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An analysis of the association between statin use and risk of endometrial and ovarian cancers in the Women's Health Initiative

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Abstract

Background—Statins have anti proliferative activity in vitro against endometrial and ovarian cancer and can affect levels of reproductive hormones. We analyzed data from the Women's Health Initiative (WHI) to assess whether statins are associated with risk of endometrial and ovarian cancer.

Methods—The WHI study included 161,808 postmenopausal women in which incident cases of endometrial (n = 1377) and ovarian cancer (n = 763) were identified over an average of 10.8 (SD + 3.3) years. Information on statin use and risk factors was collected at baseline and follow-up. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of statin use and risk of endometrial and ovarian cancer. All statistical tests were two-sided.

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Conflict of interest

No authors have disclosed any conflicts of interest with regards to this manuscript.

Results—Statins were used at baseline by 7.5% women and by up to 25% at year nine. The multivariable adjusted HR for risk of endometrial cancer for baseline statin use was 0.74, 95% C.I. 0.59–0.94 and for ovarian cancer was 1.15, 95% C.I. 0.89–1.50. In time-dependent models, statins were not associated with endometrial cancer (HR 0.91, 95% C.I. 0.76–1.08) however there was an increased risk of ovarian cancer (HR 1.30, 95% CI 1.04–1.62), largely attributed to the effect of the hydrophilic statin, pravastatin (1.89, 95% CI 1.24–2.88).

Conclusions—There was a reduction in risk of endometrial cancer among statin users at baseline but not in time-dependent models. Pravastatin use was associated with an increased risk of ovarian cancer. Analyses of larger numbers of cases are needed to evaluate these findings.

Keywords

Statins; Endometrial cancer; Ovarian cancer

1. Introduction

Statins (HMG CoA reductase inhibitors) are the most widely prescribed cholesterol lowering drugs in the United States with an estimated 25% of the US adults 45 years of age or older using statins [1]. In addition to their cardio-protective effects, statins have anti-inflammatory effects and have shown anti-proliferative, apoptotic and anti-invasive properties in cancer cell lines in vitro, suggesting a possible chemopreventive effect [2–10].

HMG CoA reductase is a key enzyme in the mevalonate pathway. Its inhibition leads to down-regulation of downstream products including farnesyl diphosphate (FPP), geranylgeranyl diphosphate (GGPP) and dolichol [2, 3, 7, 8]. FPP and GGPP are involved in multiple molecular pathways known to be deregulated in cancer including the Ras, MEK, PI3K/Akt, Rho kinases, Bcl2 and histone deacetylase pathways. Cancers that commonly carry mutations in these pathways, including endometrial and ovarian cancer [11], may be potential targets for preventive strategies utilizing statins.

Epidemiologic studies of statins and cancer risk have shown mixed results. While findings from a large US cohort showed a reduction in risk of melanoma, endometrial cancer and Non-Hodgkin's Lymphoma [12], results from another large cohort study showed no significant relationship between statins and the risk of 10 different cancers including endometrial cancer [13]. A case control study of endometrial and ovarian cancer found that statin use for >1 year was associated with a lower odds of developing endometrial cancer but not ovarian cancer [14]. Other studies have also shown mixed results for both ovarian and endometrial cancers [15–21].

The Women's Health Initiative (WHI) is the largest multicenter longitudinal study of postmenopausal women in the United States with follow-up on cancer diagnoses through September 2015 [22]. We have previously used data from the WHI to evaluate the relationship between statins and risk of breast cancer [23, 24], colorectal cancer [25], melanoma [26] and pancreatic cancer [27] and have shown a marginal reduction in colon cancer risk associated with lovastatin [25] and a marginal inverse association for pancreatic

cancer associated with low-potency statins [25]. In this report, we examined the relationship between prior statin use and risk of endometrial and ovarian cancer.

2. Methods

2.1. Study population

The population included 161,808 postmenopausal women aged 50 to 79 enrolled in the WHI Clinical Trial (CT) and Observational Study (OS) from October 1, 1993 through December 31, 1998. Study implementation details have been published previously [22, 28, 29]. Follow-up continued from study initiation until planned termination in March 2005, and thereafter for participants providing re-consent; with data collection updated through September 2012.

We excluded women for whom there was no information on statin use ($N = 2$) as well as women with a history of hysterectomy with and without bilateral salpingo-oophorectomy (BSO) from the analysis of endometrial cancer ($n = 67,788$) and women with a history of ovarian cancer at baseline ($n = 212$) or BSO or BSO status unknown ($n = 35,341$) from the analysis of ovarian cancer. In the final analyses after the above exclusions, 126,253 women were included for the ovarian cancer analysis and 94,018 women were included in the analysis for endometrial cancer.

2.2. Statin exposure

Statin exposure and duration was determined at baseline in Clinical Trial (CT) and Observational Study (OS) participants and follow-up information on statin use was updated at year 3 in the OS and years 1, 3, 6, and 9 in the CT group. For this purpose, the participants were asked to bring all prescription medications to all clinic visits and each medication name was entered from the medication containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, CA).

Statin use was defined as use of any HMG-CoA reductase inhibitor. Statins were classified as lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin) or hydrophilic (pravastatin) [30] and by potency: low potency (fluvastatin and lovastatin), medium potency (pravastatin), and high potency (simvastatin and atorvastatin) [31].

2.3. Outcomes

The outcomes of interest were pathologically confirmed invasive endometrial and ovarian cancers. Cases of endometrial cancer that were classified as carcinoma in situ as well as rare histological types (spindle cell, small cell and carcinoid) were also excluded from being counted as cases but contributed to follow up time and were censored at the time of hysterectomy. Similarly, cases of ovarian cancer that were classified as borderline malignant potential were excluded from being counted as cases but contributed to follow up time. All cases were first confirmed with review of medical records and then adjudicated by centrally trained physician adjudicators. Cases that were reported in the WHI through September 2012 were included in the study.

2.4. Covariates

Information regarding potential confounding and modifying variables were collected for each individual cancer by baseline questionnaire including baseline characteristics and known risk factors for invasive endometrial and ovarian cancer, as well as factors associated with health care utilization which might impact both statin utilization and cancer detection. Information on baseline food habits was determined by the WHI food frequency questionnaire [32]. The covariates used in the analysis are listed in Table 1. The medical history variable includes a personal history of diabetes, high cholesterol, myocardial infarction, and angina. BMI was adjusted for as a continuous variable.

2.5. Statistical analysis

The characteristics of statin users at baseline were compared with those of nonusers by Chi-square tests. Annualized rates of cancer (endometrial and ovarian) were calculated according to the use of statins at baseline. Planned selected secondary analyses were conducted by statin-use duration as determined at baseline (<1 year, 1–<3 years, and ≥3 years), type, potency, and lipophilic status. Women who reported using two or more statins were included in analyses that compared ever use of statins to non-users, but were excluded from analyses that examined details of statin use by specific statin type. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each cancer type among statin users versus nonusers, were computed from Cox proportional hazards models. Tests for the proportional hazards assumptions were conducted by fitting a Cox model that included statin use and the interaction of statin use with follow-up time, and testing for a zero coefficient on the interaction term. Base models were adjusted for age and stratified by WHI trial (Hormone Therapy (HT), Dietary Modification (DM) or (OS)), WHI extension study participation, and age group. For both ovarian and endometrial cancer analyses, an a priori set of adjustment variables was used, which included age, BMI, ethnicity, smoking status, education, current medical provider, baseline HT type and baseline HT duration. An additional set of confounders was used in a stepwise fashion to see if estimates changed >10% with the addition of the confounder. The set of confounders tested was family history of breast cancer, mammogram in the last two years, >30% energy from fat, waist circumference, alcohol, family history of colon cancer, age at first birth, ever pregnant, parity, age at menarche, exercise in MET-hours per week, self-reported health status, regular pap smear procedure compliance, history of an abnormal pap smear, aspirin use, NSAID use and medical history (yes, if any treated diabetes or high cholesterol, or history of MI and angina at WHI baseline). None of the confounders tested in the endometrial or ovarian analyses were true confounders and did not make any difference to the a priori adjusted estimates. Separate analyses were performed for endometrial and ovarian cancer subtypes whenever sufficient numbers were available among the subtypes of the specific cancer.

To evaluate the effect of change in statin use over time, final models were rerun by entering statin use as a time-dependent exposure and using updated information on statin use gathered at year three in the OS and year one, three, six and nine in the CT. We censored cancer outcomes in the OS participants 3 years after the last medication update in order to closely parallel measurement of statin exposure in the CT group as the CT group was followed every 3 years in the WHI (years 1, 3, 6, 9) whereas the OS group was followed at

baseline and year 3 only. Participants who had a hysterectomy after baseline were also censored from the endometrial cancer analyses at the time of the hysterectomy report. There was no information available on oophorectomy after baseline. Participants were followed through September 2012 and censored for death, diagnosis of endometrial/ovarian cancer and loss to follow up.

All statistical tests were 2-sided and nominal p values of .05 or less were regarded as statistically significant. Analyses were conducted using Statistical Analysis Software (SAS) version 9.4.

3. Results

The baseline characteristics of statin users and non-users are shown in Table 1. Statin users were more likely to be older (median age 65.6 vs. 63.0 yrs.), have a higher BMI and waist circumference, report a current health care provider and have a history of current or past smoking, diabetes requiring treatment and >30% intake of energy from fat.

Statins were used by 7.5% of women at baseline; 8.1% at year one, 14.2% at year three; 21% at year six and 25.6% at year nine. Table 2 shows the distribution of statin use at baseline by type, duration, potency and lipophilicity (users of more than one statins were excluded from this analysis). Simvastatin was the most common statin used with 29.2% using it at baseline. The majority of statin users took lipophilic statins (77.3%) and 39.4% of users were on a statin classified as low potency, 22.6% medium and 37.9% high potency. Among users at baseline, the percentage of participants using statins for <1 year, 1–<3 years and ≥3 years were 33.3%, 33.9% and 32.7% respectively.

3.1. Endometrial cancer (n = 1377)

The most common subtype of endometrial cancer was endometrioid adenocarcinoma (81.34%) followed by serous adenocarcinoma (8.57%), carcinosarcoma (3.92%), mucinous carcinoma (2.47%) and others (3.71%). The annualized rate of endometrial cancer among statin users and non-users was 0.10% (mean follow-up 11.47 yrs.) and 0.12% (mean follow-up 12.15 yrs.) respectively (Table 3). Statin use at baseline was associated with a statistically significant lower risk of endometrial cancer compared to non-users (HR 0.74, 95% C.I. 0.59–0.94) (Table 3). In the time-dependent analysis (Table 4), overall statin use was not associated with risk of endometrial cancer (HR 0.91, 95% C.I. 0.76–1.08). No individual statin type or statin category (either by lipophilicity or potency) was associated with the risk of endometrial cancer. In the subtype analysis by endometrial cancer histology, baseline statin use was associated with lower risk of endometrioid adenocarcinoma (HR 0.67, 95% C.I. 0.51–0.88) but this was not significant in the time dependent analysis (HR 0.89, 95% C.I. 0.74–1.08). We were not able to perform subtype analyses for other types of endometrial cancer due to the small number of cases.

3.2. Ovarian cancer (n = 763)

The most common subtype of ovarian cancer was serous adenocarcinoma (61.21%) followed by clear cell adenocarcinoma (13.11%), mucinous adenocarcinoma (3.93) and others/unknown histology (21.75%). The annualized rate of ovarian cancer among statin users and

non-users was 0.06% (mean follow-up 8.11 yrs.) and 0.04% (mean follow-up 8.80 yrs.) respectively (Table 3). Statin use at baseline was not associated with ovarian cancer risk in statin users compared to non-users (HR 1.15, 95% C.I. 0.89–1.50) (Table 3). In the time dependent analysis (Table 4), statin use was associated with an increased risk of ovarian cancer (HR 1.41, 95% C.I. 1.10–1.80). In the time dependent models, pravastatin use was associated with an increased risk of ovarian cancer (HR 1.89, 95% C.I. 1.24–2.88). This was again reflected in the hydrophilic statin and medium potency statin categories, as pravastatin is the only statin used by WHI participants in these categories. In the subtype analysis of ovarian cancer histology, baseline statin use was associated with increased risk of serous adenocarcinoma (HR 1.22, 95% C.I. 0.87–1.70) but was not significant in the time dependent analysis (HR 1.29, 95% C.I. 0.98–1.71). Clear cell adenocarcinoma was not associated with baseline statin use (HR 1.39, 95% C.I. 0.70–2.79). We were not able to perform analyses by the other histologic subtypes due to small numbers.

4. Discussion

We analyzed the association of statin use and risk of endometrial and ovarian cancer in the WHI because according to in-vitro studies, these two cancers are postulated to have alterations in molecular pathways that are potentially modulated by statins. Our results showed a significant lower risk of endometrial cancer among statin users at baseline, however these results were not seen in our time-dependent analyses, which take into account statin use over a longer period of time. Similarly we did not see any protective effect of statins in relation to ovarian cancer at baseline or in the time – dependent analyses but showed an increase in risk of ovarian cancer particularly associated with the lipophilic statin pravastatin. This finding however was based only on a small number of cases and may in fact be only due to chance. Among the endometrial cancer histologic subtypes, baseline statin use was associated with a lower risk of endometrioid adenocarcinoma but this finding was not seen in the time dependent analyses. For ovarian cancer histologic subtypes, baseline statin use was associated with higher risk of serous adenocarcinoma but again was not significant in the time dependent analyses.

Molecular evidence supports a potential chemo-preventive role for statins. FPP and GGPP, which are inhibited by statins, are involved in posttranslational modification of many proteins including the Ras proto-oncogene pathway [33]. Ras requires farnesylation by FPP in order to transmit signals from surface receptors and is involved in many intracellular pathways; it increases gene transcription and cellular proliferation through the MEK and PI3K/Akt pathways [34]. Statins reduce farnesylation of Ras and thus can have anti-proliferative effects on cancer cells [2]. Activating mutations in Ras have been reported in many different human cancers, including 20% of endometrioid endometrial cancers, the most common histologic type of endometrial cancer. Components of the Ras-related PI3K/Akt pathway have also been found to be mutated in 40% of ovarian cancer [11].

GGPP is involved in geranylgeranylation of Rho proteins including Rho GTPases which maintain function of Rho kinases through regulation of gene expression, actin cytoskeleton migration and adhesion of cells [35]. Thus by inhibiting production of GGPP, it is feasible that statins may have anti-proliferative and anti-invasive properties.

Statins are chemically classified based on their solubility as either octanol soluble (lipophilic) or water soluble (hydrophilic). Lipophilic statins penetrate the plasma membrane while hydrophilic statins do not [31]. There are reports in the literature suggesting a differential effect of statins on cancer prevention based on the type or class of statin [4, 36–38]. It is postulated that the cellular uptake of statins may be related to their inhibition of cell growth. The only differential effect that we observed in our study is the association of pravastatin (hydrophilic statin) with higher risk of ovarian cancer. This cannot be explained by prior in vitro studies and therefore further investigation is needed.

Despite studies suggesting a strong molecular rationale for an anti-cancer effect of statins, results from epidemiologic studies are conflicting. Our results showing no association of statin use with risk of endometrial cancer are not consistent with some of the published literature in which a potential protective effect of statins for endometrial cancer was demonstrated [12, 14, 16]. In a population based case–control study of 424 cases of endometrial and ovarian cancer and 341 controls, statin use of >1 year was associated with a lower risk of endometrial (OR = 0.56, 95% CI: 0.33–0.94) but not ovarian cancer [14]. Results from the Cancer Prevention Study II Nutrition Cohort also demonstrated a lower risk of endometrial cancer associated with statins (RR 0.65, 95% C.I. 0.45–0.94) [12]. When compared to both these studies, we had a larger number of cases (n = 1377) and like these two studies evaluated duration of use as well with null results overall. In a nested case control study, statin use was associated with a 70% reduction in risk of endometrial cancer (OR 0.30, C.I. 0.11–0.81) compared to users of bile acid sequestrants [16] but this study did not compare statins with non-users and hence cannot be directly compared to our study. Our results are consistent, however, with other published studies that showed no association between statins and endometrial cancer [13, 19, 20]. It is not clear as to why we demonstrated a lower incidence of endometrial cancer with baseline statin use that was not maintained in the time dependent analyses. While the time dependent analysis does take into account updated statin use, the numbers of cases identified in the OS were also censored three years after the last medication update which could have influenced the power of our analysis.

Lastly, we identified an almost two-fold increased risk of ovarian cancer associated with statin use in the time dependent analysis. This effect was largely confined to the effect of pravastatin. Other studies have shown increases in cancer risk associated with statins [12, 39–41] and also specifically with use of pravastatin (for melanoma cancer) [39] but these studies did not specifically find an increased risk with ovarian cancer. We are not aware of a mechanism of action that may explain why pravastatin was associated with an increased risk of ovarian cancer however this may be due to the molecular impact of hydrophilic statins. As stated above, the increase in ovarian cancer risk associated with pravastatin in our study was based on a very small number of cases and needs to be investigated further in the context of a larger study.

The limitations of our study include the low prevalence of statin use at baseline in the WHI and lack of information on medication compliance. However, with the time-dependent analysis we were able to capture changes in statin use over time and by year nine of the WHI approximately 25% of participants had taken a statin. We also did not have information on

oophorectomy during follow up and hence there is some chance of misclassification. The strengths of our study include the prospective cohort design, the large diverse population with detailed cancer risk factor and demographic characterization, adjudicated cancer diagnosis by central review, serial update of statin use and a long follow-up period. The comprehensive data collection in the WHI also allowed for a detailed adjustment for confounding variables.

5. Conclusion

Statin use was not associated with risk of endometrial cancer in the WHI. There was an increased risk of ovarian cancer largely associated with the hydrophilic statin, pravastatin. These results should be confirmed in future analyses of other large data sets.

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1. For a list of all the investigators who have contributed to WHI science, please visit: http://www.whiscience.org/publications/WHI_investigators_longlist.pdf.

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HIGHLIGHTS

- We analyzed statin use and incidence of endometrial & ovarian cancer using the Women's Health Initiative cohort.
- We found no association between statin use and endometrial cancer.
- We found increased risk of ovarian cancer with statin use particularly pravastatin use.

Table 1

Baseline characteristics by statin use.

Characteristics for N = 127,384 women included in either analysis		p-Value	
		Yes	No
		N	%
Age group at screening	50–59	41,816	35.42
	60–69	51,777	43.85
	70–79	24,475	20.73
Race/ethnicity	White	98,255	83.22
	Black	9822	8.32
	Hispanic	4926	4.17
	American Indian	494	0.42
	Asian/Pacific Islander	2960	2.51
	Unknown	1611	1.36
Education	<HS diploma/GED	5953	5.08
	HS diploma/GED	19,253	16.43
	>HS diploma/GED	91,971	78.49
Smoking status	Never	59,359	50.92
	Past	48,853	41.91
	Current	8352	7.17
Hormone therapy use	Never	58,147	49.28
	Past	17,328	14.69
	Current, <5 yrs	14,503	12.29
	Current, 5–<10 yrs	11,528	9.77
	Current, 10 + yrs	16,485	13.97
Hormone therapy use by type	None	58,147	49.25
	E-alone only	24,043	20.36
	E + P only	30,214	25.59
Body mass index (kg/m ²)	Both	5663	4.80
	<25	43,209	36.93
	25–<30	40,073	34.25
	30	33,710	28.81

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Characteristics for N = 127,384 women included in either analysis	No		Yes		p-Value
	N	%	N	%	
	22,190	18.79	3290	35.32	
	744	0.63	96	1.04	
	4938	4.21	1468	15.88	
	1882	1.59	808	8.68	
Current health care provider	8152	6.97	151	1.63	<.0001
	108,748	93.03	9094	98.37	
Medical history (any of diabetes, hyperlipidemia, MI, or angina at WHI baseline)	101,773	86.20	412	4.42	<.0001
Yes	16,295	13.80	8904	95.58	

Table 2

Distribution of statin use at baseline by type, duration, and other statin characteristics.

N = 9316 statin users included in either analysis		No		Yes	
		N	%	N	%
Statin type	No statin use	118,068	100.00		
	Atorvastatin calcium			715	7.67
	Fluvastatin sodium			1125	12.08
	Lovastatin			2450	26.30
	Pravastatin sodium			2056	22.07
	Simvastatin			2726	29.26
	2 or more statins			244	2.62
Statin potency	No statin use	118,068	100.00		
	Low (lovastatin, fluvastatin)			3575	39.41
	Medium (pravastatin)			2056	22.66
	High (simvastatin, atorvastatin)			3441	37.93
Lipophilicity	No statin use	118,068	100.00		
	Hydrophobic statin			7016	77.34
	Other statin			2056	22.66
Statin duration of use (years)	No statin use	118,068	100.00		
	<1			3103	33.31
	1–<3			3158	33.90
	3			3055	32.79

Table 3

Cancer hazard ratios (HRs) by baseline statin use.

Endometrial cancer ^a										Ovarian cancer ^b			
	N	Case	Annualized %	Mean fup (y)	Age-adjusted HR	Multivariable adjusted HR	N	Case	Annualized %	Mean fup (y)	Age-adjusted HR	Multivariable adjusted HR	
Statin													
No	87,365	1299	0.12%	12.15	1.00	1.00	117,028	701	0.05%	12.62	1.00	1.00	
Yes	6653	78	0.10%	11.47	0.78 (0.62–0.98)	0.74 (0.59–0.94)	9225	62	0.06%	11.87	1.09 (0.84–1.42)	1.15 (0.89–1.50)	
Statin type													
No use	87,365	1299	0.12%	12.15	1.00	1.00	117,028	701	0.05%	12.62	1.00	1.00	
Atorvastatin	6	0.11%	10.40	0.83 (0.37–1.85)	0.65 (0.27–1.56)		0	0.00%	10.84	NA	NA	NA	
Fluvastatin	508	15	0.17%	11.35	1.30 (0.78–2.17)	1.13 (0.65–1.95)	708	7	0.05%	11.63	1.01 (0.48–2.12)	1.06 (0.50–2.24)	
Lovastatin	783	18	0.09%	11.85	0.66 (0.42–1.06)	0.67 (0.42–1.06)	1110	18	0.06%	12.31	1.15 (0.72–1.83)	1.21 (0.75–1.93)	
Pravastatin	1770	17	0.10%	11.38	0.77 (0.47–1.24)	0.79 (0.49–1.27)	2428	18	0.07%	11.79	1.42 (0.89–2.27)	1.52 (0.95–2.44)	
Simvastatin	1482	21	0.09%	11.50	0.72 (0.47–1.11)	0.68 (0.43–1.05)	2042	17	0.05%	11.89	1.05 (0.65–1.70)	1.09 (0.67–1.77)	
	1947						2696						
Statin category													
No use	87,365	1299	0.12%	12.15	1.00	1.00	117,028	701	0.05%	12.62	1.00	1.00	
Lipophilic	5008	60	0.10%	11.49	0.80 (0.62–1.04)	0.74 (0.56–0.97)	6942	42	0.05%	11.89	0.98 (0.72–1.34)	1.03 (0.75–1.41)	
Hydrophilic	1482	17	0.10%	11.38	0.77 (0.47–1.24)	0.79 (0.49–1.27)	2042	18	0.07%	11.79	1.42 (0.89–2.27)	1.52 (0.95–2.44)	
Statin potency													
No use	87,365	1299	0.12%	12.15	1.00	1.00	117,028	701	0.05%	12.62	1.00	1.00	
High	2455	27	0.10%	11.27	0.74 (0.51–1.09)	0.67 (0.45–1.00)	17	0.04%	11.67	0.84 (0.52–1.37)	0.88 (0.55–1.43)		
Medium	1482	17	0.10%	11.38	0.77 (0.47–1.24)	0.79 (0.49–1.27)	3404	18	0.07%	11.79	1.42 (0.89–2.27)	1.52 (0.95–2.44)	
Low	2553	33	0.11%	11.70	0.85 (0.60–1.21)	0.80 (0.56–1.15)	2042	25	0.06%	12.09	1.10 (0.74–1.65)	1.16 (0.78–1.74)	
							3538						
Statin duration													
0	87,365	1299	0.12%	12.15	1.00	1.00	117,028	701	0.05%	12.62	1.00	1.00	
<1 year	2192	23	0.09%	11.36	0.72 (0.47–1.08)	0.64 (0.42–0.99)	3034	18	0.05%	11.73	0.97 (0.61–1.55)	1.03 (0.64–1.64)	
1–<3 years	2207	28	0.11%	11.54	0.84 (0.58–1.22)	0.80 (0.54–1.18)	2171	21	0.06%	11.92	1.12 (0.72–1.73)	1.19 (0.77–1.84)	
3 y	2091	26	0.11%	11.49	0.82 (0.55–1.20)	0.81 (0.55–1.19)	2923	21	0.06%	11.94	1.16 (0.75–1.79)	1.21 (0.78–1.87)	

All models contain strata for trial, WHI extension study, and age group. Base model was adjusted by continuous age.

Multivariate model adjusted for age (continuous), BMI (continuous), ethnicity, smoking status, education, current medical provider, baseline HT use, baseline HT duration.

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Women reporting hysterectomy at WHI baseline excluded; women with self-report of hysterectomy during follow-up were censored when reported.
Women with history of ovarian cancer, bilateral and unknown oophorectomy at WHI baseline were excluded.

Table 4

Cancer Hazard Ratios (HRs) by statin use using time dependent models.

	Endometrial cancer		Ovarian cancer	
	Age-adjusted HR	Multivariable adjusted HR	Age-adjusted HR	Multivariable Adjusted HR
Statin				
No	1.00	1.00	1.00	1.00
Yes	0.95 (0.80–1.13)	0.91 (0.76–1.08)	1.28 (1.04–1.59)	1.30 (1.04–1.62)
Statin type				
No use	1.00	1.00	1.00	1.00
Atorvastatin	0.95 (0.74–1.22)	0.92 (0.71–1.19)	1.14 (0.81–1.60)	1.13 (0.79–1.60)
Fluvastatin	0.83 (0.44–1.54)	0.76 (0.40–1.47)	1.49 (0.80–2.80)	1.31 (0.65–2.65)
Lovastatin	0.67 (0.38–1.18)	0.64 (0.36–1.13)	1.11 (0.59–2.08)	1.07 (0.55–2.07)
Pravastatin	0.96 (0.64–1.43)	0.97 (0.65–1.45)	1.73 (1.13–2.64)	1.89 (1.24–2.88)
Simvastatin	1.12 (0.84–1.48)	1.04 (0.78–1.39)	1.22 (0.83–1.79)	1.26 (0.85–1.88)
Statin category				
No use	1.00	1.00	1.00	1.00
Lipophilic	0.99 (0.83–1.19)	0.94 (0.78–1.13)	1.23 (0.97–1.56)	1.22 (0.95–1.56)
Hydrophilic	0.82 (0.56–1.22)	0.83 (0.56–1.23)	1.57 (1.05–2.34)	1.72 (1.15–2.56)
Statin potency				
No use	1.00	1.00	1.00	1.00
High	1.00 (0.83–1.22)	0.94 (0.77–1.15)	1.20 (0.93–1.56)	1.22 (0.93–1.60)
Medium	0.95 (0.64–1.42)	0.96 (0.64–1.68)	1.72 (1.12–2.62)	1.87 (1.23–2.86)
Low	0.73 (0.48–1.11)	0.68 (0.44–1.05)	1.27 (0.81–1.99)	1.16 (0.71–1.89)

All analyses were stratified by WHI trial, extension study and age group.

Base model was adjusted by age.

Multivariable model adjusted for age, BMI, ethnicity, smoking, education, current medical provider, baseline HT use, baseline HT duration.