Statin Use and Breast Cancer Risk in a Large Population-Based Setting

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Abstract

Background: **Mechanistic studies suggest that 3-hydroxy-3-methylglutaryl CoA inhibitors (statins) reduce the risk of breast cancer. Observational studies offer mixed results.**
Methods: **To evaluate the relation between statin use and breast cancer risk, we conducted a cohort study among women ages 45 to 89 years within an integrated health care delivery system. Information on statin use and covariates were obtained from automated databases. We identified breast cancer cases through the Surveillance, Epidemiology, and End Results registry. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for invasive breast cancer among statin users compared with nonusers.**
Results: **Among 92,788 women studied from 1990 to 2004, median follow-up time was 6.4 years, and 2,707 breast cancer cases were identified. During the study period, 7.4% of women used statins for at least 1 year, and the median duration of use was 3.1 years. We found no difference in breast cancer risk among statin users (HR, 1.07; 95% CI, 0.88-1.29) compared with nonusers. Risk of breast cancer did not differ by duration of use (1-2.9, 3-4.9, or ≥5 years) or hydrophobic statin use. We found a suggestive increased risk of breast cancer among statin users of ≥5 years (HR, 1.27; 95% CI, 0.89-1.81 for any statins and HR, 1.47; 95% CI, 0.89-2.44 for hydrophobic statins) and of estrogen receptor–negative tumors with increasing duration of statin use (1-2.9 years: HR, 1.33; 95% CI, 0.64-2.77; 3-4.9 years: HR, 1.68; 95% CI, 0.72-3.92; ≥5 years: HR, 1.81; 95% CI, 0.75-4.36).**
Conclusion: **This study does not support an association between statin use and breast cancer risk.** (Cancer Epidemiol Biomarkers Prev 2007;16(3):416–21)

Introduction

3-Hydroxy-3-methylglutaryl CoA inhibitors (statins) are a therapeutic class of drugs that reduce plasma cholesterol levels and are used to manage and prevent coronary heart disease (1). Statin use has increased dramatically in the past decade and is likely to continue rising. Statins are currently the most widely prescribed lipid-lowering agents on the U.S. pharmaceutical market; five of the six statins on the market were among the top 200 prescribed drugs for 2004 (2).

Although an early review of studies in rodents (3) and at least two clinical trials of pravastatin raised concerns that statins may have carcinogenic properties (4, 5), a growing body of mechanistic studies suggest statins may in fact have chemopreventive potential against cancer (6, 7). Statins seem to induce apoptosis and reduce cell invasiveness in various cell lines (7), including mammary carcinoma (8-12).

Epidemiologic studies that report on statin use and breast cancer risk are varied and report no effect on risk and both increases and decreases in risk (13-21). To assess the association between statin use and breast cancer risk, we conducted a cohort study within a large integrated health care delivery system that contains computerized information on medication use, incident cancers, and risk factors for breast cancer.

Materials and Methods

Study Population. We conducted a dynamic, retrospective cohort study among women enrolled in Group Health (GH), a non–profit-integrated delivery system that provides comprehensive health care on a prepaid basis to ~550,000 individuals throughout the western Washington State. GH Institutional Review Board approved the study.

Women were included in the study if they met all the following criteria: (*a*) between the age of 45 to 89 years during the study period of January 1, 1990 to July 31, 2004; (*b*) continuously enrolled in GH's integrated group practice for at least 2 years during the study period; (*c*) residing in 1 of 13 counties covered by the Surveillance, Epidemiology, and End Results cancer registry; (*d*) no prior history of any type of breast cancer as identified in the Surveillance, Epidemiology, and End Results registry and the self-administered Breast Cancer Screening Program risk survey; and (*e*) no prior preventive mastectomy or breast conserving surgery.

Data Collection. We used automated health plan data to ascertain information on medication use and potential confounders. Information on health plan enrollment and health care utilization, including medication use, diagnoses, and procedures, are recorded and maintained in GH automated databases that can be linked by a unique consumer number assigned to each enrollee (22). GH automated pharmacy data are considered a complete source of medication use, and it is estimated that GH enrollees obtain about 97% of their medications at GH pharmacies (23, 24). Computer linkage between active GH enrollees and the western Washington Surveillance, Epidemiology, and End Results registry provides complete ascertainment of cancer cases (25). Similarly, the Washington State Death records for active GH enrollees are regularly obtained (26).

GH has a Breast Cancer Screening Program (BCSP) that women are invited to join when they turn 40 years old or when they enroll in GH after 40 years of age (27). Women participating in the BCSP complete breast cancer risk factor questionnaires at program enrollment, and this information is updated at the time of each mammogram. Approximately 86%

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of women complete the questionnaires, and the data are available in automated databases (25). We collected risk factor data from the survey closest in time to entry into the study (median time interval between survey and study entry was 1.3 years). However, data are missing on a proportion of subjects partly because risk factor questions were added to the survey over the course of the study period (e.g., questions on race was added in 1993 and on education was added in 1996).

Statin Use. We used automated pharmacy data to identify all statins (atorvastatin, cerivastatin, lovastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin) dispensed at GH-owned pharmacies during the study period. For each statin dispensing, we estimated the date when the pills should have run out (run-out date) based on quantity dispensed and instructions for use. A new run-out date was set with each successive dispensing. A 60-day lag period between the run-out date of one dispensing and fill date of the successive dispensing was used to define continuous use. Periods of continuous use were summed for total duration of use.

We defined statin users as women with at least two dispensings for a statin within any 6-month period and who used statins for at least 1 year. Nonusers included women with no or one dispensing for a statin or less than 1 year of statin use. We considered women a current user if statins were used within the previous 12 months and a past user if statins were used >12 months before. Among statin users, we calculated the cumulative lengths of statin use. Cumulative duration of statin use was categorized as 1 to 2.9, 3 to 4.9, and ≥5 years. Statin use was further classified as hydrophobic-only users (lovastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin) or hydrophilic only users (pravastatin and rosuvastatin). We were unable to evaluate dose because there were few high-dose statin users.

Breast Cancer. We identified all incident, invasive breast cancer cases (N = 2,707) from the Surveillance, Epidemiology, and End Results registry. Only invasive breast cancer cases were included.

Covariates. The majority of information on risk factors for breast cancer was self-reported and determined from the BCSP survey completed at a time closest to the beginning of study period: weight, height, race, education, parity, menopausal status, and family history of breast cancer.

We used GH outpatient, inpatient, laboratory, pharmacy, and administrative data to identify other possible confounders. We defined diabetics as women with at least one of the following: (*a*) ≥2 fills for a medication used to treat diabetes (e.g., sulfonylureas and insulin), (*b*) a fasting glucose >125 mg/dL confirmed by a second out-of-range test within 1 year, (*c*) a random glucose >200 mg/dL also confirmed by a second test within 1 year, or (*d*) a hospital discharge of diabetes at any time during GH enrollment (28). Hormone therapy use was defined as ≥2 dispensings for systemic estrogen (oral or transdermal), either alone or in combination with progestin. Other lipid lowering drug use was defined as ≥2 dispensings for bile acid sequestrants, niacin, or fibrates.

Statistical Analysis. Follow-up of the study cohort extended from January 1, 1991 or 1 year after enrollment in GH if later than January 1, 1990 until the earliest of the following: diagnosis of an incident invasive breast cancer, 90 years of age, death, disenrollment from GH, preventive mastectomy, or the end of the study period (July 31, 2004). We used Cox proportional hazards models to examine the association between statin use and risk of incident invasive breast cancer (29). In separate subgroup analyses, we evaluated estrogen receptor–positive (ER^+) and ER-negative (ER^-) tumors.

Statin use was modeled as a time-varying exposure, and women were allowed to transition from being nonusers to users or from nonusers to current users to past users over time. For analyses of statin type, women were censored once they began using a different type of statin (hydrophobic or hydrophilic). Final models were adjusted for age at the beginning of the study period, hormone therapy use (estrogen only user, estrogen and progestin user, or nonuser), diabetes (yes or no), and other lipid-lowering drug use (yes or no), which were time-varying covariates, and body mass index, which was based on weight and height information obtained from the BCSP survey. We used a cubic smoothing spline with five and three knots to model age and body mass index, respectively. Cubic-smoothing splines provide a flexible approach for modeling the nonlinear relationship between cancer risk and these important covariates to more completely adjust for confounding (30). We tested for the difference in the effects of statin use on breast cancer risk between hormone therapy users and nonusers by including an interaction of statin use with hormone therapy use. The proportional hazard assumption was evaluated in all models by testing for the interaction of statin use with follow-up time. The assumption was met in all models (data not shown). Analyses were done using the SAS statistical package, version 9.1 (Cary, NC).

In a subgroup of women who were enrolled in GHC for at least 5 years during the study period (January 1, 1990 to July 31, 2004), we evaluated the relation between duration of statin use (1-2.9, 3-4.9, and ≥5 years) and breast cancer risk. Follow-up began on January 1, 1995 or 5 years after enrollment in GH if enrollment occurred after January 1, 1990. Women who died or developed invasive breast cancer during the first 5 years of the study period were excluded.

In sensitivity analyses, we only considered the true nonusers of statins in the comparison group by excluding women with either one dispensing for a statin or use of less than 1 year. We also adjusted for regular mammography screening in the models, which was defined as having at least one screening mammogram every 3 years among the subgroup of women enrolled in GH for at least 5 years during the study period.

Results

Among 92,788 women, the median duration of follow-up was 6.4 years (range, 2 days to 13.6 years); 7.4% of women used statins for at least a year during the study period. The prevalence of statin use gradually climbed from 0.2% in 1990 to 18.3% in first half of 2004 (Fig. 1), and the median cumulative duration of statin use during the study period was 3.1 years (range, 1-14.5 years). Lovastatin and simvastatin were the most commonly used statins overall, but specific statin use varied throughout the study period due to changes in the GH drug formulary (Fig. 2).

Characteristics of the cohort by statin use and breast cancer status are described in Tables 1 and 2. Statin users were older,

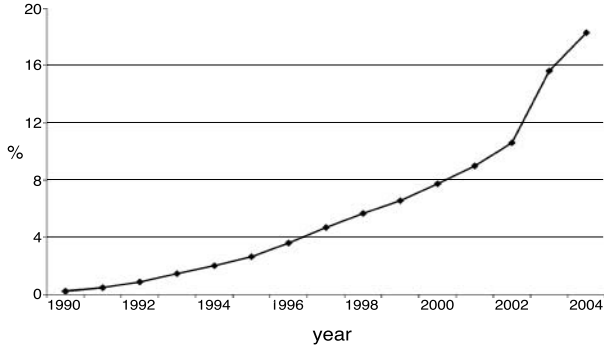

Figure 1. Prevalence of stain use by year.

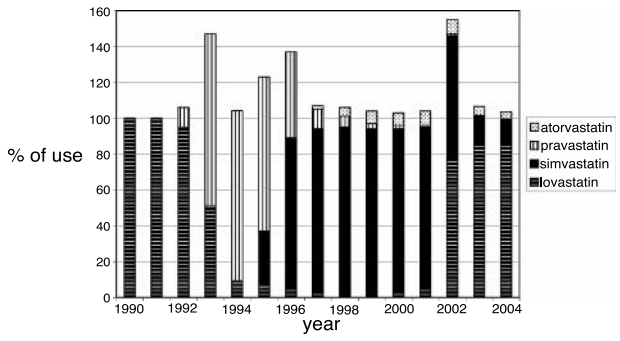

Figure 2. Specific statins used among all users by year.

less educated, had a higher body mass index, and more likely to be parous and perimenopausal/postmenopausal at the beginning of the study than nonusers (Table 1). There were a higher proportion of Caucasians, diabetics, hormone therapy users, and other lipid-lowering medication users among statin users than nonusers. Among women who were enrolled in GH for at least 5 years during the study period, a higher proportion of statin users (78.4%) than nonusers (70.1%) had at least one screening mammogram in the 3 years before end of follow-up ($P < 0.0001$). Statin users were less likely to have missing BCSP survey data on risk factors such as education, race, and family history of breast cancer than nonusers.

Breast cancer cases were older and more likely to be perimenopausal/postmenopausal and Caucasian than disease-free women (Table 2). We observed a higher frequency of hormone therapy use, other lipid-lowering medication use, and a positive family history of breast cancer among breast cancer cases than disease-free women. Cases were less likely to have missing survey data than disease-free women. The majority of breast cancer cases were diagnosed at American Joint Committee on Cancer stage I (61.7%) or stage II (28.2%); most tumors were ER^+ (84.7%); and histology was primarily ductal (80.3%). There were no differences in these breast cancer characteristics by ever use of statins compared with nonusers (data not shown).

Overall, we found no association between statin use and breast cancer risk (Table 3). Risk of breast cancer did not differ by ever use [hazard ratio (HR), 1.07; 95% confidence interval (95% CI), 0.88-1.29] or current use (HR, 1.08; 95% CI, 0.89-1.31) of statins compared with nonusers. Compared with nonusers, type of statin use was not associated with risk of breast cancer (HR, 1.01; 95% CI, 0.80-1.26 for hydrophobic only and HR, 1.01; 95% CI, 0.48-2.13 for hydrophilic only). Among women enrolled at GH for at least 5 years during the study period, examination of the risk of incident breast cancer by duration of statin use and duration of hydrophobic statin use revealed no significant trend. There was, however, a suggestive increased risk of breast cancer among the highest category of ≥5 years of statin use (HR, 1.27; 95% CI, 0.89-1.81 for any statins and HR, 1.47; 95% CI, 0.89-2.44 for hydrophobic statins).

Compared with nonusers, there was a suggestive increased risk of ER^- breast cancer tumors associated with statin use (HR, 1.28; 95% CI, 0.78-2.08 for ever use and HR, 1.16; 95% CI, 0.69-1.95 for current use), although the HRs were not statistically significant (Table 4). The suggested increased risk

Table 1. Demographic characteristics of the study population by statin use

Characteristics	Statin user (N = 6,836), n (%)	Nonuser (N = 85,952), n (%)	P*
Age (y), mean (SD)	61.4 (8.7)	59.7 (11.0)	<0.0001
Body mass index (kg/m^2), mean (SD)	27.9 (6.1)	25.9 (5.7)	<0.0001
Race			<0.0001
White	5,325 (89.3)	48,614 (87.6)	
African American	192 (3.2)	1,583 (2.9)	
Asian/Pacific Islander	316 (5.3)	3,928 (7.1)	
Other	128 (2.1)	1,366 (2.5)	
No information	875	30,461	
Education			<0.0001
Below high school	740 (12.9)	4,660 (9.3)	
High school/GED	1,920 (33.5)	14,023 (27.9)	
Some college	1,932 (33.8)	17,481 (34.8)	
College graduate	563 (9.8)	6,796 (13.5)	
Graduate school	568 (9.9)	7,263 (14.5)	
No information	1,113	35,729	
Family history of breast cancer (first- or second-degree relatives)			0.79
No	4,790 (74.3)	54,004 (74.4)	
Yes	1,660 (25.7)	18,566 (25.6)	
No information	386	13,382	
Parous			<0.0001
No	609 (9.4)	9,217 (12.6)	
Yes	5,882 (90.6)	63,981 (87.4)	
No information	345	12,754	
Diabetes			<0.0001
No	4,397 (64.3)	78,372 (91.2)	
Yes	2,439 (35.7)	7,580 (8.8)	
Hormone therapy use			<0.0001
Never	3,137 (45.9)	49,170 (57.2)	
Estrogen only	1,709 (25.0)	16,126 (18.8)	
Estrogen plus progestin	1,990 (29.1)	20,656 (24.0)	
Menopausal status			<0.0001
Premenopausal	29 (0.4)	3,655 (4.4)	
Perimenopausal or Postmenopausal	6,793 (99.6)	78,532 (95.6)	
No information	14	3,765	
Other lipid-lowering agents use			<0.0001
Never	5,070 (74.2)	83,682 (97.4)	
Ever	1,766 (25.8)	2,270 (2.6)	

*χ^2 test for categorical variables or t test for continuous variables.

Table 2. Demographic characteristics of the study population by breast cancer status

Characteristics	Breast cancer cases (N = 2,707), n (%)	Disease-free (N = 90,081), n (%)	P*
Age (y), mean (SD)	61.7 (9.9)	59.7 (10.9)	<0.0001
Body mass index (kg/m^2), mean (SD)	25.9 (5.3)	26.0 (5.8)	0.19
Race			<0.0001
White	2,206 (93.1)	51,733 (87.6)	
African American	56 (2.4)	1,719 (2.9)	
Asian/Pacific Islander	74 (3.1)	4,170 (7.1)	
Other	34 (1.4)	1,460 (2.5)	
No information	337	30,999	
Education			0.10
Below high school	223 (9.6)	5,177 (9.7)	
High school/GED	702 (30.1)	15,241 (28.4)	
Some college	770 (33.0)	18,643 (34.8)	
College graduate	284 (12.2)	7,075 (13.2)	
Graduate school	351 (15.1)	7,480 (14.0)	
No information	377	36,465	
Family history of breast cancer (first- or second-degree relatives)			<0.0001
No	1,773 (68.7)	57,021 (74.6)	
Yes	808 (31.3)	19,418 (25.4)	
No information	126	13,642	
Parous			0.39
No	306 (11.8)	9,520 (12.3)	
Yes	2,291 (88.2)	67,572 (87.7)	
No information	110	12,989	
Diabetes			0.23
No	2,434 (89.9)	80,335 (89.2)	
Yes	273 (10.1)	9,746 (10.8)	
Hormone therapy use			
Never	1,335 (49.3)	50,972 (56.6)	<0.0001
Estrogen only	522 (19.3)	17,313 (19.2)	
Estrogen plus progestin	850 (31.4)	21,796 (24.2)	
Menopausal status			<0.0001
Premenopausal	23 (0.9)	3,661 (4.2)	
Perimenopausal or Postmenopausal	2,670 (99.1)	82,655 (95.8)	
No information	14	3,765	
Other lipid-lowering agent use			<0.01
Never	2,561 (94.6)	86,191 (95.7)	
Ever	146 (5.4)	3,890 (4.3)	

*χ^2 test for categorical variables or t test for continuous variables.

of ER$^-$ tumors was also observed for increasing duration of statin use (1-2.9 years: HR, 1.33; 95% CI, 0.64-2.77; 3-4.9 years: HR, 1.68; 95% CI, 0.72-3.92; ≥5 years: HR, 1.81; 95% CI, 0.75-4.36) compared with nonusers, but the findings were limited by a small number of exposed cases.

In sensitivity analyses where only the true nonusers of statin were included in the comparison group, the results remained the same. Additional adjustment for regular mammography screening did not alter our findings. The interaction between statin use and hormone therapy use was tested in all models,

Table 3. Association between statin use and breast cancer risk

Statin use	Breast cancer cases, n = 2,707 (%)	Disease-free, n = 90,081 (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
All women				
Never	95.2	92.6	Reference	Reference
Ever	4.8	7.4	1.15 (0.96-1.38)	1.07 (0.88-1.29)
Current	4.5	6.7	1.17 (0.97-1.41)	1.08 (0.89-1.31)
Hydrophobic only†	3.1	6.3	1.09 (0.88-1.36)	1.01 (0.80-1.26)
Hydrophilic only‡	0.3	0.1	1.05 (0.50-2.21)	1.01 (0.48-2.13)
Statin use	**Breast cancer cases, n = 1,682 (%)**	**Disease-free, n = 57,666 (%)**	**Age-adjusted HR (95% CI)**	**Multivariable-adjusted HR (95% CI)***
Duration of use among women with ≥5 y of data§				
Never	93.4	89.9	Reference	Reference
All statins				
1-2.9 y	2.7	4.4	0.96 (0.71-1.29)	0.96 (0.71-1.31)
3-4.9 y	1.8	2.4	1.09 (0.76-1.55)	1.04 (0.72-1.51)
≥5 y	2.1	3.3	1.28 (0.91-1.79)	1.27 (0.89-1.81)
Hydrophobic statins only†				
1-2.9 y	2.7	4.5	0.90 (0.64-1.26)	0.90 (0.64-1.26)
3-4.9 y	1.5	2.2	1.19 (0.79-1.79)	1.12 (0.74-1.71)
≥5 y	1.0	2.2	1.51 (0.92-2.49)	1.47 (0.89-2.44)

*Multivariable-adjusted models include age, hormone therapy use, diabetes, other lipid-lowering drug use, and body mass index.
† Includes users of lovastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin.
‡ Includes users of pravastatin and rosuvastatin.
§ P = 0.3 from linear trend test for the effect of the duration of statin use and duration of hydrophobic statin use on breast cancer risk.

Table 4. Association between statin use and ER$^+$ and ER$^-$ tumors

Statin use	ER$^+$ cases		ER$^-$ cases	
	n = 2,067 (%)	Multivariable-adjusted HR (95% CI)*	n = 373 (%)	Multivariable-adjusted HR (95% CI)*
All women				
Never	95.1	Reference	94.4	Reference
Ever	4.9	1.06 (0.85-1.32)	5.6	1.28 (0.78-2.08)
Current	4.7	1.10 (0.88-1.37)	4.8	1.16 (0.69-1.95)
Statin use	ER$^+$ cases		ER$^-$ cases	
	n = 1,315 (%)	Multivariable-adjusted HR (95% CI)*	n = 218 (%)	Multivariable-adjusted HR (95% CI)*
Duration of use among women with ≥5 y of data †				
Never	93.6	Reference	90.7	Reference
1-2.9 y	2.6	0.93 (0.66-1.32)	3.7	1.33 (0.64-2.77)
3-4.9 y	1.7	0.98 (0.63-1.51)	2.8	1.68 (0.72-3.92)
≥5 y	2.1	1.24 (0.83-1.86)	2.8	1.81 (0.75-4.36)

*Multivariable-adjusted models include age, hormone therapy use, diabetes, other lipid lowering drug use, and body mass index.
† P = 0.5 from linear trend test for the effect of the duration of statin use on risk of ER$^+$ tumor; P = 0.08 from linear trend test for the effect of the duration of statin use on risk of ER$^-$ tumor.

including ER$^+$ and ER$^-$ tumors, but only significant in the model of ever statin use and overall breast cancer incidence. When we evaluated statin use and breast cancer risk separately by hormone therapy use, we found a suggestive difference in risk among nonusers of hormone therapy (HR, 1.29; 95% CI, 0.99-1.68) and estrogen plus progestin users (HR, 0.83; 95% CI, 0.59-1.17; Table 5).

Discussion

This population-based cohort study does not suggest an association between statin use and breast cancer risk. Overall, we found no significant difference in breast cancer risk by ever use, current use, duration of use, or use of hydrophobic statins compared with nonusers. We did find a suggestive increased risk of breast cancer among statin users of ≥5 years and a suggestive increased risk of ER$^-$ tumors with increasing duration of statin use compared with nonusers. However, confidence intervals included 1.0, and the findings were limited by a small number of exposed cases. We are unaware of any biological mechanisms to support an increased risk of ER$^-$ tumors with statin use; no difference was seen in the other one study that evaluated type of breast cancer tumor in relation to statin use (21).

This was the first large cohort study conducted in an integrated practice setting where women receive almost all their care within the system and where information on breast cancer risk factors is available. Other strengths of the study include the stability of the population over time, extensive and unbiased data on medication use and covariates, and reliable data on cancer incidence. Our large population-based cohort shows the dramatic increase in statin use among women over the past decade.

Although we found no association between statin use and breast cancer risk, it remains plausible that statins reduce breast cancer risk. The mechanistic data are relatively strong and suggest that statins inhibit cancer cell growth and lead to apoptotic cell death through their inhibition of the mevalonate pathway, although other mechanisms have also been suggested (6). Many products of the mevalonate pathway are necessary for critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression (6, 7). Disruptions of these processes in neoplastic cells by statins may result in control of tumor initiation, growth, and metastasis (7). Our study and others (15, 19, 21) suggest that experimental models may not apply to humans, but there may be reasons for not observing an association in our study, such as residual confounding, use of hormone therapy by the majority of statin users (54%), and a relatively short average duration of statin use.

Our results are similar to at least two other recently published large cohort studies (19, 21) and one small case-control study (15) that report no overall association between statin use and breast cancer risk. However, one of these large cohort studies by Cauley et al. found that statin use was associated with an 18% lower risk of breast cancer when statin use was limited to hydrophobic statin users among women enrolled in the Women's Health Initiative (21). Other observational studies have reported sometimes large reductions in the risk of breast cancer (30-72%) associated with use of statins (16, 18, 20). Cauley et al. also report no association between statin use and breast cancer risk among users of estrogen plus progestin or among never/past hormone therapy user but a nonstatistically significant reduced risk (22%) among users of estrogen alone. Our study and the study by Cauley et al. were not powered to evaluate an interaction between hormone therapy use and statins on breast cancer risk; therefore, findings may be due to chance.

There are several limitations in our study. First, our study subjects are from a single health care system in the western Washington State and may not be representative of other populations. Second, we cannot rule out exposure misclassification. Subjects who fill prescriptions but do not subsequently take the medication may be misclassified as users. Additionally, pharmacy utilization is only captured for

Table 5. Association of statin use and breast cancer risk by hormone use

Statin users	Breast cancer cases, n = 2,707 (%)	Disease-free, n = 90,081 (%)	Multivariable-adjusted HR (95% CI)*	P for interaction
Nonusers of hormone therapy	49.3	56.6	1.29 (0.99-1.68)	
Estrogen only users	19.3	19.2	1.02 (0.70-1.49)	0.31
Estrogen + progestin users	31.4	24.2	0.83 (0.59-1.17)	0.04

*Multivariable-adjusted models include age, hormone therapy use, diabetes, other lipid lowering drug use, and body mass index.

enrollees who fill prescriptions at GH pharmacies and for enrollees with a drug benefit through GH who fill prescriptions at contracting pharmacies. Therefore, subjects who fill prescriptions at non-GH pharmacies may be erroneously classified as nonusers. However, misclassification of medication use is relatively unlikely because previous GH studies have found that GH enrollees obtain 97% of their medications at GH pharmacies (23, 24), and we required ≥2 dispensings and a year of use to be considered a statin user. We did not have information on medication use before enrollment in GH. Any bias resulting from classifying a user as a nonuser would bias our findings towards the null. Third, BCSP survey data were disproportionately missing for nonstatin users compared with statin users and for disease-free women compared with breast cancer cases. Although these risk factors were not included in the multivariable-adjusted models, the differential missing data indicate a difference in screening practice by statin use and disease status. Lastly, residual confounding is always possible in observational studies. We lacked information on potential confounders such as diet and level of physical activity, and women prescribed and adherent to statins may differ from nonusers by factors not measured in this study.

In conclusion, our study and others indicate that statins are safe in relation to breast cancer risk, but any chemopreventive effect in humans remains to be established. Researchers have hypothesized hydrophobic statins to have antiproliferative effects on breast cancer cells (31, 32) and hydrophilic statins to promote cancer (33). We were unable to evaluate hydrophilic statin use due to the small number of hydrophilic only statin users in our cohort. Further evaluations of longer durations of statin use by type of statins (hydrophobic and hydrophilic) in relation to breast cancer risk are warranted. The effects of statins on cancer are not completely understood. The National Cancer Institute recently funded two phase II trials of (*a*) statin use and colorectal cancer risk among patients with an increased risk of colorectal cancer and (*b*) the effect of statin use on precancerous changes in atypical nevi, which are a precursor for melanoma (34). These trials are likely to be useful in disentangling the complex relation between statins and cancer. Clinical trials of the effects of statins on breast cancer risk and biological end points, such as breast density, have been suggested but are not supported by our study findings (31, 32, 35, 36).

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References

1. Sewester CS, Dombek CE, Olin BR, Kastrup EK, Hebel SK. Drug facts and comparisons. St. Louis (MO): 2004.
2. RX List. The Top 200 Prescriptions for 2004 by U.S. Sales. Available at: http://www.rxlist.com/top200_sales_2004. Accessed May 10, 2005.
3. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996;275:55–60.
4. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
5. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.
6. Wong WW, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. Leukemia 2002;16:508–19.
7. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res 2003;9:10–9.
8. Denoyelle C, Vasse M, Korner M, et al. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an *in vitro* study. Carcinogenesis 2001;22:1139–48.
9. Alonso DF, Farina HG, Skilton G, Gabri MR, De Lorenzo MS, Gomez DE. Reduction of mouse mammary tumor formation and metastasis by lovastatin, an inhibitor of the mevalonate pathway of cholesterol synthesis. Breast Cancer Res Treat 1998;50:83–93.
10. Inano H, Suzuki K, Onoda M, Wakabayashi K. Anti-carcinogenic activity of simvastatin during the promotion phase of radiation-induced mammary tumorigenesis of rats. Carcinogenesis 1997;18:1723–7.
11. Seeger H, Wallwiener D, Mueck AO. Statins can inhibit proliferation of human breast cancer cells *in vitro*. Exp Clin Endocrinol Diabetes 2003;111:47–8.
12. Denoyelle C, Albanese P, Uzan G, et al. Molecular mechanism of the anti-cancer activity of cerivastatin, an inhibitor of HMG-CoA reductase, on aggressive human breast cancer cells. Cell Signal 2003;15:327–38.
13. Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Arch Intern Med 2000;160:2363–8.
14. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Shapiro S. Statin use and the risk of breast and prostate cancer. Epidemiology 2002;13:262–7.
15. Kaye JA, Meier CR, Walker AM, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. Br J Cancer 2002;86:1436–9.
16. Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl coenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case-control study. Cancer 2004;100:2308–16.
17. Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. J Clin Epidemiol 2003;56:280–5.
18. Cauley JA, Zmuda JM, Lui LY, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt) 2003;12:749–56.
19. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med 2005;165:2264–71.
20. Kochhar R, Khurana V, Bejjanki H, Caldito G, Fort C. Statins reduce breast cancer risk: a case control study in US female veterans, 2005 ASCO Annual Meeting Proceedings [abstract 514]. Journal of Clinical Oncology 2005;23.
21. Cauley JA, McTiernan A, Rodabough RJ, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. J Natl Cancer Inst 2006;98:700–7.
22. Saunders KW, Davis RL, Stergachis A. Group Health Cooperative. In: Strom B, editor. Pharmacoepidemiology. Chichester: John Wiley and Sons; 2005. pp. 223–39.
23. Boudreau DM, Doescher MP, Jackson JE, Fishman PA. Impact of healthcare delivery system on where HMO-enrolled seniors purchase medications. Ann Pharmacother 2004;38:1317–8.
24. Buist DS, LaCroix AZ, Brenneman SK, Abbott T. A population-based osteoporosis screening program: who does not participate, and what are the consequences? J Am Geriatr Soc 2004;52:1130–7.
25. Taplin SH, Ichikawa L, Buist DS, Seger D, White E. Evaluating organized breast cancer screening implementation: the prevention of late-stage disease? Cancer Epidemiol Biomarkers Prev 2004;13:225–34.
26. Washington State Department of Health, Center for Health Statistics 2003. Washington State Vital Statistics, 2002. 2003. Available at: http://www.doh.wa.gov/ehsphl/chs/chs-data/Public/AnnSum_2002. Accessed September 17, 2004.
27. Taplin SH, Thompson RS, Schnitzer F, Anderman C, Immanuel V. Revisions in the risk-based breast cancer screening program at Group Health Cooperative. Cancer 1990;66:812–8.
28. Newton KM, Wagner EH, Ramsey SD, et al. The use of automated data to identify complications and comorbidities of diabetes: a validation study. J Clin Epidemiol 1999;52:199–207.
29. Hosmer DW, Jr., Lemeshow S. Applied survival analysis: regression modeling of time to event data. New York: John Wiley & Sons; 1999.
30. Hastie T, Tibshirani R, Friedman J, editors. The elements of statistical learning; data mining, inference, and prediction. Chapter 5. New York: Springer; 2001.
31. Prowell TM, Stearns V, Trock B. Lipophilic statins merit additional study for breast cancer chemoprevention. J Clin Oncol 2006;24:2128–9; author reply 2129.
32. Sprague JR, Wood ME. Statins and breast cancer prevention: time for randomized controlled trials. J Clin Oncol 2006;24:2129–30; author reply 2130–1.
33. Duncan RE, El-Sohemy A, Archer MC. Statins and cancer development. Cancer Epidemiol Biomarkers Prev 2005;14:1897–8.
34. Zielinski SL. Following positive epidemiologic studies, statins to enter clinical trials for cancer prevention. J Natl Cancer Inst 2005;97:1172–3.
35. Boudreau DM, Rutter CM, Buist DS. The influence of statin use on breast density. Cancer Epidemiol Biomarkers Prev 2006;15:1026–9.
36. Kumar AS, Campbell M, Benz CC, Esserman LJ. A call for clinical trials: lipophilic statins may prove effective in treatment and prevention of particular breast cancer subtypes. J Clin Oncol 2006;24:2127; author reply 2127–8.