Furthermore, a woman's use of EPT versus ET is largely dictated by the presence of her uterus, and the use of EPT is associated with a greater risk of VT than ET. Categorization of women by both prior hysterectomy/oophorectomy status and current HT use allows for estimation of VT risk specific to type and status of HT use.

Although we estimated a 25% greater risk of VT associated with prior hysterectomy with BSO and no current HT use compared with no prior hysterectomy or BSO and no current HT use, this elevation in risk may be considered modest compared with other exposures that may work through hormonal mechanisms. For example, oral contraceptive use has been associated with a 240% greater risk of VT than non-use of oral contraceptives in a meta-analysis of 9 cohort and 23 case-control studies (OR=3.4 [95% CI: 3.0, 3.9]).²⁶ In the Women's Health Initiative (WHI) trials, HT therapy that included conjugated equine estrogen and medroxyprogesterone acetate was associated with 110% greater risk of incident VT (HR=2.10 [95% CI: 1.6-2.7]).²²

Prior studies of VT risk associated with a history of hysterectomy/oophorectomy compared with no prior hysterectomy included relatively small numbers of VT cases with prior BSO and, while these studies adjusted for HT use, they did not categorize women by a

combination of their history of hysterectomy/oophorectomy and their current use of HT. In the General Practice Research Database and WHI hormone therapy trial⁷ studies that included women without a prior hysterectomy in the reference group, there was no significant evidence of a greater VT risk associated with BSO, adjusting for HT use (OR=1.7 [95% CI: 0.9, 3.1]¹³, and hazard ratio [HR]=1.0 [95% CI: 0.7, 1.3]⁷, respectively). Given the small number of VT cases with BSO in the General Practice Research Database study (n=13), and an upper confidence interval estimate of 3.1, it is unclear whether the study was underpowered to detect an association were one to exist, or if this was a true association. Our findings may differ from those reported by WHI investigators because the WHI analysis reference group included a mixture of women with and without hysterectomy and the analysis was adjusted for HT use rather than separated in exposure groups by EPT and ET use. When we conducted a relatively similar analysis in our population, evaluating the risk of VT associated with BSO compared with no BSO (with or without hysterectomy), adjusting for current HT use (any vs. none) and our other covariates, our results were similar to those in WHI (HVH study OR=1.00 [95% CI: 0.84, 1.20]).

At the time of hysterectomy, elective BSO may be performed to reduce the risk of ovarian cancer, benign neoplasms, endometriosis, and pelvic pain²⁷. In our analyses restricted to women with a prior hysterectomy, we found some evidence that concurrent BSO may be associated with a 16% greater risk of VT than hysterectomy-alone, adjusting for current ET use. This adjusted relative risk estimate of 1.16 (95% CI: 0.94, 1.43) is modest in magnitude; therefore, the suggestion that hysterectomy with BSO may be associated with a greater VT risk than hysterectomy-alone requires replication. A Nurses' Health Study analysis restricted to women with a prior hysterectomy found no evidence of an association between hysterectomy with BSO compared with hysterectomy-alone and the risk of pulmonary embolism (HR_{adj}=1.1 [95% CI: 0.85, 1.5])¹⁰. When we evaluated the risk of PE (without DVT) associated with hysterectomy with concurrent BSO, we also found no evidence that hysterectomy with BSO was associated with a greater PE risk than hysterectomy-alone (OR=1.03; 95% CI: 0.78, 1.36).

Limitations and strengths

Our study has several limitations. There is the potential for misclassification of hysterectomy and oophorectomy status if this information is inaccurately reported in the medical record. However, the majority of hysterectomies were reported via a physician's note, operative report, or pathology report (81.6% overall) and only 18.4% were from patient self-report or an unknown source. Our analyses only considered current HT use at the time of the index date. GHC pharmacy records available for this study include information only from March 1, 1977 forward, and so we were unable to account for lifetime duration of HT use. In a 2011 WHI analysis, however, VT risk associated with HT use dissipated following HT cessation²⁸. Therefore, our consideration only of HT use at the index date likely includes the period of HT use most relevant to VT risk. In this observational study we did not randomize women to hysterectomy/oophorectomy or HT use, and so the potential for residual confounding by indication or by other factors remains. Our study has a limited ability to assess the short-term risks of hysterectomy with and without BSO, given that on average, women eligible for our study had received their hysterectomy

25 years prior (range 0-64 years). Our study did not collect information regarding the indication for hysterectomy or oophorectomy or family history of cancer, but we excluded all women with any history of reproductive cancer prior to index in an effort to restrict our population to women who underwent these procedures for benign medical condition. There is the potential that some women in our study proactively had a hysterectomy/oophorectomy due to undiagnosed cancers or a family history of cancer, and that these cancers were associated with VT risk. However, in the United States, cancer is the primary indication for less than 10% of hysterectomies¹. Although our study included a larger number of VT cases with a history of hysterectomy/oophorectomy than prior studies, our ability to statistically identify an association of small magnitude was limited by the sample size.

Our study also had several strengths. The population-based design reduces the likelihood of selection bias. Furthermore, all women eligible for our study were members of a single integrated health care system, likely reducing residual confounding by health care delivery factors, provider, socioeconomic factors, and access to health care. Additional strengths include the validation of all VT events, and the use of GHC pharmacy data to classify current HT use at the index date in an identical manner for cases and controls.

Conclusions

In this population-based, case-control study, women who had a prior hysterectomy with BSO and who were currently using HT were not at an increased risk of VT relative to women with an intact uterus who were not currently using HT. There was evidence of a greater VT risk among women who had undergone a hysterectomy with BSO and who were not using HT, but this elevation in risk was modest. There was no suggestion of an increased VT risk in women who had undergone a hysterectomy without BSO, whether or not they were currently using HT. Collectively, the data from this and prior studies do not suggest a substantial impact of hysterectomy, with or without BSO, on the risk of VT among postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of VT Cases and Controls at the Index Date in the Heart and Vascular Health Study, Washington State, 1995-2010 (n=6,103).

	VT Cases n=1,623	Controls n=4,480
Age, mean (SD), years	70.9 (11.3)	69.8 (9.8)
White race/ethnicity, No. (%)	1,447 (91.1)	3,977 (88.8)
Greater than High School Education, No. (%)	683 (61.4)	2,188 (64.1)
BMI, mean (SD), (kg/m ²)	29.5 (8.0)	28.1 (6.4)
Current Smoker, No. (%)	145 (8.9)	391 (8.7)
Prevalent CVD, No. (%)	393 (24.2)	709 (15.8)
Diabetes Mellitus, No. (%)	185 (11.4)	442 (9.9)
Treated Hypertension, No. (%)	790 (48.7)	2,378 (53.1)
Total Cholesterol Level, mean (SD), mg/dL	221.0 (46.7)	222.7 (50.1)
Hysterectomy and Oophorectomy Status, No. (%)		
Intact Ovaries and Uterus	1,094 (67.4)	3,030 (67.6)
Hysterectomy-Alone	195 (12.0)	584 (13.0)
Hysterectomy with BSO	334 (20.6)	866 (19.3)
<i>Characteristics among Women with Hysterectomy</i>	<i>n=529</i>	<i>n=1,450</i>
Age at Hysterectomy, No. (%)		
<45 Years	246 (46.5)	777 (53.6)
45-54 Years	170 (32.1)	479 (33.0)
≥55 Years	113 (21.4)	194 (13.4)
Years since Hysterectomy, mean (SD)	24.2 (13.5)	25.4 (12.0)
Medical Record Source of Hysterectomy Information, No. (%)		
Patient	79 (14.9)	269 (18.9)
Doctor's Note	191 (36.1)	563 (38.8)
Operation/Pathology Report	255 (48.2)	606 (41.8)
Other/Unknown	4 (0.76)	12 (0.83)

BMI=body mass index; BSO=bilateral salpingo-oophorectomy; CVD=cardiovascular disease; SD=standard deviation; VT=venous thrombosis

Table 2

Risk of VT Associated with Combined Hysterectomy/BSO Status and Current HT Use Compared with No Hysterectomy/BSO and No Current HT Use, Heart and Vascular Health Study, Washington State, 1995-2010.

	No HT Use*						HT Use*					
	Case n	Control n	HT Type	Adjusted OR ^a	95% CI	P- value	Case n	Control n	HT Type	Adjusted OR ^a	95% CI	P- value
No Hysterectomy	906	2,567	No HT	1.0 (reference)			188	463	EPT	1.61	1.32, 1.97	<0.001
Hysterectomy-Alone	150	389	No HT	1.09	0.89, 1.35	0.4	45	195	ET	0.80	0.57, 1.12	0.2
Hysterectomy with BSO	234	524	No HT	1.25	1.05, 1.49	0.01	100	342	ET	1.00	0.78, 1.27	0.9

BSO=bilateral salpingo-oophorectomy; CI=confidence interval; EPT=estrogen plus progestogen therapy; ET=estrogen-alone therapy; HT=hormone therapy; OR=odds ratio; P=progestogen; VT=venous thrombosis

^a Adjusted for continuous age, hypertension, index year (indicator variable), white race, continuous BMI, more than high school education, current smoking status, and prevalent cardiovascular disease.

* P-value from likelihood ratio test of interaction between hysterectomy/oophorectomy and HT status=<0.0001

Table 3

Risk of VT Associated with Hysterectomy with BSO Compared with Hysterectomy-alone, on Average and by Subgroups of Menopausal Status and Age at Hysterectomy, and by Current HT Use at the Index Date, Heart and Vascular Health Study, Washington State, 1995-2010.

	Hysterectomy-Alone (reference)		Hysterectomy-with BSO		Hyster-ectomy-Alone	Hysterectomy with BSO			Likelihood Ratio Test	
	Case n	Control n	Case n	Control n		Adjusted OR ^a	95% CI	P-value	P-value	
Venous Thrombosis										
Unstratified	195	584	334	866	1.00	1.16	0.94, 1.43	0.2	-	
Menopausal Status at Hysterectomy										
Pre/Perimenopause	134	436	241	696	1.00	1.18	0.92, 1.52	0.2		
Postmenopause	46	96	84	160	1.00	1.09	0.69, 1.74	0.7	0.5	
Age at Hysterectomy										
<45 Years	112	380	134	397	1.00	1.17	0.87, 1.57	0.3		
45-54 Years	44	142	126	337	1.00	1.13	0.74, 1.71	0.6		
>=55 Years	39	62	74	132	1.00	0.87	0.51, 1.48	0.6	0.6	
Current Hormone Therapy Use at the Index Date										
Non-Use of HT	150	389	234	524	1.00	1.13	0.88, 1.45	0.4		
Use of HT	45	195	100	342	1.00	1.22	0.81, 1.84	0.3	0.7	

BSO=bilateral salpingo-oophorectomy; CI=confidence interval; HT=hormone therapy; OR=odds ratio; VT=venous thrombosis

^aAdjusted for age (linear), treated hypertension (yes vs. no), grouped index year (categorical), race (White vs. non-White), BMI (linear), education (greater than high school education vs. high school or less), tobacco smoking status (current vs. former/never), and current HT use at index assuming 80% compliance (any vs. none).

0 0.5 1 1.5 2 2.5
Adjusted Odds Ratio