Research Article

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# Long-Term Statin Use and Risk of Ductal and Lobular Breast Cancer among Women 55 to 74 Years of Age

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## Abstract

**Background:** Mechanistic studies largely support the chemopreventive potential of statins. However, results of epidemiologic studies investigating statin use and breast cancer risk have been inconsistent and lacked the ability to evaluate long-term statin use.

**Methods:** We used data from a population-based case–control study of breast cancer conducted in the Seattle–Puget Sound region to investigate the relationship between long-term statin use and breast cancer risk. Nine hundred sixteen invasive ductal carcinoma (IDC) and 1,068 invasive lobular carcinoma (ILC) cases in patients 55 to 74 years of age diagnosed between 2000 and 2008 were compared with 902 control women. All participants were interviewed in-person and data on hypercholesterolemia and all episodes of lipid-lowering medication use were collected through a structured questionnaire. We assessed the relationship between statin use and IDC and ILC risk using polytomous logistic regression.

**Results:** Current users of statins for 10 years or longer had a 1.83-fold increased risk of IDC [95% confidence interval (CI): 1.14–2.93] and a 1.97-fold increased risk of ILC (95% CI: 1.25–3.12) compared with never users of statins. Among women diagnosed with hypercholesterolemia, current users of statins for 10 years or longer had more than double the risk of both IDC (OR: 2.04, 95% CI: 1.17–3.57) and ILC (OR: 2.43, 95% CI: 1.40–4.21) compared with never users.

**Conclusion:** In this contemporary population-based case–control study, long-term use of statins was associated with increased risks of both IDC and ILC.

**Impact:** Additional studies with similarly high frequencies of statin use for various durations are needed to confirm this novel finding. *Cancer Epidemiol Biomarkers Prev; 22(9); 1529–37. ©2013 AACR.*

## Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, or statins, are a highly effective therapeutic class of drugs used to lower lipids for both primary and secondary prevention of coronary heart disease. The use of statins has increased considerably since their introduction in the United States in 1987. Approximately, a quarter of all United States women over the age of 45 report current use of one of the 7 different statin drugs on the market today (1).

Evidence from previous epidemiologic studies investigating the use of statins and risk of developing breast cancer is inconsistent, with some studies reporting an increased risk (2–11), some reporting a decreased risk (12–16), and still others reporting no association (17–23). Early studies in rodents showed a carcinogenic potential of statins (24). However, in *in vitro* breast cancer models, statins have been shown to inhibit cell proliferation and induce apoptosis (25–27). Meta-analyses have evaluated the conflicting evidence and provided summary estimates of the association between statin use and breast cancer. The meta-analysis by Bonovas and colleagues included 7 randomized trials and 9 observational studies published before 2005, and it reported a relative risk (RR) of 1.02 (95% CI: 0.89–1.18) for the association between statin use and breast cancer (28). Published in 2012, Undela and colleagues included 24 observational studies and similarly found no evidence of an association between statin use and breast cancer risk (RR: 0.99, 95% CI: 0.94–1.04; ref. 29).

Despite extensive prior research on statin use and breast cancer risk, some important questions remain unanswered. Given the increase in statin use over the past few decades, and that these medications are commonly prescribed for chronic, essentially lifetime use, the studies published to date have had limited ability to evaluate the impact of long durations of current statin use. Of the studies published since 2005, in the NHS cohort only 1.0% of women had currently used statins for 4 years or longer (15), in the WHI cohort only 2.5% had used statins for 3 years or longer (14), and in a large case–control study

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only 2.7% of controls were current statin users for 5 years or longer (20). Rates of use were highest in the most recently published study based on the Cancer Prevention Study II Nutrition Cohort, where 6.8% of women were current statin users for 5 years or longer (16). Given the frequency with which statins are used and the extended duration women are prescribed them, characterizing the relationship between long-term statin use and breast cancer risk is of clinical and public health importance. In addition, further investigation is needed regarding the impact of statin use on different types of breast cancer. We evaluated these questions using data from a recently completed large-scale population-based case–control study of postmenopausal breast cancer where use of statins was more frequent compared with populations included in prior published studies.

## Materials and Methods

We conducted a large population-based case–control study of the 2 most common histologic subtypes of breast cancer, invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), among women 55 to 74 years of age living in the three-county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties). In the United States, an estimated 70% of all invasive breast cancers diagnosed among postmenopausal women are ductal and approximately 20% are lobular (30). This study was funded in 2 continuous phases, and data from the first phase based on cases enrolled from January 2000 to March 2004 were published previously (31).

### Selection of cases and controls

Breast cancer cases with no prior history of *in situ* or invasive breast cancer, diagnosed between January 2000 and December 2008 while residing in King, Pierce, or Snohomish county were identified through the Cancer Surveillance System (CSS), the population-based tumor registry that serves western Washington state and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The 3 counties included in this analysis are among the 13 counties that comprise the Seattle-Puget Sound SEER site. All women diagnosed with an invasive breast cancer with a lobular component based on ICD-O codes 8520, 8522, and 8524 assigned by CSS were potentially eligible as lobular cases. The pathology reports of all of these cases were then centrally reviewed to confirm eligibility and re-categorize histology groupings as necessary. Given the greater frequency of IDC, an age-matched sample of approximately 25% IDC cases was selected for recruitment. IDC cases were frequency matched to the ILC case group by 5-year age group. As controls were ascertained via random digit dialing of landline home telephone numbers, to be eligible all cases were also required to have a landline home telephone. Of the 2,495 eligible cases identified, 1,984 (80%) were interviewed, including 1,068 ILC and 916 IDC cases, 424 (17%) refused and 75 (3%) were deceased.

We used the Mitofsky–Waksberg (32) method of random digit dialing to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. Controls were frequency matched within 5-year age groups and county of residence to the cases using one-step recruitment. Of the 1,313 eligible controls identified, 902 (69%) were interviewed and 411 (31%) refused.

The reference date used for each woman with breast cancer was her diagnosis date. Control reference dates were assigned to reflect the expected distribution of reference dates among the cases. Data collection was limited to exposures that occurred before each participant's reference date.

### Data collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. In addition to basic information on breast cancer diagnosis, we obtained information on tumor characteristics from CSS and from a centralized review of pathology reports. This includes data on estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) status, and tumor stage, size, and nodal status.

Cases and controls were interviewed in-person. Through a series of structured questions, detailed histories of hypercholesterolemia and all episodes of lipid lowering medication use, including beginning and ending dates, drug name, dose, route of administration, and pattern of use (number of days per month) were obtained. Study participants were also asked to show bottles of all prescription medications they were currently taking, including lipid lowering drugs, to their study interviewer who then directly transcribed data from these bottles onto our data collection form. To enhance recall of past use, a photo book containing pictures of pills and packages of commonly used lipid lowering medications was used along with a show card listing the brand and generic names of each of these medications. In addition, all participants were queried about various known or suspected breast cancer risk factors including pertinent aspects of their reproductive, medical, breast cancer screening, and family histories, as well as information about their body size and lifestyle habits. Our questioning was limited to exposures that occurred before each participant's reference date. Women were asked if they had ever smoked, drank alcoholic beverages, used a specific medication, been diagnosed with a specific condition, or ever had a mammogram; for cumulative exposure variables patterns of use from the time of first exposure through the reference date were ascertained in the interview.

### Statistical analysis

Women who never used any type of lipid lowering medication served as the reference category. Our main analysis focused on duration and recency of statin use where current users were those who ever used these

medications for 6 months or longer and were currently using them within 6 months of their reference date. Former users were ever users of these medications for 6 months or longer who last used them more than 6 months before their reference date. Short-term users were women who used these medications for less than 6 months regardless of their recency of use. Analyses also considered risk associated with each individual statin as well as when grouped as lipophilic (atorvastatin, simvastatin, lovastatin, fluvastatin, and cerivastatin) or hydrophilic (pravastatin, and rosuvastatin) statins. Finally, an analysis restricting the sample to the 273 controls, 286 IDC, and 320 ILC cases with a history of high cholesterol was conducted to investigate the existence and magnitude of potential biases due to the selection of healthy controls and to confounding by indication.

We used polytomous logistic regression to calculate odds ratios (OR) and their associated 95% confidence intervals (CI) to compare IDC and ILC cases to controls. Given the design of this study and its random sampling of IDC cases and exclusion of other histologic subtypes of breast cancer, risk estimates for breast cancer overall could not be calculated. Pearson $\chi^2$ statistic was calculated modeling categories of years of statin use as a grouped linear variable to test for a trend in duration. All analyses were conducted using Stata/SE version 11.2 (StataCorp LP). All models were adjusted for age (5-year categories), reference year (continuous), and county, as controls were frequency matched to cases on these factors. Several potential confounders and effect modifiers of the relationship between statin use and breast cancer were assessed, including: education, household income, race/ethnicity, use of menopausal hormone therapy, mammography screening history, type of menopause, first-degree family history of breast cancer, body mass index 1 year before reference date, presence of diabetes, parity, alcohol consumption, and smoking history (as grouped in Table 1). Only use of menopausal hormone therapy changed our risk estimates by more than 10% when added to the model, and so, only it was added as a covariate to our final statistical models. Excluded from all analyses were the 25 controls, 25 IDC cases, and 32 ILC cases missing data on either use of lipid lowering medications and/or menopausal hormone therapy use leaving a final analytic sample size of 877 controls, 891 IDC cases, and 1,036 ILC cases. In addition, none of the covariates were found to be a statistically significant effect modifier based on likelihood ratio testing including body mass index (all $P_{\text{interaction}}$ >0.05). To quantify differences in risk according to use of menopausal hormone therapy and mammography screening history, we also assessed risks stratified by these 2 factors. In addition, we assessed whether or not risk estimates differed among women with invasive lobular (ICD-O codes 8520 and 8524) versus invasive ductal-lobular (ICD-O code 8522) carcinomas. No appreciable differences in the magnitudes of risk were observed when the analysis was stratified in this way and none of the *P*-values comparing lobular versus ductal-lobular risk estimates were statistically significant. Thus lobular and ductal-lobular tumors were grouped together in all analyses. Finally, we conducted analyses stratified according to estrogen receptor status in 3 groupings: ER+ IDC, ER− IDC, and ER+ ILC. Given that fewer than 4% of our ILC cases were ER−, we could not evaluate risk among ER− ILC cases.

## Results

Controls, IDC cases, and ILC cases had similar distributions of age, household income, history of hypercholesterolemia, and history of heart disease (Table 1). Compared with controls and IDC cases, ILC cases were somewhat more likely to be non-Hispanic white, to have completed college, to consume greater than equal to 1 alcoholic beverage per day, to have a body mass index less than 25 kg/m$^2$, and to be current users of combined estrogen and progestin menopausal hormone therapy. IDC and ILC cases were more likely than controls to have a first-degree family history of breast cancer; however, mammography screening history was similar across all groups.

Compared with never users, women who ever used statins did not have an increased risk of IDC (OR: 1.16, 95% CI: 0.92–1.47; Table 2). There was a modest suggestion of an increased risk of ILC (OR: 1.22, 95% CI: 0.98–1.53) comparing women who ever used statins to never users. However, women using statins for greater than equal to 10 years had a 72% higher risk of IDC (95% CI: 1.10–2.71) and an 82% higher risk of ILC (95% CI: 1.17–2.82), though neither *P*-value for linear trend was statistically significant. When evaluated by recency, current long-term (≥10 years) statin users had an 83% higher risk of IDC (95% CI: 1.14–2.93, *P* for trend = 0.043) and a 97% higher risk of ILC (OR: 1.97, 95% CI: 1.25–3.12, *P* for trend = 0.021) than never users. When analyses were restricted to the 273 controls, 286 IDC cases, and 320 ILC cases with a history of high cholesterol, the associations observed were slightly greater in magnitude to those observed in our overall analyses. Current use of any statin for at least 6 months was associated with a 41% increased risk of IDC (95% CI: 0.95–2.08) and a 63% increased risk of ILC (95% CI: 1.11–2.41). Again, this increased risk was strongest among long-term statin users who had more than double the risk of both IDC (OR: 2.04, 95% CI: 1.17–3.57, *P* for trend = 0.025) and ILC (OR: 2.43, 95% CI: 1.40–4.21, *P* for trend = 0.006).

The vast majority (88%) of statin users in this population used lipophilic statins. Current use of lipophilic statins was not associated with either IDC (OR: 1.13, 95% CI: 0.88–1.45) or ILC (OR: 1.21, 95% CI: 0.95–1.54; Table 3). However, current users of lipophilic statins for greater than equal to 10 years had a 74% increased risk of IDC (95% CI: 1.05–2.86) and a 68% increased risk of ILC (95% CI: 1.02–2.76) compared with never users. The 2 most commonly used statins in this population were atorvastatin and simvastatin. Current use of atorvastatin for greater than equal to 10 years was associated with elevated risks of

**Table 1.** Demographic characteristics of the study population

| Characteristic | Controls ($n = 877$) *N* (%) | Ductal cases ($n = 891$) *N* (%) | Lobular cases ($n = 1,036$) *N* (%) |
|---|---|---|---|
| Age at reference date | | | |
| 55–59 | 252 (28.7) | 259 (29.1) | 306 (29.5) |
| 60–64 | 230 (26.2) | 245 (27.5) | 294 (28.4) |
| 65–69 | 222 (25.3) | 211 (23.7) | 241 (23.3) |
| 70–74 | 173 (19.7) | 176 (19.8) | 195 (18.8) |
| Race/ethnicity | | | |
| Non-Hispanic White | 778 (88.9) | 804 (90.4) | 960 (92.8) |
| African American | 27 (3.1) | 22 (2.5) | 14 (1.4) |
| Asian/Pacific Islander | 17 (1.9) | 35 (3.9) | 21 (2.0) |
| Native American | 24 (2.7) | 16 (1.8) | 20 (1.9) |
| Hispanic White | 29 (3.3) | 12 (1.3) | 20 (1.9) |
| Missing | 2 | 2 | 1 |
| Education | | | |
| Less than high school | 39 (4.5) | 46 (5.2) | 62 (6.0) |
| High school graduate | 207 (23.6) | 207 (23.3) | 365 (35.2) |
| Some college | 343 (39.2) | 331 (37.2) | 221 (21.3) |
| College degree or higher | 287 (32.8) | 306 (34.4) | 388 (37.5) |
| Missing | 1 | 1 | 0 |
| Annual household income | | | |
| <$20,000 | 82 (10.7) | 102 (12.9) | 100 (11.0) |
| $20,000–$34,999 | 138 (18.0) | 129 (16.3) | 173 (19.1) |
| $35,000–$69,999 | 285 (37.1) | 273 (34.6) | 294 (32.5) |
| $70,000–$89,999 | 88 (11.5) | 102 (12.9) | 132 (14.6) |
| ≥ $90,000 | 175 (22.8) | 184 (23.3) | 207 (22.8) |
| Missing | 109 | 101 | 130 |
| Alcohol use | | | |
| None | 441 (50.6) | 419 (47.4) | 480 (46.6) |
| <1 drink per day | 299 (34.3) | 312 (35.3) | 345 (33.5) |
| ≥1 drink per day | 132 (15.1) | 153 (17.3) | 205 (19.9) |
| Missing | 5 | 7 | 6 |
| Smoking status | | | |
| Never | 440 (50.2) | 445 (50.0) | 495 (47.8) |
| Former | 348 (39.7) | 342 (38.4) | 416 (40.2) |
| Current | 88 (10.0) | 103 (11.6) | 125 (12.1) |
| Missing | 1 | 1 | 0 |
| Body mass index, kg/m$^2$ | | | |
| <25 | 264 (30.4) | 285 (32.0) | 367 (35.5) |
| 25–29.9 | 300 (34.5) | 283 (31.8) | 342 (33.1) |
| ≥30 | 305 (35.1) | 322 (36.2) | 324 (31.4) |
| Missing | 8 | 1 | 3 |
| History of high cholesterol | | | |
| No | 602 (68.8) | 604 (67.9) | 713 (69.0) |
| Yes | 273 (31.2) | 286 (32.1) | 320 (31.0) |
| Missing | 2 | 1 | 3 |
| History of heart disease | | | |
| No | 385 (44.0) | 406 (45.7) | 471 (45.6) |
| Yes | 490 (56.0) | 482 (54.3) | 563 (54.4) |
| Missing | 2 | 3 | 2 |
| First-degree family history of breast cancer | | | |
| No | 697 (82.2) | 654 (76.7) | 771 (76.8) |

*(Continued on the following page)*

**Table 1.** Demographic characteristics of the study population (Cont'd)

| Characteristic | Controls ($n = 877$) N (%) | Ductal cases ($n = 891$) N (%) | Lobular cases ($n = 1,036$) N (%) |
|---|---|---|---|
| Yes | 151 (17.8) | 199 (23.3) | 233 (23.2) |
| Missing | 29 | 38 | 32 |
| Mammography screening history | | | |
| Less than annual | 394 (45.1) | 409 (46.0) | 490 (47.6) |
| Annual only | 469 (53.7) | 462 (52.0) | 521 (50.6) |
| More than annual | 11 (1.3) | 18 (2.0) | 19 (1.9) |
| Missing | 3 | 2 | 6 |
| Hormone therapy use | | | |
| Never | 249 (28.4) | 322 (36.1) | 261 (25.2) |
| Former | 310 (35.3) | 242 (27.2) | 256 (24.7) |
| Current estrogen only | 202 (23.0) | 162 (18.2) | 219 (21.1) |
| Current estrogen + progestin | 116 (13.2) | 165 (18.5) | 300 (29.0) |

both IDC and ILC but while both of these risk estimates were within the limits of chance, the trend with respect to IDC was statistically significant ($P = 0.048$). There were no clear associations between simvastatin use and IDC or ILC risk.

Stratifying by estrogen receptor status, there was evidence that while current statin use for 10 or more years was associated with 2-fold increases in risk of ER+ IDC (OR: 1.97, 95% CI: 1.21–3.20, $P$ for trend = 0.035) and ER+ ILC (OR: 2.00, 95% CI: 1.26–3.17, $P$ for trend = 0.023), it was associated with a more modest nonstatistically significant elevated risk of ER− IDC (OR: 1.33; 95% CI: 0.53–3.31; Table 4).

## Discussion

In this population-based case–control study, greater than equal to 10 years of statin use was associated with an increased risk of both IDC and ILC. Our estimate of a 26% increased risk of IDC among women using statins for 5–10 years is consistent with estimates from three previous studies reporting relative effects between 10% and 30% associated with greater than equal to 5 years of statin use (7, 16, 20). However, our estimate differs from studies reporting a decreased risk of breast cancer associated with greater than equal to 4 years of statin use (3, 22). Consistent with previous studies we did not observe evidence of associations between shorter durations of statin use and breast cancer risk. Only one prior study has reported data for statin use for 10 or more years and found no association between long-term statin use and breast cancer risk (OR: 0.8, 95% CI: 0.5–1.4; 20). We observed that risks were highest among long-term current users suggesting that statins may act as promoters of breast carcinogenesis.

This study differed from previous studies in its ability to investigate the association between statin use and breast cancer separately by histologic subtype and estrogen receptor status. Among long-term statin users, we saw substantially increased risks of both ER+ IDC and ER+ ILC, but no increased risk of ER− IDC. Given the relatively small number of ER− cases in our study and the resulting uncertainty in our estimates, it is not clear whether the association between long-term statin use and breast cancer risk differs by estrogen receptor status. While studies of the WHI and NHS cohorts found null associations for use of statins and breast cancer for both ER+ and ER− tumors, neither study had data on long-term statin users (14, 15). If in fact statins are only associated with ER+ breast cancer, this would suggest that statins may be exerting a carcinogenic effect through a hormonally driven pathway. However, the biology underlying an association between statin use and breast cancer risk is uncertain. All statins inhibit HMG-CoA reductase at the rate-limiting step of the mevalonate pathway, an intricate biochemical pathway required for the production of cholesterol, isoprenoids, dolichol, ubiquinone, and isopentenyladine (33). Laboratory studies have investigated how disrupting the melavonate pathway may lead to carcinogenesis and have discovered both pro and anticancer effects of statins (34). However, our results call into question whether the anticarcinogenic properties of statins observed in animal models apply to the long-term effects of disrupting the mevalonate pathway in humans. Our finding of an increased risk only among current long-term statin users suggests that the chronic dysregulation of the mevalonate pathway and/or long-term lowering of serum cholesterol may contribute to breast carcinogenesis. This finding does not rule out the possibility that shorter-term statin use may have no effect or possibly a transitory protective effect on the development of breast cancer.

Prior studies examining individual statins have not found increased risks of breast cancer associated with use of any individual statin, with the exception of the randomized trial of pravastatin, a hydrophilic statin, that reported a 12-fold increased risk of breast cancer (12 cases in the pravastatin arm compared with 1 case in the control arm; 35). However, other trials of pravastatin found no

**Table 2.** Associations between statin use and risk of invasive ductal or lobular breast cancer among women age 50 to 74 overall and among women with a history of high cholesterol

| | All study participants | | | | |
|---|---|---|---|---|---|
| | Controls ($n = 877$) | Ductal cases ($n = 891$) | | Lobular cases ($n = 1{,}036$) | |
| | *N* (%) | *N* (%) | OR (95% CI) | *N* (%) | OR (95% CI) |
| Never use | 674 (77) | 664 (75) | 1.00 (reference) | 782 (76) | 1.00 (reference) |
| Ever use for ≥6 months | 190 (22) | 206 (23) | 1.16 (0.92–1.47) | 237 (23) | 1.22 (0.98–1.53) |
| Duration of ever use | | | | | |
| 6 months–<5 years | 104 (12) | 93 (11) | 0.93 (0.68–1.26) | 122 (12) | 1.12 (0.84–1.49) |
| 5 yrs–<10 yrs | 50 (6) | 57 (6) | 1.26 (0.84–1.89) | 51 (5) | 1.03 (0.68–1.56) |
| ≥10 years | 35 (4) | 53 (6) | **1.72 (1.10–2.71)** | 62 (6) | **1.82 (1.17–2.82)** |
| $P_{trend}$ | | | *P = 0.173* | | *P = 0.090* |
| Recency of use | | | | | |
| Former use | 20 (2) | 20 (2) | 1.12 (0.59–2.13) | 19 (2) | 1.02 (0.53–1.95) |
| Current use | 170 (19) | 184 (21) | 1.16 (0.91–1.15) | 218 (21) | 1.25 (0.98–1.57) |
| Duration of current use | | | | | |
| 6 months–<5 years | 91 (10) | 79 (9) | 0.90 (0.65–1.24) | 109 (11) | 1.13 (0.83–1.53) |
| 5 yrs–<10 yrs | 47 (5) | 54 (6) | 1.26 (0.83–1.91) | 47 (5) | 1.00 (0.65–1.53) |
| ≥10 yrs | 31 (4) | 50 (6) | **1.83 (1.14–2.93)** | 60 (6) | **1.97 (1.25–3.12)** |
| $P$-$_{trend}$ | | | *P = 0.043* | | *P = 0.021* |
| | **Study participants with a history of high cholesterol** | | | | |
| | Controls ($n = 273$) | Ductal cases ($n = 286$) | | Lobular cases ($n = 320$) | |
| | *N* (%) | *N* (%) | OR (95% CI) | *N* (%) | OR (95% CI) |
| Never use | 85 (31) | 71 (25) | 1.00 (Ref) | 77 (24) | 1.00 (Ref) |
| Ever use for ≥6 months | 175 (64) | 195 (68) | 1.42 (0.96–2.09) | 227 (71) | **1.64 (1.12–2.41)** |
| Current use | 158 (57.9) | 175 (61) | 1.41 (0.95–2.08) | 208 (65) | **1.63 (1.11–2.41)** |
| Duration of ever use | | | | | |
| 6 months–<5 yrs | 93 (34) | 88 (31) | 1.19 (0.77–1.84) | 116 (37) | **1.55 (1.01–2.37)** |
| 5 yrs–<10 years | 48 (18) | 54 (19) | 1.46 (0.87–2.44) | 48 (15) | 1.31 (0.77–2.22) |
| ≥10 years | 33 (12) | 51 (18) | **2.04 (1.17–3.57)** | 61 (19) | **2.43 (1.40–4.21)** |
| $P_{trend}$ | | | *P = 0.025* | | *P = 0.006* |

NOTE: OR adjusted for reference year, reference age, county of residence, and HRT. Bold values signify statistically significant estimates (*P* value <0.05).

increase in breast cancer in the treatment arm (36, 37). In the WHI cohort while use of hydrophilic statins was not related to breast cancer risk, an 18% ($P = 0.02$) lower breast cancer incidence was observed among users of lipophilic statins (simvastatin, lovastatin, or fluvastatin) compared with statin nonusers (14). However, it should be noted that two thirds of statin users in the WHI cohort had used statins for less than 3 years. In contrast, a recent large case–control study found no evidence of an association between lipophilic statins and breast cancer (23). Our finding of an increased risk of breast cancer among long-term, primarily lipophilic, statin users does not support the use of statins for breast cancer prevention and suggests that the risk of breast cancer may be elevated for both users of lipophilic and hydrophilic statins.

It is also important to acknowledge the potential limitations of this study. Given its design, recall bias is a potential concern. However, our study interviewers used showcards with pictures of medications to enhance recall and had all participants bring all of their current medications to the interview to minimize misclassification. Furthermore, a validation study comparing self-reported statin use to data from pharmacy records conducted among women aged 65 to 79 years from Washington State found no significant differences in recall of recent statin use between breast cancer cases (sensitivity 83%, 95% CI: 64, 93) and controls (sensitivity 93%, 95% CI: 69, 99) and suggested that any differential misclassification would likely result in a spuriously low proportion of statin users among breast cancer cases biasing the OR for the association between statin use and breast cancer toward the null, given that cases were less likely to be correctly classified as statin users (38). Selection bias is also a possible explanation for the observation that IDC and ILC cases were more likely to be long-term statin users than controls. It is possible

**Table 3.** Relationship between use of statins and breast cancer risk by solubility and for the most commonly used statin medications

| | Controls ($n = 877$) | Ductal cases ($n = 891$) | | Lobular cases ($n = 1,036$) | |
|---|---|---|---|---|---|
| | ***N* (%)** | ***N* (%)** | **OR (95% CI)** | ***N* (%)** | **OR (95% CI)** |
| Never use | 674 (76.9) | 664 (74.8) | 1.00 (reference) | 782 (75.6) | 1.00 (reference) |
| Hydrophilic statins | | | | | |
| Current use | 13 (1.5) | 18 (2.0) | 1.56 (0.75–3.24) | 21 (2.0) | 1.65 (0.81–3.38) |
| Lipophilic statins | | | | | |
| Current use | 157 (17.9) | 166 (18.7) | 1.13 (0.88–1.45) | 196 (18.9) | 1.21 (0.95–1.54) |
| 6 months–<5 years | 84 (9.6) | 76 (8.6) | 0.95 (0.68–1.33) | 104 (10.1) | 1.17 (0.86–1.61) |
| 5 yrs–<10 yrs | 44 (5) | 45 (5.1) | 1.09 (0.70–1.69) | 44 (4.3) | 0.96 (0.62–1.50) |
| ≥10 years | 28 (3.2) | 43 (4.8) | **1.74 (1.05–2.86)** | 45 (4.4) | **1.68 (1.02–2.76)** |
| $P_{trend}$ | | | *P = 0.119* | | *P = 0.094* |
| Atorvastatin | | | | | |
| Current use | 77 (8.8) | 93 (10.5) | 1.34 (0.96–1.85) | 98 (9.5) | 1.25 (0.91–1.74) |
| 6 months–<5 years | 37 (4.2) | 47 (5.3) | 1.39 (0.88–2.17) | 56 (5.4) | 1.46 (0.94–2.25) |
| 5 yrs–<10 yrs | 28 (3.2) | 26 (2.9) | 1.01 (0.58–1.77) | 24 (2.3) | 0.85 (0.48–1.51) |
| ≥10 years | 12 (1.4) | 20 (2.3) | 1.97 (0.94–4.11) | 18 (1.7) | 1.55 (0.73–3.30) |
| $P_{trend}$ | | | *P = 0.048* | | *P = 0.254* |
| Simvastatin | | | | | |
| Current use | 50 (5.7) | 49 (5.5) | 0.97 (0.64–1.48) | 57 (5.5) | 1.05 (0.70–1.57) |
| 6 months–<5 years | 30 (3.4) | 29 (3.3) | 0.93 (0.54–1.58) | 35 (3.4) | 1.03 (0.62–1.72) |
| 5 yrs–<10 yrs | 14 (1.6) | 12 (1.4) | 0.94 (0.42–2.07) | 13 (1.3) | 0.90 (0.41–1.96) |
| ≥10 years | 6 (0.7) | 8 (0.9) | 1.30 (0.44–3.85) | 9 (0.9) | 1.49 (0.52–4.28) |
| $P_{trend}$ | | | *P = 0.729* | | *P = 0.681* |

NOTE: OR adjusted for reference year, reference age, county of residence, and hormone therapy use. Bold values signify statistically significant estimates (*P* value <0.05).

that the controls available through RDD who agreed to participate in our study were healthier than the general population, resulting in a spuriously low proportion of statin users in our controls. Our finding that controls, IDC cases, and ILC cases all had similar proportions of women with a history of high cholesterol and heart disease as well as similar mammography screening history does not suggest that the controls were exceptionally healthy. We also did not observe differences in the magnitude of the association between statin use and breast cancer when analyses were stratified by mammography screening history, suggesting that the observed results are not explained by a higher frequency of screening in among statin users. It is possible that our finding of an increased risk of breast cancer among long-term statin users is attributable to differences in characteristics of long-term statin users rather than to statin use itself. However, our finding of a greater than

**Table 4.** Associations between statin use and risk of estrogen receptor–positive or –negative breast cancer

| | Controls ($n = 877$) | ER+ ductal cases ($n = 727$) | | ER− ductal cases ($n = 149$) | | ER+ lobular cases ($n = 980$) | |
|---|---|---|---|---|---|---|---|
| | ***N* (%)** | ***N* (%)** | **OR (95% CI)** | ***N* (%)** | **OR (95% CI)** | ***N* (%)** | **OR (95% CI)** |
| Never use | 674 (77%) | 541 (74%) | 1.00 (reference) | 114 (77%) | 1.00 (reference) | 741 (76%) | 1.00 (reference) |
| Current use | 170 (19%) | 152 (21%) | 1.17 (0.90–1.51) | 27 (18%) | 1.00 (0.63–1.60) | 208 (21%) | 1.24 (0.98–1.57) |
| 6 months–<5 years | 91 (10%) | 62 (9%) | 0.86 (0.60–1.22) | 13 (9%) | 0.86 (0.46–1.61) | 104 (11%) | 1.12 (0.82–1.53) |
| 5 years–<10 years | 47 (5%) | 45 (6%) | 1.28 (0.83–1.98) | 8 (5%) | 1.08 (0.49–2.37) | 45 (5%) | 0.99 (0.64–1.53) |
| ≥10 years | 31 (4%) | 44 (6%) | **1.97 (1.21–3.20)** | 6 (4%) | 1.33 (0.53–3.31) | 58 (6%) | **2.00 (1.26–3.17)** |
| $P_{trend}$ | | | *P = 0.035* | | *P = 0.740* | | *P = 0.023* |

NOTE: OR adjusted for reference year, reference age, county of residence, and hormone therapy use. Bold values signify statistically significant estimates (*P* value <0.05).

2-fold increased risk of breast cancer among current long-term statin users in analyses restricted to study participants reporting a history of high cholesterol is evidence that confounding by indication does not account for the excess of breast cancer cases among statin users.

The finding that current, long-term use of statins may double the risk of both ductal and lobular breast cancer warrants further study. This is the first study with the power to examine long-term effects of statins on breast cancer risk. In contrast to the NHS and WHI studies where the prevalence of statin use was 2.6% and 7.5%, respectively, 25% of controls in our study population were current statin users and 18% of those had used statins for 10 or more years. As more women are taking statins and for longer durations than were previously available for study, it is possible that we will observe effects of long-term statin use that prior studies could not detect. Confirmation of these results in other studies is necessary before any changes in clinical practice would be warranted.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Disclaimer

This article and its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI, NIH.

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## References

1. Control" CfD. Data table for Figure 17. Statin drug use in the past 30 days among adults 45 years of age and over, by sex and age: United States, 1988–1994, 1999–2002, and 2005–2008. National Health and Nutrition Examination Survey. Chartbook: Centers for Disease Control; 2010.
2. Lovastatin 5-year safety and efficacy study. Lovastatin Study Groups I through IV. Arch Intern Med 1993;153:1079–87.
3. Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. J Clin Epidemiol 2003;56:280–5.
4. Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, et al. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005;114:643–7.
5. Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. Br J Cancer 2004;90:635–7.
6. Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol 2004;22:2388–94.
7. Boudreau DM, Yu O, Miglioretti DL, Buist DS, Heckbert SR, Daling JR. Statin use and breast cancer risk in a large population-based setting. Cancer Epidemiol Biomarkers Prev 2007;16:416–21.
8. 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.
9. Eaton M, Eklof J, Beal JR, Sahmoun AE. Statins and breast cancer in postmenopausal women without hormone therapy. Anticancer Res 2009;29:5143–8.
10. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol 2009;67:99–109.
11. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340:c2197.
12. 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.
13. Cauley JA, Zmuda JM, Lui LY, Hillier TA, Ness RB, Stone KL, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt) 2003;12:749–56.
14. Cauley JA, McTiernan A, Rodabough RJ, LaCroix A, Bauer DC, Margolis KL, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. J Natl Cancer Inst 2006;98:700–7.
15. 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.
16. Jacobs EJ, Newton CC, Thun MJ, Gapstur SM. Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort. Cancer Res 2011;71:1763–71.
17. Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl conenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case–control study. Cancer 2004;100:2308–16.
18. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf 2008;17:27–36.
19. Haukka J, Sankila R, Klaukka T, Lonnqvist J, Niskanen L, Tanskanen A, et al. Incidence of cancer and statin usage–record linkage study. Int J Cancer 2010;126:279–84.
20. Pocobelli G, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Hampton JM, Egan KM. Statin use and risk of breast cancer. Cancer 2008;112:27–33.
21. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. Circulation 2007;115:27–33.
22. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case–control studies. BMC Cancer 2011;11:409.
23. Woditschka S, Habel LA, Udaltsova N, Friedman GD, Sieh W. Lipophilic statin use and risk of breast cancer subtypes. Cancer Epidemiol Biomarkers Prev 2010;19:2479–87.
24. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996;275:55–60.
25. Rao S, Porter DC, Chen X, Herliczek T, Lowe M, Keyomarsi K. Lovastatin-mediated G1 arrest is through inhibition of the proteasome,

independent of hydroxymethyl glutaryl-CoA reductase. Proc Natl Acad Sci U S A 1999;96:7797–802.
26. Fritz G, Brachetti C, Bahlmann F, Schmidt M, Kaina B. Rho GTPases in human breast tumours: expression and mutation analyses and correlation with clinical parameters. Br J Cancer 2002;87:635–44.
27. 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.
28. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J Clin Oncol 2005;23:8606–12.
29. Undela K, Srikanth V, Bansal D. Statin use and risk of breast cancer: a meta-analysis of observational studies. Breast Cancer Res Treat 2012;135:261–9.
30. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. Cancer Epidemiol Biomarkers Prev 2007;16:2773–80.
31. Li CI, Malone KE, Porter PL, Lawton TJ, Voigt LF, Cushing-Haugen KL, et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:43–50.
32. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol 1984;120:825–33.
33. Clendening JW, Pandyra A, Boutros PC, El Ghamrasni S, Khosravi F, Trentin GA, et al. Dysregulation of the mevalonate pathway promotes transformation. Proc Natl Acad Sci U S A 2010;107:15051–6.
34. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. Nat Rev Cancer 2005;5:930–42.
35. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, 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.
36. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998; 339:1349–57.
37. ALLHAT Officers, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.
38. Boudreau DM, Daling JR, Malone KE, Gardner JS, Blough DK, Heckbert SR. A validation study of patient interview data and pharmacy records for antihypertensive, statin, and antidepressant medication use among older women. Am J Epidemiol 2004;159: 308–17.