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Low-Dose Aspirin and Prevention of Colorectal Cancer: Evidence From a Nationwide Registry-Based Cohort in Norway

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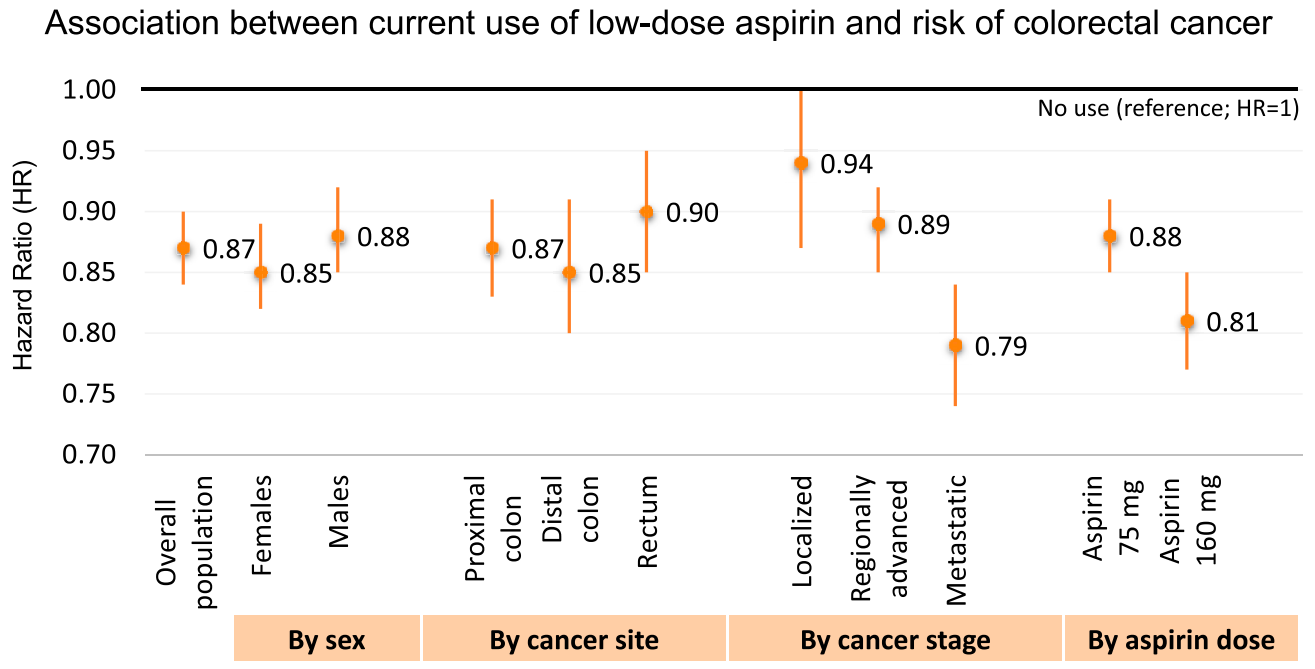
INTRODUCTION: **To examine the association between low-dose aspirin use and risk of colorectal cancer (CRC).**

METHODS: **In this nationwide cohort study, we identified individuals aged 50 years or older residing for 6 months or more in Norway in 2004–2018 and obtained data from national registers on drug prescriptions, cancer occurrence, and sociodemographic factors. Multivariable Cox regression models were used to estimate the association between low-dose aspirin use and CRC risk. In addition, we calculated the number of CRC potentially averted by low-dose aspirin use.**



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RESULTS: **We included 2,186,390 individuals. During the median follow-up of 10.9 years, 579,196 (26.5%) used low-dose aspirin, and 38,577 (1.8%) were diagnosed with CRC. Current use of aspirin vs never use was associated with lower CRC risk (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.84–0.90). The association was more pronounced for metastatic CRC (HR 0.79; 95% CI 0.74–0.84) than regionally advanced (HR 0.89; 95% CI 0.85–0.92) and localized CRC (HR 0.93; 95% CI 0.87–1.00; *P* heterogeneity = 0.001). A significant trend was found between duration of current use and CRC risk: HR 0.91 (95% CI 0.86–0.95) for <3 years, HR 0.85 (0.80–0.91) for ≥3 and <5 years, and HR 0.84 (0.80–0.88) for ≥5 years of use vs never use (*P* trend < 0.001). For past use, HR were 0.89 (95% CI 0.84–0.94) for <3 years, 0.90 (0.83–0.99) for ≥3 and <5 years, and 0.98 (0.91–1.06) for ≥5 years since last use vs never use (*P*-trend < 0.001). We estimated that aspirin use averted 1,073 cases of CRC (95% CI 818–1,338) in the study period.**

DISCUSSION: **In this nationwide cohort, use of low-dose aspirin was associated with a lower risk of CRC.**

KEYWORDS: aspirin; incidence; colorectal cancer; cohort study

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D194, http://links.lww.com/AJG/D195, and http://links.lww.com/AJG/D196

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INTRODUCTION

In 2020, colorectal cancer (CRC) had the third highest incidence rate and second highest mortality rate of all cancers worldwide, imposing substantial burden on individuals and health systems (1). Public health strategies aiming to ease this burden include developing screening programs for prevention and early detection of CRC (2,3) and raising awareness about harmful lifestyle habits that increase CRC risk, including physical inactivity, overweight and obesity, alcohol consumption, cigarette smoking, and poor diet (4,5). Chemoprevention is an additional well-studied strategy to inhibit, slow down, or reverse the carcinogenesis process (6). Aspirin has been long regarded as the most promising preventive agent against CRC (7). In a meta-analysis of 45 observational studies, regular aspirin use was associated with 27% lower CRC risk (7). Consistently, in a meta-analysis of 7 randomized controlled trials (RCT), aspirin use was associated with 26% reduced CRC risk (8). However, some large cohorts found no association between aspirin use and CRC risk when aspirin was initiated after 70 years of age (9) and when aspirin was used for less than 10 years (10) or 20 years (11). Furthermore, in 2021, the Aspirin in Reducing Events in the Elderly (ASPREE) trial, a placebo-controlled trial that included healthy individuals aged 70 years or older who were not using aspirin, found no protective effect of aspirin against CRC after a median follow-up of 4.7 years (12). Another placebo-controlled trial published in 2018, A Study of Cardiovascular Events in Diabetes, found no association between aspirin use and risk of gastrointestinal cancers, with CRC being the most common, after a mean follow-up of 7.4 years (13). So while in 2016, the US Preventive Services Task Force (USPSTF) recommended low-dose aspirin initiation for primary prevention against CRC in adults aged 50–59 years (14), in 2022, based on the recent contradictory evidence, the USPSTF revoked that recommendation (15).

Besides the aforementioned conflicting results, many published studies included a relatively small number of cases with CRC (7) and did not investigate the association between aspirin and CRC risk according to the individuals' characteristics (e.g., age and sex), cancer characteristics (e.g., location within the colorectum and stage at diagnosis), or patterns of aspirin use (e.g., dose and duration of use) (11,16–22). These limitations make it difficult to understand whether aspirin may be effective only in specific subpopulations, against particular CRC types, and in certain doses or after a certain duration of use.

Given the listed uncertainties and limitations, the protective effect of aspirin against CRC risk and the optimal pattern of use in the average-risk population remains highly debated. Therefore, we decided to conduct a nationwide population-based cohort study to investigate the association between aspirin use and CRC incidence. The large number of individuals and cases with cancer allowed stratifying the analyses by important cancer and population characteristics. Furthermore, we analyzed different doses and lengths of exposure in current aspirin users and time since aspirin discontinuation in past users. We additionally estimated the number of CRC possibly averted by aspirin in the study period.

METHODS

Study population and design

We conducted a registry-based cohort study by identifying individuals aged 18–79 years in 2004 who lived in Norway anytime between January 1, 2004, and December 31, 2018. Because low-dose aspirin is recommended for the primary prevention of cardiovascular events and possibly CRC in individuals aged 50 years or older, but not for younger adults (14,15), we decided that individuals aged 50 years or older constituted our target population. An analysis in individuals younger than 50 years would lead to possibly inaccurate estimates with large confidence intervals, given the small number of aspirin users, and would also be of limited clinical value. We excluded individuals with a history of invasive cancer (except nonmelanoma skin cancer; *International Classification of Diseases, 10th Revision* [*ICD-10*] code C44) before start of follow-up. Individuals entered the cohort on the earliest date among January 1, 2004, the date they turn 49.5 years of age, or first immigration date. We started to follow-up participants 6 months after they entered the cohort, to have data on 6 months of medication history. We followed up participants until the earliest date among CRC diagnosis (outcome of interest),

another cancer diagnosis (except C44), death, emigration, or end of follow-up (December 31, 2018).

Data sources

This cohort study used data from population-based registries, including Cancer Registry of Norway (CRN), Norwegian Prescription Database (NorPD), Cause of Death Registry, and Statistics Norway, linked by a unique personal identification number. CRN provided data on all diagnosed cancers and their characteristics, like the anatomical site and stage at the diagnosis. NorPD started registering information on prescriptions collected from pharmacies in Norway in 2004 (23) and provided data on the prescription date, the Anatomical Therapeutic Chemical (ATC) code, the number of dispensed packages, and defined daily doses (DDD). DDD is the daily average maintenance dose for the main indication in adults (24). Cause of Death Registry provided data on date of death (25). Sociodemographic data, including date of birth, migration history, educational level (none/primary school, secondary school, university, and missing), household income (categorized in quartiles and missing), marital status (married/partnered, not married/partnered, missing), and country of birth (Norway, other Nordic countries [including Denmark, Finland, Iceland, and Sweden], and rest of the world), were acquired from Statistics Norway (26).

Exposure assessment

All aspirin prescriptions (ATC codes B01AC06 and B01AC56) had low-dose formulations (75, 81, or 160 mg tablets). We had no data on use of regular-dose aspirin, which is usually an over-the-counter product and not obtained by registered prescriptions (ATC code: N02BA01). We calculated each prescription's treatment duration by assuming 1 DDD per day and extended that duration by 4 months as a grace period. When 2 or more treatment periods overlapped, we merged those into 1 treatment period.

Commencing or discontinuing a certain treatment close to cancer diagnosis could be due to an undiagnosed cancer's early symptoms. Incident drug use before cancer diagnosis increases starting from 6 months before diagnosis and leads to possible reverse causation. To limit the risk of reverse causation, we applied a lag-time period of 6 months to all prescriptions (new prescription date = original prescription date + 6 months) (27,28).

We assessed low-dose aspirin exposure in a time-dependent manner. Individuals could contribute person-time at risk as never-user, current user, and past user. An individual with no prescription during the 6 months after cohort entry started contributing person-time as never-user at the start of follow-up until the first possible low-dose aspirin prescription (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D194). Individuals contributed person-time as current users from the first prescription date until the treatment period's end. Individuals contributed person-time as past users from the end of a treatment period until the next prescription or end of follow-up. Individuals with a prescription during the 6 months after the cohort entry date were defined as prevalent users and started contributing person-time as current or past users from the start of follow-up.

Outcome assessment

The outcome of interest was first primary malignant carcinoma of the colorectum (*ICD-10*: C18-C20), excluding noncarcinomatous cancers, such as sarcomas, lymphomas, and neuroendocrine tumors. In individuals with several diagnoses in distinct sites of colorectum (n = 241), the diagnosis with highest stage was the outcome, and when the diagnoses had identical stages, only 1 was selected randomly as the outcome for those individuals (n = 316). We categorized CRC by site into proximal (from cecum and appendix to and including splenic flexure), distal (distal to splenic flexure up to and including the descending and sigmoid colon), and rectal (rectosigmoid junction and rectum). Clinical stage was categorized as localized, regionally advanced, or metastatic, according to the Surveillance, Epidemiology, and End Results Program in the United States National Cancer Institute (29).

Statistical analysis

We used descriptive statistics to illustrate the baseline sociodemographic characteristics and use of medications in low-dose aspirin users and nonusers. We used Cox regression models with age as the timescale, to estimate the hazard ratios (HR) with 95% confidence intervals (CI) for the association between low-dose aspirin use and CRC risk, in the entire population, and stratified by sex. Because the aim of this study was to investigate the potential protective effect of aspirin against CRC, cause-specific HR are more relevant than HR obtained from competing risk models (30). We tested the interaction between current aspirin use and sex using an interaction term. The association was studied by age by categorizing the cohort into 2 subcohorts where 70 years of age was considered the end of follow-up in 1 cohort (50 years or older and younger than 70 years) and the start of follow-up for the second one (70 years or older). The heterogeneity of the HR between CRC in 2 age groups was investigated using the Wald test (31). Furthermore, we studied the association between low-dose aspirin use and CRC site/stage-specific risk by censoring individuals with CRC of different site/stage in each Cox model. We investigated the heterogeneity of the HR between CRC sites and stages using the Wald test (31). All estimates were adjusted for sex, country of birth, education level, income, and marital status, all registered at cohort entry and for the use of selected medication classes (see Supplementary Table 1, Supplementary Digital Content 3, http://links.lww.com/AJG/D196). We created separate categories for missing values. A prescription containing a combination of 2 drugs was analyzed as 2 medication classes. An individual was considered a user of a specific medication class from the first prescription date until the end of follow-up. Proportional hazards assumption was investigated using Schoenfeld residuals.

We studied the association between different doses of aspirin and CRC risk by creating a new exposure variable with 5 categories: never use, current use of 75/81 mg of aspirin, current use of 160 mg of aspirin, past use of 75/81 mg of aspirin, and past use of 160 mg of aspirin. We combined 75 mg and 81 mg because of few 81 mg aspirin users. Because it would be hard to disentangle the effect of 75/81 mg and 160 mg on the risk of cancer in people who changed doses during the follow-up, we chose to right-censor the observation of those individuals at the date of first dose change, rather than building time-dependent dose models.

Besides the cohort design, we conducted a nested case-control study to evaluate the dose-response association between low-dose aspirin use and CRC risk. We chose a nested case-control design

over a time-varying exposure cohort design for computing efficiency. We matched the cases with CRC to 10 controls of the same sex, still at risk of CRC at the age and date when the corresponding case had CRC (index date). We defined the exposure based on the last exposure status before the index date (see Supplementary Figure 2, Supplementary Digital Content 2, http://links.lww.com/AJG/D195) and created a variable with 7 categories: never use, 3 levels of current use (<3, ≥3 and <5, and ≥5 years of use), and 3 levels of past use (<3, ≥3 and <5, and ≥5 years since last use). We included only individuals with at least 5 years of follow-up in the cohort to have at least 5 years of aspirin use history. Conditional logistic regression was used to estimate HR (32) and 95% CI. All estimates were adjusted for age, sex, and index date by matching, and the following possible confounders registered at index date: country of birth, education level, income, marital status, and use of selected medication classes (see Supplementary Table 1, Supplementary Digital Content 3, http://links.lww.com/AJG/D196). To test for trend for the duration of aspirin use and time since the last aspirin use, we entered 2 continuous variables in each logistic regression model: one variable for the duration of aspirin use, having value 0 for never and past use and values 1–3 for current use for <3, ≥3 and <5, and ≥5 years, and another variable for time since last aspirin use, having value 0 for never and current use and values 1–3 for use discontinued ≥5, ≥3 and <5, and <3 years before the index date. We performed a sensitivity analysis using the new-user case-control design where, instead of including only individuals with at least 5 years of follow-up, we excluded prevalent low-dose aspirin users from the study population and then built a case-control study with the same matching rules and criteria (27).

The prevented fraction for the population (PFP) and the corresponding number of cases with CRC potentially averted by low-dose aspirin use were calculated using the formulas reported by Strain and colleagues (33). The formulas incorporate the prevalence of low-dose aspirin use and the unadjusted (i.e. only adjusted for age as the timescale) and adjusted HR of CRC risk for low-dose aspirin users (either current or past users) vs never-users. To calculate the prevalence of low-dose aspirin users in the study period, we randomly selected 1 day per calendar year and estimated the year-specific prevalence as the number of users divided by the number of individuals in the cohort on each date. Next, we calculated the mean prevalence of the study period as the mean of all the year-specific prevalence estimates. The confidence interval for the PFP and number of averted cases was based on 10,000 Monte-Carlo simulations and estimated as proposed by Strain et al (33).

All tests were 2-sided, with significance set at P values <0.05. R software version 4.1.2 (http://cran.r-project.org/) was used for statistical analyses.

RESULTS

We identified 4,091,792 men and women who lived in Norway anytime from 2004 to 2018 (Figure 1). After excluding individuals who lived in Norway for less than 6 months (n = 309,423), those with a history of cancer (n = 112,230), and those younger than 50 years at the end of follow-up (n = 1,483,749), we included 2,186,390 individuals. During a median follow-up of 10.9 years, 38,577 (1.8%) were diagnosed with CRC and 579,196 (26.5%) individuals used low-dose aspirin at least once. Low-dose aspirin use was more frequent in male individuals, older individuals, individuals with lower education, lower income, and Norwegian origin, and users of antithrombotics, antihypertensives, cardiac therapy agents, statins, antidiabetics, nonsteroidal anti-inflammatory drugs, antidepressants, and menopausal hormone therapy (for female individuals) (Table 1). Of all low-dose aspirin prescriptions, 80.7% were 75 mg, 0.01% 81 mg, and 19.3% were 160 mg.

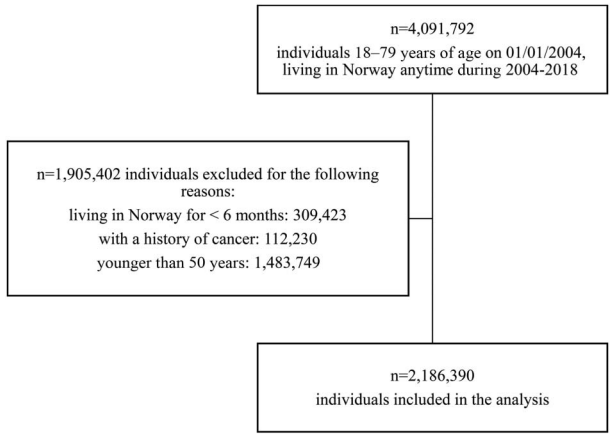

Figure 1. Flowchart for the inclusion of cohort population, 2004–2018, Norway.

Both current use (HR 0.87; 95% CI 0.84–0.90) and past use (HR 0.94; 95% CI 0.90–0.98) of low-dose aspirin use vs never use were associated with a lower CRC risk (Table 2). Similar estimates for current low-dose aspirin use vs never use were found in female individuals (HR 0.85; 95% CI 0.82–0.89) and male individuals (HR 0.88; 95% CI 0.84–0.92; P interaction = 0.251), individuals younger than 70 years (HR 0.86; 95% CI 0.82–0.91) and those aged 70 years or older (HR 0.88; 95% CI 0.85–0.91; P-heterogeneity = 0.492; see Supplementary Table 2, Supplementary Digital Content 3, http://links.lww.com/AJG/D196), and CRC in the proximal colon (HR 0.86; 95% CI 0.82–0.90), distal colon (HR 0.89; 95% CI 0.84–0.94), and rectum (HR 0.95; 95% CI 0.91–1.01; P heterogeneity = 0.361) (Table 2). The association was more profound for metastatic CRC (HR 0.79; 95% CI 0.74–0.84) than CRC diagnosed in earlier stages (regionally advanced: HR 0.89; 95% CI 0.85–0.92; localized: HR 0.93; 95% CI 0.87–1.00; P heterogeneity = 0.001). Current use of 160 mg tablets had a stronger association with CRC (HR 0.81; 95% CI 0.77–0.85) than the current use of 75 mg tablets (HR 0.88; 95% CI 0.85–0.91; P heterogeneity = 0.002).

In the nested case-control study, we included 27,673 cases and 276,730 controls (see Supplementary Table 3, Supplementary Digital Content 3, http://links.lww.com/AJG/D196). We found a trend in the association between duration of low-dose aspirin use and CRC risk: HR for current low-dose aspirin use for <3, ≥3 and <5, and ≥5 years were 0.91 (95% CI 0.86–0.95), 0.85 (0.80–0.91), and 0.84 (0.80–0.88), respectively (P trend < 0.001) (Figure 2A). Likewise, we found a trend in the association between time since last low-dose aspirin use and CRC risk: HR for past use of low-dose aspirin were 0.89 (95% CI 0.84–0.94) for <3 years, 0.90 (0.83–0.99) for ≥3 and <5 years, and 0.98 (0.91–1.06) for ≥5 years since last use (P trend < 0.001). The estimates did not change substantially after stratifying the analysis by sex (Figure 2B and C, see Supplementary Table 5, Supplementary Digital Content 3, http://links.lww.com/AJG/D196) and age groups (see Supplementary Tables 4 and 6, Supplementary

Table 1. Characteristics of the population by use of low-dose aspirin, 2004–2018, Norway

	No low-dose aspirin (n = 1,607,194)	Low-dose aspirin (n = 579,196)
Sex		
Females	832,935 (51.8)	250,694 (43.3)
Males	774,259 (48.2)	328,502 (56.7)
Age at the start of follow-up, yr		
Median (Q1, Q3)	50.0 (50.0, 58.0)	60.0 (53.0, 69.0)
Highest education level		
None/mandatory	384,800 (23.9)	191,865 (33.1)
Secondary school	709,013 (44.1)	270,713 (46.7)
University	442,659 (27.5)	110,748 (19.1)
Missing	70,722 (4.4)	5,870 (1.0)
Income (Norwegian kroner)		
Q1[a]	349,591 (21.8)	187,320 (32.3)
Q2	368,727 (22.9)	168,184 (29.0)
Q3	416,760 (25.9)	120,151 (20.7)
Q4	434,109 (27.0)	102,801 (17.7)
Missing	38,007 (2.4)	740 (0.1)
Marital status		
Married/partnered	957,157 (59.6)	377,414 (65.2)
Not married/partnered	601,303 (37.4)	198,646 (34.3)
Missing	48,734 (3.0)	3,136 (0.5)
Country of birth		
Norway	1,368,557 (85.2)	531,654 (91.8)
Other Nordic countries[b]	57,509 (3.6)	13,272 (2.3)
Rest of the world	181,128 (11.3)	34,270 (5.9)
Use of other medications		
Antithrombotics (except aspirin)	17,000 (1.1)	173,977 (30.0)
Nonselective beta-blockers	43,535 (2.7)	51,573 (8.9)
Selective beta-blockers	185,052 (11.5)	325,371 (56.2)
Calcium channel blockers	207,582 (12.9)	230,614 (39.8)
Angiotensin-converting enzyme inhibitors	119,857 (7.5)	174,839 (30.2)
Angiotensin receptor blockers	299,047 (18.6)	257,424 (44.4)
Diuretics	308,848 (19.2)	306,817 (53.0)
Cardiac therapy agents	77,244 (4.8)	208,109 (35.9)
Statins	279,261 (17.4)	441,727 (76.3)
Antidiabetics	93,732 (5.8)	108,098 (18.7)
Nonsteroidal anti-inflammatory drugs	1,015,712 (63.2)	434,264 (75.0)
Antidepressants	293,604 (18.3)	162,899 (28.1)
Menopausal hormone therapy (female individuals)	300,585 (36.1)	109,364 (43.6)

[a]Q1–Q4: quartiles for household income in Norwegian Krone (Q1 <193,000; Q2 193,000–309,300; Q3 309,301–464,500; and Q4 >464,500).
[b]Includes Denmark, Finland, Iceland, and Sweden.

Digital Content 3, http://links.lww.com/AJG/D196) and when we applied the new-user design (data not shown).

In this national cohort, the mean prevalence of low-dose aspirin use along the study period was 21.8% (95% CI 21.6–21.9). The PFP was 2.7% (95% CI 2.1–3.3), corresponding to an estimate

Table 2. Association between use of low-dose aspirin and incidence of colorectal cancer in Norway, 2004–2018, in the cohort population, overall and by sex

	Overall population			Female individuals			Male individuals		
	Cases	Person-years	HR[a] (95% CI)	Cases	Person-years	HR[a] (95% CI)	Cases	Person-years	HR[a] (95% CI)
CRC									
Never use	26,365	16,503,146	1 (ref.)	13,338	8,762,033	1 (ref.)	13,027	7,741,113	1 (ref.)
Current use	9,052	3,449,515	0.87 (0.84–0.90)	3,571	1,445,128	0.85 (0.82–0.89)	5,481	2,004,387	0.88 (0.85–0.92)
Past use	3,160	1,074,427	0.94 (0.90–0.98)	1,432	540,093	0.92 (0.86–0.97)	1,728	534,334	0.96 (0.90–1.01)
By CRC site									
Proximal colon									
Never use	10,352	16,503,146	1 (ref.)	6,099	8,762,033	1 (ref.)	4,253	7,741,113	1 (ref.)
Current use	3,906	3,449,515	0.87 (0.83–0.91)	1,892	1,445,128	0.86 (0.81–0.91)	2,014	2,004,387	0.88 (0.82–0.94)
Past use	1,438	1,074,427	0.95 (0.89–1.01)	787	540,093	0.95 (0.87–1.03)	651	534,334	0.95 (0.86–1.04)
Distal colon									
Never use	6,449	16,503,146	1 (ref.)	3,042	8,762,033	1 (ref.)	3,407	7,741,113	1 (ref.)
Current use	2,164	3,449,515	0.85 (0.80–0.91)	721	1,445,128	0.83 (0.75–0.91)	1,443	2,004,387	0.86 (0.79–0.93)
Past use	762	1,074,427	0.94 (0.87–1.02)	304	540,093	0.94 (0.83–1.07)	458	534,334	0.93 (0.84–1.04)
Rectum									
Never use	9,072	16,503,146	1 (ref.)	3,934	8,762,033	1 (ref.)	5,138	7,741,113	1 (ref.)
Current use	2,815	3,449,515	0.90 (0.85–0.95)	873	1,445,128	0.87 (0.79–0.94)	1,942	2,004,387	0.92 (0.86–0.98)
Past use	865	1,074,427	0.90 (0.84–0.97)	291	540,093	0.81 (0.71–0.92)	574	534,334	0.97 (0.88–1.06)
By CRC stage									
Localized									
Never use	4,569	16,503,146	1 (ref.)	2,338	8,762,033	1 (ref.)	2,231	7,741,113	1 (ref.)
Current use	1,923	3,449,515	0.94 (0.87–1.00)	742	1,445,128	0.91 (0.83–1.01)	1,181	2,004,387	0.95 (0.86–1.04)
Past use	684	1,074,427	1.05 (0.96–1.15)	305	540,093	1.02 (0.89–1.16)	379	534,334	1.07 (0.95–1.21)
Regionally advanced									
Never use	13,978	16,503,146	1 (ref.)	7,164	8,762,033	1 (ref.)	6,814	7,741,113	1 (ref.)
Current use	4,830	3,449,515	0.89 (0.85–0.92)	1,971	1,445,128	0.88 (0.83–0.93)	2,859	2,004,387	0.89 (0.84–0.94)
Past use	1,596	1,074,427	0.91 (0.86–0.96)	723	540,093	0.87 (0.80–0.95)	873	53,334	0.94 (0.87–1.01)
Metastatic									
Never use	6,486	16,503,146	1 (ref.)	3,166	8,762,033	1 (ref.)	3,320	7,741,113	1 (ref.)
Current use	1,782	3,449,515	0.79 (0.74–0.84)	646	1,445,128	0.75 (0.68–0.83)	1,136	2,004,387	0.81 (0.74–0.88)
Past use	628	1,074,427	0.88 (0.80–0.96)	274	540,093	0.88 (0.77–1.00)	354	534,334	0.88 (0.78–0.99)
By aspirin dose									
Never use	26,365	16,503,146	1 (ref.)	13,338	8,762,033	1 (ref.)	13,027	7,741,113	1 (ref.)
Aspirin 75 mg									
Current use	5,786	2,242,802	0.88 (0.85–0.91)	2,428	988,438	0.87 (0.83–0.91)	3,358	1,254,364	0.90 (0.86–0.94)
Past use	2,128	765,744	0.93 (0.88–0.97)	1,006	400,625	0.90 (0.84–0.97)	1,122	365,119	0.95 (0.89–1.01)
Aspirin 160 mg									
Current use	1,522	622,084	0.81 (0.77–0.85)	505	229,586	0.77 (0.70–0.85)	1,017	392,498	0.82 (0.77–0.88)
Past use	601	191,726	0.96 (0.88–1.04)	248	86,716	0.97 (0.85–1.10)	353	105,010	0.94 (0.85–1.05)

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio.

[a]Age was the underlying timescale (age adjusted), and models were additionally adjusted for sex, education level, income, marital status, country of birth, and use of antithrombotics (except aspirin), beta-blockers, calcium channel blockers, agents acting on the renin-angiotensin system, diuretics, cardiac therapy agents, statins, antidiabetics, nonsteroidal anti-inflammatory drugs, antidepressants, and menopausal hormone therapy (female individuals only).

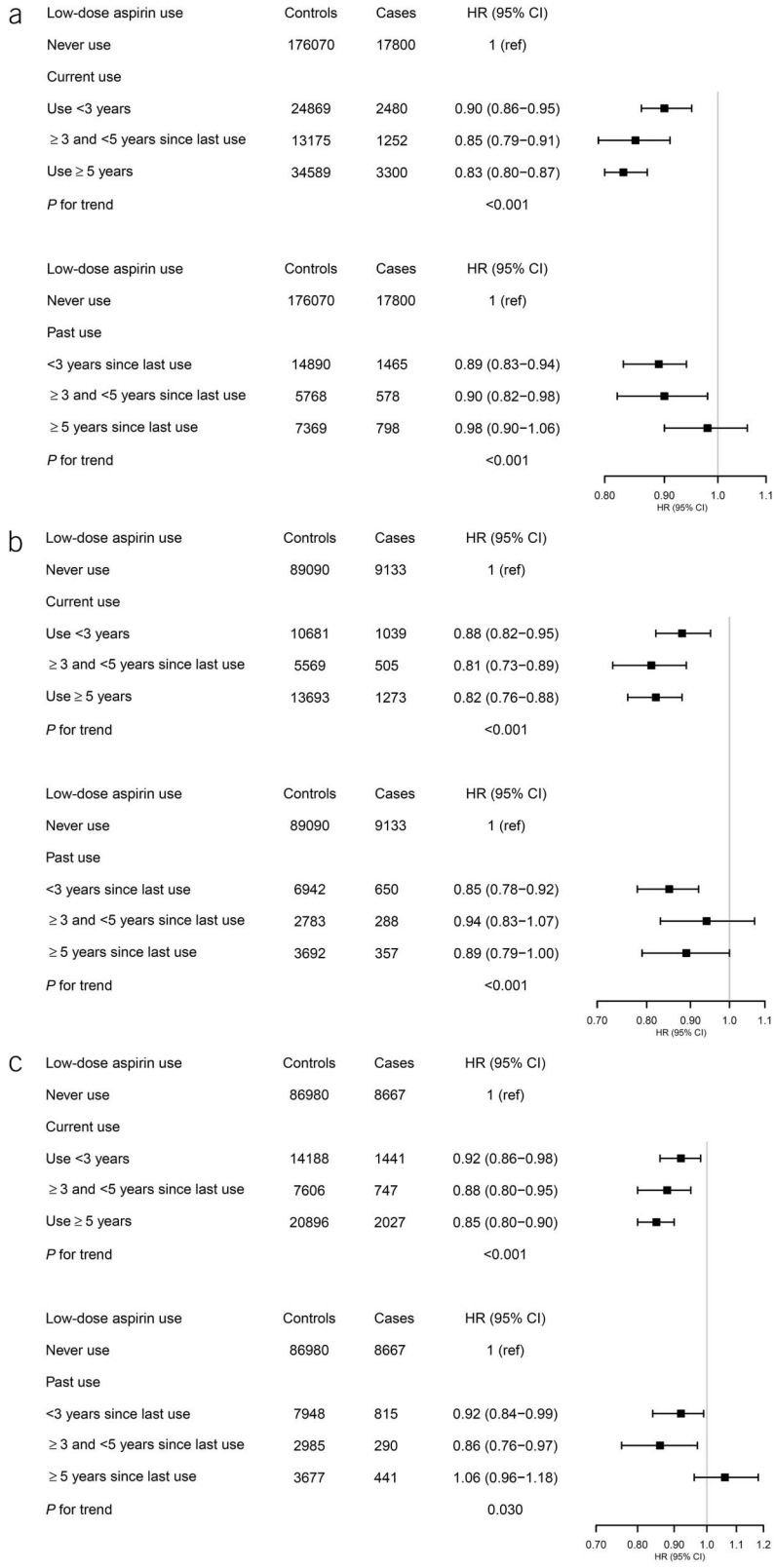

Figure 2. Association between use of low-dose aspirin and incidence of colorectal cancer in Norway in 2004–2018 in the nested case-control study, overall (**a**), and in female (**b**) and male individuals (**c**). Models were adjusted for age, sex, index date by matching, education level, income, marital status, country of birth, and use of antithrombotics (except aspirin), beta-blockers, calcium channel blockers, agents acting on the renin-angiotensin system, diuretics, cardiac therapy agents, statins, antidiabetics, nonsteroidal anti-inflammatory drugs, antidepressants, and menopausal hormone therapy (female individuals only). CI, confidence interval; HR, hazard ratio.

of 1,073 (95% CI 818–1,338) CRC cases averted by low-dose aspirin use.

DISCUSSION

In this large population-based cohort of individuals aged 50 years or older, we found an association between low-dose aspirin use and lower CRC risk. The association was similar in men and women, in individuals younger than 70 years and those aged 70 years or older, and for cancer in the proximal colon, distal colon, and rectum, but it was more profound for metastatic CRC than CRC diagnosed in earlier stages. The CRC risk decreased as the duration of low-dose aspirin use increased. Use of 160 mg tablets was associated with a greater CRC risk reduction than the use of 75 mg tablets. Furthermore, a lower CRC risk was found among individuals who had stopped taking the drug for less than 5 years.

We found a 13% lower CRC risk associated with current low-dose aspirin use vs never use, consistent with the findings of a recent large nested case-control study including 80,000 cases with CRC that reported an 11% lower CRC risk in long-term current low-dose aspirin users vs never-users (34). Moreover, in 2018, a network meta-analysis of RCT reported a 19% decrease in CRC risk in low-dose aspirin (≤100 mg) users compared with individuals receiving placebo (35). Long-term follow-up of the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial found a 12% reduced CRC risk among individuals who had used 1 or more aspirin tablets per day during the year before start of trial (18). In 2020, a large meta-analysis of 15 cohort, 11 nested case-control, and 19 case-control studies reported a 27% reduced CRC risk in regular users of aspirin (7). Noteworthy, the studies selected in that meta-analysis included individuals using all doses of aspirin and not just low dose. The same meta-analysis reported a 10% CRC risk reduction in 75 mg aspirin users, 11% in 81 mg aspirin users, and 13% in 100 mg aspirin users (7), quite consistent with our overall results and our dose-stratified results: 12% risk reduction in aspirin 75 mg users and 19% in 160 mg users. Contrary to the aforementioned evidence, in 2021, the ASPREE trial found no association between aspirin use and CRC risk after the median follow-up of 4.7 years (12). The ASPREE trial recruited adults aged 70 years or older, with only 11% having aspirin use history before joining the trial (12). It was argued later that the limited follow-up time of participants without history of aspirin use before the trial enrollment could partly explain the negative results in the ASPREE trial (9,36). As previously mentioned, the USPSTF withdrew their previous aspirin recommendations for CRC prevention based on the recent evidence including the results of the ASPREE trial (12,14,15).

We found a significant trend in CRC risk reduction with longer durations of low-dose aspirin exposure, with 9% decrease for <3 years, 15% for ≥3 and <5 years, and 16% decrease for ≥5 years of low-dose aspirin use vs never use. Consistent with our results, a meta-analysis of observational studies reported a similar trend with 4% reduced CRC risk for 1 year, 11% for 3 years, and 19% for 5 years of regular aspirin use vs never use (7). The available evidence regarding the possible protective effect of aspirin in past users is limited and controversial. Overall, we found a 6% lower CRC risk in past users vs never-users. The association between past use and CRC risk depended on the time since discontinuation, and we observed a significant association only in the first 5 years after discontinuation. A study found that past users of low-dose aspirin who used it for at least 1 year had a 22% lower CRC risk vs nonusers (19). Another study found that past users of regular-dose aspirin had the same risk as nonusers 1 year after aspirin discontinuation (37). A third study reported inconclusive results on the association between past use of low-dose aspirin and CRC risk (34).

A mechanism supporting the hypothesis that aspirin has a protective effect against CRC risk is that aspirin blocks the mutated *APC* (adenomatous polyposis coli) gene, leading to the inhibition of the KRAS pathway and the adenomatous polyp formation (38,39). Another possible explanation is the higher probability of bleeding of adenomas in aspirin users than in nonusers. Overt or occult bleeding, the latter revealed by increased use of screening tests for occult blood, might lead aspirin users more frequently than nonusers to colonoscopy and removal of adenomas and other possible CRC precursors (40).

We found a stronger inverse association between aspirin use and regionally advanced and metastatic CRC compared with localized CRC, supporting the hypothesis that aspirin slows down the progression besides preventing cancer. A possible explanation for this result is the antiplatelet mechanism of action of aspirin. Aspirin irreversibly inhibits cyclooxygenase enzyme leading to the downregulation of prostaglandin E2 levels and inhibition of cell proliferation, inflammation, and angiogenesis in the already-formed tumors (38,41). Aspirin users have an increased probability of bleeding from cancer lesions compared with nonusers, possibly resulting in early diagnosis of CRC. Furthermore, aspirin users have an increased risk of general bleeding events through the same antiplatelet pathway, possibly leading to a higher referral to colonoscopy and higher chances of early diagnosis of CRC (22,40). Besides, aspirin users tend to visit their physicians when they experience any sign of discomfort in the gastrointestinal tract, which increases the possibility of opportunistic CRC screening and early diagnosis. The indirect impact of aspirin use on time of CRC diagnosis could partly explain the stronger association observed for higher-stage CRC compared with early-stage CRC.

We found similar inverse association between aspirin use and CRC risk in female and male individuals. Similarly, Bosetti et al reported no significant difference between female and male individuals in their meta-analysis (7). We found similar association between aspirin use and CRC risk in adults aged 70 years or older and those younger than 70 years, while the ASPREE trial found no association between aspirin use and CRC risk in adults aged 70 years or older (12). The evidence on the association between aspirin and CRC according to the cancer site within the colorectal tract is controversial. We found no significant difference between the association between aspirin use and cancer risk in the distal colon, proximal colon, and rectum. This is consistent with the findings of the PLCO cancer screening trial that reported no heterogeneity by CRC site (18). A cohort study in 2006 found a stronger protective effect in aspirin users against distal colon cancer compared with that against CRC in proximal colon and rectum (11), while another study in 2010 reported a protective effect against proximal colon cancer but not against distal colon and rectal cancer (17).

By assuming a protective effect of aspirin against CRC, we estimated that 1,073 cases with CRC were prevented by aspirin use, equating to 2.7% lower CRC incidence. Another study in Australia provided the number of CRC prevented by daily aspirin use and reported 2% lower CRC incidence through daily aspirin use (42).

The main strength of our study is the large population, allowing us to obtain precise estimates of the association of interest and to study the association between aspirin use and CRC

risk in various subpopulations defined by individual and cancer characteristics. The linkage with NorPD ensured information on medication use without the risk of recall bias. Moreover, CRN has proven to provide very high-quality information on cancer (43,44). To the best of our knowledge, our study is among the rare studies presenting PFP estimates for CRC through aspirin use. To calculate the PFP estimate, we used a methodology that minimizes the risk of bias by potential confounders (33). We believe that PFP provides a useful public health indicator that can inform policymakers.

A major limitation of our study is its observational nature, which complicates the assessment of the causal association between low-dose aspirin and CRC. However, we believe that our dose-response analyses on the duration of use, years since cessation, and dose of aspirin add to the evidence of a protective effect of aspirin against CRC. Because aspirin is used for the primary prevention against cardiovascular events, aspirin users and nonusers were incomparable in terms of age or presence of comorbidities. However, we adjusted for sociodemographic variables and use of other medication as the proxies for comorbidities. We had no information on several known risk factors of CRC. If aspirin use is associated with high BMI, consumption of alcohol, smoking, low physical activity, poor diet, and family history of colorectal lesions, we can hypothesize that in our study, the association between aspirin and CRC risk was underestimated. During the study period, there was no national colorectal screening program. However, as discussed earlier, aspirin users might have attended opportunistic CRC screening more than nonusers and benefited from the screening's CRC preventive effect, for example, through the removal of polyps. This might have led to a slight overestimation of the association between aspirin use and CRC risk.

Because DDD does not always reflect the actual recommended daily dose of the prescribed medication (45), use of DDD could underestimate or overestimate the real exposure. However, low-dose aspirin pills have enteric-coated formulations, so the pills should not be divided (46). In fact, most aspirin users received 100 DDD boxes and renewed the prescription approximately every 100 days. We did not have information on the patients' adherence to the aspirin treatment, but it seems unlikely that individuals who renewed their aspirin prescriptions for long periods, a pattern generally observed in our study, did not take the drug. We had no information on regular-dose aspirin use, so comparing our results with those of previously published studies reporting regular-dose aspirin as their main exposure is not straightforward. In addition, our results could be biased by the unknown effect of high-dose aspirin consumption. If some of nonusers were regular-dose aspirin users, then the magnitude of the reported association between low-dose aspirin and CRC risk would be underestimated. However, because regular-dose aspirin is rarely used in Norway (0.2/1,000 users of all inhabitants in 2020) (47), this issue should not be a concern in this study. We had no data about the potential side effects of aspirin such as gastrointestinal ulcer and bleeding, which limits widespread aspirin use for primary prevention against CRC (48). Yet notably, the purpose was estimating the association between aspirin use and CRC incidence and not providing recommendations for aspirin use.

In conclusion, our study provided novel and strong evidence that low-dose aspirin use is associated with a lower CRC risk. The association seemed to be particularly strong for metastatic CRC and strengthened with increasing doses and increasing durations of use. With this large cohort study, we provided novel and strong evidence that supports the possible role of aspirin in the prevention of CRC. Based on our results, we believe that new RCT are urgently needed to confirm the potential protective effect of aspirin against CRC and to identify subgroups in the population who might benefit the most from the use of aspirin.

CONFLICTS OF INTEREST

Guarantor of the article: Edoardo Botteri, PhD.

Specific author contributions: All authors approved the final version of the article, including the authorship list listed below according to the contribution roles taxonomy. The work reported in the study has been performed by the authors, unless clearly specified in the text. S.N.: data curation, formal analysis, investigation, and writing—review and editing and original draft preparation, visualization. N.S.: data curation, methodology, supervision, and writing—review and editing. M.V.: methodology, supervision, writing—review and editing. K.R.: writing—review and editing. G.H.: writing—review and editing. L.L.: writing—review and editing. C.B.: writing—review and editing. E.B.: conceptualization, funding acquisition, supervision, writing—review and editing and original draft, validation, and methodology.

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Potential competing interests: The authors declare no potential conflict of interest. However, L.L.'s spouse is employed by the pharmaceutical company MSD Norway AS.

Ethics approval: This study has legal basis in accordance with Articles 6(1)(e) and 9(2)(j) of the GDPR. The linkage between national registries has received ethics approval (S-09113b 2009/2062; 2014/1854/REK sør-øst B), and the data linkage with NorPD has received approval from the Norwegian Data Protection Authority (17/00222-4/GRA). Because this is a registry-based study, informed consent from the included study subjects was not required according to Norwegian law.

Data transparency statement: Due to Norwegian law, we are not allowed to make the data publicly available. However, the data can be requested from the registry holders.

Study Highlights

WHAT IS KNOWN

- ✓ There is consistent data suggesting a reduced risk of colorectal cancer (CRC) in aspirin users.
- ✓ However, the use of aspirin for prevention of CRC is still highly debated.

WHAT IS NEW HERE

- ✓ This large nationwide study found that the use of low-dose aspirin was associated with a reduced risk of CRC.
- ✓ The association was more profound in the more advanced forms of CRC.
- ✓ The association strengthened with increasing aspirin dose and duration of use.

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