Research Article

Statin Use and Colorectal Cancer Risk According to Molecular Subtypes in Two Large Prospective Cohort Studies

Jung Eun Lee1, Yoshifumi Baba2, Kimmie Ng2, Edward Giovannucci3,5, Charles S. Fuchs2,3, Shuji Ogino2,4, and Andrew T. Chan3,6

Abstract

Use of statins is hypothesized to reduce colorectal cancer risk but the evidence remains inconsistent. This may be partly explained by differential associations according to tumor location or molecular subtypes of colorectal cancer. We examined the association between statin use and colorectal cancer risk according to tumor location, KRAS mutation status, microsatellite instability (MSI) status, PTGS2 (COX-2) expression, or CpG island methylator phenotype (CIMP) status in two large prospective cohort studies, the Nurses’ Health Study and Health Professionals Follow-up Study. We applied Cox regression to a competing risks analysis. We identified 1,818 colorectal cancers during 1990 to 2006. Compared with nonusers, current statin use was not associated with colorectal cancer [relative risk (RR) = 0.99, 95% CI = 0.86–1.14] or colon cancer (RR = 1.10, 95% CI = 0.94–1.29) but was inversely associated with rectal cancer (RR = 0.59, 95% CI = 0.41–0.84, p heterogeneity < 0.001). When we examined the association within strata of KRAS mutation status, we found no association with KRAS-mutated cancers (RR = 1.20, 95% CI = 0.87–1.67) but did observe a possible inverse association among KRAS wild-type cancers (RR = 0.80, 95% CI = 0.60–1.06, p heterogeneity = 0.06). The association did not substantially differ by PTGS2 expression, MSI status, or CIMP status. Current statin use was not associated with risk of overall colorectal cancer. The possibility that statin use may be associated with lower risk of rectal cancer or KRAS wild-type colorectal cancer requires further confirmation. Cancer Prev Res; 4(11); 1808–15. ©2011 AACR.

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are widely used in the treatment of hypercholesterolemia. In experimental studies, statins inhibit colorectal carcinogenesis. However, human studies have been inconsistent. In some case-control studies, statins are associated with a reduction in the risk of colorectal cancer, but most cohort studies and secondary analyses of randomized clinical trials have not shown a benefit (1–3).

These conflicting data may be, in part, related to the molecular heterogeneity of colorectal cancer. Cancers have distinct molecular alterations that may predict variation in clinical behavior or responsiveness to therapeutic agents as well as reflect differences in etiopathogenic mechanisms. Statins inhibit generation of mevalonate, a precursor for synthesis of isoprenoids used in prenylation, a necessary posttranslational step for functional KRAS. Similarly, statins have been hypothesized to be anti-inflammatory in some studies and function synergistically with drugs containing COX-2 [PTGS2 (COX-2)] activity such as aspirin and nonsteroidal anti-inflammatory drugs (NSAID; refs. 4–7). In addition, clinical features and risk factors appear to vary according to microsatellite instability (MSI) status, CpG island methylator phenotype (CIMP) status, or tumor location (8–13). We therefore prospectively examined whether the association of statin use and colorectal cancer risk differed by KRAS mutation status, PTGS2 (COX-2) overexpression, MSI, or CIMP status. To our knowledge, no prior prospective studies have examined the association between statin use and colorectal cancer risk in relation to these tumor subtypes.

Materials and Methods

Study population

The Nurses’ Health Study (NHS) was established in 1976 when 121,700 female registered nurses who were 30 to 55 years old returned a mailed questionnaire. The Health...
Professionals Follow-up Study (HPFS) was initiated in 1986 when 51,529 male health professionals aged 40 to 75 years returned a mailed questionnaire. Participants provided detailed information about their medical history, lifestyle, and risk factors for chronic diseases on biennial follow-up questionnaires. Because retrospective information on statin use was collected in 2000 to define statin use from 1994 forward in the NHS and from 1990 forward in the HPFS, we started follow-up in 1994 in the NHS and 1990 in the HPFS. This approach is consistent with prior analyses in these cohorts (14, 15).

We excluded participants with missing data on statin use, had been previously diagnosed with cancer (except nonmelanoma skin cancer), or had ulcerative colitis. As a result, 91,155 women in the NHS and 40,767 men in the HPFS were available for the analysis. Because there was no heterogeneity for the association of statin use and colorectal cancer between NHS and HPFS (Pr_{heterogeneity} > 0.33 for each category of statin duration), we combined data from the 2 cohorts. The Institutional Review Boards at Brigham and Women’s Hospital and the Harvard School of Public Health approved this study.

Colorectal cancer cases and their molecular markers

Self-reported information on new diagnoses of colorectal cancers was obtained on each questionnaire; participants (or next of kin for those who died) who reported a diagnosis of colorectal cancer were asked for permission to access medical records related to the diagnosis. The National Death Index was also used to identify fatalities (16). Investigators blinded to participants’ risk factor status reviewed medical records to confirm the diagnosis and classify cancers according to anatomic location and histologic types. A total of 1,818 (952 in the NHS and 866 in the HPFS) cases were included in these analyses.

We retrieved, from the pathology departments of treating hospitals, available pathologic specimens from participants diagnosed with colorectal cancer; 438 cases (51%) diagnosed in the HPFS and 449 cases (47%) in the NHS through 2006. The baseline characteristics of participants with colorectal cancer whose tumors we analyzed were similar to those of participants whose tumors we did not analyze (17). We extracted DNA from paraffin-embedded tumor tissue sections and carried out PCR and pyrosequencing targeted for KRAS codons 12 and 13 as previously described (18). MSI status was assessed using 10 microsatellite markers (D2S123, D5S346, D17S250, BAT25, BAT26, BAT40, D18S55, D18S56, D18S67, and D18S487; ref. 19). If instability of markers was 30% or more, tumors were classified as MSI-high. We quantified DNA methylation in 8 CIMP-specific promoters [CACA1G, CDKN2A (p16), CRABP1, IGFB2, MLH1, NEUROG1, RUNX3, and SOCS1; refs. 20–22]. We defined CIMP-high if 6 or more of 8 promoters were methylated, CIMP-low if 1 to 5 of 8 promoters were methylated, or CIMP-0 if none of 8 were methylated. PTGS2 (COX-2) immunohistochemical assays were conducted from incubating deparaffinized tissue sections as previously described (19, 23). Compared with adjacent normal colonic mucosa, PTGS2 overexpression in tumor cells was classified using a standardized grading system (absent, weak, moderate, or strong). The pathologist classified staining of tumor cells as “absent” if PTGS2 expression was at the same level of intensity as adjacent normal colonic epithelium; weak, moderate, or strong staining indicated progressively increasing degrees of overexpression (17, 23). Consistent with our prior analyses, absent or weak overexpression was categorized as PTGS2 negative and moderate or strong was categorized as PTGS2 positive. A pathologist (S. Ogino) blinded to statin use or any other data interpreted tumor marker status. A random sample of 108 cancers was reread by a second pathologist unaware of the data on the participants; the concordance between the 2 pathologists was 0.92 (K = 0.62; P < 0.0001; ref. 17).

Assessment of statin use

In 2000, women in the NHS were asked whether they regularly used statins and their duration of statin use in categories (0–2, 3–5, and 6+ years). Similarly, men in the HPFS were asked whether they regularly used statins and their duration of statin use in categories (1–2, 3–5, 6–9, and 10+ years). We did not specifically query participants about the dose of statin use. Consistent with prior studies (14, 15), we retrospectively defined statin use from 1994 forward in the NHS and from 1990 forward in the HPFS using the 2000 questionnaire. Participants updated their current use of statins on each biennial questionnaire after 2000. Duration of statin use was calculated by using the retrospective responses on the 2000 questionnaires and updating the subsequent responses to current use on the biennial questionnaires from 2002. Our assessment of covariates for our analyses has been previously reported (24).

Statistical analysis

We calculated the relative risks (RR) and 95% CIs associated with current statin use for each study using the Cox proportional hazards model (25) with SAS PROC PHREG (26). Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the date of colorectal cancer diagnosis, date of death, or end of follow-up (May 31, 2006, for women and January 31, 2006, for men), whichever came first. We stratified the data by study, age, and calendar year of the current questionnaire cycle. Because participants may have varied their use of statins over the study period, we used time-varying covariates such that each individual participant contributed person-time according to the statin data they provided on each biennial questionnaire. Consistent with secular patterns in the chronic use of these drugs, very few individuals who reported current use subsequently discontinued use (e.g., only 4% of those who used statins in 2000 did not continue using them through 2004). Thus, we did not have a sufficiently large enough number of former users to conduct a statistically robust analysis of former use; if a participant subsequently reported
discontinuing use, he/she then contributed person-time to the category of nonusers. In the multivariate models, we adjusted for time-varying covariates listed in the footnotes of the tables.

We used a competing risk analysis using duplication method Cox regression to examine whether the association between statin use and colorectal cancer differed by tumor sites or molecular subtypes (27, 28). To test for the difference between tumor sites or molecular subtype, we compared the model fit that produces separate associations of statin use with different tumor sites or molecular markers to the model fit that assumed a common association using the likelihood ratio test. For the test for trend, participants were assigned the median value of statin duration and this variable was entered into the model as a continuous term. To examine whether the association for statin use varied by body mass index (BMI), age, aspirin use, and alcohol intake, a likelihood ratio test was used to compare the model fit including the cross-product term of statin use and the specific modifier with the model fit without the cross-product term. All statistical tests were 2 sided, and values of \( P < 0.05 \) were considered statistically significant.

### Results

Table 1 shows the characteristics of 91,155 eligible women and 40,767 eligible men according to duration of statin use reported in 2000. Women and men who used statins were more likely to be older, to use aspirin and multivitamins, to have ever had endoscopy, and to smoke in the past than those who did not use statins. Women who used statins were more likely to have higher BMI and less likely to drink alcohol. Compared with nonusers, the prevalence of hypercholesterolemia (\( \geq 240 \text{ mg/dL} \)) was higher among those men and women who began to use statins recently. In contrast, the prevalence of hypercholesterolemia was generally lower for men and women who had been on long-term statin treatment.

| Table 1. Characteristics of participants in 2000 according to statin use in the NHS and HPFS* |
|-----------------------------------------------|------------------|------------------|------------------|
| | Nonusers | <2 y | 3–5 y | ≥6 y |
| NHS | | | | |
| No. of participants | 75,597 | 7,672 | 5,048 | 2,838 |
| Age, y | 66.4 | 67.7 | 68.3 | 69.2 |
| BMI, kg/m² | 23.0 | 27.3 | 27.5 | 26.9 |
| Alcohol intake, g/d | 5.1 | 4.3 | 4.3 | 4.5 |
| Red meat intake, servings/d | 0.9 | 0.9 | 0.9 | 0.9 |
| Aspirin use, b ≥2 tablets/wk (%) | 14.3 | 25.5 | 25.6 | 29.4 |
| Ever had endoscopy, % | 52.5 | 59.0 | 60.6 | 63.0 |
| Smoking status, % | | | | |
| Past | 45.2 | 48.4 | 48.7 | 51.7 |
| Current | 9.5 | 8.7 | 9.6 | 9.2 |
| Current multivitamin use, % | 53.6 | 67.7 | 66.6 | 67.2 |
| Serum cholesterol levels, c ≥240 mg/dL (%) | 13.0 | 23.1 | 12.3 | 14.9 |
| HPFS | | | | |
| No. of participants | 33,685 | 3,315 | 2,299 | 1,468 |
| Age, y | 67.9 | 67.4 | 68.0 | 68.7 |
| BMI, kg/m² | 20.2 | 26.0 | 26.4 | 26.3 |
| Alcohol intake, g/d | 10.8 | 11.0 | 11.1 | 11.2 |
| Red meat intake, servings/d | 1.2 | 1.0 | 1.0 | 0.8 |
| Aspirin use, b ≥2 days/wk (%) | 28.9 | 62.3 | 66.5 | 67.1 |
| Ever had endoscopy, % | 68.8 | 78.1 | 78.2 | 79.1 |
| Smoking status, % | | | | |
| Past | 48.6 | 52.8 | 55.2 | 56.5 |
| Current | 5.1 | 3.8 | 3.8 | 3.2 |
| Current multivitamin use, % | 45.7 | 66.4 | 69.0 | 66.8 |
| Serum cholesterol levels, c ≥240 mg/dL (%) | 6.3 | 7.8 | 2.7 | 4.1 |

*Values are standardized to the age distribution of the study except age. Mean values except those presented as percentages.

bStandard (326 mg) tablets.

cSelf-reported total serum cholesterol level.
We documented 1,818 colorectal cancers (952 in women and 866 in men) over 1,688,745 person-years of follow-up. We observed no significant association between the duration of statin use and overall risk of colorectal cancer (Table 2). The age-adjusted RR of colorectal cancer was 0.85 (95% CI = 0.66–1.10) comparing 6 or more years of statin use to nonusers. When we additionally adjusted for use of aspirin and history of endoscopy, the RR was attenuated (multivariate RR = 0.97, 95% CI = 0.75–1.25). Further adjustment for other covariates did not alter the association (multivariate RR = 0.97, 95% CI = 0.75–1.25).

We examined whether the association between statin use and colorectal cancer varied according to the anatomic site of the tumor (Table 3). Compared with nonusers, statin users did not have a lower risk of colon cancer (multivariate RR = 1.10, 95% CI = 0.94–1.29); similarly, there was no association with cancer of the distal colon (multivariate RR = 0.97, 95% CI = 0.79–1.34) or proximal colon (multivariate RR = 1.14, 95% CI = 0.93–1.39) cancer. In contrast, the effect of statins appeared to differ for rectal cancer compared with colon cancer (P_{heterogeneity} < 0.001). Compared with nonusers, statin users had a significantly lower risk of rectal cancer (multivariate RR = 0.59, 95% CI = 0.41–0.84).

We confirmed that the lack of association between statin use and risk of colorectal cancer was consistent for cases with tissue available for analysis of molecular subtypes (multivariate RR = 0.92, 95% CI = 0.74–1.13; Table 4) compared with cases without available tissue (multivariate RR = 1.07, 95% CI = 0.89–1.29). We evaluated the influence of statins on risk of colorectal cancer according to KRAS mutation status. Compared with nonusers, we found a lower, but nonsignificant, risk of KRAS wild-type cancer in statin users (multivariate RR = 0.80, 95% CI = 0.60–1.06). In contrast, statin use was not associated with the risk of KRAS-mutated colorectal cancer (multivariate RR = 1.20, 95% CI = 0.87–1.67). A formal test for heterogeneity for the association of statin use with KRAS-mutated or KRAS wild-type tumors approached statistical significance (P_{heterogeneity} = 0.06). When we confined the analysis to rectal cancers, we also observed a nonsignificant inverse association between statin use and risk of KRAS wild-type rectal cancers (multivariate RR = 0.65, 95% CI = 0.32–1.32) but not KRAS-mutated rectal cancer (multivariate RR = 0.90, 95% CI = 0.42–1.94).

We also examined the effect of statins according to PTGS2 (COX-2) overexpression, MSI, or CIMP status. There did not appear to be any differential association between statin use and risk of PTGS2-positive tumors compared with PTGS2-negative tumors (P_{heterogeneity} = 0.40), tumors defined as MSI-high compared with microsatellite stability (MSS) or MSI-low (P_{heterogeneity} = 0.50) or tumors defined as CIMP-high compared with CIMP-low/CIMP-0 (P_{heterogeneity} = 0.83).

Finally, we examined whether the associations between statin use and colorectal cancer varied by subgroups defined by other colorectal cancer risk factors including BMI (<23, 23 to <25, 25 to <28, 28 to <30, and ≥30 kg/m² in the NHS; <23, 23 to <25, 25 to <30, 30 to <35, and ≥35 kg/m² in the HPFS), family history of colorectal cancer in parents and siblings (yes and no), history of endoscopy (yes and no), red meat intake (quintiles), alcohol intake (never, 0.1–9.9, 10–14.9, 15–29.9, and ≥30 g/d), and total energy intake (continuous).
cancer. However, we did observe a potential inverse association with risk of rectal cancer. In addition, our results suggest a possible differential association according to KRAS mutation status. To our knowledge, our study is the first to examine statin use and colorectal cancer according to molecular features of the tumor.

Substantial experimental data support a potential anticancer effect of statins. Statins induce apoptosis, inhibit cell proliferation, attenuate angiogenesis, and delay the metastatic process in in vitro and in vivo studies (29–33). However, the results from human studies have not been consistent. Two systematic reviews observed modest reductions in colorectal cancer with statin use in case–control studies, but no clear association in randomized clinical trials or cohort studies (1–3, 34). The lack of association between statin use and overall colorectal cancer we observed in this study is largely consistent with prior cohort studies. Generally, cohort studies may be less prone to the biases of case–control studies, which include differential sampling of cases and controls and differential recall of statin use or other confounding factors by cases compared with controls.

We did observe a potential inverse association between statin use and rectal cancer. Because this finding is based on a relatively limited number of rectal cancer cases, these results should be interpreted cautiously. However, a test for heterogeneity of the association of statin use with colon or rectal cancer was statistically significant and a differential effect by site is biologically plausible. There are significant differences in risk factors, prevalence of specific molecular alterations, and gene expression levels that have been described according to cancer site (10, 35, 36). A few studies have similarly observed inverse associations between statin use and rectal cancer (37–39). Statin use was associated with 30% to 62% lower risk of rectal cancer in case–control studies that included 136 cases in United States (39) and 344 cases in Israel (38). Using information from a pharmacy database linked to hospital records in the Netherlands, a prospective cohort study observed a RR of 0.48 (0.95% CI = 0.16–1.48) of rectal cancer associated with statin use. However, others have not found inverse associations (40–44). Further investigation of the effect of statins on rectal cancer compared with colon cancer is warranted.

We examined the effect of statin use according to risk of cancers defined by KRAS mutation status. Although the specific mechanism by which statins are chemopreventive is not known, statins are hypothesized, at least in part, to modulate KRAS, which mediates downstream signaling of the epidermal growth factor receptor (EGFR). Statins inhibit the mevalonate pathway thereby suppressing biosynthesis of cholesterol as well as isoprenoids used for the posttranslational prenylation of RHO and RAS proteins including KRAS. Prenylation is a requisite step for functional KRAS in its signaling and transforming activities (6). Mutations in KRAS, found in 40% of colorectal cancers, lead to a constitutively active state of cell growth and proliferation independent of EGFR signaling. Previous work has shown that EGFR inhibitors are effective in treatment of KRAS wild-type colorectal cancer but not KRAS mutant colorectal cancer (45). Our data similarly suggest that a potential inverse association between statin use and colorectal cancer may be limited to KRAS wild-type tumors. This highlights the possibility that statins have a more important effect on KRAS signaling driven by EGFR activation than KRAS that is permanently activated through mutation. Nonetheless, these findings should be interpreted with caution, as the P value for interaction was not statistically significant, particularly in view of the multiple hypotheses tested.

Beyond mevalonate pathways, statins have been proposed to inhibit cancer through their anti-inflammatory mechanisms (46). Although experimental studies suggest that statins may act synergistically with NSAIDs (5–7), most, but not all (4), human studies have not seen significant modification of the effect of statins by concurrent use of NSAIDs (38, 39, 42, 47, 48). In our study, we also did not observe a differential effect of statin use according to use of aspirin or expression of the proinflammatory enzyme PTGS2 (COX-2). However, it remains possible that statins may have anti-inflammatory effects that are independent of aspirin- or COX-2–related pathways.

### Table 3. RRs of colon and rectal cancer according to statin use

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Nonusers</th>
<th>Current use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon and rectum&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,446</td>
<td>234</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>0.90 (0.78–1.04)</td>
</tr>
<tr>
<td>Multivariate-adjusted RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>0.97 (0.84–1.12)</td>
</tr>
<tr>
<td>Colon</td>
<td>1,083</td>
<td>199</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>1.02 (0.88–1.20)</td>
</tr>
<tr>
<td>Multivariate-adjusted RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>1.10 (0.94–1.29)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rectum</td>
<td>363</td>
<td>35</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00</td>
<td>0.54 (0.38–0.77)</td>
</tr>
<tr>
<td>Multivariate-adjusted RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>0.59 (0.41–0.84)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes cases whose cases were confirmed as colon or rectal cancer.

<sup>b</sup>Adjusted for age, calendar year, study, pack-years of smoking before age 30 (never smoker, 1–4 pack-years, 5–10 pack-years, and >11 pack-years of smoking), aspirin dose (never, past, current use 1–2, 3–5, 6–14, and >15 tablets/wk), height (continuous), BMI (<23, 23 to <25, 25 to <28, 28 to <30, and ≥30 kg/m<sup>2</sup> in the NHS; <23, 23 to <25, 25 to <30, 30 to <35, and ≥35 kg/m<sup>2</sup> in the HPFS), family history of colorectal cancer in parents and siblings (yes and no), history of endoscopy (yes and no), red meat intake (quintiles), alcohol intake (never, 0.1–9.9, 10–14.9, 15–29.9, and ≥30 g/d), and total energy intake (continuous).

<sup>c</sup>P<sub> heterogeneity</sub> for colon versus. rectum < 0.001.
Finally, we also considered the effect of statins according to tumor subtypes defined by MSI or CIMP status. About 15% of sporadic colorectal cancers are MSI-high, arising primarily through epigenetic silencing of DNA mismatch repair proteins (49). In contrast, the vast majority of sporadic colorectal cancers are MSS or MSI-low, developing through traditional chromosomal instability pathways. Colorectal cancer with CIMP-high status was associated
with MSI and is well characterized as a major epigenetic marker in colorectal cancer (13, 21, 22). However, in the present analysis, we did not observe a differential effect of statins on cancers subtyped by MSI or CIMP status.

Our study has several important strengths. First, our prospective cohort design minimized potential biases introduced by differential selection and recall found in case-control studies. Second, we collected detailed and updated information on statin use and other potential important confounding factors in a cohort with a high follow-up rate. Third, because our participants were all health professionals, the accuracy of self-reported statin use is likely to be high and is more likely to reflect their actual use than prescription records. Finally, we examined the effect of statins on molecularly defined subtypes of colorectal cancer, an example of the emerging interdisciplinary field of "Molecular Pathologic Epidemiology" (8, 50). Through molecular pathologic epidemiology studies, a known or suspected etiologic or modifying lifestyle factor, such as statin use, can be related to a specific somatic molecular change to gain insight into mechanism, provide evidence for causality, and potentially lead to more targeted approaches to prevention or therapy (8, 50).

There are several limitations to our study. First, our study is observational. Thus, we cannot rule out the possibility of residual confounding. However, our overall findings are consistent with most prospective cohort studies. Moreover, our results suggesting an inverse association with KRAS wild-type tumors have biological plausibility, given our understanding of the effect of statins on the mevalonate pathway. Second, the prevalence of statin use, especially in the longer duration categories, was relatively low. However, as a prospective cohort study, our prevalence reflects secular trends in statin use (15% of current use) in the United States over the time period of the study (1994–2006) and is consistent with the prevalence of statin use described in another U.S. population–based cohort (20% of current use) conducted in an overlapping time period (1997–2001; ref. 47). Nonetheless, as the number of individuals prescribed statins increases over time, further studies with more extended follow-up are needed. Third, we did not specifically examine different types of statins. Although it has been suggested that specific statins may have distinct effects depending on whether they are hydrophilic or lipophilic, no studies that have directly compared various statins in the same population have observed significant differences in associations. Finally, we did not have tumor tissue available from all cases of confirmed colorectal cancer ascertained in the 2 cohorts. However, the characteristics of cases without available tumor tissue did not appreciably differ from those of cases with available tumor tissue (17).

In summary, our study does not support an overall effect of statin use on risk of colorectal cancer. However, a possible inverse association with risk of rectal cancer or KRAS wild-type colorectal cancer requires further investigation. If confirmed, our results would provide mechanistic insight into the anticancer effects of statins and support the potential use of molecular markers to tailor chemoprevention.

Disclosure of Potential Conflicts of Interest

A.T. Chan has served as a consultant to Bayer HealthCare. No other potential conflicts of interest were disclosed. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH or the Damon Runyon Cancer Research Foundation.

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References

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