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ARTICLE

Relationship Between Statin Use and Colon Cancer Recurrence and Survival: Results From CALGB 89803

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Background Although preclinical and epidemiological data suggest that statins may have antineoplastic properties, the impact of statin use on patient survival after a curative resection of stage III colon cancer is unknown.

Methods We conducted a prospective observational study of 842 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial from April 1999 to May 2001 to investigate the relationship between statin use and survival. Disease-free survival (DFS), recurrence-free survival (RFS), and overall survival (OS) were investigated by Kaplan–Meier curves and log-rank tests in the overall study population and in a subset of patients stratified by *KRAS* mutation status (n = 394), and Cox proportional hazards regression was used to assess the simultaneous impact of confounding variables. All statistical tests were two-sided.

Results Among 842 patients, 134 (15.9%) reported statin use after completing adjuvant chemotherapy. DFS among statin users and nonusers was similar (hazard ratio [HR] of cancer recurrence or death = 1.04, 95% confidence interval [CI] = 0.73 to 1.49). RFS and OS were also similar between statin users and nonusers (adjusted HR of cancer recurrence = 1.14, 95% CI = 0.77 to 1.69; adjusted HR of death = 1.15, 95% CI = 0.77 to 1.71). Survival outcomes were similar regardless of increasing duration of statin use before cancer diagnosis (P_{trend} = .63, .63, and .59 for DFS, RFS, and OS, respectively). The impact of statin use did not differ by tumor *KRAS* mutation status, with similar DFS, RFS, and OS for statin use among mutant and wild-type subgroups ($P_{interaction}$ = .84, .67, and .98 for DFS, RFS, and OS, respectively).

Conclusion Statin use during and after adjuvant chemotherapy was not associated with improved DFS, RFS, or OS in patients with stage III colon cancer, regardless of *KRAS* mutation status.

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Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are widely prescribed for the treatment of hypercholesterolemia and have been shown to reduce cardiovascular events and mortality in several randomized clinical trials (1–3). Statins inhibit the conversion of HMG-CoA to the cholesterol precursor mevalonate, which is the rate-limiting step in cholesterol biosynthesis. Mevalonate is also the precursor compound for other isoprenoids, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are critical for posttranslational modification of proteins involved in cell growth, including both the RAS and RHO oncogenes (4,5). Consequently, statins are hypothesized to have antineoplastic benefits, possibly through inhibition of RAS signaling.

Several epidemiological studies have evaluated the association between statin use and the risk of colorectal cancer and yielded inconsistent results. A large retrospective case–control study in Israel demonstrated a 47% reduction in the risk of colorectal cancer after 5 years of statin use (6). Likewise, two large meta-analyses reported 12% and 13% reductions in colorectal cancer risk (7,8), respectively, after as little as 6 months of use. Nonetheless, several retrospective and prospective studies have offered conflicting results, and two other meta-analyses failed to confirm that statin use is associated with a reduction in the risk of cancer overall (9) or colorectal cancer specifically (10).

Beyond studies assessing the chemopreventative role of statins, the relationship between statin use and colon cancer patient outcome is unknown. Because of continued interest in the role of statin use in cancer risk and outcome, the National Surgical Adjuvant Breast and Bowel Project initiated the Statin Polyp Prevention Trial (protocol P-5), which is currently randomly assigning patients with resected stage I or II colon cancer to rosuvastatin (10 mg daily) or placebo treatment arms for a period of 5 years. The primary endpoint of this study is adenomatous polyp formation, metachronous colorectal carcinoma, or colon cancer recurrence. Results from this trial are not anticipated for several years. Therefore, to address the gap in knowledge, we prospectively

examined the relationship between statin use and cancer recurrence or death from any cause, cancer recurrence only, and overall mortality in stage III colon cancer patients enrolled in a completed National Cancer Institute–sponsored clinical trial of adjuvant chemotherapy. In addition, given the hypothesis that statin use may inhibit RAS signaling, we also investigated the association between statin use and patient outcome according to tumoral *KRAS* mutation status.

Methods

Study Population

Patients in this prospective cohort study were participants in the Cancer and Leukemia Group B (CALGB) trial for stage III colon cancer (89803) that compared adjuvant bolus 5-fluorouracil and leucovorin with the combination of irinotecan, bolus 5-fluorouracil, and leucovorin (11). Patients were enrolled from April 1999 to May 2001. A self-administered questionnaire that captured diet and lifestyle habits was completed by patients midway through their therapy (4 months after surgery, Questionnaire 1) and again 6 months after the completion of treatment (14 months after surgery; Questionnaire 2). The protocol amendment to survey diet and lifestyle was activated after the first 87 patients were enrolled; therefore, 1177 patients were eligible for the companion study (Figure 1).

Patients were eligible for the treatment trial if they had undergone a complete surgical resection of their primary tumor within 56 days of study entry and had regional lymph node metastases but no distant metastases. Patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0–2 and adequate bone marrow, renal, and hepatic function. Median household income was estimated using concurrent census data determined by the patient zip code. Race/ethnicity was self-reported and recorded in the hospital database at each participating center.

CONTEXT AND CAVEATS

Prior knowledge

Although several studies have investigated the potential chemopreventative activity of statins, and conflicting findings on the relationship between statin use and the risk of colon cancer have been reported, the relationship between statin use and outcome among colon cancer patients has not been studied.

Study design

The relationship between statin use and disease-free, recurrence-free, and overall survival among 842 colon cancer patients enrolled in a randomized clinical trial of adjuvant chemotherapy was analyzed. A subanalysis by *KRAS* mutation status was also done because studies have suggested that statin use may inhibit RAS signaling.

Contribution

No differences between disease-free, recurrence-free, or overall survival between statin users and nonusers were observed in the general study population or in a subanalysis by *KRAS* mutation status.

Implications

Statin use during and after adjuvant chemotherapy for the treatment of colon cancer may not improve survival outcomes. A randomized placebo-controlled prevention trial to investigate the effect of statin use on colon cancer risk and recurrence is currently underway.

Limitations

The study of statin use depended on patient self-reports in response to a questionnaire. Also, the impact of different statins on patient outcome could not be determined.

From the Editors

Classifications included white, Hispanic, black, Asian, Native Hawaiian, Native American, Indian, Filipino, other, and unknown. These and other demographic information were reported by each

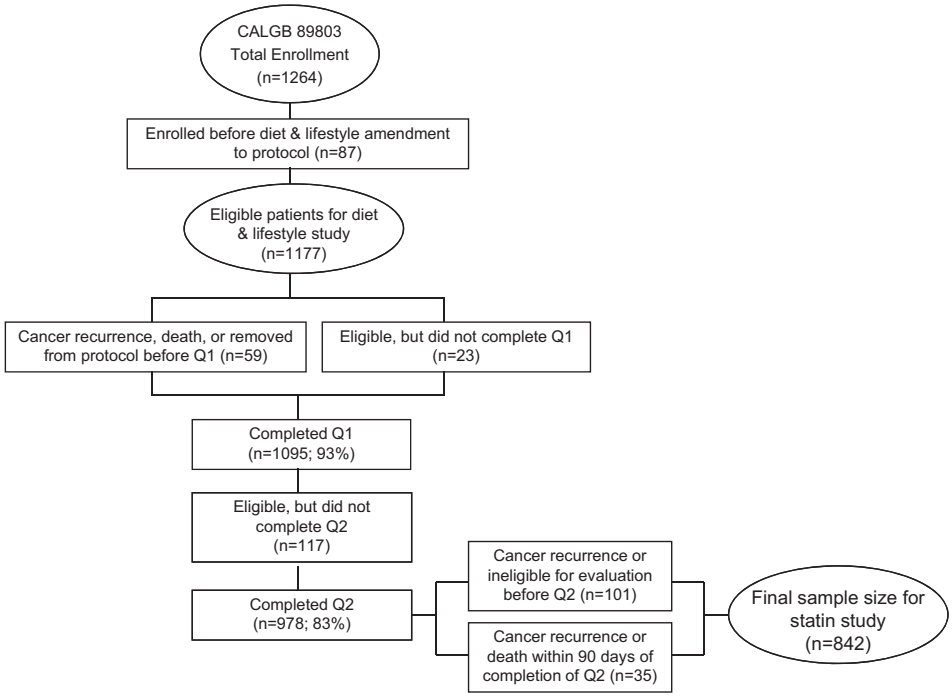

Figure 1. Flow chart of patient selection from the Cancer and Leukemia Group B (CALGB) trial 89803 for inclusion in the study cohort. Q1 = Questionnaire 1, Q2 = Questionnaire 2.

participating center to the CALGB Statistical Center. All patients gave informed consent, and the study protocol was approved by the review board of each institution.

Statin Assessment

Statin use was assessed by Questionnaire 2 after the completion of adjuvant chemotherapy. Only patients who did not experience disease recurrence or death before the second questionnaire were included in the analyses. Participants were asked whether they take any of several medications, including statin cholesterol–lowering drugs (eg, lovastatin [Mevacor], pravastatin [Pravachol], simvastatin [Zocor], and atorvastatin [Lipitor]). Those who reported current statin use were asked to provide the number of years of use (0–2, 3–5, or ≥6 years). We excluded patients whose cancer recurred or who died within 90 days of their statin assessment to avoid potential bias related to an underlying illness.

KRAS Mutation Assessment

Methods for determining the presence of a *KRAS* mutation have been previously described (12). Briefly, polymerase chain reactions and pyrosequencing spanning *KRAS* codons 12 and 13 were performed and validated against Sanger sequencing method (13). Polymerase chain reaction amplification primers for *KRAS* pyrosequencing were: *KRAS-F*, forward, 5'-nnn ggc ctg ctg aaa atg act gaa-3' and *KRAS-R*, reverse biotinylated primer, 5'-tta gct gta tcg tca agg cac tct-3'. Sequencing primers were 5'-tgt ggt agt tgg agc tg-3' and 5'-tgt ggt agt tgg agc t-3'. Similar baseline characteristics were observed for patients with available *KRAS* data and those without available tumor tissue. Moreover, similar tumor recurrence and mortality rates were observed among these two populations (13).

Study Endpoints

Study endpoints were calculated from the time of completion of statin assessment on Questionnaire 2 rather than from the start of trial treatment to avoid any biases from altered medication use and/or exposure during the period of active chemotherapy. The primary endpoint was disease-free survival (DFS), defined as the time from the completion of Questionnaire 2 to tumor recurrence, occurrence of a new primary colon cancer, or death from any cause. Recurrence-free survival (RFS) was defined as the time from the completion of Questionnaire 2 to tumor recurrence, death with evidence of recurrence, or occurrence of a new primary colon tumor; patients who died without known recurrence were censored at the last documented evaluation. Finally, overall survival (OS) was defined as the time from completion of Questionnaire 2 to death from any cause.

Statistical Analyses

Results from the CALGB trial for stage III colon cancer comparing adjuvant bolus 5-fluorouracil and leucovorin with the combination of bolus 5-fluorouracil, leucovorin, and irinotecan have been previously described (11), and results from the two chemotherapy treatment arms were similar; thus, data for patients were combined and analyzed according to categories of statin use after adjuvant chemotherapy for this study. Baseline characteristics were compared between statin users and nonusers using Fisher exact test for 2 × 2 categorical comparisons, a χ^2 test for other categorical comparisons, and the Kruskal–Wallis test for continuous variables. The median follow-up time was determined by calculating the median survival time of patients still alive on March 31, 2009.

Multivariable models were adjusted for age (in years, as a continuous variable), sex (male or female), family history of colorectal cancer (yes or no), and Eastern Cooperative Oncology Group performance status at the initiation of chemotherapy (0 or 1–2). A performance status of 0 indicated that a patient was fully active, a status of 1 indicated that the patient was restricted in physically strenuous activity but ambulatory and able to carry out light work, and a status of 2 indicated that the patient was ambulatory and capable of all self-care but unable to carry out any work activities but up and about for more than 50% of the waking hours. We adjusted for the depth of invasion through the bowel wall by assigning T1 or T2 when the level of invasion was through the bowel wall but not beyond the muscle layer, whereas T3 or T4 was assigned when the level of invasion through the bowel wall was beyond the muscle layer. The number of positive lymph nodes (1–3 or ≥4), perineural invasion (yes or no), and extravascular invasion (yes or no) were other pathological variables that were included in the model. Finally, we also adjusted for the level of postoperative carcinoembryonic antigen present in serum before the initiation of chemotherapy (<5 or ≥5 ng/mL), the treatment arm (bolus 5-fluorouracil plus leucovorin or the combination of irinotecan, bolus 5-fluorouracil, and leucovorin), body mass index (BMI) at the initiation of chemotherapy (as a continuous variable), physical activity (metabolic equivalent task hours per week, as a continuous variable), Western pattern diet (as a continuous variable), and consistent aspirin use (any aspirin use on both Questionnaires 1 and 2). Continuous variables with missing values were imputed with the median value (n = 2 for BMI and for physical activity), and categorical covariables with missing values were coded with indicator variables. DFS, RFS, and OS were examined using Kaplan–Meier curves (14) and the log-rank test (15) in the overall population and in patients stratified by *KRAS* mutation status. Cox proportional hazards regression was used to determine the simultaneous impact of potential confounders (16). The proportionality of hazards assumption for the effect of statin use was satisfied by examining it as a time-dependent covariable in the model (17). The time-dependent statin covariable was non-statistically significant, indicating that the assumption of proportional hazards was appropriate. We tested for linear trend by entering the median value of each category of duration of statin use as a continuous variable in the model (18). Statistical interactions between statin use and potentially modifying covariables were assessed using Wald test of cross-product terms. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, and logistic regression was performed to examine the association between statins and grade 3 and higher toxic effects.

All statistical tests were two-sided and *P* values less than .05 were considered statistically significant. The sample size for the cohort was determined by the chemotherapy treatment trial, which had 82% power to detect a hazard ratio (HR) for death from any cause of 0.77 on the basis of an estimated 356 deaths among 1260 patients. In a post hoc calculation of power on the basis of the

Table 1. Baseline characteristics by statin use reported after adjuvant chemotherapy in patients from the Cancer and Leukemia Group B trial 89803*

Characteristic	Statin use after completion of adjuvant chemotherapy		
	No (n = 708)	Yes (n = 134)	*P*†
Median age (range), y	59.0 (21–85)	64.0 (47–80)	<.001
Sex, No. (%)	708 (100)	134 (100)	.11
Male	390 (55.1)	84 (62.7)	
Female	318 (44.9)	50 (37.3)	
Race/ethnicity, No. (%)	705 (99.6)	134 (100)	.42
White	628 (89.1)	121 (90.3)	
Black	50 (7.1)	6 (4.5)	
Other	27 (3.8)	7 (5.2)	
Median household income (range), US dollars‡	40 742 (17 963–122 234)	40 708 (21 203–122 956)	.69
Family history of colorectal cancer, No. (%)	708 (100)	134 (100)	.63
Yes	137 (19.4)	23 (17.2)	
No	571 (80.6)	111 (82.8)	
Baseline ECOG performance status, No. (%)	692 (97.7)	133 (99.3)	.91
0	524 (75.8)	100 (75.2)	
1–2	168 (24.3)	33 (24.8)	
Invasion through bowel wall (T stage), No. (%)	691 (97.6)	133 (99.3)	.08
T1 and T2	97 (14.0)	27 (20.3)	
T3 and T4	594 (86.0)	106 (79.7)	
Positive lymph nodes (N stage), No. of patients (%)	693 (97.9)	133 (99.3)	.48
1–3 (N1)	465 (67.1)	94 (70.7)	
≥4 (N2)	228 (32.9)	39 (29.3)	
Grade of differentiation, No. (%)	693 (97.9)	133 (99.3)	.17
Well differentiated	45 (6.5)	5 (3.8)	
Moderately differentiated	488 (70.4)	104 (78.2)	
Poorly differentiated or undifferentiated	160 (23.1)	24 (18.0)	
Lymphovascular invasion, No. of patients (%)	686 (96.9)	128 (95.5)	.67
Yes	190 (27.7)	38 (29.7)	
No	496 (72.3)	90 (70.3)	
Perineural invasion, No. of patients (%)	676 (95.5)	126 (94)	1.00
Yes	40 (5.9)	7 (5.6)	
No	636 (94.1)	119 (94.4)	
Extravascular invasion, No. of patients (%)	677 (95.6)	125 (93.3)	.73
Yes	58 (8.6)	9 (7.2)	
No	619 (91.4)	116 (92.8)	
KRAS mutation, No. of patients (%)	326 (46.0)	68 (50.7)	.68
Yes	117 (35.9)	22 (32.4)	
No	209 (64.1)	46 (67.6)	
Clinical bowel perforation, No. of patients (%)	686 (96.9)	130 (97.0)	.32
Yes	24 (3.5)	7 (5.4)	
No	662 (96.5)	123 (94.6)	
Clinical bowel obstruction, No. of patients (%)	692 (97.7)	132 (98.5)	.14
Yes	159 (23.0)	22 (16.7)	
No	533 (77.0)	110 (83.3)	
Postoperative CEA, ng/mL, No. of patients (%)	660 (93.2)	124 (92.5)	.82
<5	628 (95.0)	119 (96.0)	
≥5	32 (5.0)	5 (4.0)	
Adjuvant chemotherapy arm, No. of patients (%)	708 (100)	134 (100)	.09
5-FU/LV	365 (51.6)	58 (43.3)	
IFL	343 (48.4)	76 (56.7)	
Median body mass index (range), kg/m^2	28.3 (16.8−54.5)	30.0 (17.6−45.1)	.07
Median physical activity (range), MET h/wk	7.6 (0−125.4)	7.7 (0−168.7)	.67
Western dietary pattern, median score (range)	−0.20 (−1.73 to 9.35)	−0.07 (−1.60 to 4.31)	.22
Consistent aspirin use, No. of patients (%)	698 (98.6)	125 (93.3)	.001
Yes	53 (7.6)	22 (17.6)	
No	645 (92.4)	103 (82.4)	

(Table continues)

Table 1 (Continued).

Characteristic	Statin use after completion of adjuvant chemotherapy		
	No (n = 708)	Yes (n = 134)	P†
Regular COX-2 (PTGS2) inhibitor use, No. of patients (%)	702 (99.2)	131 (97.8)	.28
Yes	33 (4.7)	9 (6.9)	
No	669 (95.3)	122 (93.1)	

* CEA = carcinoembryonic antigen; COX = cyclooxygenase; ECOG = Eastern Cooperative Oncology Group; 5-FU/LV = bolus 5-fluorouracil and leucovorin; IFL = bolus 5-fluorouracil, leucovorin, and irinotecan; IU = international units; MET = metabolic equivalent task; PTGS2 = prostaglandin–endoperoxide synthase.

† *P* values were calculated by Fisher exact test for 2 × 2 categorical comparisons including sex (male or female), family history of colorectal cancer (yes or no), Eastern Cooperative Oncology Group performance status at the initiation of chemotherapy (0 or 1–2), depth of invasion into the bowel wall (T1 and T2 or T3 and T4), the number of positive lymph nodes (1–3 or ≥4), lymphovascular invasion (yes or no), perineural invasion (yes or no), extravascular invasion (yes or no), *KRAS* mutation (yes or no), clinical bowl perforation (yes or no), clinical bowel obstruction (yes or no), CEA serum concentration (<5 or ≥5 ng/mL), adjuvant chemotherapy arm, consistent aspirin use (any aspirin use on both Questionnaires 1 and 2, yes or no), and regular COX-2 (PTGS2) use (≥3 tablets of Celebrex or Vioxx per week, yes or no). A χ^2 test was used to calculate *P* for other categorical comparisons including race/ethnicity (white, black, or a combined category that included Hispanic, Asian, Native Hawaiian, Native American, Indian, Filipino, other, and unknown race/ethnicity) and grade of differentiation (well differentiated, moderately differentiated, or poorly differentiated and undifferentiated). The Kruskal–Wallis test was used to calculate *P* values for continuous variables including age (in years), median household income, body mass index at the initiation of chemotherapy (kg/m^2), physical activity (metabolic equivalent task hours per week), and Western pattern diet. All statistical tests were two-sided.

‡ Analysis was on the basis of 1999 US census data as determined by patient zip code.

known sample size and the number of cancer recurrence or death events for this analysis, we had 80% power to detect a hazard ratio of 0.55 for cancer recurrence or death.

Patient registration and clinical data collection were conducted by the CALGB Statistical Center, and analyses were performed in conjunction with CALGB statisticians on the basis of the database freeze date of March 31, 2009. Using Clark C (19), the completeness of follow-up for this study was 84.2%; applying Wu modification (20) to adjust for unreported deaths, a more realistic assessment was 85.9%.

Results

Baseline Characteristics According to Statin Use

The questionnaire completion rates between the two treatment arms of the trial were similar. Baseline characteristics for the patients for whom data on statin use were captured are presented in Table 1. Among 842 patients who completed the second questionnaire 6 months after completion of adjuvant chemotherapy, 134 (15.9%) reported statin use. The median time from study entry (which had to be within 8 weeks of surgery) to statin assessment was 13.5 months. Patients who reported statin use were older, had slightly higher BMI (*P* = .07), and were more likely to report consistent aspirin use. Other potentially prognostic patient and tumor characteristics were similar among statin users compared with nonusers.

Impact of Statin Use on Cancer Recurrence and Death in the Overall Population

After a median follow-up of 6.5 years (10th and 90th percentiles: 4.4 and 7.3 years, respectively), 198 of the 842 eligible patients recurred and 177 died. Compared with nonusers, statin users had similar DFS (log-rank *P* = .78, Figure 2, A), RFS (*P* = .73, data not shown), and OS (*P* = .32, Figure 2, B). Similar outcomes were

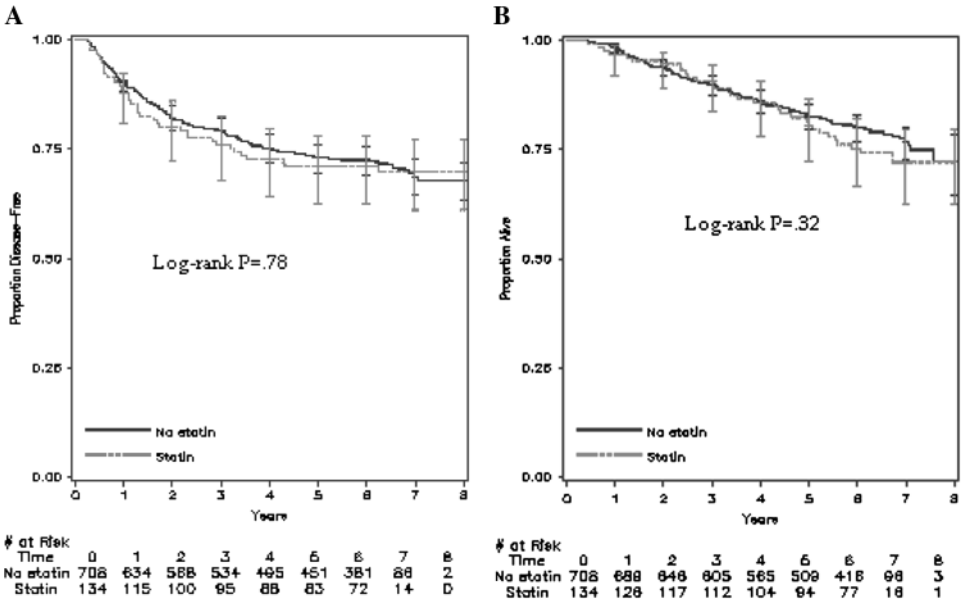

Figure 2. Survival outcomes of statin users and nonusers from the Cancer and Leukemia Group B (CALGB) trial 89803. Kaplan–Meier curves of **A**) disease-free survival and **B**) overall survival of patients (n = 842) after a median follow-up of 6.5 years. **Error bars** represent 95% confidence intervals. Statistical significance was measured by the log-rank test. All *P* values were two-sided.

again observed after adjusting for other predictors of cancer recurrence when statin users and nonusers were compared (Table 2). Compared with patients who did not report statin use following adjuvant chemotherapy, statin users had similar DFS (multivariable HR of cancer recurrence or death = 1.04, 95% confidence interval [CI] = 0.73 to 1.49). Also, statin use was not associated with a statistically significant improvement in RFS (adjusted HR of cancer recurrence = 1.14, 95% CI = 0.77 to 1.69) or OS (adjusted HR of death = 1.15, 95% CI = 0.77 to 1.71). Our results remained unchanged when we additionally adjusted our model for median household income (data not shown) and *KRAS* mutation status (Table 2).

To address the possibility that excluding recurrences and deaths within 90 days of statin assessment masked a potential benefit of statin use, we repeated the analysis using all patients who had completed Questionnaire 2, and again DFS, RFS, and OS were similar. Furthermore, after extending the exclusion period from 90 to 180 days, DFS, RFS, and OS were again similar for statin users and nonusers (data not shown).

We also investigated the effect of the duration of statin use on patient outcome (Table 3). Recent statin use as reflected by reported use for 2 years or less did not lead to statistically significantly improved DFS (adjusted HR of cancer recurrence or death = 1.12, 95% CI = 0.68 to 1.86), RFS (adjusted HR of cancer recurrence = 1.27, 95% CI = 0.74 to 2.18), or OS (adjusted HR of death = 1.25, 95% CI = 0.71 to 2.19). Moreover, increasing duration of use was not associated with patient survival (P_{trend} = .63 for DFS, .63 for RFS, and .59 for OS).

Impact of Statin Use on Cancer Recurrence and Death According to *KRAS* Mutation Status

Among the 842 patients who reported on statin use following adjuvant chemotherapy, 394 (47%) had tumor tissue available for *KRAS* sequencing and 139 (35.3%) of these patients carried a *KRAS* mutation. Of the 139 tumors carrying a *KRAS* mutation, 96 (69%) had a *KRAS* mutation in codon 12 and 43 (31%) had a mutation in codon 13. DFS among statin users and nonusers, for both *KRAS* mutant and wild-type tumors, was similar (*KRAS* mutant tumors, adjusted HR of cancer recurrence or death = 1.21, 95% CI = 0.47 to 3.13; wild-type tumors, adjusted HR of cancer recurrence or death = 0.83, 95% CI = 0.41 to 1.71; $P_{interaction}$ = .84) (Figure 3, A and B, Table 2). RFS (*KRAS* mutant tumors, adjusted HR of cancer

Table 2. Relationship between statin use and colon cancer recurrence and mortality in patients from the Cancer and Leukemia Group B trial 89803 (n = 842)

	Statin use reported after adjuvant chemotherapy					
	All		Wild-type *KRAS*		*KRAS* mutation	
Outcome	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Cancer recurrence or death from any cause						
No. of patients at risk	708	134	209	46	117	22
No. of events	201	38	57	9	35	7
Unadjusted HR (95% CI)	1.0 (referent)	1.05 (0.74 to 1.49)	1.0 (referent)	0.73 (0.36 to 1.47)	1.0 (referent)	1.09 (0.48 to 2.44)
Adjusted HR (95% CI)*	1.0 (referent)	1.04 (0.73 to 1.49)†	1.0 (referent)	0.83 (0.41 to 1.71)‡	1.0 (referent)	1.21 (0.47 to 3.13)‡
Additionally adjusted for *KRAS* mutation status	1.0 (referent)	1.05 (0.73 to 1.51)	$P_{interaction}$ = .84§			
Cancer recurrence						
No. of patients at risk	708	134	209	46	117	22
No. of events	166	32	46	9	32	5
Unadjusted HR (95% CI)	1.0 (referent)	1.07 (0.73 to 1.56)	1.0 (referent)	0.91 (0.45 to 1.86)	1.0 (referent)	0.86 (0.33 to 2.20)
Adjusted HR (95% CI)*	1.0 (referent)	1.14 (0.77 to 1.69)†	1.0 (referent)	1.07 (0.51 to 2.22)‡	1.0 (referent)	0.91 (0.30 to 2.79)‡
Additionally adjusted for *KRAS* mutation status	1.0 (referent)	1.15 (0.78 to 1.70)	$P_{interaction}$ = .67§			
Overall mortality						
No. of patients at risk	708	134	209	46	117	22
No. of events	145	32	42	8	23	5
Unadjusted HR (95% CI)	1.0 (referent)	1.22 (0.83 to 1.78)	1.0 (referent)	0.87 (0.41 to 1.85)	1.0 (referent)	1.26 (0.48 to 3.33)
Adjusted HR (95% CI)*	1.0 (referent)	1.15 (0.77 to 1.71)†	1.0 (referent)	0.88 (0.39 to 1.97)‡	1.0 (referent)	1.18 (0.38 to 3.69)‡
Additionally adjusted for *KRAS* mutation status	1.0 (referent)	1.16 (0.77 to 1.72)	$P_{interaction}$ = .98§			

* Multivariable HRs and 95% CIs were calculated by Cox proportional hazards models. CI = confidence interval; HR = hazard ratios.

† Adjusted for age (in years as a continuous variable), sex (male or female), family history of colorectal cancer (yes or no), baseline performance status (0 or 1–2), depth of invasion through bowel wall (T1, T2, T3, or T4), number of positive lymph nodes (1–3 or ≥4), perineural invasion (yes or no), extravascular invasion (yes or no), postoperative carcinoembryonic antigen (<5 or ≥5), treatment arm (bolus 5-fluorouracil and leucovorin or bolus 5-fluorouracil, leucovorin, and irinotecan), body mass index (in kg/m^2 as a continuous variable), physical activity (in metabolic equivalent task hours per week as a continuous variable), Western pattern diet (as a continuous variable), and consistent aspirin use (any aspirin use on both questionnaires).

‡ Adjusted for age (in years as a continuous variable), sex (male or female), family history of colorectal cancer (yes or no), baseline performance status (0 or 1–2), depth of invasion through bowel wall (T1–T2 or T3–T4), number of positive lymph nodes (1–3 or ≥4), postoperative carcinoembryonic antigen serum levels (<5 or ≥5 ng/mL), treatment arm (bolus 5-fluorouracil and leucovorin or the combination of irinotecan, bolus 5-fluorouracil, and leucovorin), body mass index (in kg/m^2 as a continuous variable), physical activity (in metabolic equivalent task hours per as a continuous variable), Western pattern diet (as a continuous variable), and consistent aspirin use (any aspirin use on both questionnaires).

§ Wald test of cross-product terms was used to calculate $P_{interaction}$ and was two-sided.

Table 3. The association between statin use and colon cancer recurrence and mortality by the number of years of statin use in patients from the Cancer and Leukemia Group B trial 89803 (n = 839)*

Outcome	Statin use, y				P_{trend}†
	0	≤2	3–5	≥6	
Disease-free survival					
No. of patients at risk	708	54	42	35	—
No. of events	201	17	10	11	—
Unadjusted HR (95% CI)	1.0 (referent)	1.19 (0.72 to 1.95)	0.84 (0.45 to 1.59)	1.20 (0.65 to 2.19)	.80
Adjusted HR (95% CI)	1.0 (referent)	1.12 (0.68 to 1.86)	0.83 (0.43 to 1.58)	1.25 (0.67 to 2.32)	.63
Recurrence-free survival					
No. of patients at risk	708	54	42	35	—
No. of events	166	15	8	9	—
Unadjusted HR (95% CI)	1.0 (referent)	1.26 (0.74 to 2.14)	0.82 (0.41 to 1.67)	1.17 (0.60 to 2.28)	.86
Adjusted HR (95% CI)	1.0 (referent)	1.27 (0.74 to 2.18)	0.89 (0.43 to 1.84)	1.28 (0.64 to 2.54)	.63
Overall survival					
No. of patients at risk	708	54	42	35	—
No. of events	145	14	9	9	—
Unadjusted HR (95% CI)	1.0 (referent)	1.34 (0.77 to 2.31)	1.07 (0.54 to 2.09)	1.32 (0.67 to 2.58)	.41
Adjusted HR (95% CI)	1.0 (referent)	1.25 (0.71 to 2.19)	0.94 (0.47 to 1.91)	1.28 (0.64 to 2.57)	.59

* Multivariable HRs and 95% CIs were calculated by Cox proportional hazards regression models and were adjusted for age (in years as a continuous variable), sex (male or female), family history of colorectal cancer (yes or no), baseline performance status (0 or 1–2), depth of invasion through bowel wall (T1, T2, T3, or T4), number of positive lymph nodes (1–3 or ≥4), perineural invasion (yes or no), extravascular invasion (yes or no), postoperative carcinoembryonic antigen (<5 or ≥5), treatment arm (bolus 5-fluorouracil and leucovorin or bolus 5-fluorouracil, leucovorin, and irinotecan), body mass index (in kg/m^2 as a continuous variable), physical activity (in metabolic equivalent task hours per week as a continuous variable), Western pattern diet (as a continuous variable), and consistent aspirin use (any aspirin use on both questionnaires). CI = confidence interval; HR = hazard ratios.

† A linear test for trend was performed by entering the median value of each category of duration of statin use as a continuous variable in the model.

recurrence = 0.91, 95% CI = 0.30 to 2.79; wild-type tumors, adjusted HR of cancer recurrence = 1.07, 95% CI = 0.51 to 2.22; $P_{interaction}$ = .67) (Table 2) and OS (*KRAS* mutant tumors, adjusted HR of death = 1.18, 95% CI = 0.38 to 3.69; wild-type tumors, adjusted HR of survival = 0.88, 95% CI = 0.39 to 1.97; $P_{interaction}$ = .98) (Table 2 and Figure 3, C and D) were also similar among statin users and nonusers.

Impact of Statin Use Across Strata of Other Predictors of Patient Outcome

We examined the influence of statin use during adjuvant chemotherapy on DFS across strata of other predictors of cancer outcome (Figure 4). The relationship between statin use and DFS was similar across strata of age, sex, Eastern Cooperative Oncology Group performance status, the number of positive lymph nodes, depth of invasion through the bowel wall, treatment arm, BMI, physical activity, and Western pattern diet. Notably, the association between statin use and DFS was also similar among consistent and inconsistent aspirin users ($P_{interaction}$ = .79). Moreover, regular use of cyclooxygenase-2 inhibitors (also known as prostaglandin–endoperoxide synthase-2 inhibitors) did not modify the relationship between statin use and patient outcome ($P_{interaction}$ = .56) (data not shown).

Relationship between Statin Use and Toxicity

We explored the influence of statins on the occurrence of the most common grade 3 or higher toxic effects seen in the treatment trial, as well as on cardiovascular events (Table 4) (11). The likelihood of developing grade 3 or higher toxic effects was similar for statin users of duration 2 years or more compared with nonusers after adjusting for potential confounding factors leukopenia (odds ratio [OR] = 1.10, 95% CI = 0.46 to 2.62), neutropenia (OR = 1.32, 95% CI = 0.71 to 2.44), nausea (OR = 0.68, 95% CI = 0.30 to 1.56), vomiting (OR = 0.91, 95% CI = 0.37 to 2.22), diarrhea (OR = 0.91, 95% CI = 0.54 to 1.55), and fatigue (OR = 0.77, 95% CI = 0.32 to 1.88). Also, the likelihood of developing grade 3 or higher cardiovascular toxicity was similar for statin users and nonusers, although the number of such events was small (n = 7 for nonusers and n = 1 for statin users; adjusted OR = 1.08, 95% CI = 0.13 to 9.08).

Discussion

In this large cohort of stage III colon cancer patients treated with surgery and adjuvant chemotherapy, DFS, RFS, and OS were similar for statin users and nonusers. Recent statin use during the period of cancer diagnosis and treatment conferred no improvement in DFS, RFS, or OS, and long-term regular statin use was similarly not associated with any benefit to survival. Moreover, the relationship between statin use and patient outcome was not modified by *KRAS* mutation status. Nonetheless, statin use did not increase the likelihood of chemotherapy-related adverse events. To our knowledge, this is the first study to prospectively examine the relationship between statin use and survival among patients with established colon cancer.

Because statins may interact with diverse signaling pathways that are critical for colon cancer development and progression, there has been intense interest in the potential of statins as chemopreventative and antitumor agents. A large observational study of 1953 patients with colorectal cancer and 2015 control subjects demonstrated a statistically significant reduction in the risk of colorectal cancer with 5 or more years of statin use (6), as did two recent meta-analyses (7,8). Unfortunately, these findings were not confirmed in a large meta-analysis of epidemiological studies and randomized controlled trials (10) nor in several smaller observational studies (21–28).

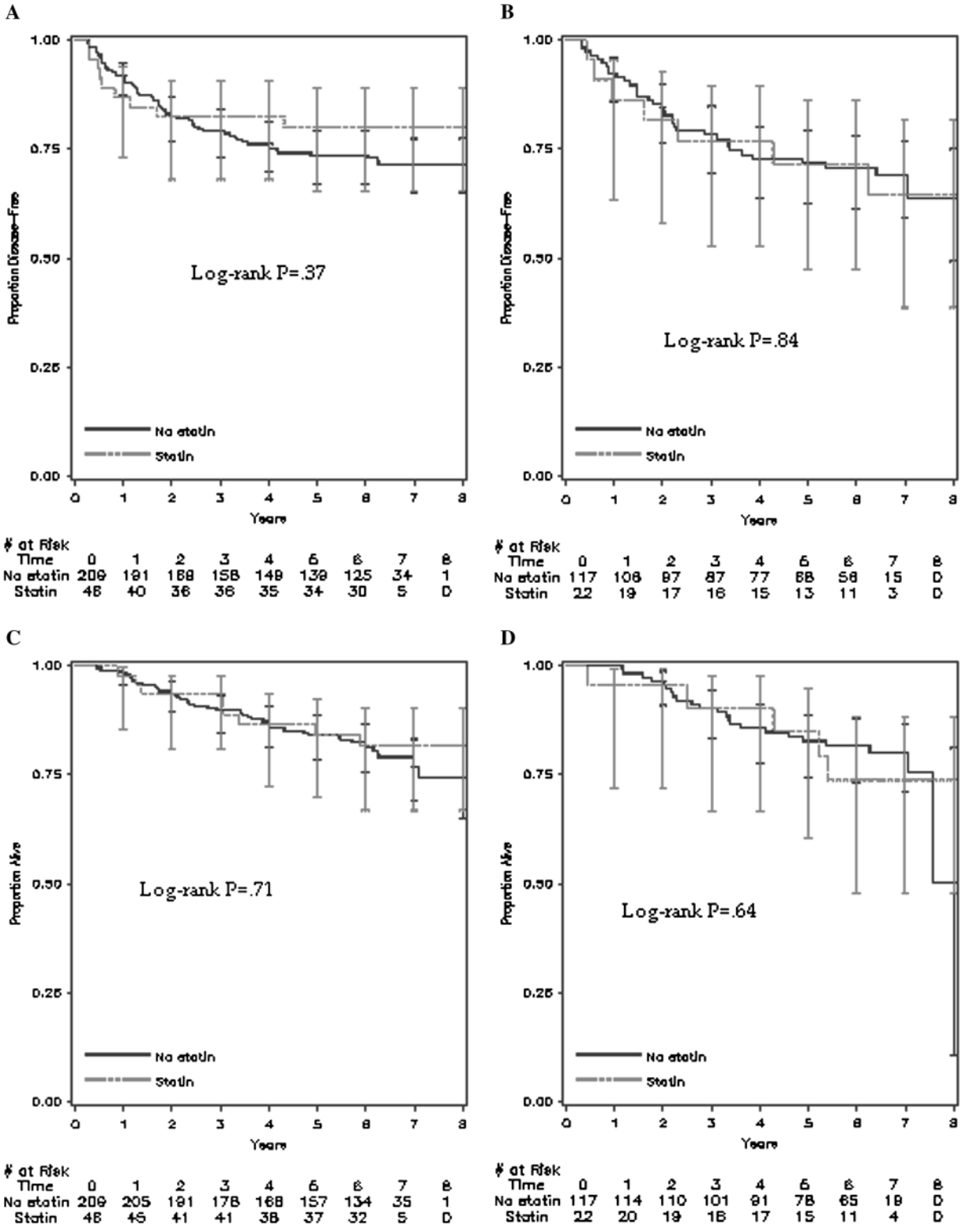

Figure 3. Survival outcomes of statin users and nonusers from the Cancer and Leukemia Group B (CALGB) trial 89803 stratified by *KRAS* mutation status. Kaplan–Meier curves of **A**) disease-free survival in *KRAS* wild-type patients, **B**) disease-free survival in *KRAS* mutant patients, **C**) overall survival in *KRAS* wild-type patients, and **D**) overall survival in *KRAS* mutant patients in those with tissue available for *KRAS* mutation testing (n = 394) after a median follow-up of 6.5 years. **Error bars** represent 95% confidence intervals. Statistical significance was measured by the log-rank test. All *P* values were two-sided.

In contrast, very few studies have addressed the role of statins among patients with established colorectal cancer. Siddiqui et al. (29) found that statin use was statistically significantly associated with less-advanced tumor stage and improved 5-year survival; however, statin use was assessed retrospectively (29). A single-arm, multicenter phase II study of infusional 5-fluorouracil, leucovorin,

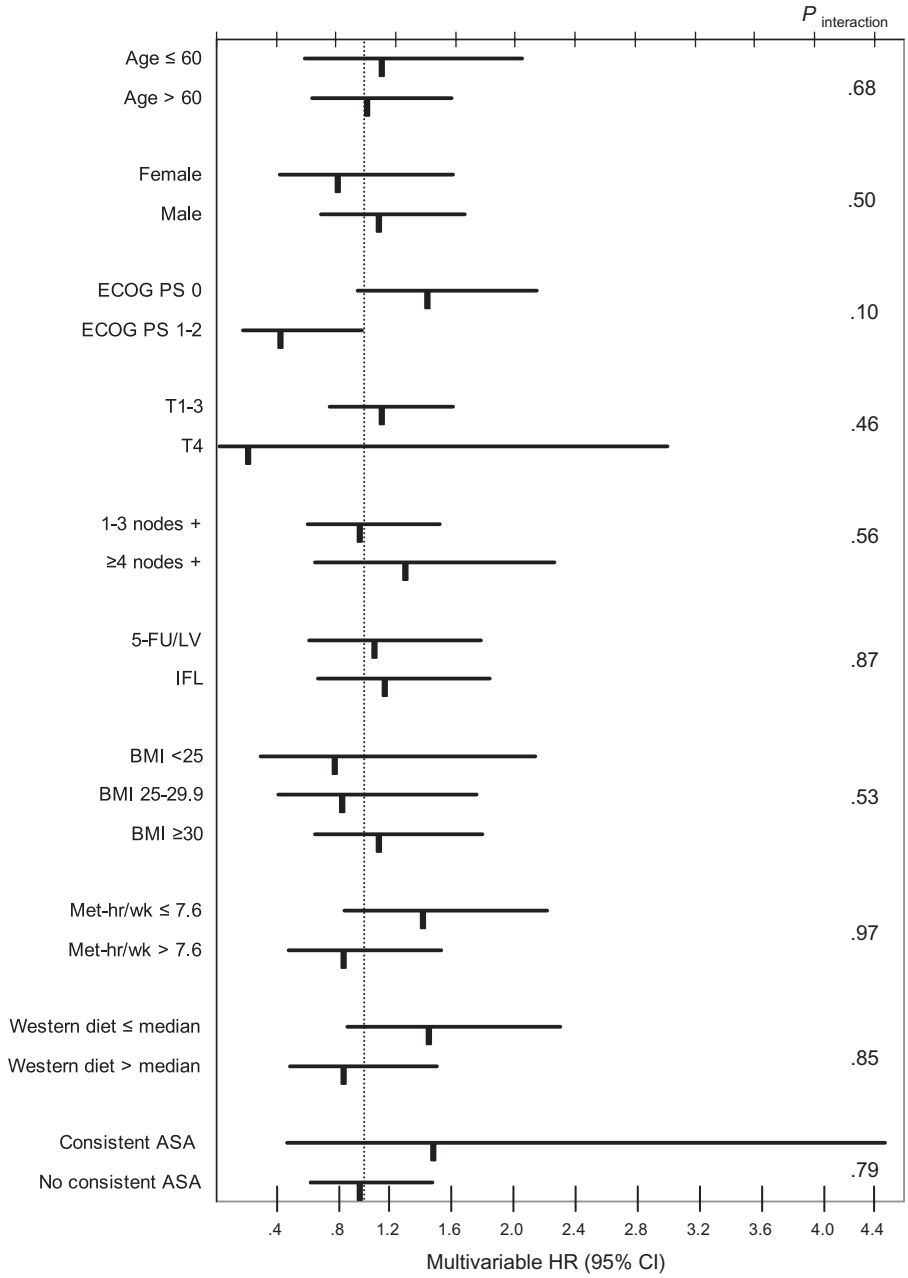

Figure 4. Risk of cancer recurrence and death among statin users and nonusers across strata of predictors of cancer outcome. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer recurrence and death (disease-free survival) were calculated by Cox proportional hazards regression models. Wald test of cross-product terms was used to calculate $P_{interaction}$ and was two-sided. ASA = aspirin; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IFL = irinotecan, bolus 5-FU, LV; MET = metabolic equivalent task; PS = performance status; T = depth of invasion through bowel wall; 5-FU/LV = bolus 5-fluorouracil/leucovorin; .

and irinotecan plus simvastatin in previously untreated metastatic colorectal cancer patients has also been reported demonstrating reasonable tolerability, an overall response rate of 47%, median time to progression of 9.9 months, and median survival of 21.8 months (30). However, the added contribution of simvastatin to chemotherapy is impossible to determine in the context of the trial's single-arm design. Finally, National Surgical Adjuvant Breast and Bowel Project protocol P-5, the Statin Polyp Prevention Trial, was recently activated and is currently enrolling patients. This large study plans to randomize 1740 patients with resected stage I or II colon cancer to rosuvastatin vs placebo for 5 years, with a primary endpoint of adenomatous polyp development, metachronous colorectal cancer, or colon cancer recurrence. Data will not be available for several years.

There are several mechanisms through which statin exposure may influence survival after a diagnosis of colon cancer. Statins have been shown to inhibit proliferation (31,32), induce apoptosis (33,34), inhibit angiogenesis (35,36), affect cell–cell adhesion (37), prevent metastasis (38), and decrease inflammation (39, 40). A leading hypothesis to explain the antitumor activity of statins in colorectal cancer revolves around the suppression of farnesylation of RAS, thus preventing RAS activation, a key oncogenic event. In fact, several pharmacological inhibitors of farnesylation have been examined in patients with *KRAS*-driven malignancies (41–44). However, in our analysis, statin use was not associated with improved survival in patients with either *KRAS*-mutated or wild-type colon tumors. Moreover, our analysis found that the relationship between statin use and patient outcome did not differ by aspirin or cyclooxygenase-2 inhibitor use.

There are several advantages to using a cohort within a clinical trial sponsored by the National Cancer Institute. First, all patients had stage III cancer, reducing the impact of heterogeneity by disease

Table 4. Association between statin use and the incidence of selected grade 3 or higher toxicities in patients from the Cancer and Leukemia Group B trial 89803 (n = 784)*

	Statin use reported after adjuvant chemotherapy, y	
Toxicity	**0**	**≥2**
Leukopenia		
No. of patients at risk, n	707	77
No. of events, n (%)	56 (8)	7 (9)
Unadjusted HR (95% CI)	1.0 (referent)	1.16 (0.51 to 2.65)
Adjusted HR (95% CI)	1.0 (referent)	1.10 (0.46 to 2.62)
Neutropenia		
No. of patients at risk, n	707	77
No. of events, n (%)	160 (23)	20 (26)
Unadjusted HR (95% CI)	1.0 (referent)	1.20 (0.70 to 2.06)
Adjusted HR (95% CI)	1.0 (referent)	1.32 (0.71 to 2.44)
Nausea		
No. of patients at risk, n	707	77
No. of events, n (%)	96 (14)	7 (9)
Unadjusted HR (95% CI)	1.0 (referent)	0.64 (0.28 to 1.43)
Adjusted HR (95% CI)	1.0 (referent)	0.68 (0.30 to 1.56)
Vomiting		
No. of patients at risk, n	707	77
No. of events, n (%)	68 (10)	6 (8)
Unadjusted HR (95% CI)	1.0 (referent)	0.79 (0.33 to 1.90)
Adjusted HR (95% CI)	1.0 (referent)	0.91 (0.37 to 2.22)
Diarrhea		
No. of patients at risk, n	707	77
No. of events, n (%)	236 (33)	23 (30)
Unadjusted HR (95% CI)	1.0 (referent)	0.85 (0.51 to 1.42)
Adjusted HR (95% CI)	1.0 (referent)	0.91 (0.54 to 1.55)
Fatigue		
No. of patients at risk, n	707	77
No. of events, n (%)	66 (9)	6 (8)
Unadjusted HR (95% CI)	1.0 (referent)	0.82 (0.34 to 1.96)
Adjusted HR (95% CI)	1.0 (referent)	0.77 (0.32 to 1.88)
Cardiovascular†		
No. of patients at risk, n	707	77
No. of events, n (%)	7 (1)	1 (1)
Unadjusted HR (95% CI)	1.0 (referent)	1.32 (0.16 to 10.84)
Adjusted HR (95% CI)	1.0 (referent)	1.08 (0.13 to 9.08)
Any of the above toxicities		
No. of patients at risk, n	707	77
No. of events, n (%)	379 (54)	41 (53)
Unadjusted HR (95% CI)	1.0 (referent)	0.99 (0.62 to 1.58)
Adjusted HR (95% CI)	1.0 (referent)	1.04 (0.64 to 1.71)

* Adverse events were rated according to the National Cancer Institute Common Toxicity Criteria version 2.0. Multivariable HRs and 95% CIs were calculated by logistic regression models. Models were adjusted for age (in years as a continuous variable), sex (male or female), baseline Eastern Cooperative Oncology Group performance status (0 or 1–2), treatment arm (bolus 5-fluorouracil and leucovorin or the combination of irinotecan, bolus 5-fluorouracil, and leucovorin), body mass index (in kg/m^2 as a continuous variable), and physical activity (in metabolic equivalent task hours per week as a continuous variable). CI = confidence interval; HR = hazard ratios.

† This category includes cardiac ischemia and/or infarction and cerebrovascular ischemia.

stage. Second, treatment and follow-up were standardized, and the date and nature of recurrence were recorded prospectively. Finally, detailed information on prognostic factors was routinely collected.

Several potential limitations deserve comment. First, the number of statin users in our cohort was small. However, the rate of statin use in our analysis is consistent with, if not higher than rates seen in other studies (6,27). Moreover, we had adequate power to detect a statistically significant treatment effect. The hazard ratios we obtained were in the 1.0–1.1 range, and no trends toward a positive or negative association were detected. Second, patients who enroll in randomized trials may differ from the population at large. However, because the study included patients from community and academic centers throughout North America, our findings should reflect the general US population. Third, because we relied on self-reported statin use, misclassification of exposure is possible. However, previous studies have demonstrated that such data are reliable (6). Furthermore, statin use was recorded before any knowledge of cancer-related outcomes, thus reducing the likelihood of reporting biases. Fourth, patients who are prescribed statins may differ from the general population by socioeconomic status (45); lifestyle factors such as diet, BMI, and physical activity; and utilization of medical care and preventative health practices (46). Our study was controlled for median household income, dietary pattern, BMI, physical activity, performance status, and other potentially prognostic variables. However, residual confounding from unknown variables is possible.

Another possible limitation is that we were unable to assess the individual impact of different statins on patient outcome, because information on the type of statin used by each patient was not collected on the questionnaires. Although some hypotheses suggest that lipophilic and hydrophilic statins may have distinct effects, previous studies have not been able to show a differential impact on colorectal cancer risk, although this has not been well studied. Finally, although many studies have reported that the presence of any *KRAS* mutation is associated with resistance to antibodies against the epidermal growth factor receptor, such as cetuximab (47–50), recent data indicate that *KRAS* codon 12 and 13 mutations may result in biologically and functionally distinct proteins, with different treatment responses to cetuximab (51). Unfortunately, we were unable to evaluate the effect of statins among tumors with specific *KRAS* mutations because of the limited number of patients with available *KRAS* data.

In conclusion, our large prospective study of stage III colon cancer patients found that DFS, RFS, and OS were similar for statin users and nonusers, independent of *KRAS* mutation. Importantly, statin use was not associated with increased toxicity in the patient population. We eagerly await the results of the Statin Polyp Prevention Trial (protocol P-5) initiated by the National Surgical Adjuvant Breast and Bowel Project. Additional studies are also needed to elucidate the potential role of statin use in colon cancer recurrence and patient outcome.

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Notes

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