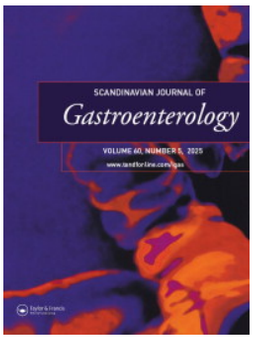

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Effects of aspirin at diagnosis on the survival of colorectal cancer patients: a 20-year population-based study

Arnar S. Agustsson[a], Sigurdis Haraldsdottir[a,b], Helgi Birgisson[c], Sigrun H. Lund[a,d], Arnar B. Ingason[e], Johann P. Hreinsson[f] and Einar S. Björnsson[a,g]

[a]Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [b]Department of Medical Oncology, Landspitali University Hospital of Iceland, Reykjavik, Iceland; [c]The Icelandic Cancer Registry, Reykjavik, Iceland; [d]Faculty of Physical Science, University of Iceland, Reykjavik, Iceland; [e]Department of Surgery, University of Vermont Larner College of Medicine, Burlington, VT, USA; [f]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [g]Department of Internal Medicine, Landspitali University Hospital of Iceland, Reykjavik, Iceland

ABSTRACT

Background: Previous studies have produced conflicting results regarding whether aspirin affects survival in colorectal cancer (CRC) patients. This study examines the relationship between regular aspirin use and survival in CRC patients within a nationwide cohort.

Methods: All patients diagnosed with CRC in Iceland from 2000 to 2019 were identified through the Icelandic Cancer Registry. Clinical variables, including medications, were extracted from medical records. Overall survival (OS) and cancer-specific survival (CSS) were calculated. The follow-up period ended on 1 October 2022. The Charlson comorbidity index was used to assess comorbidity burden, and propensity score matching was employed to balance patient characteristics.

Results: Of the 2,561 eligible patients, 22% ($n=559$) had been taking aspirin before their CRC diagnosis. Aspirin users were generally older and more frequently male (63% vs. 51%), with a higher comorbidity burden (15% vs. 4.7%). The median follow-up period was 51 months (IQR 14-110). Aspirin users were less likely to receive a stage IV diagnosis. After matching, overall survival (OS) was comparable between aspirin and non-users (HR: 0.94, 95% CI (0.83–1.06), $p=0.30$). However, cancer-specific survival (CSS) was significantly better for aspirin users (HR: 0.79, 95% CI (0.65–0.95), $p=0.01$). This benefit was not observed in patients with stages I–III CRC or those diagnosed due to gastrointestinal bleeding.

Conclusion: Aspirin use was linked to improved CSS but not OS. The findings suggest aspirin's potential role in slowing or hindering progression to stage IV cancer.

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KEYWORDS
Aspirin; Colorectal Cancer; Cancer Surviva; Chemoprevention

Background

Colorectal cancer (CRC) is the third most common cancer worldwide. It is responsible for one in every ten cancer-related deaths, with approximately 2 million people diagnosed and close to a million deaths annually [1]. Several studies have examined the effects of aspirin on CRC risk with low-dose aspirin (hereafter referred to only as aspirin), which have typically found positive chemopreventive effects on CRC incidence and precancerous colonic neoplasia [2–4].

Aspirin's effects on CRC survival have shown conflicting results, and the mechanism of the potential benefit has been debated, whether it causes direct biological effects or early detection through increased bleeding events. Many studies have demonstrated aspirin's protective effects for overall and CRC-specific survival [5–11], while others have not found any impact on survival or CRC-specific survival with aspirin use [12–15].

Aspirin is an irreversible non-selective cyclooxygenase (COX) enzyme inhibitor, and studies have demonstrated that COX-2 enzymes are overexpressed in most CRCs [16–19]. Furthermore, studies have found aspirin demonstrates survival benefits in CRCs with COX-2 over-expressive enzymes and mutations in the *PIK3CA*

CONTACT Einar S. Björnsson einarsb@landspitali.is Division of Gastroenterology and Hepatology, Landspitali-The National University Hospital of Iceland, 101 Reykjavik, Iceland

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pathway downstream from COX-2 [10,19,20]. Further supporting this biological mechanism of effect is a recent, prospective randomized controlled trial that showed aspirin users having a clear trend towards improved disease-free survival in CRC patients with the *PIK3CA mutation* at stages II-III [21]. The preliminary results from the randomized, double-blind, multicenter Nordic ALASCCA trial have also shown aspirin reducing recurrence compared to placebo in CRC patients with the *PIK3CA mutation* [22].

However, a recent large population-based study from Sweden examining CRC patients at stages I–III did not demonstrate any outcome benefit related to aspirin [15], and the authors concluded that the observed protective effects in prior studies might have resulted from early CRC diagnosis *via* bleeding events.

Considering the conflicting results from these studies and the differences in suggested mechanisms of aspirin's effects on survival, it is not clear if aspirin therapy impacts the prognosis of patients diagnosed with CRC. Given this uncertainty, the aim of the current study was to study the effects of regular aspirin use prior to CRC diagnosis on overall survival and CRC-specific survival in a nationwide cohort study.

Methods

Study design and population

This was a nationwide retrospective cohort study spanning 20 years. All patients diagnosed in Iceland from 2000 to 2019 with colorectal cancer (CRC) were identified. Survival between aspirin users and the non-users was compared.

Data sources and collection

All patients diagnosed with a first adenocarcinoma in the colon or rectum in Iceland from 2000 to 2019 were identified using the Icelandic Cancer Registry, which is over 99% complete [23]. Using the personal identification number given to all Icelandic citizens, we reviewed the electronic medical records of all patients to collect all variables. Additionally, selected clinical variables were obtained from the Icelandic Cancer Registry, including age, sex, date of diagnosis, tumor, node, and metastasis (TNM) stage, and limited clinical information for patients diagnosed in 2014 and later (details in Supplementary data). Cause of death was obtained from the Causes of Death Registry, a nationwide registry with International Classification of Diseases 10 (ICD-10) codes for the cause of death linked to a person's identification number in Iceland [24] (Supplementary Table 2).

The only tertiary hospital in Iceland, Landspitali University Hospital in Reykjavik, performed over 95% of all cancer treatment and surgeries, and together with the Regional Hospital in Akureyri, they provided over 99% of all cancer treatment.

Medical record review

Examining individual patient medical records, the following variables were collected at the first hospital visit for CRC: age, sex, primary symptoms at diagnosis, the first diagnostic investigation that raised suspicion of cancer, hemoglobin levels, mean corpuscular volume (MCV), comorbidities at CRC diagnosis through ICD-10 codes and cancer location. Gastrointestinal bleeding (GIB) events were defined as any history of physician-diagnosed lower gastrointestinal bleeding (either overt bleeding or microcytic anemia) that led to CRC diagnosis. Further details on variable collection and definitions can be found in the Supplementary data (section: Variable definition).

Selected medications of interest were collected at first hospital visit included aspirin, clopidogrel, ticagrelor, and oral anticoagulation (OACs) such as vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) like rivaroxaban, apixaban, edoxaban, and dabigatran—collectively referred to as anticoagulation therapy.

Aspirin use was identified as any regular use of 75 mg of aspirin documented in patients' medical records at the time of CRC diagnosis or in the preceding 3 months. This method was chosen to catch all users since it is possible that at the documented CRC diagnosis, aspirin had already been discontinued. In Iceland, aspirin 75 mg is available over the counter, and some regular users might opt out of refilling prescriptions while still taking their recommended aspirin by receiving it over the counter.

Aspirin is available as an over-the-counter pain medication in 500 mg tablets used on an as-needed basis; however, information on its use was not collected, nor was information on other over-the-counter pain medications, such as NSAIDs or paracetamol. Additionally, we did not examine the duration of aspirin use prior to CRC diagnosis or whether non-users had any previous history of aspirin use. The same protocol was applied to all medications of interest: OACs, NSAIDs, clopidogrel, or ticagrelor.

Patients' medical records were also examined during CRC treatment and follow-up until 1 October 2022. Data was obtained from the histopathology report, including confirmation of adenocarcinoma, and treatment and outcome variables were analyzed: Neoadjuvant and adjuvant therapy, surgical treatment, final TNM staging, recurrence of CRC, and death.

Inclusion/exclusion criteria

Only patients with confirmed adenocarcinoma on histology were included. Other histologically different tumors (e.g. carcinoid, squamous cell carcinoma, melanoma) were excluded. Patients with synchronous CRC contributed only the highest-stage CRC, and those with metachronous cancer contributed the first CRC chronologically. Patients with critical clinical data missing were excluded, i.e. any combination of no data on histopathology reports, no information on prior drug use, no information on treatment, or information lacking to assess staging.

Outcomes

All patients were followed up until death or 1st October 2022, using electronic medical records, and no patient was lost to follow-up.

Subgroup analysis

Two subgroups were analyzed further to examine the association of aspirin use with survival.

1. **Patients diagnosed at stages I–III**: This subgroup was analyzed to assess the effects of aspirin on non-metastatic disease of CRC and to examine if the previously reported survival benefits in aspirin users were mainly seen through lower rate of stage IV disease or potentially due to early detection through increased GIB events. Additionally, this subgroup analysis was conducted to compare the observations to another population-based study on CRC stages I–III [15].
2. **Patients diagnosed through bleeding events**: This subgroup included patients whose CRC diagnosis was due to gastrointestinal bleeding events. The goal was to evaluate whether the survival benefits of aspirin were likely mediated through gastrointestinal bleeding (GIB) events, leading to earlier detection and improved staging at diagnosis.

Statistical methods

Categorical variables were described by count and percentage, and continuous variables were described as medians with interquartile ranges. Pearson's Chi-squared test and Fisher's exact test were used for categorical variables, and the Wilcoxon rank sum test was used for continuous variables.

We employed a nearest-neighbor propensity score matching model to address potential confounding variables to balance the study groups for age, sex, adjuvant therapy, and Charlson comorbidity score. The variables selected for the propensity score analysis were predetermined and included variables judged as potential confounders based on clinical knowledge and previous literature. Other important variables, e.g. smoking, were judged to be too biased when collected retrospectively, and there was too much missing data, which would lead to a loss of power in the propensity score analysis. Standardized mean differences (SMD) were used to assess the balance of the groups before and after matching, guiding the control group size in whole numbers. An SMD value of <0.1 was considered the ideal balance, and an SMD of <0.2 was considered acceptable [25,26].

Primary outcomes were overall survival (OS), which was measured from the date of diagnosis to the date of death from any cause, the observations for OS were censored at death from any cause or end of follow-up. Cancer-specific survival (CSS) was measured from the date of diagnosis to the date of death from CRC; the observations for CSS were censored at death from causes other than CRC or at the end of follow-up. Comparisons were made between aspirin users and non-users. For surviving patients, analysis was censored at a loss to follow-up or at the end of follow-up on the 1st of October 2022. OS was compared using Kaplan-Meier survival analysis with log-rank tests, and hazard ratios (HR) were calculated using Cox regression models according to aspirin use or non-use. Using a Fine-Gray sub-distribution hazard ratio, CSS was compared using cumulative CRC mortality graphs and competing risk models to account for causes of death other than CRC. The same procedures were repeated for both subgroup analyses. Patients were followed up until the date of death or end of follow-up on 1 October 2022.

The database was created in Microsoft® Excel® for Microsoft 365 (Version 2311), and all statistical calculations were conducted in R (version 4.0.3) and RStudio 2023.09.1.

Results

Among the 2988 patients diagnosed with CRC during the study period, 2685 met the inclusion criteria, and 124 individuals had unknown aspirin status at diagnosis, yielding 2561 patients for the final analysis (Figure 1).

The study population

A total of 559 (22%) patients were taking aspirin at the time of CRC diagnosis. Aspirin users were older, more

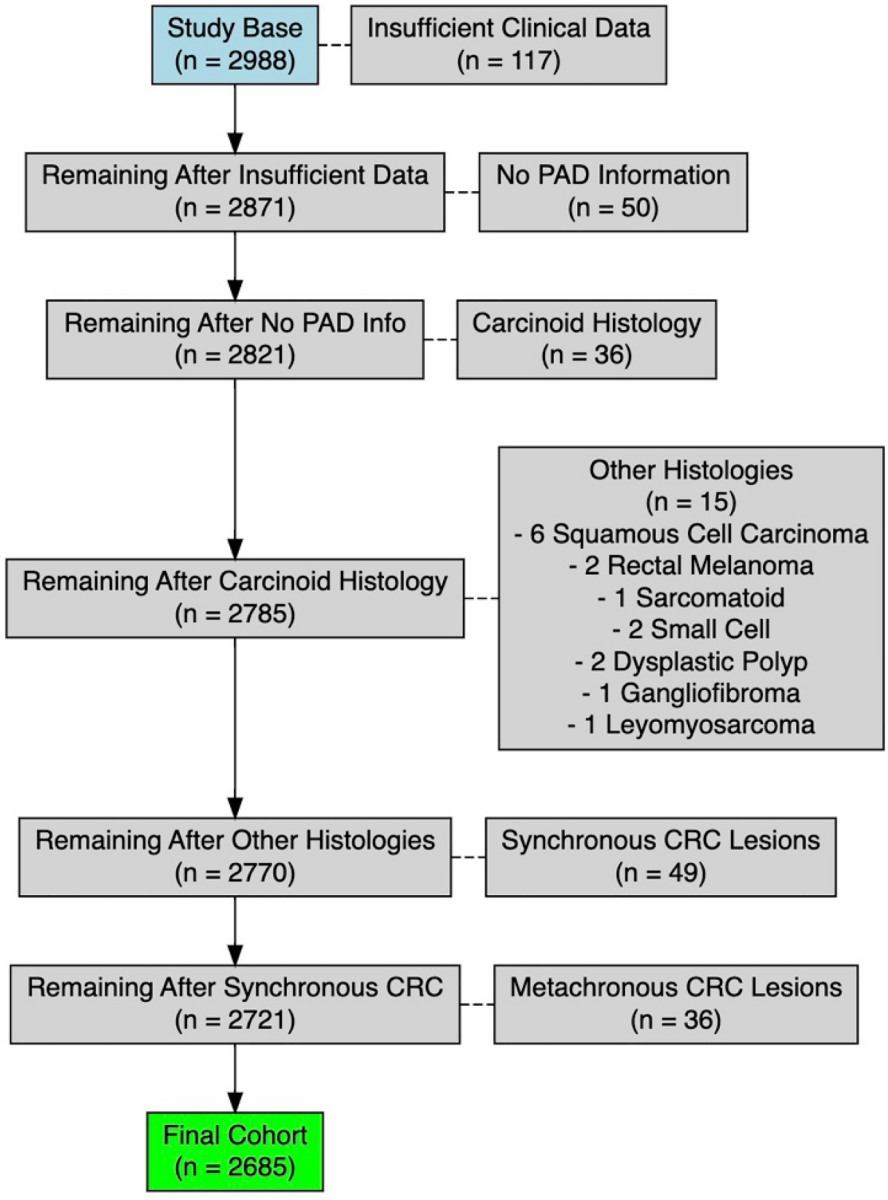

Figure 1. All patients diagnosed with colorectal cancer (CRC) in Iceland from 2000 to 2019 and the exclusion criteria to identify the final study group. Insufficient clinical data was defined as some combination of the following: missing data on the primary symptom, the first method of diagnosis, medications at diagnosis, location of CRC, and if the patient had neoadjuvant or adjuvant therapy.

often male, and had a higher comorbidity score (Table 1). Aspirin users presented with GIB events more often as the primary symptom (68% vs 58% $p<0.001$) and had lower median hemoglobin levels at presentation. Aspirin users had similar CRC location to non-users (Supplemental Table 1), and neither tumor size nor lymph node spread differed between the groups. Aspirin users were diagnosed less often at stage IV (16% vs 24% $p<0.001$). However, disease recurrence for stages I–III was similar in the two groups. The groups had similar rates of CRC surgery but aspirin users less frequently received neoadjuvant and adjuvant therapy, as shown in Table 1. Median follow-up was 49 months (IQR 14–103 months) for aspirin users and 51 months (IQR 14–112 months) for non-users. At the last follow-up, a greater percentage of aspirin users were deceased compared to non-users (Table 1).

Survival analysis

Table 2 shows aspirin users and non-users prior to and after propensity score matching. Aspirin use was not associated with improved OS (HR: 0.94 95% CI (0.83–1.06), $p=0.30$) (Figure 2). However, aspirin use was associated with improved CSS (HR: 0.79 95% CI (0.65–0.95), $p=0.01$) (Figure 3) when taking competing risks into account (Table 3). Median survival was 84 months (95% CI 75–94 months) for aspirin users and 98 months (95% CI 91–105 months) for non-users.

Table 1. Patient characteristics for all individuals diagnosed with colorectal cancer (CRC) in Iceland from 2000 to 2019, comparing aspirin users to non-users.

	N	Non-users, *N* = 2002[a]	Aspirin users, *N* = 559[a]	*p*-Value[b]
Age (years)	2,561	68 (58, 77)	76 (69, 82)	**<0.001**
Male sex	2,561	1,026 (51%)	354 (63%)	**<0.001**
Symptom	2,548			**<0.001**
Abdominal pain		405 (20%)	82 (15%)	**0.004**
Changes in bowel movements		226 (11%)	57 (10%)	0.52
Lower gastrointestinal bleeding		1,147 (58%)	376 (68%)	**<0.001**
Other		106 (5.3%)	19 (3.4%)	0.06
Screening		108 (5.4%)	22 (4.0%)	0.20
Discovery	2,556			**0.002**
Abdominal Radiography		14 (0.7%)	1 (0.2%)	0.22
Colonoscopy		1,550 (78%)	480 (86%)	**<0.001**
Computed Tomography		380 (19%)	71 (13%)	**<0.001**
Intraoperative		16 (0.8%)	3 (0.5%)	0.78
Other		17 (0.9%)	2 (0.4%)	0.40
Histopathological report		19 (1.0%)	3 (0.5%)	0.45
Hemoglobin (g/L)	2,267	125 (103, 140)	117 (97, 134)	**<0.001**
Mean corpuscular volume	2,190	86 (80, 90)	86 (79, 90)	0.7
Anticoagulation	2,558	174 (8.7%)	43 (7.7%)	0.5
Clopidogrel or Ticagrelor	2,543	22 (1.1%)	38 (6.8%)	**<0.001**
Proximal or distal tumor	2,546			0.2
Proximal		783 (39%)	238 (43%)	
Distal		698 (35%)	201 (36%)	
Rectum		507 (26%)	119 (21%)	
Tumor stage	2,561			**0.002**
I		394 (20%)	132 (24%)	**0.049**
II		533 (27%)	166 (30%)	0.17
III		537 (27%)	146 (26%)	0.78
IV		477 (24%)	89 (16%)	**<0.001**
Unknown		60 (3.0%)	27 (4.8%)	
Neoadjuvant treatment	1,656	258 (20%)	56 (15%)	**0.019**
Adjuvant treatment	2,561	708 (35%)	128 (23%)	**<0.001**
Charlson comorbidity index >2	2,560	97 (4.7%)	86 (15%)	**<0.001**
Death	2,561	1,102 (55%)	354 (63%)	**<0.001**
Colorectal cancer recurrence	1,995	282 (18%)	76 (16%)	0.4

[a]Median (IQR); *n* (%). [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Table 2. (A) Standard mean difference (SMD) of the overall aspirin users versus non-users, before and after matching, (B) SMD before and after matching subgroup only diagnosed with CRC at stages I–III, and (C) SMD before and after matching for patients diagnosed with bleeding-related symptoms.

	Before matching			After matching		
	Aspirin users	Non-users	SMD	Aspirin users	Non-users	SMD
A) All aspirin users to non-users						Match 1:2
n	559	2001[a]		556	1038	
Age, mean (SD)	75 (9)	67 (13)	0.869	75 (9)	75 (9)	0.086
Male sex	353 (63%)	1026 (51%)	0.246	353 (63%)	660 (59%)	0.073
Charlson index mean (SD)	1.17 (1.4)	0.57 (0.96)	0.434	1.14 (1.3)	0.87 (1.2)	0.095
Adjuvant chemotherapy	128 (23%)	707 (35%)	0.297	128 (23%)	235 (21%)	0.043
B) Only CRC stages I–III						Match 1:2
n	471	1524		464	842	
Age mean (SD)	75 (9)	67 (13)	0.853	75 (9)	75 (10)	0.072
Male sex	301 (64%)	764 (50%)	0.283	301 (64%)	512 (61%)	0.056
Charlson index mean (SD)	1.15 (1.4)	0.55 (1.0)	0.433	1.08 (1.3)	0.79 (1.1)	0.095
Adjuvant chemotherapy	88 (19%)	472 (31%)	0.315	88 (19%)	376 (17%)	0.047
C) Only bleeding symptom CRC's						Match 1:1
n	376	1147		371	371	
Age mean (SD)	75 (9)	68 (14)	0.835	75 (9)	76 (9)	0.101
Male sex	242 (65%)	591 (52%)	0.263	242 (65%)	232 (62%)	0.090
Charlson index mean (SD)	1.21 (1.4)	0.6 (1.01)	0.445	1.15 (1.3)	1.06 (1.3)	0.061
Adjuvant chemotherapy	81 (22%)	381 (33%)	0.284	81 (22%)	72 (19%)	0.059

[a]One non-user was excluded due to missing comorbidity information.

Subgroup analysis

Consistent with the results of the primary analysis, aspirin use was not associated with improved OS in the group of CRC stages I–III (HR: 1.06 95% CI (0.92–1.22), $p = 0.39$) (Supplementary Figure 1A) and neither in the subgroup of patients diagnosed through GIB events (HR: 0.90 95% CI (0.76–1.06), $p = 0.22$) (Supplementary Figure 2A) (Table 3). Similarly, aspirin use was not associated with improved CSS in the group of CRC stages I–III (HR:

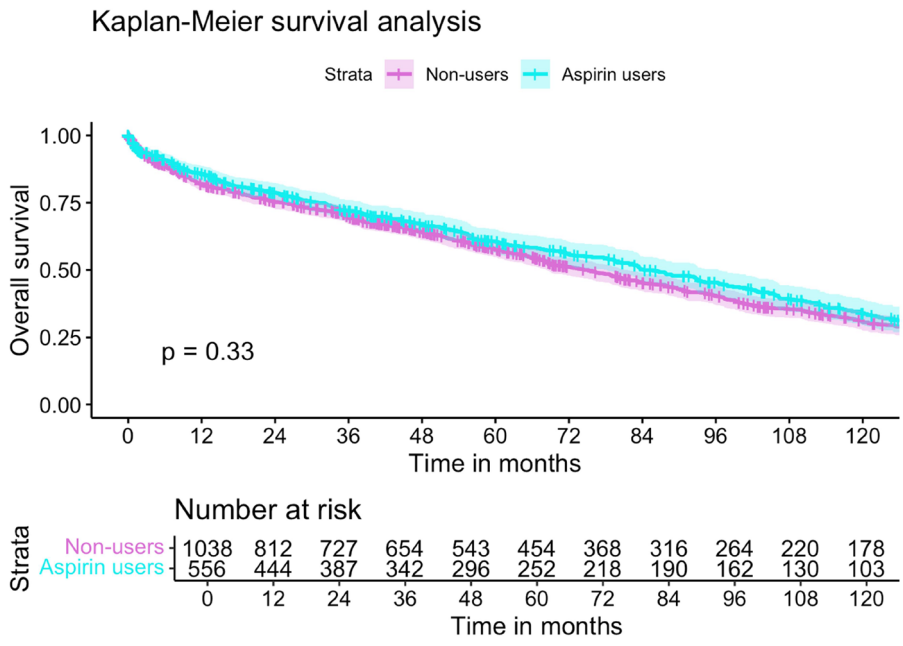

Figure 2. Kaplan-Meier Survival analysis comparing overall survival between aspirin users and non-users in patients with colorectal cancer (CRC).

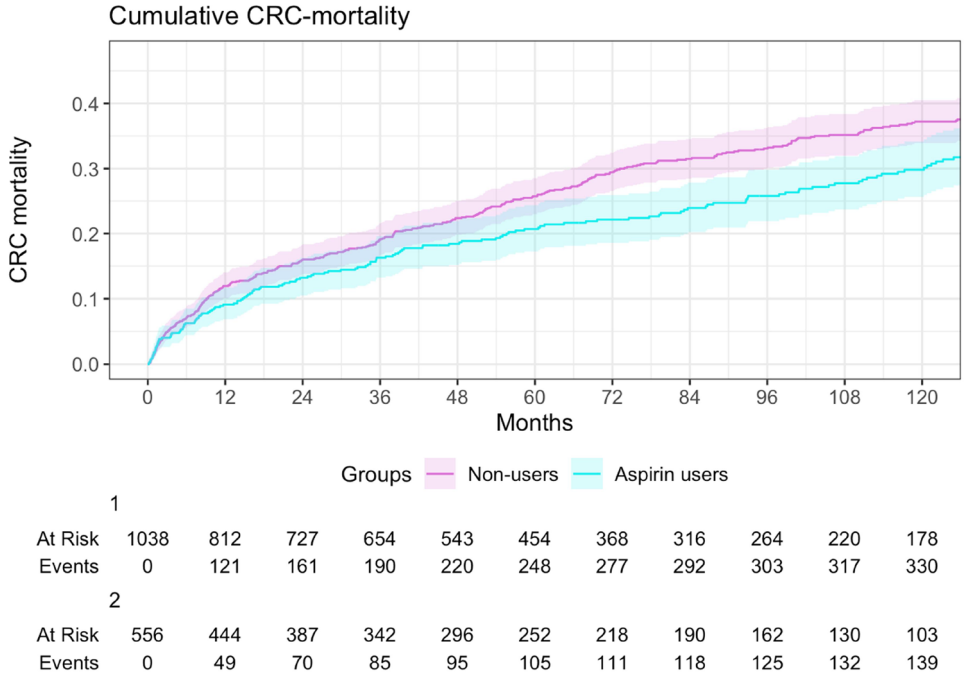

Figure 3. A comparison of the cumulative CRC-specific death between aspirin users and non-users with colorectal cancer after propensity score matching.

0.91 95% CI (0.69–1.18), $p = 0.50$) (Supplementary Figure 1B) or in the group of patients diagnosed through GIB events (HR: 0.98 95% CI (0.74–1.31), $p = 0.90$) (Supplementary Figure 2B).

Additionally, among patients diagnosed through GIB events, stage IV cancer was identified in 56 (10%) aspirin users, compared to 269 (15%) non-users. Similarly, among patients without GIB events, stage IV cancer was identified in 32 (6%) of aspirin users, compared to 165 (9%) non-users.

Using propensity score matching to assess survival probabilities at each stage of CRC, aspirin use was not associated with any significant difference in OS or CSS compared to non-users (Supplementary Table 3).

Table 3. Overall and cancer-specific survival in the propensity score matched aspirin users vs. non-users. Model A shows the overall study group of aspirin users compared to non-users. Model B shows the subgroup diagnosed with CRC at stages I–III. Model C shows only patients with bleeding-related symptoms.

	HR (95% CI)	*p*-Value
A)		
All aspirin users to non-users		
Overall survival (aspirin use)	0.94 (0.83–1.06)	0.30
CRC specific survival (aspirin use)	0.79 (0.65–0.95)	0.014
B)		
Only CRC stages I–III		
Overall survival (aspirin use)	1.06 (0.93–1.22)	0.39
CRC specific survival (aspirin use)	0.91 (0.69–1.18)	0.50
C)		
Only bleeding-related symptoms CRC's		
Overall survival (aspirin use)	0.90 (0.76–1.06)	0.22
CRC specific survival (aspirin use)	0.98 (0.74–1.31)	0.90

Discussion

In the current nationwide study spanning two decades, aspirin use was associated with improved CRC-specific survival but not overall survival. Aspirin use at diagnosis was associated with an increased proportion of CRC patients diagnosed due to gastrointestinal bleeding, and aspirin users were less commonly diagnosed at stage IV. Subgroup analysis did not reveal any association of aspirin with improved survival when examining either stages I–III CRCs or patients diagnosed with bleeding-related symptoms. This could indicate that the observed survival benefits are not equally distributed by cancer stage and further suggest that they are not derived from bleeding-related events.

Taken together, the current study's results contrast with studies finding overall survival benefits in aspirin users [5–11], but are aligned with studies demonstrating improved CRC-specific survival in aspirin users [9,11–16]. Considering the studies that did not find any survival benefits of aspirin users, two of them examined only aspirin use after CRC diagnosis and thereby examined aspirin's effects on an established and treated disease, suggesting that the protective effects of aspirin require time to have an impact [12,13]. The third study, Shahrivar et al.'s, examined only patients with stages I–III disease and did not demonstrate any survival benefits of aspirin [15]. This is in line with the current study, finding no survival advantage in population-based settings examining patients with stages I–III CRCs.

Aspirin has been proposed to hinder or delay CRC metastasis, as demonstrated in a study by Rothwell et al. They showed that daily aspirin use vs. no users resulted in 30–40% less risk of metastatic disease in solid tumors and nearly 70% in CRC patients [27]. This is further supported by our study, which found lower rates of stage IV disease in aspirin users, and studies showing that patients taking aspirin before CRC diagnosis have significantly lower rates of stage IV CRC [8,28]. The COX-2 enzyme plays a crucial role in promoting tumor metastasis [29–34]. Given the inhibitory effects of aspirin, particularly on tumors with high COX-2 expression [10,20,35], aspirin's effects may help delay progression to metastatic disease.

This theory of aspirin's inhibitory effects on metastatic disease is further supported by a recent study in Nature, which demonstrated that aspirin reverses immunosuppression caused by cancer, thereby inhibiting distant metastasis [36]. This has implications as aspirin could be included in adjuvant therapies to reduce CRC recurrence, as suggested by the improved disease-free survival in aspirin users compared to non-users with the *PIK3CA mutation* [21,22]. Additionally, aspirin use could be encouraged in high-risk populations to prevent colonic adenomas and CRCs and possibly reduce CRC mortality [2,37]. However, since evidence for reduced CRC mortality in aspirin users has been contradictory in cohort studies [14,38] and aspirin has important side effects, such as higher rates of GIB events, it has not been established as a recommendation for cancer prevention. Our study demonstrates CRC mortality benefit and a possible mechanism supported by recent literature, but there is still a great need for larger, randomized controlled trials to further validate and support the hypothesis that aspirin use might be protective against metastatic CRC.

When interpreting the subgroup findings, neither demonstrated improved outcomes for aspirin users. The lack of benefit in stages I–III aspirin users could be explained by the proposed mechanism of aspirin limiting stage IV disease. This is supported by finding improved outcomes only when stage IV patients are included in the overall analysis, as well as by a lower number of aspirin users being diagnosed with stage IV disease in the current study. Additionally, analyzing survival probabilities across each CRC stage based on aspirin use and discovering no meaningful difference further strengthens the proposed mechanism. Alternatively, the observed differences might be due to insufficient statistical power to identify a true difference in the stages I–III groups.

Despite aspirin users experiencing higher rates of GIB events and lower hemoglobin levels at CRC diagnosis, no survival benefit from aspirin was observed in the subgroup of aspirin users presenting with GIB. Aspirin use has been associated with more frequent GIB events [39], which has led to the hypothesis that it could cause early detection of CRC. Shahrivar et al. hypothesized

this in their study, as the survival benefit of aspirin shown in previous studies could be explained by more frequent healthcare visits or increased rates of bleeding-related symptoms in the aspirin group [19]. However, the subgroup of patients diagnosed through GIB events contained 67% of the overall group, and the survival benefits would also be expected to be found in the stages I–III CRC group. While power limitations cannot be excluded, the results argue against early detection *via* GIB as the primary mechanism.

Aspirin users received neoadjuvant and adjuvant therapy less often. Less frequent neoadjuvant therapy was expected due to the higher number of rectal cancers in the non-users group. Similarly, lower adjuvant therapy use was expected since aspirin users were older, had more comorbidities, and were more often diagnosed at earlier stages. Furthermore, there was no difference in histopathological variables, which aligns with prior studies that have not shown a difference in tumor grade or microsatellite instability [10,19,20].

Strengths and limitations

The current study has several strengths. This nationwide, population-based study included all individuals diagnosed with CRC, covering two decades to identify potential late effects. Data collection was based on nationwide registries and a robust review of individual medical records providing detailed phenotypic information. We examined patient's reported aspirin use at admission and drug prescription database reports.

The study has some limitations. First, the duration of aspirin use was not collected, and neither was aspirin use before CRC diagnosis, potentially incorrectly placing former aspirin users in the non-user group. However, both limitations would have decreased the likelihood of detecting a true difference. Second, inconsistent use of electronic records before 2004 increased the number of patients excluded due to missing information. Third, we could not control the over-the-counter use of NSAIDs or aspirin if it were not reported at the first hospital visit due to CRC, potentially confounding the survival benefits. Fourth, the study population is homogenous, primarily of North European descent, limiting the results' external validity. Finally, this was a retrospective study.

Summary

In a twenty-year nationwide study, aspirin use was associated with improved CRC-specific survival but not all-cause survival. Our results suggest that aspirin could mediate its beneficial effects by slowing or hindering progression to stage IV cancer. These findings support further prospective trials to determine aspirin's role in preventing CRC progression.

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The corresponding author had full access to all study data and was finally responsible for the decision to submit for publication.

Authors contributions

Guarantor of the article: Einar S. Björnsson MD, PhD. Specific author contributions: All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: A.S.A., S.H., J.P.H., and E.S.B. Acquisition, analysis, or interpretation of data: A.S.A., S.H., J.P.H. and E.S.B. Drafting of the manuscript: A.S.A., A.B.I., J.P.H., and E.S.B. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: A.S.A., S.H.L., and J.P.H. Obtained funding: A.S.A., J.P.H., and E.S.B. Administrative, technical, or material support: all authors. Supervision: E.S.B. and J.P.H. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final draft of the manuscript.

Disclosure statement

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Data availability statement

The data supporting this study's findings are available on request from the corresponding author, [ESB]. The data are not publicly available due to [restrictions, e.g. their containing information that could compromise the privacy of research participants].

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