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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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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.

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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.

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.

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-

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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

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