

Serum Lipids, Lipid-Lowering Drugs, and the Risk of Breast Cancer

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Background: Experimental evidence suggests that statins protect against breast carcinogenesis by interrupting cell cycle progression and promoting apoptosis. Evidence in humans is limited and inconsistent. The relation between serum cholesterol levels and breast cancer risk is itself unclear; because cholesterol is the precursor to sex steroid hormones, higher levels could plausibly increase risk.

Methods: The associations of statins, general lipid-lowering drugs, and reported cholesterol levels with breast cancer risk were assessed in the Nurses' Health Study, with 6 to 12 years of follow-up. A total of 79 994 women aged 42 to 69 years and free of cancer were followed prospectively for up to 12 years. Current statin use, including duration, was assessed retrospectively in 2000 in 75 828 women. Self-reported serum cholesterol level was assessed prospectively between 1990 and 2000 in 71 921 women.

Results: Overall, we documented 3177 incident cases of invasive breast cancer. Compared with nonusers, current lipid-lowering drug users experienced similar breast cancer risk (multivariate relative risk [RR], 0.99; 95% confidence interval [CI], 0.86-1.13). Current use of statins also was not significantly associated with breast cancer risk (RR, 0.91; 95% CI, 0.76-1.08). Associations by duration of current use were similarly null. Self-reported serum cholesterol levels were not associated with breast cancer risk in postmenopausal women with levels of 240 mg/dL or higher (≥ 6.22 mmol/L) compared with less than 180 mg/dL (< 4.66 mmol/L) (RR, 1.04; 95% CI, 0.91-1.17).

Conclusion: Overall, these data suggest that serum cholesterol levels and the use of lipid-lowering drugs in general and of statins in particular are not substantially associated with breast cancer risk.

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THREE-HYDROXY-3-METHYL-glutaryl coenzyme A reductase inhibitors, or statins, were first introduced in the United States in 1987 and are commonly prescribed to reduce serum cholesterol levels.^{1,2} Although initial animal studies³ and a randomized trial⁴ raised concern that statins may increase cancer risk, laboratory evidence suggests that statins inhibit tumor development by inducing cell cycle arrest⁵ and apoptosis.⁶ In addition, experimental studies suggest that statins may act synergistically with standard chemotherapy agents in cancer treatment.⁷ Findings from observational studies of the association between statins and breast cancer risk have been conflicting. Statins were weakly associated with increased risk in a case-control study⁸ and significantly inversely associated with breast cancer in a prospective study.⁹ No overall association was seen in 5 other studies.¹⁰⁻¹⁴

Serum cholesterol has long been hypothesized to affect cancer risk. Many stud-

ies have shown an inverse association between serum cholesterol level and cancer risk.¹⁵ However, this association is strongest the first 2 years after cholesterol measurement, suggesting that the lower cholesterol level observed in this subgroup may be a result of preclinical disease. Cholesterol has also been hypothesized to increase breast cancer risk^{16,17} given that cholesterol is the precursor to steroid hormone synthesis and endogenous sex steroid hormones are directly related to breast cancer risk.^{18,19} On the other hand, endogenous and exogenous estrogens decrease serum cholesterol levels.²⁰⁻²² Thus, an inverse association between cholesterol level, as a marker of low estrogen levels, and breast cancer risk is possible. Most observational studies of the association between serum cholesterol level and breast cancer risk have been small and the results inconsistent, regardless of whether cholesterol was measured before^{12,17,23-37} or after^{16,38-48} diagnosis.

We conducted an analysis within the prospective Nurses' Health Study to evalu-

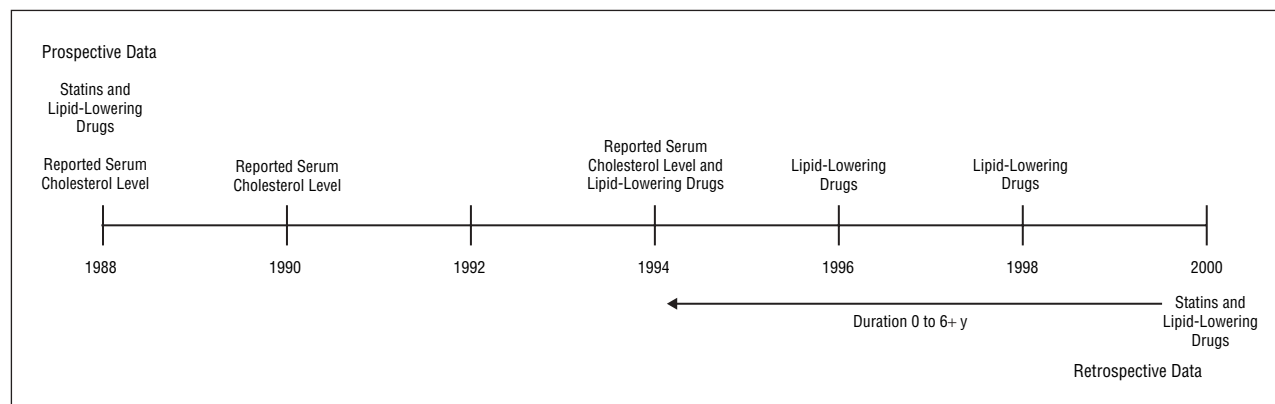


Figure. Time line of data collection in the Nurses' Health Study, 1988 to 2000.

ate the associations of statins, lipid-lowering drugs, and serum cholesterol with breast cancer risk.

METHODS

STUDY POPULATION

In 1976, 121 700 female, married registered nurses aged 30 to 55 years were enrolled in the Nurses' Health Study. At baseline, and biennially since, women have completed mailed questionnaires that collect information on lifestyle factors, including many breast cancer risk factors, and new disease diagnoses. Follow-up data are available for more than 96% of the participants in this analysis. This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital; completion of the self-administered questionnaire was considered to imply informed consent.

Three different follow-up periods were used for these analyses based on when the exposures of interest were queried. Follow-up began in 1988 for general lipid-lowering drugs, in 1990 for reported serum cholesterol levels, and in 1994 for statins using data collected in 2000 to define use from 1994 forward. Each analysis began with all women who returned the questionnaire that first queried the exposure of interest; follow-up for each of these analyses ended June 1, 2000. After excluding women with a previous cancer diagnosis (other than nonmelanoma skin cancer) and women with missing data on the primary exposures, the lipid-lowering drug analysis included 79 994 women (888 120 person-years), the serum cholesterol analysis included 71 921 women (665 743 person-years), and the statin analysis included 75 828 women (431 705 person-years).

DATA COLLECTION

In 1988, participants were asked whether they currently used cholesterol-lowering drugs at least once a week and, if so, specifically which drugs (**Figure**). In 1994, 1996, and 1998, participants were asked whether they regularly used cholesterol-lowering drugs. In 2000, participants were asked whether they regularly used statins or other cholesterol-lowering drugs. Statin users were asked to further specify duration of use, in 2-year categories up to 6 or more years. Given the range of years within the reported duration categories, we used the prospective lipid-lowering drug data to better estimate the year statin use was initiated. Dose information was not available. Women were defined as current lipid-lowering drug users in any 2-year questionnaire cycle they reported drug use, and they became past users when they no longer reported use on subsequent questionnaires. Current statin users were defined as those who re-

Table 1. Measured Total Serum Cholesterol Levels by Category of Self-reported Total Serum Cholesterol Level*

Self-reported Total Serum Cholesterol, mg/dL	Participants, No. (n = 1328)	Measured Total Serum Cholesterol, Mean (SD), mg/dL
<140	49	176 (34.3)
140-159	84	184 (31.8)
160-179	150	190 (34.1)
180-199	230	207 (33.6)
200-219	281	215 (28.7)
220-239	239	233 (30.1)
240-269	195	245 (33.6)
270-299	72	259 (35.8)
≥300	28	292 (31.3)

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Self-reported total serum cholesterol levels averaged from the 1988 and 1990 questionnaires.

ported current use on the 2000 questionnaire, with duration dating back to 1994 for those in the 6 or more years category.

Total serum cholesterol levels, if measured in the previous 5 years, were reported on questionnaires in 1988, 1990, and 1994 in 20- to 30-mg/dL (0.52- to 0.78-mmol/L) categories (**Figure**). Of the 96 597 women who answered questionnaires in 1988 or 1990, 79 422 (82%) reported cholesterol levels. To minimize measurement error,⁴⁹ we averaged reports from 1988 and 1990 for each participant. For the 10% of participants missing either 1988 or 1990 cholesterol information, a single report was used.

Blood samples collected in 1989-1990 in a subcohort of the Nurses' Health Study were used to assess the validity of self-reported cholesterol levels; details of the blood collection have previously been described elsewhere.^{50,51} As part of a breast cancer case-control study, we measured total cholesterol levels in the blood samples of 1455 women; 1328 of these women also reported cholesterol levels in 1988 and 1990. Mean measured serum cholesterol levels matched reported categories fairly well, although with some regression to the mean (**Table 1**). The correlation between measured and reported levels (Spearman $\rho=0.60$) is similar to the within-subject reproducibility of cholesterol measures across several years ($\rho=0.65$).⁵²

Cases of breast cancer, diagnosed from the start of follow-up through May 31, 2000, were identified on biennial questionnaires; the National Death Index was searched for nonresponders. To confirm cancer reports, medical records were reviewed by investigators masked to exposure status. Records were unavailable for 170 (5.4%) of 3177 cases. Given that pa-

Table 2. Age and Age-Standardized* Characteristics According to Statin Use in 2000 in 75 828 Participants† in the Nurses' Health Study

Characteristic	Nonusers (n = 59 534)	Statin Users		
		0-2 y (n = 7630)	3-5 y (n = 5034)	≥6 y (n = 2706)
Age, mean (SD), y	65.7 (7.1)	67.3 (6.9)	68.0 (6.6)	68.9 (6.3)
Age at menarche, mean (SD), y	12.6 (1.4)	12.5 (1.4)	12.5 (1.5)	12.5 (1.4)
Parity, mean (SD), No. of children‡	3.2 (1.6)	3.3 (1.6)	3.2 (1.6)	3.2 (1.6)
Age ≥30 y at first birth, %‡	8.4	8.0	8.6	7.8
Family history of breast cancer, %	16.0	17.2	16.7	16.5
History of benign breast disease, %	50.1	53.0	52.7	54.2
Age at menopause, mean (SD), y§	49.2 (5.1)	49.0 (5.1)	48.8 (5.2)	48.5 (5.5)
Current PMH use, %	41.9	40.0	43.9	48.3
Duration of PMH use, mean (SD), y	10.4 (7.4)	10.4 (8.0)	10.6 (8.6)	11.1 (7.9)
BMI, mean (SD)	26.6 (5.4)	28.1 (5.3)	28.2 (5.3)	27.6 (4.8)
BMI at age 18 y, mean (SD)	21.3 (2.9)	21.5 (3.1)	21.4 (3.1)	21.3 (2.9)
Height, mean (SD), inches	64.5 (2.4)	64.4 (2.4)	64.3 (2.4)	64.1 (2.4)
Alcohol consumption, mean (SD), g/d	5.1 (9.2)	4.3 (8.6)	4.3 (8.5)	4.4 (8.9)
Physical activity, ≥4 MET/d, %	1.3	18.0	16.8	18.1
Mammography within 2 y, %	88.2	92.6	93.8	94.1

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); MET, metabolic equivalent; PMH, postmenopausal hormones.

*Age was standardized according to 6 categories of age (<55, 55-59, 60-64, 65-69, 70-74, and ≥75 years).

†Excludes 924 statin users with unknown duration of use.

‡Among parous women only.

§Among women with natural menopause or bilateral oophorectomy only.

thology reports confirmed 99% of the reported cases, diagnoses with participant confirmation but missing medical record confirmation were included as cases.

Age was calculated from date of birth to the date of questionnaire return. Age at menarche, height, and age at first birth were queried in 1976. Parity data were collected biennially from 1976 until 1984. Diagnosis of benign breast disease, current weight, menopausal status, age at menopause, and postmenopausal hormone (PMH) use were assessed biennially. History of breast cancer in the participants' mothers and sisters was queried in 1976, 1982, 1988, 1992, and 1996. Alcohol consumption was assessed using a semiquantitative food-frequency questionnaire in 1986, 1990, 1994, and 1998. Data on physical activity were collected in 1988 and then biennially starting in 1992.

STATISTICAL ANALYSIS

Population characteristics across statin use categories were directly standardized using the cohort age distribution. We calculated person-years from the baseline questionnaire return date to the first date of diagnosis of breast or other cancer (except non-melanoma skin cancer), death, or June 1, 2000. We used Cox proportional hazards models to calculate multivariate-adjusted relative risks (RRs) and 95% confidence intervals (CIs). Multivariate models were stratified jointly by age in months and calendar year of follow-up at the beginning of each 2-year questionnaire cycle and controlled for many known breast cancer risk factors. Interactions were assessed by including interaction terms between exposure and the potential modifier in multivariate models. Statistical significance was assessed using the likelihood ratio test at the $\alpha = .05$ level. All analyses were conducted using SAS software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

We documented 3177 incident cases of invasive breast cancer between 1988 and 2000; 1727 cases were docu-

mented in the statins analysis between 1994 and 2000. Statin users accounted for 8% of person-years between 1994 and 2000. Statin users were older than women who did not use any lipid-lowering drugs (**Table 2**). After adjusting for age, compared with nonusers, statin users were slightly younger at menopause, were heavier, exercised less, and consumed less alcohol. Statin users had a higher prevalence of factors related to health care use, including PMH use, benign breast disease, and having had a mammogram within 2 years.

Current lipid-lowering drug use was not associated with breast cancer risk (RR, 0.99; 95% CI, 0.86-1.13), and neither was duration of use (**Table 3**). The relationship between current statin use and breast cancer was similarly null (RR, 0.91; 95% CI, 0.76-1.08). Categorizing current use by duration again did not alter the results. Similar results were observed with statins and lipid-lowering drugs when in situ cases were included in the analyses. We also found no relation between current statin use and breast cancer risk among longer-term statin users (mean duration, 8 years) who were current users in 1988 (RR, 1.12; 95% CI, 0.76-1.67). There also was no association with statin use among never PMH users. Similarly, no associations were observed when defining cases according to the estrogen and progesterone receptor status of the tumor, although there were few cases in several of these groups. For example, the RR of estrogen receptor- and progesterone receptor-positive breast cancer among current statin users (vs nonusers) was 0.98 (95% CI, 0.79-1.22). The associations with statins and lipid-lowering drugs also did not differ by histologic subtype of the tumor (data not shown).

Health care-seeking behavior could create a spurious association between drug use and breast cancer if

Table 3. Adjusted Relative Risks (RRs) of Breast Cancer According to General Lipid-Lowering Drug and Statin Use

Variable	Nonuse	Past Use	Current Use			Total
			<2 y	2-4 y	>4 y	
Lipid-lowering drug use*						
Invasive cases, No.	2908	32	110	71	56	237
Person-years	824 230	6860	27 108	14 698	15 224	57 030
Age-adjusted RR	1.00 (Referent)	1.00	0.99	1.13	0.84	0.99
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	0.98 (0.69-1.40)	1.00 (0.82-1.21)	1.14 (0.89-1.45)	0.83 (0.63-1.09)	0.99 (0.86-1.13)
Invasive plus in situ cases, No.	3439	44	131	83	72	286
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	1.14 (0.84-1.54)	1.00 (0.83-1.19)	1.13 (0.90-1.41)	0.90 (0.71-1.14)	1.00 (0.89-1.14)
Statin use‡						
Invasive cases, No.	1472	NA	78	53	21	152
Person-years	370 718	NA	20 644	11 357	4256	36 257
Age-adjusted RR	1.00 (Referent)	NA	0.85	0.98	0.94	0.90
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	NA	0.86 (0.68-1.08)	0.99 (0.75-1.31)	0.93 (0.60-1.44)	0.91 (0.76-1.08)
Invasive plus in situ cases, No.	1781	NA	101	63	28	192
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	NA	0.93 (0.76-1.14)	0.99 (0.77-1.28)	1.05 (0.72-1.54)	0.96 (0.83-1.12)
Among never PMH users						
Invasive cases, No.	319	NA	21	11	2	34
Age-adjusted RR	1.00 (Referent)	NA	0.95	0.90	0.42	0.87
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	NA	0.93 (0.59-1.45)	0.89 (0.48-1.64)	0.40 (0.10-1.62)	0.85 (0.59-1.23)
ER+/PR+						
Invasive cases, No.	847	NA	47	34	13	94
Age-adjusted RR	1.00 (Referent)	NA	0.90	1.09	0.99	0.97
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	NA	0.91 (0.67-1.22)	1.11 (0.78-1.57)	0.98 (0.56-1.71)	0.98 (0.79-1.22)
ER-/PR-§						
Invasive cases, No.	197	NA	8	10	3	21
Age-adjusted RR (95% CI)	1.00 (Referent)	NA	0.66 (0.32-1.34)	1.40 (0.73-2.66)	1.16 (0.36-3.70)	0.96 (0.60-1.51)

Abbreviations: CI, confidence interval; ER, estrogen receptor; NA, not available; PMH, postmenopausal hormone; PR, progesterone receptor; +, positive; -, negative.

*Prospective assessment with follow-up between 1988 and 2000.

†Relative risk was adjusted for time in 2-year intervals, age in months, age at menarche (≤ 12 , 13, or ≥ 14 years, or missing), parity and age at first birth (nulliparous, 1-2 children and < 25 years, 1-2 children and 25-29 years, 1-2 children and ≥ 30 years, 3-4 children and < 25 years, 3-4 children and 25-29 years, 3-4 children and ≥ 30 years, ≥ 5 children and < 25 years, ≥ 5 children and 25-29 years, ≥ 5 children and ≥ 30 years, or missing), height (< 63 , 63-63.9, 64-65.9, or ≥ 66 inches), body mass index (calculated as weight in kilograms divided by the square of height in meters) (< 21 , 21-22.9, 23-24.9, 25-29.9, or ≥ 30), first-degree family history of breast cancer (yes or no), benign breast disease (yes or no), alcohol consumption (none, < 5 , 5-14.9, or ≥ 15 g/d or missing), physical activity (< 3 , 3-8.9, 9-17.9, 18-26.9, or ≥ 27 metabolic equivalents/wk, or missing), and menopausal status, age at menopause, and use of postmenopausal hormones (premenopausal; postmenopausal, < 45 years, and never use; postmenopausal, 45-52 years, and never use; postmenopausal, ≥ 53 years, and never use; postmenopausal, < 45 years, and current use < 5 years; postmenopausal, 45-52 years, and current use < 5 years; postmenopausal, ≥ 53 years, and current use < 5 years; postmenopausal, < 45 years, and current use ≥ 5 years; postmenopausal, 45-52 years, and current use ≥ 5 years; postmenopausal, ≥ 53 years, and current use ≥ 5 years; or missing).

‡Retrospective assessment with follow-up between 1994 and 2000.

§No multivariate results owing to the small number of cases.

women using lipid-lowering drugs were more likely to visit their health care provider, be screened, and be diagnosed as having breast cancer. To address this possibility, we conducted an analysis restricted to women who received mammograms regularly (at least every 2 years), and again, the results were unchanged (data not shown).

Further adjustment for self-reported serum cholesterol level did not appreciably alter the lipid-lowering drug or statin results (data not shown). In addition, when we stratified by recently reported serum cholesterol levels (1994), the association between current statin use and breast cancer did not vary significantly: for cholesterol levels less than 200 mg/dL (< 5.18 mmol/L), 200 to 249 mg/dL (5.18-6.45 mmol/L), and 250 mg/dL or greater (≥ 6.47 mmol/L), the RRs were 1.06 (95% CI, 0.71-1.59), 0.94 (95% CI, 0.70-1.26), and 1.00 (95% CI, 0.71-1.32), respectively. The associations of statins and lipid-lowering drugs with breast cancer were also similar across levels of age and body mass index (data not shown).

The restriction of the statins analysis to current users in 2000 could have caused bias if cases were less likely than noncases to continue use through 2000. To evalu-

ate the impact of this restriction, we used the prospective lipid-lowering drug data to compare use patterns and breast cancer risk among users between 1994 and 1998 with those who continued use in 2000. Given the high prevalence (93%) of statin use among lipid-lowering drug users in 2000, this comparison is likely a good approximation of statin use. Among those who used lipid-lowering drugs between 1994 and 1998, continued use in 2000 was similar for cases (83%) and noncases (86%). The association between lipid-lowering drug use and breast cancer risk in the subset of users who remained current users in 2000 (RR, 0.91; 95% CI, 0.77-1.07) was similar to the association in the prospective analysis (RR, 0.98; 95% CI, 0.85-1.13).

No association was observed between reported total serum cholesterol levels and breast cancer risk in either premenopausal or postmenopausal women (**Table 4**). There was also no association in postmenopausal never PMH users or when the analysis was conducted by estrogen and progesterone receptor status of the tumor. Analyses adjusting for lipid-lowering drug use or restricted to nonusers did not differ from the overall re-

Table 4. Adjusted Relative Risks (RRs) of Breast Cancer by Reported Total Serum Cholesterol Level Among 71 921 Women Followed Up Between 1990 and June 2000

	Reported Total Serum Cholesterol, mg/dL					P Value*
Variable	<180	180-199	200-219	220-239	≥240	
Premenopausal women						
Invasive cases, No.	85	35	33	20	16	
Age-adjusted RR	1.00 (Referent)	0.72	0.82	0.73	0.94	
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	0.73 (0.48-1.09)	0.82 (0.54-1.24)	0.72 (0.43-1.19)	0.94 (0.54-1.64)	.35
Postmenopausal women						
Invasive cases, No.	512	393	484	386	504	
Age-adjusted RR	1.00 (Referent)	1.06	1.02	0.92	1.05	
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	1.05 (0.92-1.20)	1.01 (0.89-1.14)	0.90 (0.78-1.03)	1.04 (0.91-1.17)	.29
Among never PMH users						
Invasive cases, No.	124	92	114	104	128	
Age-adjusted RR	1.00 (Referent)	1.02	0.97	1.01	1.00	
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	1.00 (0.76-1.31)	0.95 (0.73-1.23)	0.96 (0.73-1.25)	0.95 (0.74-1.23)	.66
ER +/PR +						
Invasive cases, No.	264	207	251	189	253	
Age-adjusted RR	1.00 (Referent)	1.08	1.03	0.87	1.00	
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	1.05 (0.88-1.26)	1.00 (0.84-1.19)	0.85 (0.70-1.02)	1.00 (0.83-1.19)	.36
ER-/PR-						
Invasive cases, No.	76	58	70	51	75	
Age-adjusted RR	1.00 (Referent)	1.06	1.04	0.87	1.16	
Multivariate-adjusted RR (95% CI)†	1.00 (Referent)	1.05 (0.75-1.49)	1.03 (0.74-1.44)	0.85 (0.59-1.23)	1.15 (0.83-1.60)	.76

Abbreviations: CI, confidence interval; ER, estrogen receptor; PMH, postmenopausal hormone; PR, progesterone receptor; +, positive; -, negative.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*P value determined using test for trend.

†Relative risk was adjusted as described in Table 3.

sults (data not shown). In addition, the association between cholesterol levels and breast cancer risk did not vary by body mass index (data not shown). To rule out preclinical disease affecting the association, we repeated the analysis excluding cases diagnosed in the first 2 years of follow-up; the results were similar. Results were also similar when in situ cases were included (data not shown).

COMMENT

In this large, prospective cohort study, use of lipid-lowering drugs in general and of statins in particular was not associated with breast cancer risk. Longer duration of use was similarly unrelated to risk. Serum cholesterol levels were not appreciably associated with breast cancer risk. This analysis has several strengths, including the number of exposed women, many breast cancer cases, high levels of follow-up, detailed covariate information, and updated exposure status. Our exposure data are likely to be accurate given that participants are registered nurses familiar with prescription drugs and health-related exposures. Except for the statin inquiry in 2000, exposure data were collected before diagnosis, precluding the possibility of recall bias.

This study also has several potential limitations. Because statin use was assessed retrospectively in women who were current users in 2000, women who discontinued use before 2000 were not included as users in our analysis. However, the proportion of lipid-lowering drug users who continued use in 2000 was similar in cases and noncases. In addition, the associations between lipid-

lowering drug use and breast cancer were similar in the prospective and retrospective analyses. Because biennial questionnaires were administered, we were unable to assess the effect of very short-term statin use. However, statins are generally prescribed for long periods, and with relatively few adverse effects, short-term use is unlikely.⁵³ We also cannot rule out modest associations or associations with longer durations of use; thus, more follow-up is necessary. Finally, we were unable to assess the effects of specific types of statins.

Experimental studies have raised hopes that statins may provide benefits beyond lowering cardiovascular disease risk. Statins lower cholesterol levels by blocking 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step in the mevalonate pathway.⁵⁴ This pathway not only leads to the production of cholesterol but also includes intermediate products that are essential to cell cycle progression.^{55,56} Statins have inhibited tumor growth in murine models of brain, pancreatic, and breast cancer⁵⁷⁻⁵⁹ and have induced apoptosis in leukemic, colon cancer, and breast cancer cell lines.⁶⁰⁻⁶² However, statins have been designed to be hepatospecific, given that cholesterol production occurs primarily within the liver, and less than 5% of some statins taken orally reach the peripheral circulation.⁶³ Thus, even if statins are beneficial in experimental models, the effects may not be applicable to humans. In addition, estradiol has been shown to counteract the antiproliferative effects of statins in vitro.⁶⁴ Thus, if statins reach the breast tissue, the hormonal milieu of the breast may negate any beneficial effect of statins.

Our results of no overall association between statin use and breast cancer risk are consistent with those of 1

cohort study¹¹ and 3 case-control studies.^{10,12,13} In addition, no association was observed in 2^{65,66} of 3^{4,65,66} cardiovascular prevention trials with breast cancer data. A positive association was observed in 1 trial,⁴ although there were few cases, some of which were breast cancer recurrences. Increased risk was also observed in a case-control study,⁸ but the association was present only among in situ cases, suggesting heightened screening in statin users. There seemed to be somewhat greater health care use among statin users in our study given the slightly higher prevalence of PMH use, benign breast disease, and recent mammograms. However, no association was observed with statins either using all breast cancer cases or restricting the cases to invasive disease. Our results contrast those of the most recent cohort study,⁹ with 240 breast cancer cases (6 exposed cases), in which statins were associated with a significantly decreased breast cancer risk (RR, 0.28; 95% CI, 0.09-0.86). However, it is possible that the apparent protective effect was a chance finding. Our findings are consistent with the overall results of the most recent case-control study¹⁴ in which ever use of statins was not associated with breast cancer. However, in contrast to our results, a decreased risk was observed with more than 5 years of statin use (RR, 0.7; 95% CI, 0.4-1.0).

In contrast to statins, there is little laboratory evidence to support an association between nonstatin lipid-lowering drugs and cancer, although fibrates have been associated with liver cancer incidence in animals.³ If cholesterol is directly related to cancer, then lowering cholesterol levels with any lipid-lowering drugs might decrease breast cancer risk. The few previous epidemiologic studies of lipid-lowering drugs and breast cancer have had inconsistent results, with null,⁶⁷ nonsignificant positive,¹² and significant inverse⁹ associations reported. In the present study, the largest to date, no association was observed, even with more than 4 years of use.

The relation of cholesterol to sex steroid hormones and breast cancer is complex. Cholesterol is the precursor to steroid hormone synthesis and could potentially be associated with higher sex steroid hormone production due to increased substrate availability. However, estrogen lowers cholesterol levels by increasing low-density lipoprotein (LDL) receptor expression in the liver and other tissues, which increases cholesterol uptake and excretion.^{20,21,68,69} Additional evidence of the inverse association between estrogen and cholesterol includes the increase in total and LDL cholesterol levels at menopause, likely due to the decline in estrogen levels,⁷⁰ and the association between high total or LDL cholesterol levels and lower bone density^{71,72} and higher risk of osteopenia,⁷³ conditions strongly associated with low estrogen levels. The association between cholesterol and breast cancer is unclear. Although LDL receptors are overexpressed in cancer cell lines⁷⁴⁻⁷⁷ and have been associated with breast cancer invasiveness⁷⁸ and poorer survival,⁷⁹ this may be a result of tumor requirements for membrane and hormone production⁸⁰ rather than high total or LDL cholesterol levels leading to carcinogenesis. Further complicating the association is whether serum levels of cholesterol and sex steroid hormones are correlated with tissue levels. Although correlation data are limited and inconsistent,⁸¹⁻⁸⁴ epidemiologic evidence that

circulating sex steroid hormone levels are directly associated with breast cancer risk supports a correlation.^{18,19}

The relation between serum cholesterol and breast cancer has been examined in several case-control studies,^{12,16,38-48} with inconsistent results. The association has also been investigated in several cohort studies, although most have been small^{23-28,33,34} or have not had complete covariate information.^{17,29-31,35,36} In the most recent cohort study,³⁷ an inverse association was observed between high-density lipoprotein cholesterol level and breast cancer, suggesting that lower high-density lipoprotein cholesterol levels may be a hormonal marker of increased risk. Amid the inconsistencies of previous studies, our results suggest no association between total cholesterol levels and breast cancer risk.

In summary, the results of this study suggest that the beneficial effect of statins on breast cancer observed in experimental studies may not be applicable to humans. We also found no associations of general lipid-lowering drugs and serum cholesterol levels with breast cancer risk. Further study is warranted to evaluate the associations of longer durations of statin use and specific types of statins with breast cancer risk.

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