

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

Anjali S. Kumar,^{1,2} Christopher C. Benz,^{3,5} Veronica Shim,¹ Christina A. Minami,² Dan H. Moore,⁴ and Laura J. Esserman²

¹Department of Surgery, Kaiser Permanente Oakland Medical Center, Oakland, California; ²Department of Surgery, University of California-San Francisco; ³Department of Medicine, Division of Hematology and Oncology, and ⁴Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, California; and ⁵Buck Institute for Age Research, Novato, California

Abstract

Background: Preclinical studies have shown the anti-cancer potential of HMG-CoA reductase enzyme inhibitors (statins), whereas epidemiologic studies remain controversial. Because lipophilic statins show preclinical anticancer activity against hormone receptor [estrogen receptor (ER)/progesterone receptor (PR)]–negative breast cancer models, we explored the hormone receptor phenotype of breast cancers that arise 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 (85%), 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 ≥ 1 year before breast cancer diagnosis compared with statin use < 1 year (including nonuse). Breast cancers in patients with ≥ 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). (Cancer Epidemiol Biomarkers Prev 2008;17(5):1028–33)

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

Received 8/7/07; revised 12/29/07; accepted 2/15/08.

Grant support: Breast Cancer Research Foundation and The Association of Women Surgeons Foundation.

Requests for reprints: Laura J. Esserman, Carol Franc Buck Breast Care Center, 2nd Floor, 1600 Divisadero Street, San Francisco, CA 94115. Phone: 415-885-7691; Fax: 415-353-9571. E-mail: laura.esserman@ucsfmedctr.org

Copyright © 2008 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-07-0726

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 χ^2 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

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

Statin use	Breast cancers	ER/PR-negative tumors (%)	OR (95% CI) of ER/PR-negative tumor	P*
Never	1,754	323 (18)	1.0 (reference)	
<1 y	84	17 (20)	1.25 (0.72-2.17)	0.42
≥1 y	303	34 (11)	0.63 (0.43-0.92)	0.02

*P values for test against "Never."

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 ≥ 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 ≥ 3 years were associated with a similar reduction in odds ratios (OR). For the remainder of the analyses, we therefore selected a cutoff of ≥ 1 year of statin use to dichotomize patients by statin use. This increased our power to detect statistically significant differences.

Statin use for ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 1 year. Although statin use ≥ 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

Table 2. Tumor characteristics by statin use

Tumor characteristics	Statin use (%)		OR (95% CI)
	None or <1 y	≥1 y	
ER/PR negative	340 (19)	34 (12)	0.64*
HER-2 positive [†]	184 (12.6)	22 (9.2)	0.71
Grade			
Low	332 (21)	73 (27)	1.44 [‡]
Moderate	709 (44)	122 (46)	
High	565 (35)	72 (27)	
Total	1,606	267	
Stage			
<i>In situ</i>	199 (11)	39 (13)	1.42 [§]
Local	1,054 (58)	188 (63)	
Distant	49 (3)	10 (3)	
Regional	522 (29)	63 (21)	
Total	1,825	300	

*Adjusted for age.

[†]HER-2 data were available for $n = 1,700$ patients.

[‡]Low versus other grades.

[§]*In situ* or local versus other stages.

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

Age group	Breast cancers	ER/PR-negative tumors (%)	OR (95% CI) of ER/PR-negative tumor with ≥ 1 y* statin use
<40	78	25 (32)	0 [†]
40-49	350	62 (18)	0.77 (0.17-3.52)
50-59	564	128 (23)	0.76 (0.35-1.69)
60-69	535	83 (16)	0.70 (0.36-1.35)
70-79	424	49 (12)	0.62 (0.29-1.32)
>80	190	27 (14)	0.47 (0.13-1.67)
All ages	2,141	374 (17)	0.63 [‡] (0.43-0.92)

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

*Referenced to statin users <1 y (including nonusers) within each age group.

[†]No patients under 40 used statins >1 y.

[‡]Age-adjusted OR of developing an ER/PR-negative tumor referenced to statin users <1 y (including nonusers).

KPNC breast cancer patients would be less likely to be diagnosed with ER-negative breast cancer. The most striking observation from the present study is that lipophilic statin use for ≥ 1 year appeared to result in a significant 37% reduction (age-adjusted OR, 0.63; 95% CI, 0.43-0.92; *P* = 0.002) in receptor-negative breast cancers relative to the proportion of receptor-negative breast cancers diagnosed in age-matched women who never used statins. Published longitudinal studies evaluating breast cancer incidence in statin users have not reported on the hormonal phenotype (ER/PR status) of tumors arising during statin use. Moreover, in a recent meta-analysis of statin use and cancer risk, the only significant *Q* statistic was noted for breast cancer cases (*Q* statistic *P* = 0.047), indicating marked statistical heterogeneity among reported statin effects on the risk of developing breast cancer (8). Such heterogeneity could be explained by dissimilar statin effects on breast cancers of different hormonal phenotypes and/or by potentially confounding influences from the use of pharmacologically different statin types (lipophilic versus hydrophilic). 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, 0.7-0.97; *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 4. Comparison of studies investigating statin use and ER phenotype

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

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

†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 statins 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- κ B) 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.⁶ Another strategy would be to test statin-endocrine therapy combinations (e.g., statins and tamoxifen or aromatase inhibitors) in specific racial or ethnic populations

⁶ A phase II trial of lovastatin for modification of abnormal breast duct cytology and risk-associated biomarkers in women at high inherited risk of breast cancer (BRSNSTU0010). Stanford University. Principal investigator: James Ford (http://cancer.stanford.edu/trials/adult/Breast_Cancer/BRSNSTU0010.html).

(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.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Sam Pollock and Kelly O'Neal (Kaiser Permanente Oakland Medical Center), Michael Oehrli (KPNC Cancer Registry), and Mary Callahan (KPNC Breast Cancer Tracking System Oakland) for data collection support and Elisabeth Garwood, Pamela Derish, and John Parr (University of California-San Francisco) for editorial support.

References

- Graaf MR, Richel DJ, van Noorden CJ, Guchelaar HJ. Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. *Cancer Treat Rev* 2004;30:609–41.
- Liao JK. Statins: potent vascular anti-inflammatory agents. *Int J Clin Pract Suppl* 2004;143:41–8.
- Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005;45:89–118.
- Nakagami H, Liao JK. Statins and myocardial hypertrophy. *Coron Artery Dis* 2004;15:247–50.
- Amin-Hanjani S, Stagliano NE, Yamada M, Huang PL, Liao JK, Moskowitz MA. Mevastatin, an HMG-CoA reductase inhibitor, reduces stroke damage and upregulates endothelial nitric oxide synthase in mice. *Stroke* 2001;32:980–6.
- Katz MS. Therapy insight: potential of statins for cancer chemoprevention and therapy. *Nat Clin Pract Oncol* 2005;2:82–9.
- 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.
- Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. *JAMA* 2006;295:74–80.
- Kumar AS, Benz CC, Esserman LJ. Clinical trials are required to prove the chemopreventive worth of statins. *Arch Intern Med* 2006;166:1143.
- Kumar AS, Campbell M, Benz CC, Esserman LJ. A call for clinical trials: lipophilic statins may prove effective in treatment and prevention of particular breast cancer subtypes. *J Clin Oncol* 2006;24:2127; author reply 2127–8.
- Prowell TM, Stearns V, Trock B. Lipophilic statins merit additional study for breast cancer chemoprevention. *J Clin Oncol* 2006;24:2128–9; author reply 2129.
- Sprague J, Wood M. Breast cancer prevention: time for randomized controlled trials with statins. *Arch Intern Med* 2006;166:1143–4.
- Sprague JR, Wood ME. Statins and breast cancer prevention: time for randomized controlled trials. *J Clin Oncol* 2006;24:2129–30; author reply 2130–21.
- Vogel VG. Can statin therapy reduce the risk of breast cancer? *J Clin Oncol* 2005;23:8553–5.
- 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.
- 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.
- Kochhar R, Khurana V, Bejjanki H. Statins to reduce breast cancer risk: a case control study in U.S. female veterans. *J Clin Oncol* 2005 ASCO Annu Meet Proc 2005;23:514.
- Cauley JA, McTiernan A, Rodabough RJ, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. *J Natl Cancer Inst* 2006;98:700–7.
- Chan KK, Oza AM, Siu LL. The statins as anticancer agents. *Clin Cancer Res* 2003;9:10–9.
- Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. *Nat Rev Cancer* 2005;5:930–42.
- Hindler K, Cleland CS, Rivera E, Collard CD. The role of statins in cancer therapy. *Oncologist* 2006;11:306–15.
- Stamm JA, Ornstein DL. The role of statins in cancer prevention and treatment. *Oncology (Huntingt)* 2005;19:739–50; discussion 753–4.
- Laufs U, Liao JK. Direct vascular effects of HMG-CoA reductase inhibitors. *Trends Cardiovasc Med* 2000;10:143–8.
- Wright RS, Murphy JG, Bybee KA, Kopecky SL, LaBlanche JM. Statin lipid-lowering therapy for acute myocardial infarction and unstable angina: efficacy and mechanism of benefit. *Mayo Clin Proc* 2002;77:1085–92.
- Campbell MJ, Esserman LJ, Zhou Y, et al. Breast cancer growth prevention by statins. *Cancer Res* 2006;66:8707–14.
- Bates MC, Warren SG, Grubb S, Chillag S. Effectiveness of low-dose lovastatin in lowering serum cholesterol. Experience with 56 patients. *Arch Intern Med* 1990;150:1947–50.
- Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243–53.
- White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002;42:963–70.
- Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999;84:413–28.
- Ho RH, Tirona RG, Leake BF, et al. Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. *Gastroenterology* 2006;130:1793–806.
- Hsiang B, Zhu Y, Wang Z, et al. A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J Biol Chem* 1999;274:37161–8.
- 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.
- Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl coenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case-control study. *Cancer* 2004;100:2308–16.
- Cauley JA, Zmuda JM, Lui LY, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. *J Womens Health* 2003;12:749–56.
- Mortimer JE, Axelrod R, Zimbro K. Effect of statins on breast cancer incidence: findings from the Sentara Health Plan. *Proc Am Soc Clin Oncol* 2003;22:93.
- Zhou Q, Atadja P, Davidson NE. Histone deacetylase inhibitor LBH589 reactivates silenced estrogen receptor α (ER) gene expression without loss of DNA hypermethylation. *Cancer Biol Ther* 2007;1:64–9.
- Massarweh S and Schiff R. Unraveling the mechanisms of endocrine resistance in breast cancer: new therapeutic opportunities. *Clin Cancer Res* 2007;13:1950–4.
- Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437–45.
- Loman N, Johannsson O, Bendahl PO, Borg A, Ferno M, Olsson H. Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. *Cancer* 1998;83:310–9.
- Chu KC, Anderson WF. Rates for breast cancer characteristics by estrogen and progesterone receptor status in the major racial/ethnic groups. *Breast Cancer Res Treat* 2002;74:199–211.
- Quong J, Eppenberger-Castori S, Moore D III, et al. Age-dependent changes in breast cancer hormone receptors and oxidant stress markers. *Breast Cancer Res Treat* 2002;76:221–36.