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Association of statins, aspirin, and venous thromboembolism in women with endometrial cancer

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Abstract

Objective—The anti-thrombogenic effects of statins and aspirin have been reported in various malignancies but have not been well examined in endometrial cancer. This study examined the association between statin and/or aspirin use and venous thromboembolism (VTE) risk in endometrial cancer.

Methods—This is a multi-center retrospective study examining 2527 women with endometrial cancer between 2000 and 2015. Statin and aspirin use at diagnosis was correlated to VTE risk during follow-up on multivariable analysis.

Results—There were 132 VTE events with a 5-year cumulative incidence rate of 6.1%. There were 392 (15.5%) statin users and 219 (8.7%) aspirin users, respectively. On multivariable analysis, statin use was associated with an approximately 60% decreased risk of VTE when

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Conflict of interest statement

Honorarium, Chugai Pharmaceutical Co.,Ltd.and Astra Zeneca (T.E.);research grant, Pfizer Inc., Yakult Honsha Co., Ltd., and OncoThreapy Science Inc. (K.H.); honorarium, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Eisai Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Bayer Yakuhin Ltd. (K.H.); advisory role, Merck Sharp and Dohme K. K (K.H.); honorarium, Chugai Pharmaceutical Co., Ltd. (K.M.); consultant, Tempus Labs (L.D.R.); none for others.

Appendix A. Supplementary data

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compared to non-users (5-year cumulative rates 2.5% *versus* 6.7%, adjusted-hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.19–0.92, $P = 0.030$) whereas aspirin did not demonstrate statistical significance (2.0% *versus* 6.5%, adjusted-HR 0.54, 95%CI 0.19–1.51, $P = 0.24$). There was a trend of joint effect between statin and aspirin although it did not demonstrate statistical significance: VTE risks for dual statin/aspirin user (adjusted-HR 0.27, 95%CI 0.04–2.07), statin alone (adjusted-HR 0.40, 95% CI 0.18–0.93), and aspirin alone (adjusted-HR 0.51, 95%CI 0.16–1.64) compared to non-use after adjusting for patient characteristics, tumor factors, treatment types, and survival events (*P*-interaction = 0.090). When stratified by statin type, simvastatin demonstrated the largest reduction of VTE risk (5-year cumulative rates 1.1% versus 6.7%, adjusted-HR 0.17, 95%CI 0.02–1.30, $P = 0.088$). Obesity, absence of diabetes mellitus, type II histology, and recurrent disease were the factors associated with decreased VTE risk with statin use (all, P-interaction<0.05).

Conclusion—Our study suggests that statin use may be associated with decreased risk of VTE in women with endometrial cancer.

Keywords

Endometrial neoplasms; Hydroxymethylglutaryl-CoA reductase Inhibitors; Aspirin; Venous thromboembolism; Incidence

1. Introduction

Endometrial cancer continues to be the most common gynecologic malignancy in the United States, with >63,000 women projected to be diagnosed in 2018 [1]. Gynecologic malignancies are associated with an increased risk of venous thromboembolism (VTE) [2–5], and certain groups of women with endometrial cancer harbor a disproportionally high risk (>40%) [6]. VTE can not only result in fatality due to pulmonary thrombosis but also in high treatment-related costs, decreased quality of life due to symptoms or treatment, and increased risk of treatment-related complications. VTE is also a surrogate marker for decreased survival in endometrial cancer [6]. Therefore, any efforts to reduce the risk of VTE will be useful.

Recently, reductions in VTE risk have incidentally been observed with certain medications. Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, are generally used for the treatment of hypercholesterolemia, however multiple studies have demonstrated that statin use is also associated with a reduced risk of VTE in cancer populations [7–10] and in the non-oncologic setting [11]. Similarly,aspirin, which permanently inhibits cyclooxygenase 1 on platelets and exerts both anti-inflammatory and anti-thrombotic effects [12], is also associated with protective effects on cancer-related VTE development [13,14].

Women with endometrial cancer often have multiple medical comorbidities, and statin and aspirin use seems to be prevalent [15,16]. Nevertheless, the effects of statin and aspirin use on VTE risk have not been examined in the endometrial cancer population. The objective of this study was to examine the association between statin and/or aspirin use and VTE risk in women with endometrial cancer.

2. Materials and methods

2.1. Eligibility

This retrospective multicenter study examined consecutive cases of women with endometrial cancer from two U.S. centers and four Japanese centers between 2000 and 2015. Institutional Review Board approval was obtained at each site. Eligible women were those with a histologic diagnosis of endometrial cancer and available information for medication usage at endometrial cancer diagnosis. Exclusion criteria included synchronous secondary primary malignancy, VTE prior to endometrial cancer diagnosis, and lack of medication information. Some of the cases were included within the context of our prior study, which examined effects of aspirin on endometrial cancer survival [15].

2.2. Clinical information

Among eligible cases for the study, salient variables pertaining to VTE risk and cancer diagnosis were abstracted, including patient demographics, medical comorbidities, medications, tumor characteristics, treatment type, and survival events. Patient demographics included age, race/ethnicity, and body habitus. Medical comorbidities at diagnosis included hypertension, diabetes mellitus, and hypercholesterolemia, and medications included use of statins and aspirin at endometrial cancer diagnosis. Tumor characteristics included histologic type of endometrial cancer, serum cancer antigen 125 (CA-125) level at diagnosis, and cancer stage. Treatment type included use and type of hysterectomy and chemotherapy use. Survival information included endometrial cancer recurrence.

2.3. Study definition

For patient demographics, age was grouped by quartile, and obesity was classified per the CDC criteria (body mass index <30, 30–34.9, 35.0–39.9, and ≥40 kg/m^2)[17]. Cancer stage was re-classified based on the 2009 International Federation of Gynecology and Obstetrics staging system [18]. Type I endometrial cancer was defined as grade 1–2 endometrioid adenocarcinomas, whereas type II endometrial cancer was defined as other histology types [19].

Information regarding chemotherapy use was collected, as chemotherapy can be associated with increased risk of VTE [20]. Per the prior criteria for VTE risk in endometrial cancer [6], cancer stage was grouped as stage I–II *versus* III–IV and CA-125 levels were grouped as <35 *versus* ≥35 IU/L. Hysterectomy type was grouped as laparotomy, minimally invasive, or no hysterectomy based on a prior study associating hysterectomy mode and VTE risk [21].

VTE events were assessed during follow-up, and the time interval between endometrial cancer diagnosis and VTE was collected. Cases without VTE were censored at last follow-up. Cases lost to follow-up were also censored at the last known visit. The type of VTE was also collected (deep vein thrombosis [DVT] alone, pulmonary embolism [PE] alone, or both). In our institutions, diagnosis of VTE was generally made radiographically *via* Doppler studies, computer tomography, or ventilation-perfusion scans that were performed when VTE is clinically suspected, and routine scans to diagnose subclinical VTE are not performed.

2.4. Study population

There were 2527 women with histology-confirmed primary endometrial cancer and without a history of VTE or synchronous malignancy who had information regarding medication type available at diagnosis. The median follow-up time was 43.0 months (interquartile range, 24.6–64.4). There were 132 women who were diagnosed with VTE, resulting in a 5-year cumulative risk of 6.1% estimated by a time-dependent life table. The most common VTE type was DVT alone (n = 79, 59.8%), followed by both DVT and PE (n =31,23.5%)andPE alone (n = 22, 16.7%).

2.5. Study objectives

The primary objective of the study was to examine the association between statin and/or aspirin use and VTE risk in women with endometrial cancer. The secondary objective of the study was to identify the clinico-pathological factors associated with the benefit of statin and/or aspirin use on VTE risk.

Normality of continuous variables was examined with the Kolmogorov-Smirnov test, and continuous variables were expressed with mean (±standard deviation) or median (interquartile range) valuesasappropriate. Differences in continuous variables were assessed with the Student's t-test or the Mann-Whitney U test, as appropriate. Differences in ordinal and categorical variables were examined by the Fisher's exact test or chi-squared tests, as appropriate.

The cumulative incidence curves of VTE were constructed with the Kaplan-Meier method, and the difference between curves was assessed with log-rank testing. Cox proportional hazard regression models were used for multivariable analysis, and magnitude of statistical significance was expressed with hazard ratios (HR) and 95% confidence interval(CI). Proportional hazard assumption was tested and showed no interaction with time.

To examine the independent association between statin, aspirin use and VTE risk, multiple adjustments were performed in various layers. This stepwise-adjustment in various models was used to assess and visualize the interaction of statin use, aspirin use, and VTE risk in each layer. In a stepwise fashion, adjustment was performed for clinically relevant factors in the management of endometrial cancer, including patient demographics, medical comorbidity, tumor characteristics, treatment types, and survival sequentially. That is, the first adjustment model included patient demographics only. In the second model, medical comorbidity was added to patient demographics. In the third model, tumor characteristics were further added. In the fourth model, treatment type was added. In the last model, survival event was added.

Logic behind this stepwise approach was as follows: First, we assumed that (*i*) medical comorbidities are commonly affected by patient demographics and that (*ii*) statin/aspirin use largely depends on these two factors. Next, tumorigenesis in endometrial cancer is generally divided into two pathways, type I (obesity and metabolic syndrome) *versus* type II tumors (elderly), which also depend on patient demographics and comorbidities. Treatment type then depends on tumor and patient factors. Lastly, survival is largely affected by tumor factors. As stated earlier, each layer of variables independently impacts VTE risk. As long as

stability of HR for VTE risk was observed, we moved forward to construct the next adjustment model. In this study, we observed that statin-related VTE risk reduction remained constant throughout the five adjustment models. Thus, interpretation of analysis was based on the last adjustment model.

In a sensitivity analysis, the particular impact of statin subtypes on VTE risk was examined. This is based on the rationale that the type-specific risk reduction in VTE has not been examined previously. In addition, the joint effect of combined statin and aspirin use on VTE risk was examined, as use of both medications is common in women with endometrial cancer [15,16]. The interaction between statin and/or aspirin use and clinico-pathological variables was assessed.

All statistical analyses were based upon two-tailed hypotheses, and a $P < 0.05$ was considered statistically significant. Statistical Package for the Social Sciences (IBM SPSS, version 24.0, Armonk, NY, USA) was used for the analyses. The STROBE guidelines were consulted to outline the results of this retrospective observational study [22].

3. Results

Patient demographics are shown in Table 1. There were 392 (15.5%, 95%CI 14.1–16.9) statin users, and atorvastatin was the most commonly used statin ($n = 113$, 28.8%) followed by simvastatin ($n = 101$, 25.8%) (Table 2). Statin users were more likely to be young, Caucasian or Hispanic, obese, hypertensive, diabetic, and dyslipidemic compared to non-users (all, $P < 0.05$). Statin users were less likely to have undergone laparotomy for hysterectomy and less likely to have received chemotherapy (both, $P < 0.05$).

There were 219 (8.7%, 95%CI 7.6–9.8) aspirin users recorded (aspirin daily dose: 81–100 mg $n = 217$ and 325 mg $n = 2$). Aspirin users were more likely to be young, Caucasian or Hispanic, obese, hypertensive, diabetic, and dyslipidemic compared to non-users (all, $P < 0.05$). Aspirin users were less likely to have undergone laparotomy for hysterectomy and to have received chemotherapy (both, $P < 0.05$). Aspirin users had asignificantly lower rates of endometrial cancer recurrence compared to non-users ($P = 0.004$).

On univariable analysis, statin users had a significantly lower incidence of VTE compared to non-users (5-year cumulative rates: 2.5% *versus* 6.7%, $P = 0.005$). Similarly, on univariable analysis, aspirin use was significantly associated with decreased VTE risk (5-year cumulative incidence: 2.0% *versus* 6.5%, $P = 0.017$).

Multivariable analysis was performed to examine the independent association between statin and/or aspirin use and VTE risk in endometrial cancer (Table 3). After controlling for patient characteristics, medical comorbidity, tumor factors, treatment types, and survival events, the association between statin use and decreased VTE risk remained independent. Statin use was associated with an approximately 60% reduction in VTE risk (adjusted-HR 0.42, 95%CI 0.19–0.92, $P = 0.030$). Aspirin use did not retain an independent association with decreased VTE risk in this model (adjusted-HR 0.54, 95%CI 0.19–1.51, $P = 0.24$).

The joint effects of combined statin and aspirin use were examined (Table 4). Among 392 statin users, 92 (23.5%) used both a statin and aspirin Among 219 aspirin users, there were 127 (59.6%) women who used aspirin alone without a statin. On univariable analysis, dual users had lower VTE risk compared to those who used a statin or aspirin alone (5-year cumulative rates: dual statin and aspirin users 1.2%, statin alone 2.9%, aspirin alone 2.6%, and neither of two 7.0%, respectively, $P = 0.039$). When type of VTE was examined (Table S1), dual users had the lowest incidence of PE among the groups, although this did not reach statistical significance (0% for dual statin and aspirin use, 1.0% for statin only, 1.6% for aspirin only, and 2.4% for neither of two; $P = 0.06$).

On multivariable analysis adjusting for patient characteristics, medical comorbidity, tumor factors, treatment types, and survival events (Table 4), we observed statistically non-significant joint effect of dual statin and aspirin use on VTE risk compared to non-use (*P*-interaction = 0.090). Albeit statistically non-significant findings, dual statin/aspirin use conferred qualitatively lower VTE risk than statin alone or aspirin alone: adjusted-HR for dual statin/aspirin use 0.27 (95%CI 0.04–2.07), statin alone 0.40 (95%CI 0.18–0.93), aspirin alone 0.51 (95%CI 0.16–1.64) compared to non-use.

When stratified by statin type (Table 5), simvastatin demonstrated the highest reduction of VTE risk on multivariable analysis, although it did not quite reach statistical significance (5-year cumulative rates: 1.1% *versus* 6.7%, adjusted-HR 0.17, 95%CI 0.02–1.30, $P = 0.088$).

The impact of clinical-pathological factors on VTE risk reduction with statin usewas examined (Table 6).We observed statistically significant interaction for statin use in terms of body habits, diabetic status, histology type, tumor marker, hysterectomy mode, chemotherapy use, and disease status on multivariable analysis (all, *P*-interaction < 0.05). Specifically, obesity (adjusted-HR 0.21, 95%CI 0.05–0.90), absence of diabetes mellitus (adjusted-HR 0.52, 95%CI 0.29–0.96), type II histology (adjusted-HR 0.28, 95%CI 0.08–0.96), and recurrent disease (adjusted-HR 0.37, 95%CI 0.14–0.99) were all factors associated with decreased VTE risk with statin use (all, *P*-interaction<0.05).

4. Discussion

A key finding of this study is that statin use is associated with decreased risk of VTE in women with endometrial cancer. Simvastatin use, in particular, seems to greatly reduce the risk of VTE. Moreover, a possible synergistic effect of dual statin/aspirin use on VTE risk reduction may be suggested. This study also suggests that obese women and those with aggressive tumor characteristics may benefit from statin use to decrease VTE risk.

The results of this study are consistent with other studies demonstrating reduced cancer-related thrombosis with statin use [7–10]. However, these studies were conducted in mixed study populations of various cancer types, and endometrial cancer-specific data has been previously missing. Therefore, our study is unique to show the association between statin use and decreased VTE risk in the endometrial cancer population.

The findingsof this study differ from prior studies that demonstrated no association between statin use and cancer-related VTE risk [13,23]. These studies examined either a different

statin type (rosuvastatin) or a different gynecologic malignancy. Of note, our study also found no association between rosuvastatin use and VTE. These results suggest that effects on VTE risk may vary based on the type of statin used and the type of malignancy.

Aspirin use did not decrease the risk of VTE in our study. Prior studies mainly examined the impact of aspirin on cancer incidence or survival [12], and the association of aspirin and VTE has not been addressed in endometrial cancer. Aspirin use seems to protect against cancer-related thrombosis in various other cancers including ovarian cancer (one of the most thrombogenic malignancies) [13,14]. More data would be useful to examine the effects of aspirin on VTE in malignancies, including endometrial cancer.

While the exact mechanism remains uncertain, a biological plausibility to explain the protective effects of statin and aspirin use against endometrial cancer-related VTE is that both drugs possess anti-inflammatory properties [24]. Statins inhibit the interleukin 6-related pro-inflammatory pathway, whereas aspirin inhibits platelet-related or the prostaglandin E_2-mediated inflammatory mechanism [12,25]. Endometrial cancer in particular often affects obese women, in whom excess adiposity may lead to a pro-inflammatory state [26]. Moreover, aggressive tumor states also may contribute to increased inflammation. These cancer-related pro-inflammatory states are known to cause thrombosis in both direct and indirect fashions [4]. Thus, statins and aspirin may reduce the inflammatory milieu as a whole and reduce the riskof VTE. Indeed, ourstudyfoundthat obese women (representing inflammatory status in excess adiposity) or type II tumor histology/recurrent disease (representing inflammatory status from aggressive tumor behavior) benefitted from statin use to reduce VTE risk.

Another biological mechanism may include the anti-tumor effects of statins and aspirin. In endometrial cancer, VTE is strongly associated with recurrent disease [6]. Agents that might reduce cancer recurrence may indirectly reduce the risk of VTE. Recent clinical data have shown that statins and aspirin may be protective against disease progression in endometrial cancer [15,16]. However, these studies did not examine VTE, and this association remains understudied.

Our results showed that type of statin also affects VTE incidence in endometrial cancer. Specifically, simvastatin demonstrated the largest reduction of VTE risk compared to other statins (Table 4). Our findings are consistent with a recent large-scale population-based prospective study in that simvastatin significantly reduced VTE risk whereas other higher potency statins did not as shown in a general population [25]. However, possibility for a lack of adequate sample size may be a concern. That is, rosuvastatin and fluvastatin uses were suggestive for decreased VTE risk but it did not quite reach statistical significance in their study. Whether different statin types exert different anti-inflammatory or -tumor effects resulting in altered VTE risk in endometrial cancer would be of interest and further study is warranted.

Strengths of this study include the large sample size, allowing various adjustment models and rigorous analysis to ensure the durability of the association between statin use and VTE risk. Weaknesses of this study include lack of information on the dose and duration of

medications, which may suggest a volume-dependent risk reduction [24]. Data on compliance in medication usage or discontinuation of medication during follow-up was not available. A relatively short follow-up time additionally limits the accuracy of capturing VTE events. Side effects related to statin and aspirin use were also not available, and a composite endpoint together with risks and benefits was not assessable.

An indication bias inherent to this type of retrospective study is a major concern [27]. Our study showed that statin or aspirin users were more likely to have factors associated with decreased risk of VTE (young, minimally-invasive surgery, or non-chemotherapy). While we addressed these confounding factors with multivariable models, exact risk adjustment for VTE remains immeasurable in retrospective study. A potential solution could be to compare to the active comparator with a new-user design [27]. However, such a study may favor more healthy patients as those with the worst disease prognosis probably do not receive statins/aspirin. We have previously addressed survival effects of statin/aspirin [13]: aspirin use was protective for endometrial cancer survival whereas statin use was not.

Another limitation is the relatively small event number for VTE, which made sub-analyses difficult to conduct. Thus, there may be a possible type II error in the association between aspirin use and VTE risk. With an α-level of 0.05, the power of our study to detect a statistically significant impact of aspirin use on occurrence of VTE was <30%, and >400 aspirin users would be needed to reach a power of 80%. Similarly, fewer than expected VTE events in the statin as well as aspirin groups in our study may possibly make the interpretation of adjustment models less reliable due to the possibility of over-adjustment. Given the large number of comparisons, some statistically significant findings would be possibly expected by chance alone. However, throughout the layers of adjustment, the magnitude of statistical significance of the protective effects of statins on VTE was consistent (HR range, 0.33–0.42), implying that the association of statin use and decreased VTE risk holds likely true.

Our study population was predominantly Asian and Hispanic, lying in two continents. Thus, generalizability and reproducibility in different populations may be limited. In a post-hoc analysis, we assessed country of origin, which demonstrated similar results as the original cohort (Table S2). Last, less frequent use of rosuvastatin likely resulted in lack of power to detect the statistical difference as above.

A clinical implication of this study is the possible use of a statin to prevent VTEin women with endometrial cancer. Currently, VTE prevention is not an approved indication for statin or aspirin use, so effects of these medications on the risk of VTE would need to be confirmed with randomized trials. If this effect persists, the use of certain statins and/ or aspirin may also be cost-effective for VTE prophylaxis in high-risk patients as compared to the current standard prophylactic agent(low-molecular-weight heparin). Effects of concurrent statin and aspirin use on VTE risk reduction is also of interest. Additional studies with improved measurement and closer monitoring of medication use are warranted to address this potential role for statins and/or aspirin in endometrial cancer treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Association of statins and VTE remains understudied in endometrial cancer.
- Statin use may be associated with decreased risk of VTE in endometrial cancer.
- Obese non-diabetic women may benefit from statin use to reduce VTE risk.
- Women with aggressive tumors may benefit from statin use to reduce VTE risk.

Table 1

Patient demographics based on statin, aspirin use.

Medication type	**Statin**			**Aspirin**		
Characteristic	**No**	**Yes**	***P*-value**	**No**	**Yes**	***P*-value**
Number	***n* = 2135**	***n* = 392**		***n* = 2308**	***n* = 219**	
Age (years)	60.6 (±10.6)	56.0 (±11.8)	**<0.001**	58.3 (±11.0)	56.6 (±11.8)	**0.031**
Race/ethnicity			**0.003**			**<0.001**
Caucasian	162 (7.6%)	44 (11.3%)		180 (7.8%)	26 (12.0%)	
African	45 (2.1%)	2 (0.5%)		43 (1.9%)	4 (1.9%)	
Hispanic	569 (26.7%)	119 (30.7%)		566 (24.6%)	122 (56.5%)	
Asian	1354 (63.6%)	223 (57.5%)		1513 (65.7%)	64 (29.6%)	
Obesity			**0.001**			**<0.001**
No	1366 (64.6%)	215 (55.4%)		1505 (65.8%)	76 (34.9%)	
Yes	750 (35.4%)	173 (44.6%)		781 (34.2%)	142 (65.1%)	
Hypertension			**<0.001**			**<0.001**
No	1417 (66.4%)	107 (27.3%)		1480 (64.1%)	44 (20.1%)	
Yes	718 (33.6%)	285 (72.7%)		828 (35.9%)	175 (79.9%)	
Diabetes mellitus			**<0.001**			**<0.001**
No	1784 (83.6%)	204 (52.0%)		1899 (82.3%)	89 (40.6%)	
Yes	351 (16.4%)	188 (48.0%)		409 (17.7%)	130 (59.4%)	
Hypercholesterolemia			**<0.001**			**<0.001**
No	1954(91.5%)	69 (17.6%)		1914 (82.9%)	109 (49.8%)	
Yes	181 (8.5%)	323 (82.4%)		394(17.1%)	110 (50.2%)	
CA-125 (IU/L)	19 (IQR 35)	19 (IQR 30)	0.94	19.5 (IQR 35)	18 (IQR 23)	0.26
Histology			0.48			0.74
Type I	1598 (75.0%)	301 (76.8%)		1732 (75.1%)	167 (76.3%)	
Type II	534 (25.0%)	91 (23.2%)		573 (24.9%)	52 (23.7%)	
Cancer stage			0.35			0.14
I-II	1644 (78.2%)	312 (80.4%)		1780 (78.2%)	176 (82.6%)	
III-IV	458 (21.8%)	76 (19.6%)		497 (21.8%)	37 (17.4%)	
Hysterectomy			**0.010**			**0.002**

Medication type	Statin			Aspirin		
Characteristic	**No**	**Yes**	***P*-value**	**No**	**Yes**	***P*-value**
Number	***n* = 2135**	***n* = 392**		***n* = 2308**	***n* = 219**	
Laparotomy	1413 (66.2%)	237 (60.5%)		1531 (66.3%)	119 (54.3%)	
Minimally invasive	612 (28.7%)	141 (36.0%)		666 (28.9%)	87 (39.7%)	
None	110 (5.2%)	14 (3.6%)		111 (4.8%)	13 (5.9%)	
Chemotherapy			**0.009**			**<0.001**
No	1345 (64.8%)	281 (71.7%)		1495 (64.8%)	170 (77.6%)	
Yes	751 (35.2%)	111 (28.3%)		813 (35.2%)	49 (22.4%)	
Cancer recurrence			0.99			**0.004**
No	1792 (84.1%)	330 (84.2%)		1923 (83.5%)	199 (90.9%)	
Yes	339 (15.9%)	62 (15.8%)		381 (16.5%)	20 (9.1%)	

Patient demographics are grouped based on the medication use. Student *t*-test, Mann-Whitney *U* test, Fisher exact test, or chi-square test for *P*-values. Significant *P*-values are emboldened. Abbreviations: CA-125, cancer antigen 125; and IQR, interquartile range.

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Tabe 2

Statin types.

Characteristic	No. (%)
Atorvastatin	113 (28.8%)
Simvastatin	101 (25.8%)
Rosuvastatin	67 (17.1%)
Pravastatin	53 (13.5%)
Fluvastatin	37 (9.4%)
Lovastatin	6 (1.5%)
Cerivastatin	1 (0.3%)
Type not specified	14 (3.6%)
Total	392 (100%)

Table 3

Adjustment models for association of statin, aspirin use and venous thromboembolism risk.

Adjustment model	Demographics alone		Demographics and comorbidity		Demographics, comorbidity, and tumor factors		Demographics, comorbidity, tumor factors, and treatment type		Demographics, comorbidity, tumor factors, and treatment type, and survival events	
Characteristic	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**
Statin										
No	1		1		1		1		1	
Yes	0.42 (0.21–0.83)	**0.012**	0.33 (0.15–0.73)	**0.006**	0.34 (0.15–0.74)	**0.007**	0.38 (0.17–0.85)	**0.018**	0.42 (0.19–0.92)	**0.030**
ASA										
No	1		1		1		1		1	
Yes	0.30 (0.11–0.83)	**0.02**	0.32 (0.12–0.90)	**0.031**	0.41 (0.15–1.14)	0.087	0.41 (0.15–1.14)	0.087	0.54(0.19–1.51)	0.24

Cox proportional hazard regression models for *P*-values. Significant *P*-values are emboldened. Demographics included age (every quartile), race/ethnicity (Asian *versus* non-Asian), and obesity (<30.0, 30–34.9, 35.0–39.9, and ≥40.0). Comorbidities included hypertension (yes *versus* no), diabetes mellitus (yes *versus* no), and hypercholesterolemia (yes *versus* no). Tumor factors included histology (type I *versus* type II), cancer stage (I–II *versus* III–IV), and CA-125 (<35 *versus* ≥35 IU/L). Treatment factors included hysterectomy (none, minimally-in-vasive, and laparotomy) and chemotherapy use (yes *versus* no). Survival events included endometrial cancer recurrence (yes *versus* no). Country type was not entered in the model because of concern for multicollinearity for race. Abbreviations: HR, hazard ratio; CI, confidence interval; and ASA, aspirin.

Table 4

Joint effects of statin and aspirin use on venous thromboembolism risk.

Adjustment model	Demographics alone		Demographics and comorbidity		Demographics, comorbidity, and tumor factors		Demographics, comorbidity, tumor factors, and treatment type		Demographics, comorbidity, tumor factors, treatment type, and survival events	
Characteristic	**Adjusted-HR (95%CI)**	***P*-value***	**Adjusted-HR (95%CI)**	***P*-value***	**Adjusted-HR (95%CI)**	***P*-value***	**Adjusted-HR (95%CI)**	***P*-value***	**Adjusted-HR (95%CI)**	***P*-value***
None	1	**0.004**	1	**0.005**	1	**0.013**	1	**0.028**	1	0.090
Statin alone	0.41 (0.20–0.85)		0.33 (0.14–0.75)		0.33 (0.14–0.75)		0.37 (0.16–0.86)		0.40 (0.18–0.93)	
ASA alone	0.29 (0.09–0.93)		0.31 (0.10–1.00)		0.39 (0.12–1.25)		0.39 (0.12–1.26)		0.51 (0.16–1.64)	
Both	0.14 (0.02–0.97)		0.12 (0.02–0.92)		0.16 (0.02–1.22)		0.18 (0.02–1.37)		0.27 (0.04–2.07)	

Cox proportional hazard regression models forvenous thromboembolism risk.

**P*-values represent interaction. Significant *P*-values are emboldened. Demographics included age (every quartile), race/ethnicity (Asian *versus* non-Asian), and obesity (<30.0,30–34.9,35.0–39.9, and ≥40.0). Comorbidities included hypertension (yes *versus* no), diabetes mellitus (yes *versus* no), and hypercholesterolemia (yes *versus* no).Tumor factors included histology (type I *versus* type II), cancerstage (I–II *versus* III–IV), and CA-125 (<35 *versus* ≥35 IU/L). Treatment factorsincluded hysterectomy (none, minimally-invasive, and laparotomy) and chemotherapy use (yes *versus* no). Survival events included endometrial cancer recurrence (yes *versus* no). Country type was not entered in the model because of concern for multicollinearity for race. Abbreviations: HR, hazard ratio; CI, confidence interval; and ASA, aspirin.

Table 5

Statin type-specific effects on venous thromboembolism.

Adjustment model	Demographics alone		Demographics and comorbidity		Demographics, comorbidity, and tumor factors		Demographics, comorbidity, tumor factors, and treatment type		Demographics, comorbidity, tumor factors, treatment type, and survival events	
Characteristic	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**	**Adjusted-HR (95%CI)**	***P*-value**
None	1		1		1		1		1	
Simvastatin	0.12 (0.02–0.88)	**0.037**	0.11 (0.02–0.86)	**0.035**	0.13 (0.02–0.98)	**0.048**	0.14(0.02–1.03)	0.053	0.17 (0.02–1.30)	0.088
Atorvastatin	na	0.94	na	0.94	na	0.94	na	0.96	na	0.96
Other statins	0.86 (0.42–1.78)	0.69	0.74 (0.32–1.68)	0.47	0.71 (0.31–1.66)	0.43	0.87 (0.37–2.04)	0.75	0.93 (0.39–2.20)	0.87

Cox proportional hazard regression models for *P*-values. Significant *P*-values are emboldened. Demographics included age (every quartile), race/ethnicity (Asian *versus* non-Asian), and obesity (<30.0, 30–34.9, 35.0–39.9, and ≥40.0). Comorbidities included hypertension (yes *versus* no), diabetes mellitus (yes *versus* no), and hypercholesterolemia (yes *versus* no). Tumor factors included histology (type I *versus* type II), cancer stage (I–II *versus* III–IV), and CA-125 (<35 *versus* ≥ 35 IU/L). Treatment factors included hysterectomy (none, minimally-invasive, and laparotomy), chemotherapy use (yes *versus* no), and aspirin use (yes *versus* no). Survival events included endometrial cancer recurrence (yes *versus* no). Country type was not entered in the model because of concern for multicollinearity for race. Abbreviations: HR, hazard ratio; and CI, confidence interval.

Table 6

Interaction of patient demographics and statin use for venous thromboembolism risk.

Characteristic	Adjusted-HR (95%CI)	*P*-value (interaction)
Obesity		
Obese/statin(−)	1	
Obese/statin(+)	0.21 (0.05–0.90)	
Non-obese/statin(−)	0.59 (0.37–0.94)	
Non-obese/statin(+)	0.36 (0.14–0.92)	**0.019**
Diabetes mellitus		
Non-diabetic/statin(−)	1	
Non-diabetic/statin(+)	0.52 (0.29–0.96)	
Diabetic/statin(−)	0.32 (0.12–0.88)	
Diabetic/statin(+)	0.34(0.11–1.02)	**0.020**
Histology		
Type II/statin(−)	1	
Type II/statin(+)	0.28 (0.08–0.96)	**0.023**
Type I/statin(−)	0.63 (0.41–0.96)	
Type I/statin(+)	0.34(0.13–0.91)	
CA-125		
≥35/statin (−)	1	
≥35/statin (+)	0.42 (0.16–1.15)	
<35/statin (−)	0.48 (0.30–0.77)	
<35/statin (+)	0.28 (0.09–0.87)	**0.031**
Surgery type		
MIS/statin (−)	1	
MIS/statin (+)	0.26 (0.06–1.15)	
Laparotomy/statin (−)	1.18 (0.73–1.91)	
Laparotomy/statin (+)	0.64(0.24–1.73)	**<0.001**
Chemotherapy		
Chemotherapy (+)/statin (−)	1	
Chemotherapy (+)/statin (+)	0.42 (0.17–1.06)	
Chemotherapy (−)/statin (−)	0.63 (0.37–1.07)	
Chemotherapy (−)/statin (+)	0.25 (0.07–0.90)	**0.045**
Survival events		
Recurrence (+)/statin (−)	1	
Recurrence (+)/statin (+)	0.37 (0.14–0.99)	
Recurrence (−)/statin (−)	0.22 (0.14–0.37)	
Recurrence (−)/statin (+)	0.11 (0.04–0.34)	**<0.001**

Cox proportional hazard regression models for venous thromboembolism risk. *P*-values represent interaction. All covariates shown in Table 1 were examined, and only significant covariates with $P < 0.05$ are listed. Significant *P*-values are emboldened. Demographics, comorbidity, tumor factors, treatment type, and survival events were entered in the final model. Demographics included age (every quartile), race/ethnicity (Asian versus non-Asian), and obesity (<30.0,30–34.9,35.0–39.9, and ≥40.0). Comorbidities included hypertension (yes *versus* no), diabetes mellitus (yes *versus* no), and hypercholesterolemia (yes *versus* no). Tumor factors included histology (type I *versus* type II), cancerstage (I–II *versus* III–IV), and CA-125 (<35 *versus* ≥35 IU/L). Treatment factors included hysterectomy (none, minimally-invasive, and laparotomy), chemotherapy use (yes *versus* no),

and aspirin use(yes *versus* no). Survival events included endometrial cancer recurrence (yes *versus* no).Country type was not entered in the model because of concern for multicollinearity forrace. Abbreviations: CA-125, cancer antigen 125; MIS, minimally invasive surgery; HR,hazard ratio; and CI, confidence interval.