Neither Long-Term Statin Use nor Atherosclerotic Disease Is Associated With Risk of Colorectal Cancer

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BACKGROUND & AIMS: Statin use has been reported to reduce risk for colorectal cancer (CRC) whereas atherosclerotic disease has been reported to increase risk, but findings have been inconsistent. We aimed to establish the association of statin use and coronary atherosclerosis with CRC.

METHODS: We performed a population-based case control study of patients with a first diagnosis of CRC cancer between January 1, 1991, and December 31, 2008 (n = 9979), using the Danish National Registry of Patients. As many as 10 population controls were matched to each patient using risk set sampling (n = 99,790). Statin use before cancer diagnosis (or control index date) was determined via county prescription databases and evidence of coronary atherosclerosis using International Classification of Diseases codes. We calculated incidence rate ratios using conditional logistic regression, adjusted for multiple covariates.

RESULTS: Among patients with CRC, statin use was modest (7.7%), but 23.5% of use was long term (≥5 years). Ever use of statins (≥2 prescriptions) slightly reduced CRC risk, compared with relative to never/rare use (incidence rate ratio [IRR] = 0.87, 95% confidence interval = 0.80–0.96). However, long-term use did not affect risk compared with never/rare use (IRR = 0.95, 95% confidence interval = 0.80–1.12). No associations were observed between atherosclerosis, myocardial infarction, or stroke, and CRC incidence.

CONCLUSIONS: Although there is a weak inverse association between ever use of statins and CRC incidence, there was no trend with increasing duration of use, so statins do not appear to reduce CRC risk. We did not confirm the reported association between atherosclerosis and CRC risk.

Keywords: ICD; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Colorectal Neoplasms; Epidemiology; Myocardial Infarction.

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Colorectal cancer (CRC) is the second most common cause of cancer death in the United States1 and so prevention is of significant public health importance.2 While screening for this cancer is likely to be a major factor in reducing disease burden, chemoprevention may also play an important role.

Some have suggested that statins, a drug class widely prescribed for the treatment of hypercholesterolemia, may be a potential agent for chemoprevention.3,4 Statin drugs are potentially attractive agents as chemopreventive agents because they are safe and complications that would merit discontinuation are rare.5–7 These drugs reduce lipid levels by inhibiting the enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate.8,9 While the precise mechanisms by which these drugs may prevent cancer growth have not been elucidated, the inhibition of mevalonate synthesis appears to be important.5,10 Specifically, mevalonate is a precursor for the synthesis of substances that may serve as regulators of cell growth. However, antineoplastic mechanisms independent of the mevalonate pathway have also been suggested,11 and increasing evidence suggests that statins have potent anti-inflammatory effects that contribute to their beneficial effects.12 In vitro studies have shown that these agents can induce growth arrest and apoptosis.5,10,13,14

Epidemiological studies examining the association of statin use and CRC have reported inconsistent findings. One large population-based case control study from Israel suggested that long-term (>5 years) statin use was associated with a 50% reduction in cancer risk.15 A similar reduction in CRC risk has recently been reported in a large cohort of veteran patients.16 However, other large case control studies from the United States17 and United Kingdom18,19 showed no statistical association between statin use and cancer incidence.

Similar to the epidemiologic evidence linking statins and CRC, studies examining coronary atherosclerosis and CRC have also been inconsistent. CRC and coronary artery disease share common risk factors (eg, diabetes, smoking) and so an association between the 2 is plausible. In a cross-sectional analysis of autopsies (n = 842), the presence of atherosclerotic lesions of the aorta was significantly associated with adenomatous polyps in both white and black men.20 A recent Israeli cohort study found that colon cancer incidence was significantly higher in subjects with known coronary heart disease when compared with population controls (relative risk = 1.41; 95% confidence interval [CI], 1.11–1.80).21 In Hong Kong, a group of patients, all of whom underwent coronary angiography, subsequently underwent screening colonoscopy. After adjusting for age and sex, those with coronary artery disease were significantly more

Abbreviations used in this paper: ATC, Anatomical Therapeutical Chemical; CI, confidence interval; CRC, colorectal cancer; DDD, defined daily dose; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; ICD, International Classification of Diseases; IRR, incidence rate ratio; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

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likely to have a colorectal neoplasm (adjusted odds ratio [OR], 1.88; 95% CI, 1.25–2.70).22

Members of our group, using Danish Cancer Registry data, have previously performed a population-based cohort study of cancer risk among statin users and found a modest, but statistically significant, reduction in all cancer incidence among statin users (0.86; 95% CI, 0.78–0.95).23 However, that study was not designed to specifically evaluate risk for CRC, nor did it assess risk among long-term users. Therefore, we performed a large population-based case control study specifically focused on long-term users of the drug and with adjustment for relevant confounders. Given the recent interest in atherosclerotic disease and CRC, we also examined that association.

Methods

We performed a population-based case control study using the combined counties of Aarhus and North Jutland County, Denmark. The entire Danish population is provided tax-supported health care by the National Health Service, allowing free access to health care. Through the use of a unique 10-digit civil registry number assigned to all Danish citizens at birth, which incorporates sex and date of birth, complete hospital discharge and prescription histories can be obtained, and linked to specific individuals. Our outcome of interest was incident CRC. In the analyses, our primary exposure was statin use while secondarily examining the association of atherosclerosis with CRC. This study was approved by the Danish Protection Agency (record number 2004-41-4693).

Identification of CRC Cases

To identify cases, we utilized the Danish National Registry of Patients covering all Danish hospitals. These registries include the civil registry number and detailed individual data on all acute care nonpsychiatric hospital admissions (since 1977), and hospital outpatient and emergency room contacts (since 1995) in Denmark including up to 20 discharge diagnoses per admission or contact using International Classification of Diseases (ICD) coding.24,25

Using the Danish National Registry of Patients, we identified all patients with a first diagnosis of CRC (ICD-8: 153.00–153.99, 154.00–154.19; ICD-10: C18.0–C18.9, C19.9, C20.9) in North Jutland County during the period from January 1, 1991, through December 31, 2008, and in Aarhus County during the period January 1, 1998, through December 31, 2008. To be a case, an individual had to live in either North Jutland County or Aarhus County for the 2 calendar years prior to cancer diagnosis.

Identification of Population Controls

To identify controls, we utilized the Danish Civil Registration System. Through the civil registry number, all changes in vital status and migration are tracked. We chose up to 10 controls for each case, matched by birth, gender, and county of residence using risk set sampling. Therefore, the controls had to be alive and at risk for a first hospital admission of CRC at the time the corresponding case was diagnosed, and have 2 years residence in-county. When using risk set sampling, the estimated exposure odds ratio in a case-control design is an unbiased estimate of the incidence rate ratio.26

Identification of Statin Use and Atherosclerotic Disease

We assessed statin use from the Prescription Databases from Aarhus and North Jutland County. Data from North Jutland County were available from January 1, 1989. Data from Aarhus County were available from January 1, 1996. The prescription databases include the civil registry number, the date the prescription was filled, number of tablets and quantity dispensed, and information on the drug prescribed using the Anatomical Therapeutical Chemical (ATC) classification system.27–29 Statins registered during the study period were: simvastatin (C10AA01, B04AB01), lovastatin (C10AA02), pravastatin (C10AA03), fluvastatin (C10AA04), atorvastatin (C10AA05), cerivastatin (C10AA06), rosuvastatin (C10AA07), and pitavastatin (C10AA08).

To identify those with atherosclerotic disease appropriate diagnostic (ICD) codes for atherosclerotic disease (ICD-8: 411–414, 440; ICD-10: I20, I24, I25, I70), myocardial infarction (ICD-8: 410; ICD-10: I21.0–I23.9) and stroke (ICD-8: 431–434; ICD-10: I16, I163, I164) were employed.

Ascertainment of Potential Confounding Factors

We controlled for a number of potentially important confounders including aspirin (ATC codes: B01AC06, N02BA01, N02BA51) and nonaspirin (ATC codes: M01A) nonsteroidal anti-inflammatory drug (NSAID) use, and cholecystectomy (Nordic Classification of Surgical Procedures and Therapies30 codes: 4736 [1977–1995] and JKA20 and JKA21 [1996–2005]). ICD coding for diabetes (ICD-8 codes 249–250 and ICD-10 codes E10–E14) was used as a marker of that disease, and a prior hospital diagnosis for alcoholism (ICD-8: 291, 303, 577.10, 979, 980; ICD-10: F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, R78.0, T51, T72.1) was employed as a proxy measure for heavy alcohol use.

Statistical Analysis

For each subject, we identified prescriptions for all statins filled before the first hospitalization with CRC, or the corresponding index date in the matched controls. We ignored any statin prescription filled within 1 year prior to index date because it is likely that CRC among the cases had already developed. Contingency tables and ORs computed with conditional logistic regression were used to assess the association of statin use and relevant confounders with case control status.

Individuals identified to have had 2 or more statin prescriptions during the observation period (prior to CRC detection) were identified as “ever users” of the drug with all others defined as never/rare users. Then, to examine the effect of temporality of statin use on cancer risk, we subdivided “ever users” into “recent users” and “former users” of the drug. Recent use was defined as having at least 1 prescription within 1–3 years of index date, and former use was defined as having received all prescriptions more than 3 years prior to the date of cancer diagnosis (or the corresponding index date in the controls).

The intensity of statin use (estimate of number of tablets/day by subject) was determined by dividing the total number of pills prescribed by the duration of use (as defined above). To determine whether longer duration of statin use was associated with cancer development we calculated duration of use for each ever user by counting the number of days from the
date of the first prescription to the date of the last prescription in the registry and adding the “duration” of the last prescription (determined by the number of pills in that last prescription). Arbitrarily, we defined short-term use as <3 years, medium-term use as 3–5 years and long-term use as >3 years. Conditional logistic regression was used to estimate ORs for CRC with never/rare users defined as the reference group.

In addition to analyses performed based on counts of prescription data, to further refine our estimates we examined prescription data in terms of “defined daily dose” (DDD). Using DDD, each drug is assigned a value that represents the average maintenance dose per day (http://www.whocc.no/atcddd). We used data on DDD obtained from the prescription databases and performed 2 supplementary analyses examining length of use and average daily dose. We defined short-, medium-, and long-term use identically as above and performed conditional regression (adjusting for the same factors) categorizing use by DDD and again using never/rare use as the reference group. Similarly, we categorized statin users by average daily dose (<1.0 DDD/day, 1.0 to <1.5 DDD/day, ≥1.5 DDD/day) and compared categories of users to the never/rare reference group using logistic regression.

We performed separate subgroup analyses examining risk based on the specific type of statin drug prescribed.

For each analysis, adjustment for the potential confounding effects of other medications and diseases was performed. Medication use was categorized in the same manner as our main exposure variable. To be considered an “ever user” 2 or more prescriptions were required. Recent use was defined as having at least 1 prescription within 1–3 years of index date, and former use was defined as having received all prescriptions more than 3 years prior to the date of cancer diagnosis (or the corresponding index date in the controls).

### Results

During the study period, we identified 9979 cases of CRC and 99,790 population controls. The characteristics of the study population are summarized in Table 1. The mean age of the population was 71.2 years and 50.6% of the group was male. With regard to potential confounding factors, cases were more likely than controls to carry a diagnosis of alcoholism or diabetes and to have undergone cholecystectomy. Recent NSAID use (≥2 prescriptions during 1–3 years prior to index date) was significantly more common in the cases (23.3%; P = .0002). However, prescriptions for aspirin were similarly common in the 2 groups.

When considering statin use in the total population, 8440 (7.7%) were classified as users (2 or more prescriptions during the period of observation) and of these, 1983 (23.5%) were long-term (>5 years) users. Nearly all users were recent users (97%) reflecting the fact that once on the drug, few discontinued it. Also, based on assessment of intensity of use, most appeared to use a single tablet per day (median intensity among all statin users = 0.98; interquartile range, 0.87–1.03).

Ever use of statins was associated with a small, but statistically significant, reduction in risk of subsequent CRC when compared with never/rare use of the drug. In a crude analysis, 7729 (7.8%) of the controls had used statins compared with 711 (7.1%) of the cases. After adjustment for covariates, ever users remained less likely to develop colorectal cancer than never/rare users (IRR = 0.87, 95% CI, 0.80–0.96). However, longer-term use was not associated with any reduction in CRC incidence (Table 2). In fully adjusted models, the relative risk for long-term users versus never/rare users of the drug was 0.95 (95% CI, 0.80–1.12). In secondary analyses, defining statin use byDDD, findings in fully adjusted models were unchanged. When comparing with never/rare use, short-term use was associated with a small reduction in cancer incidence (0.79, 95% CI, 0.70–0.89), but long-term statin use was not significantly associated with risk (0.92, 95% CI, 0.80–1.07). Similarly, while those users with

### Table 1. Characteristics of Colorectal Cancer Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 9979)</th>
<th>Controls (n = 99,790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.2</td>
<td>71.2</td>
</tr>
<tr>
<td>Male sexa (%)</td>
<td>50.6</td>
<td>50.6</td>
</tr>
<tr>
<td>Use of NSAIĐs (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare</td>
<td>61.7</td>
<td>60.3</td>
</tr>
<tr>
<td>Recent</td>
<td>23.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Former</td>
<td>15.0</td>
<td>14.5</td>
</tr>
<tr>
<td>Use of aspirin (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare</td>
<td>85.2</td>
<td>84.9</td>
</tr>
<tr>
<td>Recent</td>
<td>12.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Former</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>12.5</td>
<td>12.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

NSAIĐs, nonsteroidal anti-inflammatory drugs.

aMatching variable.

### Table 2. Effect of Duration of Statin Use on Colorectal Cancer Incidence

<table>
<thead>
<tr>
<th>Statin use</th>
<th>Cases, n (%)</th>
<th>Control, n (%)</th>
<th>Adjusted OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or rareb</td>
<td>9268 (92.9)</td>
<td>92,061 (92.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Short term (0–3 y)</td>
<td>370 (3.7)</td>
<td>4186 (4.2)</td>
<td>0.84 (0.75–0.95)</td>
</tr>
<tr>
<td>Medium term (3–5 y)</td>
<td>162 (1.6)</td>
<td>1739 (1.7)</td>
<td>0.88 (0.74–1.04)</td>
</tr>
<tr>
<td>Long term (&gt;5 y)</td>
<td>179 (1.8)</td>
<td>1804 (1.8)</td>
<td>0.95 (0.80–1.12)</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

aAdjusted for all variables in Table 1.

b≥2 prescriptions for any statin during the entire period of observation.
the lowest average DDD (<1.0/day) had a small reduction in risk relative to never/rare users (0.83, 95% CI, 0.72–0.96), there was no association in those with the highest average DDD (>1.5/day) relative to the same control group (0.92, 95% CI, 0.80–1.07).

When considering individual statin agents (Table 3), ever use of simvastatin, the most commonly prescribed statin, was associated with a subsequent reduction in CRC risk. This difference remained statistically significant in fully adjusted models (IRR, 0.88; 95% CI, 0.79–0.98). In adjusted models, the association of simvastatin with a reduction in CRC risk was confined to short-term users (IRR, 0.84; 95% CI, 0.73–0.96) and was not seen in long-term users of the drug (IRR, 1.06; 95% CI, 0.84–1.34). No other single statin was associated with a significant reduction in CRC risk; although atorvastatin use strongly trended toward an association with reduced risk (IRR, 0.73; 95% CI, 0.52–1.01). The hydrophilic statin, pravastatin (OR, 0.85; 95% CI, 0.61–1.20), had a similar risk profile to the other lipophilic statins.

In crude analysis, the occurrence of a diagnosis of atherosclerosis, myocardial infarction, or stroke was similar when comparing cases of CRC and corresponding controls. In fully adjusted models, there were no associations between risk of CRC and previous myocardial infarction (IRR, 0.99; 95% CI, 0.89–1.10), previous stroke (IRR, 0.99; 95% CI, 0.89–1.09), or a diagnosis of atherosclerotic disease (IRR, 1.04; 95% CI, 0.97–1.12).

### Discussion

In this large population-based case control study, we found that ever use of statins was associated with a small reduction in cancer incidence. However, when examining subgroups most likely to show benefit (ie, long-term users), that association disappeared. When examining individual agents, risk estimates were similar for both the hydrophilic and lipophilic statins.

Statin drugs are potentially attractive as chemotherapeutic agents. As a class, they are generally well tolerated with a low frequency of adverse events. The most important adverse effects are myopathy, abnormal liver function tests, and potential liver toxicity, all of which are rare.

Our results suggest that if statins have any effect in preventing CRC, it is modest. In fully adjusted models, ever use was associated with a 13% reduction in risk. This finding is significantly less pronounced that that reported in a case control study from Israel, which suggested a 50% reduction in risk for those with 5 or more years of statin exposure. In fact, when we analyzed those with 5 or more years of exposure we found no risk reduction.

Our findings are much more consistent with case control studies from 4 other groups. In a large population-based study from the United Kingdom examining statin risk in 5686 cases of CRC and 24,982 controls, the adjusted odds ratio associated with any statin prescription was 0.93 (95% CI, 0.88–1.00). As in our study, long-term users (>5 years) had no reduction in risk (OR, 1.00; 95% CI, 0.67–1.48) and there was no trend with longer duration of use. In a separate study from the United Kingdom using the General Practice Research Database, including 4432 incident colorectal cancer cases and 44,292 controls, long-term statin use (>5 years) was not associated with CRC (adjusted OR, 1.1; 95% CI, 0.5–2.2). In a US study, using data from the Massachusetts Cancer Registry, 1809 cases of CRC were matched to 1809 controls. Neither ever use (OR, 0.92; 95% CI, 0.78–1.09) or use greater than 10 years (OR, 0.86; 95% CI, 0.51–1.45) was significantly associated with risk for CRC. Finally, most recently, a case control study was completed in the US veteran population. When comparing 6080 cases to 24,320 controls, ever statin use was associated with a small reduction in risk of CRC (OR, 0.88; 95% CI, 0.83–0.93), consistent with our findings.

Our results are also generally consistent with a large meta-analysis of randomized clinical trials in which statins were studied and cancer was a secondary end point. Colon cancer was specifically reported as an outcome in 4 trials. There was no significant difference between those prescribed a statin and controls in subsequent cancer incidence (OR, 0.95; 95% CI, 0.73–1.25). A separate meta-analysis specifically focusing on CRC (summarizing both randomized trial and observational data) also concluded that statins did not appear to strongly reduce the risk of CRC when taken for the management of hypercholesterolemia. It is possible that statins may be protective, but only after a longer latent period of 10 or more years or at dosages above those prescribed for prevention of cardiovascular disease. Therefore, trials (of limited duration) or observational studies like ours where very few “long-term” users have that length of exposure may not be adequate to detect such an effect.

There has been some suggestion that individual statins vary in their association with CRC risk. For example, it has been hypothesized that pravastatin, and other hydrophilic statins, may actually promote the development of extrahepatic cancers by causing an induction of HMG-CoA reductase and, hence, mevalonate synthesis in extrahepatic cells. This hypothesis is based on the fact that, lipophilic statins, including simvastatin and lovastatin, can counteract the increase in extrahepatic HMG-CoA activity and mevalonate synthesis that accompanies the decrease in serum cholesterol caused by the inhibition of hepatic HMG-CoA reductase, whereas pravastatin does not possess this ability due to its limited uptake in most extrahepatic cells. In fact, the Prosper trial, which evaluated pravastatin in elderly individuals at risk for vascular disease, found that incident cancer diagnoses were more frequent on pravastatin than

<table>
<thead>
<tr>
<th>Statin</th>
<th>Cases, n (%)</th>
<th>Control, n (%)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never/rare⁵</td>
<td>9268 (92.9)</td>
<td>92,061 (92.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>441 (4.4)</td>
<td>4762 (4.8)</td>
<td>0.88 (0.79–0.98)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>37 (0.4)</td>
<td>416 (0.4)</td>
<td>0.85 (0.61–1.20)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>38 (0.4)</td>
<td>494 (0.5)</td>
<td>0.73 (0.52–1.01)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>14 (0.1)</td>
<td>176 (0.8)</td>
<td>0.78 (0.45–1.35)</td>
</tr>
<tr>
<td>Other statins⁶</td>
<td>11 (0.1)</td>
<td>159 (0.2)</td>
<td>0.65 (0.35–1.15)</td>
</tr>
<tr>
<td>Mix of statins</td>
<td>170 (1.7)</td>
<td>1722 (1.7)</td>
<td>0.98 (0.81–1.17)</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*Adjusted for all variables in Table 1.

⁵≤2 prescriptions for any statin during the entire period of observation.

⁶Fluvastatin, cerivastatin, rosuvastatin, and pitavastatin.
placebo (relative risk, 1.25; 95% CI, 1.04–1.51).38 Our results are reassuring in this regard; we showed no increased risk for pravastatin users.

There has been recent interest in the association between coronary artery disease and the subsequent development of CRC, and 1 recent study demonstrated an increased prevalence of CRC in those with prior angiographically demonstrated coronary artery disease (OR, 1.88; 95% CI, 1.25–2.70).22 In our nested case control design, we found no association between either atherosclerosis or myocardial infarction and CRC. Our results are also consistent with at least 1 other case control study that has examined coronary heart disease in relation to colorectal cancer and found no association.39

Our study has a number of strengths. It is large and population based, with a prospective (nested) design. This study population is quite stable with little migration into, or out of, the study area. Because statins have been available and recorded in our prescription databases for many years, we were able to identify a relatively large number of long-term (>5 years) cases (n = 179) and matched controls (n = 1804) to specifically assess risk reduction in that group. We were also able to control for a number of potentially important confounders including aspirin and NSAID use.

Over the counter (OTC) NSAID and aspirin use could be a particular threat to the validity of our approach that relied upon the prescription registry. However, use of nonaspirin NSAIDs in Denmark has been estimated as low (14% of the population).40 In addition, low dose aspirin (ie, for cardioprotection) is reimbursed and this likely limits over-the-counter use of this product. Given the Danish National Health Care System with ready access to affordable prescriptions, the “healthy cohort” effect described by others relative to statin users should be minimized (although not eliminated)41 in this data set.

Limitations of our work include the use of prescription data as a surrogate for actual use, although former studies have shown a good correlation between self reported use of asthma42 and hormone43 drugs with prescription data. Also, for our long-term users, it seems unlikely that patients would repeatedly fill prescriptions, but not use them. While our study is based on administrative hospital coding, the data are quite good for outcomes such as myocardial infarction.44 A particular concern is that we relied upon hospital coding to identify cases of CRC and so would have missed patients not admitted to hospital. However, prior work by our group suggests close correlation of hospital data with those from the Danish Cancer Registry data for CRC, and so this factor seems unlikely to influence our results.45 Unfortunately, we were unable to adjust for lifestyle factors related to risk of CRC, including exercise, cigarette smoking, obesity, and various aspects of diet.

In summary, we evaluated the association between statin exposure in the Danish population and subsequent CRC development. We did observe a modest reduction in risk. However, a cumulative dose response effect was not observed, because the longest users of the drug appeared to have no benefit. The size of the effect, combined with the lack of a dose response, argues against an important biological effect of statin use on CRC incidence.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.08.010.

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Conflicts of Interest
These authors disclose the following: Dr Baron was previously a consultant to Merck (Mevacor/lovastatin) and is currently a consultant to Pfizer as a member of a safety and data monitoring committee. Dr Sørensen reports receiving no fee, honoraria, or consultancies. The Department of Clinical Epidemiology is involved in studies with funding from various pharmaceutical companies as research grants to and administered by Aarhus University. None of these studies is related to the present study. The remaining authors disclose no conflicts.

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