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Statin use and female reproductive organ cancer risk in a large population-based setting

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Abstract

Objective—Statins are an effective and commonly used cholesterol-lowering medication class, but their hypothesized effects on cancer risk remain uncertain. We evaluated the association between statin use and endometrial as well as ovarian cancer risks.

Methods—We conducted a retrospective study with two cohorts of women aged 45–89 years during 1990–2004 within an integrated healthcare delivery system. Information on statin use and covariates were obtained from automated databases. We identified cancer cases through the Surveillance, Epidemiology, and End Results registry. Multivariable Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for incident invasive endometrial and ovarian cancers among statin users compared to nonusers.

Results—Women were followed for a median of about six years. Among 73,336 women studied, 568 endometrial cancer cases were identified. During the study period, 6% of women used statins for at least one year and the median duration of use was 3.1 years. Although not statistically significant, we found a reduction in endometrial cancer risk among statin users (HR = 0.67; 95% CI: 0.39–1.17) compared to nonusers. We identified 326 ovarian cancer cases in a cohort of 93,619 women. There was also a nonsignificant decrease in ovarian cancer risk among statin users (HR = 0.69; 95% CI: 0.32–1.49).

Conclusion—Our study does not support an association between statin use and endometrial as well as ovarian cancers, but a reduced risk cannot be ruled out.

Keywords

Statins; Endometrial cancer; Ovarian cancer; HMG-CoA reductase inhibitors

Introduction

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) are an effective therapeutic class of drugs in reducing plasma cholesterol levels and in preventing cardiovascular disease [1]. Use of statins has increased dramatically since their introduction to the United States in 1987, and five of the six statins on the market were among the top 200 prescribed drugs in 2006 [2].

Despite benefits on cardiovascular disease, statins were found to have carcinogenic properties in a review of studies in rodents [3], and two clinical trials reported an increased cancer risk among pravastatin users compared to placebo [4,5]. However, mechanistic studies suggest statins may in fact have chemopreventive potential against cancer [6,7]. These mechanistic data are relatively strong and suggest statins inhibit cancer cell growth and lead to apoptotic cell death through their inhibition of the mevalonate pathway, although other mechanisms have been suggested [6]. Many products of the mevalonate pathway are necessary for critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression [6,7]. Disruptions of these processes in neoplastic cells by statins may result in control of tumor initiation, growth, and metastasis [7].

While the association between statin use and risk of breast, prostate, and colorectal cancer are relatively well studied, there are only a few studies of statin use and female reproductive cancer risk [8–12]. Of the few published studies, one reported a significant decreased risk of uterine cancer among statin users [8], and another a suggested decreased risk of ovarian cancer among women with more than five years of statin use [12]. We conducted a cohort study within a large integrated healthcare delivery system to assess the association between statin use and risk of endometrial as well as ovarian cancers. We previously published results on the association of statin use and breast cancer risk [13], and prostate cancer risk [14] using a similar methodology as described below.

Materials and methods

Study population

We conducted a dynamic, retrospective cohort study among women enrolled in Group Health, a nonprofit integrated delivery system that provides comprehensive health care on a pre-paid basis to approximately 550,000 individuals throughout western Washington State. Group Health's Institutional Review Board approved the study.

We identified 97,159 women who were (1) between the age of 45 and 89 years during the study period of January 1, 1990 to July 31, 2004; (2) continuously enrolled in Group Health's integrated group practice for at least two years during the study period unless death occurred; and (3) residing in one of 13 counties covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry.

The first cohort was selected to evaluate the association between statin use and endometrial cancer risk. Women who had a prior history of endometrial cancer, either in-situ or invasive, as identified by the International Classification of Diseases for Oncology (ICD-O) code of C54.0–C54.9 in the SEER cancer registry were excluded. We also excluded women with a history of hysterectomy prior to study entry as identified in Group Health's health encounter databases and the self-administered Breast Cancer Screening Program (BCSP) risk survey [15].

We assessed the association between statin use and risk of ovarian cancer in the second cohort. Women who had a prior history of ovarian cancer (in-situ or invasive) as recorded in

the SEER cancer registry (ICD-O code C56.9) or in the BCSP risk survey were excluded. We also excluded women with a history of unilateral or bilateral oophorectomy prior to study entry as identified in Group Health's health encounter databases and the BCSP risk survey [15].

Data collection

In both cohorts, we ascertained information on health plan enrollment, health care utilization including medication use, diagnoses, and procedures that are recorded and maintained in Group Health's automated databases [16]. Group Health's automated pharmacy data are considered a complete source of medication use and it is estimated that enrollees obtain about 97% of their medications at Group Health pharmacies [17,18]. Computer linkage between active Group Health enrollees and the western Washington SEER cancer registry provides complete ascertainment of cancer cases [19]. Similarly, Washington State Death records for active enrollees are regularly obtained [20].

Women are invited to join Group Health's Breast Cancer Screening Program (BCSP) when they turn 40-year-old or when they enroll in Group Health after 40 years of age [15]. Women participating in the BCSP complete breast cancer risk factor questionnaires at program enrollment and this information is updated at the time of each mammogram. Approximately 86% of women complete the questionnaires, and the data are available in automated databases [19]. We collected risk factor data from the survey closest in time to entry into the study. However, data are missing on a proportion of women partly because risk factor questions were added to the survey over the course of the study period.

Statin use

We identified all statins (atorvastatin, cerivastatin, lovastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin) dispensed at Group Health pharmacies during the study period through the automated pharmacy database. For each statin dispensing, we estimated the date when the prescription should have run out (run-out date) based on the date dispensed, quantity dispensed, and instructions for use. A new run-out date was set with each successive dispensing. Successive dispensings with less than a 60-day time interval between the run-out date of one dispensing and fill date of the subsequent dispensing were considered continuous use. Total duration of statin use was calculated as the sum of all periods of continuous use during the study period.

We defined statin users as women with at least two dispensings for a statin within any six-month period, who used statins for at least one year. Nonusers included women with no or one dispensing for a statin or less than one year of statin use. Among statin users, we calculated the cumulative length of statin use since they became users and categorized them into 1–2.9 years, 3–4.9 years, and 5+ years of use. We were unable to evaluate dose because there were few high dose statin users.

Covariates

The majority of information on potential confounders for endometrial and ovarian cancers was determined from the BCSP risk survey completed at a time closest to the beginning of study period: weight and height [to calculate body mass index (BMI, in kg/m²)], smoking status, and parity.

We used Group Health outpatient, inpatient, laboratory, pharmacy, and administrative data to identify other possible confounders. We defined diabetics as women with at least one of the following: (1) 2+ fills for a medication used to treat diabetes (e.g., sulfonylureas, insulin), (2) a fasting glucose >125 mg/dL confirmed by a second out-of range test within

one year, (3) a random glucose >200 mg/dL also confirmed by a second test within one year, or (4) a hospital discharge of diabetes at any time during enrollment [21]. Hormone therapy use was defined as 2+ dispensings for systemic estrogen (oral or transdermal) either alone or in combination with progestin. Other lipid lowering drug use was defined as 2+ dispensings for bile acid sequestrants, niacin, or fibrates. Hypercholesterolemia was defined as low density lipoprotein ≥ 160 mg/dL or total cholesterol ≥ 240 mg/dL. High triglyceride was defined as triglyceride level ≥ 150 mg/dL. We also ascertained smoking status and history of endometriosis from outpatient encounter data.

Statistical analysis

Follow-up of both study cohorts extended from January 1, 1991 or one year after enrollment in Group Health if later than January 1, 1990 until the earliest of the following: diagnosis of an incident invasive female reproductive organ cancer of interest (i.e., endometrial or ovarian cancer), 90 years of age, death, disenrollment from Group Health, hysterectomy (for endometrial cancer study cohort) or oophorectomy (for ovarian cancer study cohort), or the end of the study period (July 31, 2004). In both analyses, we continued to follow women if they developed cancer in other reproductive organs.

Statin use was modeled as a time-varying exposure. Once a woman had at least two dispensings for statin within any six-month period and used statin for at least one year, she would be considered a user for the rest of the follow-up period. We used Cox proportional hazards models with calendar time as the time scale to examine the association between statin use and risk of incident invasive reproductive organ cancer in both study cohorts [22].

We used a stepwise selection method to identify important covariates in the models. In both study cohorts, final models were adjusted for age and BMI in the beginning of the study period, diabetes, high triglyceride and other lipid lowering drug use, which were treated as time-varying covariates. We used a cubic smoothing spline with five knots to model age and body mass index. Cubic smoothing splines provide a flexible approach for modeling the nonlinear relation between cancer risk and these important covariates to more completely adjust for confounding [23]. The proportional hazards assumption was evaluated in all models by testing the interaction of statin use with the logarithm of follow-up time. The assumption was met in all models (data not shown). Analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, NC).

Results

Endometrial cancer

Among 97,159 women who met the eligibility criteria, we excluded 520 women with a prior history of endometrial cancer; 22,651 with a history of hysterectomy prior to study entry; and 652 who reached 90 years of age when follow-up began (January 1, 1991 or one year after enrollment in Group Health). There were 73,336 women included in the analysis and 7,331 (10%) had a hysterectomy during the follow-up period. Five hundred and sixty-eight (0.8%) women developed an invasive endometrial cancer during the follow-up period. Distribution of SEER summary stage at the time of endometrial cancer diagnosis was 76% localized, 16% regional, 6% distant, and 2% unstaged.

After the one-year enrollment at Group Health, women were followed for a range of one day to 13.6 years, with a median of 5.6 years of follow-up. About 6% of women used statins for at least a year during the study period. The prevalence of statin use gradually climbed from 0.2% in 1990 to 16.8% in first half of 2004 and the median cumulative duration of statin use during the study period was 3.1 years (range, 1–14.5 years). Almost half (49%) of the statin users had cumulatively used statin for one to 2.9 years, 23% for three to 4.9 years and 28%

for at least five years during the study period. Lovastatin and simvastatin were the most commonly used statins overall, but specific statin use varied throughout the study period due to changes in the Group Health drug formulary [13].

Characteristics of the endometrial cancer study cohort by statin use are described in Table 1. Statin users were older, had a higher BMI, and were more likely to be parous in the beginning of the study than nonusers (Table 1). Compared to nonusers, statin users were more likely to have diabetes, hypercholesterolemia, and high triglycerides. They were also more likely to use hormone therapy and other lipid lowering medications. Approximately 0.8% of nonusers and 0.4% of statin users developed an invasive endometrial cancer during the study period.

The multivariable model results suggested a reduction in endometrial cancer risk among ever users of statins (hazard ratio (HR) = 0.67; 95% confidence interval (CI): 0.39–1.17) compared with nonusers, but the difference was not statistically significant (Table 2).

Ovarian cancer

Among 97,159 women who met the eligibility criteria, we excluded 161 women with a prior history of ovarian cancer; 2,631 with a history of oophorectomy prior to study entry; and 748 who reached 90 years of age when follow-up began. A total of 93,619 women remained in the analysis, of which 11,097 (11.9%) had an oophorectomy, and 326 (0.4%) were diagnosed with an incident invasive ovarian cancer during the follow-up period. Twenty percent of the ovarian cancer cases were diagnosed at localized SEER summary stage, 11% regional stage, 66% distant stage, and 3% unstaged.

Women were followed for a range of one day to 13.6 years, with a median of 5.8 years of follow-up. Almost 7% of women used statins for at least a year during the study period. The pattern and prevalence of statin use over the 15-year study period was similar to that of the endometrial cancer study cohort described above.

Characteristics of the ovarian cancer study cohort by statin use are shown in Table 1, and they were similar to those described for the endometrial cancer cohort. We also found a nonsignificant reduction in ovarian cancer risk among statin users (HR = 0.69; 95% CI: 0.32–1.49) (Table 2).

Discussion

In our cohort study of women between 45 and 89 years of age, we did not find a significant association between statin use and reproductive organ cancer risk, specifically, endometrial and ovarian cancer risk. Although our results suggest a reduced cancer risk among statin users, the differences were not statistically significant. There are only a few epidemiologic studies that evaluated statin use and risk of female reproductive organ cancer risk (Table 2). Our results are similar to two recently published case-control studies [9,10], and two cohort studies [11,12] that reported no association between statin use and endometrial or ovarian cancer risk. In a matched case-control study using the General Practice Research Database in the United Kingdom, Kaye and Jick reported a relative risk of 1.0 (95% CI: 0.4–2.7) for ovarian cancer comparing current statin users to nonusers, and a relative risk of 0.5 (95% CI: 0.1–1.9) for endometrial cancer [9]. Coogan et al. also evaluated endometrial cancer risk in a hospital-based case-control study of women 40–79 years of age and reported that regular statin users and nonusers had similar risk of endometrial cancer (odds ratio = 1.3; 95% CI: 0.7–2.4) [10]. In addition, they did not find any difference in cancer risk between hydrophobic statin users and nonusers (odds ratio = 0.9; 95% CI: 0.4–2.0) [24]. In a large cohort study of women 20 years and older conducted by Friedman et al., the hazard ratio

was 1.1 (95% CI: 1.0–1.3) for endometrial cancer and 0.8 (95% CI: 0.7–1.1) for ovarian cancer among statin users compared to nonusers [12]. When they compared statin users of more than five years to nonusers, the hazard ratio for ovarian cancer reduced to 0.54 (95% CI: 0.27–1.09). Another cohort study conducted in Denmark by Friis et al. also did not find an overall association between statin use and female genital cancer (relative risk = 0.9; 95% CI: 0.6–1.4), although the definition of genital cancer was not specified in the article [11].

In contrast, a nested case–control study by Blais et al. in Canada found a reduced risk of cancer in the uterus among statin users compared with bile acid sequestrant users [8]. The study included 26 cancer cases in the cervix, endometrium and ovary between 1988 and 1994, and statin users were 70% less likely than users of bile acid sequestrants to develop cancer in the uterus (rate ratio: 0.30; 95% CI: 0.11–0.81). The study did not evaluate the difference in cancer risk between statin users and nonusers since the study population was all lipid-lowering medications users. The number of cancer cases was small and it included cancers in different parts of the uterus which may have different etiologies and thus, association with statin.

Our study was conducted in an integrated practice setting where women receive almost all their care within the system, and information on medication use and risk factors are available. Our large population-based cohort demonstrates the dramatic increase in statin use among women over the past decade. Other strengths of our study include the stability of the population over time, extensive data on risk factors and other covariates from subjects' self-report as well as administrative databases, and reliable data on cancer incidence. We also have unbiased data on medication use from our automated pharmacy data. Previous Group Health studies have found that enrollees obtain 97% of their medications at Group Health pharmacies [17,18]. Thus, our study has relatively complete capture of medication use that is not subject to recall bias.

Our study cohort was 86% Caucasian and 30% of women had at least a four-year college degree. Study subjects were from a single healthcare system in western Washington State and may not be representative of other populations. Over the 15 years study period, there were only 18 endometrial cancer cases and 12 ovarian cancer cases among statin users versus 550 and 314 corresponding cancer cases among nonusers. Since small number of cancer cases among statin users, we observed estimates with wide confidence intervals that included one (i.e., no effect). It is therefore likely that only large effects would be detected in our study. We observed a nonsignificant but clinically meaningful decrease in risk of endometrial and ovarian cancer associated with statin use, and we cannot rule out this protective effect of statin given we did not have adequate power to detect a hazard ratio of this size. Another limitation of our study is that we cannot rule out statin exposure misclassification. We did not have information on the actual intake of statins. Subjects who received statin dispensings but did not subsequently take the medication may be misclassified as users. To reduce this possibility, we required at least two dispensings and a year of cumulative use to be considered a statin user. Any bias resulting from classifying a user as a nonuser would bias our findings toward the null. Lastly, residual confounding is always possible in observational studies. We lacked information on potential confounders such as social economic status, diet and level of physical activity, and women prescribed and adherent to statins may differ from nonusers by factors not measured in this study [25]. We also did not have complete collection of family history of ovarian cancer in a first degree relative for women in this cohort, because we only started collecting this information in the BCSP survey in 2001. Family history of other reproductive organ cancers such as endometrial cancer is not collected in the BCSP survey.

In conclusion, our study suggests a nonsignificant reduced risk of endometrial and ovarian cancers among statin users compared with nonusers. Hypothesized chemopreventive effects of statins in humans remains to be established. Duncan et al. hypothesized that hydrophilic pravastatin promotes cancer risk by increasing mevalonate synthesis in extrahepatic tissues [26]. We were unable to evaluate the associations between cancer risk and duration of statin use, and type (hydrophobic and hydrophilic) of statin use given the small number of cancer cases among statin users in our cohort. Due to lingering questions regarding the association between statin use and cancer risk and the limited studies evaluating endometrial and ovarian cancers, a larger study with more statistical power to assess duration and type of statin may be warranted. It may also be worthwhile to conduct a meta-analysis that combines results from our study together with others to increase statistical power.

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Table 1

Demographic characteristics of the study populations by statin use

Characteristics ^a	Endometrial cancer study cohort		Ovarian cancer study cohort	
	Statin user (n = 4,661)	Nonuser (n = 68,675)	Statin user (n = 6,264)	Nonuser (n = 87,355)
	n (%)	n (%)	n (%)	n (%)
Years of follow-up, mean (SD)	10.4 (4.2)	6.6 (4.7)	10.2 (4.2)	6.7 (4.5)
Age in years, mean (SD)	61.4 (8.8)	59.3 (11.1)	61.6 (8.7)	60 (11.1)
BMI in kg/m ² , mean (SD)	27.7 (6.2)	25.7 (5.7)	27.7 (6.2)	25.7 (5.7)
No information	371	13,850	1,810	
<18.5 (underweight)	30 (0.7)	1,531 (2.8)	33 (0.7)	1,524 (2.8)
18.5–24.9 (normal)	1,675 (39.1)	28,121 (51.3)	1,706 (38.3)	27,970 (51.4)
25–29.9 (overweight)	1,361 (31.7)	15,077 (27.5)	1,435 (32.2)	14,935 (27.4)
30+ (obese)	1,224 (28.5)	10,096 (18.4)	1,280 (28.8)	10,000 (18.4)
Parity				
No information	345	12,757	346	12,811
No	454 (10.5)	7,481 (13.4)	547 (9.2)	9,432 (12.7)
Yes	3,862 (89.5)	48,437 (86.6)	5,371 (90.8)	65,112 (87.3)
Endometriosis				
No	4,645 (99.7)	68,481 (99.7)	6,242 (99.6)	87,122 (99.7)
Yes	16 (0.3)	194 (0.3)	22 (0.4)	233 (0.3)
Diabetes				
No	2,993 (64.2)	63,027 (91.8)	4,043 (64.5)	79,728 (91.3)
Yes	1,668 (35.8)	5,648 (8.2)	2,221 (35.5)	7,627 (8.7)
Hypercholesterolemia				
No	790 (16.9)	44,819 (65.3)	1,012 (16.2)	54,946 (62.9)
Yes	3,871 (83.1)	23,856 (34.7)	5,252 (83.8)	32,409 (37.1)
High triglycerides				
No	1,592 (34.2)	61,560 (89.6)	2,008 (32.1)	77,054 (88.2)
Yes	3,069 (65.8)	7,115 (10.4)	4,256 (67.9)	10,301 (11.8)
Hormone therapy use				
No	2,597 (55.7)	45,210 (65.8)	4,153 (66.3)	64,123 (73.4)
Estrogen only	206 (4.4)	4,192 (6.1)	267 (4.3)	4,058 (4.6)
Estrogen + Progestin	1,858 (39.9)	19,273 (28.1)	1,844 (29.4)	19,174 (21.9)
Other lipid lowering agents use				
No	3,507 (75.2)	67,128 (97.7)	4,611 (73.6)	85,022 (97.3)
Yes	1,154 (24.8)	1,547 (2.3)	1,653 (26.4)	2,333 (2.7)

^a All characteristics except a history of endometriosis were statistically different between statin users and nonusers in both cohorts (p -value <0.05 from χ^2 test for categorical variables or t -test for continuous variables)

Table 2

Association between statin use and female reproductive organ cancer risk from the current study and previously published studies

Author (year of publication)	Study cohort Age (years)	Study period and design	Definition of statin use	Endometrial cancer		Ovarian cancer	
				No. cases User	Nonuser	No. cases User	Nonuser
Yu (current study)	45–89	1990–2004 Cohort study	Ever versus never users Ever use: 2+ dispensings for 1+ year of cumulative use	18	550	12	314
Coogan (2007)	40–79	1991–2005 Hospital-based case–control study	(1) Regular versus never users	19	194	–	–
			Regular use: use 4+ times per week for 3+ continuous month and began use 12+ months before hospital admission				
			(2) Hydrophobic statin versus never users	8	194		
Friedman (2008)	20 and older	1994–2003 Cohort study	(3) Hydrophilic statin versus never users	5	194		
			(1) Ever versus never users	199	Did not report	79	Did not report
			Ever use: 1+ dispensing				
Friis (2005)	30–80	1989–2002 Cohort study	(2) > 5 years of use versus never users	29		8	
			Ever versus never users	24	1,738	–	–
Kaye (2004)	50–89	1990–2002 Matched case–control study	Ever use: 2+ dispensings				
			Current versus never users	3	70	6	85
			Current use: 1+ dispensing within the year before index date				
Blais (2000)	65 and older	1988–1994 Nested case–control study	Statin versus bile acid-binding resins users	26	Did not report	–	–
			Cancer in cervix, endometrium and ovary				

HR hazard ratio; OR odds ratio; RR relative risk; 95% CI 95% confidence interval