

*Editorial***Statins, Breast Cancer, and an Invisible Switch?****Tim Byers**

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In this issue, Kumar et al. (1) report a provocative finding—that, among a large group of women diagnosed with breast cancer in the Northern California Kaiser Permanente population, those who had been users of lipophilic statin drugs (e.g., simvastatin, lovastatin, and fluvastatin) before their diagnosis were more likely to present cancers having a more favorable prognostic profile. Specifically, statin users were less likely to have breast cancers not expressing estrogen and progesterone receptors (ER and PR negative; 11% of statin users had cancers that were ER–/PR– versus 19% of nonusers,  $P = 0.02$ ). Statin users were also less likely to have breast cancers that were of high histologic grade (27% versus 35%), and they were less likely to have regional stage disease (21% versus 29%). A very recent report by another research group that is following Northern California and Utah Kaiser Permanente breast cancer patients may also be relevant to these observations. Kwan and colleagues have observed that breast cancer patients who took statins after diagnosis were less likely to have had recurrences than were patients who did not take statins (4.7% versus 13.2%,  $P$  for linear trend with duration of use = 0.02; ref. 2). Is it really possible that statins might switch breast cancers to a more favorable phenotype?

A full explanation of Kumar and colleagues' observed association between statin use and the breast cancer phenotype is precluded by the fact that they studied only women with breast cancer. In case-only studies of this type, there are three possible explanations, apart from chance, for any observed association: effects on numerators, effects on denominators, or effects on both. Here, I will briefly comment on the strength of the evidence for each of these three possible explanations for the observation by Kumar: that statins might increase risk of ER+ breast cancer, that statins might decrease risk of ER– breast cancer, or that statins might somehow switch early breast cancers from an ER– to an ER+ phenotype.

The possibility that statins might substantially increase risk for ER+ cancers seems unlikely. Systematic reviews and meta-analyses clearly show that there is no meaningful association between statin use and risk for all-sites cancer (3-5) nor, specifically, for breast cancer (6, 7). Among the three trials of lipophilic statins, the

relative risk for breast cancer was marginally lower than among the four trials using a nonlipophilic statin (0.89 versus 1.15), but this was not a statistically significant difference (6). Three large case-control studies and two examinations of large administrative databases showed no association between breast cancer risk and statin use, but none of those studies assessed risk separately by ER status (8-12). Despite this limitation, this large body of evidence suggests that any effects of statins on ER+ breast cancer would need to be quite small, as more than 80% of all incident breast cancers in the age group taking statins would have been ER+.

The possibility that statins might affect risk for ER– cancers is less certain. Three cohort studies have reported findings stratified by ER status (13-15). In the Nurses' Health Study, neither ER+ nor ER– breast cancer risk was associated with statin use (based on 21 exposed ER–/PR– cases; ref. 13). In the Women's Health Initiative cohort, lipophilic statins were associated with lower breast cancer risk than were other statins (relative risk, 0.82; 95% confidence interval, 0.70-0.97 versus relative risk, 1.14; 95% confidence interval, 0.92-1.42). Although the Women's Health Initiative report did not present risks separately by ER status, overall statin users (about 65% of whom used lipophilic statins) had a somewhat lower proportion of cancers that were ER– than did nonusers (15.9% versus 17.5% based on 37 exposed ER– cases,  $P > 0.05$ ; ref. 14). In a study of a cohort of women from the Group Health Cooperative in the Seattle area, no evidence of reduced risk for either ER+ or ER– breast cancer was observed for statin users (based on 20 ER–/PR– exposed cases; ref. 15). In total then, including the case-only study by Kumar et al. (based on 34 ER–/PR– exposed cases), the observational studies are inconclusive about whether lipophilic statins might reduce risk for ER–/PR– breast cancer. There are, however, biological mechanisms that might explain an effect of statins specific to ER– breast cancer. Lipophilic statins have been shown, in preclinical model systems, to be capable of affecting proliferation, apoptosis, and cell cycle regulation pathways that are preferentially used by ER–/PR– cancer cells (16, 17).

The possibility posed by Kumar and colleagues that statins might be capable of throwing an invisible switch to induce the expression of hormone receptors in breast cancers before their clinical diagnosis is an especially intriguing new idea: "One possible explanation of the discrepant data is that statins may exert their effect by altering the phenotype of emergent breast cancers, reducing the proportion of ER–/PR– cancers rather than reducing the total number of breast cancers that develop(1)." The potential to switch-on ER is not only imaginable, but it has been proven in the example of

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histone deacetylase inhibitors, which can induce ER expression in ER- cell lines (18). Recent trends in breast cancer incidence are consistent with the hypothesis that there may be factors at play in the population that are switching the breast cancer phenotype. Glass et al. (19) recently reported on trends in breast cancer over time, showing a remarkable mirror image of decreasing incidence of ER- breast cancer coincident with increases in incidence of ER+ breast cancer. If statin use is throwing this type of switch, then the apparently contradictory observations of no overall effect of statins on breast cancer risk but an effect of statins on the phenotype of breast cancer at presentation could be explained.

Researchers now need to examine their data on the specific effects of lipophilic statins on cancers defined by both ER and PR status. In addition, effects on human epidermal growth factor receptor 2 expression and on "triple-negative" breast cancers should also be assessed. More preclinical research is needed on the potential phenomenon of switching of breast cancer phenotypes by statins. Finally, a high priority needs to be placed on assessing the effects of statins on recurrence and survival after breast cancer.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References

1. Kumar AS, Benz CC, Shim V, Minami CA, Moore DH, Esserman LJ. Estrogen receptor negative breast cancer is less likely to arise among lipophilic statin users, this issue.
2. Kwan ML, Habel LA, Flick ED, Quesenberry CP, Caan B. Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. *Breast Cancer Res Treat*. Epub ahead of print 2007.
3. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006;24:4808-17.
4. Dale KM, Coleman CI, Henyan NN, White CM. Statins and cancer risk: a meta-analysis. *JAMA* 2006;295:74-80.
5. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. *J Am Coll Cardiol* 2007;50:409-18.
6. Browning DRL, Martin RM. Statins and risk of cancer: a systematic review and meta-analysis. *Int J Cancer* 2006;120:833-43.
7. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized controlled clinical trials and nine observational studies. *J Clin Oncol* 2005;23:8606-12.
8. Pocobelli G, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Hampton JM, Egan KM. Statin use and risk of breast cancer. *Cancer* 2008;112:27-33.
9. 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.
10. Coogan PF, Rosenberg L, Strom BL. Statin use and the risk of 10 cancers. *Epidemiology* 2007;18:213-9.
11. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf* 2008;17:27-36.
12. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007;115:27-33.
13. 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.
14. 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.
15. Boudreau DM, Yu O, Miglioretti DL, Buist DSM, Heckbert SR, Daling JR. Statin use and breast cancer risk in a large population-based setting. *Cancer Epidemiol Biomarkers Prev* 2007;16:416-21.
16. Sassano A, Plataniotis LC. Statins in tumor suppression. *Cancer Lett*. Epub ahead of print 2008.
17. Brown AJ. Cholesterol, statins, and cancer. *Clin Exp Pharmacol Physiol* 2007;34:135-41.
18. Zhou Q, Atadja P, Davidson NE. Histone deacetylase inhibitor LBH589 reactivates silenced estrogen receptor  $\alpha$  (ER) gene expression without loss of DNA hypermethylation. *Cancer Biol Ther* 2007;6:64-9.
19. Glass AG, Lacey JV, Jr., Carreon JD, Hoover RN. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;99:1152-61.