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Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study

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The study used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and endorsement by the Cancer Registry of Norway is not intended nor should be inferred. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

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ABSTRACT

Purpose
Regular use of aspirin (acetylsalicylic acid) is associated with reduced incidence and mortality of colorectal cancer (CRC). However, aspirin as primary prevention is debated because of the risk of hemorrhagic adverse effects. Aspirin as secondary prevention may be more justified from a risk-benefit perspective. We have examined the association between aspirin use after the diagnosis of CRC with CRC-specific survival (CSS) and overall survival (OS).

Materials and Methods
An observational, population-based, retrospective cohort study was conducted by linking patients diagnosed with CRC from 2004 through 2011 (Cancer Registry of Norway) with data on their aspirin use (The Norwegian Prescription Database). These registries cover more than 99% of the Norwegian population and include all patients in an unselected and consecutive manner. Exposure to aspirin was defined as receipt of aspirin prescriptions for more than 6 months after the diagnosis of CRC. Multivariable Cox-proportional hazard analyses were used to model survival. The main outcome measures of the study were CSS and OS.

Results
A total of 23,162 patients diagnosed with CRC were included, 6,102 of whom were exposed to aspirin after the diagnosis of CRC (26.3%). The median follow-up time was 3.0 years. A total of 2,071 deaths (32.9%, all causes) occurred among aspirin-exposed patients, of which 1,158 (19.0%) were CRC specific. Among unexposed patients (n = 17,060), there were 7,218 deaths (42.3%), of which 5,375 (31.5%) were CRC specific. In multivariable analysis, aspirin exposure after the diagnosis of CRC was independently associated with improved CSS (hazard ratio [HR], 0.85; 95% CI, 0.79 to 0.92) and OS (HR, 0.95; 95% CI, 0.90 to 1.01).

Conclusion
Aspirin use after the diagnosis of CRC is independently associated with improved CSS and OS.

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INTRODUCTION

Worldwide, 1.3 million patients are diagnosed with colorectal cancer (CRC) each year.[1] Norway, with a population of 5.1 million, has an annual incidence of approximately 4,000 cases.[2] Evidence from randomized controlled trials and experimental and observational studies indicates that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the incidence and mortality of CRC when used before diagnosis.[3-5] However, use of aspirin as primary prevention in the general public is debated, because aspirin-induced gastric and cerebral hemorrhages affect the risk-benefit assessment.[6,7] In contrast, secondary prevention in patients already diagnosed with CRC may offer more advantages with respect to risk of recurrence and a different risk-versus-benefit profile. Accordingly, our main interest was to examine the potential efficacy of aspirin after the diagnosis of CRC.

In Norway, a free public health care system and the assignment of a unique identification number to each resident make patient traceability nearly complete. Norway is also privileged to have well-curated high-quality data from national population-based registries, including a database of all types of cancer incidences and a prescription database containing detailed information on all drugs dispensed on prescription from pharmacies.

This study is a large, population-based, retrospective, cohort study to assess whether use of aspirin can influence overall survival (OS) and CRC-specific survival (CSS) in patients with CRC; virtually no patients were lost to follow up.

MATERIALS & METHODS

Data Sources

The study linked data between the Cancer Registry of Norway (CRN) and the Norwegian Prescription Database (NorPD) at the Norwegian Institute of Public Health. The CRN records detailed information on each occurrence of cancer diagnosed in Norway, including tumor topography and morphology, treatment, outcome, and demographic information (including emigration status), on the basis of data from several sources (clinical and pathologic reports, data from radiotherapy, and death certificates). Data on vital status are integral in the CRN provided by the national cause of death registry and define patients as alive, dead as a result of cancer, dead as a result of other cause, or dead as a result of unknown reason, according to the International Classification of Diseases, 10th revision (ICD-10). Classification of lesions by the CRN is based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).[8] The NorPD is a national population-based prescription registry that contains data on all prescription drugs dispensed to individuals in ambulatory care by pharmacies since 2004. All drugs in Norway are classified according to the Anatomic Therapeutic Chemical (ATC) classification system.[9] Both the CRN and NorPD have an estimated coverage of 99% in the population and contain validated data of documented high quality.[10,11] Data from the CRN and the NorPD were linked using the national identification number that was encrypted according to standard procedures. Informed written consent was not needed from included study patients, because the use of national registry data for scientific purposes is regulated by the Personal Health Data Filing System Act when unidentifiable data are used.[12]

Study Design

Data were extracted from the CRN on all Norwegian patients diagnosed with CRC (ICD-O-3 code C18-C20.9) between January 2004 and December 2011 (N = 29,495). Patients with stage I to IV disease were included if they fulfilled the following inclusion criteria (n = 23,162): first incidence of CRC, tumor histology classified as adenocarcinoma, secure tumor diagnosis with ascertained malignancy, confirmed topography, and age $\geq$ 18 years.[2] For patients included in the study, prescription data were withdrawn from the NorPD, and the study was further designed as a retrospective cohort. The follow-up for each patient was from 30 days after diagnosis (T0) until death, emigration, or end of study (June 30, 2013), whichever first occurred. Inclusion was established as of 30 days from date of diagnosis, because the mortality rate is increased perioperatively (n = 715 [2.8%] died within 30 days after diagnosis), and these patients are thus unable to use aspirin after diagnosis. To avoid immortal time bias, aspirin exposure was handled as a time-varying covariate, for which each patient contributed person-time in the unexposed group until time of exposure was settled. In addition, the start of follow-up of both exposed and unexposed patients was delayed 6 months, which is the minimum of time needed to fulfill the criteria of exposure (three prescriptions collected). By using the intention-to-treat approach, we presumed a lasting effect of aspirin in patients whose aspirin use was discontinued after a state of exposure was settled. The outcomes of interest were death and cancer-specific death, defined as those deaths with an underlying cause associated with ICD-10 C18-C20.9.

Assessment of Aspirin Use

Detailed information on aspirin dispensed to individuals in the study population was extracted from the NorPD on the basis of ATC code (B01AC06). Enteric-coated aspirin tablets available by prescription in Norway are offered in two different dosages, 75 mg and 160 mg. These cannot be purchased over the counter in Norway.

In total, there were 10,368 unique aspirin users. Exposed patients were defined as having received three or more prescriptions after the date of diagnosis + 30 days (T0), which resulted in a total of 6,102 of the aspirin-using patients in the exposed group. Aspirin prescriptions lasted 3 months at a time (100-tablet packets, one tablet once per day), so the follow-up for aspirin-exposed patients started 6 months after T0 and continued until time of death, emigration, or the end of the follow-up period, whichever occurred first. Patients who had fewer than three prescriptions were classified as unexposed. Average adherence to aspirin use was calculated by dividing the total amount of defined daily doses (DDDs) on the number of days from exposure to end of follow-up; adherence was, on average, 0.99 DDD/day for the aspirin-exposed patients, which indicated a high level of compliance.

In separate analyses, patients who used aspirin before the diagnosis of CRC and who continued to use aspirin after the time of diagnosis (pre and post; n = 4,391) or who used aspirin solely after the diagnosis (post; n = 1,711) were compared with unexposed patients. Pre- and post-diagnosis users were defined as patients who initiated aspirin use before the time of diagnosis, and post-diagnosis users were defined as patients who filled their first aspirin prescriptions after diagnosis of CRC.

Statistical Analysis

Continuous data were described with means and standard deviations (SDs) if normally distributed, and categoric data were described with counts and percentages. Pairs of continuous data were compared with the *t* test, and χ^2 test was used for categoric data. Cox regression models were used to estimate hazard ratios (HRs) with 95% CIs for CSS and OS in aspirin-exposed versus unexposed patients, by using the time-varying covariate explained in the Study Design section. Likelihood ratio tests were performed for overall testing of categoric variables. Correction for multiple comparisons was done with the Benjamini-Hochberg procedure (false discovery rate $<$ 5%).

Covariates available from the CRN and NorPD included age, sex, tumor differentiation grade, site of disease, disease stage, and surgery. Adjustments were also made for the following drugs because of emerging evidence to suggest that they also have cancer-protective properties[13-16]: statins, metformin, beta blockers, NSAIDs, cyclooxygenase-2 inhibitors (coxibs), angiotensin-converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARBs); drug use was determined from the NorPD (on the basis of more than one prescription after diagnosis). The covariates that were entered into a multivariable Cox proportional hazard model all contained less than 10% missing data (except differentiation grade, for which 14% was missing).

Several supplementary tests were also carried out, in which the effect of aspirin was analyzed when aspirin-exposed patients were defined as having received four or more prescriptions and in which the lag-time was increased to 1 year, 2 years, 3 years, and 5 years. Furthermore, analyses were carried out in which the material was stratified by variables such as site of disease, disease stage, age, sex, differentiation grade, potential confounding drugs, and surgery. A competing-risk analysis was carried out as an additional survival assessment (Appendix Fig A1, online only) to assess the probability of cancer death.

All data handling and statistical analyses were performed with SPSS version 22 (SPSS, Chicago, IL) and STATA SE version 14 (STATA, College Station, TX).

RESULTS

Characteristics of the Cohort

In total, 23,162 patients were diagnosed with CRC between 2004 and 2011 and met the inclusion criteria. The mean age was

71.5 years (SD, 11.7 years). Of these, 6,102 patients (26.3%) were exposed to aspirin according to the predefined criteria (three or more prescriptions of aspirin starting from 30 days after the diagnosis of CRC [T0]). The remaining 17,060 patients with CRC were unexposed. The median patient follow-up time was 3.0 years after CRC diagnosis. Surgical treatment of the CRC was performed in 88.9% of the patients. Baseline characteristics stratified by aspirin exposure are listed in Table 1.

Table 1. Baseline Characteristics of the Study Cohort by Aspirin Use

Characteristic	No. at Risk	Aspirin Use		*P*
		No	Yes	
No. (%) overall	23,162	17,060 (73.7)	6,102 (26.3)*	
Patient characteristic				
No. (%) by sex				< .001
Female	11,486	8,821 (51.7)	2,665 (43.7)	
Male	11,676	8,239 (48.3)	3,437 (56.3)	
Mean (SD) age, years		69.0 (12.6)	74.0 (9.3)	< .001
No. (%) by tumor characteristic				
Tumor differentiation grade				< .001
Well	1,518	1,066 (7.3)	452 (8.4)	
Moderate	14,717	10,653 (72.8)	4,064 (75.4)	
Poor	3,740	2,878 (19.7)	862 (16.0)	
Undifferentiated	42	30 (0.2)	12 (0.2)	
Site of disease				.004
Right	7,163	5,171 (30.7)	1,992 (33.1)	
Transverse	1,523	1,118 (6.6)	405 (6.7)	
Left	6,166	4,553 (27.0)	1,613 (26.8)	
Rectum	8,018	6,008 (35.7)	2,010 (33.4)	
AJCC disease stage				< .001
I	5,231	3,600 (21.9)	1,631 (27.7)	
II	6,952	4,840 (29.4)	2,112 (35.9)	
III	6,410	4,829 (29.3)	1,581 (26.8)	
IV	3,753	3,188 (19.4)	565 (9.6)	
Survival status				< .001
Alive	13,873	9,842 (57.7)	4,031 (66.1)	
Dead as a result of colorectal cancer	6,533	5,375 (31.5)	1,158 (19.0)	
Dead as a result of another reason	2,038	1,375 (8.1)	663 (10.9)	
Dead as a result of unknown reason	718	468 (2.7)	250 (4.1)	
No. (%) by treatment characteristic				
Primary surgery				.689
No	9	6 (0.0)	3 (0.1)	
Yes	21,429	15,563 (100.0)	5,866 (99.9)	
Drug covariate				
ACE inhibitor/ARB				< .001
No	22,603	16,787 (98.4)	5,816 (95.3)	
Yes	559	273 (1.6)	286 (4.7)	
Statin				< .001
No	22,685	16,876 (98.9)	5,809 (95.2)	
Yes	477	184 (1.1)	293 (4.8)	
Beta blocker				< .001
No	22,486	16,719 (98.0)	5,767 (94.5)	
Yes	676	341 (2.0)	335 (5.5)	
Metformin				< .001
No	22,994	16,974 (99.5)	6,020 (98.7)	
Yes	168	86 (0.5)	82 (1.3)	
NSAID/coxib				< .001
No	22,212	16,443 (96.4)	5,769 (94.5)	
Yes	950	617 (3.6)	333 (5.5)	
Aspirin use characteristic				
Adherence, mean (SD) DDD	—	—	1.00 (0.21)	
Aspirin use before and/or after diagnosis				< .001
Post	—	—	1,711 (28.0)	
Pre and post	—	—	4,391 (72.0)	
Prescribed daily dose of aspirin, mg				
75	—	—	4,503 (73.8)	
160	—	—	901 (14.8)	
Both	—	—	698 (11.4)	

Abbreviations: ACE, angiotensin converting enzyme; AJCC, American Joint Committee on Cancer; ARB, angiotensin II receptor blocker; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; post, post diagnosis use of aspirin; pre and post, use of aspiring both before and after diagnosis; SD, standard deviation.
*The number of aspirin users throughout the study period.

Patients in the aspirin-exposed group were more likely to be older (74.0 *v* 69.0 years) and male (56.3% *v* 48.3%, $P < .001$). They were also more likely to use potential confounding drugs, such as statins, ACE inhibitors/ARBs, metformin, beta blockers, and NSAIDs/coxibs. Aspirin-exposed patients were also more likely to have a well-differentiated to moderately differentiated tumor and to have stage I to II disease. There was no difference in site of disease between aspirin-exposed and -unexposed patients.

Among included patients who used aspirin, 1,711 patients (28.0%) had no record of aspirin use before diagnosis (ie, post-diagnosis group), whereas the remaining 4,391 used aspirin both before and after the CRC diagnosis (ie, pre- and post-diagnosis group). Regarding the daily dose of aspirin used in the cohort, 4,503 (73.8%) used 75 mg once per day, and 901 (14.8%) used 160 mg once per day, over the longest period. Of these, 698 patients alternated between the two doses during the study period.

Association Between Aspirin Use and Survival

By June 30, 2013, a total of 9,289 deaths were recorded in the study population, of which 6,533 were a result of CRC. Among the aspirin-exposed patients (n = 6,102), a total of 2,071 deaths (33.9%) were recorded, of which 1,158 (19.0%) were CRC specific. Among the aspirin-unexposed patients (n = 17,060), a total of

Table 2. Cox Proportional Hazard Model for Colorectal Cancer Survival and Overall Survival

	Colorectal Cancer Survival			Overall Survival		
Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)*	*P*†	Univariable HR (95% CI)	Multivariable HR (95% CI)*	*P*†
Aspirin use						
No (reference)			< .001			.076
Yes	0.84 (0.78 to 0.89)	0.85 (0.79 to 0.92)		1.02 (0.97 to 1.08)	0.95 (0.90 to 1.01)	
Age, years‡						
< 60 (reference)			< .001			< .001
60-69	1.01 (0.93 to 1.09)	1.19 (1.08 to 1.31)		1.09 (1.02 to 1.17)	1.26 (1.16 to 1.38)	
70-79	1.14 (1.06 to 1.23)	1.69 (1.54 to 1.85)		1.43 (1.34 to 1.53)	1.96 (1.81 to 2.13)	
≥ 80	1.54 (1.43 to 1.65)	2.56 (2.33 to 2.81)		2.45 (2.29 to 2.61)	3.71 (3.42 to 4.02)	
Sex						
Female (reference)			< .001			< .001
Male	1.10 (1.04 to 1.15)	1.17 (1.10 to 1.24)		1.10 (1.06 to 1.15)	1.23 (1.17 to 1.29)	
Site of disease						
Right colon (reference)			.064			.059
Left colon/rectum	0.94 (0.89 to 0.99)	0.94 (0.89 to 1.00)		0.91 (0.87 to 0.94)	0.95 (0.91 to 1.00)	
Tumor differentiation grade						
Well (reference)			< .001			< .001
Moderate	1.73 (1.51 to 1.97)	1.37 (1.19 to 1.59)		1.35 (1.22 to 1.48)	1.17 (1.05 to 1.30)	
Poor	3.01 (2.62 to 3.46)	1.97 (1.69 to 2.29)		2.09 (1.88 to 2.32)	1.54 (1.37 to 1.73)	
Undifferentiated	2.30 (1.32 to 4.02)	2.11 (1.18 to 3.78)		1.67 (1.03 to 2.71)	1.56 (0.95 to 2.58)	
AJCC disease stage						
I (reference)			< .001			< .001
II	1.19 (1.08 to 1.31)	1.38 (1.22 to 1.55)		1.06 (0.99 to 1.13)	1.12 (1.03 to 1.21)	
III	2.47 (2.26 to 2.69)	3.29 (2.94 to 3.68)		1.61 (1.51 to 1.72)	2.01 (1.86 to 2.17)	
IV	10.72 (9.85 to 11.66)	13.14 (11.74 to 14.72)		6.20 (5.82 to 6.61)	7.29 (6.72 to 7.90)	
Primary surgery						
No (reference)			.121			.299
Yes	0.74 (0.24 to 2.28)	0.26 (0.07 to 1.05)		0.81 (0.31 to 2.17)	0.43 (0.11 to 1.73)	
ACE inhibitor/ARB						
No (reference)			.337			.898
Yes	0.76 (0.61 to 0.94)	0.88 (0.68 to 1.15)		1.01 (0.87 to 1.17)	0.99 (0.83 to 1.18)	
Statin						
No (reference)			.479			.257
Yes	0.70 (0.55 to 0.90)	0.90 (0.68 to 1.20)		0.88 (0.74 to 1.04)	0.89 (0.73 to 1.09)	
Beta blocker						
No (reference)			.361			< .001
Yes	1.06 (0.89 to 1.25)	1.10 (0.90 to 1.36)		1.36 (1.20 to 1.53)	1.32 (1.14 to 1.53)	
NSAID/coxib						
No (reference)			.356			.827
Yes	0.96 (0.83 to 1.11)	1.08 (0.92 to 1.27)		0.91 (0.81 to 1.02)	0.99 (0.87 to 1.12)	
Metformin						
No (reference)			.4			.162
Yes	1.09 (0.77 to 1.53)	1.19 (0.80 to 1.78)		1.19 (0.92 to 1.53)	1.23 (0.93 to 1.64)	

Abbreviations: ACE, angiotensin converting enzyme; AJCC, American Joint Committee on Cancer; ARB, angiotensin II receptor blocker; coxib, cyclooxygenase-2 inhibitor; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

*Analyses were adjusted for sex, age, site of disease, tumor differentiation, disease stage, surgery, ACE inhibitor/ARB use, NSAID/coxib use, statin use, beta blocker use, and metformin use.

†*P* values are from the likelihood-ratio test for overall testing of categoric variables.

‡For additional age adjustments, we performed analyses that increased categorization to six age groups, included age as a continuous variable, and modeled age by using splines. None of these approaches led to any changes in the estimates of survival.

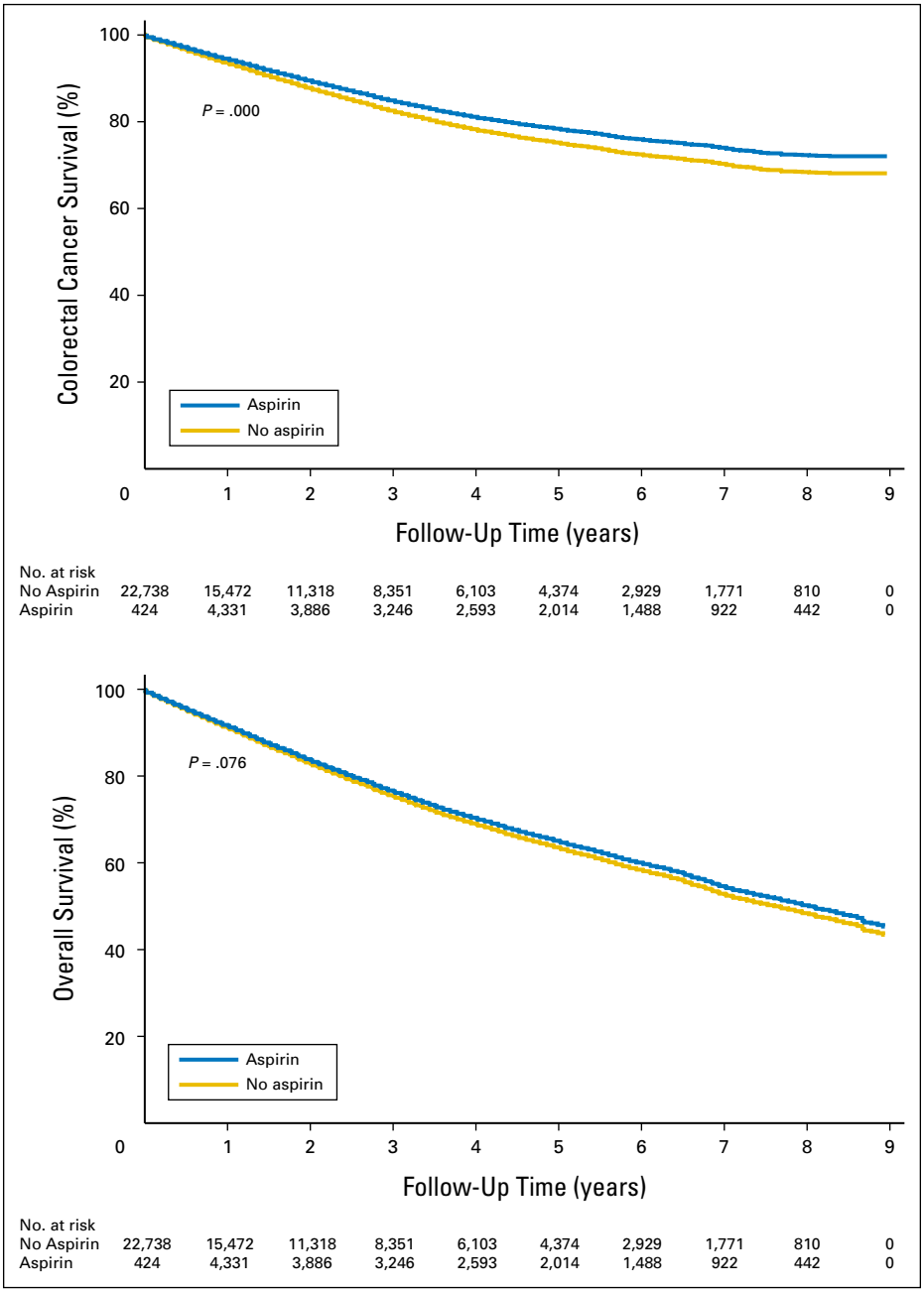

Fig 1. Colorectal cancer-specific survival and overall survival according to aspirin use after colorectal cancer diagnosis. Cox proportional hazard plot shows colorectal cancer-specific survival and overall survival between aspirin-exposed and -unexposed patients. Start of follow-up was T0 + 6 months, which was the earliest time an aspirin-exposed patient could be defined as an aspirin user according to the definition used (ie, three prescriptions collected, each for 3 months of use). Numbers at risk refer to the actual number of aspirin users at each time point after start of follow-up. The total number of aspirin users over the course of the follow-up time was 6,102 patients. The survival curve is only valid given independence between cause-specific mortality and other causes of death.

7,218 deaths (42.3%) were recorded, of which 5,375 (31.5%) were CRC specific.

In the current cohort, the use of aspirin after CRC diagnosis was associated with improved CSS (HR, 0.85; 95% CI, 0.79 to 0.92) and OS (HR, 0.95; 95% CI, 0.90 to 1.01) in multivariable analysis (Table 2; Fig 1). Stratified analysis also revealed that patients who used aspirin both before and after diagnosis (ie, pre and post group) had additional improvement in CSS (HR, 0.77; 95% CI, 0.71 to 0.84) and OS (HR, 0.86; 95% CI, 0.81 to 0.92; Table 3). The survival curves in Figure 1 are only valid given independence between cause-specific mortality and other causes of death. The survival curves in Appendix Figure A1 show the survival from a Fine and Gray (competing risk) model, which does not assume independence. Furthermore, by using a time-dependent coefficient model, we showed that the effect of aspirin use was most beneficial in the first 2 to 3 years after diagnosis (Table 4).

Supplementary Analysis

Supplementary analysis of CSS and OS did not reveal any marked differences in associations by sex, age (by exclusion of patients < 50 years), surgical status, or the use of confounding drugs (Appendix Tables A1 and A2, online only). Notably, patients with poorly and moderately differentiated tumors experienced the greatest benefits of aspirin exposure (poorly differentiated: HR, 0.83; 95% CI, 0.71 to 0.98; moderately differentiated: HR, 0.84;

Table 3. Risk of Colorectal Cancer Survival and Overall Survival According to Use of Aspirin Before and After Diagnosis

Aspirin Use by Survival Type*	No. of Events/ No. at Risk	Univariable Analysis HR (95% CI)	Univariable Analysis P	Multivariable Analysis HR (95% CI)†	Multivariable Analysis P
Colorectal cancer survival					
No use	5,375/17,060	1 (reference)	—	1 (reference)	—
Post	290/1,711	0.94 (0.84 to 1.06)	.337	1.00 (0.87 to 1.14)	.951
Pre and post	868/4,391	0.75 (0.70 to 0.81)	< .001	0.77 (0.71 to 0.84)	< .001
Overall survival					
No use	7,218/17,060	1 (reference)	—	1 (reference)	—
Post	549/1,711	1.11 (1.01 to 1.21)	.028	1.06 (0.96 to 1.18)	.227
Pre and post	1,522/4,391	0.94 (0.89 to 1.00)	.044	0.86 (0.81 to 0.92)	< .001

Abbreviation: HR, hazard ratio.
*Post are patients that used aspirin solely after diagnosis. Pre and post are patients that used aspirin before and after diagnosis.
†Adjusted for sex, age, site of disease, tumor differentiation, disease stage, surgery, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use, nonsteroidal anti-inflammatory drug/cyclooxygenase-2 inhibitor use, statin use, beta blocker use, and metformin use.

95% CI, 0.77 to 0.91). Patients with stage II disease experienced the most benefits of aspirin exposure (HR, 0.71; 95% CI, 0.60 to 0.83). Furthermore, when the material was stratified according to tumor localization, tumors located in the transverse and left colon experienced no significant effect of aspirin use on CSS, whereas tumors located in the rectum had the most improved CSS (HR, 0.79; 95% CI, 0.69 to 0.90), followed by right-sided tumors (HR, 0.88; 95% CI, 0.77 to 0.99). However, the overlapping CIs indicate a tendency rather than a significant difference.

To additionally investigate whether the effect of aspirin use was time dependent, the lag was increased to 1, 2, 3, and 5 years; thus, only exposed and unexposed patients who survived were compared (Appendix Tables A1 and A2). This demonstrated a protective effect of aspirin with a lag time up to 1 year, and the CSS HR was 0.86 (95% CI, 0.80 to 0.93).

DISCUSSION

In this study, aspirin use initiated or continued after CRC diagnosis was associated with significantly improved CSS and OS. Among all of the factors associated with CSS and OS included in the multivariable analyses, aspirin use was the strongest predictor. In addition, exposure of aspirin before the CRC diagnosis (ie, pre and post group) had the most advantage of aspirin use with respect to CSS and OS. Furthermore, aspirin use was most beneficial the first 2 to 3 years after diagnosis (Table 4). This is not fully in line with previous reports presented in the meta-analyses by Li et al[17] and Ye et al.[18] One explanation may be that patients who regularly take aspirin and who do develop CRC tend to be diagnosed with a more differentiated tumor. In our study, aspirin users were more likely to have CRC in a less advanced stage (American Joint Committee on Cancer stage I to II) and to have a tumor with less aggressive properties (well to moderate tumor differentiation). Many preceding studies have shown that prediagnostic aspirin use significantly reduces the incidence and mortality of CRC. We speculate that aspirin may have an immunomodulating affect, and we assume that prediagnostic aspirin users develop a less aggressive form of CRC, with fewer metastatic properties.[4]

Table 4. Time-Dependent Coefficient Analysis of Aspirin Effect Over Time

Follow-Up Interval by Survival Type (years)	Aspirin Effect HR	95% CI	P
Colorectal cancer survival			
0-1	0.737	0.627 to 0.866	< .001
1-2	0.832	0.723 to 0.957	0.010
2-3	0.856	0.727 to 1.008	0.062
3-5	0.990	0.843 to 1.163	0.901
> 5	0.955	0.742 to 1.230	0.721
Overall survival			
0-1	0.798	0.696 to 0.914	< .001
1-2	0.877	0.782 to 0.984	.026*
2-3	0.881	0.772 to 1.005	.060
3-5	1.101	0.978 to 1.239	.106
> 5	1.183	1.021 to 1.371	.025*

Abbreviation: HR, hazard ratio.
**P* values were not significant after correction for multiple comparisons.

In 2009, Chan et al[19] were the first to report that regular aspirin use after CRC diagnosis was associated with increased survival, especially in tumors with cyclooxygenase 2 (COX-2) overexpression. Since then, several studies have confirmed an association between postdiagnosis aspirin use and improved CSS and OS.[17-26] However, these studies had limitations in the sample size, the selected populations, and the patient-based questionnaires to assess aspirin use.

In this study, generalization bias was avoided, because the national databases include more than 99% of the population in an unselected manner. In addition, population screening for CRC was not conducted in Norway in the time period of the study, which reduced the risk of lead-time bias. Recall bias was avoided, because data about aspirin use was based on automatically recorded prescriptions from pharmacies that provided precise information on use and dose. An accurate dose-response analysis was not feasible with the design of this study, because patients were prescribed aspirin 75 or 160 mg/day for varying periods and also switched between the doses. Finally, the cohort in this study is the largest, to date, to report on the secondary preventive effect of aspirin use in CRC.

The molecular mechanisms underlying the anticancer effect of aspirin as a primary or secondary prevention method are still incompletely understood. Experimental studies have suggested several mechanisms of action, such as inhibition of cancer cell proliferation

and angiogenesis, enhancement of antitumor immunity, and inhibition of metastasis through the antiplatelet effect.[27-29] Given the fact that pre- and post-diagnostic aspirin use reduced CSS and OS in this study, the predominant effect may result from a combined effect of reduced tumor growth, a decreased ability of circulating tumor cells to metastasize,[22] and enhancement of an antitumor immune response.[30] Other reports showed that the benefit from aspirin use after CRC diagnosis is associated with a strong COX-2 expression and the presence of *PI3KCA* mutations, which might prove useful as biomarkers to predict treatment response.[19,25] In our study, we showed a stronger effect of aspirin use on survival in patients who had stage II disease. This might suggest that adjuvant aspirin treatment should be restricted to certain disease stages, although more data are needed.

Interestingly, when aspirin exposure was adjusted for non–cancer-related survival and unknown survival, it showed no benefit, with a nonsignificant HR of 1.06 for OS. Aspirin-exposed patients were more prone to die as a result of a non–cancer-related death, which may in part be explained by the higher age and frequency of other comorbidities among these patients. Aspirin-exposed patients were more likely to use other drugs, such as metformin, beta blockers, ACE inhibitors/ARBs, statins, and NSAIDs/coxibs, which might imply a higher frequency of type 2 diabetes, hypercholesterolemia, and heart disease in this group. This reflects the main indication of cardiovascular disease prevention for aspirin prescriptions in Norway.

The following limitations warrant a remark in this study. Our study was an observational retrospective cohort and the data were nonrandomized. As such, we were unable to adjust for unknown and potential confounding factors correlated with aspirin use. However, cardiovascular protection is the main indication for aspirin prescription in Norway. Furthermore, data about an association between aspirin and colorectal malignancies were not widely available during most of the study period; therefore, it is unlikely that study patients received aspirin for cancer prevention. In addition, no significant association between aspirin and available predictors of cancer outcome was observed (Table 2), and the findings remained unchanged after adjustment for other available and potential risk factors for CSS and OS. Moreover, although precise data on all pharmaceutically dispensed aspirin drugs were available, there were no records of the use of unprescribed over-the-counter aspirin (available in Norway as 300 mg and 500 mg, in 20- and 24-tablet packs, respectively) and NSAIDs (nor of aspirin use by patients admitted to hospitals or nursing homes). However, over-the-counter drugs are strictly regulated, expensive, limited to only small packets, and not subject to reimbursement, which restricts extensive use. Another limitation of this study was the lack of data on *PI3KCA* mutations and COX-2 expression, which are not routinely measured in Norway. This made it impossible to stratify the aspirin effect according to these possible predictors that have been reported by others.[19,20,25] Beyond causes of mortality, data on cancer recurrence and metastases were limited by the short follow up-time. Also, because of the big sample size, some small effects seemed to be statistically significant but did not have clinical significance.

In conclusion, exposure to aspirin after diagnosis of CRC was associated with a favorable outcome in a large, unselected, and consecutive cohort of patients, although the greatest benefit was seen in patients who initiated aspirin use before the time of diagnosis (ie, pre and post group). Routine use of aspirin as a secondary prevention method cannot be recommended on the basis of these findings in light of concerns about aspirin toxicities and because of the observational nature of our data. Randomized, placebo-controlled clinical trials are warranted to additionally address the role of aspirin after the diagnosis of CRC, specifically with regard to dose, duration, and subgroups of patients who may benefit the most.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study

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Appendix

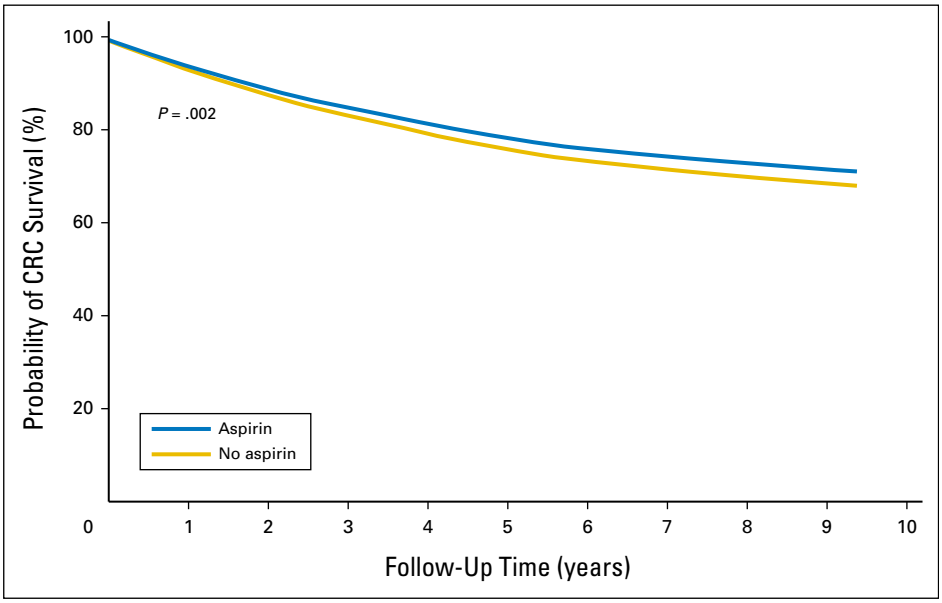

Fig A1. Colorectal cancer–specific survival according to aspirin use after colorectal cancer diagnosis. A competing-risk plot displays colorectal cancer-specific survival differences between aspirin-exposed and -unexposed patients from a Fine and Gray model, which does not assume independence between cause-specific mortality and other causes of death.

Table A1. Stratified Analysis for CRC-Specific Survival

Variable	No of Events/No. at Risk		CRC-Specific Survival		
	No Aspirin	Aspirin	Univariable HR (95% CI), *P*	Multivariable* HR (95% CI), *P*	Interaction *P*†
Main analysis	5,375/17,060	1,158/6,102	0.84 (0.78 to 0.89), < .001	0.85 (0.79 to 0.92), < .001	
> 4 aspirin prescriptions	5,565/17,555	968/5,607	0.70 (0.65 to 0.75), < .001	0.70 (0.65 to 0.76), < .001	
Tumor differentiation grade					
Well	169/1,066	60/452	1.18 (0.87 to 1.59), .292	1.18 (0.85 to 1.63), .329	
Moderate	3,024/10,653	746/4,064	0.86 (0.79 to 0.93), < .001	0.84 (0.77 to 0.91), < .001	
Poor	1,217/2,878	206/862	0.78 (0.67 to 0.90), .001	0.83 (0.71 to 0.98), .028‡	
Undifferentiated	10/30	3/12	1.20 (0.31 to 4.67), .790	6.49 (0.90 to 46.90), .064	< .001
AJCC disease stage					
I	542/3,600	153/1,631	0.88 (0.73 to 1.06), .175	0.90 (0.71 to 1.13), .373	
II	813/4,840	240/2,112	0.87 (0.75 to 1.01), .064	0.71 (0.60 to 0.83), < .001	
III	1,450/4,829	382/1,581	1.11 (0.99 to 1.25), .071	0.91 (0.81 to 1.03), .151	
IV	2,346/3,188	337/565	0.90 (0.80 to 1.01), .085	0.85 (0.74 to 0.98), .025‡	.104
Surgically treated	4,267/1,5563	1,038/5,866	0.87 (0.81 to 0.94), < .001	0.85 (0.79 to 0.92), < .001	.279
Sex					
Female	2,659/8,821	465/2,665	0.83 (0.75 to 0.92), < .001	0.85 (0.76 to 0.96), .008	
Male	2,716/8,239	693/3,437	0.82 (0.75 to 0.89), < .001	0.84 (0.76 to 0.93), .001	.099
Site of disease					
Right colon	1,664/5,171	370/1,992	0.83 (0.74 to 0.93), .002	0.88 (0.77 to 0.99), .042‡	
Transverse colon	363/1,118	74/405	0.86 (0.67 to 1.12), .265	0.98 (0.74 to 1.30), .879	
Left colon	1,383/4,553	297/1,613	0.83 (0.73 to 0.94), .004	0.87 (0.76 to 1.00), .057	
Rectum	1,843/6,008	391/2,010	0.84 (0.75 to 0.94), .003	0.79 (0.69 to 0.90), .001	.400
Excluded variable					
Age < 50 years	5,068/15,837	1,145/6,052	0.82 (0.76 to 0.87), < .001	0.85 (0.79 to 0.91), < .001	.199§
ACE inhibitor/ARB use	5,318/16,787	1,130/5,816	0.84 (0.79 to 0.90), < .001	0.86 (0.80 to 0.93), < .001	< .001
Statin use	5,345/16,876	1,123/5,809	0.84 (0.78 to 0.89), < .001	0.85 (0.79 to 0.92), < .001	< .001
Beta blocker use	5,288/16,719	1,104/5,767	0.83 (0.78 to 0.89), < .001	0.85 (0.78 to 0.91), < .001	< .001
NSAID use	5,227/16,443	1,110/5,769	0.84 (0.78 to 0.89), < .001	0.85 (0.79 to 0.92), < .001	< .001
Metformin use	5,354/16,974	1,146/6,020	0.83 (0.78 to 0.89), < .001	0.85 (0.79 to 0.92), < .001	< .001
Follow-up start time after CRC diagnosis, years					
1	3,689/15,092	1,057/5,970	0.85 (0.80 to 0.91), < .001	0.86 (0.80 to 0.93), < .001	
2	2,040/12,056	717/5,216	0.91 (0.84 to 0.99), .031	0.91 (0.83 to 1.01), .065	
3	1,138/9,024	457/4,256	0.95 (0.86 to 1.06), .394	0.95 (0.84 to 1.07), .384	
5	311/4,966	142/2,530	0.95 (0.78 to 1.16), .591	0.95 (0.76 to 1.19), .669	

Abbreviations: ACE, angiotensin converting enzyme; AJCC, American Joint Committee on Cancer; ARB, angiotensin II receptor blocker; coxib, cyclooxygenase-2 inhibitor; CRC, colorectal cancer; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

*Adjusted for sex, age, site of disease, tumor differentiation, disease stage, surgery, ACE inhibitor/ARB use, NSAID/coxib use, statin use, beta blocker use, and metformin use.

†Interaction was tested by using the likelihood ratio test.

§Test for interaction by age group.

‡*P* values were not significant after correction for multiple comparisons.

Table A2. Stratified Analysis for Overall Survival

Variable	No of Events/ No. at Risk		Overall Survival		
	No Aspirin	Aspirin	Univariable HR (95% CI), *P*	Multivariable* HR (95% CI), *P*	Interaction *P*†
Main analysis	7,218/17,060	2,071/6,102	1.02 (0.97 to 1.08), .352	0.95 (0.90 to 1.01), .076	
> 4 aspirin prescriptions	7,490/17,555	1,799/5,607	0.87 (0.83 to 0.92), < .001	0.80 (0.75 to 0.85), < .001	
Tumor differentiation grade					
Well	301/1,066	125/452	1.27 (1.03 to 1.57), .026	1.22 (0.97 to 1.53), .094	
Moderate	4,175/10,653	1,354/4,064	1.05 (0.99 to 1.12), .094	0.93 (0.87 to 0.99), .034‡	
Poor	1,491/2,878	338/862	0.95 (0.84 to 1.07), .375	0.94 (0.83 to 1.08), .397	
Undifferentiated	13/30	4/12	1.11 (0.35 to 3.57), .856	3.50 (0.79 to 15.59), .100	< .001
AJCC disease stage					
I	1,049/3,600	422/1,631	1.13 (1.01 to 1.27), .039	0.98 (0.85 to 1.13), .811	
II	1,379/4,840	572/2,112	1.14 (1.03 to 1.26), .012	0.88 (0.79 to 0.98), .018	
III	1,888/4,829	576/1,581	1.24 (1.13 to 1.36), < .001	0.98 (0.88 to 1.08), .683	
IV	2,581/3,188	407/565	0.96 (0.86 to 1.07), .463	0.91 (0.80 to 1.03), .133	< .001
Surgically treated	5,922/15,563	1,912/5,866	1.08 (1.02 to 1.14), .005	0.95 (0.89 to 1.00), .072	.260
Sex					
Female	3,580/8,821	861/2,665	1.04 (0.96 to 1.12), .358	0.95 (0.87 to 1.04), .253	
Male	3,638/8,239	1,210/3,437	1.00 (0.93 to 1.06), .883	0.94 (0.87 to 1.01), .109	.080
Site of disease					
Right colon	2,262/5,171	697/1,992	1.02 (0.94 to 1.11), .641	0.96 (0.87 to 1.06), .451	
Transverse colon	496/1,118	144/405	1.10 (0.91 to 1.33), .345	1.07 (0.86 to 1.32), .558	
Left colon	1,874/4,553	522/1,613	1.00 (0.91 to 1.11), .963	0.94 (0.84 to 1.05), .262	
Rectum	2,447/6,008	670/2,010	1.03 (0.94 to 1.12), .545	0.91 (0.82 to 1.02), .097	.540
Excluded variable					
Age < 50 years	6,874/15,837	2,055/6,052	0.99 (0.94 to 1.04), .642	0.94 (0.89 to 1.00), .036‡	.671§
ACE inhibitor/ARB use	7,111/16,787	1,987/5,816	1.03 (0.97 to 1.08), .330	0.95 (0.90 to 1.01), .106	< .001
Statin use	7,163/16,876	1,988/5,809	1.02 (0.97 to 1.08), .364	0.95 (0.90 to 1.01), .082	< .001
Beta blocker use	7,056/16,719	1,945/5,767	1.02 (0.97 to 1.07), .472	0.95 (0.89 to 1.01), .084	< .001
NSAID use	7,006/16,443	1,973/5,769	1.02 (0.97 to 1.08), .408	0.95 (0.89 to 1.00), .061	< .001
Metformin use	7,183/16,974	2,045/6,020	1.02 (0.97 to 1.08), .360	0.95 (0.89 to 1.00), .060	< .001
Follow-up start time after CRC diagnosis, years					
1	5,254/15,092	1,939/5,970	1.05 (1.00 to 1.11), .064	0.96 (0.90 to 1.02), .140	
2	3,209/12,056	1,447/5,216	1.13 (1.06 to 1.20), < .001	0.99 (0.92 to 1.06), .698	
3	1,958/9,024	1,051/4,256	1.24 (1.15 to 1.34), < .001	1.02 (0.94 to 1.11), .594	
5	692/4,966	463/2,530	1.36 (1.21 to 1.53), < .001	1.04 (0.91 to 1.19), .537	

Abbreviations: ACE, angiotensin converting enzyme; AJCC, American Joint Committee on Cancer; ARB, angiotensin II receptor blocker; coxib, cyclooxygenase-2 inhibitor; CRC, colorectal cancer; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

*Adjusted for sex, age, site of disease, tumor differentiation, disease stage, surgery, ACE inhibitor/ARB use, NSAID/coxib use, statin use, beta blocker use, and metformin use.

†Interaction was tested by using the likelihood ratio test.

‡*P* values were not significant after correction for multiple comparisons.

§Test for interaction by age group.