

Statin Use and Breast Cancer Risk in the Nurses' Health Study

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Abstract

Preclinical studies support an anticancer effect of statin drugs, yet epidemiologic evidence remains inconsistent regarding their role in breast cancer primary prevention. Here, we report an updated analysis of the association between statin use and breast cancer incidence in the Nurses' Health Study (NHS) cohort. Postmenopausal NHS participants without a cancer history were followed from 2000 until 2012 ($n = 79,518$). Data on statin use were retrieved from biennial questionnaires. We fit Cox regression models to estimate associations between longitudinal statin use and breast cancer incidence. Over 823,086 person-years of follow-

up, 3,055 cases of invasive breast cancer occurred. Compared with never users, both former and current statin users had similar rates of invasive breast cancer incidence [former users: HR_{adj} 0.96; 95% confidence interval (CI), 0.82–1.1; current users: HR_{adj} 1.1; 95% CI, 0.92–1.3]. Associations did not differ by estrogen receptor (ER) status or histology (ductal vs. lobular carcinoma). Statin use was not associated with risk of invasive breast cancer, irrespective of histologic subtype and ER status. Statin drugs do not appear to modify processes involved in breast cancer initiation. *Cancer Epidemiol Biomarkers Prev*; 25(1); 201–6. ©2016 AACR.

Introduction

Statins (HMG-CoA reductase inhibitors) are widely used cholesterol-lowering drugs, which have received substantial attention for their purported antineoplastic effects (1, 2). Initial epidemiologic evidence showed lower breast cancer incidence among statin users (3, 4). Other studies found no association between statin use and breast cancer risk (5, 6)—a conclusion shared by two recent meta-analyses (7, 8). In contrast, a recent case-control study showed increased odds of both invasive ductal and lobular carcinomas among long-duration (>10 years) statin users, compared with nonusers (9).

The association between use of statins and other lipid-lowering drugs and breast cancer incidence was previously investigated in the Nurses' Health Study (NHS) cohort (10). That analysis was based on breast cancer follow-up from 1994 through May 2000 and relied on retrospective statin exposure reported on the 2000 questionnaire. The study reported no association between statin use and breast cancer risk [HR , 0.91; 95% confidence interval (CI),

0.76–1.08]. Herein, we report an analysis of the association between statin use and breast cancer incidence, with up to 12 years of follow-up, based on prospectively ascertained statin exposures from 2000 onward.

Materials and Methods

Study population

The NHS began in 1976 with the enrolment of 121,700 female U.S. registered nurses ages 30 to 55 who returned baseline questionnaires reporting medical and reproductive histories. Participants have since returned biennial questionnaires to report demographic, lifestyle, and health-related characteristics such as body mass index (BMI), use of menopausal hormone therapy (MHT), reproductive history, dietary habits, medication usage, and new diagnoses. Questionnaire items regarding use of prescription and over-the-counter medications have evolved to reflect changes in the U.S. formulary, and the response rate at each questionnaire cycle has been approximately 90%. For our main analysis of any statin use in relation to breast cancer risk, the study population consisted of all postmenopausal NHS participants who returned a 2000 questionnaire (the year in which statin use was first assessed) and who were without a cancer history. For analyses of solubility-based exposure definitions, we began follow-up in 2004 (when use of specific statins was reported) and limited the study population to postmenopausal women without a cancer history who had not used a statin before 2004.

Breast cancer cases and pathologic information

Self-reported breast cancer cases were confirmed by physician review of medical records. Information on clinical pathologic parameters, such as invasiveness, histology, and estrogen receptor (ER) status was retrieved from clinical pathology reports. Incident invasive breast cancer, irrespective of hormone receptor status or histology, was the main outcome. We also evaluated incidence of breast carcinoma *in situ* as well as incidence of invasive ductal

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carcinoma (IDC), invasive lobular carcinoma (ILC), ER-positive, and ER-negative breast cancer.

Definitions of analytic variables

We considered as separate study outcomes any invasive breast carcinoma, IDC, ILC, ER-positive disease, ER-negative disease, and breast carcinoma *in situ*. Statin use was classified as time-varying cumulative duration of exposure (current user \geq 8 years, current user for 4 to 8 years, current user $<$ 4 years, former user of any duration, or never user). Exposure duration increased by 2 years for each biennial report of use. A missing statin response on the questionnaire was treated as nonuse. If a woman stopped using a statin for one or more questionnaire periods and later resumed use, the period of nonuse was omitted from her cumulative duration of exposure. Questionnaires from 2004 onward asked which specific statins were used. With this information, we defined current and former use of atorvastatin, lovastatin, simvastatin, pravastatin, and rosuvastatin. We also defined current and former exposure to hydrophilic (pravastatin or rosuvastatin) and lipophilic (atorvastatin, lovastatin, and simvastatin) statins.

We evaluated several potential confounders in our analyses. These were modeled as time-varying covariates using information from the most recent questionnaire (except for age at menarche, which was defined at baseline). Attained age served as the time axis for Cox regression models. Age at menarche, age at menopause, and BMI were modeled as continuous variables. Age at first birth and parity were converted into a categorical variable (see Table 1). MHT was categorized as never used MHT, formerly used MHT, currently using MHT for less than 5 years, and currently using MHT for at least 5 years. History of breast cancer in a first-degree female biologic relative and personal history of benign breast disease (BBD) were coded dichotomously. Use of individual co-medications was classified dichotomously. Screening mammography was characterized as whether or not the participant underwent a screening mammogram within the past 2 years. Alcohol intake was defined as the cumulative average daily consumption between 1980 and the follow-up cycle in question.

Statistical analyses

We fit age-adjusted and multivariable Cox proportional hazards models to estimate associations between statin exposures and breast cancer outcomes. In analyses of specific breast cancer subtypes, women diagnosed with a different subtype were censored on their date of diagnosis. Participants were followed from the date they returned their 2000 questionnaire until the first of breast cancer incidence, death from any cause, diagnosis with another malignancy, or the end of available follow-up in 2012. Women who were pre-menopausal at baseline entered the cohort when they became postmenopausal. Polytomous variables were modeled with indicator variables to allow for nonlinear effects across levels. Proportionality of hazard functions was evaluated with Wald tests for the interaction between statin exposure and attained age.

Analyses were conducted with SAS v.9.3 (SAS Institute), and statistical tests were two-sided ($\alpha = 0.05$). This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital. Subjects' participatory consent was implied by their completion and return of study questionnaires.

Table 1. Characteristics of postmenopausal NHS participants at baseline in 2000 according to statin exposure ($n = 77,845$)

Characteristic	Statin users ($n = 15,151$)	Nonusers ($n = 62,694$)
Age, mean (SD)	68.1 (6.6)	66.1 (7.0)
Age at menarche, mean (SD)	12.5 (1.8)	12.4 (1.8)
Age at menopause, mean (SD)	49.4 (5.2)	49.4 (5.8)
Personal history of BBD, n (%)	7,711 (51)	31,079 (50)
First-degree family history of breast cancer, n (%)	2,560 (17)	9,393 (15)
BMI, mean (SD)		
Number of missing observations	27.8 (5.2)	26.7 (5.4)
Reproductive history		
Nulliparous, n (%)	760 (5.0)	3,371 (5.4)
Parity, mean (SD) ^a	3.2 (1.5)	3.2 (1.5)
Age at first birth, mean (SD) ^a	25.1 (3.3)	25.0 (3.3)
(Missing)	232	1,120
MHT, n (%)		
Never used hormones	3,425 (24)	13,626 (22)
Former user	4,367 (31)	15,531 (25)
Current user, duration $<$ 5 years	1,059 (7.5)	5,323 (8.5)
Current user, duration \geq 5 years	5,336 (38)	23,863 (38)
(Missing)	964	4,351
Co-medications, n (%)		
Aspirin	4,987 (33)	13,019 (21)
Ibuprofen	3,979 (26)	14,867 (24)
Beta-blockers	3,969 (26)	7,268 (12)
Calcium channel blockers	2,452 (16)	4,467 (7.1)
ACE inhibitors	2,782 (18)	5,351 (8.5)
Tamoxifen (preventive)	943 (6.2)	3,216 (5.1)
Digoxin	651 (4.3)	1,352 (2.2)
Diabetes history, n (%)	1,789 (12)	3,441 (5.5)
Screening mammogram in past 2 years, n (%)	14,048 (93)	48,803 (78)
Alcohol consumption, median (q1–q3)	1.7 (0.2–6.3)	2.0 (0.3–7.7)
Number of missing observations	233	2,482
Physical activity, weekly metabolic equivalents		
METs $<$ 3	4,045 (27)	12,367 (23)
(3 \leq METs $<$ 9)	3,610 (24)	11,830 (22)
(9 \leq METs $<$ 18)	2,994 (20)	10,822 (20)
(18 \leq METs $<$ 27)	1,790 (12)	6,816 (13)
METs \geq 27	2,544 (17)	11,221 (21)
(Missing)	168	9,638

^aAmong parous women. Age at first birth (AFB) and parity were converted into a categorical variable with the following categories: nulliparous, 1 or 2 children and AFB \leq 30, 1 or 2 children and AFB $>$ 30, 3 or 4 children and AFB \leq 30, 3 or 4 children and AFB $>$ 30, 5 or more children and AFB \leq 30, and 5 or more children and AFB $>$ 30.

Results

Baseline characteristics of the cohort

Table 1 displays the distribution of characteristics according to statin exposure among the study population in the baseline (year 2000) questionnaire cycle ($n = 77,845$). Compared with nonusers, statin users were somewhat older, had a higher mean BMI, were more likely to be users of aspirin, beta blockers, calcium channel blockers, digoxin, and ACE inhibitors, had a higher prevalence of diabetes, and were more likely to undergo mammographic screening.

Statin use and risk of breast cancer

Table 2 reports associations between breast cancer incidence and longitudinal statin exposure. Over the entirety of follow-up, 79,518 postmenopausal women contributed 823,086 person-years of follow-up to the analysis. Models for any invasive breast

Table 2. Associations between statin use and breast cancer incidence in the NHS, 2000–2012

	Cases, <i>n</i>	Age-adjusted HR (95% CI)	Multivariate ^a HR (95% CI)
All invasive cases (<i>n</i> = 3,055)			
Never users	1,977	1.0 (ref)	1.0 (ref)
Former users	202	0.93 (0.80–1.1)	0.96 (0.82–1.1)
Current users			
Duration <4 y	330	1.1 (0.95–1.2)	1.0 (0.92–1.2)
4 y ≤ duration < 8 y	349	0.99 (0.88–1.1)	0.95 (0.84–1.1)
Duration ≥ 8 y	197	1.2 (1.0–1.4)	1.1 (0.92–1.3)
Invasive ductal carcinoma (<i>n</i> = 1,952)			
Never users	1,323	1.0 (ref)	1.0 (ref)
Former users	113	0.91 (0.74–1.1)	0.92 (0.75–1.1)
Current users			
Duration < 4 y	212	1.0 (0.87–1.2)	0.95 (0.82–1.1)
4 y ≤ duration < 8 y	214	0.94 (0.81–1.1)	0.88 (0.75–1.0)
Duration ≥ 8 y	90	1.1 (0.88–1.4)	1.0 (0.79–1.3)
Invasive lobular carcinoma (<i>n</i> = 313)			
Never users	206	1.0 (ref)	1.0 (ref)
Former users	18	0.86 (0.52–1.4)	0.87 (0.53–1.4)
Current users	89	1.1 (0.82–1.4)	0.98 (0.75–1.3)
ER-positive cases (<i>n</i> = 2,162)			
Never users	1,430	1.0 (ref)	1.0 (ref)
Former users	125	0.89 (0.74–1.1)	0.90 (0.75–1.1)
Current users			
Duration < 4 y	245	1.1 (0.95–1.3)	1.0 (0.91–1.2)
4 y ≤ duration < 8 y	249	0.98 (0.85–1.1)	0.91 (0.79–1.0)
Duration ≥ 8 y	113	1.2 (0.94–1.4)	1.0 (0.84–1.3)
ER-negative cases (<i>n</i> = 405)			
Never users	252	1.0 (ref)	1.0 (ref)
Former users	30	1.2 (0.81–1.8)	1.3 (0.85–1.9)
Current users			
Duration < 4 y	41	1.1 (0.77–1.5)	1.0 (0.74–1.5)
4 y ≤ duration < 8 y	56	1.2 (0.88–1.6)	1.1 (0.82–1.5)
Duration ≥ 8 y	26	1.6 (1.0–2.5)	1.5 (0.93–2.3)
<i>In situ</i> cases (<i>n</i> = 608)			
Never users	385	1.0 (ref)	1.0 (ref)
Former users	34	1.1 (0.80–1.6)	1.2 (0.83–1.7)
Current users			
Duration < 4 y	82	1.4 (1.1–1.8)	1.4 (1.1–1.7) ^b
4 y ≤ duration < 8 y	76	1.2 (0.95–1.6)	1.1 (0.88–1.5)
Duration ≥ 8 y	31	1.7 (1.1–2.5)	1.5 (0.99–2.2)

^aAdjusted for body mass (continuous), first-degree family history of breast cancer (dichotomous), personal history of BBD (dichotomous), parity and age at first birth (design variables: see categories in Materials and Methods), age at menarche (<12, 12–13, or 14+), cumulative average ethanol consumption (design variables: see categories in Materials and Methods), MHT use (design variables: see categories in Materials and Methods), prevalent diabetes, and concomitant use of aspirin, ibuprofen, preventive tamoxifen, beta-blockers, calcium channel blockers, ACE inhibitors, and digoxin.

^bThis association was near null in the subset of cohort members who had consistently undergone mammography screening (HR_{adj}, 1.2; 95% CI, 0.96–1.6).

cancer, IDC, ILC, ER-positive disease, ER-negative disease, and *in situ* disease were based on 3,055, 1,952, 313, 2,162, 405, and 608 cases, respectively.

Compared with never users, current users of any statin had a similar rate of invasive breast cancer incidence, regardless of cumulative duration (for current use of <4 years' duration, multivariate HR, 1.0; 95% CI, 0.92–1.2; for current use of 4 to <8 years' duration, multivariate HR, 0.95; 95% CI, 0.84–1.1, for current use of ≥8 years' duration, multivariate HR, 1.1; 95% CI, 0.92–1.3, respectively). Former use of any statin was not associated with breast cancer risk (multivariate HR, 0.96; 95% CI, 0.82–1.1; Table 2).

Statin use was not associated with the risk of either IDC (for current use of <4 years' duration, HR_{adj}, 0.95; 95% CI, 0.82–1.1) or ILC (for current use, HR_{adj}, 0.98; 95% CI, 0.75–1.3). Rates of ER-positive and ER-negative breast cancer were similar among current users and never users (for ER-positive disease: current use of <4 years' duration, HR_{adj}, 1.0; 95% CI, 0.91–1.2; for ER-negative disease: current use of <4 years' duration, HR_{adj}, 1.0;

95% CI, 0.74–1.5). Risk of *in situ* carcinoma appeared to be associated with statin exposure (for current use of <4 years' duration, HR_{adj}, 1.4; 95% CI, 1.1–1.7), but the association was near null in the subset of cohort members who had consistently undergone mammography screening (for current use of <4 years' duration, HR_{adj}, 1.2; 95% CI, 0.96–1.6).

When assessing class of statins, neither former nor current use of lipophilic or hydrophilic statins was associated with incidence of breast cancer, both overall and by subtypes (Table 3). Furthermore, no specific type of statin was associated with breast cancer risk (Supplementary Table S1).

Discussion

In this updated analysis from the NHS, we observed no associations between use of any statin and risk of invasive breast cancer, regardless of cumulative duration of exposure. Furthermore, this study showed no impact of statin use on risk of breast cancer defined by histologic subtype (ILC/IDC) or ER status.

Table 3. Associations between statin exposure based on solubility and breast cancer incidence in the NHS, among new initiators of statins 2004–2012

	Cases, <i>n</i>	Age-adjusted HR (95% CI)	Multivariate ^a HR (95% CI)
All invasive cases (<i>n</i> = 1,337)			
Lipophilic statins			
Never user of any statin	849	1.0 (ref)	1.0 (ref)
Former users	76	1.1 (0.84–1.4)	1.0 (0.79–1.3)
Current users	185	1.2 (1.0–1.4)	1.1 (0.94–1.3)
Hydrophilic statins			
Never user of any statin	849	1.0 (ref)	1.0 (ref)
Former users	90	1.1 (0.89–1.4)	1.1 (0.84–1.3)
Current users	101	1.1 (0.89–1.4)	1.0 (0.81–1.3)
Invasive ductal carcinoma (<i>n</i> = 802)			
Lipophilic statins			
Never user of any statin	515	1.0 (ref)	1.0 (ref)
Former users	40	1.1 (0.79–1.5)	0.99 (0.71–1.4)
Current users	94	1.1 (0.90–1.4)	1.0 (0.82–1.3)
Hydrophilic statins			
Never user of any statin	515	1.0 (ref)	1.0 (ref)
Former users	35	0.94 (0.66–1.4)	0.87 (0.60–1.3)
Current users	63	1.1 (0.87–1.5)	1.0 (0.79–1.4)
Invasive lobular carcinoma (<i>n</i> = 123)			
Lipophilic statins			
Never user of any statin	76	1.0 (ref)	(not estimable)
Former users	6	0.91 (0.39–2.1)	
Current users	16	1.2 (0.70–2.1)	
Hydrophilic statins			
Never user of any statin	76	1.0 (ref)	(not estimable)
Former users	6	0.83 (0.35–2.0)	
Current users	9	0.99 (0.49–2.0)	
ER-positive cases (<i>n</i> = 919)			
Lipophilic statins			
Never user of any statin	581	1.0 (ref)	1.0 (ref)
Former users	45	1.0 (0.75–1.4)	0.94 (0.69–1.3)
Current users	107	1.1 (0.90–1.4)	1.0 (0.83–1.3)
Hydrophilic statins			
Never user of any statin	581	1.0 (ref)	1.0 (ref)
Former users	44	0.95 (0.69–1.3)	0.91 (0.66–1.3)
Current users	71	1.1 (0.86–1.4)	1.0 (0.79–1.3)
ER-negative cases (<i>n</i> = 168)			
Lipophilic statins			
Never user of any statin	107	1.0 (ref)	1.0 (ref)
Former users	12	1.6 (0.85–2.9)	1.5 (0.78–2.7)
Current users	24	1.4 (0.88–2.2)	1.3 (0.83–2.1)
Hydrophilic statins			
Never user of any statin	107	1.0 (ref)	1.0 (ref)
Former users	7	0.93 (0.42–2.1)	0.86 (0.38–2.0)
Current users	13	1.1 (0.62–2.0)	1.0 (0.56–1.9)
<i>In situ</i> cases (<i>n</i> = 210)			
Lipophilic statins			
Never user of any statin	136	1.0 (ref)	(not estimable)
Former users	9	0.98 (0.49–2.0)	
Current users	25	1.2 (0.77–1.8)	
Hydrophilic statins			
Never user of any statin	136	1.0 (ref)	(not estimable)
Former users	8	0.97 (0.46–2.1)	
Current users	14	0.99 (0.56–1.8)	

^aAdjusted for body mass (continuous), first-degree family history of breast cancer (dichotomous), personal history of BBD (dichotomous), parity and age at first birth (design variables: see categories in Materials and Methods), age at menarche (<12, 12–13, or 14+), cumulative average ethanol consumption (design variables: see categories in Materials and Methods), MHT use (design variables: see categories in Materials and Methods), prevalent diabetes, and concomitant use of aspirin, ibuprofen, preventive tamoxifen, beta-blockers, calcium channel blockers, ACE inhibitors, and digoxin.

Current use of shorter duration appeared to be associated with incidence of *in situ* breast cancer, but the lack of an association among consistent users of screening mammography suggests this may be a spurious association.

Our analysis of specific statins and statin solubility classes from 2004 onward showed null associations between current use and invasive breast cancer incidence. These observations are incon-

gruent with past evidence that shows lipophilic statins to be most strongly associated with anticancer effects (11).

Epidemiologic studies have shown inconsistent evidence for statins' role in breast cancer primary prevention (3–7, 9, 12), with the most recent study showing an increased risk of ILC and IDC among long-duration statin users (9). The latter study, by McDougall and colleagues (9), collected pharmaceutical

exposures retrospectively, so the positive associations may be an artifact of higher-sensitivity drug exposure recall among cases. The McDougall study's chief advantage over prior literature was its assessment of long-term statin exposure (>10 years of use). Our study improves on the evidence from the McDougall report by making a comparable assessment of long-term statin exposure (>8 years of use) while capitalizing on prospectively collected exposure information. An updated prospective analysis from the Women's Health Initiative revealed no associations between statin use and breast cancer risk, irrespective of drug duration or drug product (13), contrary to a previous analysis showing a decreased breast cancer risk among users of lipophilic statins (3). Two meta-analyses assessing the association between statin use and breast cancer risk showed no associations (7, 8). The meta-analysis by Bonovas and colleagues (8) included nine observational studies and seven randomized trials—although breast cancer incidence was not the primary endpoint in any of those trials. The meta-analysis by Undela and colleagues (7) reviewed a total of 24 studies (including the previous NHS analysis) comprising 76,759 breast cancer cases (10). In contrast with the earlier NHS analysis (10), which showed no association between statin use and invasive breast cancer risk (RR, 0.91; 95% CI, 0.76–1.08), this updated analysis includes up to 12 years of follow-up, uses only prospectively ascertained exposure, and includes nearly twice as many cases. The number of statin users also increased considerably, from 15,370 to 38,663 statin users in the present study.

This study has several additional strengths, including its large size and physician confirmation of breast cancer diagnoses. Importantly, information on established lifestyle risk factors for breast cancer was available for most participants, and was accounted for in our analyses.

Some limitations affect the interpretation of our results. First, statin use was self-reported and may be less accurate than registry-derived prescription data. The combination of false-positive and false-negative exposure reporting could have masked a truly non-null association. Such misclassification may have particularly affected analyses of specific statin exposures, which may be more difficult to recall accurately. Second, our analysis of specific statins and solubility-based exposures made use of a new-initiator subcohort from 2004 onward, which may be susceptible to selection bias (14).

Summary

In this updated analysis from the NHS, we observed no associations between current statin use and breast cancer inci-

dence, supporting previous reports on neutral effects of statins in the primary prevention setting. Notably, statin use did not increase the risk of invasive breast cancer, regardless of histologic type. Future epidemiologic studies should focus more on differential risk by type of statin and specific breast cancer subtype.

Disclosure of Potential Conflicts of Interest

J.E. Garber reports receiving commercial research support from Myriad Genetic Labs and Novartis, and is a consultant/advisory board member for Pfizer, SV Life Sciences, and Sequenom. No conflicts of interest were disclosed by the other authors.

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