Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prospective Analysis of Association between Statin Use and Breast Cancer Risk in the Women's Health Initiative

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Abstract

Background: Statins are a class of cholesterol-lowering drugs that affect many intracellular pathways that may have implications for chemoprevention against cancer. Epidemiologic data on statins and breast cancer are conflicting. We analyzed updated data from the Women's Health Initiative (WHI) to assess the relationship between statins and breast cancer risk.

Methods: The population included 154,587 postmenopausal women ages 50 to 79 years, with 7,430 pathologically confirmed cases of breast cancer identified over an average of 10.8 (SD, 3.3) years. Information on statins was collected at baseline and years one, three, six, and nine. Self- and interviewer-administered questionnaires were used to collect information on risk factors. Cox proportional hazards regression was used to calculate HRs with 95% confidence intervals (CI) to evaluate the relationship between statin use and cancer risk. Statistical tests were two-sided.

Results: Statins were used by 11,584 (7.5%) women at baseline. The annualized rate of breast cancer was 0.42% among statin users and 0.42% among nonusers. The multivariable adjusted HR of breast cancer for users versus nonusers was 0.94 (95% CI, 0.83–1.06). In the multivariable-adjusted, time-dependent model, the HR for simvastatin was 0.87 (95% CI, 0.71–1.07). There was no significant trend by overall duration of use (*P* value for trend 0.68). There was no effect of tumor stage, grade, or hormone receptor status.

Conclusion: Overall, statins were not associated with breast cancer risk.

Impact: Our study is one of the largest prospective observational studies on this topic, and substantially adds to the literature suggesting no relationship between statins and breast cancer risk. *Cancer Epidemiol Biomarkers Prev; 22(10); 1868–76. ©2013 AACR.*

Introduction

Preclinical evidence suggests that statins, the most commonly used cholesterol-lowering medications, may influence mammary cancer growth (1, 2), but the clinical evidence is inconsistent (3). Observational studies of statins and breast cancer risk have shown mixed results, with some studies reporting an increase in risk, (4–9), others showing a protective effect (10–14), and others showing no association (15, 16). In a previous analysis of the Women's Health Initiative (WHI) cohort, Cauley and colleagues reported that, after a mean of 6.7 years follow-up, there was an 18% lower risk of invasive breast cancer seen among women who had reported use of lipophilic statins (11). However, in further analyses limited by the small numbers of cases in medication subgroups, no specific statin was associated with a lower risk of breast cancer. We now reexamine the relationship between statins and breast cancer risk in the WHI with approximately four additional years of follow-up and 3,047 additional breast cancer cases.

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Materials and Methods

Study population

The population included 154,587 postmenopausal women enrolled in the WHI clinical trial (67,327) and

Table 1. Baseline characteristics by statin use at study entry

	No	Yes	
	N (%)	*N* (%)	*P* value
Age group at screening, y			<0.0001
50–59	49,623 (34.70)	2,093 (18.07)	
60–69	63,399 (44.33)	6,039 (52.13)	
70–79	29,983 (20.97)	3,452 (29.80)	
Race/ethnicity			<0.0001
White	118,055 (82.55)	9,485 (81.88)	
Black	12,855 (8.99)	1,054 (9.10)	
Hispanic	5,859 (4.10)	371 (3.20)	
American Indian	629 (0.44)	45 (0.39)	
Asian/Pacific Islander	3,621 (2.53)	459 (3.96)	
Unknown	1,986 (1.39)	170 (1.47)	
Education			<0.0001
<High school diploma/GED	7,478 (5.27)	757 (6.58)	
High school diploma/GED	24,041 (16.94)	2,444 (21.24)	
>High school diploma/GED	110,418 (77.79)	8,305 (72.18)	
Smoking status			<0.0001
Never	72,383 (51.22)	5,592 (48.93)	
Past	58,917 (41.69)	5,126 (44.85)	
Current	10,014 (7.09)	710 (6.21)	
Alcohol			<0.0001
Nondrinker	41,604 (29.29)	4,006 (34.79)	
≤1 drink/d	46,840 (32.98)	3,876 (33.66)	
>1 drink/d	53,593 (37.73)	3,633 (31.55)	
Hormone therapy use			<0.0001
Never	61,619 (43.12)	5,221 (45.13)	
Past	21,947 (15.36)	1,988 (17.18)	
Current, <5 y	16,902 (11.83)	1,210 (10.46)	
Current, 5–<10 y	14,762 (10.33)	981 (8.48)	
Current, 10+ y	27,657 (19.36)	2,169 (18.75)	
Hormone therapy use by type			<0.0001
None	61,619 (43.09)	5,221 (45.07)	
E-alone only	43,048 (30.10)	3,819 (32.97)	
E+P only	30,301 (21.19)	1,954 (16.87)	
Both	8,035 (5.62)	590 (5.09)	
BMI, kg/m^2			<0.0001
<25	50,787 (35.83)	2,854 (24.84)	
25–<30	48,675 (34.34)	4,557 (39.67)	
≥30	42,297 (29.84)	4,077 (35.49)	
Physical activity, MET/wk			<0.0001
Inactive 0 METs	21,822 (16.01)	1,683 (14.89)	
[0,3.75) METs	19,896 (14.59)	1,739 (15.38)	
[3.75, 8.75) METs	27,942 (20.49)	2,506 (22.17)	
[8.75, 17.5) METs	30,722 (22.53)	2,627 (23.24)	
≥17.5 METs	35,954 (26.37)	2,750 (24.33)	
Waist circumference > 88 cm	55,542 (38.98)	5,725 (49.58)	<0.0001
≥30% energy from fat	93,057 (65.19)	6,522 (56.38)	<0.0001
Gail risk score ≥ 1.67	57,163 (39.97)	5,453 (47.07)	<0.0001
Age at menarche			0.5281
Less than 12 years old	31,248 (21.91)	2,580 (22.33)	
12–13 years old	78,419 (54.98)	6,334 (54.83)	
14–15 years old	32,964 (23.11)	2,638 (22.84)	

(Continued on the following page)

Table 1. Baseline characteristics by statin use at study entry (Cont'd)

	No	Yes	
	N (%)	*N* (%)	*P* value
Ever pregnant	129,807 (90.90)	10,471 (90.55)	0.2024
Number of live births			0.0006
None	16,790 (11.80)	1,374 (11.92)	
1–2	48,327 (33.95)	3,714 (32.22)	
3+	77,221 (54.25)	6,440 (55.86)	
Age at first birth, y			0.3471
Never pregnant	12,990 (10.01)	1,093 (10.53)	
No term pregnancy	3,800 (2.93)	281 (2.71)	
<20	18,450 (14.22)	1,468 (14.14)	
20–29	83,989 (64.74)	6,716 (64.68)	
30+	10,495 (8.09)	825 (7.95)	
Bilateral oophorectomy	27,484 (19.29)	2,496 (21.64)	<0.0001
Hysterectomy	59,243 (41.45)	5,262 (45.45)	<0.0001
Benign breast disease			<0.0001
No	106,733 (78.75)	8,672 (77.21)	
Yes, 1 biopsy	20,293 (14.97)	1,752 (15.60)	
Yes, 2+ biopsies	8,502 (6.27)	808 (7.19)	
Family history of female relative with breast cancer	24,639 (18.19)	2,044 (18.71)	0.1803
Aspirin use $\geq$ 80 mg for at least 30 days	27,129 (18.97)	4,050 (34.96)	<0.0001
NSAIDs use	47,420 (33.16)	5,471 (47.23)	<0.0001
Self-reported health status			<0.0001
Excellent	25,664 (18.05)	875 (7.60)	
Very good	59,167 (41.62)	3,912 (33.98)	
Good	45,322 (31.88)	5,019 (43.60)	
Fair	11,014 (7.75)	1,575 (13.68)	
Poor	1,010 (0.71)	130 (1.13)	
Diabetes requiring treatment	5,664 (3.96)	1,137 (9.83)	<0.0001
History of angina	6,575 (4.62)	1,904 (16.55)	<0.0001
History of MI	2,442 (1.71)	1,022 (8.83)	<0.0001
Current healthcare provider	132,133 (93.31)	11,311 (98.42)	<0.0001

observational study (87,266). Study implementation details have been published previously (17–19). In brief, women aged 50 to 79 were enrolled in one or more of four clinical trials [Hormone therapy which included estrogen alone and estrogen plus progesterone trials; dietary modification; and calcium and vitamin D supplementation] or an observational study cohort in 40 U.S. clinical centers from October 1, 1993 through December 31, 1998. Follow-up continued from study initiation until planned termination on March, 2005 and thereafter for participants providing reconsent, with data collection updated through September, 2010 for an average of 10.8 (SD, 3.3) years of follow-up. For the purposes of this analysis, we excluded 7,217 women who had a self-reported prior history of breast cancer at baseline entry into the WHI, and two women for whom information on statin intake was not available.

Statin exposure

Participants in the WHI were asked to bring all current prescription medications to their first screening interview. Reported medications were then matched to the Master Drug Database (First DataBank, Inc.) and duration of use for each medication was recorded. The procedures for collection of data on medication use were repeated in years one, three, six, and nine of follow-up in the clinical trial, and in year three in the observational study. Memory aides were not used for collection of medication use information.

Statin use was defined as any use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor at baseline entry into the WHI. Updated information collected at subsequent participant visits were used to measure statin use as a time-dependent exposure for a secondary analysis. Statins were classified as lipophilic (lovastatin, simvastatin, fluvastatin) or hydrophilic (pravastatin and atorvastatin; ref. 20) and, by potency, as low potency (fluvastatin and lovastatin), medium potency (pravastatin), and high potency (simvastatin and atorvastatin; refs. 21–23).

Outcome

Reported invasive breast cancer cases were initially confirmed by medical record review by trained physician

adjudicators at the clinical centers. Final adjudication and coding for stage using the Surveillance Epidemiology and End Results (SEER) system was done at the Clinical Coordinating Center. Hormone receptor status and HER2 status was based on local laboratory criteria (24).

Covariates

Information on potential confounding and modifying variables were collected by baseline questionnaire including baseline characteristics and known risk factors for invasive breast cancer, as well as factors associated with health-care use and cancer screening, which might impact both statin use and breast cancer detection. Information on baseline food habits was determined by the WHI food frequency questionnaire (25), and interviewer-administered questionnaires were used to determine hormone therapy use, which was defined as any use of hormones for three or more months after menopause. Mammograms and breast exams were mandated by study protocol annually in the two hormone therapy trials and biennially in the dietary modification trial. Mammograms and breast exams were not mandated in the observational study and were left to the discretion of the participant's physician. Information on mammography and breast exams was collected annually in the observational study. The covariates used in the analysis are listed in Table 1.

Statistical methods

The characteristics of statin users at baseline were compared with those of nonusers by χ^2 tests. Annualized rates of breast cancer were calculated for statin users and nonusers at baseline. Planned selected subgroup 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 statin use to none, but were excluded from analyses that examined details of statin use by type, potency or lipophilic status. Separate analyses were conducted for women with ER/PR-positive and ER/PR-negative breast cancer. HRs for breast cancer among statin users versus nonusers, and 95% confidence intervals (CI) were computed from Cox proportional hazards analyses. Tests for the proportional hazards assumptions were conducted by 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.

Cox proportional hazards models were used to assess associations between statin use at baseline and risk of invasive breast cancer. An *a priori* selection of covariates with a 10% backward selection in Cox modeling was used to create a final multivariable-adjusted model. The base model was adjusted for age and baseline hormone therapy use and stratified by trial participation (hormone therapy, dietary modification, or observational study), WHI extension study participation, and age group. The final multivariable model was adjusted for age, body mass index (BMI), ethnicity, smoking status, baseline hormone therapy use and duration of use, family history of breast cancer, education, hysterectomy, bilateral oophorectomy, mammogram within the last two years, age at first birth, parity, age at menarche, alcohol use, percentage energy from fat, nonsteroidal anti-inflammatory drug (NSAID) use, and physical activity. Comparisons of breast cancer tumor characteristics between statin users and nonusers were based on χ^2 and Fisher exact tests.

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 observational study and years one, three, six, and nine in the clinical trial. We censored breast cancer outcomes three years after the last medication update in the observational study to more closely parallel statin exposure in the clinical trial. In addition, we conducted the analysis including censored outcomes. Moreover, we conducted a sensitivity analysis by excluding breast cancer cases diagnosed within two years from baseline in order to allow for sufficient statin exposure to have an effect on risk of breast cancer.

All statistical tests were two-sided with a significance level of 0.05. Analyses were conducted using the Statistical Analysis Software (SAS) version 9.2.

Results

The baseline characteristics of statin users and nonusers are outlined in Table 1. Most of the variables listed were statistically significant due to large numbers. Statin use was reported at baseline by 11,584 women (7.5%) in the WHI cohort. Statin users were more likely to be older, have higher past use of tobacco, and to have larger BMI

Table 2. Distribution of statin use at baseline by type, duration, and other statin characteristics

	N (%)
Statin type	
Atorvastatin calcium	890 (7.68)
Fluvastatin sodium	1,405 (12.13)
Lovastatin	3,037 (26.22)
Pravastatin sodium	2,552 (22.03)
Simvastatin	3,398 (29.33)
2 or more statins	302 (2.61)
Statin potency	
Low (lovastatin, fluvastatin)	4,442 (39.37)
Medium (pravastatin)	2,552 (22.62)
High (simvastatin, atorvastatin)	4,288 (38.01)
Lipophilicity	
Lipophilic statin	7,840 (69.49)
Hydrophilic statin	3,442 (30.51)
Duration of statin use, y	
<1	3,852 (33.25)
1–<3	3,932 (33.94)
≥3	3,800 (32.80)

and waist circumference. Other variables associated with statin use included: bilateral oophorectomy, hysterectomy, history of benign breast disease, mammography within the past two years, use of aspirin and NSAIDS, as well as history of diabetes, angina, and myocardial infarction. Nonuse of statins was associated with current hormone therapy use, less physical activity, and a diet with more than 30% of body energy from fat. There was no association between statin use and age at menarche, prior pregnancies, age at first full-term pregnancy, and family history of breast cancer.

Table 2 shows the distribution of statin use at baseline by type, duration, potency, and lipophilicity. Simvastatin was the most common statin used, with 29.3% reporting it's use at baseline. The majority of statin users took lipophilic statins (69.5%) and 39.4% of users were on a statin classified as low potency, 38% high potency, and 22.6% medium potency. Among users at baseline, the percentage of participants using statins for <1 year, 1–<3 years, and ≥3 years was 33.25%, 33.94%, and 32.8%, respectively.

Table 3 shows the risk of invasive breast cancer by statin use at baseline. The annualized rate of breast cancer was 0.42% among statin users and 0.42% among nonusers. In the multivariable-adjusted model, there was no significant relationship between statin use and breast cancer risk (HR, 0.94; 95% CI, 0.83–1.07). There was no significant reduction in breast cancer risk for prior use of simvastatin (HR, 0.87; 95% CI, 0.70–1.09) or other types of statins, use of two or more statins, lipophilicity, or statin potency. Statin use for less than one year duration was associated with a trend toward an inverse association (HR, 0.78; 95% CI, 0.63–0.98); however, there was no significant trend by overall duration of use (HR, 1.19; 95% CI, 0.91–1.33 for 1–<3 years and HR, 0.97; 95% CI, 0.79–1.19 for ≥3 years; *P*-trend, 0.68). There were no significant differences in the results observed with or without censoring breast cancer outcomes three years after last medication update in the observational study or after exclusion of breast cancer cases diagnosed within two years from baseline (data not shown). Table 4 shows the risk of invasive breast cancer by statin use in a multivariable-adjusted time-dependent

Table 3. Invasive breast cancer incidence (annualized%) and HRs by statin use

	N	Breast cancer	Annualized%	Mean follow-up (y)	Age adjusted[a,b] HR (95% CI)	Multivariable adjusted[a,c] HR (95% CI)
Statin	11,584	366	0.41%	7.71	0.93 (0.83–1.03)	0.94 (0.83–1.06)
Statin type						
No statin use	143,005	5061	0.43%	8.30	1.00	1.00
Two or more statins	302	13	0.53%	8.15	1.26 (0.73–2.18)	0.94 (0.47–1.89)
Atorvastatin calcium	890	24	0.39%	6.85	0.86 (0.57–1.28)	1.04 (0.69–1.57)
Fluvastatin sodium	1,405	40	0.37%	7.63	0.85 (0.62–1.16)	0.82 (0.57–1.17)
Lovastatin	3,037	103	0.42%	8.05	0.95 (0.78–1.16)	0.98 (0.79–1.23)
Pravastatin sodium	2,552	86	0.43%	7.75	0.98 (0.79–1.22)	1.07 (0.85–1.35)
Simvastatin	3,398	100	0.39%	7.60	0.88 (0.72–1.07)	0.87 (0.70–1.09)
Lipophilicity						
No statin use	143,005	5061	0.43%	8.30	1.00	1.00
Lipophilic statin	7,840	243	0.40%	7.78	0.90 (0.79–1.03)	0.91 (0.78–1.05)
Hydrophilic statin	3,442	110	0.43%	7.52	0.95 (0.79–1.15)	1.06 (0.87–1.30)
Statin potency						
No statin use	143,005	5061	0.43%	8.30	1.00	1.00
Low	4,442	143	0.41%	7.91	0.92 (0.78–1.09)	0.93 (0.77–1.13)
Medium	2,552	86	0.43%	7.75	0.98 (0.79–1.22)	1.07 (0.85–1.35)
High	4,288	124	0.39%	7.45	0.87 (0.73–1.05)	0.90 (0.74–1.10)
Duration						
0	143,005	5061	0.43%	8.30	1.00	1.00
<1 y	3,852	104	0.35%	7.81	0.79 (0.65–0.96)	0.78 (0.63–0.98)
1–<3 y	3,932	137	0.45%	7.70	1.03 (0.87–1.22)	1.10 (0.91–1.33)
≥3 y	3,800	125	0.43%	7.62	0.96 (0.80–1.15)	0.97 (0.79–1.19)

[a]Stratified by trial, WHI extension study, and age group.

[b]Base model was adjusted by age and baseline hormone therapy use.

[c]Multivarite model adjusted for age, BMI, ethnicity, smoking status, baseline hormone therapy use, baseline hormone therapy duration, family history of breast cancer, education, hysterectomy, mammogram last two years, age at first birth, parity, age at menarche, alcohol, percentage energy from fats, physical activity, and NSAID.

Table 4. Invasive breast cancer incidence (annualized%) and HRs by time-dependent statin

	Age adjusted[a,b] HR (95% CI)	Multivariable adjusted[a,c] HR (95% CI)
Statin use	0.98 (0.89–1.08)	0.97 (0.87–1.08)
Statin type		
Atorvastatin calcium	0.91 (0.69–1.20)	1.00 (0.75–1.35)
Fluvastatin sodium	1.02 (0.78–1.33)	1.05 (0.78–1.42)
Lovastatin	1.01 (0.83–1.22)	0.98 (0.78–1.23)
Pravastatin sodium	0.97 (0.79–1.19)	1.00 (0.79–1.25)
Simvastatin	0.90 (0.75–1.08)	0.88 (0.71–1.07)
Cerivastatin sodium	0.73 (0.10–5.16)	NA
2 or more statins	1.24 (0.65–2.39)	0.83 (0.34–1.99)
Lipophilicity		
Lipophilic statin	0.98 (0.86–1.11)	0.94 (0.81–1.09)
Hydrophilic statin	0.93 (0.81–1.08)	0.98 (0.83–1.15)
Stain potency		
Low	1.01 (0.86–1.18)	1.01 (0.84–1.21)
Medium	0.98 (0.80–1.20)	1.02 (0.81–1.28)
High	0.90 (0.77–1.05)	0.92 (0.77–1.09)

Abbreviation: NA, not applicable.

[a]Stratified by trial, WHI extension study, and age group.

[b]Base model was adjusted by age and baseline hormone therapy use.

[c]Multivarite model adjusted for age, BMI, ethnicity, smoking status, baseline hormone therapy use, baseline hormone therapy duration, family history of breast cancer, education, hysterectomy, mammogram last two years, age at first birth, parity, age at menarche, alcohol, percentage energy from fats, physical activity, and NSAID.

model. In this model, there was no significant reduction in risk of breast cancer for users of simvastatin (HR, 0.87; 95% CI, 0.71–1.07). Similarly, no significant associations were seen for other statin types, lipophilicity, or statin potency.

Table 5 shows the distribution of breast cancer tumor characteristics by statin use at baseline. There were no significant differences in the distribution of tumor characteristics including stage, grade, ER/PR receptor, and HER2neu status by use of statins. In addition, we looked at the relationship between statin use at baseline and breast cancer risk stratified by other important breast cancer risk factors including hormone therapy, family history of breast cancer, waist circumference, and BMI. There were no significant interactions seen (Table 6).

Discussion

Our updated results from the WHI cohort showed no significant relationship between statin use and breast cancer risk; however, there was a nonsignificant reduction in risk for simvastatin in the multivariable analyses and no significant relationship was seen for lipophilic statins as a group. These results are contrary to the previous analysis by Cauley and colleagues (11) that showed a statistically significant reduction in risk of breast cancer associated with lipophilic statins. However, our results did not show this same reduction in risk. In addition, we showed a modestly protective effect associated with statin use of less than 1-year duration compared with multiple years, which argues against biological plausibility. In our analysis, we censored breast cancer outcomes after year six in the observational study participants in order to closely parallel exposure information available for clinical trial participants, which was different than the methodology used in the earlier WHI analysis by Cauley and colleagues. Moreover, we analyzed the data without censoring, and no significant differences in the results were observed (data not shown).

A number of preclinical findings support the biologic plausibility of a protective effect for statins in relationship to the development of breast cancer. Statins act by inhibition of HMG-CoA reductase and have pleomorphic properties in the cell. The multiple downstream effects of statins may have antiproliferative, anti-invasive, and apoptotic activities (26–29). Farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP), downstream products of the mevalonate pathway, are both involved in posttranslational modification of many proteins (30), such as the Ras molecule, which in turn helps transmit downstream signaling from surface receptors (31). Ras is involved in many intracellular pathways and increases gene transcription and proliferation by acting through the MEK and phosphoinositide 3-kinase (PI3K)/Akt pathways (32) and inhibition of this pathway can have antiproliferative effects on cancer cells (33). In addition, statins have been implicated in reducing cell migration, proliferation, and invasion by inhibiting production of GGPP, which is involved in geranylgeranylation of Rho proteins including Rho GTPases (27) that maintain function of Rho kinases involved in various cellular functions including gene expression, actin cytoskeleton migration, adhesion, and contractility of cells (34).

Earlier observational studies of statins and breast cancer risk have shown mixed results. Individual studies have reported a protective effect (10–14); however, two meta-analyses published in 2005 reported no significant association (15, 16). The most recent meta-analyses, which included 13 cohort and 11 case-control studies with 2.4 million participants and 76,759 breast cancer cases identified through January 2012, also showed no significant relationship between statins and breast cancer risk (RR, 0.99; 95% CI, 0.94–1.04; ref. 3).

Class differences in statins and anticancer efficacy have been explored in previous studies. Lipophilic statins (lovastatin, simvastatin, fluvastatin) penetrate the plasma membrane whereas hydrophilic statins (pravastatin and atorvastatin) do not (22, 35) Cellular uptake of lipophilic statins may be related to their inhibition of cell growth, and this has been supported by a cell culture study in which only lipophilic statins were shown to have anticancer activity (36).

Table 5. Breast cancer characteristics by statin use measured at baseline

	No statin use *N* (%)	Stain use *N* (%)	*P*
Tumor size, cm			0.1103
<5 mm	607 (12.00)	49 (13.39)	
(5–10) mm	1,290 (25.49)	102 (27.87)	
(10–20) mm	1,922 (37.98)	136 (37.16)	
(20–50) mm	878 (17.35)	46 (12.57)	
>50 mm	363 (7.17)	33 (9.02)	
Summary stage (SEER)			0.5670
In situ	54 (1.07)	7 (1.93)	
Localized	3,676 (72.99)	266 (73.48)	
Regional	1,182 (23.47)	82 (22.65)	
Distant	66 (1.31)	3 (0.83)	
Unknown	58 (1.15)	4 (1.10)	
Morphology—grading			0.5786
Well differentiated	1,264 (28.18)	84 (26.25)	
Moderately differentiated	1,954 (43.57)	135 (42.19)	
Poorly differentiated	1,137 (25.35)	89 (27.81)	
Anaplastic	130 (2.90)	12 (3.75)	
Estrogen receptor assay			0.8400
Positive	3,869 (84.87)	277 (84.45)	
Negative	690 (15.13)	51 (15.55)	
Progesterone receptor assay			
Positive	3,207 (71.76)	235 (73.44)	0.5194
Negative	1,262 (28.24)	85 (26.56)	
Her 2/Neu			
Positive	571 (18.09)	35 (15.28)	0.2853
Negative	2,586 (81.91)	194 (84.72)	
Number of positive lymph nodes			0.7701
None	3,321 (65.95)	234 (64.64)	
1–3	817 (16.22)	58 (16.02)	
4+	898 (17.83)	70 (19.34)	
Lymph nodes positive	1,715 (34.05)	128 (35.36)	0.6132

The results from epidemiologic studies which have analyzed specific statin preparation or class have been mixed showing either no relationship (37, 38), an increased risk of breast cancer (6, 7, 39), or a reduced breast cancer risk (10–14). In one case–control study, only fluvastatin was associated with a decreased risk of breast cancer (OR, 0.50; 95% CI, 0.30–0.80) with no association seen overall or with lipophilic statins as a group (12) and, in another case–control study, the specific type of statin was not associated with breast cancer risk, although use of statins for more than five years was related to a trend toward decreased risk (OR, 0.70; 95% CI, 0.40–1.0; ref. 13). In a record-linkage cohort study from Finland, a marginal reduction in breast cancer risk was noted for users of simvastatin (HR, 0.97; 95% CI, 0.95–0.99; ref. 14). In the meta-analysis by Bonovas and colleagues, seven randomized clinical trials were included together with nine cohort studies. Although the overall result of the meta-analysis showed no significant relationship (HR using fixed effects model of 1.04; 95% CI, 0.81–1.33), only two randomized trials were undertaken using simvastatin. Of these, the Heart Protection Study (39), which had 38 incident cases of invasive breast cancer in the simvastatin group and 51 breast cancer cases in the nonstatin group, did not show a protective effect (HR, 0.75; 95% CI, 0.49–1.13) and, in the Scandinavian Simvastatin Survival Study (40), there were only seven incident breast cancer cases in the simvastatin arm and five in the non-statin arm (HR, 1.44; 95% CI, 0.46–4.52).

The strengths of our study include the prospective cohort design, the large diverse population which was well characterized for breast cancer and cardiovascular risk, breast cancer verification by central review, serial update of statin use, and adjustment for mammography frequency as well as the long follow-up period. In addition, the comprehensive data collection in the WHI allows for a detailed adjustment for confounding variables. Limitations include the low prevalence of statin use at baseline and lack of information on medication compliance, interval data collection rather than continuous, recall bias, and bias due to loss of follow-up. Moreover, the

Table 6. Interaction of statin and other risk factors

		No annualized	Yes annualized	Age adjusted[a,b]		Multivariable adjusted[a,c]	
		N (%)	*N* (%)	HR (95% CI)	*P*	HR (95% CI)	*P*
Hormone	None/past	1,795 (0.38%)	158 (0.42%)	0.94 (0.79–1.10)	0.03	0.94 (0.78–1.14)	0.11
	E-alone only	1,324 (0.39%)	84 (0.30%)	1.35 (1.09–1.69)		1.32 (1.02–1.69)	
	E+P only	1,616 (0.52%)	106 (0.53%)	1.04 (0.85–1.26)		1.04 (0.84–1.30)	
Family history	No	3,658 (0.40%)	264 (0.38%)	1.07 (0.94–1.21)	0.73	1.08 (0.94–1.24)	0.78
	Yes	1,167 (0.57%)	83 (0.53%)	1.12 (0.90–1.40)		1.04 (0.82–1.32)	
BMI	<25	1,594 (0.40%)	83 (0.40%)	1.05 (0.84–1.30)	0.63	1.03 (0.80–1.31)	0.69
	25–<30	1,692 (0.41%)	128 (0.36%)	1.18 (0.98–1.41)		1.16 (0.95–1.42)	
	≥30	1,742 (0.47%)	154 (0.47%)	1.06 (0.90–1.25)		1.06 (0.88–1.27)	
Waist circumference > 88 cm	No	2,824 (0.40%)	168 (0.39%)	1.08 (0.93–1.27)	0.79	1.04 (0.88–1.24)	0.50
	Yes	2,227 (0.46%)	198 (0.44%)	1.12 (0.97–1.29)		1.13 (0.96–1.33)	

[a]Stratified by trial, WHI extension study, and age group.

[b]Base model was adjusted by age and baseline hormone therapy use.

[c]Multivarite model adjusted for age, BMI, ethnicity, smoking status, baseline hormone therapy use, baseline hormone therapy duration, family history of breast cancer, education, hysterectomy, mammogram last two years, age at first birth, parity, age at menarche, alcohol, percentage energy from fats, physical activity, and NSAID.

study lacked updated information on use of rosuvastatin and the more recently available pitavastatin as they were not widely in use during the time of the study. Our results may be biased toward the null as participants on statins could potentially not be compliant with taking the medication whereas nonusers at baseline did not have this bias. In addition, due to the observational nature of our study, the results may be biased because of unknown variables that may be associated with both breast cancer and statin use. It is unclear why a protective effect was seen associated with short duration of statin use.

In conclusion, we found no overall association between statin use and breast cancer risk; however, our findings raise the possibility of a marginal reduction in risk associated with simvastatin use. Genetic variation in statin metabolism has been linked to the efficacy of statins in the treatment of coronary artery disease (41) and may possibly have an impact on the effect of statins on colorectal cancer risk (42). Future studies should assess the effect of statins on cancer risk in selected populations based on genotype.

Disclosure of Potential Conflicts of Interest

L.W. Martin has commercial research grants from Amarin, Amgen, Sanofi, and Novartis, and is a consultant/advisory board member of WHI Publication committee NIH. No potential conflicts of interest were disclosed by the other authors.

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