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Statin Therapy and Association with Ovarian Cancer risk in the New England Case Control (NEC) Study

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Abstract

Statins are widely used to lower blood cholesterol and reduce risk for cardiovascular diseases, but attention has recently focused on a role in cancer prevention or therapy. Here we present data from a large case-control study addressing whether statin use can lower the risk for epithelial ovarian cancer (EOC).

Between 1992 and 2008, data including medications used for at least six months were collected from 2040 cases with EOC and 2100 frequency-matched controls without the disease who participated in the New England Case Control study. We used unconditional logistic regression controlling for matching factors and potential confounders to examine the association between statin use and the risk for EOC.

Overall, women who used statins had 32% lower risk of ovarian cancer compared to non-users (Odds ratio (OR) 0.68, 95% Confidence Interval (CI): 0.54 – 0.85), adjusting for the matching factors and other covariates. The reduced risk was most apparent in women taking a lipophilic statin who began use after age 49, and who had used them 2 – 4.9 years. Statin use was associated with lower risks for both serous and non-serous histologic subtypes with strongest effect seen for mucinous and mixed epithelial subtypes. The association became apparent about a decade after the introduction of statins and did not appear to be confounded by indications for use of statins or medications used concomitantly.

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In this case-control study, statins were found to lower the risk for both serous and non-serous EOC and especially mucinous EOC.

Keywords

Hydroxy-methylglutaryl-CoA reductase inhibitors; Ovarian Cancer; Risk and Prevention; Case-Control

Introduction

Statins inhibit 3-hydroxy-methylglutaryl (HMG) Co-enzyme A reductase and block a rate-limiting step in the biosynthesis of cholesterol ¹. As such they are prescribed for individuals with high cholesterol who have had or are at risk for atherosclerotic cardiovascular disease. Statins have become one of the most widely used drugs in the United States and some other parts of the world ^{2,3}. According to the National Health and Nutrition Examination Survey from 2011–2012, an estimated 38.6 million Americans were using a statin ⁴.

Besides prevention of cardiovascular disease (CVD), statins could impact cancer occurrence or progression based upon cholesterol's role as a precursor of steroid hormones synthesis, activator of the inflammasome, and its involvement in cellular homeostasis and the biologic function of cell membranes. Studies have addressed use of statins as an adjunct to initial chemotherapy or radiotherapy ^{5,6}, in reducing the risk of recurrence ^{6,7}, or as a chemopreventive agent for several types of cancers including colorectal, esophageal, gastric, and liver ^{8–11}.

Because of its high case fatality ratio, chemoprevention is an especially important issue for ovarian cancer. Although the data on ovarian cancer prevention by statins have been mixed ^{12–15}, a meta-analysis of existing studies suggested a lower risk for ovarian cancer associated with statin use ¹⁶. Here we present the association between statin use and ovarian cancer risk in the New England Case-Control (NEC) Study.

Materials and Methods

Study population

We recruited women with ovarian cancer and healthy controls who were residing in Eastern Massachusetts or New Hampshire. As described previously ¹⁷, there were three enrollment phases: 1992 – 1998, 1998 – 2002, and 2003 – 2008. Overall, 3957 women diagnosed with ovarian cancer between ages 18 and 80 years were initially identified through tumor boards and registries, of which 3,083 cases were eligible and 2,203 (71%) cases were enrolled. Information on ovarian cancer characteristics including the histologic subtypes, grades, and stage of the disease were obtained from case pathology reports. Excluding 128 nonepithelial and 35 mixed mesodermal tumors, 2040 cases with epithelial tumors of ovarian, primary peritoneal, and fallopian tube origin, including borderline malignancies (henceforth, epithelial ovarian cancer (EOC)) were included.

Controls were identified through random digit dialing, driver license lists, and town resident lists. From 1992 through 1997, 420 (72%) controls identified through random digit dialing and 102 (51%) identified through lists agreed to participate. From 1998 to 2008, 4,366 potential controls were identified of whom 1,426 (33%) were ineligible. Of the eligible controls, 1,578 (54%) were enrolled making a total of 2100 controls. The controls were frequency matched to cases by five-year age groups and region of residence. Written informed consent was obtained in all phases of the study following which the participants completed an in-person interview. The study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, Massachusetts and Dartmouth College, Hanover, New Hampshire.

Medical conditions and covariates

Information was obtained about women's sociodemographic background, reproductive and family history. Detailed information on medical history including disease diagnoses, surgeries and medications was collected. All questions were asked with respect to a reference date of one year before diagnosis for those with ovarian cancer (cases) and one year before the date of interview for controls. Obesity was defined as BMI $\geq 30\text{kg/m}^2$.

Medications

The participants were asked if they ever used statins for at least six consecutive months prior to their reference date, age at first use of statins, type and quantity, and the duration of use were obtained for statin users. The statin dose was recorded as quantity of tablets they took or their usual number of pills per day, week or per month, and the type of statin characterized by fat (lipophilic) or water (hydrophilic) solubility. Information on use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and bisphosphonate was also collected.

Statistical methods

We calculated the frequency of participant characteristics in cases and controls and statin users and non-users and compared them using chi-square tests. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) to describe the association between statin use and the risk of ovarian cancer. In our initial models, OR were adjusted for age at interview, study center (Massachusetts or New Hampshire) and study phase (1, 2, and 3). Additional models contained terms for body mass index (kg/m^2 , continuous), parity (continuous), educational status (≤ 12 grade, >12 grade), use of oral contraceptive pills (ever, never), history of tubal ligation (no, yes), family history of ovarian cancer (no, yes), smoking status (never, former, current) and menopausal status (pre, postmenopausal). Among the covariates, only BMI had missing data ($n=11$). To prevent records with missing data from being dropped from models, we assigned the median BMI of the sample to records with missing data. To examine how indication for statin use influences the association between statins and ovarian cancer, we examined the association between statins and ovarian cancer risk by whether participants did or did not have common indications for statin use including hypercholesterolemia/atherosclerosis, hypertension, coronary artery disease, obesity, and diabetes. Similarly, we stratified by commonly used drugs that may be used with or interact with statins. We also performed a test of interaction by adding interaction terms to models to

determine if the indications for statin use or concomitant use of other drugs above modify the association observed. The analysis was performed using SAS v 9.4 (SAS Institute, Gary NC, USA). The two-sided P value (Wald test) was used and the level of statistical significance was set at P value = 0.05.

Results

Table 1 illustrates key demographic and reproductive factors that distinguished cases from controls (regardless of statin use) and statin users and non-users (among controls).

Compared to controls, cases were more likely to be white, have less education, and have a family history of ovarian cancer and were less likely to be parous, have used oral contraceptive, and have had tubal ligation. Among controls, statin users compared to non-users were more likely to be from later survey periods, older, less educated, overweight or obese, former smokers, multiparous, and less likely to have used oral contraceptives.

About 9% of cases had used statins compared to 11% of controls (Table 2). The multivariate adjusted OR for the association between statin use and ovarian cancer risk was 0.68 (95% CI: 0.54–0.85). An association between statin use and ovarian cancer was not apparent in the 1992–1998 data; but reduced risk became apparent in the 1998–2002 and significant in the 2003 to 2008 data. An association was not apparent among women who were premenopausal at study entry. Most statin users were taking a lipophilic type of statin.

Although use of either type was associated with similar ORs, only the OR for use of lipophilic statins achieved statistical significance. Compared to non-users, women who took lipophilic statins were 32% less likely to have EOC (OR 0.68, 95% CI: 0.54 – 0.86). The average age at first use of a statin was 58 years and the average duration of use was 5 years. No association between statin use and ovarian cancer was seen in women who began use before age 50, but significant associations were found for women who were 50–59 (OR 0.63, 95% CI: 0.46 – 0.87) and women who were 60 years or older (adjusted OR 0.61, 95% CI: 0.44 – 0.85) at first use. A decreased risk for EOC was most apparent in women who had used statins for 2 to 4.9 years compared to women who never used statins. Among users, there was no association between duration of use and EOC, p -trend=0.34.

In Table 3, we show the association between statin use and EOC risk by histologic subtypes, grade, and invasiveness, stage of EOC, and statin use subdivided by age of first use (<60, 60+) and duration of use (<5, 5+ years). For ever-use, the decreased risk was apparent for all invasive cancers, (OR 0.65, 95% CI: 0.52 – 0.82), serous invasive cancers (OR 0.69, 95% CI: 0.53 – 0.90), high grade serous cancer, (OR 0.70, 95% CI: 0.54 – 0.92), all non-serous invasive cancers, (OR 0.56, 95% CI 0.40 – 0.79), and mucinous cancers, both borderline and invasive combined, OR 0.39, 95% CI 0.18 – 0.82). For the invasive serous tumors, the decreased risk was more apparent for first statin use after age 60 but was seen for both short (< 5) and long > 5) years of use. For mucinous tumors, the decreased risk was more apparent for those who began use at less than 60 years of age and short term use. For all EOC, decreased risk was seen both for early stage (I, II) and late stage (III, IV) disease with the decreased risk mainly apparent in women beginning use at 60 or older and having short term use.

In Table 4, associations between ovarian cancer and statin are examined within strata of possible indications for statin use and use of other medications. For hypercholesterolemia/ atherosclerosis, the main indications for statin use, only about 1% of cases and controls without this diagnosis were taking a statin, whereas 71% of controls and 65% of cases with this diagnosis were using statins. Although reduced ovarian cancer risk was similar for statin users with and without this condition, associations were not statistically significant in either group. Reductions in risk were also found for women with and without hypertension and with and without coronary artery disease with the association being significant in women without hypertension, (OR 0.63, 95% CI: 0.47 – 0.86) and women without coronary artery disease (OR 0.68, 95% CI: 0.53 – 0.86). Reduced risk for ovarian cancer from statin use was seen only in women who did not have obesity, BMI <30, (OR 0.56, 95% CI: 0.43 – 0.74) and did not have type 1 or 2 diabetes, (OR 0.63, 95% CI: 0.50 – 0.80), and the interaction between statin use and obesity was borderline statistically significant ($p = 0.06$). No significant interaction was seen between statin use and smoking although the reduction in risk was most apparent in current smokers. Reductions in risk for EOC associated with statin use were seen whether or not the woman also used aspirin, NSAIDS, or bisphosphonates. A significant interaction was seen with aspirin use such that women using both aspirin and statins had an adjusted OR (and 95% CI) of 0.55 (0.38 – 0.82).

Discussion

In this population-based case-control study, we observed a 32% lower risk of EOC for statin users compared to non-users. The association became apparent in the data collected after 1998. The reduced risk was most apparent in women taking a lipophilic statin, who began use after age 49, and for women who had used them for at least 2 and up to 5 years. Statin use was associated with lower risks of both serous and non-serous histologic subtypes; the strongest and most consistent effect across characteristics of statin use was seen for the mucinous subtype. Except for obesity, where the reduced risk was more apparent in non-obese women, no significant interactions were seen by other indications for statin use including high cholesterol, hypertension, diabetes, NSAID, or bisphosphonate use. Statin users who had also taken aspirin had a lower risk than those who did not use aspirin. Our discussion will focus on the rationale for a role of statins in cancer occurrence and progression, what has been found for cancer, in general, and for ovarian cancer, in particular, and what new information is added by this study.

The ability of statins to lower cholesterol has been convincingly linked to lower the risk for atherosclerotic cardiovascular disease (CVD) in randomized clinical trials (RCTs)¹⁸. But lowering cholesterol might also impact cancer risk deriving from cholesterol's role as a steroid precursor, in cellular homeostasis and biologic function of cell membranes, through activation of the inflammasome and as anti-angiogenic agents¹⁹. Although the RCTs related to CVD prevention would seem ideal for assessing cancer risk as a secondary endpoint, these studies were not powered for cancer occurrence and participants assigned to placebo were allowed to take statins after the trial, which may explain the largely null results²⁰. Thus, there is a need for well-designed cohort and case-control studies to address the role of statins in reducing cancer risk or progression. Regarding prevention, evidence for a role for statins is perhaps strongest for gastric, esophageal, liver and colorectal cancer^{8–11}, but some

studies suggest roles for certain hematologic²¹, lung²², and pancreatic malignancies²³. Regarding cancer recurrence and progression, a role for statins as an adjunct therapy has been suggested for breast^{6,7}, colorectal²⁴, and rectal cancers⁵.

Evidence that statins can induce apoptosis in ovarian cancer cell lines²⁵ suggests a role for statins in ovarian cancer risk or recurrence. Graaf and colleagues²⁶ reported a 20% reduction in ovarian cancer risk among statin users compared to non-users. Liu et al performed a systematic review and reported a 21% reduction in ovarian cancer risk among statin users overall and a 52% reduction with long term (> 5 years) statin use¹⁶. Baandrup et al used data from a Danish nationwide case-control study to look at EOC risk and survival. No overall association with EOC for both risk and survival was observed, but the authors did identify a marginally significant decreased risk of mucinous ovarian tumors among statin users (OR 0.63, 95% CI: 0.39 – 1.00)²⁷. In contrast, a recent study from the Women's Health Initiative (WHI) cohort reported an increased risk of ovarian cancer among statin users, especially for the hydrophilic statin, pravastatin²⁸. Our study is in agreement with lower overall risk for EOC for ever use of statin reported by Graf et al²⁶ and Liu et al¹⁶.

Concerning dose-response there was not a clear drop in risk in our study with > 5 years of use as reported by Liu et al for ovarian cancer and Singh et al for liver cancer²⁹. One limitation of addressing dose-response in our study is that our study began shortly after statins were introduced in the late 1980's and the prevalence of use in all subjects only reached 18.3% in the last phase of our study. This limits the number of subjects who could potentially have had long-term use. However, risks by duration of use in Table 2 did not materially change when the data was restricted to the last phase of the study (data not shown). A second limitation of our data was an absence of information on the dosage of statins used by cases and controls. It is noteworthy that Zhong et al¹¹ reported a non-linear decrease in risk for liver cancer when dosage was taken into consideration.

In our study, the greatest reduction in risk was found for mucinous EOC (borderline and invasive combined). Among the previous studies on ovarian cancer, only the Danish study looked at risk for EOC by subtype²⁷. In this study, the only subtype showing decreased risk with statin use was mucinous. We think this is noteworthy because the epidemiologic evidence for reduction in cancer risk or progression with statins may be strongest for cancers of the gastrointestinal (GI) tract including esophageal, gastric, and colorectal. Histologic similarities between ovarian cancer and especially colorectal cancers can be the source of confusion in whether the diagnosis is a primary mucinous tumor of the ovary or metastasis from a GI tumor³⁰. We consider it unlikely that the stronger association with mucinous tumors occurred in our study because metastatic tumors from the colon were mistakenly recorded as ovarian primaries. Pathology reports were uniformly reviewed and about 75% of cases (Massachusetts) were enrolled from Harvard teaching hospitals with academic pathologists reading the tissue. Additionally, smoking is known to be a risk factor for several of the cancers likely to be reduced by statin use including esophageal, gastric, liver cancers³¹, as well as mucinous ovarian cancer³². The additional fact from this study that the reduction in overall risk for EOC associated with statins was most apparent for current smokers suggests that the pathway by which smoking causes cancer may involve elements that can be inhibited by statins. Based on only 1 exposed case, the risk associated statin use

for mucinous cancers of the ovary for current smokers was (OR 0.18, 95% CI: 0.02 – 1.41) compared to the risk for mucinous tumors overall (OR 0.3, 95% CI: 0.13–0.82).

Statins have been characterized by their solubility in fat (lipophilic) or water (hydrophilic) and may differ in their bioavailability and potency, side-effect profiles, and interaction with other drugs or foods. Lipophilic statins achieve higher levels in non-hepatic tissue and may be more potent because of longer half-life, lower dose to achieve maximal effect, and higher volume of distribution³³. Hydrophilic (water soluble) statins are more hepatoselective and rely mostly on active transport via the organic anion transporting polypeptide (OATP) expressed in liver tissues for their hepatic uptake and action³⁴. Some studies suggest that lipophilic statins are associated with a greater reduction in risk of cancer recurrence and improved survival^{7,35,36}, while another study found no difference in the associations between statins and cancer incidence either by their solubility or other characteristics³⁷. In our study, use of either a hydrophilic or lipophilic statin was associated with a 25% reduction in ovarian cancer risk overall. However, the reduction in risk was significant only for use of a lipophilic statin. This may be a simple matter of study power since most of our study participants were using a lipophilic statin (88% vs 12%), but type of statin is an important issue to consider in future epidemiologic studies of statins and ovarian cancer. Future studies should also consider use of nutraceutical alternatives to statins such as red yeast rice—information not systematically collected in this study.

In our study 90% of both cases and controls taking statins had a diagnosis of hypercholesterolemia/atherosclerosis; and, among this group, the decrease in risk for ovarian cancer for statin users was not significant, albeit less than one. Whether this indicates confounding depends upon the underlying relationship between cholesterol and ovarian cancer risk. If high cholesterol per se lowered ovarian cancer risk, this could lead to confounding by indication for use. Alternatively, if low cholesterol actually increased ovarian cancer risk, as has been argued for cancer in general³⁸, then this could lead to confounding by lack of indication for use. From cohort studies there is no evidence that high dietary cholesterol lowers ovarian cancer risk³⁹ or, if anything, raises it;⁴⁰ and cohort studies of women who had serum cholesterol measured prior to ovarian cancer indicate either no association⁴¹ with ovarian cancer risk or increased risk with higher serum cholesterol⁴². Concerning other potential indications for statin use, the effect of statin use on ovarian cancer risk was more apparent in women without coronary artery diseases, hypertension, obesity, or diabetes—reinforcing the idea that statin use, not the indication (or lack of indication) for use for use, is driving the protective effect.

We also examined the effect of statins on ovarian cancer risk with concomitant use of other drugs like aspirin, NSAIDs and bisphosphonates because of previous reports of interactions of these medications with statins in cancer chemoprevention and because these compounds have also been individually associated with lower incidence of common cancers^{43,44}. In our study, we found the risk reduction for EOC with combined use of statins and NSAIDs or combined use of statins and aspirin was greater than that for statin use without NSAIDs or aspirin. The test for interaction was significant for aspirin and statin.

A synergistic effect was not found with bisphosphonates where the risk reduction for EOC was apparent in both users and non-users of bisphosphonates. Despite this, there is biologic credibility for such a synergy. Bisphosphonates have been shown to demonstrate anti-proliferative and pro-apoptotic activities in ovarian cancer cells and in vivo animal models, inhibit cell proliferation and angiogenesis, and induce apoptosis and activation of immune cells⁴⁵. In addition, bisphosphonates inhibit mevalonate pathway and they specifically inhibit farnesyl pyrophosphate synthase which is also along the pathway of mevalonate inhibited by statins⁴⁶ hence their likelihood of interactions with statins. Finally, the use of bisphosphonate with or without statins have also been reported to be associated with reduced risk of ovarian cancer in one epidemiologic study⁴⁷. The topic of synergy between statins and other drugs that may individually lower cancer risk is an important one but may require large studies that have enough women in combined categories of drug use. Our analysis did not consider the precise timing of statin use in relation to aspirin, NSAID, or bisphosphonate use which also may impact on ovarian cancer risk.

To our knowledge, this is the first population-based case-control study to report a reduced risk for EOC, along with its major histologic subtypes, associated with statin use. There was no indication this association is due to a confounding effect of ovarian cancer risk factors and no epidemiologic basis for proposing that high cholesterol as an indication for statin use accounts for the association. The overall association was confined to women who first used statins at age 50 or more suggesting benefit primarily for disease arising postmenopausally. However, when analyzed by histologic subtype, the data suggested reduced risk for serous and all non-serous subtypes with first use at age 60 or more. Results were less striking with first use before age 60, and there was no evidence of reduced risk of clear cell tumors. We think it is noteworthy that the reduction in risk was seen within a decade of their introduction, with relatively short-term use, these observations could reflect that statins operate relatively late in cancer development in preventing precursor lesions from progressing - a model that seems to explain the reduction in colorectal cancer in individual with inflammatory bowel diseases⁸ or esophageal cancer in individuals with Barrett's esophagus¹⁰. Over the past several decades, a decline in both the incidence and mortality of ovarian cancer in the US has been described and attributed to cumulative effects of past oral contraceptive use⁴⁸. We believe that changing patterns of statin use over the past three decades should also be considered as a possible explanation.

The strengths of our study include the relatively large sample size, extensive data on medical history of the participants, and detailed data on the histologic type of ovarian cancer. Limitations of our study include the fact that medication use was self-reported and not verified from pharmacy records. In 2008, data from the National Center for Health Statistics found that about 19% of U.S. women over age 40 were taking a statin⁴⁹ compared to the 20% of controls in the 2003–2008 study. Recall bias is unlikely since a reduction of risk, not an elevated one, was found. Further studies are warranted with an eye towards defining histology-specific relationships and defining interactions with other medications that may impact on ovarian cancer risk. Because of the increasing frequency of statin use and the fact that ovarian cancer is largely a disease of postmenopausal women, it is likely that ovarian cancer incidence will continue to decrease in the coming years, if the association is causal.

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Novelty and Impact:

The ability of statins to lower cholesterol may be relevant to cancer. In a large case-control study spanning sixteen years, statin use was associated with a significantly reduced risk for epithelial ovarian cancer, especially of mucinous histology. The association was not confounded by risk factors for ovarian cancer, indications for statin use, or medications used concomitantly. It is noteworthy that the association became apparent within a decade of the introduction of statins.

Table 1:

Associations between temporal and demographic features and ovarian cancer in all participants and statin use among controls.

	All participants			Controls		
Variable	Cases N (%)	Controls N (%)	p-value [*]	Non-users N (5)	Statin users N (%)	p-value [*]
Study Center						
Massachusetts	1615 (49)	1709 (51)	0.07	1515 (89)	194 (11)	0.35
New Hampshire	425 (52)	391 (48)		340 (87)	51 (13)	
Survey Period						
1992-1998	557 (52)	522 (48)	0.15	513 (98)	9 (2)	<0.0001
1998-2002	658 (48)	721 (52)		660 (92)	61 (8)	
2003-2008	825 (49)	857 (51)		682 (80)	175 (20)	
Age (years)						
Less than 40	316 (47)	361 (53)	0.16	361 (100)	0 (0)	<0.0001
40 to 49	494 (51)	474 (49)		467 (99)	7 (1)	
50 to 59	598 (51)	578 (49)		507 (88)	71 (12)	
60 years and above	632 (48)	687 (52)		520 (76)	167 (24)	
Race						
White	1932 (49)	2031 (51)	0.001	1794 (88)	237 (12)	0.98
Non-white	108 (61)	69 (39)		61 (88)	8 (12)	
Education						
12	616 (54)	516 (46)	<0.0001	440 (85)	76 (15)	0.01
12 and above	1424 (47)	1584 (53)		1415 (89)	169 (11)	
BMI [†]						
<25	1024 (49)	1074 (51)	0.005	997 (93)	77 (7)	<0.0001
25-29.9	556 (47)	628 (53)		528 (84)	100 (16)	
30	458 (54)	389 (46)		322 (83)	67 (17)	
Smoking status						
Never smoked	959 (49)	1007 (51)	0.01	907 (90)	100 (10)	0.004
Former smoker	727 (48)	798 (52)		681 (85)	117 (15)	
Current smoker	354 (54)	295 (46)		267 (90)	28 (10)	
Parity						
0	649 (63)	378 (37)	<0.0001	347 (92)	31 (8)	<0.0001
1-2	826 (47)	931 (53)		841 (90)	90 (10)	
3 and above	565 (42)	791 (58)		667 (84)	124 (16)	
Oral contraceptive use 3months						
No	974 (56)	766 (44)	<0.0001	643 (84)	123 (16)	<0.0001
Yes	1066 (44)	1334 (56)		1212 (91)	122 (9)	
History of tubal ligation						
No	1763 (51)	1681 (49)	<0.0001	1491 (89)	190 (11)	0.30
Yes	277 (40)	419 (60)		364 (87)	55 (13)	

Variable	All participants			Controls		
	Cases N (%)	Controls N (%)	p-value*	Non-users N (5)	Statin users N (%)	p-value*
Menopausal Status						
Pre-menopausal	899 (49)	932 (51)	0.84	916 (98)	16 (2)	<0.0001
Post-menopausal	1141 (49)	1168 (51)		939 (80)	229 (20)	
Hormone replacement therapy [‡]						
Never used	787 (52)	737 (48)	0.002	589 (80)	148 (20)	0.74
Estrogen only	178 (43)	239 (57)		198 (83)	41 (17)	
Estrogen and progesterone	129 (51)	122 (49)		96 (79)	26 (21)	
Other	47 (40)	70 (60)		56 (80)	14 (20)	
Family history of ovarian cancer						
No	1945 (49)	2046 (51)	0.0003	1807 (88)	239 (12)	0.90
Yes	95 (64)	54 (36)		48 (89)	6 (11)	

^{*} p-values from chi-square tests.

[†] BMI was missing for 11 participants.

[‡] Among postmenopausal women.

Table 2:

Association between statin use and ovarian cancer risk.

Characteristic	Cases N (%)	Controls N (%)	Adjusted* OR (95% CI)
Statin use			
No	1852 (91)	1855 (88)	1.00 (referent)
Yes	188 (9)	245 (12)	0.68 (0.54 - 0.85)
Statin use by study period			
1992 – 1998	11 (6)	9 (4)	0.99 (0.39 - 2.53)
1998 – 2002	42 (22)	61 (25)	0.70 (0.45 – 1.08)
2003 – 2008	135 (72)	175 (71)	0.64 (0.49 - 0.85)
Statin use by menopausal status			
Premenopausal	22 (12)	16 (7)	1.17 (0.58 – 2.36)
Postmenopausal	166 (88)	229 (93)	0.68 (0.53 - 0.86)
Type of statin use[†]			
Hydrophilic	23 (12)	29 (12)	0.67 (0.38 - 1.19)
Lipophilic	162 (88)	211 (88)	0.68 (0.54 - 0.86)
Age at first statin (years)[†]			
< 50	34 (18)	26 (11)	1.18 (0.69 - 2.02)
50 to 59 years	76 (40)	110 (45)	0.63 (0.46 - 0.87)
60 years and above	78 (42)	107 (44)	0.61 (0.44 - 0.85)
Duration of statin use[†]			
<2	38 (20)	54 (22)	0.70 (0.45 - 1.08)
2 to 4.9 years	67 (36)	94 (39)	0.63 (0.45 - 0.88)
5 years	83 (44)	95 (39)	0.73 (0.53 - 1.02)

* Adjusted for age (continuous), study site (Massachusetts, New Hampshire), study phase (1, 2, 3), BMI (continuous), parity (continuous), educational status (< 12 grade, >12 grade), oral contraceptive use (yes/no), tubal ligation (yes/no), family history of ovarian cancer (yes/no), smoking status (never, former, current smoker), menopausal status and HRT use (premenopausal, postmenopausal no HRT use, postmenopausal and used HRT).

[†] Among statin users, 8 could not remember the type of statin used and 2 could not recall the age at first use and duration of use.

Table 3:

Characteristic	Statin use			Age at first use (years)			Duration of statin use (years)				
	No N (%)	Yes N (%)	Adjusted* OR (95% CI)	<60	Adjusted* OR (95% CI)	60	Adjusted* OR (95% CI)	<5	Adjusted* OR (95% CI)	5	Adjusted* OR (95% CI)
Controls	1855 (88)	245 (12)	1.00 (referent)	136 (56)	1.00 (referent)	107 (44)	1.00 (referent)	148 (61)	1.00 (referent)	95 (39)	1.00 (referent)
Ovarian cancer											
By histologic type, grade, and invasiveness											
All invasive	1445 (90)	169 (10)	0.65 (0.52 - 0.82)	96 (57)	0.72 (0.54 - 0.97)	73 (43)	0.57 (0.41 - 0.80)	98 (58)	0.66 (0.50 - 0.88)	71 (42)	0.64 (0.45 - 0.90)
Serous all invasive	850 (88)	117 (12)	0.69 (0.53 - 0.90)	61 (52)	0.76 (0.55 - 1.07)	56 (48)	0.63 (0.44 - 0.91)	68 (58)	0.72 (0.52 - 0.99)	49 (42)	0.67 (0.45 - 0.97)
Serous low grade	46 (94)	3 (6)	0.41 (0.12 - 1.41)	1 (33)	0.25 (0.03 - 1.91)	2 (67)	0.67 (0.15 - 3.01)	2 (67)	0.44 (0.10 - 1.91)	1 (33)	0.37 (0.05 - 2.84)
Serous high grade	804 (88)	114 (12)	0.70 (0.54 - 0.92)	60 (53)	0.79 (0.57 - 1.11)	54 (47)	0.62 (0.43 - 0.90)	66 (58)	0.73 (0.53 - 1.01)	48 (42)	0.68 (0.46 - 1.00)
All non-serous invasive	595 (92)	52 (8)	0.56 (0.40 - 0.79)	35 (67)	0.68 (0.45 - 1.03)	17 (33)	0.41 (0.23 - 0.71)	30 (58)	0.55 (0.35 - 0.85)	22 (42)	0.58 (0.35 - 0.96)
Endometrioid invasive	297 (91)	30 (9)	0.70 (0.45 - 1.09)	19 (63)	0.78 (0.45 - 1.33)	11 (37)	0.61 (0.31 - 1.22)	18 (60)	0.72 (0.42 - 1.25)	12 (40)	0.69 (0.35 - 1.35)
Clear cell invasive	104 (91)	10 (9)	0.67 (0.32 - 1.38)	8 (80)	1.01 (0.46 - 2.25)	2 (20)	0.27 (0.06 - 1.16)	6 (60)	0.70 (0.29 - 1.73)	4 (40)	0.61 (0.21 - 1.80)
Mucinous [†]	234 (97)	8 (3)	0.39 (0.18 - 0.82)	4 (50)	0.32 (0.11 - 0.89)	4 (50)	0.51 (0.18 - 1.46)	4 (50)	0.30 (0.11 - 0.85)	4 (50)	0.56 (0.20 - 1.60)
All borderline	407 (96)	19 (4)	0.70 (0.42 - 1.17)	14 (74)	0.83 (0.46 - 1.49)	5 (26)	0.50 (0.20 - 1.29)	7 (37)	0.40 (0.18 - 0.88)	12 (63)	1.30 (0.68 - 2.50)
Serous borderline	236 (94)	14 (6)	0.94 (0.51 - 1.72)	12 (86)	1.27 (0.66 - 2.43)	2 (14)	0.40 (0.09 - 1.68)	5 (36)	0.53 (0.21 - 1.34)	9 (64)	1.84 (0.86 - 3.90)
All non-serous borderline	171 (97)	5 (3)	0.40 (0.16 - 1.03)	2 (40)	0.26 (0.06 - 1.10)	3 (60)	0.63 (0.19 - 2.10)	2 (40)	0.25 (0.06 - 1.04)	3 (60)	0.70 (0.21 - 2.34)
Stage											
I - II	991 (93)	74 (7)	0.63 (0.47 - 0.85)	48 (65)	0.72 (0.50 - 1.03)	26 (35)	0.52 (0.32 - 0.83)	41 (55)	0.57 (0.39 - 0.84)	33 (45)	0.73 (0.47 - 1.13)
III - IV	854 (88)	113 (12)	0.69 (0.53 - 0.90)	61 (54)	0.76 (0.54 - 1.06)	52 (46)	0.63 (0.44 - 0.92)	64 (57)	0.69 (0.50 - 0.95)	49 (43)	0.71 (0.49 - 1.04)

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* Adjusted for age (continuous), study site (Massachusetts, New Hampshire), study phase (1, 2, 3), BMI (continuous), parity (continuous), educational status (12 grade, >12 grade), oral contraceptive use (yes/no), tubal ligation (yes/no), family history of ovarian cancer (yes/no), smoking status (never, former, current smoker), menopausal status and HRT use (premenopausal, postmenopausal no HRT use, postmenopausal and used HRT).

[†] Includes borderline and invasive cases. The OR (95% CI) for statin use in borderline and invasive mucinous invasive cases is 0.32 (0.10–1.06) and 0.42 (0.16–1.11), respectively.

Table 4:

Association between statin use and risk of ovarian cancer among participants with and without hypercholesterolemia, hypertension, coronary heart disease, obesity, diabetes, smoking, or medication use.

Variable	Controls		Cases		Adjusted* OR (95% CI) for ovarian cancer risk	P Int
	Non-users N (%)	Statin users N (%)	Non-users N (%)	Statin users N (%)		
Hypercholesterolemia/atherosclerosis						
No	1763 (99)	22 (1)	1762 (99)	22 (1)	0.87 (0.47 - 1.63)	
Yes	92 (29)	223 (71)	90 (35)	166 (65)	0.71 (0.48 - 1.06)	0.52
Hypertension						
No	1604 (93)	124 (7)	1592 (94)	92 (6)	0.63 (0.47 - 0.86)	
Yes	251 (67)	121 (33)	260 (73)	96 (27)	0.76 (0.53 - 1.08)	0.77
Coronary heart disease						
No	1815 (90)	202 (10)	1799 (92)	157 (8)	0.68 (0.53 - 0.86)	
Yes	40 (48)	43 (52)	53 (63)	31 (37)	0.54 (0.27 - 1.09)	0.48
Obesity						
No	1525 (90)	177 (10)	1466 (93)	114 (7)	0.56 (0.43 - 0.74)	
Yes	322 (83)	67 (17)	384 (84)	74 (16)	1.12 (0.75 - 1.69)	0.06
Diabetes						
No	1798 (89)	214 (11)	1798 (92)	158 (8)	0.63 (0.50 - 0.80)	
Yes	57 (65)	31 (350)	54 (64)	30 (36)	1.35 (0.64 - 2.86)	0.13
Smoking status						
Never	907 (90)	100 (10)	873 (91)	86 (9)	0.77 (0.55 - 1.08)	
Former	681 (85)	117 (15)	647 (89)	80 (11)	0.66 (0.47 - 0.92)	
Current	267 (91)	28 (9)	332 (94)	22 (6)	0.45 (0.24 - 0.86)	0.46
Aspirin use						
No	1532 (91)	143 (9)	1499 (92)	125 (8)	0.78 (0.59 - 1.03)	
Yes	323 (76)	102 (24)	353 (85)	63 (15)	0.55 (0.38 - 0.82)	0.03
NSAIDS use						
No	1112 (91)	109 (9)	1162 (92)	99 (8)	0.74 (0.54 - 1.01)	
Yes	743 (85)	136 (15)	690 (89)	89 (11)	0.65 (0.47 - 0.89)	0.29
Bisphosphonate use						

Variable	Controls		Cases		Adjusted* OR (95% CI) for ovarian cancer risk	P Int
	Non-users N (%)	Statin users N (%)	Non-users N (%)	Statin users N (%)		
No	1800 (89)	219 (11)	1807 (92)	167 (8)	0.68 (0.54 - 0.85)	
Yes	55 (68)	26 (32)	45 (68)	21 (32)	0.51 (0.20 - 1.26)	0.76

* Adjusted for age (continuous), study site (Massachusetts, New Hampshire), study phase (1, 2, 3), BMI (continuous), parity (continuous), educational status (< 12 grade, ≥12 grade), oral contraceptive use (yes/no), tubal ligation (yes/no), family history of ovarian cancer (yes/no), smoking status (never, former, current smoker), menopausal status and HRT use (premenopausal, postmenopausal no HRT use, postmenopausal and used HRT).