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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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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 8391 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 1064 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.

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].

Abbreviations: CI, confidence interval; CRC, colorectal cancer; DDD, daily defined dose; HR, hazard ratio.

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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 [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–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).