ELSEVIER

Prospective Analysis of Association Between Use of Statins or Other Lipid-Lowering Agents and Colorectal Cancer Risk

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PURPOSE: To determine whether 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) are associated with a decreased risk of colorectal cancer.
METHODS: The population included 159,219 postmenopausal women enrolled in the Women's Health Initiative in which 2000 pathologically confirmed cases of colorectal cancer were identified during an average of 10.7 (S.D. 2.9) years. Information on statins was collected at baseline and years 1, 3, 6, and 9. Self- and interviewer-administered questionnaires were used to collect information on other risk factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by the use of Cox proportional hazards regression to evaluate the relationship between statin use and risk. Statistical tests were two-sided.
RESULTS: Statins were used by 12,030 (7.6%) women at baseline. The annualized colorectal cancer rate was 0.13% among users and 0.12% among nonusers. The multivariable adjusted HR for users versus nonusers was 0.99 (95% confidence interval [CI], 0.83–1.20, $p = .95$), and 0.79 (95% CI, 0.56–1.11) for users of $\geqslant$3 years. In the multivariable adjusted time-dependent model, the HR for lovastatin was 0.62 (95% CI, 0.39–0.99). There was no effect of tumor location, stage or grade.
CONCLUSIONS: There was a reduction in colorectal cancer risk associated with lovastatin and a nonsignificant association with longer duration of use.
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KEY WORDS: Colorectal Cancer, Statins, Cancer Risk, Cohort Study.

INTRODUCTION

Colorectal cancer is the third-leading cause of cancer incidence and death among women in the United States, with an estimated 70,480 new cases and 24,790 deaths reported in 2010 (1). With the appropriate use of treatment, colorectal cancer is potentially curable, especially if discovered at an early stage; however, the clinical presentation can be insidious, and patients frequently present at an advanced stage (2). Although regular screening of asymptomatic patients by fecal occult blood testing, sigmoidoscopy, or colonoscopy is effective in decreasing the mortality associated with colorectal cancer, the majority of the population receives no screening or inadequate screening (3, 4), and rates of screening are much lower than for other common malignancies. The high death rate from colorectal cancer and inadequate acceptance of screening support the need to focus on chemoprevention as a way to more effectively impact colorectal cancer mortality.

A number of measures, including regular intake of aspirin or nonsteroidal anti-inflammatory drugs (5), calcium and vitamin D intake (6), and dietary changes including increased fiber (7) and whole grain intake (8), have been associated with lower colorectal cancer risk in observational studies; however, validation by randomized controlled trials have been disappointing (9, 10). Colorectal cancer involves the progression through well-defined morphological, cellular, and genetic events in the adenoma to carcinoma pathway (11). Statins are a logical candidate for chemoprevention

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Selected Abbreviations and Acronyms

WHI = Women's Health Initiative
OS = observational study
CT = clinical trial

in that they have pleiotropic effects in addition to cholesterol-lowering including, inhibition of rho GTPases (12–14), induction of apoptosis (12, 15–18), decrease in markers of chronic inflammation (19), inhibition of cell proliferation (20–22), and decrease in formation and progression of aberrant crypt foci (23). In a population based case-control study, Poynter et al. (24) demonstrated a 47% reduction in colorectal cancer risk among users of statins for 5 or more years. The relationship between statins and reduction in colorectal cancer risk has been reviewed in four recently completed meta-analyses (25–28). Overall, the authors of observational studies have shown a modest reduction in risk; however, these findings have not been demonstrated in randomized controlled trials.

The purpose of this study was to test whether statins and other lipid-lowering agents are associated with a lower risk of colorectal cancer among participants in the Women's Health Initiative (WHI), which is the largest multicenter longitudinal study of postmenopausal women in the United States. In the WHI, detailed information on statin use and duration of use was collected at study entry, and additional follow-up information was collected at years 1, 3, 6, and 9. Cancer outcome data is available for an average (SD) of 10.7 (2.9) years of follow-up.

METHODS

Study Population

The WHI includes an observational study (OS; n = 93,676) and three clinical trials (CTs; n = 68,132) of hormone therapy, dietary modification, and calcium/vitamin D supplementation in postmenopausal women of mixed race and ethnicity (29). Recruitment was conducted between October 1, 1993, and December 31, 1998, at 40 clinical centers in the United States. Eligibility criteria included women ages 50–79 years who were postmenopausal, planned to remain in area where they were recruited, and had an estimated survival of at least 3 years. Study methods have been described in detail elsewhere (30, 31). Participants were followed through March 2005 and were invited to enroll in an extension study which lasted from April 2005 through September 2010.

The current analysis includes 91,912 women enrolled in the OS and 67,307 enrolled in the CT (159,219 total), and excludes 963 women with a previous diagnosis of colorectal cancer, 1624 women with an unknown previous history of colorectal cancer, and 2 women with unknown information on previous statin use. All participants signed informed consent forms, and all protocols and procedures were approved by institutional review boards of the participating institutions. Follow-up was through August 14, 2009, for a mean (SD) follow-up of 10.7 (2.9) years and a maximum of 15.6 years.

Statin Exposure

At study entry, participants brought in all of their current prescriptions and each medication name was directly entered by study personnel into the WHI database, which assigned national drug codes by the use of Medispan software (First DataBank, Inc., San Bruno, CA). Participants also reported duration of use for each medication. Information on prescription medications was similarly updated at years 1, 3, 6, and 9 in the CT, and at year 3 in the OS.

Statins were defined as any 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and were classified on the basis of solubility in octanol (lipophilicity) or water (hydrophilicity) (32, 33). Lipophilic (or hydrophobic) statins (lovastatin, simvastatin, fluvastatin, cerivastatin) penetrate the plasma membrane whereas hydrophilic statins (pravastatin, atorvastatin and rosuvastatin) do not (34–36). Statins were classified by potency on the basis of lipid-lowering efficacy as low (fluvastatin and lovastatin), medium (pravastatin), and high (simavastatin, atorvastatin, cerivastatin and rosuvastatin) (34, 35, 37). Data were collected on other lipid-lowering medications, including fibrates, colestipol, probucol, cholestyramine, niacin, and nicotinic acid.

Colorectal Cancer Diagnosis and Screening

Cancer diagnoses were updated annually in the OS or semi-annually in the CT by mail and/or telephone questionnaires. Participant or next-of-kin reports of colorectal cancer were verified by centrally trained physician adjudicators after review of medical records and pathology reports using the Surveillance Epidemiology and End Results coding system (38). Only invasive colorectal cancer cases were included and the following unusual or rare histologic types were censored: adenocarcinoma in the setting of polyposis coli (n = 1), malignant carcinoid tumor (n = 14), neuroendocrine carcinoma (n = 9), infiltrating ductal carcinoma, NOS (n = 2), medullary carcinoma (n = 1), and malignant melanoma, not otherwise specified (n = 3). Information on the frequency of screening tests, including fecal occult blood tests, rectal examinations, and sigmoidoscopy or colonoscopy was collected at baseline and updated semiannually in the CT and annually in the OS. Screening rates were not protocol defined.

Covariates

Baseline questionnaires were used to collect information on race or ethnicity (White, African American, Hispanic, Native American, Asian/Pacific Islander, or unknown), physician-diagnosed diabetes, high serum cholesterol that required treatment with pills, history of coronary artery disease, educational level (<high school, high school diploma/GED, or > high school diploma/GED), family colorectal cancer history, use of nonsteroidal anti-inflammatory drugs or aspirin (yes/no), current and past smoking, and physical activity in metabolic equivalents. Alcohol consumption (none/past drinker, <1 drink/week, or ⩾1 drink/week), percentage of calories from fat (⩾30% versus <30% of calories from fat) and other dietary data were estimated from the WHI food-frequency questionnaire (39). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Current and previous use of menopausal hormones and oral contraceptives were ascertained by interviewer administered questionnaires that queried type, route of administration, number of pills per day/week, and duration for each preparation ever taken. Hormone therapy users were defined as those who used estrogen (with or without progestin) for at least 3 months after menopause.

Statistical Methods

Characteristics of statin users at baseline were compared with those of nonusers by χ^2 tests. Annualized rates of colorectal cancer were calculated as the percentage of women with an event divided by total follow-up time in years by statin use categories and other lipid-lowering agents at baseline. An a priori plan specified that we perform selected subgroup analyses by duration (<1 year, 1 to <3 years, and ⩾3 years), type, potency, and hydrophobic status. Women who used two or more statins were included in analyses that compared statin use to none, but were excluded from analyses that examined details of use (by type, potency or lipophilic). Separate analyses were conducted for proximal, distal and rectal sites as well as other clinical characteristics including stage, tumor size, lymph node involvement and grade. Hazard ratios (HRs) for colorectal cancer among statin users versus nonusers, and 95% confidence intervals (CIs) were computed from Cox proportional hazards analyses. Tests for the proportional hazards assumptions were conducted by a Cox model that included statin use and the interaction of statin use with follow-up time, and testing for a zero coefficient on the interaction term. Results of these analyses showed that the assumptions were not violated.

Cox proportional hazards analyses were used to assess associations between statins and colorectal cancer. Two models were developed including an age-adjusted model and a multivariable-adjusted model. Both sets of models were stratified as to allow the baseline hazard function to vary by assignment to active hormone or placebo in the two WHI hormone trials (estrogen plus progestin and estrogen alone), assignment to intervention or control in the dietary modification trial, or enrollment in the OS, and/or WHI extension study participation. To control for confounding, the multivariable model was additionally adjusted for age, ethnicity, education, smoking, alcohol use, physical activity, BMI, percent energy from fat, fruit and vegetable intake, dietary calcium, calcium supplement use, selenium supplement use, current healthcare provider, last medical visit within one year, colon screening at baseline, current HT use, family history of colorectal cancer, history of colon polyp removal, use of nonsteroidal anti-inflammatory drugs, hypertension, history of stroke and history of coronary artery disease.

To evaluate the effect of the change in statin use over time, we conducted time-dependent models in which we incorporated updated information on statins (whether or not participants had started statins, statin type, category and potency) at years 1, 3, 6, and 9 in the CT and year 3 in the OS. We conducted time-dependent Cox models to examine the effect of colon screening during the study, where any report of screening (rectal examination, hemoccult guaiac, colonoscopy, sigmoidoscopy, flexible sigmoidoscopy, or barium enema x-ray), was incorporated on a yearly basis. Comparisons of colorectal cancer tumor characteristics between statin users and nonusers were based on χ_2 and Fisher exact tests. We evaluated interaction effects of age, family history, BMI, colonoscopy screening, and hormone therapy with statin use on the association with colorectal cancer. All analyses were conducted with Statistical Analysis Systems (SAS) software, version 9.2 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided with a significance level of .05.

RESULTS

The WHI cohort consisted of 12,030 statin users (7.6%)at baseline. Table 1 shows characteristics of WHI participants by statin use. Although most of the absolute differences between statin users and nonusers were small, many were statistically significant because of the large sample size. Statin users were more likely to be older than nonusers (mean age, SD, 65.6 [6.5] and 63.0 [7.2] years, respectively) and to have a greater BMI (28.9 [5.5] and 27.9 [6.0] kg/m^2). Statin use was associated with tobacco consumption, previous colon screening, a family history of colorectal cancer, one or more co-morbid medical conditions, and use of nonstatin lipid-lowering medications or aspirin. Non-use of statins was associated with greater levels of education and family income, greater alcohol intake, more physical activity, use of hormone therapy and a diet with >30% calories from fat.

TABLE 1. Baseline characteristics of WHI CT and OS participants by statin use

	Statin use				
	No (n = 147,189)		Yes (n = 12,030)		
	N	%	N	%	*p*-value*
Age group at screening, years					<.0001
50–59	50824	34.5	2165	18.0	
60–69	65227	44.3	6273	52.1	
70–79	31138	21.2	3592	29.9	
Ethnicity					<.0001
White	121067	82.6	9873	82.1	
Black	13230	9.0	1092	9.1	
Hispanic	5984	4.1	378	3.1	
American Indian	648	0.4	46	0.4	
Asian/Pacific Islander	3680	2.5	468	3.9	
Unknown	2040	1.4	173	1.4	
Education					<.0001
None-some HS	7653	5.2	780	6.5	
High school diploma/GED	24679	16.9	2520	21.1	
>HS diploma/GED	113758	77.9	8651	72.4	
Family income					<.0001
<$10,000	6265	4.6	506	4.5	
$10,000–$19,999	16648	12.1	1487	13.3	
$20,000–$34,999	32974	24.0	3095	27.7	
$35,000–$49,999	28000	20.4	2444	21.9	
$50,000–$74,999	27465	20.0	2041	18.3	
$75,000+	26048	19.0	1602	14.3	
Marital status					<.0001
Never married	6446	4.4	523	4.4	
Divorced/Separated	23860	16.3	1552	12.9	
Widowed	24788	16.9	2522	21.0	
Presently married/living as married	91397	62.4	7389	61.6	
Smoking					<.0001
Never	74508	51.2	5791	48.8	
Past	60694	41.7	5347	45.1	
Current	10250	7.0	725	6.1	
Alcohol intake					<.0001
Non/past drinker	42828	29.3	4137	34.6	
<1 drink/wk	48122	32.9	4027	33.7	
⩾1 drink/wk	55246	37.8	3795	31.7	
Total expenditure from physical activity quartiles, METs/wk					<.0001
<2.25	35720	25.4	2899	24.7	
2.25–<8.34	35046	24.9	3147	26.8	
8.34–<17.75	34532	24.6	3017	25.7	
⩾17.75	35215	25.1	2686	22.9	
BMI, kg/m^2					<.0001
<25	52476	36.0	2975	24.9	
25–<30	50044	34.3	4734	39.7	
⩾30	43369	29.7	4221	35.4	
Waist circumference ⩾88 cm	59340	40.5	6197	51.7	<.0001
Daily dietary intake					
Percent calories from fat					<.0001
<30	49853	34.9	5025	43.5	
30–<35	34336	24.0	2594	22.5	
35–<40	31237	21.9	2278	19.7	
⩾40	27463	19.2	1655	14.3	
Folacin quartiles, μg					<.0001
⩽180.7159	35896	25.1	2715	23.5	
180.7159–238.6261	35907	25.1	2703	23.4	
238.6261–312.9879	35841	25.1	2770	24.0	

(*Continued*)

TABLE 1. (Continued)

	Statin use				
	No (n = 147,189)		Yes (n = 12,030)		
	N	%	N	%	*p*-value*
>312.9879	35245	24.7	3364	29.1	
Calcium quartiles, mg					<.0001
≤505.105	35458	24.8	3151	27.3	
505.105–733.503	35692	25.0	2919	25.3	
733.503–1047.099	35852	25.1	2759	23.9	
>1047.099	35887	25.1	2723	23.6	
Vitamin D quartiles, IU					0.01
≤93.0457	35685	25.0	2924	25.3	
93.0457 – 146.4375	35617	24.9	2994	25.9	
146.4375 – 221.2653	35847	25.1	2764	23.9	
>221.2653	35740	25.0	2870	24.8	
Fruit and vegetable servings					0.08
<2.51	35891	25.1	2797	24.2	
2.51–<3.75	35530	24.9	2881	24.9	
3.75–<5.34	35917	25.1	2897	25.1	
≥5.34	35547	24.9	2976	25.8	
Supplement use					
Calcium	33014	22.4	2573	21.4	.01
Vitamin D	5839	4.0	437	3.6	.07
Alpha-toc eq	43549	29.6	4252	35.3	<.0001
Selenium	4007	2.7	318	2.6	.61
Zinc	5126	3.5	332	2.8	.05
Vitamin C	38818	26.4	3232	26.9	.24
Beta-carotene	6565	4.5	507	4.2	.21
Vitamin A	9391	6.4	688	5.7	.004
Multivitamin (with or without minerals)	114326	77.7	9844	81.8	<.0001
Geographic region by latitude					.27
Southern: <35 degrees N	46503	31.6	3868	32.2	
Middle: 35–40 degrees N	40090	27.2	3208	26.7	
Northern: >40 degrees N	60596	41.2	4954	41.2	
Current health care provider	136102	93.4	11749	98.4	<.0001
Last medical visit within 1 year	115178	81.0	10947	93.5	<.0001
Colonoscopy/sigmoidoscopy/flexible sigmoidoscopy					<.0001
Never	68873	49.2	4843	41.4	
Within 5 years	44465	31.8	4456	38.1	
More than 5 years ago	26593	19.0	2397	20.5	
Hemoccult test/rectal examination					<.0001
Never	35655	25.5	2228	19.1	
Within 5 years	77426	55.4	7332	62.8	
More than 5 years ago	26646	19.1	2121	18.2	
Current HT use by type (includes HT trial use)					<.0001
Never/past	77132	52.4	6790	56.5	
E alone	36767	25.0	3058	25.5	
E + P	33182	22.6	2167	18.0	
Previous OC use	62105	42.2	4051	33.7	<.0001
Family history of colorectal cancer	22078	16.4	1965	17.9	<.0001
Number of first degree relatives with colorectal cancer					<.0001
None	112422	84.8	8996	83.1	
1	17992	13.6	1595	14.7	
2+	2200	1.7	236	2.2	
History of cancer (excludes nonmelanoma skin cancer)	12265	8.3	1185	9.9	<.0001
Breast	4782	3.2	515	4.3	<.0001
Lung	214	0.1	22	0.2	.30
Ovarian	785	0.5	58	0.5	.46
Melanoma	1366	0.9	133	1.1	.05

(*Continued*)

TABLE 1. (Continued)

	Statin use				
	No (n = 147,189)		Yes (n = 12,030)		
	N	%	N	%	*p*-value*
History of nonmelanoma skin cancer	10816	7.4	1010	8.4	<.0001
History of polyp removal	11908	8.6	1457	12.7	<.0001
History of coronary artery disease (MI/angina)	8001	5.4	2383	19.8	<.0001
History of diabetes	7988	5.4	1446	12.0	<.0001
History of hypertension					<.0001
Never	94589	67.7	5404	46.3	
Untreated	11318	8.1	921	7.9	
Treated	33757	24.2	5335	45.8	
Nonstatin lipid-lowering medication use	1912	1.3	297	2.5	<.0001
History of stroke	1749	1.2	358	3.0	<.0001
History of gallbladder removal	18599	12.7	1685	14.1	<.0001
Nonsteroidal anti-inflammatory medication use	22540	15.3	1870	15.5	.50
Aspirin use (⩾80 mg)	27913	19.0	4208	35.0	<.0001
WHI trial participation					<.0001
E alone trial only	6621	4.5	606	5.0	
E + P trial only	10941	7.4	867	7.2	
DM trial only	37760	25.7	2559	21.3	
HT and DM trials	7511	5.1	442	3.7	
OS	84356	57.3	7556	62.8	

BMI = body mass index; E = estrogen; P = progestin; DM = diet modification; HS = high school; HT = hormone therapy; MET = metabolic equivalents; NSAID = nonsteroidal anti-inflammatory drugs; OC = oral contraceptive; OS = observational study.
*Includes ibuprofen and prescription NSAID use.

Table 2 shows the distribution of statin users by type of statin, potency, lipophilicity, and duration of use. Simvastatin was the most commonly used single statin, and the majority of women used either a low- or a high-potency statin and/or a statin classified as lipophlilic. Among statin users at baseline, 3980 (33.1%) took statins for less than 1 year, 4088 (34) took statins for 1–3 years, and 3962 (32.9%) took statins for 3 or more years. Table 3 shows the incidence of invasive colorectal cancer (annualized %) and HRs by statin use and other lipid-lowering medications. There were 2000 women diagnosed with invasive colorectal cancer with a yearly incidence of 0.13% for statin users compared to 0.12% for non-users. There were no significant differences in risk of colorectal cancer for statin versus nonstain users at baseline in the age and WHI trial adjusted model (HR, 0.95; 95% CI, 0.81–1.12) or in the multivariable adjusted model (HR, 0.99; 95% CI, 0.83–1.20).

TABLE 2. Distribution of statin use at baseline by type, duration, and other statin characteristics

	N (n = 12,030)	%
Type of statin used		
Atorvastatin calcium	940	7.8
Fluvastatin sodium	1457	12.1
Lovastatin	3159	26.3
Pravastatin sodium	2640	21.9
Simvastatin	3523	29.3
Two or more statins	311	2.6
Statin potency		
Low (lovastatin, fluvastatin)	4723	39.3
Medium (pravastatin)	2717	22.6
High (simvastatin, atorvastatin)	4590	38.2
Statin category		
Hydrophobic (fluvastatin, lovastatin, simvastatin)	8139	67.7
Other (atorvastatin, pravastatin)	3580	29.8
Statin use duration, years		
<1	3980	33.1
1–<3	4088	34.0
⩾3	3962	32.9

There were no significant differences in risk on the basis of type of statin, potency or category. There was a 21% decrease in colorectal cancer risk for statin use of >3 years' duration (HR, 0.79; 95% CI, 0.56–1.11) but this difference was not statistically significant ($p = .13$). There was no significant association for other lipid-lowering medications and colorectal cancer risk. There was also no significant association between risk of proximal, distal, or rectal cancer and statin use, and no significant association between statins and colorectal cancer risk for any of the observed tumor characteristics at diagnosis (Table 4). There were no other significant interaction effects (data not shown).

When statin use reported at years 1, 3, 6, and 9 was incorporated into a multivariable time-dependent model, there was no overall effect on colorectal cancer risk (HR, 1.02; 95% CI, 0.89–1.16; Table 5). There was no significant association with colorectal cancer risk by statin potency or category or with other lipid-lowering medications in the time

TABLE 3. Invasive colorectal cancer incidence (annualized %)* and HRs by statin use and other lipid-lowering medications

			Age-adjusted†			Multivariate-adjusted‡		
	N	(Ann %)	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Statin use					.57			.95
No	1843	(0.12%)	1.00			1.00		
Yes	157	(0.13%)	0.95	(0.81–1.12)		0.99	(0.83–1.20)	
Type of statin					.74			.67
No statin use	1843	(0.12%)	1.00			1.00		
Atorvastatin	8	(0.09%)	0.69	(0.34–1.38)		0.88	(0.44–1.76)	
Fluvastatin	24	(0.17%)	1.20	(0.80–1.79)		1.19	(0.76–1.88)	
Lovastatin	37	(0.11%)	0.81	(0.59–1.13)		0.72	(0.49–1.08)	
Pravastatin	36	(0.13%)	0.98	(0.71–1.37)		1.09	(0.76–1.55)	
Simvastatin	48	(0.14%)	1.03	(0.77–1.37)		1.10	(0.80–1.50)	
2 or more statins	4	(0.13%)	0.96	(0.36–2.55)		1.19	(0.45–3.18)	
Statin potency					.94			.74
No statin use	1843	(0.12%)	1.00			1.00		
Low	62	(0.13%)	0.93	(0.72–1.19)		0.87	(0.65–1.18)	
Medium	37	(0.13%)	0.98	(0.71–1.36)		1.08	(0.76–1.54)	
High	58	(0.13%)	0.97	(0.75–1.26)		1.07	(0.80–1.42)	
Statin category					.80			.94
No statin use	1843	(0.12%)	1.00			1.00		
Hydrophobic	109	(0.13%)	0.97	(0.80–1.18)		0.97	(0.78–1.21)	
Other	44	(0.12%)	0.91	(0.68–1.23)		1.04	(0.75–1.43)	
Duration of statin use					.10			.13
No statin use	1843	(0.12%)	1.00			1.00		
<1 year	43	(0.11%)	0.81	(0.60–1.10)		0.91	(0.66–1.27)	
1–<3 years	68	(0.16%)	1.22	(0.96–1.56)		1.28	(0.97–1.68)	
>3 years	46	(0.11%)	0.82	(0.61–1.10)		0.79	(0.56–1.11)	
Other lipid-lowering medications					.67			.71
No	1971	(0.12%)	1.00			1.00		
Yes	29	(0.13%)	0.92	(0.64–1.33)		0.92	(0.61–1.41)	

CI = confidence interval; HR = hazard ratio; HT = hormone therapy; NSAID = nonsteroidal anti-inflammatory drugs; WHI = Women's Health Initiative.
*Annualized percents are calculated by category as the percentage of women with an event divided by total follow-up time in years.
†Cox proportional hazards models are adjusted for age and stratified by WHI trial randomization and extension study participation.
‡Cox proportional hazards models are adjusted for age, ethnicity, education, smoking, alcohol use, physical activity, body mass index, percent energy from fat, fruit and vegetable intake, dietary calcium, calcium supplement use, selenium supplement use, current healthcare provider, last medical visit within one year, colon screening, current HT use, family history of colorectal cancer, history of colon polyp removal, NSAID use, hypertension, history of stroke and history of coronary artery disease and stratified by WHI trial randomization and extension study participation.

dependent models. However, when statin type was taken into account, there was a marginally significant lower risk associated with use of lovastatin in the multivariable model (HR, 0.62; 95% CI, 0.39–0.99, $p = .05$).

DISCUSSION

We hypothesized that statins are associated with a lower risk of colorectal cancer on the basis of in vitro and in vivo data suggesting that the mechanism of anticancer effects are through inhibition of small GTPases (Ras and Rho) (12–14) induction of apoptosis (12, 16–18, 25), and regression of aberrant crypt foci (23). The authors of previous epidemiologic studies have reported an association of statins with either a reduction in risk of cancer overall (40, 41), or specifically a reduction in colorectal cancer risk (27, 28). In our analysis, we found no overall protective effect of statins, or when statins were considered by potency or category; however, we observed a significant reduction in colorectal cancer risk for lovastatin specifically in a time-dependent analysis, and a modest, although not significant reduction for overall statin use of ⩾3 years. We also found no association of colorectal cancer risk with use of nonstatin lipid-lowering agents, although only 1.4% of the cohort reported use of these medications at baseline.

Results from previous studies have been mixed. In a 2007 meta-analysis of 18 studies involving more than 1.5 million patients, there was no significant association between statins and colorectal cancer in six randomized controlled trials, and in 3 cohort studies, although among the nine case-control studies cited (including two studies presented as abstracts), there was an overall modest reduction in risk (26). This risk reduction was mainly attributed to the findings of a population-based study completed by Poynter et al. (24) in which statin use was compared among 1953 cases and 2015 controls in Northern Israel. Their results showed that statin use of 5 or more years was associated with a 47% reduction in risk.

TABLE 4. Invasive colorectal cancer incidence (annualized %)* and HRs by tumor characteristics and statin use

	No statin use		Statin use		Age-adjusted†			Multivariate-adjusted‡		
Tumor characteristic	N	(Ann %)	N	(Ann %)	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Proximal	961	(0.06%)	90	(0.07%)	1.03	(0.83–1.28)	.81	1.04	(0.81–1.33)	.77
Distal	437	(0.03%)	38	(0.03%)	1.01	(0.72–1.41)	.96	1.02	(0.69–1.50)	.92
Rectal	357	(0.02%)	26	(0.02%)	0.85	(0.57–1.27)	.43	1.02	(0.65–1.59)	.95
Tumor size <30 mm	464	(0.03%)	48	(0.04%)	1.18	(0.87–1.59)	.28	1.08	(0.76–1.55)	.65
Tumor size 30–49 mm	419	(0.03%)	42	(0.03%)	1.12	(0.81–1.54)	.50	1.27	(0.89–1.82)	.19
Tumor size ⩾50 mm	490	(0.03%)	32	(0.03%)	0.73	(0.51–1.04)	.08	0.77	(0.52–1.15)	.21
Localized stage	771	(0.05%)	66	(0.05%)	0.97	(0.75–1.25)	.80	0.92	(0.69–1.23)	.59
Regional stage	746	(0.05%)	64	(0.05%)	0.96	(0.74–1.23)	.73	1.02	(0.77–1.37)	.87
Distant stage	225	(0.01%)	21	(0.02%)	1.07	(0.68–1.67)	.78	1.36	(0.83–2.22)	.22
Well-differentiated grade	141	(0.01%)	13	(0.01%)	1.08	(0.61–1.91)	.80	0.93	(0.48–1.81)	.83
Moderately differentiated grade	1100	(0.07%)	96	(0.08%)	0.98	(0.80–1.21)	.86	1.06	(0.83–1.34)	.65
Poorly differentiated/anaplastic grade	397	(0.03%)	35	(0.03%)	0.99	(0.70–1.39)	.93	0.93	(0.62–1.38)	.71
Positive nodes	548	(0.03%)	53	(0.04%)	1.09	(0.82–1.45)	.55	1.19	(0.86–1.64)	.29
No positive nodes	1009	(0.06%)	82	(0.07%)	0.91	(0.73–1.15)	.44	0.94	(0.73–1.21)	.61

CI = confidence interval; HR = hazard ratio; HT = hormone therapy; NSAID = nonsteroidal anti-inflammatory drugs; WHI = Women's Health Initiative.
*Annualized percents are calculated by category as the percentage of women with an event divided by total follow-up time in years.
†Cox proportional hazards models are adjusted for age and stratified by WHI trial randomization and extension study participation.
‡Cox proportional hazards models are adjusted for age, ethnicity, education, smoking, alcohol use, physical activity, body mass index, percent energy from fat, fruit and vegetable intake, dietary calcium, calcium supplement use, selenium supplement use, current healthcare provider, last medical visit within one year, colon screening, current HT use, family history of colorectal cancer, history of colon polyp removal, NSAID use, hypertension, history of stroke and history of coronary artery disease and stratified by WHI trial randomization and extension study participation.

In a recently updated meta-analysis of 11 randomized controlled trials, 13 case-control, and 8 cohort studies, authors estimated the overall effect of statins and reported an 8% reduction in risk, although again there were no significant effects seen in randomized controlled trials (25). It should be noted that the randomized trials were designed to assess the impact of statins on cardiovascular health and were not powered to assess the role of statins in cancer prevention. In a review of eight cohort studies, the authors revealed heterogeneous findings with one study showing a significantly increased risk (42), two other studies showing a reduction in risk (43, 44), and five others showing no association (45–49). Overall cohort studies revealed a nonsignificant marginal reduction in risk among users of statins (HR. 0.89; 95% CI, 0.75–1.05) (25).

Our results showing a marginal reduction in risk of colorectal cancer associated with statins are consistent with other cohort studies (25). The reduction in risk associated with lovastatin in the time-dependent analyses though was of marginal significance, and could have been due to chance because of multiple comparisons. It is of note that at baseline, lovastatin was the second most commonly used statin in the WHI and accounted for 47% of individuals that used statins for more than 3 years. By study year 9, lovastatin accounted for only 5% of those who used statins for more than 3 years, 55% of whom reported taking atorvastatin (data not shown). It is also possible that the results by duration of use, did not reach statistical significance because of the relatively uncommon baseline use of statins in the WHI for women enrolling from 1993 through 1998 (7.6%), compared with other studies in which the prevalence of statin use ranges from 1.8% to 76%. Also, in the WHI there were only a few cases (n = 46) who used statins for 3 or more years, and additional analyses of statin use of 5 or more years reported in 26 women were not significant (data not shown). It is of note that the WHI analysis of statins and breast cancer risk revealed a reduction in breast cancer risk associated with lovastatin as well as simvastatin and fluvastatin which are also both lipophilic statins (50); however, simvastatin and fluvastatin were not associated with a reduction in colorectal cancer risk in the current analysis.

The strengths of the WHI include the prospective design; information on statin use through multiple years of follow-up; inclusion of a large, racially diverse sample of well-characterized women; large number of colorectal cancer cases; collection of detailed information on a comprehensive range of risk factors; complete follow-up of outcomes; assessment of screening at baseline and follow-up; blinded adjudication of colorectal cancer via pathology report review; description of colorectal cancer clinical characteristics; and the ability to examine associations by statin category. Limitations include the relatively low prevalence of statin use, lack of information on dose, and low power to examine long-term effects. Although statin use was determined by self-report, the actual data were derived from medications that WHI participants brought in to their clinic visits and were directly recorded by study personnel. Other limitations include the fact that there may be residual confounding by unmeasured factors and that participants were not required to have colorectal cancer screening.

TABLE 5. Invasive colorectal cancer incidence (annualized %)* and HRs by time-dependent statin use and other lipid-lowering medications

	Age-adjusted†			Multivariate-adjusted‡		
	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Statin use			.79			.82
No	1.00			1.00		
Yes	1.02	(0.91–1.14)		1.02	(0.89–1.16)	
Type of statin			.78			.47
No statin use	1.00			1.00		
Atorvastatin	1.07	(0.90–1.28)		1.06	(0.87–1.29)	
Fluvastatin	1.03	(0.72–1.48)		1.06	(0.71–1.59)	
Lovastatin	0.73	(0.50–1.05)		0.62	(0.39–0.99)	
Pravastatin	1.06	(0.82–1.37)		1.19	(0.90–1.58)	
Simvastatin	1.06	(0.87–1.30)		1.03	(0.82–1.30)	
Cerivastatin§	0.73	(0.30–1.76)		0.55	(0.18–1.71)	
Rosuvastatin§	–	–		–	–	
2 or more statins	1.24	(0.46–3.30)		1.43	(0.54–3.83)	
Statin potency			.50			.32
No statin use	1.00			1.00		
Low	0.85	(0.65–1.10)		0.80	(0.59–1.09)	
Medium	1.04	(0.81–1.36)		1.17	(0.89–1.56)	
High	1.05	(0.92–1.21)		1.03	(0.88–1.20)	
Statin category			.90			.59
No statin use	1.00			1.00		
Hydrophobic	0.99	(0.84–1.16)		0.94	(0.77–1.14)	
Other	1.03	(0.89–1.19)		1.06	(0.90–1.25)	
Other lipid-lowering medications			.58			.25
No	1.00			1.00		
Yes	0.92	(0.69–1.23)		0.81	(0.57–1.16)	

CI = confidence interval; HR = hazard ratio.
*Annualized percents are calculated by category as the percentage of women with an event divided by total follow-up time in years.
†Cox proportional hazards models are adjusted for age and stratified by WHI trial randomization and extension study participation.
‡Cox proportional hazards models are adjusted for age, ethnicity, education, smoking, alcohol use, physical activity, body mass index, percent energy from fat, fruit and vegetable intake, dietary calcium, calcium supplement use, selenium supplement use, current healthcare provider, last medical visit within one year, colon screening, current HT use, family history of colorectal cancer, history of colon polyp removal, NSAID use, hypertension, history of stroke and history of coronary artery disease and stratified by WHI trial randomization and extension study participation.
§Cerivastatin and Rosuvastatin came on the market after baseline data collection was complete. None of the women who reported use of Rosuvastatin developed colorectal cancer during the study, thus the HR for Rosuvastatin is inestimable.

In conclusion, despite sound scientific plausibility, the association of statins with a reduced risk of colorectal cancer is not clearly evidenced in the WHI cohort. Although the reduction in risk associated with lovastatin in the time-dependent analysis is provocative, and the marginal reduction in risk with longer term exposure was consistent with the literature, our results are still not conclusive. Recent studies suggest that the efficacy of statins in reducing both cardiovascular (51) and colorectal cancer risk (52) may be related to genetic variation in 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. The results from these studies support the need for randomized trials of statin use among individuals at high risk for colorectal cancer based on family history or genetic predisposition.

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Women's Health Initiative Memory Study

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