Gastroenterology 2014;146:700–708

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Low-Dose Aspirin Use After Diagnosis of Colorectal Cancer Does Not Increase Survival: A Case–Control Analysis of a Population-Based Cohort

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BACKGROUND & AIMS: Individuals who began taking low-dose aspirin before they were diagnosed with colorectal cancer were reported to have longer survival times than patients who did not take this drug. We investigated survival times of patients who begin taking low-dose aspirin after a diagnosis of colorectal cancer in a large population-based cohort study. **METHODS:** We performed a nested case-control analysis using a cohort of 4794 patients diagnosed with colorectal cancer from 1998 through 2007, identified from the UK Clinical Practice Research Datalink and confirmed by cancer registries. There were 1559 colorectal cancer–specific deaths, recorded by the Office of National Statistics; these were each matched with up to 5 risk-set controls. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI), based on practitioner-recorded aspirin usage. **RESULTS:** Overall, low-dose aspirin use after a diagnosis of colorectal cancer was not associated with colorectal cancer–specific mortality (adjusted OR = 1.06; 95% CI: 0.92–1.24) or all-cause mortality (adjusted OR = 1.06; 95% CI: 0.94–1.19). A dose–response association was not apparent; for example, low-dose aspirin use for more than 1 year after diagnosis was not associated with colorectal cancer–specific mortality (adjusted OR = 0.98; 95% CI: 0.82–1.19). There was also no association between low-dose aspirin usage and colon cancer–specific mortality (adjusted OR = 1.02; 95% CI: 0.83–1.25) or rectal cancer–specific mortality (adjusted OR = 1.10; 95% CI: 0.88–1.38). **CONCLUSIONS:** In a large population-based cohort, low-dose aspirin usage after diagnosis of colorectal cancer did not increase survival time.

Keywords: Antiplatelet Drugs; Pharmacoepidemiology; Colorectal Neoplasms; CPRD.

Platelets play a complex role in cancer growth and metastasis.[1–3] Evidence from randomized controlled trials of aspirin to prevent vascular events show that low-dose aspirin reduces colorectal cancer risk,[4] and it has been proposed it could improve survival. In support of this hypothesis, a meta-analysis of 5 randomized controlled trials of low-dose aspirin to prevent vascular events showed that colorectal cancer patients initiating aspirin treatment before cancer diagnosis had a reduced risk of metastasis and improved survival.[5] However, as these patients were taking aspirin before colorectal cancer diagnosis, it remains unclear whether low-dose aspirin use after cancer diagnosis, a time point more relevant for clinical intervention, confers any benefit.

Only 2 independent observational studies have investigated aspirin use after colorectal cancer diagnosis and cancer-specific mortality.[6–8] The larger[6] of 2 overlapping studies[6,7] using Nurses Health and Health Professionals Follow-Up data investigated 1279 colorectal cancer patients (including 222 colorectal cancer–specific deaths) and found that self-reported post-diagnostic aspirin use (but not specifically low-dose aspirin use) was associated with a 30% reduction in colorectal cancer–specific mortality. More recently, a Scottish study of 2990 colorectal cancer patients (including 1021 colorectal cancer–specific deaths) observed a more marked 40% reduction in cancer-specific mortality with low-dose aspirin usage after diagnosis.[8] However, their analysis might have exaggerated the true association if aspirin was withdrawn from cancer patients in whom death was suspected to be imminent. Other observational studies[6–11] have investigated low-dose aspirin usage and all-cause mortality, but the observed associations could reflect non–cancer-related mortality.

This study aimed to investigate low-dose aspirin usage after colorectal cancer diagnosis and colorectal cancer–specific mortality in a large cancer registry defined population-based cohort of colorectal cancer patients. Importantly, this study focused solely on low-dose aspirin usage, used epidemiological methods that reduce reverse causality and is the largest cohort study to date to investigate this association.

Abbreviations used in this paper: **CI, confidence interval; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HR, hazard ratio; NCDR, National Cancer Data Repository; ONS, Office of National Statistics; OR, odds ratio.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.11.005

Materials and Methods

Data Source

The study utilized recent linkages between the National Cancer Data Repository (NCDR), Clinical Practice Research Datalink (CPRD), and Office of National Statistics death registration data (ONS).[12] The NCDR contains data on all cancer patients identified in English cancer registries, including date and site of primary cancer diagnosis, stage, and treatment data. The CPRD is the world's largest computerized database of longitudinal patient records, comprising approximately 6% of the UK population and includes demographic information, clinical diagnoses, and prescription data of documented high quality.[13] Linkages between data sources were conducted using a deterministic algorithm based on National Health Service number, sex, date of birth, and postcode. Ethical approval for all observational research using CPRD data has been obtained from a multicenter research ethics committee. CPRD also contains ONS mortality data providing date and cause of death for deaths up to 2012.

Study Design

A colorectal cancer cohort was identified from individuals with a CPRD colorectal cancer diagnosis code and NCDR primary diagnosis of colorectal cancer (based on International Classification of Diseases codes of the colon [C18] or rectum [C20], including the rectosigmoid junction [C19]) from 1998 to 2006. Cohort members with previous NCDR cancer diagnosis, apart from in situ neoplasms and nonmelanoma skin cancers, were excluded. This cohort was initially analyzed using a nested case-control approach, a common approach[14,15] that accounts for immortal time bias[16] without requiring complicated statistical techniques[17] (and is therefore easier to understand and communicate to a clinical audience) with minimal loss of precision.[18] Time-varying covariate analyses were also applied and presented and will be described here. Cases were patients who had died due to colorectal cancer (with an ONS-recorded underlying cause of death of International Classification of Diseases code of C18, C19, C20, or other and ill-defined digestive organs [C26]) and these were matched on age (in 5-year intervals), year of cancer diagnosis (in 2-year intervals), sex, and site (colon or rectum and rectosigmoid junction) to up to 5 risk-set controls who lived at least as long after their cancer diagnosis. The exposure period in cases was the period from colorectal cancer diagnosis until 6 months before cancer-specific death. The exposure period in the controls was of the same duration as their matched cases starting from the date of colorectal cancer diagnosis. Prescriptions in the 6-month period before death were removed, as these might reflect end-of-life treatment (sensitivity analyses were conducted excluding prescriptions in the 3 months and excluding the year before death, not shown as produced similar results). The main analyses were restricted to individuals with at least 1 year of follow-up.

Exposure Data

Aspirin prescriptions in the exposure period (from general practitioner [GP] data) were classified as low dose if $\leq$75 mg (0.3% of prescriptions after cancer diagnosis were 25 mg, 98.5% were 75 mg, and 1.2% were $\geq$300 mg). Duration of use was determined from quantity of tablets. A quantity of 28 tablets was assumed for approximately 2% of prescriptions where quantity was missing or assumed incorrect. Number of tablets per day was calculated by dividing the number of tablets by the duration of the exposure period.

Covariates

Data available from NCDR included cancer stage; histological grade; and surgery, chemotherapy, and radiotherapy in the 6 months after diagnosis. Smoking, alcohol, and body mass index were determined from the closest GP record before colorectal cancer diagnosis (values more than 10 years before diagnosis were ignored). Comorbidities were determined from GP diagnosis codes using a recent adaptation of the Charlson Comorbidity Index.[19] Adjustments were made for statin and metformin use (used after diagnosis by 34% [1610 of 4794] and 9% [433 of 4794] of the final cohort) determined from GP prescription records (based on 1 or more prescription after diagnosis in the exposure period) because emerging evidence suggests these could have anti-cancer properties.[20,21]

Statistical Analysis

In the main analysis, conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Adjusted analyses were initially conducted adjusting for only potential confounders available for the entire cohort (including surgery; chemotherapy; radiotherapy; statin use; metformin use; and comorbidities including myocardial infarction, cerebrovascular disease, congestive heart disease, chronic pulmonary disease, peripheral vascular disease, peptic ulcer disease, renal disease and rheumatological disease, and diabetes). A separate analysis was conducted that was restricted to individuals with available stage and grade data and additionally adjusting for stage, grade, and smoking status. Analyses were conducted after stratification by site, stage, and prediagnostic low-dose aspirin usage (based on any use in the previous 2 years) after rematching within strata for stage and prediagnostic usage. Secondary analyses investigated any aspirin usage in the 2 years before colorectal cancer diagnosis, restricted to individuals with 2 years of medication records before diagnosis, not excluding deaths in the year after diagnosis. These analyses of prediagnosis aspirin omitted stage from adjustments for potential confounders to avoid overadjustment,[22,23] as stage could be on the causal pathway for the association between prediagnosis aspirin and colorectal cancer–specific mortality. Interaction tests were conducted using Z tests.[24] Sensitivity analyses were conducted restricting the analysis to 4 cancer registries with high-stage recording (>90%) using a separate category for missing stage, matching on stage and using multiple imputation of missing stage (results from method using multiple imputation not shown as similar to overall). Sensitivity analyses were also conducted analyzing the entire cohort, before conversion to case-control data, applying survival analysis investigating aspirin as a time-varying covariate[16] (individuals were considered nonusers before first use after diagnosis and users after a lag of 6 months after their first aspirin prescription, to mimic the case-control analysis). A similar dose-exposure analysis was conducted with individuals considered nonusers before 6 months after first use, a short-term user between 6 months after first use and 6 months after 365 tablets, and a longer-term user after this time. Finally, for comparison with a previous study,[8] a start/stop