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ORIGINAL ARTICLE

Statin use is associated with a reduced incidence of colorectal adenomatous polyps

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Abstract
Background Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have been shown to have potentially useful anticancer effects against colorectal cancers in experimental studies, but clinical studies have shown inconsistent results on colorectal cancer incidence. Most colorectal cancers are believed to develop through the polyp-cancer sequence. We hypothesized that statins may protect against the development of adenomatous polyps, and this may contribute to the apparent cancer-protective effects.
Objective This study aims to compare previous statin use in patients with newly diagnosed adenomatous polyps against a control group without polyps.
Method A case–control study involving 264 patients attending for diagnostic colonoscopy at the Norfolk and Norwich University Hospital was used. Polyp cases were age and sex matched against controls with normal colonoscopies. Structured patient interviews and clinical notes were used to ascertain drug and risk factor. Logistic regression was used to compare statin exposure and correct for confounding factors.
Results There was a significant negative association between prior statin use and a diagnosis of adenomatous polyps [odds ratio (OR)=0.40 (0.24–0.76)]. The association was significantly stronger with higher statin doses [≥40 mg simvastatin or equivalent; OR 0.33 (0.10–0.53)] or longer duration of use [>5 years; OR 0.36 (0.10–0.67)]. Statin use was negatively associated with both high- and low-risk polyps.
Conclusions Statins may have a protective effect against the development of adenomatous polyps. The negative association between statin use and polyp incidence showed a significant dose and duration relationship.

Keywords Aspirin · Chemoprevention · Hydroxymethylglutaryl-CoA reductase inhibitors · Colorectal adenocarcinoma · Colorectal adenomas

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Introduction

Colorectal cancer (CRC) is a common and important cause of morbidity and mortality. The overall incidence is 20.1/100,000/year in men and 14.6/100,000/year in women [1]. Although improvements in screening, surgical, and oncological techniques all have had positive impacts on the disease, the prospect of an effective chemotherapeutic strategy at the population level provides yet another way to minimize the burden of the disease. Of the currently most promising agents, cyclo-oxygenase-2-selective inhibitors are effective in reducing adenomatous polyp formation [2], but at the cost of increased cardiovascular morbidity [3], and although aspirin has consistently been shown to reduce the incidence of CRC, it is generally not recommended for widespread chemoprevention because of the increased risk of bleeding [4]. Statins [hydroxymethylglutaryl coenzyme (HMG-CoA) reductase inhibitors] have been reported to have potentially useful actions against CRC in cell line studies, inhibiting proliferation and inducing apoptosis [5], and statins have been reported to reduce the incidence of CRC in animal models and, overall, have an excellent safety profile [6, 7].

However, clinical studies examining the relationship between statins and CRC incidence have provided mixed results. One widely reported case–control study showed an approximately 50 % reduction in CRC incidence in statin users [8], and although other case–control and cohort studies and a meta-analysis [9–14] have also shown a protective (albeit usually less pronounced) effect, other case–control and cohort studies have failed to demonstrate a protective effect of statins against CRC [15–20]; differences in the populations studied, with differing underlying CRC risk; different study methodologies; and in particular, different periods of statin exposure (some studies included only 3 months of statin exposure) may all have contributed to these different results. Most of the negative studies tended to assess less than 5 years of exposure to statins, and a more prolonged period may be required to demonstrate a reduced cancer risk. At least 3 years of exposure to lovastatin was associated with a 38 % reduction in colon cancer [21]. Recently, two major reviews on the subject have concluded that although the protective effect of statins against colon cancer was not consistently shown, more studies were definitely indicated because the situation was sufficiently unclear [22, 23]. Modest protective effects were generally seen in the cohort and case–control studies, but randomized studies (not originally designed with cancer as an outcome) tended to show smaller and nonsignificant reduction on colon cancer incidence [22]. Protective effects have been reported with simvastatin and pravastatin in addition to lovastatin [5, 24].

As most sporadic CRCs are believed to develop through the adenomatous-polyp-cancer sequence [25, 26], we have hypothesized that statins may reduce the incidence of adenomatous polyps (APs), and this may contribute to the reduction in CRC incidence seen in longer-term studies. As the polyp-cancer sequence is believed to take 10–15 years on average [27], it is quite possible that the period of statin exposure has not been long enough in many clinical studies to detect an anticancer effect, and by studying the effects of statins on the incidence of adenomatous polyps, we may be able to further examine the potential chemopreventive effects of statins.

Despite the obvious interest in statins and CRC, there are surprisingly few studies examining the effect, specifically on polyps. In the $Min^{-/-}$ mouse model, statin treatment reduces polyp formation [28]. While in human clinical studies, Siddiqui et al. showed reduced post-polypectomy recurrence of polyps [odds ratio (OR) 0.51, 95 % confidence interval (CI) 0.43–0.60] and high-risk polyps (OR 0.74, 95 % CI 0.52–0.96) as well as diminished polyp size and number in patients that used statins continuously for up to 5 years [29]. However, another study examining detection of recurrent polyps following initial colonoscopic polypectomy found no protective effect of statins (OR 1.36, 95 % CI 0.35–8.27) [30], although the follow-up interval may have been too short to show an effect. In the latter study, the mean duration until follow-up colonoscopy was only 453 days perhaps not long enough to demonstrate an effect of statins; yet despite this short interval, polyp recurrence rate was rather high at 55 % (compared to 35 % at 3.5 years in the study by Siddiqui et al. [29]), possibly suggesting that initial colonoscopic clearance was not total. A further study by Siddiqui et al. showed that polyp recurrence on those taking statins was significantly lower in those with the greatest fall in low-density lipoprotein cholesterol, suggesting that reducing the tissue bioavailability of cholesterol may contribute to a reduced adenoma recurrence [31]. Other studies have examined the effects of coincidental use of statins on post-polypectomy polyp recurrence in randomized trials of other putative chemopreventive agents; results from a combination of three separate studies showed no effect on adenoma recurrence (OR 1.03, 95 % CI 0.70–1.25) [32], but this study may have had insufficient statistical power as only 8.1 % of patients had any use of statin during follow-up. In the celecoxib adenoma prevention trial, statin use was not associated with a significant reduction in adenoma recurrence, and in subgroup analysis of >3 years, continuous statin use seemed to be associated with a slight increase in adenoma recurrence (OR 1.39, 95 % 1.04–1.86) [33]. One potential problem with all the trials examining polyp recurrence is that because the inclusion criteria was the presence of colonic adenomas, these studies may have selected those "statin-resistant" polyp formers, having already developed an adenoma while taking a statin and, hence, be less responsive to continued statin therapy during the follow-up period. It is possible that on a wider population scale, statin use could be associated with protection against the development of de novo polyps. Therefore, to further examine the relationship between statin use and the development of colonic adenomas, we have performed a case–control study comparing statin use in patients with newly diagnosed colorectal adenomatous polyps with a control group, all of whom were free from polyps.

Methods

Study design and population

All cases and controls were recruited from patients undergoing their first ever diagnostic colonoscopy at the Norfolk and Norwich University Hospital from 1 September 2009 to 31 August 2010. This is a large university teaching hospital and one of the UK's national endoscopy training centers, serving a predominantly rural population of approximately 600,000 people. The stability of and consistent referral patterns within the catchment population has been noted in

previous epidemiological studies [34], and drug histories could almost always be verified by clinical notes.

Adult patients aged >18 were invited to participate, prior to having their colonoscopy. Exclusions were colonoscopies for surveillance for dysplasia in inflammatory bowel disease or for surveillance following previous cancer or adenomatous polyps or for cancer screening in high-risk populations. Subjects in which polyps were not retrieved for histological analysis were excluded, as were all cases with invasive adenocarcinoma. Information on drug exposure and other putative risk factors was gathered during a structured interview by a trained researcher before subjects underwent their colonoscopy and was verified through subsequent review of the clinical and referral notes. Information on statin use was gathered, including the dose, duration, and type of statin that was used. Drug exposure (statin or aspirin) was regarded as positive if the drug had been taken continuously for more than 6 months prior to the colonoscopy because the potential chemopreventive effects of drugs may not have materialized after such short-term use. Statin use was regarded as positive if more than five daily doses were taken per week; aspirin and nonsteroidal anti-inflammatory drug (NSAID) use was regarded as positive if one or more doses were taken weekly. Colonoscopy was performed by accredited colonoscopists or by trainees under the direct supervision of accredited colonoscopists, independently of the study. The histology of all removed and recovered polyps was reviewed by a specialized gastrointestinal pathologist (JS).

Cases

All cases had histologically confirmed adenomatous polyps found at colonoscopy.

Controls

All controls had no evidence of colorectal cancer or adenomatous polyps at their subsequent diagnostic colonoscopy. If histological analysis of removed polyps showed only hyperplastic polyps, these were included in the control group. However, if removed polyps were not recovered for histological analysis, the patients were excluded from further analysis. Also excluded were those patients in whom experienced colonoscopists detected what were thought to be hyperplastic polyps, but no histological confirmation was available. Controls were age (within 5 years) and sex matched to cases.

Ethics and research governance

All patients gave written informed consent, and the study was approved by the Norfolk Research Ethics Committee and the Norfolk and Norwich University Hospital Trust Research Governance Committee.

Statistical analysis

The analyses were performed using SPSS version 16.0. The percentage of participants that had previously used statins in each case group was compared against the control group using a chi-square statistic. The differences between the groups were quantified using the calculated odds ratios and 95 % confidence intervals, with the significance level set at $p<0.05$. Further preplanned analyses were performed, examining the effects of duration, dose, and type of statin use. The duration of statin use was divided into three categories: <2, 2–5, and >5 years. The statin dose category was split into low dose (<40 mg simvastatin or equivalent/day) and high dose (≥40 mg/day). The type of statin used was separated into two categories: simvastatin (the majority) and other types of statin. When there was exposure to more than one statin drug or dose, exposure was classified according to the most recent exposure. Subgroup analysis was also performed as the adenomatous polyp group that was dichotomized into low-risk polyps (one to two adenomas, all of <1 cm) and high-risk polyps (greater than three or more adenomas, or any of >1 cm). The polyp subgroups were based on the guidelines for polyp surveillance by Cairns et al. [35]. In the current study, intermediate- and high-risk polyps as defined by the UK guidelines were grouped together as the higher-risk group because of low numbers in individual groups. Unconditional logistic regression was used to assess whether any potential confounder had a statistically significant association with either case group. All odds ratios were recalculated using unconditional logistic regression, correcting for potential confounding factors.

Sample size

An initial sample size of at least of 93 cases and 93 controls was planned; this had 80 % power to detect a 50 % relative risk reduction in the incidence of adenomatous polyps in statin users, assuming a statin use rate of 40 % in controls.

Results

Baseline characteristics and confounding variables

A total of 132 patients with adenomatous polyps and 132 controls were included in the study. A total of 434 subjects were interviewed, and the 132 controls were selected and matched from a total of 197 subjects with eligible normal colonoscopies. Baseline characteristics and demographic information for cases and controls are shown in Table 1. The groups were generally well matched for all variables, although there was an excess of patients with type 2 diabetes in the control group. In all other respects, the groups are

Table 1 Baseline characteristics

	Normal	APs
Frequency	132	132
Male (%)	61 (46.2)	61 (46.2)
Mean age, year (SD)	63.8 (12.2)	64.2 (11.5)
Type 2 diabetes (%)	26 (19.7)	14 (10.6)*
Inflammatory bowel disease (%)	6 (4.5)	4 (3)
Family history[a] (%)	19 (14.4)	20 (15.2)
Smokers[b] (%)	55 (41.7)	50 (37.8)
Mean smoking, pack years (SD)	8.3 (12.6)	9.4 (15.5)
Alcohol drinkers[b] (%)	89 (67.4)	90 (68.2)
Mean alcohol, units/week[c] (SD)	6.5 (6.3)	7.3 (6.7)
BMI (SD)	27.1 (4.4)	27.5 (3.7)
HRT (% of women)	9 (12.7)	13 (18.3)
Mean parity (% of women)	2.25 (1.13)	2.2 (1.2)
Number of parous women (%)	65/71 (91.5)	60/71 (84.5)

BMI body mass index, *HRT* hormone replacement therapy

[a] First degree relative with family history of CRC

[b] Current or ex-smokers/alcohol drinkers

[c] Current weekly alcohol consumption

*$p<0.05$

typical of those undergoing colonoscopy and having polyps detected in the UK. Overall, the indications for diagnostic colonoscopy were typical of that in the UK (diarrhea and/or change in bowel habit 34 %, iron deficiency anemia 28 %, rectal bleeding 11 %, abdominal pain 9 %, positive fecal occult screening test 16 %, abnormal or equivocal previous imaging 1 %, and unexplained weight loss 1 %).

Table 2 shows that previous aspirin and metformin use was both significantly less common in the polyp group compared to the controls. There were no significant differences between the cases and controls with regard to the use of NSAIDs, calcium channel modulator, and other diabetes medications. There was a suggestion of a protective effect of NSAIDs (odds ratio 0.79), but there were only small numbers of patients, and conventional statistical significance was not shown. The multivariable regression analyses were adjusted for all potential confounding factors. This included age, gender, type 2 diabetes, weekly alcohol intake, and a history of aspirin or metformin use.

Table 2 Other medications taken

	Control	Adenomatous polyps			
	n (%)	*n* (%)	OR	95 % CI	*p* value
Aspirin	43 (32.6)	23 (17.4)	0.43	(0.24–0.77)	<0.01
NSAIDs	16 (12.1)	13 (9.8)	0.79	(0.35–1.73)	0.51
CCMs	12 (9.1)	15 (11.4)	1.28	(0.57–2.92)	0.58
Metformin	18 (13.6)	8 (6.0)	0.41	(0.16–0.97)	<0.05
Other diabetes	8 (6.1)	3 (2.2)	0.36	(0.07–1.35)	0.08

CCM calcium channel modulators

Prior use of statins

There was a significant inverse association between previous statin use of at least 6 months duration and a diagnosis of adenomatous polyps. As shown in Table 3, there was an inverse association [unadjusted OR 0.18 (0.09–0.32)], which persisted after adjustment for potential confounders [0.40 (0.24–0.76), $p<0.01$].

Duration of statin use

The inverse association between statin use and adenomatous polyps strengthened as the duration of statin use increased. [Less than 2 years OR=0.72 (0.12–1.49), $p=0.18$], [2–5 years OR=0.62 (0.12–0.87), $p=0.03$], and [>5 years OR=0.36 (0.10–0.67), $p=0.01$]. There was a significant linear trend for the duration–response relationship between statin use and polyps [test for trend, x^2 (1)=32.0, $p<0.001$].

Dose of statin

The inverse association between statin use and adenomatous polyps was stronger at the higher statin dosage [OR=0.33 (0.10–0.53), $p<0.01$] compared to the lower statin dosage [OR=0.56 (0.14–0.93), $p=0.04$]. There was a significant linear trend for the dose–response relationship between statin use and polyp diagnosis [test for trend, x^2 (1)=31.4, $p<0.01$].

Type of statin

Simvastatin was the most commonly used statin (63/89; 70.8 %) (Table 4), so the type of statin used was separated into simvastatin and others. Patients with adenomatous polyps were significantly less likely to have used simvastatin than the controls [OR=0.39 (0.08–0.75), $p<0.01$], and there was a similar association with the use of other statins, but with much smaller numbers, this did not reach statistical significance [OR=0.59 (0.14–1.08), $p=0.07$].

Polyp subgroup analysis

We further examined the relationship between statin use and higher-risk adenomatous polyps. As shown in Table 3, statin use associated with a lower incidence of both low-risk [OR=0.35 (0.14–0.90), $p=0.03$] and high-risk polyps [OR=0.27 (0.10–0.76), $p=0.01$]. Patients with higher-risk polyps were less likely to have previously used statins 7/58 (12.1 %) than patients in the lower-risk group 11/58

Table 3 Statin use and adenomatous polyps

	Controls (%)	APs (%)	*p* value	Odds ratios (95 % CI)	
				Unadjusted	Adjusted[a]
Previous use	68/132 (51.5)	21/132 (15.9)	<0.01	0.18 (0.09–0.32)	0.40 (0.24–0.76)
Duration (years)					
<2	14 (10.6)	6 (4.5)	0.18	0.41 (0.13–1.07)	0.72 (0.12–1.49)
2–5	23 (17.4)	7 (5.3)	<0.01	0.27 (0.10–0.65)	0.62 (0.12–0.87)
>5	31 (23.5)	8 (6.0)	<0.01	0.21 (0.09–0.47)	0.36 (0.10–0.67)
Dose (mg/day)					
<40	28 (21.2)	10 (7.5)	0.04	0.31 (0.13–0.65)	0.56 (0.14–0.93)
≥40	40 (30.3)	11 (8.3)	<0.01	0.21 (0.10–0.42)	0.33 (0.10–0.53)
Statin type					
Simvastatin	49 (37.1)	14 (10.7)	<0.01	0.20 (0.10–0.39)	0.39 (0.08–0.75)
Other	19 (14.4)	7 (5.3)	<0.05	0.33 (0.12–0.80)	0.59 (0.14–1.08)

CI confidence interval

[a]Adjusted for age, gender, type 2 diabetes, aspirin use, metformin use, and weekly alcohol intake

(17.2 %), although the difference between those rates was not statistically significant.

Statins and aspirin

Aspirin use was associated with a lower incidence of adenomatous polyps [unadjusted OR=0.43 (0.24–0.77), p= 0.01]; however, this became nonsignificant when adjusted for the use of statin [adjusted OR=1.56 (0.67–3.63), p= 0.30]. Although the combination of aspirin and statin was associated with a significantly lower incidence of polyps compared to controls [adjusted OR=0.12 (0.04–0.30), p< 0.01], this was not significantly different from the use of statin alone.

Discussion

In this case–control study, statin use was associated with a significantly reduced incidence of adenomatous polyps. There was a significant duration– and dose–response relationship with greater statin exposure seeming to be associated with a greater reduction in polyp incidence. When analyzed for statin type, the use of simvastatin was associated with a reduction in polyp incidence, but there were insufficient patients taking other types of statin to produce statistically significant findings, although the pattern of responses was similar. This supports a causal relationship between statin exposure and reduced risk of colorectal adenomatous polyps. These data are consistent with in vitro cell line studies [5, 24], $Min^{-/-}$ mouse polyp models [28, 36] and two single clinical studies [29, 31]. These data do suggest that statins may protect against the development of colorectal polyps and that this effect may contribute to the development of colorectal cancer, as reported in some previous studies [40, 43].

Table 4 Type of statin used

	Control (%)	AP (%)
Simvastatin	49 (37.1)	14 (10.7)
Atorvastatin	7 (5.3)	4 (3.0)
Pravastatin	4 (3.0)	2 (1.5)
Rosuvastatin	8 (6.1)	1 (1.0)
Total	68 (51.5)	21 (15.9)

Similarly, if the most prominent effect of stains in the carcinogenic sequence is at the relatively early and intermediate stages of polyp initiation and development, rather than later stages or progression, this may contribute to the variability of results in different studies examining cancer-protective effects of statins [9–13, 17, 18, 37]. If statins are generally initiated at a later age, once polyps have developed, the cancer-protective effect may be less prominent and more difficult to detect in cohort and case–control studies. However, given the apparent protective effect of statins against adenomatous polyps, it is possible that cohort studies that failed to find a protective effect against colorectal cancer were simply of insufficient duration. Several of the studies used prescribing databases and included patients in the statin-treated group if as little as one prescription or a 3-month treatment was taken [16, 17], while more protective effects were seen in studies that only included at least 5 years or a mean of 9-year follow-up [8, 10].

The dose and duration data in the current paper, in combination with the experimental laboratory studies, show that our hypothesis has biological plausibility. There are further hints that biological variability may contribute to the differences seen with statins. Previous laboratory studies have suggested that HMG-CoA reductase is overexpressed in CRC cells, and the action of statins causing apoptosis is more pronounced in these cells [12, 38]. Recently, it has

been shown that left-sided cancers relatively over express HMG-CoA reductase more than right-sided cancers [39], and given the differences in biology between right and left colonic cancers, with more of the latter going through the classic polyp-cancer sequence [39], it is possible that because statins appear to act early in the polyp-cancer sequence, statins would be more protective against left-sided cancers. In keeping with this, one case–control study has shown that statins seemed to protect against rectal cancer but were less effective against more proximal cancers [40]. Although we did not predefine polyp location as a study variable in our study, there was a trend for greater protection against rectal [adjusted OR 0.44 (0.15–0.88)] and left-sided polyps [adjusted OR 0.38 (0.17–0.47)] than right-sided polyps [adjusted OR 0.66 (0.29–0.95)], although with small numbers in each group, this trend was not statistically significant.

In keeping with a direct effect of statins on polyp-cancer tissues, it is the recent description of the effect of HMG-CoA genotype on the protective effect of statins against colon cancer, and significant protection was seen in higher activity alleles [12]. While these data lend support to the concept that statins may protect against the development of polyps and cancer and may partly explain differences in results between different populations, it is not yet clear whether such information can be used to inform decisions on a population or individual scale.

The biological mechanisms underlying any putative proactive effect of statins against the polyp-cancer sequence are still under investigation. Most attention has been given to the inhibition of the mevalonate synthetic pathway by statins reducing the cellular availability of farnesyl and geranylgeranyl intermediates that are required for the prenylation of small signaling G proteins and are essential for their membrane localization and subsequent role in growth factor-related signaling [24, 39]. Cell line studies have shown that as cancer cells accumulate, further activating mutations in signaling molecules downstream of the small G proteins, the effects of statins are negated [40, 41]. In general, these data would be consistent with statins acting relatively early in the polyp-cancer sequence. Other possible protective mechanisms have been proposed, including diminution of inflammation, reduction of hyperlipidemia, and a beneficial effect on adipokine secretion [42]. The methodology employed in our case–control study did not allow us to relate the effects of statins on polyp incidence with the longer-term effects on serum cholesterol, and further studies examining this are warranted. Indeed, the majority of published clinical studies examining the relationships between statin use and either colon cancer or polyp development have not examined serum cholesterol [8, 10, 11, 13, 14, 16, 18, 19, 30]. As serum cholesterol is a product of the whole body's combination of synthesis, transport, and catabolism, this may not directly relate to activity of the mevalonate pathway in the colonic epithelium, and hence, changes in serum cholesterol may or may not be good predictors of prenylation intermediates and statin effects at the colonic epithelial level. However, in light of the one study showing a correlation between falls in serum cholesterol and polyp recurrence [31], it will be very interesting to examine if absolute or relative falls in serum cholesterol do relate to polyp incidence.

The strengths of our study are the full and accurate history of drug exposure, and that the control group, all underwent colonoscopy. Some previous case–control and cohort studies have used prescribing records, and while these have strengths, they may not accurately capture actual consumption due to non-concordance, and aspirin, ibuprofen, diclofenac, and simvastatin are available to purchase over the counter without prescription in the UK. Asymptomatic adenomatous polyps are common, and hence, when examining the effects on polyp incidence, a control group with a clear colonoscopy is essential. The potential weaknesses of our study are the relatively small size and the potential bias inherent in all nonrandomized studies. However, recruitment exceeded our predefined sample size and had sufficient power to detect our primary outcome of a significant reduction in polyp incidence; further studies in larger groups are warranted, not only to confirm these findings but to investigate other variables such as polyp location, histology, and statin type. It is very difficult to refute the potential bias inherent in statin users being a generally more health-conscious group and this contributing to the perceived reduction in polyp burden. Although this needs to be considered, we feel that this is unlikely to the explanation of the effects; there was no obvious difference in factors such as alcohol use or body mass index between the groups, and in fact, smoking was more common in the control group. It has been shown that patients with documented obesity, coronary artery disease, or diabetes mellitus are at increased risk for colorectal neoplasia [43–45], and these effects would be expected to have decreased the inverse association noted between statins and adenomatous polyps. Hypercholesterolemia has also been reported to be an independent risk factor for the development of colon cancer [46]. The majority of the statin prescribing in our population is, by primary care physicians, for the primary prevention of circulatory diseases, and as such, any such effect of baseline hypercholesterolemia would also be expected to reduce the negative association between statin use and polyp incidence.

Similarly, the apparent risk reduction associated with the use of statins persisted after statistical adjustment for risk and confounding factors. We also showed an apparently protective effect of aspirin comparable to that seen in many other studies [11, 19] and replicated the apparent protective

effect of metformin against colorectal neoplasia [47]; this suggests that our study has external validity. Chronic statin use is associated with a very low incidence of gastrointestinal side effects, so we think it unlikely that referral bias has contributed to overrepresentation of statins in the control group [48].

Investigating the effect of statins and aspirin produced interesting findings. The use of statins or aspirin was associated with a lower incidence of adenomatous polyps. However, the inverse association with aspirin was apparently negated when adjustment was made for statin use, whereas the negative association between polyp incidence and statin use remained significant after adjustment for aspirin use. This requires further study, and we suggest that future studies of chemoprevention should correct for any effects of statins. In vitro cell line studies suggest that statins and cyclooxygenase inhibitors have synergistic effects when used in combination [49]; a similar interaction has been reported in the $Min^{-/-}$ mouse model [36], and further clinical studies exploring the interaction of aspirin or other cyclooxygenase with statins would be welcomed [42].

Conclusion

In conclusion, this case–control study suggests that statins may have a protective effect against the development of colorectal adenomatous polyps. The negative association between statin use and polyp incidence was associated with a significant dose-and duration response, suggesting biological plausibility. Statins may have a role in colon cancer chemoprevention by acting at a relatively early stage in the polyp-cancer sequence, and further studies are warranted to explore this further.

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Conflict of interest None.

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