

ORIGINAL ARTICLE

## Statins and the Risk of Colorectal Cancer

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### ABSTRACT

#### BACKGROUND

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Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase and effective lipid-lowering agents. Statins inhibit the growth of colon-cancer cell lines, and secondary analyses of some, but not all, clinical trials suggest that they reduce the risk of colorectal cancer.

#### METHODS

The Molecular Epidemiology of Colorectal Cancer study is a population-based case–control study of patients who received a diagnosis of colorectal cancer in northern Israel between 1998 and 2004 and controls matched according to age, sex, clinic, and ethnic group. We used a structured interview to determine the use of statins in the two groups and verified self-reported statin use by examining prescription records in a subgroup of patients for whom prescription records were available.

#### RESULTS

In analyses including 1953 patients with colorectal cancer and 2015 controls, the use of statins for at least five years (vs. the nonuse of statins) was associated with a significantly reduced relative risk of colorectal cancer (odds ratio, 0.50; 95 percent confidence interval, 0.40 to 0.63). This association remained significant after adjustment for the use or nonuse of aspirin or other nonsteroidal antiinflammatory drugs; the presence or absence of physical activity, hypercholesterolemia, and a family history of colorectal cancer; ethnic group; and level of vegetable consumption (odds ratio, 0.53; 95 percent confidence interval, 0.38 to 0.74). The use of fibric-acid derivatives was not associated with a significantly reduced risk of colorectal cancer (odds ratio, 1.08; 95 percent confidence interval, 0.59 to 2.01). Self-reported statin use was confirmed for 276 of the 286 participants (96.5 percent) who reported using statins and whose records were available.

#### CONCLUSIONS

The use of statins was associated with a 47 percent relative reduction in the risk of colorectal cancer after adjustment for other known risk factors. Because the absolute risk reduction is likely low, further investigation of the overall benefits of statins in preventing colorectal cancer is warranted.

**C**OLORECTAL CANCER IS THE THIRD most commonly diagnosed cancer in the United States, with approximately 145,000 new cases and 56,300 deaths projected for 2005.<sup>1</sup> An intensive search to identify chemopreventive agents as a means to reduce the complications and deaths due to colorectal cancer has revealed aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) as attractive candidates,<sup>2-6</sup> although concern about toxicity may limit broad application of these agents.

The rate-limiting enzyme in mevalonate synthesis is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.<sup>7,8</sup> The statins are a class of agents designed to inhibit HMG-CoA reductase, and they are effective in the management of hypercholesterolemia. Owing to the involvement of HMG-CoA reductase in cholesterol synthesis and growth control, statins may have chemopreventive activity against cancer.<sup>9</sup> In vitro data support a potential role for the use of statins in colorectal cancer. HMG-CoA reductase is overexpressed in colorectal-cancer cells,<sup>10</sup> and statins have been shown to induce apoptosis in cancer cell lines in vitro.<sup>11,12</sup>

Several randomized clinical trials designed to assess the safety of statins and cardiovascular outcomes among patients receiving them have also assessed the incidence of cancer. The results were not consistent: in some trials, more cases of cancer occurred among patients treated with statins than among those who did not receive these agents, and in other trials, fewer cases occurred.<sup>13-21</sup> Since all these studies were designed to assess end points related to cardiovascular disease, the small numbers of cancers observed limit their statistical power to detect associations between statin use and the risk of cancer. To clarify this association, we evaluated data gathered in a population-based, epidemiologic, case-control study.

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## METHODS

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### PARTICIPANTS

The Molecular Epidemiology of Colorectal Cancer study is a population-based case-control study of incident colorectal cancer in northern Israel. Patients were eligible for participation if they had received a diagnosis of colorectal cancer between May 31, 1998, and March 31, 2004, and lived in a geographically defined area of northern Israel. Controls were identified from the same source population with the use of the Clalit Health Services (CHS) database.

CHS is the largest health care provider in Israel and covers approximately 70 percent of the older population (persons at least 60 years of age). Health care coverage in Israel is mandated and is provided by four groups akin to health maintenance organizations. Thus, all study participants (patients and controls) had similar health insurance and similar access to health services. Controls were individually matched to patients according to the year of birth, sex, primary clinic location, and ethnic group (Jewish vs. non-Jewish). Potential controls were excluded if they had a history of colorectal cancer. Participants provided written informed consent at the time of enrollment.

Participants were interviewed to obtain demographic information and information about their personal and family history of cancer, reproductive history, medical history, medication use, and health habits; they also completed a dietary questionnaire. Diagnoses of colorectal cancer were confirmed by means of a standardized pathological review by one pathologist. The institutional review boards at the Carmel Medical Center, Haifa, and the University of Michigan, Ann Arbor, approved all procedures.

### EXPOSURE DATA

Participants were asked to recall each medication they had used for at least five years, and statin use was determined on the basis of this list. The use of aspirin and other NSAIDs was also assessed; information gathered included dose, duration of use, and indication for use. For analyses of aspirin or other NSAIDs, exposure was defined as five or more years of total use, and no exposure was defined as less than five years of use or no use.

A complete, three-generation pedigree and information on the family history of cancer were also recorded for each participant. The report of colon or rectal cancer in at least one first-degree relative was considered to represent a family history of colorectal cancer. Assessment of physical activity was based on a validated instrument<sup>22</sup> used to evaluate three dimensions of physical activity: sports, leisure, and occupational activities. Sports activity was the dimension considered in these analyses since it is the dimension most strongly associated with colorectal cancer in this analysis.

Ethnic group was determined by assessing participants' religious affiliation, self-described ethnic group, and the country of birth of their parents and grandparents. Ashkenazi Jewish heritage was determined as previously described.<sup>23</sup>

Characteristic	Patients	Controls	P Value
All subjects — no.	1953	2015	
Sex — no. (%)†			0.70
Male	1004 (51.4)	1024 (50.8)	
Female	949 (48.6)	991 (49.2)	
Age — yr†	69.9±11.7	71.0±11.5	0.51
Ethnic group — no. (%)†			<0.001
Jewish			
Ashkenazi	1352 (69.2)	1278 (63.4)	
Sephardi	334 (17.1)	476 (23.6)	
Mixed	14 (0.7)	13 (0.6)	
Other or unspecified	23 (1.2)	17 (0.8)	
Arab			
Christian	77 (3.9)	72 (3.6)	
Muslim	81 (4.1)	102 (5.1)	
Other	30 (1.5)	27 (1.3)	
Christian, non-Arab	42 (2.2)	30 (1.5)	
Hypercholesterolemia — no. (%)	408 (20.9)	528 (26.2)	<0.001
History of colorectal cancer in first-degree relative — no. (%)	137 (7.0)	85 (4.2)	<0.001
Sports participation — no. (%)	611 (31.3)	814 (40.4)	<0.001
Vegetable consumption — no. (%)‡			<0.001
Low	779 (41.8)	652 (32.6)	
Medium	546 (29.3)	687 (34.4)	
High	538 (28.9)	661 (33.0)	

Comprehensive dietary histories were obtained with the use of a validated food-frequency questionnaire modified for the Israeli diet. Vegetable consumption was categorized into three groups on the basis of the number of servings consumed per day in the control group (fewer than 5.2, 5.2 to 7.5, and more than 7.5 servings per day). The lowest category of consumption was used as the reference category. Red-meat consumption was also categorized into three groups on the basis of the number of servings consumed per day in the control group. A participant's history of medical conditions was elicited by asking whether he or she had ever received a diagnosis of any of 15 medical conditions, including hypercholesterolemia, ischemic heart disease, and inflammatory bowel disease.

#### VALIDATION OF STATIN USE

Participants' reports of statin use were matched against CHS prescription records to verify use. Prescription records were available for 1998 through 2004 and included the number of prescriptions

filled per year. The prescription file was started in 1998, so any prescriptions filled before 1998 could not be validated by this means. Prescription records for statins during the year before diagnosis were reviewed for all patients who were invited to participate in the study; for controls, prescription records during the year before enrollment in the study were reviewed. In this way, potential differences between participating and nonparticipating patients and controls in terms of statin use were evaluated.

#### STATISTICAL ANALYSIS

Statistical analyses were performed with the use of SAS software (version 8.2), and all reported P values are two-sided. A contingency table was used to assess crude associations between statin use and the risk of colorectal cancer. Stratified analyses and unconditional logistic regression were used to assess the association between statin use and the risk of colorectal cancer, to adjust for confounding, and to identify any potential effect modification. To account for the study design, matched analyses were

**Table 1. (Continued.)**

Characteristic	Patients	Controls	P Value
Matched pairs — no.	1651	1651	
Sex — no. (%)†			1.00
Male	845 (51.2)	845 (51.2)	
Female	806 (48.8)	806 (48.8)	
Age — yr‡	70.0±11.6	70.6±11.6	0.88
Ethnic group — no. (%)			<0.001
Jewish			
Ashkenazi	1130 (68.4)	1032 (62.5)	
Sephardi	293 (17.7)	408 (24.7)	
Mixed	11 (0.7)	10 (0.6)	
Other or unspecified	21 (1.3)	12 (0.7)	
Arab			
Christian	64 (3.9)	59 (3.6)	
Muslim	73 (4.4)	83 (5.0)	
Other	30 (1.8)	25 (1.5)	
Christian, non-Arab	29 (1.8)	22 (1.3)	
Hypercholesterolemia — no. (%)	344 (20.8)	425 (25.7)	<0.001
History of colorectal cancer in first-degree relative — no. (%)	107 (6.5)	68 (4.1)	<0.001
Sports participation — no. (%)	533 (32.3)	677 (41.0)	<0.001
Vegetable consumption — no. (%)§			<0.001
Low	630 (39.9)	522 (31.8)	
Medium	469 (29.7)	564 (34.4)	
High	479 (30.4)	553 (33.7)	

\* Plus-minus values are means ±SD.

† This was a matching variable, with matching for ethnic group (Jewish vs. non-Jewish).

‡ This category excludes 90 patients and 15 controls with missing data on the food-frequency questionnaire.

§ This category excludes 73 patients and 12 controls with missing data on the food-frequency questionnaire.

performed with the use of both contingency-table methods and conditional logistic regression.

## RESULTS

Of the 3181 potentially eligible patients in whom colorectal cancer was ascertained during the study period, 618 (19.4 percent) could not be located or approached, including 275 (8.6 percent) who had died. Thus, 2563 patients were approached and invited to participate. Forty-two were subsequently excluded as too sick to participate or unable to communicate in Hebrew, Russian, Arabic, or English. Of the 2521 remaining eligible patients, 335 declined to participate (13.3 percent). Therefore, 2186 eligible patients agreed to participate, and 2146 completed the in-person interview, which corresponds to a response rate of 67.5 percent of all eli-

gible patients. In addition, 2162 matched controls provided consent and were interviewed, representing 52.1 percent of the eligible controls who were invited to participate. Findings reported here are based on data from the 1953 patients and 2015 controls, corresponding to 1651 matched pairs, for whom data were available at the time of a planned analysis in July 2004. For ease of presentation, results are given first for the unmatched analysis and then for the matched analysis.

Ashkenazi Jews were overrepresented among the patients, a finding corresponding to the known increased risk of colorectal cancer among Ashkenazi as compared with non-Ashkenazi Jews.<sup>24</sup> Hypercholesterolemia was reported in 20.9 percent of the patients and 26.2 percent of the controls (Table 1).

The use of statins for at least five years was reported more often by controls than by patients (11.6

**Table 2. Crude and Adjusted Associations between Statin Use and the Risk of Colorectal Cancer in the Unmatched Study Population.\***

Variable	Patients	Controls	Total No.	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) <sup>†</sup>
	<i>no. of subjects (%)</i>				
Statin use				0.50 (0.40–0.63)	0.57 (0.44–0.73)
Yes	120 (6.1)	234 (11.6)	354		
No	1833 (93.9)	1781 (88.4)	3614		

\* CI denotes confidence interval.

<sup>†</sup> Analyses were adjusted for age; sex; use or nonuse of aspirin or other NSAIDs; ethnic group; the presence or absence of sports participation, hypercholesterolemia, and a history of colorectal cancer in a first-degree relative; and level of vegetable consumption.

percent vs. 6.1 percent) and was associated with a significant reduction in the risk of colorectal cancer (odds ratio, 0.50; 95 percent confidence interval, 0.40 to 0.63) (Table 2). After adjustment for potential confounders (including age; sex; the use or nonuse of aspirin or other NSAIDs; ethnic group; the presence or absence of sports participation, hypercholesterolemia, and a history of colorectal cancer in a first-degree relative; and level of vegetable consumption), the association between statins and the reduced risk of colorectal cancer remained significant. The level of education and level of red-meat consumption were also evaluated as potential confounders but were not included in the final model, since they did not measurably influence the odds ratio. Matched analyses of 1651 pairs revealed that the crude and adjusted odd ratios for statin use were similar in magnitude to those found in the unmatched analysis and remained significant (Table 3). When the analysis was limited to the 1520 patients who were members of CHS, the association was unchanged (odds ratio, 0.50; 95 percent confidence interval, 0.39 to 0.64). The frequency of statin use increased with increasing year of detection among both patients ( $P$  for trend=0.08) and controls ( $P$  for trend=0.02). After controlling for the year of detection, we found that the association between statin use and the reduced risk of colorectal cancer remained virtually unchanged (odds ratio, 0.51; 95 percent confidence interval, 0.40 to 0.64).

Simvastatin and pravastatin were the two most commonly used statins in this population, accounting for 55.6 percent and 41.5 percent of use, respectively. In unadjusted analyses, the strength of the association between statin use (vs. no statin use) and

a reduced risk of colorectal cancer was similar for simvastatin (odds ratio, 0.49; 95 percent confidence interval, 0.36 to 0.67) and pravastatin (odds ratio, 0.44; 95 percent confidence interval, 0.31 to 0.63).

To assess whether the association was due to a general effect of cholesterol lowering or to a specific effect of statins, we also evaluated the association between other cholesterol-lowering drugs and the risk of colorectal cancer. Twenty-one patients and 20 controls used the fibric-acid derivative bezafibrate. There was no significant association between bezafibrate use and the risk of colorectal cancer (odds ratio, 1.08; 95 percent confidence interval, 0.59 to 2.01). It is worthwhile to note that only 1 percent of the study population reported using bezafibrate, so it is unlikely that we would be able to identify small effects associated with the use of fibric-acid derivatives. No other class of cholesterol-lowering agent or specific drug was reported as being commonly used.

After adjustment for the use of aspirin or other NSAIDs for at least five years as well as other risk factors for colorectal cancer, statin use was still associated with a significant reduction in the risk of colorectal cancer (odds ratio, 0.55; 95 percent confidence interval, 0.40 to 0.74) (Table 4). Because of reports of a synergistic effect in vitro between NSAIDs and statins, we evaluated whether the use of aspirin or other NSAIDs modified the protective effect of statins. We could find no evidence of an effect modification on a multiplicative scale ( $P=0.36$ ).

A stratified analysis was performed to determine whether statins appeared equally protective among patients with and those without a family history of colorectal cancer. The protective association remained significant among patients with a family history of colorectal cancer (odds ratio, 0.41; 95 percent confidence interval, 0.19 to 0.93), and we noted no interaction between family history and statin use ( $P$  for interaction=0.67).

We analyzed the data separately for cancers of the colon and the rectum and observed a significant inverse association for both (Table 3). Statin users were almost as likely as nonusers to have colorectal cancer diagnosed at an early stage of disease (stage I or II) as compared with a later stage (stage III or IV) (odds ratio, 0.90; 95 percent confidence interval, 0.54 to 1.50;  $P=0.69$ ). Colorectal cancer was somewhat less likely to be poorly differentiated among statin users (6.4 percent) than among nonusers (8.6 percent), although this difference was not significant ( $P=0.48$ ).

**Table 3. Effect of Statins on the Risk of Colorectal Cancer, Colon Cancer, and Rectal Cancer in Matched Pairs.\***

Subgroups of Patients	Controls		Total No.	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
	Statin Use	No Statin Use			
	no. of subjects				
Patients with colorectal cancer					
Statin use	21	76	97		
No statin use	168	1386	1554		
Total	189	1462	1651	0.45 (0.35–0.59)†	0.53 (0.38–0.74)
Patients with colon cancer					
Statin use	11	43	54		
No statin use	78	737	815		
Total	89	780	869	0.55 (0.38–0.80)	
Patients with rectal cancer					
Statin use	1	12	13		
No statin use	32	299	331		
Total	33	311	344	0.38 (0.19–0.73)	

\* CI denotes confidence interval.

† Analyses were adjusted for use or nonuse of aspirin or other NSAIDs; ethnic group; the presence or absence of sports participation, hypercholesterolemia, and a history of colorectal cancer in a first-degree relative; and level of vegetable consumption.

To evaluate the possibility of confounding by indication, we investigated statin use and the risk of colorectal cancer among patients who reported a previous diagnosis of hypercholesterolemia or ischemic heart disease, and the protective effect of statins was similar in these patients (Table 5). Because of our interest in the antiinflammatory properties of statins, we also examined the relationship between statin use and the risk of colorectal cancer among 55 patients with inflammatory bowel disease, and we observed a protective effect of statins in this subgroup (P=0.006 for the comparison between users and nonusers of statins) (Table 5).

We validated regular statin use on the basis of prescription records from the CHS database for the 286 self-reported statin users who were members of CHS. When we classified regular users of statins as persons who filled a prescription for statins three or more times per year, self-reports were validated for 276 of 286 participants (96.5 percent). Self-reported use could not be confirmed on the basis of prescription records for six patients and four controls.

We also used data from prescription records to evaluate differences in statin use among patients and controls who declined to participate in the study.

The use of statins during the year before diagnosis (for patients) and the year before enrollment (for controls) was compared. No significant difference in the rate of statin use was observed between patients who were interviewed and those who declined to participate (5.2 percent vs. 6.0 percent, P=0.51). The findings were similar among participating controls and those who declined to participate (6.3 percent and 5.7 percent, respectively; P=0.39).

#### DISCUSSION

Our data indicate that there is a strong inverse association between the risk of colorectal cancer and the long-term use of statins. This association is consistent with preclinical data suggesting that it is biologically plausible that statins may have a role in colorectal cancer, as well as with evidence from secondary analyses of some, but not all, randomized, controlled trials. These data are also consistent with the results of a small, nested case-control study from Quebec, Canada, that reported a significant reduction in the occurrence of all cancers among statin users as compared with persons who did not use statins (but who did take bile acid-binding resins to lower cholesterol) and a nonsignificant

**Table 4. Crude and Adjusted Associations between the Use of Statins and Aspirin or Other NSAIDs and the Risk of Colorectal Cancer.\***

Variable	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†	P Value
Statin use for ≥5 yr (vs. use for <5 yr or no use)	0.50 (0.40–0.63)	0.55 (0.40–0.74)	<0.001
Use of aspirin or other NSAIDs for ≥5 yr (vs. use for <5 yr or no use)	0.63 (0.51–0.77)	0.70 (0.55–0.90)	0.005
Interaction term	—	1.30 (0.74–2.27)	0.36

\* CI denotes confidence interval.

† Analyses were adjusted for age; sex; ethnic group; the presence or absence of sports participation, hypercholesterolemia, and a history of colorectal cancer in a first-degree relative; and level of vegetable consumption.

**Table 5. Association between Statin Use and the Risk of Colorectal Cancer among Participants with Hypercholesterolemia, Ischemic Heart Disease, or Inflammatory Bowel Disease.**

Variable	Patients	Controls	Total No.	Odds Ratio (95% CI)*
	<i>no. of subjects (%)</i>			
<b>Hypercholesterolemia</b>				
Statin use	91 (22.3)	190 (36.0)	281	
No statin use	317 (77.7)	338 (64.0)	655	
Total	408	528	936	0.51 (0.38–0.68)
<b>Ischemic heart disease</b>				
Statin use	59 (14.0)	136 (24.4)	195	
No statin use	361 (86.0)	421 (75.6)	782	
Total	420	557	977	0.51 (0.36–0.71)
<b>Inflammatory bowel disease</b>				
Statin use	1 (2.6)	5 (31.2)	6	
No statin use	38 (97.4)	11 (68.8)	49	
Total	39	16	55	0.06 (0.006–0.55)

\* CI denotes confidence interval.

protective effect of statin use among 56 patients with colon cancer (odds ratio, 0.83; 95 percent confidence interval, 0.37 to 1.89).<sup>25</sup> A nested case-control study from the Netherlands also showed a significant reduction in the incidence of all cancers among statin users as compared with nonusers, which increased with increasing duration of use, and a nonsignificant reduction in risk among 292 patients with colon cancer (odds ratio, 0.87; 95 percent confidence interval, 0.48 to 1.57) and 148

patients with rectal cancer (odds ratio, 0.48; 95 percent confidence interval, 0.16 to 1.48).<sup>26</sup> In contrast, an analysis of data from the General Practice Research Database found a marginally increased risk of cancers of the colon and rectum among persons who had used statins for longer than 60 months as compared with those who had not used statins.<sup>27</sup> All these previous observational studies are limited by the small numbers of cases of colorectal cancer.

In vitro data suggest that statins may have a synergistic effect with NSAIDs.<sup>28,29</sup> However, our results do not provide evidence of an interaction between statins and aspirin or other NSAIDs (P for interaction=0.36). Rodent models may not perfectly represent human disease, and it is worth noting that the end point in the rat azoxymethane model is polyp formation rather than the development of colorectal cancer.

Statins have been shown to be associated with an acceptable adverse-effect profile in patients with hypercholesterolemia,<sup>30</sup> with a discontinuation rate of approximately 3 percent owing to such effects.<sup>31</sup> If statins were to be considered for chemopreventive studies in subjects without elevated cholesterol levels, the safety of such an application would need to be evaluated in this population.

We evaluated the potential absolute reduction in the risk of colorectal cancer after treatment with statins by estimating the number of cancers that could be prevented by statin use in both the Israeli population and a high-risk population. In 2002, the age-adjusted incidence of colorectal cancer was 42 per 100,000 Jewish men,<sup>32</sup> and the rate was similar among Jewish women. Using the matched, adjusted odds ratio of 0.53 as an approximation for the relative risk in order to calculate the absolute reduction in risk,<sup>33</sup> we determined that statin therapy could prevent 20.8 cases per 100,000 Jewish men. In the average-risk Israeli population, 4814 persons would need to be treated with statins to prevent one case of colorectal cancer. In a high-risk population, such as those with a family history of colorectal cancer, approximately half as many would need to be treated in order to prevent one case.

Our study has several limitations. Exposure data were collected retrospectively and are therefore sensitive to recall bias. However, since participants are not likely to expect that the use of statins is related to the risk of colorectal cancer, any resulting misclassification is most likely nondifferential and would

tend to attenuate true associations. Furthermore, we were able to validate self-reported statin use through a prescription database. The participation rate was lower among controls than among patients, suggesting the possibility of selection bias. Selection bias seems unlikely, however, since the rate of statin use was similar among those who participated and those who declined. It is also possible that some controls had undiagnosed colorectal cancer, and this type of misclassification would be likely to attenuate any observed association. Assessment of potential confounders was also self-reported; measurement error for these variables could limit our ability to control adequately for confounding. We had very limited information on the dose and dura-

tion of use of statins and therefore could not analyze the data for evidence of a dose response.

We found that the use of statins is associated with a 47 percent relative reduction in the risk of colorectal cancer after adjustment for other known risk factors and is specific to this class of lipid-lowering agents. Our finding suggests that statins deserve further investigation in chemoprevention and therapeutic clinical trials.

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Dr. Greenon reports having served as an expert witness for Parke-Davis (now Pfizer) with respect to a class of medications not discussed in this article. Mr. Bonner reports having been employed by Parke-Davis (now Pfizer) and owning stock in Pfizer.

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