Statin Use and Breast Cancer: Prospective Results From the Women's Health Initiative

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Background: **Despite experimental observations suggesting that 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) have antitumor activity, clinical studies have reached mixed conclusions about the relationship between statin use and breast cancer risk.** ***Methods:*** **To investigate associations between potency, duration of use, and type of statin used and risk of invasive breast cancer, we examined data for 156 351 postmenopausal women who were enrolled in the Women's Health Initiative. Information was collected on breast cancer risk factors and on the use of statins and other lipid-lowering drugs. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical tests were two-sided.** ***Results:*** **Over an average follow-up of 6.7 years, 4383 invasive breast cancers were confirmed by medical record and pathology report review. Statins were used by 11 710 (7.5%) of the cohort. Breast cancer incidence was 4.09 per 1000 person-years (PY) among statin users and 4.28 per 1000 PY among nonusers. In multivariable models, the hazard ratio of breast cancer among users of any statin, compared with nonusers, was 0.91 (95% CI = 0.80 to 1.05, *P* = .20). There was no trend in risk by duration of statin use, with HR = 0.80 (95% CI = 0.63 to 1.03) for <1 year of use, HR = 0.99 (95% CI = 0.80 to 1.23) for 1–<3 years of use, and HR = 0.94 (95% CI = 0.75 to 1.18) for ≥3 years of use. Hydrophobic statins (i.e., simvastatin, lovastatin, and fluvastatin) were used by 8106 women, and their use was associated with an 18% lower breast cancer incidence (HR = 0.82, 95% CI = 0.70 to 0.97, *P* = .02). Use of other statins (i.e., pravastatin and atorvastatin) or nonstatin lipid-lowering agents was not associated with breast cancer incidence.** ***Conclusions:*** **Overall statin use was not associated with invasive breast cancer incidence. Our finding that use of hydrophobic statins may be associated with lower breast cancer incidence suggests possible within-class differences that warrant further evaluation. [J Natl Cancer Inst 2006;98:700–7]**

Statins are widely prescribed, effective cholesterol-lowering drugs. Indeed, atorvastatin and simvastatin were the most commonly prescribed drugs in the United States in 2004, with over 70 million prescriptions written for atorvastatin alone *(1)*. The statins are pleiotropic agents, and, after an early study of patients with coronary heart disease showed a lower than expected incidence of cancers *(2)*, preclinical studies were carried out that have supported the potential anticancer activity of these compounds *(3,4)*. However, clinical reports on the relationship between statin use and breast cancer risk have yielded mixed results, with no association *(5,6)* and both positive *(7,8)* and negative *(9)* associations being observed. Prior observational studies have not evaluated the statin–breast cancer link by statin potency or category (i.e., hydrophobic versus not). Because breast cancer is the most frequent cancer in U.S. women, any link between statin use and breast cancer risk would have major public health implications.

The objective of the current study was to examine the associations between the potency, duration, and type of statin used and invasive breast cancer risk among women enrolled in the Women's Health Initiative (WHI). A secondary objective was to assess the association between use of other lipid-lowering agents and breast cancer.

Subjects and Methods

Study Population

The WHI includes an observational study (n = 93 676) and clinical trials (n = 68 132) of hormone therapy, dietary modification, and/or calcium and vitamin D supplementation in postmenopausal women of many races and ethnicities. Recruitment to the WHI was conducted between October 1, 1993, and December 31, 1998, at 40 clinical centers in the United States. Women were eligible if they were aged 50–79 years, were postmenopausal, planned to remain in the area where they lived at recruitment, and had an estimated survival of at least 3 years. Study methods have been described in detail elsewhere *(10)*. This analysis included

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See "Notes" following "References."

DOI: 10.1093/jnci/djj188

women enrolled in the observational study and clinical trial components of the WHI, excluding those who had previously been diagnosed with breast cancer or who had used tamoxifen or any selective estrogen receptor modulator. The final sample included 88 322 women enrolled in the observational study and 68 029 women enrolled in the clinical trials (156 351 women total).

All participants signed informed consent forms. All protocols and procedures were approved by institutional review boards at participating institutions. Follow-up for this report is through February 2004, for a mean ± SD of 6.7 ± 1.5 years.

Statin Exposure

Participants were asked to bring all current prescription medications to their first screening interview. Clinic interviewers entered each medication name directly from the containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, CA). Women reported duration of use for each current medication. Information on dose was not recorded. Current medication use was updated at the year 3 clinic visit with identical methods.

Current statin use was defined as use of any 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Statins were further classified as hydrophobic (lovastatin, simvastatin, and fluvastatin) or other (pravastatin and atorvastatin) and by potency: low (fluvastatin and lovastatin), medium (pravastatin), and high (simvastatin and atorvastatin) *(11)*. Other lipid-lowering medications included fibrate, colestipol, probucol, cholestyramine, niacin, and nicotinic acid.

Breast Cancer Screening and Diagnosis

Medical history was updated annually (in the observational study) or semiannually (in the clinical trials) by mail and/or telephone questionnaires. For women in the clinical trial components of the WHI, the frequency of clinical breast examination and mammography was protocol defined (annually for women in the hormone trials and biennially for women in the dietary trial). Clinical breast examination and mammography were not protocol defined for women in the observational study. Data on the frequency of clinical breast examination and mammography were collected annually from all participants.

Self-report of breast cancer was locally verified at each clinic by medical record and pathology report review by centrally trained WHI physician adjudicators. Central adjudication and coding of histology, extent of disease, and estrogen receptor (ER) and progesterone receptor (PR) status (positive or negative per pathology report) were performed at the Clinical Coordinating Center using the Surveillance, Epidemiology, and End Results Program (SEER) coding system *(12,13)*. Only invasive breast cancer cases confirmed by adjudication were included in the analysis (4383 cases). Information on ER status was available for 3793 invasive breast cancer cases.

Covariates

Information on all covariates was collected at study entry. Current and previous use of menopausal hormone therapy and oral contraceptives were ascertained by interview using a detailed questionnaire that included type, route of administration, number of pills per day or week, and duration of use for each hormonal preparation ever taken. Hormone therapy users were defined as those who used estrogen (with or without progestin) after menopause for at least 3 months.

Baseline questionnaires ascertained information on race or ethnicity (white, black, Hispanic, American Indian, Asian/Pacific Islander, or unknown), history of physician-diagnosed diabetes (yes/no), high serum cholesterol level that required treatment with pills (yes/no), history of myocardial infarction or angina (yes/no), history of benign breast disease (yes/no), educational level (<high school, high school diploma/GED, or >high school diploma/GED), family history of female breast cancer (yes/no), hysterectomy and oophorectomy status (yes/no), ages at menarche (≤11, 12–13, or ≥14 years) and first birth (never pregnant, no term pregnancy, or <20, 20–29, or ≥30 years), parity (none, 1–2, or ≥3), use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (yes/no), current and past smoking status, and time (minutes per week) spent in mild, moderate, or strenuous physical activity (none, 10–<115, or 115–≥250 minutes/week). Alcohol consumption (none/past drinker, <1 drink/week, or ≥1 drink/week) and percentage of calories from fat (≥30% versus <30% of calories from fat) were estimated from a food-frequency questionnaire *(14)*. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The Gail 5-year breast cancer risk estimate was calculated. A woman was considered at high risk if her Gail score was >1.7% *(15)*.

Statistical Methods

The characteristics of statin users at baseline were compared with those of nonusers by chi-square or Fisher exact tests (for categorical variables) or two-sample *t* tests (for continuous variables). Incidence rates of breast cancer per 1000 person-years were calculated according to the use of statins and other lipid-lowering agents. An a priori plan of analysis specified that we perform selected subgroup analyses by statin use duration (<1 year, 1–<3 years, and ≥3 years), potency, and hydrophobic 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 (i.e., by potency or type). Separate analyses were conducted for women with ER-positive and ER-negative breast cancer. Hazard ratios (HRs) for breast cancer among statin users versus nonusers and 95% confidence intervals (CIs) 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. Results of these analyses showed that the assumptions were not violated.

All models were adjusted for assignment to active hormone or placebo in the two WHI hormone trials (estrogen plus progestin and estrogen alone), assignment to intervention or control in the dietary modification trial, or enrollment in the observational study. We also adjusted for prior hormone use at baseline (none, prior estrogen alone, prior estrogen plus progestin, or prior use of both estrogen alone and estrogen plus progestin). These adjustments resulted in what we refer to as the base model. The base model was further adjusted by age; these age-adjusted base models included 155 530 women. To control for potential confounding factors, we used multivariable Cox proportional hazards analyses with a forced-entry approach for variable selection. In addition to the variables in the age- and base factor–adjusted

Table 1. Baseline characteristics by statin use*

Characteristic	No statin use		Statin use	
	N	%	*N*	%
Total	144 641	92.5	11 710	7.5
Age at baseline, y				
50–59	50 088	34.6	2111	18.0
60–69	64 073	44.3	6093	52.0
70–79	30 478	21.1	3506	29.9
Race/ethnicity				
White	119 309	82.5	9582	81.8
Black	13 058	9.0	1078	9.2
Hispanic	5984	4.1	376	3.2
American Indian	647	0.4	46	0.4
Asian/Pacific Islander	3644	2.5	458	3.9
Unknown	1997	1.4	170	1.5
Education				
None–some high school	7631	5.3	766	6.6
High school diploma/GED	24 283	16.9	2474	21.3
>High school diploma/GED	111 615	77.8	8390	72.1
Smoking				
Never	73 087	51.2	5644	48.9
Past	59 534	41.7	5183	44.9
Current	10 130	7.1	715	6.2
Alcohol use				
Non/past drinker	42 106	29.3	4058	34.9
<1 drink/week	47 319	33.0	3912	33.6
≥1 drink/week	54 174	37.7	3665	31.5
Physical activity, min/wk				
None	22 022	16.0	1697	14.9
10–<115	38 130	27.7	3287	28.8
115–<250	37 964	27.6	3298	28.9
≥250	39 370	28.6	3128	27.4
≥30% energy from fat	97 541	69.5	6848	61.0
Body mass index, kg/m^2				
<25	51 333	35.8	2879	24.8
25–<30	49 239	34.3	4613	39.7
≥30	42 786	29.8	4119	35.5
Have a current medical care provider	133 597	93.3	11 427	98.4
Mammogram in the last 2 years	116 030	82.9	10 147	89.3
Gail risk of breast cancer >1.7%	54 512	37.7	5226	44.6
Family history of breast cancer†	24 887	18.2	2052	18.6
Age at menarche, y†				
≤11	31 559	21.9	2603	22.3
12–13	79 186	55.0	6403	54.9
14+	33 307	23.1	2662	22.8
Ever pregnant†	131 118	90.9	10 575	90.5
Age at first birth, y†				
Never pregnant	13 120	10.0	1104	10.5
No term pregnancy	3853	2.9	283	2.7
<20	18 638	14.2	1488	14.2
20–29	84 768	64.7	6771	64.6
≥30	10 593	8.1	829	7.9
Number of live births†				
None	17 133	11.9	1398	12.0
1–2	50 011	34.8	3883	33.4
≥3	76 545	53.3	6358	54.6
Benign breast disease				
No	107 450	78.6	8735	77.1
Yes, 1 biopsy	20 629	15.1	1783	15.7
Yes, ≥2 biopsies	8566	6.3	815	7.2
Hysterectomy	60 022	41.5	5336	45.6
Bilateral oophorectomy	27 800	19.7	2534	22.3
Hormone therapy use				
Never	62 337	43.1	5277	45.1
Past	22 189	15.4	2012	17.2
Current, <5 y	17 123	11.8	1221	10.4
Current, 5–<10 y	14 892	10.3	988	8.4
Current, ≥10 y	27 979	19.4	2197	18.8
Current HT use by type (includes HT trial use)				
Never/past user	72 930	50.5	6390	54.6
Estrogen alone	37 732	26.1	3103	26.5
Estrogen plus progestin	33 863	23.4	2202	18.8
Prior oral contraceptive use	61 026	42.2	3921	33.5
Nonstatin lipid-lowering medication use	1874	1.3	288	2.5
Aspirin use	27 142	18.8	4074	34.8
NSAID use	38 264	26.5	3606	30.8
General health rating				
Excellent	25 886	18.0	882	7.6
Very good	59 741	41.6	3960	34.0
Good	45 843	31.9	5066	43.6
Fair/poor	12 231	8.5	1722	14.8
Medical history				
Diabetes	7818	5.4	1414	12.1
High cholesterol, requiring pills	9658	7.1	10 957	96.4
Myocardial infarction	2489	1.7	1038	8.9
Angina	6656	4.6	1919	16.5
WHI participation				
Estrogen-alone trial only	6720	4.6	614	5.3
Estrogen plus progestin trial only	11 058	7.6	874	7.5
Dietary modification trial only	38 127	26.4	2580	22.1
HT and dietary modification trials	7593	5.2	447	3.8
Observational study	81 139	56.1	7159	61.3

**P*-values from chi-square tests comparing statin users to nonusers are <.001 for all characteristics except as indicated. HT = hormone therapy; NSAID = nonsteroidal anti-inflammatory drug; WHI = Women's Health Initiative.

†*P* values for comparison are not statistically significant.

models, the multivariable models were adjusted for race and ethnicity, BMI, physical activity, current and past smoking, family history of breast cancer, hysterectomy status, mammogram in the past 2 years, educational level, ages at menarche and first birth, parity, alcohol consumption, and percentage of calories from fat. Multivariable models were based on the 115 683 individuals remaining after the exclusion of participants with missing values for any of the covariates. To evaluate the effects on the results 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 the year 3 clinic visit. We examined the risk for breast cancer by statin use separately in users of estrogen plus progestin, users of estrogen alone, and never/past users of hormone therapy.

Comparisons of breast cancer tumor characteristics between statin users and nonusers were based on chi-square tests, two-sample *t* tests, or Brown–Mood tests of medians. All analyses were conducted using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided.

Results

In this cohort of 156 351 women, 11 710 (7.5%) were statin users (Table 1). Women using statins at baseline were older at enrollment than nonusers (65.6 and 63.0 years, respectively) and had a higher BMI (mean 28.9 and 27.9 kg/m^2, respectively). Statin users were less likely than nonusers to have more than a high school education, to drink alcohol, to be physically active,

Table 2. Statin use details for the 11 710 users of any statin

	n	%
Type of statin used		
Simvastatin (Zocor)	3515	30.0
Lovastatin (Mevacor)	3140	26.8
Pravastatin (Pravachol)	2645	22.6
Fluvastatin (Lescol)	1451	12.4
Atorvastatin (Lipitor)	923	7.9
Miscellaneous	7	0.1
Two or more statins	29	0.2
Duration of statin use, y		
<1	3898	33.3
1–<3	3964	33.9
≥3	3848	32.9

to have used hormone therapy, and to report that they obtained ≥30% calories from fat. Statin users were more likely than nonusers to have smoked, to have had a hysterectomy or bilateral oophorectomy, and to report use of NSAIDs and aspirin. A higher proportion of statin users reported having had a mammogram in the past 2 years, although ≥80% of both users and nonusers had had a mammogram in the past 2 years. A higher proportion of statin users than nonusers were considered at high risk of breast cancer, i.e., to have a Gail 5-year breast cancer risk of >1.7%. Of the 2162 women who reported using nonstatin lipid-lowering agents, 288 women reported also using a statin. Although most of the absolute differences between statin users and nonusers were small, many were statistically significant because of the large number of women in the cohort.

Of the 11 710 statin users, 4591 (39.2%) used a low-potency statin, 2645 (22.6%) used a medium-potency statin, and 4438 (37.9%) used a high-potency statin (Table 2). A total of 8106 (69.2%) of the women who used statins reported using at least one hydrophobic statin. A year 3 medication history was available for 135 772 women (82% of the cohort). Among cohort members who used statins at baseline, 8274 women (82.5%) were still using a statin at the year 3 clinic visit; among those who did not use statins at baseline, 11 583 women newly reported taking a statin at the year 3 visit.

During a total of 1 041 518 person years (PY) of observation, 4383 women were diagnosed with invasive breast cancer. The incidence of breast cancer was approximately 4.4% lower among women reporting statin use (4.09 per 1000 PY) than among nonusers (4.28 per 1000 PY). In the age-adjusted base model, the relative risk of breast cancer was 8% lower among statin users than among nonusers (HR = 0.92, 95% CI = 0.82 to 1.03) (Table 3). In the full multivariable-adjusted model, breast cancer incidence was approximately 9% lower in statin users than in non-users (HR = 0.91, 95% CI = 0.80 to 1.05, $P = .20$).

Examination of the relative risk of breast cancer by duration of statin use (Table 3) revealed no consistent trend. Short-term use (<1 year) was associated with a non–statistically significant 20% reduction in invasive breast cancer, whereas use for 1 to 3 years and for more than 3 years was not associated with the risk of breast cancer.

We also examined breast cancer risk by statin potency and category (Table 3). Use of low- and high-potency statins was associated with non–statistically significant reductions in breast cancer incidence (of 15% and 17%, respectively), but use of medium-potency statins showed no such association. Use of hydrophobic statins was associated with a statistically significant 18% reduction in risk of

Table 3. Incidence and hazard ratios of invasive breast cancer by use of statins and other lipid-lowering medications*

	Breast cancer cases	Incidence per 1000 PY	HR (95% CI) from age-adjusted base model	HR (95% CI) from multivariable-adjusted† model
Statin use				
No (referent)	4086	4.28	1.00	1.00
Yes	297‡	4.09	0.92 (0.81 to 1.03)	0.91 (0.80 to 1.05)
Type of statin				
Lovastatin	81	3.87	0.87 (0.70 to 1.09)	0.84 (0.65 to 1.09)
Simvastatin	80	3.75	0.84 (0.68 to 1.05)	0.80 (0.62 to 1.04)
Fluvastatin	32	3.60	0.81 (0.57 to 1.15)	0.80 (0.53 to 1.19)
Pravastatin	81	4.92	1.10 (0.88 to 1.37)	1.17 (0.92 to 1.49)
Atorvastatin	22	4.63	0.99 (0.65 to 1.51)	1.05 (0.66 to 1.67)
Statin category§				
Hydrophobic	194	3.79	0.85 (0.74 to 0.98)	0.82 (0.70 to 0.97)
Other	103	4.85	1.08 (0.89 to 1.31)	1.14 (0.92 to 1.42)
Statin potency‖				
Low	113	3.79	0.85 (0.71 to 1.03)	0.83 (0.66 to 1.03)
Medium	81	4.92	1.10 (0.88 to 1.37)	1.17 (0.91 to 1.49)
High	102	3.91	0.87 (0.72 to 1.06)	0.85 (0.68 to 1.07)
Duration of statin use				
<1 year	84	3.51	0.80 (0.65 to 1.00)	0.80 (0.63 to 1.03)
1–<3 years	104	4.23	0.95 (0.79 to 1.16)	0.99 (0.80 to 1.23)
>3 years	108	4.52	0.99 (0.82 to 1.20)	0.94 (0.75 to 1.18)
Other lipid-lowering medication				
No (referent)	4324	4.27	1.00	1.00
Yes	58	4.04	0.92 (0.71 to 1.19)	0.88 (0.64 to 1.19)

*PY = person-year; HR = hazard ratio; CI = confidence interval.

†Age-adjusted base model was further adjusted for body mass index, race, smoking, family history of breast cancer, education, hysterectomy, mammogram in the last 2 years, age at menarche, parity/age at first birth, alcohol use, percentage of calories from fat, physical activity, and nonsteroidal anti-inflammatory drug use.

‡Information on specific statin use was available for 296 of the 297 statin users with breast cancer.

§Hydrophobic statins are simvastatin, lovastatin, and fluvastatin; others are pravastatin and atorvastatin.

‖Low-potency statins are lovastatin and fluvastatin, the medium-potency statin is pravastatin, and the high-potency statins are simvastatin and atorvastatin.

Table 4. Incidence of invasive breast cancer by statin and hormone use* at baseline

Current hormone use	No statin use		Statin use		HR (95% CI)‡	*P* for interaction
	Cases	Rate†	Cases	Rate†		
Never/past	1789	3.68	161	4.06	1.09 (0.93 to 1.28)	
E-alone only	979	4.00	60	3.15	0.78 (0.60 to 1.02)	
Any E + P	1314	5.89	74	5.46	0.93 (0.74 to 1.18)	
						.09

*If a woman had been randomly assigned to the estrogen plus progestin (E + P) group or reported active use of estrogen plus progestin at baseline, she was considered an estrogen plus progestin user. If a woman was randomly assigned to the active estrogen (E)-alone group or reported estrogen-alone use at baseline, she was considered in the estrogen-alone group. Women randomly assigned to placebo groups and women who reported past or never use at baseline were considered never/past users.

†Rate given per 1000 person-years.

‡HR = hazard ratio; CI = confidence interval.

breast cancer (HR = 0.82, 95% CI = 0.70 to 0.97, $P = .02$), whereas use of other statins was not associated with breast cancer incidence (HR = 1.14, 95% CI = 0.92 to 1.42, $P = .24$).

To test for possible interactions between statin use and postmenopausal hormone use, we examined the association between statin use and breast cancer separately in women who used estrogen plus progestin, those who used estrogen alone, and never/past users of hormones (Table 4). Statin use was not associated with breast cancer risk among users of estrogen plus progestin or among never/past hormone users (Table 4). Among users of estrogen alone, statin use was associated with a non–statistically significant 22% reduction in the risk of breast cancer (P for the interaction between hormone use and statin use = .09). The multivariable-adjusted hazard ratio for ER-positive breast cancer among statin users compared with non-users was 0.97 (95% CI = 0.83 to 1.13), and that for ER-negative breast cancer was 0.83 (95% CI = 0.55 to 1.25). The breast cancers in statin users and nonusers were similar in size, number of positive lymph nodes, SEER stage, histology, tumor grade, and ER and PR status (Table 5).

Finally, we analyzed breast cancer risk according to the use of lipid-lowering agents other than statins. The incidence of breast cancer in users of such agents (4.04 per 10 000 PY) was 5.4% lower than that in non-users (4.27 per 1000 PY), but the difference was not statistically significant in the multivariable model (HR = 0.88, 95% CI = 0.64 to 1.19, $P = .41$).

Discussion

The current report is the largest cohort study, to our knowledge, to evaluate statin use and invasive breast cancer in terms of the number of incident breast cancers. We studied 156 361 women, who were followed for 1 041 518 person-years, and 4383 incident breast cancers. The full multivariable model used in the analysis adjusted for a comprehensive set of breast cancer risk factors, including age, race, BMI, family history of breast cancer, alcohol consumption, physical activity, mammography utilization, past and current menopausal hormone therapy, smoking, percentage of calories from fat, educational level, NSAID use, and reproductive history. When we considered statins as a class, we found no association between statin use and breast cancer risk. Although the relative risk of breast cancer was approximately 9% lower among statin users than among nonusers, the difference was not statistically significant. Breast cancer incidence was also not associated with duration of statin use or statin potency. There was an interaction between statin use and hormone therapy that was of borderline statistical significance: current users of both estrogen alone and a statin had a somewhat lower risk of breast cancer than women who had never used a statin. This interaction was not observed among users of estrogen plus progestin, however, and these results also conflict with results from the Nurses' Health Study *(5)*. Finally, women using hydrophobic statins (simvastatin, lovastatin, or fluvastatin) had an 18% lower breast cancer incidence than nonstatin users ($P = .02$).

Previous reports on statin use and breast cancer risk, which include both randomized trials of subjects with coronary heart disease and risk factors for coronary heart disease *(2,8,16–21)* and observational studies *(5–7,9,22–27)*, have provided mixed results. For example, in two randomized trials of pravastatin in older people at risk of vascular disease, a nonhydrophobic statin, more breast cancers were seen in the statin group. In one of these studies, the Cholesterol and Recurrent Events (CARE) study, one woman of 291 in the placebo group and 12 women of 291 in the pravastatin group developed breast cancer ($P = .002$) *(8)*. Of the 12 breast cancers, however, three occurred in women who previously had breast cancer and one occurred in a woman who took pravastatin for only 6 weeks. In the second of these trials of pravastatin, more breast cancers were diagnosed in women taking pravastatin than in women taking placebo (HR = 1.65, 95% CI = 0.78 to 3.49), but the difference was not statistically significant *(19)*. In contrast, the Long Term Intervention with Pravastatin in Chronic Disease (LIPID) trial, with 1516 women randomly assigned to pravastatin or placebo, found no increase in breast cancer with pravastatin use *(17)*. The Heart Protection study found slightly fewer breast cancers among women randomly assigned to the hydrophobic statin simvastatin than among those assigned to placebo, but the difference was not statistically significant *(18)*. Other randomized trials of simvastatin *(21)* or pravastatin *(20)* found no association with breast cancer risk. In a recent meta-analysis of 90 056 participants in 14 randomized trials of statins, statin users did not have an increase in risk of cancer death or cancer incidence, including breast cancer *(28)*.

Among the observational studies, an increase in breast cancer incidence for statin users has been observed in some case–control studies *(4,21)*, especially for short-term users of statins and past long-term users of hormone therapy *(7)*. However, neither a large case–control study from the General Practice Research Database, an automated data source containing drug prescription and medical information on more than 3 million people in the United Kingdom *(24)*, nor three other large cohort studies *(5,6,26)* found an association between statin use and breast cancer. In a large case–control study of nearly 1000 women with breast cancer identified from the

Table 5. Breast cancer characteristics by statin use

	No Statin Use		Statin Use		
	n	Mean (SD) or %	n	Mean (SD) or %	*P* value*
Tumor size, cm†	2669	1.6 (1.2)	189	1.4 (1.4)	.33
No primary mass	21		5		
Microscopic focus or foci	139	4.7	10	4.8	
≤0.5 cm	278	9.5	18	8.6	
>0.5–1 cm	791	27.0	69	32.9	
>1–2 cm	1139	38.9	74	35.2	
>2–5 cm	504	17.2	28	13.3	
>5 cm	56	1.9	6	2.9	
Missing	1014	25.7	81	27.8	.43
Lymph nodes examined					.49
No	386	10.0	32	11.3	
Yes	3455	90.0	250	88.7	
Missing	101	2.6	9	3.1	.58
Number of lymph nodes examined†	3841	10.2 (8.1)	283	9.9 (8.3)	.21
Number of positive lymph nodes†	3488	1.0 (3.2)	251	0.6 (1.6)	.64‡
Number of positive lymph nodes					.35
None	2594	74.4	190	75.7	
1–3	644	18.5	49	19.5	
4+	250	7.2	12	4.8	
Missing	454	11.5	40	13.7	.25
Lymph nodes positive					.64
No	2594	74.4	190	75.7	
Yes	894	25.6	61	24.3	
Missing	454	11.5	40	13.7	.25
SEER stage§					.93
Localized	2932	75.9	219	76.6	
Regional	897	23.2	65	22.7	
Distant	34	0.9	2	0.7	
Missing	79	2.0	5	1.7	.74
Histology					.19
Ductal	2516	63.8	173	59.5	
Lobular	360	9.1	32	11.0	
Ductal and lobular	543	13.8	49	16.8	
Tubular	163	4.1	7	2.4	
Other	360	9.1	30	10.3	
Tumor grade					.78
Well differentiated	979	28.4	71	27.6	
Moderately differentiated	1457	42.2	103	40.1	
Poorly differentiated	907	26.3	75	29.2	
Anaplastic	108	3.1	8	3.1	
Missing	491	12.5	34	11.7	.70
Estrogen receptor assay					.54
Positive	2980	84.3	223	85.8	
Negative	553	15.7	37	14.2	
Missing	409	10.4	31	10.7	.88
Progesterone receptor assay					.32
Positive	2439	84.2	190	86.6	
Negative	1015	15.8	65	13.4	
Missing	488	12.4	36	12.4	1.00

**P* values are from a two-sample *t* test for continuous variables or from a chi-square test for categorized variables. The first *P* value for a given characteristic tests the association with statin use by using only known values of the characteristic. The *P* value corresponding to the "missing" rows tests the association of percent missing for the given characteristic with statin use.

†Mean (SD) only applies to those with known tumor size or known number of lymph nodes examined or positive.

‡*P* value for number of positive lymph nodes based on Brown–Mood test of medians.

§SEER = Surveillance, Epidemiology, and End Results Program.

Cancer Surveillance System, a population-based tumor registry that serves 13 counties in western Washington State, no overall association of statins with breast cancer incidence was seen, but women who had used statins for more than 5 years had an approximately 30% lower breast cancer incidence than never users *(25)*. A statistically significantly decrease in breast cancer incidence in statin users has been seen in only two *(9,27)* of eight cohort studies. However, the number of breast cancers in one of these reports was small *(9)*, and limited information on breast cancer risk factors was provided in the second report, which was an abstract *(27)*.

Our results, taken together with the existing literature, indicate that breast cancer risk is at least not increased in statin users. Whether or not statin use is associated with reduced breast cancer risk is less certain. In the current study, after adjustment for breast cancer risk factors, statin users had a somewhat lower breast cancer incidence than nonusers. However, the differences were statistically significant only in women who reported using hydrophobic statins. This observation is consistent with a cell culture study in which only hydrophobic statins (lovastatin, simvastatin, and fluvastatin) but not a hydrophilic statin (pravastatin)

had anticancer activity *(29)*. Pravastatin may promote the development of cancer by causing an induction of mevalonate synthesis in extrahepatic tissues *(30)*, an effect that is not observed with other statins. This increase in mevalonate appears to promote the growth of breast cancer cells *(30)*. In the randomized trials of statins, an increase in breast cancer was observed only in the two trials of pravastatin *(8,19)*. Moreover, in the cohort study that reported a 72% lower risk of breast cancer among statin users, the majority of these users (247 of 284) used a hydrophobic statin *(9)*. Thus, the inconsistency in previous results may reflect differences in the association with specific statins.

Considering all other nonstatin lipid-lowering medications together, we found no statistically significant association between their use and breast cancer risk. However, because the multivariable-adjusted relative risk of breast cancer was 12% lower among users of these other agents than among nonusers and because one previous cohort study also reported a statistically significantly lower breast cancer risk among users of other lipid-lowering agents than among nonusers *(9)*, further study of the influence of individual lipid-lowering agents on breast cancer incidence may be warranted.

Strengths of this study include the prospective design; inclusion of a large, racially diverse sample of well-characterized women; collection of detailed information on a comprehensive range of breast cancer risk factors; complete follow-up for breast cancer outcomes; regular assessment of mammography use; blinded adjudication of breast cancers via pathology report review; description of breast cancer histologic characteristics and hormone receptor status; and the ability to examine associations by statin category. The limitations of this study include its observational design. Although we adjusted for many factors that could confound the association between statin use and breast cancer, there may be residual confounding by unmeasured factors. Indeed, a recent comparison of observational study and randomized clinical trial results, with respect to findings regarding postmenopausal hormone use and coronary heart disease, showed that the discrepancy in findings can be substantially explained by confounding *(31)*. Study limitations also include the relatively low prevalence of statin use, lack of information on dose, and limited power to examine long-term (>5 years) effects.

In conclusion, in this large population of postmenopausal women with well-characterized breast cancer risk factors, when all statins were considered together as a class, no statistically significant association with breast cancer incidence was seen. However, use of hydrophobic statins was associated with statistically significantly lower breast cancer incidence, a finding that warrants further evaluation. Future studies of statins and breast cancer should assess associations with individual statins or statin categories because class differences may exist.

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Notes

The Women's Health Initiative (WHI) program is funded by the National Heart, Lung and Blood Institute, U.S. Department of Health and Human Services. The sponsor played a role in the design and analysis of the WHI.

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Funding to pay the Open Access publication charges for this article was provided by the University of Pittsburgh Research and Development Funds.

Manuscript received October 14, 2005; revised March 8, 2006; accepted March 28, 2006.