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

A. Heather Eliassen, ScD; Graham A. Colditz, MD, DrPH; Bernard Rosner, PhD; Walter C. Willett, MD, DrPH; Susan E. Hankinson, ScD

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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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 79,922 women (888,120 person-years), the serum cholesterol analysis included 71,921 women (665,743 person-years), and the statin analysis included 79,828 women (431,703 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 reported duration categories up to 6 or more years. Given the range of years within the lipid-lowering drug analysis included 79,922 women (888,120 person-years), the serum cholesterol analysis included 71,921 women (665,743 person-years), and the statin analysis included 79,828 women (431,703 person-years).

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

<table>
<thead>
<tr>
<th>Self-reported Total Serum Cholesterol, mg/dL</th>
<th>Participants, No. (n = 1328)</th>
<th>Measured Total Serum Cholesterol, Mean (SD), mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;140</td>
<td>49</td>
<td>176 (34.3)</td>
</tr>
<tr>
<td>140-159</td>
<td>84</td>
<td>184 (31.8)</td>
</tr>
<tr>
<td>160-179</td>
<td>150</td>
<td>190 (34.1)</td>
</tr>
<tr>
<td>180-199</td>
<td>230</td>
<td>207 (33.6)</td>
</tr>
<tr>
<td>200-219</td>
<td>281</td>
<td>215 (28.7)</td>
</tr>
<tr>
<td>220-239</td>
<td>239</td>
<td>233 (30.1)</td>
</tr>
<tr>
<td>240-269</td>
<td>195</td>
<td>249 (33.6)</td>
</tr>
<tr>
<td>270-299</td>
<td>72</td>
<td>259 (35.8)</td>
</tr>
<tr>
<td>≥300</td>
<td>28</td>
<td>292 (31.3)</td>
</tr>
</tbody>
</table>

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

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. 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 ρ = 0.60) is similar to the within-subject reproducibility of cholesterol measures across several years (ρ = 0.65).

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 (3.4%) of 5177 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonusers (n = 59,534)</th>
<th>0-2 y (n = 7630)</th>
<th>3-5 y (n = 5034)</th>
<th>≥6 y (n = 2706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65.7 (7.1)</td>
<td>67.3 (6.9)</td>
<td>68.8 (6.6)</td>
<td>68.9 (6.3)</td>
</tr>
<tr>
<td>Age at menarche, mean (SD), y</td>
<td>12.6 (1.4)</td>
<td>12.5 (1.4)</td>
<td>12.5 (1.5)</td>
<td>12.5 (1.4)</td>
</tr>
<tr>
<td>Parity, mean (SD), No. of children‡</td>
<td>3.2 (1.6)</td>
<td>3.3 (1.6)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.6)</td>
</tr>
<tr>
<td>Age ≥ 50 y at first birth, %‡</td>
<td>8.4</td>
<td>8.0</td>
<td>8.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Family history of breast cancer, %</td>
<td>16.0</td>
<td>17.2</td>
<td>16.7</td>
<td>16.5</td>
</tr>
<tr>
<td>History of benign breast disease, %</td>
<td>50.1</td>
<td>53.0</td>
<td>52.7</td>
<td>54.2</td>
</tr>
<tr>
<td>Age at menopause, mean (SD), y§</td>
<td>49.2 (5.1)</td>
<td>49.0 (5.1)</td>
<td>48.8 (5.2)</td>
<td>48.5 (5.5)</td>
</tr>
<tr>
<td>Current PMH use, %</td>
<td>41.9</td>
<td>40.0</td>
<td>43.9</td>
<td>48.3</td>
</tr>
<tr>
<td>Duration of PMH use, mean (SD), y</td>
<td>10.4 (7.4)</td>
<td>10.4 (8.0)</td>
<td>10.6 (8.6)</td>
<td>11.1 (7.9)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.6 (5.4)</td>
<td>28.1 (5.3)</td>
<td>28.2 (5.3)</td>
<td>27.6 (4.8)</td>
</tr>
<tr>
<td>BMI at age 18 y, mean (SD)</td>
<td>21.3 (2.9)</td>
<td>21.5 (3.1)</td>
<td>21.4 (3.1)</td>
<td>21.3 (2.9)</td>
</tr>
<tr>
<td>Height, mean (SD), inches</td>
<td>64.5 (2.4)</td>
<td>64.4 (2.4)</td>
<td>64.3 (2.4)</td>
<td>64.1 (2.4)</td>
</tr>
<tr>
<td>Alcohol consumption, mean (SD), g/d</td>
<td>5.1 (9.2)</td>
<td>4.3 (8.6)</td>
<td>4.3 (8.5)</td>
<td>4.4 (8.9)</td>
</tr>
<tr>
<td>Physical activity, &gt; 4 MET/d, %</td>
<td>1.3</td>
<td>18.0</td>
<td>16.8</td>
<td>18.1</td>
</tr>
<tr>
<td>Mammography within 2 y, %</td>
<td>88.2</td>
<td>92.6</td>
<td>93.8</td>
<td>94.1</td>
</tr>
</tbody>
</table>

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.

RESULTS

We documented 3177 incident cases of invasive breast cancer between 1988 and 2000; 1727 cases were documented 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 risk was observed (RR, 0.99; 95% CI, 0.86-1.13). 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 was also 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...
The association between lipid-lowering drug use and breast cancer risk among users 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 lipido-lowering drug use or restricted to nonusers did not differ from the overall results.
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 we did not 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. 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. This pathway not only leads to the production of cholesterol but also includes intermediate products that are essential to cell cycle progression. Statins have inhibited tumor growth in murine models of brain, pancreatic, and breast cancer and have induced apoptosis in leukemic, colon cancer, and breast cancer cell lines. 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. 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. 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 other studies (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).
circulating sex steroid hormone levels are directly associated with breast cancer risk supports a correlation. 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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Correspondence: A. Heather Eliassen, ScD, Channing Laboratory, Brigham and Women’s Hospital, 181 Longwood Ave, Boston, MA 02115 (heather.eliassen@channing.harvard.edu).

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Additional Information: All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


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