Statins and the Risk of Lung, Breast, and Colorectal Cancer in the Elderly

Soko Setoguchi, MD, DrPH; Robert J. Glynn, PhD, ScD; Jerry Avorn, MD; Helen Mogun, MS; Sebastian Schneeweiss, MD, ScD

Background—Although most randomized trials and meta-analyses suggest a slight or no increase in the risk of cancer in statin users, results from observational studies have been conflicting, and some have even suggested a large protective effect of statins on certain cancers. Long-term statin users tend to be healthier, less frail, and more adherent to therapy than nonusers, however. This could explain such apparent “protective” effects.

Methods and Results—We conducted the present cohort study by linking data from a large state drug benefit program with cancer registry data and Medicare healthcare utilization data. We identified all initiators of statins; initiators of glaucoma medications, another preventive drug, served as a comparison group. Outcomes included all registry-identified cases of colorectal, lung, and breast cancer. Multivariable Cox proportional models were used to adjust for confounding. Patient characteristics were similar in both groups, but statin initiators (n=24,439) were slightly younger and used some services more frequently than glaucoma drug initiators (n=7,284). The mean follow-up was 2.9 years, with the longest follow-up being 8.4 years. Incidence rates of colorectal, lung, and breast cancers in both groups were very similar to rates in the general population. Adjusted hazard ratios were 0.96 (95% CI, 0.70 to 1.31) for colorectal cancer, 1.11 (95% CI, 0.77 to 1.60) for lung cancer, and 0.99 (95% CI, 0.74 to 1.33) for breast cancer.

Conclusions—These data from a large population of typical older patients who began using statins indicate that it is unlikely that statins confer a clinically important decrease or increase in the risk of colorectal, lung, or breast cancer over the durations studied. (Circulation. 2007;115:27-33.)

Key Words: statins cancer morbidity age
utilization data from Medicare and Pennsylvania State Cancer Registry data. Pharmaceutical Assistance Contract for the Elderly is a state program of reimbursement for drug expenses for nonindigent elderly (age ≥65 years) who meet criteria for an annual income (<$13,000 if single and <$16,200 if married). The Medicare/Pharmaceutical Assistance Contract for the Elderly data provide basic demographic information and coded diagnostic, procedural, and pharmacy-dispensing information. The quality and completeness of Medicare claims data and Pharmaceutical Assistance Contract for the Elderly dispensing data are well characterized.27-29 The Pennsylvania Cancer Registry is a population-based registry that routinely collects data on demographics, primary tumor site, morphology, and stage at diagnosis for all cancer patients in that state. It is certified as "gold" (the highest quality) by the North American Association of Central Cancer Registries.30 The Institutional Review Board of the Brigham and Women's Hospital approved the present study, and data use agreements were established. All potentially traceable personal identifiers were removed from the data before analyses to protect patients' privacy.

The study population consisted of all subjects aged 65 years or older who were enrolled in Medicare and the drug benefit programs from 1994 to 2003. To ensure active system use, subjects were required to have had at least 1 clinical encounter and a prescription for any drug during each of 2 consecutive 6-month periods before cohort entry. Patients were excluded if they had a previous diagnosis of a cancer of interest recorded in the registry (1988 to 2003) before cohort entry.

Cohort Definition
We first identified all patients who filled a prescription for a statin during the period 1994–2002. To achieve a more homogeneous mix of users with regard to disease risk, we restricted the cohort to initiators of statins by ensuring that the patients had not filled a prescription for at least 12 months before the first prescription. We studied statin initiators to reduce the potential for attrition of susceptible individuals because of side effects or treatment failures, which could introduce bias.31 The design also allowed us to account for duration of exposure. As a comparison group, we identified initiators of glaucoma drugs in the same study population. Users of glaucoma drugs were selected as a reference group for the following reasons. Previous studies suggested that long-term users of statins tend to be healthier, less frail physically and cognitively, and more adherent to therapy and screening than nonusers.24-28 Glaucoma drugs are another type of preventive drug, and their users are likely to have characteristics similar to those of statin users with regard to health-seeking behavior and adherence to other preventive procedures. We have previously found that statins and glaucoma drugs were both prescribed less frequently to subjects at the end of life,23 and there is no evidence that glaucoma drug users pose an increased risk of cancer compared with the general population.32,33

Exposure Definition
Adherence to statin use declines most rapidly during the first 6 months, and these nonadherent users are likely to have very different characteristics with regard to health-seeking behaviors and/or preventive procedures.24,34,35 It is also difficult to establish the association between statin use and the occurrence of cancer in nonadherent patients. Therefore, we required statin initiators to fill 3 or more prescriptions of any statin (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, or cerivastatin) during the first 180 days after initiation of the drug from this rate calculation to avoid immortal person-time bias and to account for 6 months of induction time.36 We used multivariable Cox proportional hazards regression to estimate the effects of statin use on incidence of cancer compared with glaucoma drug use. Statistical significance was assessed with 95% CIs. We tested the proportional hazards assumption by including an interaction term between time and exposure in the model. All statistical analyses were performed with the SAS statistical program (version 9, SAS, Cary, NC).

Assessment for Unmeasured Confounding With External Data and Sensitivity Analyses
Using data from the Medicare Current Beneficiary Survey (MCBS), we assessed the balance of variables not measured in our healthcare utilization data. The MCBS is conducted in a sample of Medicare beneficiaries selected each year to be representative of the current Medicare population, including both aged and disabled beneficiaries living in the community or in institutions. Previously, the data have been used to estimate the likelihood of confounding bias.37 We identified users of statins and glaucoma drugs in MCBS data from 1999 to 2001 and excluded subjects with history of breast, colorectal, or lung cancers. We estimated the prevalence of smoking status, body mass index, functional status, education, and aspirin use in users of statins versus glaucoma drugs.

We further conducted quantitative sensitivity analyses to assess the impact of important unmeasured confounders, ie, smoking, aspirin use, and family history of cancer, using the estimated prevalence of these covariates in glaucoma users from MCBS data.38 We assumed that the rate ratio (RR) of the association between smoking (ever versus never) and lung cancer was 11.6 from the estimates for current smoking versus nonsmoking in US data39 and that the effect of aspirin was RR = 0.6 for colorectal cancer.40 Because prevalence of family history of cancer was not available in MCBS data, we assumed the prevalence of family history of lung and breast cancer was 15%41,42 in glaucoma drug users, with an effect size of approximately RR = 2.0 (RR = 1.8 for lung cancer, with greater risk in younger subjects43 and RR = 1.5 for breast cancer in elderly women44). We did not perform sensitivity analyses for family
history with regard to colorectal cancer because family history is a strong risk factor in younger populations (especially those aged <45 years) but not in older populations.45

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Patients and Their Characteristics
After the application of exclusion and inclusion criteria, the cohort consisted of 24,439 statin initiators and 7284 glaucoma drug initiators. The characteristics of the study population measured during the 12-month period before the initiation of either drug class are shown in Table 1. In general, glaucoma users were slightly older than statin users but had comparable characteristics for health service utilization, use of preventive services, and observable risk factors for the cancers of interest.

Incidence Rates of Cancers
Table 2 shows the number of cancers, person-years of follow-up, and incidence of colorectal, lung, and invasive breast cancer in the cohort and in the general population standardized for age and gender with Surveillance, Epidemiology, and End Results data.46 The majority of cases in statin users (61% of colorectal cancers and 77% of breast cancers) occurred after 3 years of drug use, whereas 41% of lung cancers occurred after 3 years. The cancer rates we observed in the present study population were comparable to cancer incidence rates in the US general population.

Cancer Risk in Statin Users
Table 3 shows unadjusted, age/gender/race–adjusted, and multivariable adjusted hazard ratios (HRs) of invasive colorectal cancer, lung cancer, and invasive breast cancers. The total numbers of cancers after the exclusion of in situ cancers were 233 for colorectal cancer and 268 for breast cancer. We found no meaningful increase or decrease in the risk of cancers in statin users compared with that in glaucoma drug users. In a secondary analysis, we included in situ cases in the outcome for colorectal and breast cancers. The multivariable adjusted HRs including in situ cases were unchanged: 0.97 (95% CI, 0.74 to 1.28) for colorectal cancer and 0.93 (95% CI, 0.68 to 1.26) for breast cancer. We also examined the effects of different types of statins. The HR estimates for hydrophobic statins (simvastatin, lovastatin, fluvastatin, and atorvastatin47) and for pravastatin were not meaningfully different from the overall result (point estimates ranged from 0.87 to 1.18).

The test for proportional hazard was statistically significant for breast cancer (P=0.003), which indicates that the effect of statin use might be different over time. It was not significant for colorectal cancer (P=0.39) or lung cancer (P=0.65). Table 4 shows point estimates for short-term effects of statins (=3 years) and longer-term effects (>3 years). The short-term effect of statins tended to be protective for breast cancer.

Balance in Unmeasured Factors in MCBS Data
Compared with glaucoma drug users, statin users were more educated, less functionally limited, had a slightly higher mean body mass index, and were more likely to have been smokers and to take aspirin (Table 5).

Sensitivity Analyses on Unmeasured Confounders
The Figure shows the impact of 3 important unmeasured confounders on our observed null effect of statin use on incident cancer. Given the estimated prevalence of smoking and aspirin use in the MCBS survey data, we concluded that the corrected HR would be 0.90 for smoking and 1.02 for aspirin use (see the 2 circled points in the Figure). Because there is no evidence that family history of cancer is associated with statin use versus glaucoma drug use, we can assume that the prevalence in statin users would reasonably be in the
range of 5% to 30% compared with the prevalence of 15% in the general population; then, the corresponding range of corrected HR was 0.87 to 1.07.

**Discussion**

We estimated the risk of common solid cancers among new users of statins compared with new users of glaucoma drugs, and we found no significant increase or decrease in the risk of cancers among statin users. The present study has several strengths compared with earlier studies. First, we restricted the analysis to new users of statins, eliminating the biases that can occur when prevalent drug users are included.31 Second, we used a comparison group likely to have similar characteristics in health-seeking behaviors and adherence to screening procedures.23 Third, the present study considered of a very large group of older adults at high risk of cancer. Finally, we used registry-validated cancer diagnosis to measure outcomes.

An overview11 of RCTs of statins reported no significantly increased risk of cancer (RR, 1.07; 95% CI, 0.90 to 1.26), and 3 meta-analyses found the same result.6,12,13 A nested case-control study using healthcare utilization databases in Quebec, Canada, compared statin users with resin users aged 65 years and older and found no increase but a decrease in cancer outcomes.14 The incidence of colorectal cancer among long-term statin users was 33% lower in observational studies compared with short-term users or nonusers among the elderly (aged ≥65 years) and reported a 68% reduction in the risk of breast cancer in statin users. A population-based case-control study of 3 Washington counties showed no significant reduction of the risk for invasive breast cancer (RR ranged from 0.9 to 1.2). Most recently, large cohort studies in the United States found no association between statin use and colorectal and breast cancer. Although the populations in most trials and these observational studies were relatively young compared with the present study population, our findings are similar to the meta-analyses and the most recent studies, and the point estimates from all the other studies are included within the 95% CIs of our estimates.

The results of the present study exclude the strong protective effect of statins found in observational studies in the elderly by Cauley et al and Poynter et al. Cauley et al conducted a prospective cohort study in US elderly women (aged ≥65 years) and reported a 68% reduction in the risk of breast cancer in statin users. A population-based case-control study in northern Israel by Poynter et al reported a 47% reduction in colorectal cancer among long-term statin users (≥5 years) compared with short-term users or nonusers among the elderly (aged ≥60 years). As we have pointed out, however, long-term statin users are likely to be systematically different from nonusers of statins. Health-seeking behavior and the healthier lifestyle of long-term compliant statin users may independently lower the risk of colorectal cancer. In addition, prevention-oriented statin users may be more likely to have precancerous colorectal polyps detected and removed early, which would make statins appear protective. These studies by Poynter et al and Cauley et al may have failed to adjust adequately for these factors, likely leading to residual confounding. The present study attempted to adjust for these possible biases by choosing equally compliant glaucoma drug users as a comparison group. These patients take another kind of preventive drug that, like statins,

**Table 2. Unadjusted Incidence Rate of Cancer and Its Comparison With Surveillance, Epidemiology, and End Results Data**

<table>
<thead>
<tr>
<th></th>
<th>Statin Users</th>
<th>Glaucoma Drug Users</th>
<th>SEER Population (Aged ≥65 Years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-Years of Follow-Up</td>
<td>Incidence Rate</td>
<td>Incidence Rate</td>
<td>Incidence Rate</td>
</tr>
<tr>
<td><strong>No.</strong></td>
<td><strong>(per 100 000)</strong></td>
<td><strong>(per 100 000)</strong></td>
<td><strong>(per 100 000)</strong></td>
</tr>
<tr>
<td>All colorectal cancer</td>
<td>190</td>
<td>59640.9</td>
<td>318.6</td>
</tr>
<tr>
<td>All lung cancer</td>
<td>179</td>
<td>59907.7</td>
<td>298.8</td>
</tr>
<tr>
<td>All breast cancer</td>
<td>227</td>
<td>49910.6</td>
<td>454.8</td>
</tr>
<tr>
<td>Invasive colorectal cancer</td>
<td>178</td>
<td>59640.9</td>
<td>298.5</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>203</td>
<td>49910.6</td>
<td>406.7</td>
</tr>
</tbody>
</table>

*SEER indicates Surveillance, Epidemiology, and End Results.
†SEER-based general population incidence rate standardized for the age and gender of the study population.

**Table 3. Effects of Statin Use on Invasive Colorectal Cancer, Lung Cancer, and Invasive Breast Cancer**

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Invasive Colorectal Cancer</th>
<th>Lung Cancer</th>
<th>Invasive Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
</tr>
<tr>
<td>Unadjusted*</td>
<td>0.92</td>
<td>0.68</td>
<td>1.24</td>
</tr>
<tr>
<td>Adjusted for sex/age/race†</td>
<td>0.99</td>
<td>0.72</td>
<td>1.36</td>
</tr>
<tr>
<td>Multivariable‡</td>
<td>0.96</td>
<td>0.70</td>
<td>1.31</td>
</tr>
</tbody>
</table>

* Cox proportional hazard regression with study time as a time scale.
† Cox proportional hazard regression with study time as a time scale and age, race, and sex in the model.
‡ Multivariable Cox proportional hazard regression with study time as a time scale and including covariates in Table 1 in the model.
is less frequently prescribed to subjects at the end of life.23,54
We found that use of preventive procedures in glaucoma drug
users was comparable to that of statin users (Table 1).

Long-term statin users have survived and stayed healthy
enough to continue to take statins. As a result, in many
studies, patients who are vulnerable or susceptible to cancer
or other morbid conditions drop out of the long-term statin
user cohort, leaving those who are healthier and less suscep-
tible to the risk of cancer (attrition of susceptible individuals).
This bias can be avoided by employing a study design that
enrolls only initiators of statins or a comparison drug and by
comparing their risk at the same point over the course of drug
exposure in a Cox model, as we did here. A naïve case-
control design (without risk-set sampling) simply comparing
long-term users of statins with nonusers has difficulty han-
dling this bias.

The present results raise the possibility that the short-term
effect of statins on breast cancer might differ from that of

long-term use, with short-term use appearing modestly pro-
tective and long-term use seeming to raise the risk slightly,
although not significantly. Although we have adjusted for
screening behaviors of the study patients, it is possible that
statin users had relatively more extensive screening before
they reached 65 years of age that was not captured in our data
and therefore had fewer events during the first years after
their enrolment into Medicare and initiation of statins. The
present data do not rule out a possibly increased risk of cancer
for long-term statin users beyond the range of our data.

Several limitations of the present study should be noted. A
number of possible confounders were not measured in the
data (eg, aspirin use and family history of cancer) or were
measured incompletely (eg, tobacco use and obesity). These
unmeasured risk factors might have biased results if they
were differentially associated with statin versus glaucoma
drug use. We might have been able to reduce much of this
confounding by the choice of comparison group. Using
MCBS data, we found that some of the possible confounding
factors unmeasured in our data, such as body mass index,
smoking, functional status, and aspirin use, were slightly
imbalanced; however, sensitivity analyses showed that these
differences were not substantial enough to cause significant

### Table 4. Short-Term vs Long-Term Effect of Statin Use on Selected Cancers

<table>
<thead>
<tr>
<th></th>
<th>Short-Term Users (&lt;3 Years)</th>
<th>Long-Term Users (≥3 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Exposed Cases</td>
<td>HR</td>
</tr>
<tr>
<td>Invasive colorectal cancer*</td>
<td>74</td>
<td>0.93</td>
</tr>
<tr>
<td>Lung cancer*</td>
<td>99</td>
<td>1.18</td>
</tr>
<tr>
<td>Invasive breast cancer*</td>
<td>47</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Multivariable Cox proportional hazard regression with study time as a time scale and including covariates in Table 1 in the model.

### Table 5. Unmeasured Patient Characteristics by Drug Use Categories in Noninstitutionalized Medicare Beneficiaries Aged ≥65 Years (MCBS 1999 and 2001)

<table>
<thead>
<tr>
<th></th>
<th>Statin Users</th>
<th>Glaucoma Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>3569</td>
<td>894</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>75 (6)</td>
<td>80 (7)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>27 (5)</td>
<td>25 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Bedridden status, %</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bedridden</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>Not bedridden</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Functional limitation, %</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Any difficulty in activities of daily living</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>No difficulty in activities of daily living</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>High school or less</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or more</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Taking aspirin, %</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Sensitivity analysis: effect of unmeasured confounding factors.
The curves represent how the “true” or corrected RR changes
with various values of prevalence of unmeasured confounders in
statin users. For glaucoma drug users, the prevalence of aspirin
use and smoking is fixed using the estimates for glaucoma
users in the MCBS data, and the prevalence of family history of
lung and breast cancer is assumed to be 15% based on esti-
mates from the general population. The 2 circled points repre-
sent the corrected RR for the values of prevalence of smoking
and aspirin use in statin versus glaucoma users in MCBS data.
No estimates for family history of cancer were available from
MCBS data, but we expect that the prevalence in statins users
will be similar to 15%, which is the estimate for the general
population.
bias in our estimates. Finally, although we believe that new glaucoma drug users are a more valid comparison group than nonusers of statins, the size of the group was smaller than the statin user group and resulted in less precise estimates.

The mean duration of drug use in the present study population was 2.9 years, slightly longer than that of the RCTs criticized for having a relatively short follow-up.6,11–13 Nonetheless, the study population included patients with various durations of follow-up (maximum of 8.4 years), and 40% of the patients had a follow-up of more than 3 years, with 60% of cancers occurring after 3 years of follow-up. Assessment of the possibility of different risk with longer use will require studies with greater exposure durations.

The present data indicate that in the first several years of statin use, it is unlikely that elderly patients have a clinically important decrease or increase in the risk of colorectal, lung, or breast cancer compared with elderly patients using other, unrelated preventive medications. The present data do not rule out a possibly increased risk of long-term statin use beyond the period of exposure studied, however.

Disclosures
Dr Glynn reports that he has a contract with AstraZeneca to serve as the independent statistical monitor of its trial of Crestor (rosuvastatin; JUPITER trial). The remaining authors report no conflicts.

References
CLINICAL PERSPECTIVE

In addition to extensive evidence proving the benefit of statins on cardiovascular morbidity and mortality, recent observational studies have suggested that these drugs might reduce the risk of several cancers; however, long-term statin users tend to be healthier, less frail, and more adherent to therapy and screenings than nonusers. This could explain such apparent “protective” effects of the drug on other outcomes. In contrast, most randomized trials and meta-analyses suggest little or no change in the risk of cancer among patients taking statins. We conducted a cohort study to assess the effect of statins on the incidence of lung, colorectal, and breast cancer in a large population of typical older patients. The present study supports the conclusion that statins are not associated with a clinically important decrease or increase in the risk of cancer in the elderly over the duration studied (mean follow up was 2.9 years, with the longest follow-up being 8.4 years). Until proven otherwise in clinical trials, physicians may not prescribe statins for cancer prevention. These findings suggest that statin use in the elderly should be based solely on the evidence of its cardioprotective effects and previously documented adverse effects rather than on any supposed effect on cancer risk.
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