Estrogen Receptor–Negative Breast Cancer Is Less Likely to Arise among Lipophilic Statin Users

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Abstract

Background: Preclinical studies have shown the anticancer potential of HMG-CoA reductase enzyme inhibitors (statins), whereas epidemiologic studies remain controversial. Because lipophilic statins show preclinical antitumor activity against hormone receptor–negative breast cancer models, we explored the hormone receptor phenotype of breast cancer that arises in statin users.

Methods: We did a retrospective cohort analysis via electronic pharmacy records from the Kaiser Permanente Northern California Cancer Registry on 2,141 female patients listed in 2003 as incident cases of breast malignancy. Measures included tumor grade, stage, and receptor phenotype in statin users versus nonusers and controlled for hormone replacement therapy and race. Results: 387 of the 2,141 breast cancer patients used lipophilic statins [lovastatin (68%), simvastatin, and atorvastatin]. Fifty-one women developed ER/PR-negative tumors. The age-adjusted odds ratio (OR) of developing an ER/PR negative tumor was 0.63 (95% confidence interval, 0.43-0.92; \( P = 0.02 \)) for statin use \( \geq 1 \) year before breast cancer diagnosis compared with statin use \( < 1 \) year (including nonuser). Breast cancers in patients with \( \geq 1 \) year of statin use were more likely to be low grade (OR, 1.44) and less invasive stage (OR, 1.42).

Conclusions: Breast cancer patients with exposure to statins have proportionately fewer ER/PR-negative tumors that are of lower grade and stage. Although our data set cannot address whether statins affect the incidence of breast cancer, we show that statin use may influence the phenotype of tumors. This suggests a new potential strategy for breast cancer prevention, that of combining statins with agents that prevent ER-positive cancer (tamoxifen, aromatase inhibitors).

Introduction

Statins, the drugs originally introduced to reduce cholesterol by inhibition of HMG-CoA reductase, can also affect immune and inflammatory responses as well as reduce cellular proliferation, survival, motility, and invasion—all potentially important factors affecting cancer development (1). Cardiovascular studies have shown that the risk reduction statins confer for stroke events occur via cholesterol-independent mechanisms (2-5). The cholesterol-independent and pleiotropic effects of lipophilic statins in particular may not only be responsible for cardiovascular health benefits but also may confer some degree of cancer prevention (6).

The rapidly growing number of epidemiologic studies addressing statins and cancer incidence has been both provocative and mixed, prompting several recent meta-analyses, which have generally concluded that there is no convincing clinical evidence supporting either a cancer-promoting or cancer-preventing effect for statins (7, 8). However, subsequent commentaries have detailed many perceived deficiencies in these meta-analyses and the studies they analyzed (9-14), including the confounding effect of combining lipophilic (e.g., lovastatin and simvastatin) and hydrophilic (e.g., pravastatin) statin users, lack of assessment of duration of statin use, and failure to consider clinically important cancer subtypes, such as breast cancers typed according to estrogen receptor (ER) and progesterone receptor (PR) status (ER/PR positive, ER/PR negative). Additionally, data from three large retrospective studies and one large prospective study were not included in these meta-analyses, as they had not yet been published. Analysis of retrospective data through the Nurses’ Health Study by Eliassen et al. (\( n = 75,828 \)) as well as a large retrospective population-based study by Boudreau et al. (\( n = 92,788 \)) found no difference in breast cancer risk with statin use (15, 16). However, one retrospective study of 40,421 women found a protective benefit of statins (relative risk, 0.49) that increased with increasing duration of statin use (17). In a prospective analysis of the Women’s Health Initiative data (\( n = 156,351 \)), Cauley et al. suggested that lower breast cancer incidence depends on within-class differences in statin use (18). Specifically, lipophilic statins were associated with decreased risk of breast cancer development [hazard ratio (HR), 0.82], but other agents were not (HR, 1.14). Thus, the broader question of whether statin use reduces cancer risk remains unanswered, as does the more specific question about any differential effect of lipophilic statins in preventing...
or influencing ER/PR-negative versus positive breast cancer or in altering the phenotype of tumors that develop.

Although epidemiologic evidence for statin use and cancer prevention remains controversial, preclinical evidence supporting the anticancer potential of lipophilic but not hydrophilic statins is quite strong, prompting numerous reviews and prominent calls for prospective clinical assessment of statins as cancer therapeutics and prevention agents (1, 6, 19-22). In vitro and in vivo treatment of cancer models by lipophilic statins invariably reduces intracellular levels of mevalonate and its downstream products, including the isoprenoid intermediates that provide lipid attachment sites for activated Ras, Rac, and Rho family members (23). Many of these downstream products mediate intracellular pathways critical for cancer cell growth and survival, including membrane integrity, cell signaling, cell cycle progression, and cellular motility and invasiveness as well as specific immune, inflammatory, and stromal cell responses supporting cancer development and growth (19, 24).

With regard to statins and breast cancer, a recent in vitro and in vivo preclinical study has now shown that different human breast cancer phenotypes are differentially responsive to statins (25), with ER/PR-negative breast cancers being most responsive to the anticancer effects of lipophilic statins like lovastatin, simvastatin, and fluvastatin; no breast cancer phenotype was responsive to the commonly studied hydrophilic statin pravastatin.

In the present study, we sought to determine if lipophilic statin use could be shown to have any effect on the ER/PR phenotype of breast cancers in a medical population of breast cancer patients who used statins, and if this effect was dependent on duration of statin use.

Materials and Methods

Study Design. We conducted a retrospective cohort analysis of all cases of primary ductal carcinoma in situ and invasive breast cancer diagnosed within the Kaiser Permanente Northern California (KPNC) healthcare system from January 1, 2003 to December 31, 2003, where electronic pharmacy records were available to document the type and duration of lipophilic statin use.

After institutional review board approval was obtained, the KPNC Cancer Registry provided us with a consecutive list of female patients diagnosed with ductal carcinoma in situ and primary breast cancer during the study period. As our goal was to capture pharmacy data for at least 1.5 years on this patient cohort, those patients who joined KPNC after June 2001 were excluded. Additionally, we only included those patients whose ER status, positive or negative, was known. Individual electronic chart review was conducted on each of the included subjects (n = 2,141).

Statin Use. We recorded the type and dosage of statin prescribed (atorvastatin, lovastatin, or simvastatin). Only lipophilic statins were on the KPNC formulary; thus, no patient took hydrophilic statins. We noted the earliest recorded prescription date and correlated this with pathology specimen date to confirm and quantify time (in days) that statins were used before breast cancer diagnosis. The data registry only provides information on prescriptions filled. As maximal decrease in total cholesterol levels occur within 6 weeks of initiation of low-dose therapy (26), we defined “statin ever users” as those who were prescribed statins >6 weeks before the date of the pathology specimen.

Tumor Type. The ratio of cells staining positive for estrogen, progesterone, and HER-2/neu receptor versus unstained cells (represented by a percentage of positivity) was documented by KPNC pathologists in the data registry. The Kaiser Permanente Regional Immunohistochemistry Laboratory developed this immunoperoxidase panel and The Permanente Medical Group Northern California determined its performance characteristics. According to the estrogen and progesterone immunohistochemical receptor analysis used in this system, tumors with <5% nuclear staining are considered negative for the respective antibody. Although final determination is dependent on the subjective measurement by the pathologist, all tumor specimens from KPNC are read, and confirmed, by a team of five pathologists at a single pathology laboratory (Kaiser San Francisco).

ER/PR-negative patients included those who were either ER negative/PR negative or ER negative/PR unknown (n = 15). ER/PR-positive patients included those who were either ER positive, PR positive, or both.

Tumor grade is determined by the pathologist according to Scarff Bloom Richardson scoring based on histologic features and is coded in the KPNC Cancer Registry as the highest numerical value: I (low grade), II (moderate grade), and III (high grade). Stage in the KPNC Cancer Registry is recorded according to the Surveillance, Epidemiology, and End Results guidelines: IS (in situ carcinoma), LOC (localized malignancy), REG (regional malignancy), and DIS (distant metastases).

Statistical Analyses. All analyses were done, and all listings and tables were prepared using STATA version 9. Summary statistics for continuous variables include mean, SD, median, minimum value, and maximum value; categorical variables are presented as counts and percentages. Standard baseline characteristics are summarized for each group. For continuous variables, means were compared using ANOVA. Logistic regression was used to estimate the effects of age (as a continuous variable), race, tumor grade, stage, and exogenous hormone use on ER/PR negativity. Categorical variables were compared using the χ² test for contingency tables. P < 0.05 was considered to be statistically significant.

Results

Registry Data. Of incident cases of breast malignancy in 2003 (n = 2,830) listed in the KPNC Cancer Registry, 2,320 (82%) were invasive and 510 (18%) were ductal carcinoma in situ. We evaluated only those patients for whom ER status was known and who were members of Kaiser Permanente for at least 1 year. ER status was entered into the registry for 83% of patients overall. The vast majority (90%) of patients with invasive cancers had known ER status (2,080 of 2,320), whereas only 51% (260 of 510) of ductal carcinoma in situ patients had known ER status. Of patients with known ER status, 92% of combined invasive (1,903 of 2,080) and ductal carcinoma in situ (238 of 260) cases were Kaiser Permanente members before June 2001 (n = 2,141). The distribution
of tumor stage and grade for those with unknown ER status was nearly identical to those with known ER status.

As would be expected in a predominantly Caucasian population with median age of 61.3 years, most tumors were ER/PR positive (81%). The proportion of ER/PR-negative tumors by age followed a normal distribution. Logistic regression analysis showed that the proportion of ER/PR-negative tumors decreased significantly with patient age at diagnosis ($P < 0.001$).

**Effects of Statin Use.** Eighteen percent of the 2,141 patients had ever used lipophilic statins ($n = 387$) and 17% had documented sustained use of lipophilic statins for $\geq 1$ year before breast cancer diagnosis. All statins prescribed were lipophilic: most patients were prescribed lovastatin (85%), whereas the minority was prescribed simvastatin (13.8%) and rarely atorvastatin (1%) or fluvastatin (0.02%). Essentially all patients who had sustained use of statins took lovastatin and simvastatin, which are incontrovertibly lipophilic statins.

Table 1 shows the distribution of ER/PR-negative tumors as a function of length of statin use. Increasing length of statin exposure beyond 1 year did not appear to affect the effect of statins on reducing the development of ER-negative tumors, as subcategories 1 to 3 and $\geq 1$ year of statin use to dichotomize patients by statin use. This increased our power to detect statistically significant differences.

Statin use for $\geq 1$ year before diagnosis resulted in a significantly decreased proportion of ER/PR-negative tumors when compared with no statin use or use for $<1$ year [12% versus 19%; $P = 0.001$ (based on $2 \times 2 \chi^2$ analysis); Table 1]. Statin use also led to a statistically significant downward shift in grade and stage, with an increase in the percentage of low grade (grade I) and low stage (in situ of localized) tumors (Table 2). ER-negative tumors of higher pathologic grade (less differentiated) and more advanced clinical stage showed the greatest proportional reduction associated with statin use $\geq 1$ year (data not shown).

Because statin users were older than nonusers [median age, 68.3 (range, 40.2-92.8) for users versus 60.3 (range, 15.3-95.7) years for nonusers ($P < 0.001$)], we calculated an age-adjusted OR for ER/PR-negative breast cancer. The age-adjusted OR was still statistically significant [OR, 0.63; 95% confidence interval (95% CI), 0.43-0.92; $P = 0.017$]. The probability of having an ER/PR-negative tumor was reduced as age at diagnosis increased. The reduced likelihood of having an ER/PR-negative tumor with statin use of $\geq 1$ year compared with statin use $<1$ year (including nonuse) was seen across all age groups (Table 3).

Sustained use of combination estrogen + progesterone hormone therapy has also been shown to result in a proportionate increase in ER-positive tumors (27). For this reason, we investigated whether the observed decrease in ER/PR-negative tumors in our data set could be explained by an increase in ER-positive tumors combination hormone replacement therapy. In our data, hormone therapy use before diagnosis ($n = 1,005$) had no effect on ER/PR phenotype of the tumors that developed. Hormone therapy use was balanced in statin users versus nonusers (data not shown).

We observed that patients of Asian, Hispanic, and African American ethnicity were more likely to be diagnosed with ER/PR-negative tumors than their Caucasian counterparts ($P < 0.005$ for African American and Hispanic groups), with African American tumors being twice as likely to be ER and PR negative. The reduction in the proportion of ER/PR-negative tumors associated with statin use of $\geq 1$ year was shown among all ethnic groups. In the largest ethnic group, Caucasians, the age-adjusted OR for their tumor being ER/PR negative was 0.62 when statin use was sustained for $\geq 1$ year. Although statin use $\geq 1$ year appears to have the greatest effect on tumors in Hispanics and least in Asians, the numbers of tumors in these ethnic groups were not sufficient to show a statistically significant difference.

**Discussion**

Recent *in vitro* and *in vivo* preclinical evidence indicates that lipophilic statins can prevent breast cancer growth by inhibiting critical cell proliferation and survival signals used preferentially by ER/PR-negative breast cancers (19, 25). Based on this evidence, we explored the possibility that lipophilic statin users among a cohort of

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**Table 1. Age-adjusted OR of ER-negative tumor development by statin use before diagnosis of breast cancer**

<table>
<thead>
<tr>
<th>Statin use</th>
<th>Breast cancers</th>
<th>ER/PR-negative tumors (%)</th>
<th>OR (95% CI) of ER/PR-negative tumor</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1,754</td>
<td>323 (18)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>$&lt;1$ y</td>
<td>84</td>
<td>17 (20)</td>
<td>1.25 (0.72-2.17)</td>
<td>0.42</td>
</tr>
<tr>
<td>$\geq 1$ y</td>
<td>303</td>
<td>34 (11)</td>
<td>0.63 (0.43-0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* $P$ values for test against “Never.”

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**Table 2. Tumor characteristics by statin use**

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>Statin use (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None or $&lt;1$ y</td>
<td>$\geq 1$ y</td>
</tr>
<tr>
<td>ER/PR negative</td>
<td>340 (19)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>HER-2 positive†</td>
<td>184 (12.6)</td>
<td>22 (9.2)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>332 (21)</td>
<td>73 (27)</td>
</tr>
<tr>
<td>Moderate</td>
<td>709 (44)</td>
<td>122 (46)</td>
</tr>
<tr>
<td>High</td>
<td>565 (35)</td>
<td>72 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>1,606</td>
<td>267</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ</td>
<td>199 (11)</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Local</td>
<td>1,054 (58)</td>
<td>188 (63)</td>
</tr>
<tr>
<td>Distant</td>
<td>49 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Regional</td>
<td>522 (29)</td>
<td>63 (21)</td>
</tr>
<tr>
<td>Total</td>
<td>1,825</td>
<td>300</td>
</tr>
</tbody>
</table>

*Adjusted for age.
† HER-2 data were available for $n = 1,700$ patients.
†† Low versus other grades.
†In situ or local versus other stages.
Kumar et al. KPNC 2,141 386 34 OR, 0.63 0.47-0.97 Yes Lipophilic

The prospective study by Cauley et al. reported that use of lipophilic statins is associated with a significant reduction in risk of developing breast cancer (HR, 0.82; 95% CI, 0.70-0.97; P = 0.02) not seen when other statins are used (HR, 1.14; 95% CI, 0.92-1.42; ref. 18). Unfortunately, this prospective study did not evaluate the tumor ER/PR status of breast cancer patients taking lipophilic statins to determine if their risk reduction was generated from a lower incidence of receptor-negative breast cancers. To date, this study is the only study powered to detect a difference in ER-negative tumors and lipophilic statins. The prospective study by Cauley et al. reported that use of lipophilic statins is associated with a significant reduction in risk of developing breast cancer (HR, 0.82; 95% CI, 0.70-0.97; P = 0.02) not seen when other statins are used (HR, 1.14; 95% CI, 0.92-1.42; ref. 18). Unfortunately, this prospective study did not evaluate the tumor ER/PR status of breast cancer patients taking lipophilic statins to determine if their risk reduction was generated from a lower incidence of receptor-negative breast cancers. To date, this study is the only study powered to detect a difference in ER-negative tumors and lipophilic statins.

An important strength of the present study is that virtually all KPNC statin users are prescribed only lipophilic statins, including atorvastatin, lovastatin, or simvastatin. Because there has been some discrepancy in the classification of lipophilic versus hydrophilic statins in reported epidemiologic studies of cancer risk in statin users (7, 8, 15-17), we adopted a pharmacologic classification widely used by cardiovascular researchers in which pravastatin and rosuvastatin are considered hydrophilic statins, whereas other approved statins are considered lipophilic (28, 29).

The chemical structures of lovastatin, simvastatin, and pravastatin appear similar. However, pravastatin lacks the closed lactone ring found in simvastatin and lovastatin, which must be intracellularly hydrolyzed to inhibit HMG-CoA reductase, producing a near 100-fold greater lipophilicity over pravastatin. Unlike the widespread intracellular distribution seen following lipophilic statin intake, pravastatin enters the liver but does not otherwise traverse cellular membranes. Importantly, the systemic pleiotropic effects of lipophilic statins are independent of hepatic cholesterol-lowering effects produced by both lipophilic and hydrophilic statins, although the latter must enter hepatocytes via a Na+-independent bile acid transporter mechanism (active carrier-mediated uptake) not found in most peripheral cell types (30, 31). Thus, whereas lipophilic statins exhibit some variability in their preclinical anticancer activity, hydrophilic statins like the commonly prescribed pravastatin are generally inactive when tested in vitro against human cancer cells (25).

In several other regards, the KPNC System and patient database offered an ideal opportunity to explore the association between lipophilic statins and their effect on breast cancer hormonal phenotypes. The electronic pharmacy database allowed for precise calculation of total exposure to statins; the duration of statin use was accurately reflected in the number of prescriptions dispensed, as few Kaiser patients fill prescriptions outside the Kaiser formulary system. This produces a

### Table 3. OR for ER-negative tumor development by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Breast cancers</th>
<th>ER/PR-negative tumors (%)</th>
<th>OR (95% CI) of ER/PR-negative tumor with ≥1 y* statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>78</td>
<td>25 (32)</td>
<td>0.77 (0.17-3.52)</td>
</tr>
<tr>
<td>40-49</td>
<td>350</td>
<td>62 (18)</td>
<td>0.76 (0.35-1.69)</td>
</tr>
<tr>
<td>50-59</td>
<td>564</td>
<td>128 (23)</td>
<td>0.62 (0.29-1.32)</td>
</tr>
<tr>
<td>60-69</td>
<td>535</td>
<td>83 (16)</td>
<td>0.70 (0.36-1.35)</td>
</tr>
<tr>
<td>70-79</td>
<td>424</td>
<td>49 (12)</td>
<td>0.67 (0.33-1.36)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>190</td>
<td>27 (14)</td>
<td>0.47 (0.13-1.67)</td>
</tr>
<tr>
<td>All ages</td>
<td>2,141</td>
<td>374 (17)</td>
<td>0.63 (0.43-0.92)</td>
</tr>
</tbody>
</table>

NOTE: P values based on OR from a 2 × 2 table.

*Statins ever use among ER-negative cases was reported as 21; presumably, the number of cases of statin use >1 y is less.

### Table 4. Comparison of studies investigating statin use and ER phenotype

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study population</th>
<th>Breast cancer cases</th>
<th>ER-negative cases</th>
<th>ER-negative cases &gt;1 y statin use</th>
<th>Risk 95% CI</th>
<th>P &lt; 0.05 Statin type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliassen et al.</td>
<td>Nurses' Health Study</td>
<td>3,439</td>
<td>218</td>
<td>&lt;21*</td>
<td>RR 0.96</td>
<td>0.60-1.50 No</td>
</tr>
<tr>
<td>Boudreau et al.</td>
<td>Group Health of Western</td>
<td>2,440</td>
<td>373</td>
<td>20</td>
<td>HR 1.33-1.81</td>
<td>0.64-4.36 No</td>
</tr>
<tr>
<td></td>
<td>Washington State</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No Mixed</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>KPNC</td>
<td>2,141</td>
<td>386</td>
<td>34</td>
<td>OR 0.63</td>
<td>0.47-0.97 Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lipophilic only</td>
</tr>
</tbody>
</table>

*HRs were given for 1 to 2, 2 to 5 and >5 y; therefore, the range of combined HRs and 95% CIs are represented.
more accurate estimate of lifetime statin exposure than self-reporting and provides an advantage over randomized trials, because total time on statin is known rather than estimated. Although software to extract pharmacy data from the general Kaiser Permanente patient population (n > 1.3 million) is still under development, we were able to tap into the electronic pharmacy resource by manually extracting data from individual patients listed in the cancer registry. Another key study advantage is Kaiser centralized pathology review, because all ER and PR immunohistochemical results were evaluated and quality controlled by a team of five pathologists located at one facility (Kaiser San Francisco). This single reference laboratory system minimizes misclassification of breast cancer histology and hormone receptor status and precludes concerns regarding interinstitutional variations in immunohistochemical reagents, methods, and result interpretation.

Our study design did not allow us to assess potential overall breast cancer risk reduction by lipophilic statins, although several studies have addressed this point (17, 18, 32-35). Only two studies have investigated the effect of statin on specific histologic type. At first glance, our results seem to be at odds with two large retrospective studies (Nurses’ Health Study and Group Health of Western Washington State), which report data on statin use and breast cancer phenotype by ER (16, 18). The disputed results may be explained by inclusion of both lipophilic and hydrophilic (that is, pravastatin) in their analysis of statin use on ER. Also, analysis of fewer ER-negative tumors and even fewer ER-negative patients who took statins for ≥1 year may not have provided sufficient power to see the differences we have observed (Table 4).

Most recently, a large cohort study by Boudreau et al. designed to evaluate statin use and breast cancer risk failed to identify any significant risk reduction benefit among lipophilic statin users ≥1 year (HR, 1.07; 95% CI, 0.88-1.29) compared with nonusers and likewise found no significant benefit according to type of statin used or reduction in the specific risk of developing receptor-negative breast cancer (16). However, although powered to address breast cancer risk reduction on statins, the study by Boudreau et al. may not have been sufficiently powered to discern a statin-induced decline in the number of newly diagnosed receptor-negative breast cancers. The total number of breast cancers diagnosed in statin users of ≥1 year in the study by Boudreau et al. (n = 111) was less than half the number of breast cancer cases identified in this study (n = 303). Similarly the total number of receptor-negative breast cancers among statin users of ≥1 year in Boudreau et al. (n = 20) was significantly fewer than those examined in our study (n = 34; Table 4).

One possible explanation for the discrepant data is that statins may exert their effect by altering the phenotype of emergent breast cancers, reducing the proportion of ER/PR-negative cancers rather than reducing the total number of breast cancers that develop. The relative reduction in the proportion of receptor-negative breast cancers observed among statin users in our study, assuming total breast cancer incidence is unchanged in this population, implies a relative increase in the incidence of ER/PR-positive breast cancer among the patients who used statins in this cohort. This possibility is potentially as significant as a total reduction in breast cancer incidence, because a statin-induced reduction in higher-grade, ER/PR-negative breast cancers would ultimately improve the outcome of incident lower-grade, ER/PR-positive breast cancers especially with the use of adjuvant endocrine therapy. Consistent with this possibility, the breast cancers that developed among statin users in our study population were of significantly lower grade and invasive stage than those that developed in nonusers (Table 2).

Breast cancer investigators have recently become interested in potential therapeutic approaches designed to convert receptor-negative to receptor-positive breast cancers, because this would improve patient outcome by enabling treatment with clinically effective and well-tolerated endocrine agents (antiestrogens, aromatase inhibitors). Enthusiasm for this novel strategy has increased given recent preclinical evidence for its feasibility, with histone deacetylase inhibitors and signal transduction (mitogen-activated protein kinase) inhibitors both shown to be capable of converting a significant proportion of ER-negative breast cancer models into antiestrogen-responsive ER-positive breast cancer models (36, 37). Statins may also be capable of inducing this phenotypic conversion, because early treatment effects noted in receptor-negative breast cancer models growth inhibited by lipophilic statins include interruption of two tumorigenic pathways (mitogen-activated protein kinase and nuclear factor-κB) known to reduce ER expression (19, 25). Other mechanisms underlying statin potential to alter the breast cancer phenotype that may be most pertinent would be their known vascular anti-inflammatory properties (38), particularly because inflammation is an important component of hormone receptor-negative breast cancers. Preclinical studies can now be designed to look for evidence of statin-induced conversion in breast cancer hormonal phenotype.

If statin use for ≥1 year shows little or no effect on total breast cancer incidence, it might still significantly reduce a woman’s likelihood of developing receptor-negative breast cancer. We can ill afford to ignore this possibility because receptor-negative breast cancers are much more aggressive and more difficult to treat. Unfortunately, epidemiologic evidence addressing the question of statin use and breast cancer risk is driven largely by the fact that >80% of breast cancers arising after age 45 are ER/PR positive, as seen in the Group Health Western Washington study by Boudreau et al. (16). Additional cohort studies enriched in populations at greater risk for developing ER/PR-negative breast cancer cases are needed to address this question with greater statistical precision. Specific forms of familial and hereditary breast cancers (e.g., BRCA1) are associated with the more likely development of receptor-negative breast cancers (39), and studies testing the prevention of these tumors by statins are already underway. Another strategy would be to test statin-endocrine therapy combinations (e.g., statins and tamoxifen or aromatase inhibitors) in specific racial or ethnic populations.

(African Americans or Hispanics) at greater risk of developing receptor-negative breast cancer (40, 41). In the present study, lipophilic statin use was associated with a reduction in the proportion of receptor-negative breast cancers across all age-adjusted ethnic groups. Given the absence of chemoprevention approaches for receptor-negative breast cancer, a form of breast cancer most common in underserved American populations, the data in the current study point to a potential new prevention approach for these populations. With the well-established tolerability and general health-promoting benefits of statins (reduction in heart attacks and strokes), we cannot afford to overlook the possibility that lipophilic statins also reduce the risk of developing aggressive receptor-negative breast cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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