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

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For the Women's Health Initiative Research Group

Background: Despite experimental observations suggesting that 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) have antitumor activity, clinical studies have reached mixed conclusions about the relationship between statin use and breast cancer risk. Methods: To investigate associations between potency, duration of use, and type of statin used and risk of invasive breast cancer, we examined data for 156,351 postmenopausal women who were enrolled in the Women's Health Initiative. Information was collected on breast cancer risk factors and on the use of statins and other lipid-lowering drugs. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical tests were two-sided. Results: Over an average follow-up of 6.7 years, 4383 invasive breast cancers were confirmed by medical record and pathology report review. Statins were used by 11,710 (7.5%) of the cohort. Breast cancer incidence was 4.09 per 1000 person-years (PY) among statin users and 4.28 per 1000 PY among nonusers. In multivariable models, the hazard ratio of breast cancer among users of any statin, compared with nonusers, was 0.91 (95% CI = 0.80 to 1.05, P = .20). There was no trend in risk by duration of statin use, with HR = 0.80 (95% CI = 0.63 to 1.03) for <1 year of use, HR = 0.99 (95% CI = 0.80 to 1.23) for 1–3 years of use, and HR = 0.94 (95% CI = 0.75 to 1.18) for ≥3 years of use. Hydrophobic statins (i.e., simvastatin, lovastatin, and fluvastatin) were used by 8106 women, and their use was associated with an 18% lower breast cancer incidence (HR = 0.82, 95% CI = 0.70 to 0.97, P = .02). Use of other statins (i.e., pravastatin and atorvastatin) or nonstatin lipid-lowering agents was not associated with breast cancer incidence. Conclusions: Overall statin use was not associated with invasive breast cancer incidence. Our finding that use of hydrophobic statins may be associated with lower breast cancer incidence suggests possible within-class differences that warrant further evaluation. [J Natl Cancer Inst 2006;98:700–7]
women enrolled in the observational study and clinical trial components of the WHI, excluding those who had previously been diagnosed with breast cancer or who had used tamoxifen or any selective estrogen receptor modulator. The final sample included 88,322 women enrolled in the observational study and 68,029 women enrolled in the clinical trials (156,351 women total).

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

Statin Exposure

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

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

Breast Cancer Screening and Diagnosis

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

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

Covariates

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

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

Statistical Methods

The characteristics of statin users at baseline were compared with those of nonusers by chi-square or Fisher exact tests (for categorical variables) or two-sample t tests (for continuous variables). Incidence rates of breast cancer per 1000 person-years were calculated according to the use of statins and other lipid-lowering agents. An a priori plan of analysis specified that we perform selected subgroup analyses by statin use duration (<1 year, 1–<3 years, and ≥3 years), potency, and hydrophobic status. Women who reported using two or more statins were included in analyses that compared statin use to none but were excluded from analyses that examined details of statin use (i.e., by potency or type). Separate analyses were conducted for women with ER-positive and ER-negative breast cancer. Hazard ratios (HRs) for breast cancer among statin users versus nonusers and 95% confidence intervals (CIs) were computed from Cox proportional hazards analyses. Tests for the proportional hazards assumptions were conducted by a Cox model that included statin use and the interaction of statin use with follow-up time and testing for a zero coefficient on the interaction term. Results of these analyses showed that the assumptions were not violated.

All models were adjusted for assignment to active hormone or placebo in the two WHI hormone trials (estrogen plus progesterin and estrogen alone), assignment to intervention or control in the dietary modification trial, or enrollment in the observational study. We also adjusted for prior hormone use at baseline (none, prior estrogen alone, prior estrogen plus progesterin, or prior use of both estrogen alone and progesterone alone). These adjustments resulted in what we refer to as the base model. The base model was further adjusted by age; these age-adjusted base model included 155,530 women. To control for potential confounding factors, we used multivariable Cox proportional hazards analyses with a forced-entry approach for variable selection. In addition to the variables in the age- and base factor-adjusted
<table>
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<th>N</th>
<th>%</th>
<th>Statin use</th>
<th>N</th>
<th>%</th>
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<td>&gt;High school diploma/GED</td>
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<td>≥1 drink/week</td>
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<td>Have a current medical care provider</td>
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<td>8735</td>
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<td>Yes, 1 biopsy</td>
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<td>1783</td>
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<td>Yes, &gt;2 biopsies</td>
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<td>Bilateral oophorectomy</td>
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<tr>
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<td>1221</td>
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<tr>
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<td>908</td>
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<tr>
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<td>19.4</td>
<td>2197</td>
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</table>

Table 1. Baseline characteristics by statin use*

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

†P-values for comparison are not statistically significant.

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

**RESULTS**

In this cohort of 156351 women, 11 710 (7.5%) were statin users (Table 1). Women using statins at baseline were older at enrollment than nonusers (65.6 and 63.0 years, respectively) and had a higher BMI (mean 28.9 and 27.9 kg/m², respectively). Statin users were less likely than nonusers to have more than a high school education, to drink alcohol, to be physically active, models, the multivariable models were adjusted for race and ethnicity, BMI, physical activity, current and past smoking, family history of breast cancer, hysterectomy status, mammogram in the past 2 years, educational level, ages at menarche and first birth, parity, alcohol consumption, and percentage of calories from fat. Multivariable models were based on the 115683 individuals remaining after the exclusion of participants with missing values for any of the covariates. To evaluate the effects on the results of change in statin use over time, final models were rerun by entering statin use as a time-dependent exposure and using updated information on statin use gathered at the year 3 clinic visit. We examined the risk for breast cancer by statin use separately in users of estrogen plus progestin, users of estrogen alone, and never/past users of hormone therapy.

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

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

Of the 11710 statin users, 4591 (39.2%) used a low-potency statin, 2645 (22.6%) used a medium-potency statin, and 4438 (37.9%) used a high-potency statin (Table 2). A total of 8106 (69.2%) of the women who used statins reported using at least one hydrophobic statin. A year 3 medication history was available for 135772 women (82% of the cohort). Among cohort members who used statins at baseline, 8274 women (82.5%) were still using a statin at the year 3 clinic visit; among those who did not use statins at baseline, 11583 women newly reported taking a statin at the year 3 visit.

During a total of 1041518 person years (PY) of observation, 4383 women were diagnosed with invasive breast cancer. The incidence of breast cancer was approximately 4.4% lower among women reporting statin use (4.09 per 1000 PY) than among nonusers (4.28 per 1000 PY). In the age-adjusted base model, the relative risk of breast cancer was 8% lower among statin users than among nonusers (HR = 0.92, 95% CI = 0.82 to 1.03) (Table 3). In the full multivariable-adjusted model, breast cancer incidence was approximately 9% lower in statin users than in non-users (HR = 0.91, 95% CI = 0.80 to 1.05, *P* = .20).

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

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

### Table 2. Statin use details for the 11710 users of any statin

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<th>HR (%)</th>
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<td>4.28</td>
</tr>
<tr>
<td>Yes</td>
<td>297‡</td>
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#### Type of statin used

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Hydrophobic</td>
<td>194</td>
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<tr>
<td>Other</td>
<td>103</td>
</tr>
</tbody>
</table>

#### Duration of statin use

| <1 year          | 84    |
| 1–<3 years       | 104   |
| ≥3 years         | 18    |

#### Other lipid-lowering medication

| No (referent)  | 4324  |
| Yes            | 58    |

#### Duration of statin use

<table>
<thead>
<tr>
<th>Duration of statin use</th>
<th>HR (95% CI) from age-adjusted base model</th>
<th>HR (95% CI) from multivariable-adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>0.89 (0.68 to 1.15)</td>
<td>0.86 (0.63 to 1.03)</td>
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<tr>
<td>1–&lt;3 years</td>
<td>0.95 (0.79 to 1.16)</td>
<td>0.99 (0.80 to 1.23)</td>
</tr>
<tr>
<td>≥3 years</td>
<td>0.99 (0.82 to 1.20)</td>
<td>0.94 (0.75 to 1.18)</td>
</tr>
</tbody>
</table>

#### Other lipid-lowering medication

| Yes | 4.04 |

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

<table>
<thead>
<tr>
<th>Statin use</th>
<th>Breast cancer cases</th>
<th>Incidence per 1000 PY</th>
<th>HR (95% CI) from age-adjusted base model</th>
<th>HR (95% CI) from multivariable-adjusted† model</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (referent)</td>
<td>4086</td>
<td>4.28</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>297‡</td>
<td>4.09</td>
<td>0.92 (0.81 to 1.03)</td>
<td>0.91 (0.80 to 1.05)</td>
</tr>
</tbody>
</table>

#### Type of statin

<table>
<thead>
<tr>
<th>Statin category</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobic</td>
<td>194</td>
</tr>
<tr>
<td>Other</td>
<td>103</td>
</tr>
</tbody>
</table>

#### Statin potency

<table>
<thead>
<tr>
<th>Statin category</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>113</td>
</tr>
<tr>
<td>Medium</td>
<td>81</td>
</tr>
<tr>
<td>High</td>
<td>102</td>
</tr>
</tbody>
</table>

#### Duration of statin use

<table>
<thead>
<tr>
<th>Duration of statin use</th>
<th>HR (95% CI) from age-adjusted base model</th>
<th>HR (95% CI) from multivariable-adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>0.89 (0.68 to 1.15)</td>
<td>0.86 (0.63 to 1.03)</td>
</tr>
<tr>
<td>1–&lt;3 years</td>
<td>0.95 (0.79 to 1.16)</td>
<td>0.99 (0.80 to 1.23)</td>
</tr>
<tr>
<td>≥3 years</td>
<td>0.99 (0.82 to 1.20)</td>
<td>0.94 (0.75 to 1.18)</td>
</tr>
</tbody>
</table>

#### Other lipid-lowering medication

| Yes | 4.04 |

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

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

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

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

||Low-potency statins are lovastatin and fluvastatin, the medium-potency statin is pravastatin, and the high-potency statins are simvastatin and atorvastatin.
breast cancer (HR = 0.82, 95% CI = 0.70 to 0.97, \( P = .02 \)), whereas use of other statins was not associated with breast cancer incidence (HR = 1.14, 95% CI = 0.92 to 1.42, \( P = .24 \)).

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

Finally, we analyzed breast cancer risk according to the use of lipid-lowering agents other than statins. The incidence of breast cancer in users of such agents (4.04 per 10000 PY) was 5.4% lower than that in non-users (4.27 per 1000 PY), but the difference was not statistically significant in the multivariable model (HR = 0.88, 95% CI = 0.64 to 1.19, \( P = .41 \)).

**Discussion**

The current report is the largest cohort study, to our knowledge, to evaluate statin use and invasive breast cancer in terms of the number of incident breast cancers. We studied 156361 women, who were followed for 1041518 person-years, and 4383 incident breast cancers. The full multivariable model used in the analysis adjusted for a comprehensive set of breast cancer risk factors, including age, race, BMI, family history of breast cancer, alcohol consumption, physical activity, mammography utilization, past and current menopausal hormone therapy, smoking, percentage of calories from fat, educational level, NSAID use, and reproductive history. When we considered statins as a class, we found no association between statin use and breast cancer risk. Although the relative risk of breast cancer was approximately 9% lower among statin users than among nonusers, the difference was not statistically significant. Breast cancer incidence was also not associated with duration of statin use or statin potency. There was an interaction between statin use and hormone therapy that was of borderline statistical significance: current users of both estrogen alone and a statin had a somewhat lower risk of breast cancer than women who had never used a statin. This interaction was not observed among users of estrogen plus progesterin, however, and these results also conflict with results from the Nurses’ Health Study (5). Finally, women using hydrophobic statins (simvastatin, lovastatin, or fluvastatin) had an 18% lower breast cancer incidence than nonstatin users (\( P = .02 \)).

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

<table>
<thead>
<tr>
<th>Current hormone use</th>
<th>No statin use</th>
<th>Statin use</th>
<th>HR (95% CI)</th>
<th>( P ) for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Rate†</td>
<td>Cases</td>
<td>Rate†</td>
</tr>
<tr>
<td>Never/past</td>
<td>1789</td>
<td>3.68</td>
<td>161</td>
<td>4.06</td>
</tr>
<tr>
<td>E-alone only</td>
<td>979</td>
<td>4.00</td>
<td>60</td>
<td>3.15</td>
</tr>
<tr>
<td>Any E + P</td>
<td>1314</td>
<td>5.89</td>
<td>74</td>
<td>5.46</td>
</tr>
</tbody>
</table>

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

†Rate given per 1000 person-years.
‡HR = hazard ratio; CI = confidence interval.
Cancer Surveillance System, a population-based tumor registry that serves 13 counties in western Washington State, no overall association of statins with breast cancer incidence was seen, but women who had used statins for more than 5 years had an approximately 30% lower breast cancer incidence than never users (25).

A statistically significant decrease in breast cancer incidence in statin users has been seen in only two (9, 27) of eight cohort studies. However, the number of breast cancers in one of these reports was small (9), and limited information on breast cancer risk factors was provided in the second report, which was an abstract (27).

Our results, taken together with the existing literature, indicate that breast cancer risk is at least not increased in statin users. Whether or not statin use is associated with reduced breast cancer risk is less certain. In the current study, after adjustment for breast cancer risk factors, statin users had a somewhat lower breast cancer incidence than nonusers. However, the differences were statistically significant only in women who reported using hydrophobic statins. This observation is consistent with a cell culture study in which only hydrophobic statins (lovastatin, simvastatin, and fluvastatin) but not a hydrophilic statin (pravastatin)
had anticancer activity (29). Pravastatin may promote the development of cancer by causing an induction of mevalonate synthesis in extrahepatic tissues (30), an effect that is not observed with other statins. This increase in mevalonate appears to promote the growth of breast cancer cells (30). In the randomized trials of statins, an increase in breast cancer was observed only in the two trials of pravastatin (8,19). Moreover, in the cohort study that reported a 72% lower risk of breast cancer among statin users, the majority of these users (247 of 284) used a hydrophobic statin (9). Thus, the inconsistency in previous results may reflect differences in the association with specific statins.

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

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

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

REFERENCES


NOTES

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