Statin use and survival in colorectal cancer: Results from a population-based cohort study and an updated systematic review and meta-analysis

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TITLE

Statin use and survival in colorectal cancer: results from a population-based cohort study and an updated systematic review and meta-analysis.

RUNNING HEAD

Statin use and survival in colorectal cancer.

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ABBREVIATIONS

CI – Confidence interval

CRC – Colorectal cancer

DDD – Daily defined dose

HR – Hazard ratio

ABSTRACT

Background

The aim of this study was to investigate the association between statin use and survival in a population-based colorectal cancer (CRC) cohort and perform an updated meta-analysis to quantify the magnitude of any association.

Methods

A cohort of 8,391 patients with newly diagnosed Dukes' A-C CRC (2009-2012) was identified from the Scottish Cancer Registry. This cohort was linked to the Prescribing Information System and the National Records of Scotland Death Records (until January 2015) to identify 1,064 colorectal cancer-specific deaths. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer-specific mortality by statin use were calculated using time dependent Cox regression models. The systematic review included relevant studies published before January 2016. Meta-analysis techniques were used to derive combined HRs for associations between statin use and cancer-specific and overall mortality.

Results

In the Scottish cohort, statin use before diagnosis (HR=0.84, 95%CI 0.75-0.94), but not after (HR=0.90, 95% CI 0.77-1.05), was associated with significantly improved cancer-specific mortality. The systematic review identified 15 relevant studies. In the meta-analysis, there was consistent (I^2=0%,heterogeneity P=0.57) evidence of a reduction in cancer-specific mortality with statin use before diagnosis in 6 studies (n=86,622, pooled HR=0.82, 95% CI 0.79-0.86) but this association was less apparent and more heterogeneous (I^2=67%,heterogeneity P=0.03) with statin use after diagnosis in 4 studies (n=19,152, pooled HR=0.84, 95% CI 0.68-1.04).

Conclusion

In a Scottish CRC cohort and updated meta-analysis there was some evidence that statin use was associated with improved survival. However, these associations were weak in magnitude and, particularly for post-diagnosis use, varied markedly between studies.

KEY WORDS

Hydroxymethylglutaryl-CoA Reductase Inhibitors; Colorectal Neoplasms; Survival; Pharmacoepidemiology; Review, Systematic; Meta-Analysis

1. INTRODUCTION

It is currently estimated that there are 1.4 million incident cases of colorectal cancer (CRC) per year worldwide.[1] In the United Kingdom (UK), CRC is the second most common cause of cancer death with an associated 5-year survival of 50-55%.[2,3] Unfortunately there have been no major advances in the treatment of locally advanced CRC since the MOSAIC study (oxaliplatin in addition to standard chemotherapy) was published over a decade ago,[4] therefore research into novel agents or novel use of existing agents is required.[5,6]

Like aspirin, statins have been identified as potential novel anti-cancer agents that are cost-effective and safe to administer.[7,8] They inhibit the mevalonate pathway and have been shown to have anti-cancer effects in-vitro.[9] Our research group previously reported an association between both pre- and post-diagnostic statin use and improved survival in CRC using observational data.[10] However, not all observational studies assessing the role of statins in CRC survival support our findings.[8,10–19] A recent meta-analysis of these studies suggests the associated reduction in cancer-specific mortality was limited to pre-diagnostic statin users.[20] However two other meta-analyses conclude that the benefit is observed for both pre- and post-diagnostic statin users.[21,22] Importantly though, none of these meta-analyses capture all of the currently available data and they all include hazard ratios for post-diagnostic statin use from one study[13] at risk of immortal time bias.[23] To clarify the association between post-diagnostic statin use and CRC survival we describe a further observational study using an independent population-based UK dataset. We also performed an updated systematic review and meta-analysis to include all additional data for post-diagnostic use that is not at risk of immortal time bias.

2. MATERIALS AND METHODS

2.1. Cohort study

2.1.1. Data source

The study utilised linkages between national datasets from Scotland including the Scottish Cancer Registry (SMR06), the Prescribing Information System (available from January 2009 to January 2015),[24] the General / Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records. A more detailed description of these data resources is described in Supplementary File 1. Linkages between data sources were conducted using the Community Health Index number (unique to individuals in Scotland). The Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland (NSS) approved the study.

2.1.2. Study population

A cohort of newly diagnosed CRC patients was identified on the basis of a Scottish Cancer Registry recorded primary diagnosis of CRC (comprising ICD codes of the colon C18 or rectum C20 including the recto-sigmoid junction C19) between January 2009 and December 2012. Cohort members with a previous Scottish Cancer Registry cancer diagnosis (after January 1999), apart from in situ neoplasms and non-melanoma skin cancers, were excluded.

As post-diagnostic medication usage is unlikely to influence survival in cases with incident metastatic disease, the analysis of medication use after diagnosis was restricted to patients with incident Dukes' A-C disease. Deaths were identified from

National Records of Scotland with coverage up to 1st January 2015 (or from Scottish Cancer Registry death records) with CRC-specific deaths defined as those with underlying cause of death ICD code C18, C19, C20, C21 (anus) or C26 (other and ill-defined digestive organs). Deaths in the first year after CRC diagnosis were removed, this restriction reduces the likelihood of including patients who were not recurrence-free at exposure.[25] Patients were therefore followed from one year after CRC diagnosis to death, the date they left Scotland or 1st January 2015, whichever occurred first.

2.1.3. Exposure data

Statins dispensed in the community (identified from the Prescribing Information System) consisted of all medications in the Statins section of the British National Formulary (Section 2.12).[26] A quantity of 28 tablets was assumed for the less than 0.1% of prescriptions where quantity was deemed incorrect. Daily defined doses (DDD) in each prescription were calculated by multiplying the quantity by strength (in mg) and dividing by the World Health Organization defined DDD (in mg) for individual statins as defined by the).[27] Statin use was investigated as a time-varying covariate (patients were initially considered non-users and then users after a lag of 6 months after their first statin prescription).[23] The use of a lag is recommended[25] and in this study prescriptions in the 6 month period prior to death were not considered as these may reflect end of life treatment (in sensitivity analyses the duration of this lag was varied). Dose-response analyses were conducted with individuals considered non-users prior to 6 months after first use, a short term user between 6 months after first use and 6 months after the 12th prescription (or 365 DDDs) and a longer term user after this time.

2.1.4. Covariates

Data available from the Scottish Cancer Registry included Dukes' stage, histological grade and surgery, chemotherapy and radiotherapy in the six months after diagnosis. Comorbidities that contribute to the Charlson index were determined prior to diagnosis based upon ICD10 diagnosis codes, as described previously,[28] in Scottish hospital inpatient (SMR01) and outpatient data (SMR00). A deprivation measure was determined using the 2009 Scottish Index of Multiple Deprivation based upon postcode of residence.[29] Low-dose aspirin use was determined from dispensing records.

2.1.5. Statistical analysis

In the main analysis, time-dependent Cox regression models were used to calculate hazard ratios (HRs) for CRC-specific death and 95% confidence intervals (95% CI) for post-diagnostic statin users compared with non-users using a time-varying covariate as described previously. Deaths from other causes were censored in cancer-specific analyses. Adjusted analyses were conducted including the following potential confounders: sex, age, year of diagnosis, deprivation (in fifths), grade, site (colon or rectal), Dukes' stage, surgery (within 6 months of diagnosis), radiotherapy (within 6 months of diagnosis), chemotherapy (within 6 months of diagnosis), comorbidities (dichotomised as absent or present prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin usage (as time-varying covariate). Other commonly prescribed medications with potential anti-cancer effects (metformin, drugs affecting the renin-angiotensin system and beta-blockers) were not included in the final models, as they

did not alter the hazard ratio estimates. Analyses were conducted by number of prescriptions, number of DDDs and type of statin and repeated for all-cause mortality. Subgroup analyses were conducted by site (colon or rectal), stage (I-III), treatment (surgery alone versus surgery and adjuvant therapy) and finally for post-diagnostic statin users, *de novo* versus pre- and post-diagnostic statin use.

Sensitivity analysis was conducted by increasing the lag to 1 year. A simplified analysis was also performed using Cox regression to compare statin users to non-users in the first year after CRC diagnosis in individuals living more than 1 year after diagnosis; this controls for immortal time bias without requiring time-varying covariates.[30] Finally, an analysis was conducted based upon statin prescriptions in the year prior to diagnosis (excluding patients diagnosed in 2009 for whom a full year of prescription records prior to diagnosis may not be available), not excluding deaths in the first year after diagnosis and including all CRC patients regardless of Dukes' stage. To avoid overadjustment this analysis did not adjust for stage and grade, or restrict the cohort to Dukes' stage A to C disease, because these variables could be on the causal pathway for the association between pre-diagnostic statin use and CRC–specific mortality.[31,32] For comparison between studies a fully adjusted model was also included. Finally, as the prevalence of commonly prescribed medications may increase in the period before cancer diagnosis an alternative definition of pre-diagnostic statin use in the 12-month period one to two years prior to diagnosis was also assessed (this definition requires the exclusion of patients diagnosed in 2009 and 2010).

2.2. Systematic review and meta-analysis

2.2.1. Search strategy

The review protocol was undertaken according to the principles recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) group[34] statements. It was registered with the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO, registration number CRD42015017915). A systematic search of the literature was performed using Medline (US National Library of Medicine, Bethesda, Maryland, USA), Embase (Reed Elselvier PLC, Amsterdam, Netherlands) and Web of Science (Thompson Reuters, New York, USA). The search encompassed all studies published from database inception to January 12 2016. Keywords and Medical Subject Headings (MeSH) relating to statins and CRC were used following the strategies detailed in Supplementary File 1. References of all eligible studies were also searched for additional relevant studies.

2.2.2. Study selection and eligibility criteria

Two independent reviewers (R.T.G. and H.G.C.) screened all titles and abstracts to identify eligible studies. Full-text manuscripts were reviewed in cases where the title and abstract provided insufficient information to determine eligibility. Disagreements were resolved after discussion with a third party (L.J.M.). Studies were considered for inclusion if (i) they identified a cohort of CRC patients in which exposure to statin treatment was measured and recorded and (ii) they determined an estimate of progression of CRC (i.e. overall, cancer-specific, recurrence-free, progression-free or disease free survival) in a statin user group compared with non-users using

measures of effect or association (HR, relative risk (RR) or odds ratio (OR)) and corresponding 95% CI, or enough information to allow these to be calculated. Abstracts and non-English language articles were included if they met the criteria above. Authors were contacted for further information when required. Results from the current cohort study were also included in the final pooled analyses.

2.2.3. Data extraction and study quality assessment

Standardised data extraction forms were used to collect information on the variables listed in Supplementary File 1 (R.T.G). When the information was not clear this was discussed with a second investigator (H.G.C). The methodological quality of the studies included in the meta-analysis was assessed (R.T.G.) using the Newcastle-Ottawa scale for cohort studies[35] and the Cochrane risk of bias tool for randomised controlled trials (RCTs).[36] When the judgement of the domain was not immediately clear it was discussed with a second investigator (H.G.C. or C.R.C.).

2.2.4. Statistical analysis

The statistical analysis was conducted using Review Manager (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random effects model was used to produce pooled estimates from the fully adjusted HRs and CIs of included studies. If these were not available estimates of the HR and standard error were produced using the indirect method proposed by Parmar *et al.*[37] Meta-analyses were conducted separately on statin use before and after diagnosis. Study outcomes for post-diagnostic statin use deemed to be at risk of immortal time bias, where the exposed group acquire follow-up from a fixed time point (such as diagnosis date) but do not actually commence statin

therapy to later in their follow-up, were not included in the pooled analyses.[23] Between-study heterogeneity was assessed using the Cochrane Q statistic (χ^2 test) and the I^2 statistic.[38] Funnel plot asymmetry was visually assessed to determine the potential for publication bias. A number of *a priori* subgroup analyses were considered including tumour location (colon versus rectum), sex, age (>65 years versus ≤65 years) and disease stage. Finally, sensitivity analyses were performed by systematically removing each individual study in order to assess its effect on the pooled result estimates and accompanying heterogeneity.

3. RESULTS

3.3. Cohort study

3.3.1. Patient cohort

A total of 8,391 incident Dukes' A to C CRC cases met the inclusion criteria (Supplementary Figure 1), in which there was, on average, 2.4 years of exposure-related follow-up starting one year after diagnosis (sd=1.3, minimum=0, maximum=5 years). Patient characteristics by statin use are shown in Table 1. Statin users were more likely to be older and male. Stage and grade were generally similar by statin use, but a smaller proportion of statin users compared with statin non-users had Dukes' C disease (post-diagnostic use 32.5% versus 36.2% respectively). Statin users were more likely to have comorbidities (particularly cerebrovascular disease, diabetes and myocardial infarction) and use concomitant aspirin, but a smaller proportion received adjuvant chemotherapy.

3.3.2. Association between post-diagnostic statin use and survival

Overall, there was no statistically significant reduction in CRC-specific mortality when post-diagnostic statin users were compared with statin non-users (Table 2). Similarly, there was no evidence of a dose-response association when exposure was investigated using DDDs. The absence of an association with CRC-specific survival persisted when simvastatin was assessed and after adjustment for potential confounders. Similar results were observed for adjusted all-cause mortality in terms of marginal non-significant reductions in mortality.

3.3.3. Sensitivity / subgroup analyses

Sensitivity / subgroup analyses are shown in Table 3. Stratifying by tumour location, overall mortality was reduced for post-diagnostic statin users compared to statin non-users in patients with colon cancer (HR=0.85, 95% CI 0.74 to 0.98). However, this subgroup benefit was less apparent for CRC-specific mortality (HR=0.88, 95% CI 0.74 to 1.06). There was some evidence of reduced CRC-specific mortality for statin users compared to non-users when the analysis was restricted to stage II tumours but this was only of marginal statistical significance (HR=0.75, 95% CI 0.56 to 1.00, Supplementary Table 1). There was no evidence of a differential association when cases were stratified by treatment with surgery alone compared to those receiving additional adjuvant therapies (Supplementary Table 1). Increasing the lag period to one year did not alter the results for post-diagnostic statin use and CRC-specific mortality (adjusted HR=0.93, 95% CI 0.79 to 1.08). Repeating the analysis using a simplified 1 year analysis also did not demonstrate a survival benefit for post-diagnostic statin use (Table 3). When post-diagnostic statin use versus non-use was stratified by *de novo* compared to prior statin use, *de novo* post-diagnostic statin users had a more pronounced reduction in cancer-specific and overall mortality. However, the interactions for CRC-specific and overall mortality (P for interaction=0.34 and 0.35, respectively) were not significant. Finally, in contrast to the non-significant association observed for post-diagnostic statin use, CRC-specific mortality and overall mortality were significantly improved by 16% (HR=0.84, 95%CI 0.75 to 0.94) and 11% (HR=0.89, 95% CI 0.80 to 0.98) respectively comparing pre-diagnostic statin users (in the year prior to diagnosis) with statin non-users. These associations were not significantly altered when the definition of pre-diagnostic use

was changed to include any use in the one year period one to two years prior to diagnosis (results not shown).

3.4. Systematic review and meta-analysis

3.4.1. Search results and study characteristics

Fifteen studies were deemed eligible for inclusion in the final review after screening 1192 titles and abstracts (Figure 1). There was one RCT,[39] six prospective population-based studies,[8,10,11,16,18,40] two cohorts within RCTs,[12,15] one prospective cohort within a population-based case-control study[13] and five retrospective hospital-based cohorts(Table 4).[14,17,19,41,42] Seven studies assessed stage I-IV disease,[11,13,14,17–19,40] three assessed stage I-III disease,[10,16,41] two stage III disease only,[15,42] two stage IV disease only,[12,39] and one did not report stage.[8] Two studies reported outcomes for only rectal cancer patients,[14,41] one study consisted of only male subjects[17] while another related to patients with diabetes mellitus only.[18] Eleven studies reported outcomes for post-diagnostic statin use[10–15,18,19,39,40,42] and six reported pre-diagnostic statin use.[8,10,13,16,17,41] The methodological quality of these 15 studies (n=14 observational, n=1 RCT) was evaluated using relevant risk of bias tools (Supplementary Table 2 and 3). In addition to these studies, we also included the results from our own population-based cohort study (described above).

3.4.2. Post-diagnostic statin use

Four studies with 19,152 patients reported CRC-specific mortality in post-diagnostic statin users compared to statin non-users but only two of them, the current study and Cardwell *et al,*[10] assessed statin use as a time-varying covariate. The pooled HR

was 0.84 (95% CI 0.68 to 1.04) with evidence of significant heterogeneity (heterogeneity P=0.03; I^2=67%) (Figure 2A). Removing the study by Cardwell *et al*.[10] in sensitivity analysis reduced this statistical heterogeneity but moved the association closer to null (Supplementary Table 4).

Twelve studies reported overall mortality in relation to post-diagnostic statin use but the HR reported by Lakha *et al*.[13] was excluded as it has previously been identified as being at risk of immortal time bias.[10,20] Eleven studies (21,030 patients) were subsequently included in the pooled analysis for which the HR was 0.84 (95% CI 0.73 to 0.98). Again, there was a high level of statistical heterogeneity (heterogeneity P=0.0004; I^2=69%) (Figure 2B). There was also methodological heterogeneity amongst the studies included in this analysis. Only four studies (the current study, Cardwell *et al*.,[10] Voorneveld *et al*.[40] and Zanders *et al*.[18]) assessed post-diagnostic statin use as a time-varying covariate, one considered a diabetic cohort only[18] and a further two assessed the role of statins in stage IV disease only.[12,39] Removing individual studies in sensitivity analysis did not markedly alter the result or associated heterogeneity for overall mortality and post-diagnostic statin use (Supplementary Table 4).

3.4.3. Pre-diagnostic statin use

Six studies with 86,622 patients reported CRC-specific mortality in pre-diagnostic statin users compared to statin non-users. The pooled HR was 0.82 (95% CI 0.79 to 0.86) with no evidence of heterogeneity (heterogeneity P=0.57; I^2=0%) (Figure 3A). Statin exposure was determined through linkage to dispensing or prescribing

databases in all of the studies included in this pooled analysis and four of the six were large population-based studies.

Six studies (44,026 patients) also reported overall mortality in relation to pre-diagnostic statin use. The pooled HR for overall mortality was 0.85 (95% CI 0.76 to 0.95) although there was evidence of significant heterogeneity in this analysis (heterogeneity P=0.0009; I^2=76%) (Figure 3B). There was also greater methodological heterogeneity associated with this analysis as one study[41] relied on medical record review rather than data linkage and only three were prospective population-based cohorts (current study, Cardwell *et al*.[10] and Shao *et al*.[16]). The heterogeneity associated with the pooled analysis for pre-diagnostic statin use and overall mortality reduced from 76% to 48% when the only study associated with increased mortality was removed (Supplementary Table 4). Removing the other studies individually had no significant impact on the result or associated heterogeneity.

3.4.4. Subgroup analyses and publication bias

Survival estimates stratified by age, sex, stage and tumour location were not consistently reported therefore the planned subgroup analysis could not be reliably performed. Funnel plots showed no evidence of asymmetry for cancer-specific or overall mortality in pre- or post-diagnostic statin use (Supplementary Figure 2).

4. DISCUSSION

In a large Scottish cohort of CRC patients we identified some evidence of an inverse association between CRC-specific mortality and statin use before diagnosis but less evidence of an association with statin use after diagnosis. In particular, while *de novo* post-diagnostic statin use was associated with reduced cancer-specific mortality in a subgroup analysis, this association was based on relatively few events and the interaction term for this stratification was not statistically significant. An updated systematic review and meta-analysis was subsequently performed which demonstrated an association with relatively small reductions in cancer-specific and all-cause mortality with statin use before and after diagnosis. However, these associations generally lacked consistency and the association between cancer-specific mortality and post-diagnostic statin use did not reach statistical significance.

We previously reported an association between improved survival outcomes and post-diagnostic statin use in a cohort of 7,657 patients within the UK National Cancer Data Repository.[10] However, despite using very similar methodology, the association with reduced mortality was smaller and non-significant in this current Scottish cohort of 8,391 patients. In addition to the possibility of differences in unknown lifestyle factors, one potential explanation for the failure to demonstrate a significant inverse association between post-diagnostic statin use and mortality in the current study is that it is more contemporaneous (2009-2012 versus 1998-2009). In more recent years important changes in the detection and management of CRC occurred including the full implementation of the bowel cancer screening programme in Scotland in 2009[43] and the availability of oxaliplatin-based adjuvant chemotherapy from 2006.[44] It is possible that undergoing screening (with the potential to have an

earlier stage tumour) or receiving oxaliplatin-based chemotherapy could be associated with statin use. Therefore, potential confounding by these factors could contribute to the different findings observed in our studies.

The results of other studies assessing post-diagnostic statin use are similarly heterogeneous (I^2 67%-69%) and may represent the absence of a standardised methodological approach. The numerous different methods could explain some of this heterogeneity. For example, the use of patient self-reporting measures to determine statin use potentially introduces recall bias and limiting the study population to stage IV disease or diabetic patients reduces external validity. Finally, only four studies reported cancer-specific mortality in post-diagnostic statin users compared to 11 studies reporting overall mortality. The inverse association with survival outcomes and post-diagnostic statin use was only statistically significant for overall mortality in the subsequent meta-analysis. However, as this could reflect non-cancer related mortality, further studies assessing cancer-specific mortality are required.

In comparison to the results for post-diagnostic statin use, the significant association between improved survival outcomes and pre-diagnostic statin use observed in the UK National Cancer Data Repository cohort[10] persisted in the Scottish cohort study, albeit the magnitude of the effect was smaller. The subsequent pooled analysis demonstrated pre-diagnostic statin use was associated with an 18% reduction in cancer-specific mortality. The absence of statistical heterogeneity in this analysis contrasts with the other pooled analyses and could represent a more homogeneous

methodological approach. In this case, the majority of studies used large-scale population-based designs and utilised prescribing or dispensing database information. Overall there were also four times as many patients in the pre- compared to post-diagnostic pooled analysis for cancer-specific mortality. However, the consistent association observed for pre-diagnostic users is perhaps less clinically useful, as it is difficult to intervene before diagnosis, whereas an association with post-diagnostic use could represent the potential for use as a novel adjuvant agent.

It remains unclear if the molecular phenotype of CRC developing in pre-diagnostic statin users is different to statin non-users and whether this difference conveys a survival benefit. While no benefit for statin use was identified when survival analyses were stratified by KRAS status[11,15] or MSI,[11] the field of personalised cancer treatment is evolving and further studies should consider the molecular profile of the tumour. Additional molecular pathological epidemiology studies assessing CRC risk and progression could provide further insights into the anti-cancer effect of statins and identify potential biomarkers to tailor treatment.[45] In particular TP53 mutations,[46] immunohistochemical expression of hydroxymethylglutaryl-CoA reductase[47,48] and single nucleotide polymorphisms in the genes which encode proteins involved in statin metabolism[48] have been identified as potential biomarkers to differentiate potentially statin sensitive tumours and warrant further study.

The strengths of the Scottish cohort study include its large population-based design and use of dispensing information with detailed information on the type, timing and dose of statins being used. One of the main limitations is that this is an observational

study and there is the potential for residual confounding for which we could not control. The follow-up period was also relatively short (average 3.4 years from diagnosis with 2.4 years of follow-up) and may not be sufficient to fully assess the potential beneficial effect of statins. However, three studies included in the review have similar follow-up periods (average/median 3.4-3.8 years),[11,18,40] two of which demonstrated a survival benefit for post-diagnostic statin use and overall mortality.[18,40] While dispensing information is more robust than prescribing information, compliance cannot be confirmed. Cause of death can also be misclassified when relying on data from national statistics records.[8] Healthy-user bias[49] could be responsible for the observed improvement in survival for pre-diagnostic users but co-morbidities were actually higher in statin users. Finally, statin users had a smaller proportion of Dukes' C cancers but the adjusted analyses should correct for this difference.

Compared to prior systematic reviews and meta-analyses,[20–22] the present updated one benefits from the ability to include data from the Scottish cohort study and at least five further studies.[19,39–42] The three previous reviews[20–22] also incorporated results from one study[13] identified as being at risk of immortal time bias,[10,20] whereas it was excluded from our pooled analysis. In addition, the review by Zhong *et al*.[20] excluded the estimate reported by Nielsen *et al*.[8] (n=43,487 patients) for colon cancer-specific mortality and pre-diagnostic statin use despite identifying the study. The review by Ling *et al*.[21] included the HR from both the nationwide cohort study and nested matched study reported by Nielsen *et al.*[8] adding inappropriate extra weight to this study as individuals were counted twice. Finally Ling *et al*.[21] and Cai *et al*.[22] have misclassified the HR for overall mortality reported by Siddiqui *et al*.[17] as

cancer-specific mortality. Therefore, we believe our review adds improved rigour to prior systematic evaluations of this topic.

In summary, combining the results of this cohort study and the updated systematic review and meta-analysis suggests that statin use appears to be associated with reduced mortality in CRC. However the magnitude of the effect is weak and the association may not be causal. The association also varies markedly between studies for statin use after diagnosis, the only time point at which clinical intervention is possible. Importantly, the only RCT assessing adjuvant statin therapy after surgery for early stage colon cancer (NCT01011478)[50] has been terminated due to poor accrual (predominantly due to limited numbers of statin-naïve patients - *personal communication, NSABP, 2015*). To inform the decision to conduct future trials, further observational studies reporting cancer-specific survival outcomes are therefore required to clarify the association between post-diagnostic statin use and CRC-specific survival.

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Table 1. Characteristics of colorectal cancer patients by post-diagnostic statin use

	Statin use in first year after cancer diagnosis*			
	Yes		No	
	n	%	n	%
Age				
<50	20	0.6	425	8.1
50-59	248	7.9	996	19.0
60-69	927	29.6	1,632	31.1
70-79	1,348	43.0	1,462	27.8
≥ 80	594	18.9	739	14.1
Men	1,913	61.0	2,761	52.6
Deprivation (fifth)				
1 (most deprived)	632	20.1	854	16.3
2	711	22.7	1,058	20.1
3	618	19.7	1,074	20.4
4	641	20.4	1,132	21.5
5 (least deprived)	535	17.1	1,135	21.6
Colon	2204	70.3	3,516	66.9
Rectum†	933	29.7	1,738	33.1
Dukes' stage				
A	931	29.7	1,349	25.7
B	1,187	37.8	2,004	38.1
C	1,019	32.5	1,901	36.2
Grade				
Well differentiated	119	3.8	166	3.2
Moderately differentiated	2,450	78.1	3,992	76.0
Poorly differentiated	432	13.8	851	16.2
Missing	136	4.3	245	4.7
Treatment (within 6 months)				
Surgery	2,972	94.7	4,956	94.3
Radiotherapy	258	8.2	613	11.7
Chemotherapy	693	22.1	1,946	37.0
Comorbidity before cancer diagnosis				
Acute myocardial infarction	352	11.2	51	1.0
Congestive heart failure	166	5.3	63	1.2
Peripheral vascular disease	181	5.8	44	0.8
Cerebral vascular accident	244	7.8	59	1.1
Pulmonary disease	277	8.8	313	6.0
Peptic ulcer	101	3.2	109	2.1
Liver disease	7	0.2	24	0.5
Diabetes	467	14.9	108	2.1
Renal disease	109	3.5	80	1.5
Aspirin use	1,647[a]	52.5[a]	503[a]	9.6[a]

*Restricted to patients who survived at least one year after diagnosis
†Includes recto sigmoid junction
a – Refers to aspirin use in the year after diagnosis
Abbreviation: n – number.

Table 2. Association between statin use after diagnosis and cancer-specific and all-cause mortality in patients with colorectal cancer.

	Mortality	Patients	Person Years	Unadjusted HR (95% CI)	P	Adjusted[1] HR (95%CI)	P
				Cancer-specific mortality			
Statin non-user	639	4,766	13,224	1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	425	3,625	8,910	1.01 (0.89, 1.14)	0.89	0.90 (0.77, 1.05)	0.17
1-12 prescriptions vs. non-user	257	1,199	4,927	1.00 (0.86, 1.16)	0.98	0.89 (0.75, 1.06)	0.19
≥ 12 prescriptions vs. non-user	168	2,426	3,983	1.03 (0.86, 1.23)	0.78	0.91 (0.74, 1.12)	0.39
1 to 365 DDDs vs. non-user	271	1,470	5,196	1.02 (0.89, 1.18)	0.75	0.90 (0.77, 1.07)	0.23
≥ 365 DDDs vs. non-user	154	2,155	3,714	0.98 (0.82, 1.18)	0.85	0.90 (0.72, 1.10)	0.29
Simvastatin non-user	761	5,789	15,799	1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	303	2,602	6,335	1.02 (0.89, 1.17)	0.76	0.96 (0.83, 1.12)	0.63
				Overall mortality			
Statin non-user	906	4,766	13,224	1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	729	3,625	8,910	1.20 (1.09, 1.33)	<0.001	0.90 (0.80, 1.02)	0.09
1-12 prescriptions vs. non-user	405	1,199	4,927	1.16 (1.03, 1.30)	0.02	0.89 (0.78, 1.02)	0.11
≥ 12 prescriptions vs. non-user	324	2,426	3,983	1.27 (1.11, 1.45)	0.001	0.91 (0.78, 1.07)	0.25
1 to 365 DDDs vs. non-user	436	1,470	5,196	1.21 (1.07, 1.35)	0.001	0.91 (0.80, 1.04)	0.18
≥ 365 DDDs vs. non-user	293	2,155	3,714	1.21 (1.05, 1.38)	0.007	0.88 (0.75, 1.03)	0.11
Simvastatin non-user	1,126	5,789	15,799	1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	509	2,602	6,335	1.14 (1.02, 1.26)	0.02	0.94 (0.83, 1.05)	0.26

[1]Model contains age, sex, year of diagnosis, deprivation, site (colon or rectum), stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time-varying covariate).

Table 3. Sensitivity analysis of association between statin use and cancer-specific and all-cause mortality in patients with colorectal cancer.

	Medication User			Medication Non-user						
	Cancer \ All Mortality	Patients	Person Years	Cancer \ All Mortality	Patients	Person Years	Unadjusted HR (95% CI)	P	Adjusted HR (95%CI)	P
Cancer-specific mortality										
Subgroup analyses: Statin users versus non-users[1]										
Colon cancer	300	3,132	6,238	442	3,309	8,766	0.99 (0.85, 1.14)	0.88	0.88 (0.74, 1.06)	0.17
Rectal cancer[†]	125	1,397	2,673	197	1,618	4,458	1.06 (0.85, 1.32)	0.62	0.98 (0.74, 1.30)	0.88
Use in first year after diagnosis										
Statin user vs. non-user[2]	408	3,137	8,257	656	5,254	13,877	1.04 (0.92, 1.18)	0.50	0.95 (0.81, 1.11)	0.51
Simvastatin vs. versus non-user[2]	288	2,149	5,655	776	6,242	16,480	1.08 (0.94, 1.24)	0.26	1.03 (0.89, 1.20)	0.70
Post-diagnostic use stratified by pre-diagnostic use[1]										
Statin user (pre- plus post-diagnostic) vs. non-user (excludes 2009 cases)	255	2223	4952	19	116	304	0.83 (0.52, 1.32)	0.43	0.95 (0.59, 1.53)	0.83
Statin user (*de-novo* post-diagnostic) vs. non-user (excludes 2009 cases)	24	444	698	434	3543	8317	0.69 (0.46, 1.05)	0.08	0.64 (0.42 ,0.99)	0.05
Use in year before CRC diagnosis										
Statin user vs. non-user[3]	1,418	3,967	9,297	2,237	6,441	15,815	1.06 (1.00, 1.14)	0.06	0.83 (0.77, 0.90)	<0.001
Statin user vs. non-user (fully adjusted)[4]									0.84 (0.75, 0.94)	0.002
Simvastatin user vs. non-user[3]	1,006	2,755	6,373	2,649	7,653	18,738	1.10 (1.02, 1.18)	0.01	0.92 (0.85, 1.00)	0.05
Simvastatin vs. non –user (fully adjusted)[4]									0.95 (0.85, 1.06)	0.33
All-cause mortality										
Subgroup analyses: Statin users versus non-users[1]										
Colon cancer	516	3,132	6,238	636	3,309	8,766	1.16 (1.03, 1.30)	0.02	0.85 (0.74, 0.98)	0.03
Rectal cancer[†]	213	1,397	2,673	270	1,618	4,458	1.31 (1.09, 1.57)	0.003	1.03 (0.82, 1.29)	0.82
Use in first year after diagnosis										
Statin user vs. non-user[2]	691	3,137	8,257	944	5,254	13,877	1.23 (1.11, 1.36)	<0.001	0.93 (0.82, 1.05)	0.24
Simvastatin user vs.non-user[2]	474	2,149	5,655	1,161	6,242	16,480	1.19 (1.07, 1.32)	0.001	0.98 (0.87, 1.10)	0.74
Post-diagnostic use stratified by pre-diagnostic use[1]										
Statin user (pre- plus post-diagnostic) vs. non-user (excludes 2009 cases)	422	2223	4952	31	116	304	0.82 (0.57, 1.18)	0.29	0.92 (0.62, 1.36)	0.67
Statin user (*de-novo* post-diagnostic) vs. non-user (excludes 2009 cases)	42	444	698	587	3543	8317	0.87 (0.63, 1.19)	0.38	0.68 (0.48, 0.96)	0.03
Use in year before CRC diagnosis										
Statin user vs.non-user[3]	1,907	3,967	9,297	2,716	6,441	15,815	1.18 (1.11, 1.25)	<0.001	0.86 (0.80, 0.92)	<0.001
Statin user vs. non-user (fully adjusted)[4]									0.89 (0.80, 0.98)	0.02
Simvastatin user vs. non-user[3]	1,336	2,755	6,373	3,287	7,653	18,738	1.18 (1.11, 1.26)	<0.001	0.93 (0.87, 1.00)	0.04
Simvastatin vs. non-user (fully adjusted)[4]									0.97 (0.88, 1.06)	0.47

[†]Includes rectosigmoid junction
[1]Based upon main time-varying covariate analysis adjusted model containing age, sex, year of diagnosis, deprivation, site (colon or rectum), stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time-varying covariate).
[2]Model contains age, sex, year of diagnosis, deprivation, site (colon or rectum), stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (in first year after diagnosis).
[3]Excluding patients diagnosed in 2009 (who do not have complete prescription records for year before diagnosis) but not excluding patients who die within 1 year of diagnosis; adjusted model contains age, sex, year of diagnosis, deprivation, site (colon or rectum), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (in year prior to diagnosis).
[4]Adjusting for variables in (3) but additionally adjusting for stage, grade and cancer treatment within 6 months (radiotherapy, chemotherapy, surgery).

Table 4. Baseline characteristics of included studies investigating statin use and survival outcomes in colorectal cancer.

First Author (year) Country	Study design (Exposure Ascertainment)	Study Period (Follow-up)	No. of Patients	Tumour Location	Stage	Statin Use	Outcome	Adjusted Variables
Lim (2015)[39] Korea	RCT (N/A)	2010-2013 (NR)	269	CRC	IV	Post	OM¶	Unadjusted hazard ratio provided by the study authors through personal communication.
Current study Scotland	Prospective population-based cohort (Dispensing database)	2009-2012 (Censored 2015, mean 3.4 years)	8391	CRC	I-III	Post	CSM & OM	Age, sex, year of diagnosis, deprivation, site (colon or rectum), stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time-varying covariate).
Cardwell (2014)[10] England	Prospective population-based cohort (Prescribing database)	1998-2009 (Censored 2012, mean 5 years)	7657	CRC	I-III	Pre & Post†	CSM & OM	Year of diagnosis, age at diagnosis, sex, stage, surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, site, comorbidities, low-dose aspirin, ACEIs, and metformin use after diagnosis as time-varying covariates, grade, deprivation, and smoking before diagnosis. Post- but not pre-diagnostic analyses adjusted for stage and grade as potentially on causal pathway.
Hoffmeister (2015)[11] Germany	Prospective population-based cohort (Patient reported)	2003-2009 (Median 3.4 years)	2697	CRC	I-IV	Post‡	CSM & OM	Age at diagnosis, sex, stage, site, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, BMI, lifetime pack-years of active smoking, physical activity, diabetes, ever regular use of NSAIDs including aspirin, ever use of HRT among women, previous large bowel endoscopy, hypercholesterolemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, late entry into the study, and time-dependent effect chemotherapy.
Nielsen (2012)[8] Denmark	Prospective population-based cohort (Dispensing database)	1995-2007 (Censored 2009)	43487	Colon	NR	Pre	CSM	Age at diagnosis, stage, chemotherapy, radiotherapy, cardiovascular disease, diabetes mellitus, year of birth, sex, descent, education, and size of residential area. **Tumour staging only available for 3 years (2004-2007).
Shao (2015)[16] Taiwan	Prospective population-based cohort (Insurance database)	2004-2008 (Censored 2011, median 4.2 years)	17115	CRC	I-III	Pre	CSM & OM	Age, sex, tumour stage, adjuvant therapy and a propensity score for statin use modelled on age, sex, year of diagnosis, physician visits and hospitalisation 1 year prior to diagnosis, aspirin, NSAIDs, insulin, oral anti-diabetic medication, ACEIs, ARBs and comorbidities.
Zanders (2015)[18] Netherlands	Prospective population-based cohort (Dispensing database)	1998-2011 (Censored 2011, mean 3.4 years)	1043	CRC	I-IV	Post†	OM¶	Metformin, sulfonylurea derivatives, insulin, other diabetes medication, statins and aspirin after diagnosis as time-dependent ever-never terms, the use of these drugs before diagnosis as a dichotomised variable, and the time-fixed variables: sex, age at CRC diagnosis, calendar year of CRC diagnosis, type of CRC, stage and administration of surgery, radiotherapy and/or chemotherapy.
Voorneveld (2015)[40] Netherlands	Prospective population-based cohort (Dispensing database)	1998-2007 (Censored 2012, median 3.8 years)	999	Colon	I-IV	Post†	OM¶	Unadjusted hazard ratio estimated using Parmar's method based on the log rank test provided through personal communication.
Krens (2014)[12] Netherlands	Prospective cohort within RCT (Patient reported)	2005-2006 (NR)	529	CRC	IV	Post‡	OM	Age, prior adjuvant therapy, aspirin use, > 1 organ affected by metastatic spread, treatment arm, KRAS mutation status, and a KRAS*statin interaction term.
Ng (2011)[15] USA	Prospective cohort within RCT (Patient reported)	1999-2001 (Censored 2009, median 6.5 years)	842	Colon	III	Post‡	OM	Age, sex, family history of colorectal cancer, ECOG performance status (0 *vs*. 1-2), T stage (T1/T2 *vs*. T3/T4), number of positive lymph nodes (1-3 *vs*. ≥4), perineural invasion, extravascular invasion, postoperative CEA (<5 *vs*. ≥5 ng/mL), treatment arm, BMI, physical activity, Western pattern diet, KRAS mutation status, and aspirin use.
Lakha (2012)[13] Scotland	Prospective cohort within case-control study (Dispensing database)	1999-2006 (Censored 2009)	309	CRC	I-IV	Pre & Post§	CSM & OM	Stage, age, and sex.
Anderson (2014)[19] USA	Retrospective cohort (Medical record review)	2005-2009 (Censored 2013)	230	CRC	I-IV	Post‡	OM¶	Age at diagnosis, stage, margin status and chemotherapy use.

Table 4 continued. Baseline characteristics of included studies investigating statin use and survival outcomes in colorectal cancer.

First Author (year) Country	Study design (Exposure Ascertainment)	Study Period (Follow-up)	No. of Patients	Tumour Location	Stage	Statin Use	Outcome	Adjusted Variables
Armstrong (2015)[41] Canada	Retrospective cohort (Medical record review)	2005-2012 (Median 3.7 years)	891	Rectum	I-III	Pre	OM¶	Age at diagnosis, pathologic stage, performance status, sex and adjuvant chemotherapy use
Kim (2015)[42] Korea	Retrospective cohort (Medical record review)	2007-2009 (NR)	239	CRC	III	Post¶	CSM	Age, sex, comorbidity, pre-diagnosis aspirin use, medication, cancer site, initial stage and pathological differentiation
Mace (2013)[14] USA	Retrospective cohort (Medical record review)	2000-2012 (Report 5 year outcomes)	394	Rectum	I-IV	Post‡	CSM & OM	Age, BMI, ASA class (III/IV *vs*. I/II), AJCC tumour regression grade, and stage.
Siddiqui (2009)[17] USA	Retrospective cohort (Dispensing database)	1997-2003 (Report 5 year outcomes)	1309	CRC	I-IV	Pre	CSM & OM	Stage, anatomical site (right *vs*. other), presence of metastases, NSAIDs, and BMI for OM. Unadjusted hazard ratio for CSM estimated using Parmar's method based on the log rank test reported in the manuscript.

Abbreviations: RCT – randomised controlled trial; CRC – colorectal cancer; NR – not reported; CSM – cancer-specific mortality; OM – overall mortality; ACEIs – angiotensin converting enzyme inhibitors; BMI – body mass index; NSAIDs – non-steroidal anti-inflammatory drugs; HRT – hormone replacement therapy; ARBs – angiotensin receptor blockers; AJCC – American Joint Committee on Cancer; ECOG – Eastern Cooperative Oncology Group; CEA – Carcinoembryonic antigen. Footnotes: † Time-varying covariates of post-diagnostic statin use considered in the survival analysis; ‡ Statin use ascertained at a single time point in the early post-diagnosis period to negate the risk of immortal time bias; § Study at risk of immortal time bias as ever/never drug exposure was determined based on use at any time in the follow-up period but did not include a time-varying covariate; ¶ Authors provided additional information upon request.

FIGURE LEGENDS

Figure 1. Flow chart of the selection of publications included in the meta-analysis.

Figure 2. Forest plot of post-diagnostic statin use and (A) colorectal cancer-specific survival and (B) overall survival. † - Parmar method used to estimate hazard ratio from log rank test; ‡ - Authors contacted for additional information including adjusted hazard ratios.

Figure 3. Forest plot of pre-diagnostic statin use and (A) colorectal cancer-specific survival and (B) overall survival. † - Parmar method used to estimate hazard ratio from log rank test; ‡ - Authors contacted for additional information including adjusted hazard ratios.