CLINICAL–ALIMENTARY TRACT

Risk of Colorectal Cancer in Patients Prescribed Statins, Nonsteroidal Anti-Inflammatory Drugs, and Cyclooxygenase-2 Inhibitors: Nested Case-Control Study

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Background & Aims: **Several studies suggest that statins prevent some cancers, with one study finding a 47% reduction in colorectal cancer risk after ≥5 years of regular use.** ***Methods:*** **A nested case-control study was conducted within 454 general practices in the United Kingdom using the QRESEARCH database. Cases with colorectal cancer were diagnosed between 1995 and 2005. The effects of statins, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and aspirin on colorectal cancer were estimated with conditional logistic regression adjusted for morbidity, smoking status, body mass index, and socioeconomic status.** ***Results:*** **We analyzed 5686 cases and 24,982 matched controls with ≥4 years of records. The adjusted odds ratio for colorectal cancer associated with any statin prescription was 0.93 (95% confidence interval: 0.83–1.04), with no trend in duration of use or number of prescriptions. For any nonsteroidal anti-inflammatory drug prescription the adjusted odds ratio was 0.94 (95% confidence interval: 0.88–1.00), with a significant decrease in risk with increasing number of prescriptions and an adjusted odds ratio of 0.76 (0.60–0.95) for ≥25 prescriptions. Prolonged use of cyclooxygenase-2 inhibitors was minimal, but for those receiving ≥25 prescriptions the adjusted odds ratio was 0.34 (0.14–0.85). Results were similar in the subset of participants with ≥8 years of records; the adjusted odds ratio for ≥61 months of statin prescriptions was 1.00 (0.67–1.48).** ***Conclusions:*** **In this large population-based case-control study prolonged use of nonsteroidal anti-inflammatory drug and cyclooxygenase-2 inhibitor was associated with a reduced colorectal cancer risk, but prolonged statin use was not.**

Colorectal cancer is the third most common cancer worldwide,[1] and effective chemoprevention agents would have important implications for public health. Laboratory data (mostly from studies in rodents) suggest that statins may be chemoprophylactic against various types of cancer, including colon[2] and breast cancers.[3,4] Statins appear to suppress the growth of cancer cells in vitro by causing the cells to pause in the G_1 phase of the mitotic cycle and by increasing cell death.[5] In contrast to the overwhelming evidence from randomized clinical trials for the beneficial effect of statins in vascular disease, their effects on the risk of cancer remains unclear. Greater clarity is obviously needed because statins are already being used for prolonged periods in large numbers of patients also at risk of colorectal cancer.[6]

Several clinical trials have reported on the risk of cancer in patients on statins, but generally the results were equivocal because of inadequate power. Three randomized trials involving statins reported no difference in the overall incidence of cancers,[7–9] whereas the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, which included more elderly patients, reported a 46% increased risk of gastrointestinal cancer in the pravastatin arm.[10] A meta-analysis of the various cardiovascular trials performed to examine the impact of statins on cancer incidence was recently reported.[11] Of the 26 trials included, only 4 reported specific data on colorectal cancer incidence. Altogether there were 320 colorectal cancers reported, with no evidence of a reduced risk in the statin takers. However, only 2 of the 4 trials lasted >5 years, leaving open the possibility of some benefit from prolonged statin use.

Several observational cohort studies have also examined statin use and cancer risk but have been generally limited by small numbers of participants developing colorectal cancer and by short duration of statin exposure.[12–15] Nevertheless, a recent case-control study from Israel reported a 47% reduction in risk of colorectal cancer in patients reporting statin use of ≥5 years.[16]

We have undertaken a study to determine the risk of colorectal cancer in patients prescribed statins by using a

Abbreviations used in this paper: CI, confidence interval; COX-2, cyclooxygenase-2; GPRD, General Practice Research Database; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

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large population-based general practice database. In addition, we included in the protocol an analysis to determine the risk of colorectal cancer in patients prescribed nonsteroidal anti-inflammatory drugs (both traditional [NSAIDs] and cyclooxygenase-2 [COX-2] inhibitors). This inclusion was to substantiate previous findings from British primary care for traditional NSAIDs[17,18] and to offer new data on COX-2 inhibitors in the light of recent colorectal adenoma prevention trials that were terminated because of safety concerns.[19,20]

Materials and Methods

Study Population and Data Source

We conducted the study using general practices in the United Kingdom contributing to the QRESEARCH database (http://www.qresearch.org). This is a new clinical database containing the records of almost 8 million patients ever registered with 454 practices during the past 16 years. The information recorded in the database includes patient demographics (year of birth, sex, and socioeconomic data associated with postcode area), characteristics (height, weight, smoking status), symptoms, clinical diagnoses (Read codes), consultations, referrals, prescribed medication, and results of investigations. Version 8 of the QRESEARCH database was used for this analysis.

The QRESEARCH database has been validated by comparing birth rates, death rates, consultation rates, and prevalence and mortality rates with other data sources, including the General Household Survey and the General Practice Research Database (GPRD).[21] Correspondence is good for all of these measures (results available on request), although in some instances QRESEARCH prevalence figures of chronic diseases such as diabetes, hypertension, and stroke are marginally higher than less recent data.[22] The age-sex structure of the QRESEARCH population is similar to that reported in the United Kingdom 2001 census. We have also compared practices taking part in regional research networks on these and other measures and found a good correspondence.[23] Detailed analyses have shown good levels of completeness and consistency.[24] The database has been used for studies that investigate effects of NSAIDs[25,26] and statin.[27] The diagnosis of cancer in primary care databases was found to be sufficiently reliable to allow analysis of cancer risk in relation to the prescribing of calcium channel blockers.[28]

Cohort Definition

Our study period for this analysis was the 10 years between January 1, 1995 and July 31, 2005 (the date of the most recent download available at the time of the study). We identified an open cohort of patients registered on or after January 1, 1995. Our left censor date was the latest of the patients' registration date or January 1, 1995. Our right censor date was the earliest of the dates on which they developed colorectal cancer, died, left the practice, or the study period ended.

Cases of colorectal cancer were identified on the basis of a first-time computer-recorded diagnosis of colorectal cancer during the 10-year study period. Patients with a recorded malignancy before the study period were excluded.

We determined the crude incidence rate of colorectal cancer for men and women and compared this to national incidence data as part of our validation processes.

Cancer Cases and Controls

We assembled matched case-control sets in which cases were all patients with an incident colorectal cancer during the 10-year study period. With the use of incidence density sampling, we matched up to 5 controls to each case by age (within a year), calendar time, sex, and practice. All controls were alive and registered with the practice and free of colorectal cancer at the time their matched case was diagnosed. We derived an index date for each control which corresponded to the first recorded date of diagnosis of colorectal cancer in the matched case.

Assessment of Exposure

We restricted the main statistical analyses to subjects with $\geq$4 years of records available before their index date. We reviewed the medical history and extracted data on prescribed medications before the index date for each set of cases and controls.

For the analyses, a patient was assumed to be exposed to a drug if the patient had received $\geq$1 prescription for that drug in the 13 to 48 months before his or her index date. We ignored prescriptions issued in the 12 months immediately preceding the date of diagnosis of colorectal cancer or the equivalent date in controls. This was done to minimize issues of reverse causality; for example, patients with prodromal symptoms could consult in the year before diagnosis and have a serum cholesterol measurement as part of a general screening procedure and hence be prescribed statins as a result.

We grouped the drugs as follows: statins (atorvastatin, cerivastatin, fluvastatin, pravastatin, and simvastatin), NSAIDs (ibuprofen, diclofenac, naproxen, and other nonselective NSAIDs), COX-2 inhibitors (meloxicam, celecoxib, rofecoxib, etoricoxib, etodolac, valdecoxib), and aspirin. Apart from ibuprofen and aspirin, none of these drugs was available without prescription during the study period.

For each statin, we identified each prescription issued during the 13–48 months before the index date, then extracted dose and duration in days for each statin prescription. We estimated the cumulative duration in days for all statin prescriptions during the 13- to 48-month interval and converted the duration to months, assuming

that 12 months were equivalent to 365 days. Because prescribing of the other drugs under analysis was less continuous and recommended dosage was more variable, we restricted our calculations of duration of exposure to number of prescriptions for these drugs. General practitioners in the United Kingdom issue patients with sufficient drugs to last ≥1 calendar month, so one prescription is approximately equivalent to 1 month of treatment. We grouped the number of prescriptions in the last 13–48 months as only 1 prescription, 2–12, 13–24, and ≥25 prescriptions.

For our primary exposure of interest (statins), we also conducted analyses for each individual type of statin medication. For the analyses of interactions between drugs, we considered statins to have been prescribed at the same time as NSAIDs or COX-2 inhibitors if the drugs were prescribed within 90 days of each other.

Confounding Variables

We considered smoking and obesity to be possible confounding factors for colorectal cancer.[1] We also took account of the following morbidities if they were diagnosed ≥13 months before the index date: ulcerative colitis, diabetes, ischemic heart disease with and without a history of myocardial infarction, hypertension, stroke, rheumatoid arthritis, and osteoarthritis. We adjusted for socioeconomic status with the Townsend deprivation score based on 2001 postcode-related census data. This is an area-level composite score based on unemployment, overcrowding, lack of home ownership, and lack of car ownership, and it is strongly related to morbidity.[29] Higher scores indicate greater levels of material deprivation.

Statistical Analysis

We estimated the odds ratio of colorectal cancer for each drug group using conditional logistic regression analysis for individually matched case-control studies. The odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for possible confounding effects of morbidity (as listed previously), smoking status (smoker, not smoker, not recorded), body mass index (calculated as weight in kilograms divided by the square of height in meters [kg/m^2]; <25, 25 to 29.9, ≥30, not recorded), socioeconomic status (in fifths), and use of the other drug groups (statins, any traditional NSAID, any COX-2 inhibitor, and aspirin).

We undertook tests for trend across the number of prescriptions and the duration of statin use, using ordinal variables and examining the significance of the coefficients with adjusted Wald's tests. We tested for interactions between statins and NSAIDs and statins and COX-2 inhibitors. We preselected a P value of .01 as indicating statistical significance, to take account of the size of the dataset and the potential for multiple comparisons. All P values are two-sided.

Additional Analyses

We repeated the analysis, restricting it to patients with ≥8 years of complete prescribing data. In this analysis we grouped the number of prescriptions in the past 13–96 months as only 1 prescription; 2–12; 13–24; 25–36; 37–48; ≥49. The duration of statin use was grouped as none, ≤12 months, 13–24 months, 25–36 months, 37–48 months, 49–60 months, and ≥61. We also conducted analyses restricted to patients with complete data for smoking status, body mass index, and deprivation.

The study was approved by the Trent Multicentre Ethics committee and the QRESEARCH Scientific Advisory Board. The study had no external funding and was conducted independently of the pharmaceutical industry.

Results

The total number of patients included in the cohort was 1,896,944 patients registered within a total of 454 practices. We identified 9694 incident cases of colorectal cancer between January 1995 and July 2005 arising from 8,823,664 person-years of observation. The crude incidence rate of colorectal cancer was 49.8 per 100,000 person years (56.1 in men and 43.6 in women). In comparison colorectal cancer in 2003 in the United Kingdom has been reported as 62.3 per 100,000 in men and 49.5 per 100,000 in women.[30] Of the 9694 cases of incident colorectal cancer, 5686 cases, matched to 24,982 controls, had a minimum of 4 years of registration with that general practice.

Baseline Characteristics

Table 1 shows the baseline characteristics of cases with colorectal cancer and their matched controls: 3181 of the colorectal cancer patients were men (55.9%); and their median age at diagnosis was 72 years (interquartile range: 64–79). Of the cases, 3460 (60.9%) had colon cancer and 2226 (39.1%) had rectal cancer.

An average of 4.4 controls was identified for each case. The median number of months of prior data for both case and control groups was 88 months (interquartile range: 66–117). Cases and controls had similar patterns of comorbidity except for a higher prevalence of diabetes (8.7% cases vs 6.8% controls) and colitis (1% cases vs 0.6% controls) in cases and a lower prevalence of rheumatoid arthritis (0.9% cases vs 1.4% controls). The baseline characteristics for the subset of 2425 cases and 9706 matched controls with ≥8 years of medical records were similar to the sample with ≥4 years of records (data available from the authors).

Use of Statins

Table 2 shows the frequencies and ORs for use of statins in cases and controls, by duration of prescriptions in months, and the number of prescriptions in the previous 13–48 months. Ninety-five percent of cases and of

Table 1. Characteristics of Cases and Matched Controls with ≥4 Years of Records and Odds Ratios for the Variables

Characteristics	Cases n = 5686	Controls n = 24,982	Odds ratios (95% confidence interval)[a]
Men, n (%)	3181 (55.9)	14,014 (56.1)	
Females, n (%)	2505 (44.1)	10,968 (43.9)	
Age group			
<55 y, n (%)	522 (9.2)	2128 (8.5)	
55–64 y, n (%)	1007 (17.7)	4412 (17.7)	
65–74 y, n (%)	1818 (32.0)	8103 (32.4)	
75–84 y, n (%)	1867 (32.8)	8340 (33.4)	
≥85 y, n (%)	472 (8.3)	1999 (8.0)	
Deprivation			
Townsend score, median (interquartile range)	−1.26 (−3.05, 1.57)	−1.43 (−3.16, 1.46)	
Townsend quintile 1 most affluent, n (%)	1302 (22.9)	5945 (23.8)	1.00
Townsend quintile 2, n (%)	1208 (21.3)	5495 (22.0)	1.01 (0.92–1.10)
Townsend quintile 3, n (%)	1163 (20.5)	4788 (19.2)	1.11 (1.02–1.22)
Townsend quintile 4, n (%)	946 (16.6)	4070 (16.3)	1.07 (0.97–1.18)
Townsend quintile 5 most deprived, n (%)	899 (15.8)	3753 (15.0)	1.10 (0.98–1.23)
Townsend quintile missing, n (%)	168 (3.0)	931 (3.7)	
Body mass index			
<25 kg/m^2, n (%)	1686 (29.7)	6928 (27.7)	1.00
25–29.9 kg/m^2, n (%)	1835 (32.3)	7687 (30.8)	0.99 (0.92–1.07)
≥30 kg/m^2, n (%)	839 (14.8)	3581 (14.3)	0.95 (0.87–1.05)
Not recorded, n (%)	1326 (23.3)	6786 (27.2)	
Smoking status			
Nonsmoker, n (%)	3845 (67.6)	16,212 (64.9)	1.00
Smoker, n (%)	985 (17.3)	4060 (16.3)	1.02 (0.95–1.11)
Smoking status not recorded, n (%)	856 (15.1)	4710 (18.9)	
Morbidity			
Ischemic heart disease			
No myocardial infarction, n (%)	488 (8.6)	2067 (8.3)	1.01 (0.90–1.14)
Myocardial infarction, n (%)	271 (4.8)	1313 (5.3)	0.90 (0.78–1.05)
Diabetes, n (%)	493 (8.7)	1697 (6.8)	1.26 (1.13–1.41)
Hypertension, n (%)	1716 (30.2)	7312 (29.3)	1.01 (0.94–1.08)
Osteoarthritis, n (%)	684 (12.0)	3033 (12.1)	0.99 (0.90–1.09)
Colitis, n (%)	57 (1.0)	145 (0.6)	1.70 (1.25–2.32)
Rheumatoid arthritis, n (%)	52 (0.9)	353 (1.4)	0.65 (0.48–0.87)
Stroke, n (%)	306 (5.4)	1292 (5.2)	1.04 (0.91–1.19)

[a]Odds ratios for the model which includes smoking, obesity, deprivation, morbidity (diabetes, ischemic heart disease, hypertension, stroke, rheumatoid arthritis, and osteoarthritis) and use of any statin, any cyclooxygenase-2 inhibitor, any nonsteroidal anti-inflammatory drug, aspirin.

controls who were prescribed statins for >24 months in this period continued to use them in the 12 months before the index date. The majority of statin use was continuous: 90% of cases and controls who had >1 statin prescription in the previous 13–48 months had no break in prescribing of >3 months and 96% of cases and controls had no break of >6 months. No statistically significant trends were observed in the adjusted ORs associated with either the duration or the number of statin prescriptions (Figure 1). Although the upper 95% CI for a single statin prescription is less than unity, the *P* value of .04 is not considered statistically significant.

Table 2 also shows the frequencies and ORs for use of statins in the subgroup with ≥8 years of records available. The adjusted ORs for any use of statins was 0.94 (95% CI: 0.79–1.11), and no significant associations were observed with the duration of use or the number of prescriptions.

The statins most frequently prescribed were atorvastatin (4.4% of cases and 3.8% of controls) and simvastatin (5.0% of cases and 5.7% of controls) with <1% of cases and controls having prescriptions for other statins (cerivastatin, fluvastatin, and pravastatin) (Table 3).

We found some variation in the ORs for colorectal cancer associated with individual statins. In the unadjusted analysis, any use of atorvastatin or cerivastatin was associated with increased ORs for colorectal cancer, although these did not reach the 0.01 significance level before or after adjustment. Although any use of simvastatin, after adjustment for confounders, including use of other statins, was associated with a 17% decrease in cancer risk (adjusted OR: 0.83; 95% CI: 0.72–0.96; $P = .013$), no significant trend was observed with the number of simvastatin prescriptions.

Use of NSAIDs, COX-2 Inhibitors, and Aspirin

Table 4 show the frequencies and the ORs for COX-2 inhibitors, traditional NSAIDs, and aspirin use by the number of prescriptions for these medications in the

Table 2. Use of Statins Before Index Date in Cases and Controls

	Cases n (%)	Controls n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	P[a]
Use in 13–48 mo[b]					
Any statin	538 (9.5)	2424 (9.7)	0.99 (0.89–1.09)	0.93 (0.83–1.04)	.22
Duration in 13–48 mo[b]					
None	5148 (90.5)	22,558 (90.3)	1.00	1.00	.69[c]
1–12 mo	183 (3.2)	911 (3.6)	0.90 (0.76–1.06)	0.84 (0.71–1.00)	
13–24 mo	122 (2.1)	526 (2.1)	1.04 (0.85–1.27)	0.99 (0.80–1.22)	
25+ mo	233 (4.1)	987 (4.0)	1.04 (0.90–1.21)	0.99 (0.84–1.16)	
No. prescriptions in 13–48 mo[b]					
None	5148 (90.5)	22,558 (90.3)	1.00	1.00	.99[c]
1	32 (0.6)	189 (0.8)	0.74 (0.51–1.08)	0.67 (0.46–0.98)	
2–12	206 (3.6)	1007 (4.0)	0.91 (0.78–1.07)	0.85 (0.72–1.01)	
13–24	170 (3.0)	726 (2.9)	1.05 (0.88–1.24)	1.01 (0.84–1.21)	
25+	130 (2.3)	502 (2.0)	1.15 (0.94–1.40)	1.13 (0.91–1.41)	
Use in 13–96 mo[d]					
Any statin	302 (12.5)	1220 (12.6)	1.01 (0.87–1.16)	0.94 (0.79–1.11)	.44
Duration in 13–96 mo[d]					
None	2123 (87.5)	8486 (87.4)	1.00	1.00	.44[c]
1–12 mo	115 (4.7)	440 (4.5)	1.06 (0.85–1.31)	0.98 (0.78–1.23)	
13–24 mo	60 (2.5)	259 (2.7)	0.96 (0.72–1.28)	0.90 (0.67–1.22)	
25–36 mo	43 (1.8)	167 (1.7)	1.05 (0.75–1.48)	0.97 (0.68–1.39)	
37–48 mo	27 (1.1)	124 (1.3)	0.87 (0.57–1.34)	0.82 (0.53–1.27)	
49–60 mo	22 (0.9)	98 (1.0)	0.90 (0.56–1.44)	0.83 (0.51–1.35)	
61+ mo	35 (1.4)	132 (1.4)	1.07 (0.73–1.57)	1.00 (0.67–1.48)	
No. of prescriptions in 13–96 mo[d]					
None	2123 (87.5)	8486 (87.4)	1.00	1.00	.63[c]
1	23 (0.9)	97 (1.0)	0.99 (0.63–1.57)	0.87 (0.55–1.40)	
2–12	122 (5.0)	469 (4.8)	1.06 (0.86–1.31)	1.00 (0.80–1.25)	
13–24	58 (2.4)	271 (2.8)	0.87 (0.65–1.16)	0.81 (0.59–1.10)	
25–36	46 (1.9)	176 (1.8)	1.05 (0.75–1.48)	0.97 (0.68–1.38)	
37–48	22 (0.9)	96 (1.0)	0.95 (0.60–1.52)	0.88 (0.55–1.43)	
49+	31 (1.3)	111 (1.1)	1.11 (0.73–1.67)	1.11 (0.72–1.72)	

[a]Adjusted for smoking, obesity, deprivation, morbidity (diabetes, ischemic heart disease, hypertension, stroke, colitis, rheumatoid arthritis, and osteoarthritis), use of the other medications (number of prescriptions).
[b]Cases (n = 5686) and controls (n = 24,982).
[c]Trend test.
[d]Cases (n = 2425) and controls (n = 9706).

previous 13–48 and 13–96 months. Patients receiving ≥25 prescriptions for traditional NSAIDs in the past 13–48 months had a lower risk of colorectal cancer than patients not prescribed NSAIDs (adjusted OR: 0.76; 95% CI: 0.60–0.95), and the test for trend was highly significant (Table 4; Figure 1). In this group receiving ≥25 NSAID prescriptions in the past 13–48 months 77% of cases and 80% of controls continued to use these drugs in the 12 months before the index date. A significant decrease in risk was observed in patients who had ≥25 prescriptions of COX-2 inhibitors in the past 13–48 months (adjusted OR: 0.34; 95% CI: 0.14–0.85) compared with patients not prescribed COX-2 inhibitors, although the test for trend was not statistically significant. In the group receiving ≥25 COX-2 inhibitor prescriptions in the 13–49 months before the index date 100% of cases and 91% of controls also received COX-2 inhibitor prescriptions in the 12 months before the index date. For aspirin use, for which 70% of prescriptions were for ≤75 mg/day, about a 10% reduction was observed in risk associated with ≥13 prescriptions in the past 13–48 months, but the trend was not significant. In the group with ≥25 aspirin prescriptions, most continued to take aspirin in the year before the index date (95% of cases and 90% of controls).

The adjusted OR for use of any traditional NSAID in the past 13–96 months was 0.91 (95% CI: 0.83–1.00), with longer use showing a more protective effect (*P* for trend = 0.001) (Figure 2). For aspirin use about a 10% to 15% reduction in risk associated with ≥37 prescriptions was observed in the past 13–96 months, but the trend was not significant. For this analysis it is important to note that COX-2 inhibitors were not in use for the first 5 years of the study period. No significant interactions were observed between any of the drug groups (statins, NSAIDs, and COX-2 inhibitors).

We repeated all of the above analyses separately for colon and rectal cancers and found similar results for the separate diagnoses. We also repeated the analyses, restricting them to cases and controls with complete data on

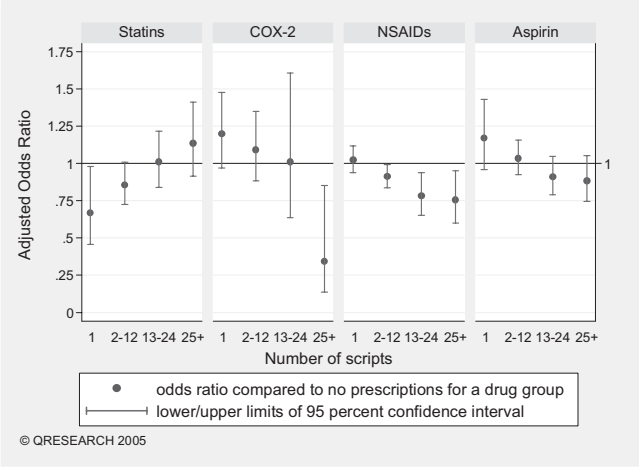

Figure 1. Number of prescriptions for the different drugs in 13–48 months before the index date and adjusted odds ratios for colorectal cancer.

smoking, body mass index, and deprivation (71% of cases and 54% of controls) and restricting them to patients aged ≥65 years, and obtained similar results for all groups of drugs and individual types of statins. Finally, to check on the possibility of confounding by hyperlipidemia as the indication for statin use, we included a variable for this diagnosis (recorded in 4.9% of cases and 4.8% of controls) and found our results were essentially unchanged.

Discussion

This is a large population-based study designed to determine the association between the use of statins and development of colorectal cancer. Although we were able to confirm previous protective associations between colorectal cancer and traditional NSAIDs, we were unable to confirm the large reduction in colorectal cancer risk with prolonged statin use reported in the recent case-control study from Israel.[16] However, equally, it also provides reassurance that statins as a class do not increase the risk of colon cancer, a concern raised within the PROSPER pravastatin trial.[10]

In contrast to our findings on statin use, prolonged use of NSAIDs was associated with a ≥25% reduction in colorectal cancer risk, similar to that found in a previous case-control study of colorectal cancer using another British primary care database, GPRD.[18] In that study the adjusted OR for colorectal cancer among patients using traditional NSAIDs for >2 years was 0.66 (95% CI: 0.40–0.80), which is similar to our value of 0.76 (95% CI: 0.60–0.95) for ≥25 prescriptions of NSAIDs in the past 13–48 months. Other established risk factors (such as diabetes and ulcerative colitis) also showed a positive

Table 3. Use of Individual Statins in 13–48 Months Before the Index Date in 5686 Cases and 24,982 Controls

	Cases n (%)	Controls n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	*P*[a]
Atorvastatin	250 (4.4)	954 (3.8)	1.19 (1.02–1.38)	1.11 (0.95–1.30)	.17
Simvastatin	287 (5.0)	1420 (5.7)	0.88 (0.77–1.01)	0.83 (0.72–0.96)	.013
Pravastatin	27 (0.5)	136 (0.5)	0.90 (0.59–1.37)	0.84 (0.55–1.28)	.41
Fluvastatin	44 (0.8)	150 (0.6)	1.35 (0.95–1.91)	1.21 (0.85–1.74)	.29
Cerivastatin	56 (1.0)	179 (0.7)	1.40 (1.03–1.91)	1.34 (0.97–1.86)	.07
Duration of atorvastatin use					
None	5436 (95.6)	24,028 (96.2)	1.00	1.00	.14[b]
1–12 mo	111 (1.6)	452 (1.8)	1.12 (0.90–1.38)	1.07 (0.85–1.33)	
13–24 mo	60 (1.1)	223 (0.9)	1.20 (0.90–1.61)	1.13 (0.84–1.53)	
25+ mo	79 (1.4)	279 (1.1)	1.29 (1.00–1.67)	1.20 (0.92–1.56)	
Duration of simvastatin use					
None	5399 (95.0)	23,562 (94.3)	1.00	1.00	.07[b]
1–12 mo	119 (2.1)	586 (2.4)	0.89 (0.73–1.09)	0.82 (0.66–1.01)	
13–24 mo	56 (1.0)	317 (1.3)	0.78 (0.58–1.04)	0.73 (0.54–0.98)	
25+ mo	112 (2.0)	517 (2.1)	0.94 (0.76–1.16)	0.92 (0.74–1.15)	
No. of prescriptions for atorvastatin					
None	5436 (95.6)	24,028 (96.2)	1.00	1.00	.10[b]
1	16 (0.3)	99 (0.4)	0.72 (0.42–1.22)	0.66 (0.39–1.14)	
2–12	122 (2.1)	457 (1.8)	1.21 (0.98–1.49)	1.14 (0.92–1.42)	
13–24	74 (1.3)	248 (1.0)	1.36 (1.04–1.77)	1.28 (0.97–1.69)	
25+	38 (0.7)	150 (0.6)	1.16 (0.80–1.67)	1.13 (0.78–1.65)	
No. of prescriptions for simvastatin					
None	5399 (95.0)	23,562 (94.3)	1.00	1.00	.11[b]
1	24 (0.4)	138 (0.6)	0.75 (0.48–1.15)	0.67 (0.43–1.04)	
2–12	127 (2.2)	631 (2.5)	0.89 (0.73–1.08)	0.82 (0.67–1.01)	
13–24	70 (1.2)	415 (1.7)	0.74 (0.57–0.96)	0.73 (0.56–0.95)	
25+	66 (1.2)	236 (0.9)	1.20 (0.91–1.59)	1.22 (0.91–1.64)	

[a]Adjusted for smoking, obesity, deprivation, morbidity (diabetes, ischemic heart disease, hypertension, stroke, colitis, rheumatoid arthritis, and osteoarthritis), use of nonsteroidal anti-inflammatory drug, cyclooxygenase-2, aspirin, and the other statins.
[b]Trend test.

Table 4. Use of Anti-Inflammatory Medication Before the Index Date

	Cases (%)	Controls (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	P[a]
Use in 13–48 mo[b]					
Any COX-2	263 (4.6)	1101 (4.4)	1.05 (0.91–1.21)	1.07 (0.92–1.24)	.37
Any NSAID	1871 (32.9)	8460 (33.9)	0.96 (0.90–1.02)	0.94 (0.88–1.00)	.048
Aspirin	1226 (21.6)	5369 (21.5)	1.01 (0.94–1.09)	0.99 (0.90–1.08)	.79
No. of COX-2 prescriptions in 13–48 mo[b]					
None	5423 (95.4)	23,881 (95.6)	1.00	1.00	.88[c]
1	118 (2.1)	444 (1.8)	1.18 (0.96–1.45)	1.20 (0.97–1.48)	
2–12	117 (2.1)	487 (1.9)	1.06 (0.86–1.31)	1.09 (0.88–1.35)	
13–24	23 (0.4)	103 (0.4)	0.93 (0.59–1.48)	1.01 (0.64–1.61)	
25+	5 (0.1)	67 (0.3)	0.33 (0.13–0.83)	0.34 (0.14–0.85)	
No. of NSAID prescriptions in 13–48 mo[b]					
None	3815 (67.1)	16,522 (66.1)	1.00	1.00	.001[c]
1	765 (13.5)	3130 (12.5)	1.06 (0.97–1.15)	1.02 (0.94–1.12)	
2–12	864 (15.2)	3992 (16.0)	0.94 (0.87–1.02)	0.91 (0.84–0.99)	
13–24	151 (2.7)	822 (3.3)	0.80 (0.67–0.96)	0.78 (0.65–0.94)	
25+	91 (1.6)	516 (2.1)	0.76 (0.61–0.96)	0.76 (0.60–0.95)	
No. of aspirin prescriptions in 13–48 mo[b]					
None	4460 (78.4)	19,613 (78.5)	1.00	1.00	.19[c]
1	132 (2.3)	494 (2.0)	1.17 (0.96–1.42)	1.17 (0.96–1.43)	
2–12	541 (9.5)	2281 (9.1)	1.06 (0.96–1.17)	1.03 (0.92–1.16)	
13–24	334 (5.9)	1563 (6.3)	0.95 (0.83–1.07)	0.91 (0.79–1.05)	
25+	219 (3.9)	1031 (4.1)	0.94 (0.80–1.10)	0.88 (0.74–1.05)	
Use of medications in 13–96 mo[d]					
Any NSAID	1211 (49.9)	4989 (51.4)	0.94 (0.86–1.03)	0.91 (0.83–1.00)	.06
Aspirin	636 (26.2)	2529 (26.1)	1.03 (0.92–1.14)	0.98 (0.86–1.12)	.77
No. of NSAID prescriptions in 13–96 mo[d]					
None	1214 (50.1)	4717 (48.6)	1.00	1.00	.001[c]
1	377 (15.5)	1456 (15.0)	1.00 (0.88–1.14)	0.97 (0.85–1.10)	
2–12	639 (26.4)	2513 (25.9)	0.98 (0.88–1.09)	0.94 (0.84–1.05)	
13–24	93 (3.8)	422 (4.3)	0.86 (0.68–1.09)	0.83 (0.65–1.06)	
25–36	46 (1.9)	243 (2.5)	0.74 (0.54–1.02)	0.73 (0.52–1.01)	
37–48	21 (0.9)	159 (1.6)	0.50 (0.31–0.79)	0.48 (0.30–0.77)	
49+	35 (1.4)	196 (2.0)	0.69 (0.48–1.00)	0.69 (0.48–1.00)	
No. of aspirin prescriptions in 13–96 mo[d]					
None	1789 (73.8)	7177 (73.9)	1.00	1.00	.47[c]
1	72 (3.0)	273 (2.8)	1.07 (0.82–1.40)	1.03 (0.79–1.36)	
2–12	190 (7.8)	782 (8.1)	1.01 (0.85–1.20)	0.95 (0.79–1.14)	
13–24	149 (6.1)	539 (5.6)	1.11 (0.91–1.34)	1.06 (0.86–1.31)	
25–36	94 (3.9)	361 (3.7)	1.07 (0.84–1.36)	1.01 (0.78–1.32)	
37–48	54 (2.2)	237 (2.4)	0.95 (0.70–1.29)	0.91 (0.66–1.26)	
49+	77 (3.2)	337 (3.5)	0.90 (0.69–1.17)	0.85 (0.63–1.14)	

[a]Adjusted for smoking, obesity, deprivation, morbidity (diabetes, ischemic heart disease, hypertension, stroke, colitis, rheumatoid arthritis, and osteoarthritis), use of the other medications (number of prescriptions).
[b]Cases (n = 5686) and controls (n = 24,982).
[c]Trend test.
[d]Cases (n = 2425) and controls (n = 9706).

association with colorectal cancer in our study as reported elsewhere.[1] Like the GPRD study, we found around a 10% reduction in risk associated with prolonged aspirin use (≥13 prescriptions in the past 13–48 months), which was not statistically significant. Other studies have suggested that the benefit as a result of aspirin may take more than a decade to accrue[31] and requires a dose >75 mg daily, which is likely to explain our findings in this context.

We also found some evidence that prolonged use of COX-2 inhibitors was associated with a significantly reduced risk of colorectal cancer; we found a 66% reduction in risk in patients who had ≥25 prescriptions than patients who had not been prescribed COX-2 inhibitors. This is of interest in view of recent trials with celecoxib which reported a ≥50% reduction in the occurrence of advanced adenoma and the overexpression of COX-2 that was shown in colorectal cancers.[20,32] However, examining the risk of colorectal cancer in patients taking COX-2 inhibitors was a secondary aim of our study, overall usage was low, and the test for trend was not significant, so this finding needs to be interpreted with caution.

Our study has several strengths. It is substantially larger and has greater statistical power than previous

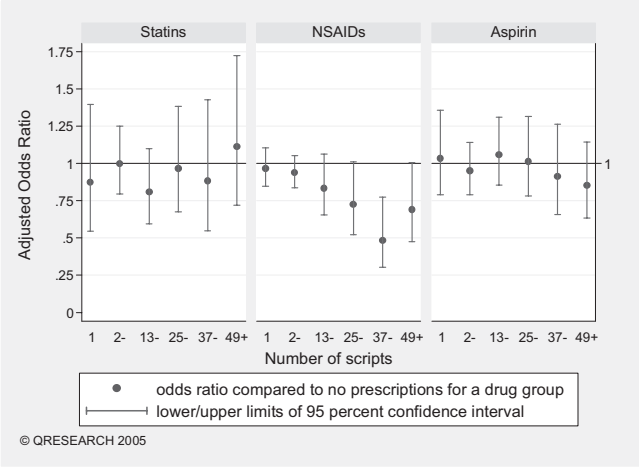

Figure 2. Number of prescriptions for the different drugs in 13–96 months before the index date and adjusted odds ratios for colorectal cancer.

studies.[12–16,33] Because it is based on computer-recorded prescribing and morbidity data collected prospectively, we were able to include all patients (including those who had died) rather than being restricted to a survivor volunteer population as in the study of Poynter et al[16] in which only two thirds of eligible cases and half of the eligible controls were included.

Matching of controls to cases on age, sex, calendar time, and practice removed confounding by these factors. Unlike the Israeli study[16] and a recent Massachusetts study,[34] recall bias for the type and duration of statin and other drug use is not an issue because information about the patient and drugs prescribed was recorded on computer before the diagnosis of cancer was made, and so the information was unaffected by the cancer diagnosis itself. Any bias from misclassification is likely to be minimal because recording of clinical diagnoses and prescribed medication in general practice was shown to have high levels of accuracy and completeness.[35] In addition, statins were available only on prescription throughout the study period. The similar results for ibuprofen and aspirin use in patients aged ≥65 years, who are entitled to free prescribed medications and so unlikely to buy them over the counter, suggest that misclassification of use of these medications because of over-the-counter purchase is not an explanation for our findings.

Our study also had some limitations. Information on certain risk factors for colorectal cancer, such as sedentary lifestyle, family history, and diet,[1] are not recorded on the database and could not be included in the analysis. No information was available on cancer stage, and information on how the cancer was treated was incomplete. Other factors such as body weight, alcohol intake, and smoking status are less consistently recorded, because the general practitioner either does not ask or does not record the relevant information; hence, there may be some misclassification for these factors. Some confounding may remain if these factors are also associated with statin use. Nevertheless, in the study by Poynter et al,[16] which was able to adjust for sports participation, a family history of colorectal cancer, and level of vegetable consumption, the effect of adjustment was small.

Our incidence rates were slightly lower than national figures, suggesting possible under-ascertainment of cases. The under-ascertainment is likely to be due to some colorectal cancers only being registered at the time of death which may go unrecorded in the general practitioner records.[36] However, making the assumption that the underrecording rate is ≤10%, <16 of the 24,982 sampled controls are likely to be unrecorded cases, a level of under-ascertainment unlikely to have an influence on our findings. It is also possible that statin users might be more likely to have colorectal cancer detected as an indirect consequence of more frequent practice attendance. Although ignoring statin prescribing in the 12 months before the diagnosis date will have reduced this bias, it will not entirely eliminate the possibility of detection bias.

Although our data contain detailed information on drug prescriptions, this may not reflect actual use. However, there is no reason to think that any nonadherence would systematically differ between cases and controls. Even though this is the largest study of its kind, there were only a relatively small number of participants (1.4% of cases and controls) with ≥8 years of records and prolonged exposure to statins. Thus, the 95% CI for the most prolonged statin use (61+months) is consistent with both a 33% reduction in colorectal cancer risk as well as a 48% increase. Nevertheless, there was no hint of any dose-response relationship with statin use in this subset or in the full dataset. We also cannot exclude the possibility that protection from colorectal cancer is confined to a particular statin. In this regard the data for simvastatin could be interpreted as hinting at some reduction in cancer risk. However, we had no prior hypothesis here, and it is notable that there was no indication of a protective effect specific to simvastatin in previous case-control studies.[16,34]

In summary, we have conducted a large population-based case-control study that examined the effect of statins on the risk of colorectal cancer and found that, although prolonged NSAID and COX-2 inhibitor use are associated with reduced colorectal cancer risk, prolonged statin use is not.

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All authors declare that they have no conflict of interest to disclose.