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Timing of Aspirin Use Among Patients With Colorectal Cancer in Relation to Mortality: A Systematic Review and Meta-Analysis

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Abstract

Background: Exposure of aspirin has been associated with reduced risk of colorectal cancer (CRC) incidence, but aspirin use in relation to CRC patients' mortality remains undetermined. It is necessary to quantify the association between aspirin use and CRC mortality. **Methods:** Two authors independently searched the electronic databases (PubMed, Embase, and the Cochrane Library) from 1947 through April 25, 2020. All observational studies assessing the association between different timing of aspirin use and CRC mortality were included. The effect size on study outcomes was calculated using random-effect model and presented as risk ratio (RR) with 95% confidence interval (CI). Heterogeneity, publication bias, and quality of included studies were also assessed. **Results:** A total of 34 studies were included in this systematic review and meta-analysis. Prediagnosis aspirin use was not associated with CRC-specific mortality (RR = 0.91, 95% CI = 0.79 to 1.05) and all-cause mortality (RR = 0.87, 95% CI = 0.57 to 1.31). A statistically significant association between continued aspirin use and improvement in both CRC-specific mortality (RR = 0.76, 95% CI = 0.70 to 0.81) and all-cause mortality (RR = 0.83, 95% CI = 0.74 to 0.93) was observed. Postdiagnosis use of aspirin was associated only with reduced all-cause mortality (RR = 0.80, 95% CI = 0.69 to 0.94). **Conclusions:** Continued aspirin use before and after CRC diagnosis has the most advantage regarding the improvement of CRC mortality. Nevertheless, further prospective trials and mechanistic studies are highly warranted.

Colorectal cancer (CRC) remains the second leading cause of cancer-related death worldwide (1), and the incidence rate in young adults (aged younger than 50 years) is increasing in recent years (2). Numerous evidence has demonstrated the protective role of aspirin on colorectal neoplasia among general populations (3) and even among high-risk populations (4). Low-dose aspirin also seems to be equally effective as colonscopy or fecal occult blood testing to reduce CRC incidence and even mortality (5). Regarding its potential biological mechanism for tumor suppression, aspirin has been identified to inhibit cyclooxygenase 2 (COX2) and related eicosanoids that promote malignant transformation (6,7), induce apoptosis via COX-dependent or -independent pathway (8), and modulate gut microbiota (9).

Nevertheless, the regular use of aspirin in the prevention of cancers is still a debated subject, because aspirin-induced bleeding, especially gastrointestinal bleeding, affects the risk-benefit assessment (10). In this way, secondary prevention in patients already diagnosed with CRC may offer a different risk-benefit profile. In support of this, some prospective studies designed for cardiovascular diseases prevention showed that aspirin use reduced the risk of metastasis and improved prognosis of patients with CRC (11-13). Recently, an increasing number of population-based observational studies have assessed the association between aspirin use and CRC patients' survivorship, but inconsistent conclusions were reported regarding the difference in starting time of aspirin use (14-17), as well as different subtypes of CRC (18-22). Nevertheless, these publications also formed the driving force for the conduct of several ongoing clinical trials assessing the efficacy of aspirin as an adjuvant agent in CRC treatment (summarized in Supplementary Table 1, available online), though relevant data or papers are not published yet. On the other hand, given that it is at least 5 years since the publication of 2 meta-analyses concerning this controversy (23,24), the fact that there will now be more published studies leads us to reexamine this issue.

Therefore, the present systematic review and meta-analysis was performed to provide up-to-date and comprehensive estimates for the association between aspirin use and CRC survival. We investigated the different starting time to aspirin use in relation to CRC survival among total CRC patients, and subgroup analysis was further explored regarding different anatomical sites or molecular signs whenever sufficient data were available.

Methods

Search Strategy and Selection Criteria

A systematic search of PubMed, Embase, and Cochrane Library was performed from 1947 to April 25, 2020, to identify potential studies, without language restriction. Reference lists of retrieved articles and previous systematic reviews were checked for further eligible publications. Abstracts published from American Society of Clinical Oncology, European Society for Medical Oncology, the American Digestive Disease Week, and the United European Gastroenterology Week were also searched manually.

Studies were eligible for inclusion if all the following criteria were fulfilled: 1) the study type was restricted to observational study; 2) the study assessed the association between aspirin use and CRC mortality (mainly including all-cause mortality and cancer-specific mortality); 3) effect estimates (the hazard ratio [HR], risk ratio [RR], odds ratio [OR]) and 95% confidence interval (CI) were available; 4) if datasets overlapped, the recent information was extracted.

Two investigators (SYX and WHX) conducted the literature search, independent of each other. Search terms used in the search strategy were *colorectal neoplasms, colorectal cancer, colorectal carcinoma, colorectal adenocarcinoma, colon cancer, colonic neoplasms, rectal neoplasms, rectal cancer, rectum cancer, aspirin, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), nonsteroidal anti-inflammatory drugs, survival, death,* and *mortality.* The search strategy is detailed in the Supplementary Methods (available online). SYX and WHX then independently evaluated all abstracts identified by the search for eligibility and further evaluated all potentially relevant papers in more detail according to predesigned criteria. Disagreements between the 2 investigators were resolved by discussion.

Data Analysis

A data extraction form was used to finish data collection. Extracted data mainly include author, publication year, country, study design, cancer type, number of participants, sex , age at cancer diagnosis, stage, follow-up duration, assessment of outcome, dose and duration-based response, and estimates in each study. The primary outcome is the impact of aspirin use in different timing (timing 1 = ever-use; timing 2 = prediagnosis use; timing 3 = aspirin use only before diagnosis; timing 4 = continued use; timing 5 = postdiagnosis use; timing 6 = aspirin use after diagnosis regardless of its usage before diagnosis) on the mortality of CRC patients (assessed by CRC-specific mortality, all-cause mortality). A graphical illustration of the timing categories are depicted in Supplementary Figure 1 (available online). Ever-users are those who have a history of aspirin use at any time in the context of established CRC. Prediagnosis use refers to the usage of aspirin prior to CRC diagnosis with or without aspirin use after diagnosis. Postdiagnosis aspirin users are defined as those who initiate aspirin use only after the diagnosis of CRC. Continued aspirin users refer to those who initiate aspirin use prior to CRC diagnosis and continue to use after diagnosis. The secondary outcome is whether the effect size of aspirin is different regarding the clinical stage, anatomical site of tumor (colon vs rectum), and molecular marker (*PIK3CA* mutation status and *COX2* expression). It should be noted that the same study simultaneously reported multiple outcomes regarding different timing of aspirin use. Quality assessment was carried out using the Newcastle-Ottawa scale.

The hazard ratio, risk ratio, or odds ratio with 95% confidence interval from maximally adjusted models whenever possible were extracted to estimate the summary effect. The pooled effect was calculated with a random-effect model. Heterogeneity of included studies was assessed with I^2, whereby a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (25). Publication bias was examined by Egger and Begg test (26,27). Sensitivity analysis was also performed to evaluate whether any study had excessive influence on the results of pooled analysis. All analyses were conducted using the statistical software package Stata13.0. Two-sided *P* values were calculated, with a *P* value less than .05 considered statistically significant for all tests. Data were reported in accordance to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines (Supplementary Methods, available online) (28).

Results

Using our search strategy, 942 potentially relevant articles were identified. Finally, 34 studies [31 in full-text (14-22,29-50) and 3 in conference abstract (51-53)] were included in this systematic review and meta-analysis. The detailed literature screening process is shown in Figure 1. Most of the studies were conducted in the United States and European countries. Except for 3 case-control studies (16,31,48), the remaining studies adopted a cohort design. Among the included studies, 5 (20,21,37,38,46) enrolled patients with colon cancer or rectal cancer only, and the remaining studies included patients with both colon and rectal cancer; 10 studies also provided detailed information on site-specific outcomes (colon vs rectum). In addition, 3 (29,33,47) and 4 (16,17,30,33) studies, respectively, reported the dose- and duration-dependent association between aspirin use and CRC survival. In terms of molecular markers, 9 studies reported this association (18,19,22,29,36,40,44,51,52). The general characteristics of included studies are summarized in Table 1, and the estimated hazard ratio, risk ratio, or odds ratio with 95% confidence interval and adjustment factors for each study are listed in Supplementary Table 2 (available online). According to the Newcastle-Ottawa scale, the methodology of these included studies was generally moderate to good, as shown in Supplementary Table 3 (available online; for cohort study) and Supplementary Table 4 (available online; for case-control study).

Six studies (21,37,39,48,49,51) reported the relation between ever-use of aspirin (timing 1) and CRC patients' outcome. Pooled results showed a positive association between ever-use of aspirin and CRC-specific mortality (pooled RR = 0.59, 95% CI = 0.57 to 0.62; I^2 = 0.0%) (Table 2; Supplementary Figure 2, A, available online) but not all-cause mortality (pooled RR = 1.10, 95% CI = 0.93 to 1.29; I^2 = 94.8%) (Table 2; Supplementary Figure 2, B, available online). For CRC patients without distant metastasis (stage I-III), ever-use also did not show a positive association regarding all-cause death (pooled RR = 0.82, 95% CI = 0.66 to 1.01; I^2 = 5.9%) (Figure 2, B). Stratified by tumor site, ever-use of aspirin was associated with reduced risk of both cancer-specific
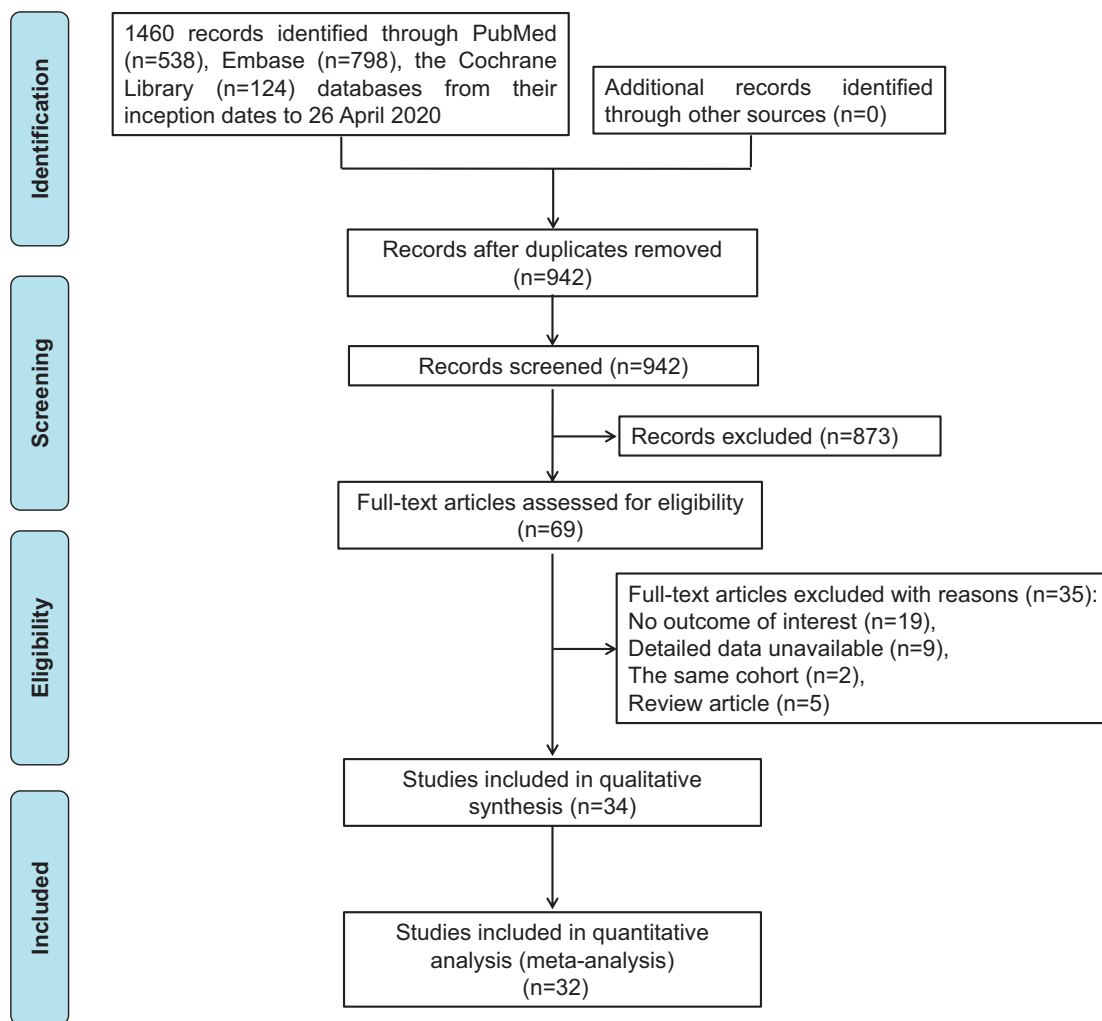
Figure 1. Flow diagram of included studies.

mortality (pooled RR = 0.60, 95% CI = 0.57 to 0.64; $I^2 = 0$) (Figure 2, A) and all-cause mortality (pooled RR = 0.74, 95% CI = 0.60 to 0.91; $I^2 = 0$) (Figure 2, B) among colon cancer patients and only cancer-specific mortality in rectal cancer (pooled RR = 0.56, 95% CI = 0.52 to 0.62; $I^2 = 0$) (Figure 2, A). It should be noted, however, that the estimate for site-specific outcome from Tsoi and colleague's study (48) was not an adjusted value which might induce bias .

To better characterize the association between the starting time of aspirin use relative to CRC diagnosis and patients' survival, we divided aspirin use into prediagnosis use, postdiagnosis use, and continued use. It was found that prediagnosis aspirin use (timing 2) was not associated with CRC-specific mortality (pooled RR = 0.91, 95% CI = 0.79 to 1.05; $I^2 = 60.0\%$) (Table 2; Supplementary Figure 3, A, available online) and all-cause mortality (pooled RR = 0.87, 95% CI 0.57 to 1.31; $I^2 = 96.1\%$) (Table 2; Supplementary Figure 3, B, available online). Site-specific cancer-related mortality was 0.82 (95% CI = 0.52 to 1.28) and 1.09 (95% CI = 0.92 to 1.30) for colon cancer and rectal cancer, respectively, among these patients (Figure 2, A). Additionally, 2 studies respectively reported the CRC-specific mortality (unadjusted HR = 1.76, 95% CI = 1.09 to 2.83) (35) and overall mortality (adjusted HR = 1.05, 95% CI = 0.63 to 1.74) (17) among those taking aspirin only before CRC diagnosis (timing 3).

For continued users (timing 4) (15-17,29,33,41,47,50), there was a statistically significant association between aspirin use and improvement in both CRC-specific mortality (pooled RR = 0.76, 95% CI = 0.70 to 0.81; $I^2 = 0\%$) and all-cause mortality (pooled RR = 0.83, 95% CI = 0.74 to 0.93; $I^2 = 83.3\%$) (Table 2; Supplementary Figure 4, available online). In subgroup analysis, continued use of aspirin was associated with lower cancer-specific mortality in colon cancer patients (pooled RR = 0.66, 95% CI = 0.53 to 0.82; $I^2 = 11.7\%$) but not rectal cancer patients (pooled RR = 0.75, 95% CI = 0.34 to 1.64; $I^2 = 61.0\%$) (Figure 2, A), whereas all-cause mortality was not modified by continued aspirin use regarding separate tumor site (colon cancer RR = 0.70, 95% CI = 0.44 to 1.12; rectal cancer RR = 0.75, 95% CI = 0.54 to 1.02) (Figure 2, B).

Postdiagnosis use of aspirin (timing 5) was associated with improved all-cause mortality (pooled RR = 0.80, 95% CI = 0.69 to 0.94; $I^2 = 84.4\%$) but not CRC-specific mortality (pooled RR = 0.89, 95% CI = 0.73 to 1.08; $I^2 = 75.0\%$) (Table 2; Supplementary Figure 5, available online). For those diagnosed in stage I-III, aspirin use also did not show an improved trend regarding cancer-specific death (pooled RR = 0.66, 95% CI = 0.43 to 1.00; $I^2 = 36.2\%$) (Figure 2, A). Stratifying by tumor anatomical site, pooled risk ratio for cancer-specific death was 0.88 (95% CI = 0.79 to 0.99) and for overall death was 0.60 (95% CI = 0.50 to 0.72) among

Table 1. Baseline characteristics of included studies

Study	Country	Study design	Cancer type	Sample size	Age at CRC diagnosis, y	Stage (AJCC/Duke)	Follow-up duration, y	Outcome indicators	Dose-response	Duration-response
Chan AT et al. 2009 (29)	US	Cohort study (NHS/HPFS)	CRC	1279[a]	NA	I-III	Median = 11.8	CRC-specific mortality, overall mortality	0.5-5 tablets/wk, ≥6 tablets/wk	—
Zell JA et al. 2009 (30)	US	Cohort study (CTS)	CRC	621[b]	NA	I-IV	Median = 2.8; mean = 3.4	CRC-specific mortality, overall mortality	—	<5y, ≥5y
Din FV et al. 2010 (31)	UK	Case-control study (SOCCS)	CRC	2063[a]	Mean = 62.2	NA	NA	CRC-specific mortality, all-cause mortality	—	—
Coghill AE et al. 2011 (14)	US	Cohort study	CRC[d]	1737[a]	NA	I-IV	Mean = 8	CRC-specific mortality	—	—
Bastiaannet E et al. 2012 (15)	Netherland	Cohort study	CRC[d]	4481[a]	Median = 69	I-IV	Median = 3.5	Overall survival	—	—
Liao X et al. 2012 (18)	US	Cohort study (NHS/HPFS)	CRC	964[a]	Mean = 68	I-IV	Median = 12.7	CRC-specific mortality, overall mortality	—	—
Reimers MS et al. 2012 (32)	Netherland	Cohort study	CRC	536[a]	Median = 77.6	I-IV	NA	Overall survival	—	—
Walker AJ et al. 2012 (33)	UK	Cohort study	CRC	13 944[a]	User, mean = 68.3; Nonuser, mean = 74.5	I-IV	NA	All-cause mortality	Prophylaxis dose, high dose	0-5y, 5-10y, >10y
Chae YK et al. 2013 (51)[c]	US	Cohort study	CRC	243[a]	Mean = 58	NA	NA	All-cause mortality	—	—
Domingo E et al. 2013 (19)	UK	Cohort study (VICTOR trial)	CRC	896[a]	Median = 64.6	II-III	Median = 5.1	Overall survival, RFS	—	—
McCowan C et al. 2013 (34)	UK	Cohort study	CRC[d]	2990[a]	Median = 73	Duke A-D	NA	CRC-specific mortality, all-cause mortality	—	—
Sun R et al. 2013 (52)[c]	US	Cohort study (NHS/HPFS)	CRC	931[a]	NA	I-IV	NA	CRC-specific mortality	—	—
Cardwell CR et al. 2014 (16)	UK	Nested case-control study	CRC[d]	4794[a]	NA	I-IV	NA	CRC-specific mortality, all-cause mortality	—	<1y, ≥1y
Goh CH et al. 2014 (35)	Singapore	Cohort study	CRC	726[a]	Median = 65	I-III	NA	CRC-specific mortality, RFS	—	—
Reimers MS et al. 2014 (20)	Netherland	Cohort study	CC	999[a]	NA	I-IV	NA	Overall survival	—	—
Kothari N et al. 2015 (36)	Australia	Cohort study	CRC	185[a]	Median = 72	I-IV	Median = 4.5	Cancer-specific survival, overall survival	—	—
Ng K et al. 2015 (37)	US	Cohort study (CALGB89803 trial)	CC	799[a]	NA	III	Median = 6.5	Overall survival, RFS, DFS	—	—

(continued)

Table 1. (continued)

Study	Country	Study design	Cancer type	Sample size	Age at CRC diagnosis, y	Stage (AJCC/Duke)	Follow-up duration, y	Outcome indicators	Dose-response	Duration-response
Restivo A et al. 2015 (38)	Italy	Cohort study	RC	241[a]	Median = 65	II-III	Median = 3.08	Overall survival, PFS	—	—
Zanders MM et al. 2015 (39)	Netherland	Cohort study	CRC[d]	1043[a]	Mean = 73.2	I-IV	Mean = 3.4	All-cause mortality	—	—
Babic A et al. 2016 (40)	US	Cohort study (NHS/HPFS)	CRC	544[a]	NA	I-IV	NA	Overall mortality	—	—
Bains SJ et al. 2016 (41)	Norway	Cohort study	CRC[d]	23162[a]	Mean = 71.5	I-IV	Median = 3	Cancer-specific survival, overall survival	—	—
Frouws MA et al. 2017 (42)	Netherland	Cohort study	CRC	6335[a]	NA	I-IV	NA	Overall survival	—	—
Frouws MA et al. 2017 (43)	Netherland	Cohort study	CRC	7006[a]	NA	I-IV	NA	Overall survival	—	—
Frouws MA et al. 2017 (44)	Netherland	Cohort study	CRC	599[a]	NA	I-IV	NA	Overall survival	—	—
Giampieri R et al. 2017 (45)	Italy	Cohort study	CRC	66[a]	NA	NA	NA	Overall survival, PFS, disease control rate	—	—
Gray RT et al. 2017 (21)	Northern Ireland	Cohort study	CC	740[a]	NA	II-III	Mean = 5.7	Cancer-specific survival, overall survival	—	—
Hamada T et al. 2017 (22)	US	Cohort study (NHS/HPFS)	CRC	617[a]	Mean = 68.6	I-IV	Median = 11.5	Cancer-specific survival, overall survival	—	—
Hua XW et al. 2017 (17)	US	Cohort study	CRC	2419[a]	Mean = 54	I-IV	Median = 10.8	Cancer-specific survival, overall survival	—	≤3 y, >3 y
Murphy C et al. 2017 (46)	Australia	Cohort study	CC	488[a]	Median = 72	II	NA	Overall survival, RFS	—	—
Gray RT et al. 2018 (47)	Northern Ireland	Cohort study	CRC[d]	8391[a]	NA	Dukes A-C	Median = 3.6	CRC-specific survival, overall survival	1-365 daily defined dose, >365 daily defined dose	—
Rouette J et al. 2018 (53)[c]	Canada	Cohort study	CRC	7478[a]	NA	NA	NA	All-cause mortality	—	—
Tsoi KK et al. 2018 (48)	China	Case-control study	CRC[d]	612 509[a]	NA	NA	NA	CRC-specific mortality, all-cause mortality, GIB/CVD/CBVD-related mortality	—	—
Ventura L et al. 2018 (49)	Italy	Cohort study	CRC[d]	22 7011[a]	NA	NA	NA	CRC-specific mortality, all-cause mortality, CVD/major bleeding-related mortality	—	—

(continued)

Table 1. (continued)

Study	Country	Study design	Cancer type	Sample size	Age at CRC diagnosis, y	Stage (AJCC/Duke)	Follow-up duration, y	Outcome indicators	Dose-response	Duration-response
Sung JJY et al. 2019 (50)	China	Cohort study	CRC[d]	13 528[a]	NA	NA	NA	CRC-specific mortality, all-cause mortality, CVD/CBVD-related mortality	—	—

[a]Participants were both male and female. AJCC = American Joint Committee on Cancer; CBVD = cerebrovascular diseases ; CC = colon cancer; CRC = colorectal cancer; CTS = California Teachers Study; CVD = cardiovascular diseases; DFS = disease-free survival; GIB = gastrointestinal bleeding; HPFS = Health Professionals Follow-up Study; NA = not available; NHS = Nurses' Health Study; PFS = progression-free survival; RC = rectal cancer; RFS = recurrence-free survival; SOCCS = Study of Colorectal Cancer in Scotland .

[b]Participants were female only.

[c]Conference abstract only.

[d]Studies report the subgroup result regarding the anatomical site of CRC (CC and RC).

Note: "—" represents data not available.

colon cancer patients, and no statistical association was observed in patients with rectal cancer (cancer-specific mortality: 1.00, 95% CI = 0.83 to 1.20; overall mortality: 0.54, 95% CI = 0.22 to 1.30) (Figure 2). For those taking aspirin after diagnose regardless of its usage before diagnosis (timing 6), statistical association regarding CRC-specific mortality (pooled RR = 0.80, 95% CI = 0.66 to 0.97; I^2 = 84.8%) or all-cause mortality (pooled RR = 0.87, 95% CI = 0.77 to 0.98; I^2 = 85.1%) (Table 2; Supplementary Figure 6, available online) was observed. Further analysis of site-specific cancer outcome showed no association with aspirin use among these patients (Figure 2).

In terms of molecular biomarkers in predicting the adjunctive function of aspirin, only 4 studies (18-20,29) targeting *PIK3CA* or *COX2* were available to pool the estimates. Meta-analysis showed that aspirin use after diagnosis irrespective of its usage before diagnosis was associated with improved all-cause mortality among patients with tumor *PIK3CA* mutation (pooled RR = 0.58, 95% CI = 0.37 to 0.9) or *COX2* overexpression (pooled RR = 0.65, 95% CI = 0.50 to 0.85) (Figure 2, B).

Furthermore, sensitivity analysis was performed to test the robustness of this relationship. We first assessed the effect of study design on the pooled estimate. The results revealed that pooled relative risk was not disturbed by the stratification of study design (Table 2). The influence of study design on pooled estimates was not evaluated in subgroup analysis because of the small number of included studies. Omitting each study iteratively was then performed. It was found that the stability was affected by exclusion of a particular study in assessing the relation between postdiagnosis use (timing 5) or aspirin use after diagnosis irrespective of its use before diagnosis (timing 6) and CRC survival. The detailed results are listed in Table 3. For publication bias test, it was only tested in primary outcome analysis but not in subgroup analysis because of their limited number of available studies. No small study effect existed in each analysis (Table 2).

Discussion

This updated comprehensive systematic review and meta-analysis suggests that continued aspirin use is associated with lower cancer-specific and overall mortality, and postdiagnosis use is only associated with reduced overall mortality. In addition, the association between aspirin use and lower mortality seems to be more pronounced in tumors with *PIK3CA* mutation or *COX2* overexpression. Thus, our data support the hypothesis that aspirin might be served as an adjuvant agent to treat CRC.

Optimizing the timing of aspirin use as an adjuvant treatment is clinically important. Our data first suggest that exposure of aspirin before and after CRC diagnosis is associated with reduced 24% cancer-specific mortality and 17% all-cause mortality. One explanation may be that patients who were exposed to aspirin prior to CRC development were more likely to have CRC in a less advanced stage and with less aggressive properties (41,54). Postdiagnosis use, which is most clinically relevant when considering recommendations for CRC treatment, was associated only with reduced 20% overall mortality. Notably, the observed benefit in overall mortality may be partially due to an improvement in cardiovascular-related mortality, because cancers increase the risk of some specific cardiovascular diseases such as thromboembolism (55). Thus, the improvement in overall mortality for aspirin use is less sensitive regarding its antitumor effect. In this way, those who take aspirin for heart disease reasons or for other indications might enjoy additional benefit

Table 2. Timing of aspirin use and CRC patients' mortality[a]

	CRC-specific mortality						All-cause mortality					
	Random-effect model		Test of heterogeneity		Test of publication bias		Random-dffect model		Test of heterogeneity		Test of publication bias	
Timing of aspirin use[b]	No. of studies	RR (95% CI)	I^2, %	P	Begg P	Egger P	No. of studies	RR (95% CI)	I^2, %	P	Begg P	Egger P
Timing 1												
All studies	3	0.59 (0.57 to 0.62)	0.0	.38	1.00	.10	6	1.10 (0.93 to 1.29)	94.8	<.001	1.00	.09
Cohort studies	2	0.70 (0.55 to 0.89)	0.0	.91	—	—	5	0.97 (0.76 to 1.24)	73.0	.005	—	—
Case-control studies	1	0.59 (0.56 to 0.62)	—	—	—	—	1	1.43 (1.42 to 1.44)	—	—	—	—
Timing 2												
All studies	6	0.91 (0.79 to 1.05)	60.0	.04	.46	.14	5	0.87 (0.57 to 1.31)	96.1	<.001	.71	.88
Cohort studies	4	0.81 (0.64 to 1.02)	66.1	.05	—	—	4	0.82 (0.51 to 1.33)	96.5	<.001	—	—
Case-control studies	2	1.03 (0.92 to 1.15)	0.0	1.00	—	—	1	1.12 (0.90 to 1.39)	—	—	—	—
Timing 3												
All studies	1	1.76 (1.09 to 2.83)	—	—	—	—	1	1.05 (0.63 to 1.74)	—	—	—	—
Cohort studies	1	1.76 (1.09 to 2.83)	—	—	—	—	1	1.05 (0.63 to 1.74)	—	—	—	—
Case-control studies	0	—	—	—	—	—	0	—	—	—	—	—
Timing 4												
All studies	6	0.76 (0.70 to 0.81)	0.0	.67	.71	.59	7	0.83 (0.74 to 0.93)	83.3	<.001	.37	.90
Cohort studies	5	0.76 (0.70 to 0.81)	0.0	.53	—	—	7	0.83 (0.74 to 0.93)	83.3	<.001	—	—
Case-control studies	1	0.72 (0.44 to 1.18)	—	—	—	—	0	—	—	—	—	—
Timing 5												
All studies	7	0.89 (0.73 to 1.08)	75.0	.001	.55	.63	11	0.80 (0.69 to 0.94)	84.4	<.001	.16	.10
Cohort studies	6	0.87 (0.70 to 1.10)	79.1	<.001	—	—	11	0.80 (0.69 to 0.94)	84.4	<.001	—	—
Case-control studies	1	0.95 (0.69 to 1.32)	—	—	—	—	0	—	—	—	—	—
Timing 6												
All studies	7	0.80 (0.66 to 0.97)	84.8	<.001	.76	.38	9	0.87 (0.77 to 0.98)	85.1	<.001	.25	.17
Cohort studies	6	0.75 (0.59 to 0.94)	84.8	<.001	—	—	8	0.84 (0.73 to 0.96)	85.6	<.001	—	—
Case-control studies	1	1.06 (0.92 to 1.24)	—	—	—	—	1	1.06 (0.94 to 1.19)	—	—	—	—

[a]All statistical tests were 2-sided. CI = confidence interval; CRC= colorectal cancer; RR= risk ratio. "—" represents data not available.
[b]Timing 1 = ever-use; timing 2 = prediagnosis use; timing 3 = aspirin use only before diagnosis; timing 4 = continued use; timing 5 = postdiagnosis use; timing 6 = aspirin use after diagnosis regardless of its usage before diagnosis.

from adjunctive aspirin therapy once they develop CRC. Our analysis did not obtain robust results for those who take aspirin after diagnosis irrespective of its usage before diagnosis, which was not in line with previous reports presented by Ye et al. (23) and Li et al. (24). These results support that aspirin use before diagnosis might be one of the key confounders when assessing the association between aspirin use and patients' survival. No evidence of an association between prediagnosis aspirin use and improved patients' survival was observed in our analysis and previous study (CRC-specific mortality: pooled HR = 0.93, 95% CI = 0.82 to 1.05; overall mortality: pooled HR = 1.10, 95% CI = 0.96 to 1.06) (24).

CRC is a heterogeneous disease with different molecular characteristics that would lead to different response to therapy, and adverse events of aspirin use (such as bleeding) are concerning in clinical practice. Thus, molecular biomarkers are needed to better identify individuals deriving a benefit from aspirin. The present meta-analysis noted a protective association for aspirin with all-cause mortality in PIK3CA-mutant (reduced by 10%) or COX2-overexpressed (reduced by 15%) tumors, which is consistent with the previous studies (23,24,56). PIK3CA mutation that frequently results in activated PI3K-signaling pathway is present in about 15%-20% of CRC (57). Activation of PI3K enhances COX2 activity and prostaglandin E_2 synthesis, resulting in inhibition of apoptosis in CRC. Upregulated COX2 expression is common in about 70% CRC, and high expression predicts poor prognosis of CRC (58). Thus, aspirin use can inhibit the 2 targets to induce apoptosis of CRC cells. However, it should be

noted that whether the adjuvant efficacy of aspirin use after diagnosis in relation to mortality is dependent in its usage before diagnosis or is different in anatomical site of tumor for these 2 targets is not determined because of the limited information. Except for these 2 targets, studies also indicated that CTNNB1 (gene encoding β-catenin) (52), BRAF or KRAS mutation status (44), and CD724 (also known as PD-L1) expression (22) might be candidate molecular biomarkers for the personalized use of aspirin in CRC patients. Of them, KRAS and BRAF are currently used in the precision treatment (59), and a prospective study also demonstrated that regular use of aspirin was associated with risk reduction of CRC without BRAF mutation (60,61). However, among these studies, the number of participants is limited, so the results might be less definitive. Therefore, the prospective trials of aspirin as an adjuvant therapy in specific molecular subtype with large sample size are warranted.

Questions still remain about the optimal dose and duration of aspirin use for secondary prevention. Available individual studies did not suggest potential dose-dependent association of aspirin use and CRC prognosis (29,33), whereas the most recent meta-analysis has confirmed that the favorable effect of aspirin tended to increase with longer duration of use and increasing dose for primary prevention of CRC incidence (3). In addition, only 2 ongoing trials assessed dose-dependent relation: 100 mg vs 200 mg (NCT02607072) or 100 mg vs 300 mg (NCT02804815). Duration-dependent response was only reported in 4 studies with different time spans (16,17,30,33). Hua and colleagues (17) found that compared with those taking aspirin for less than
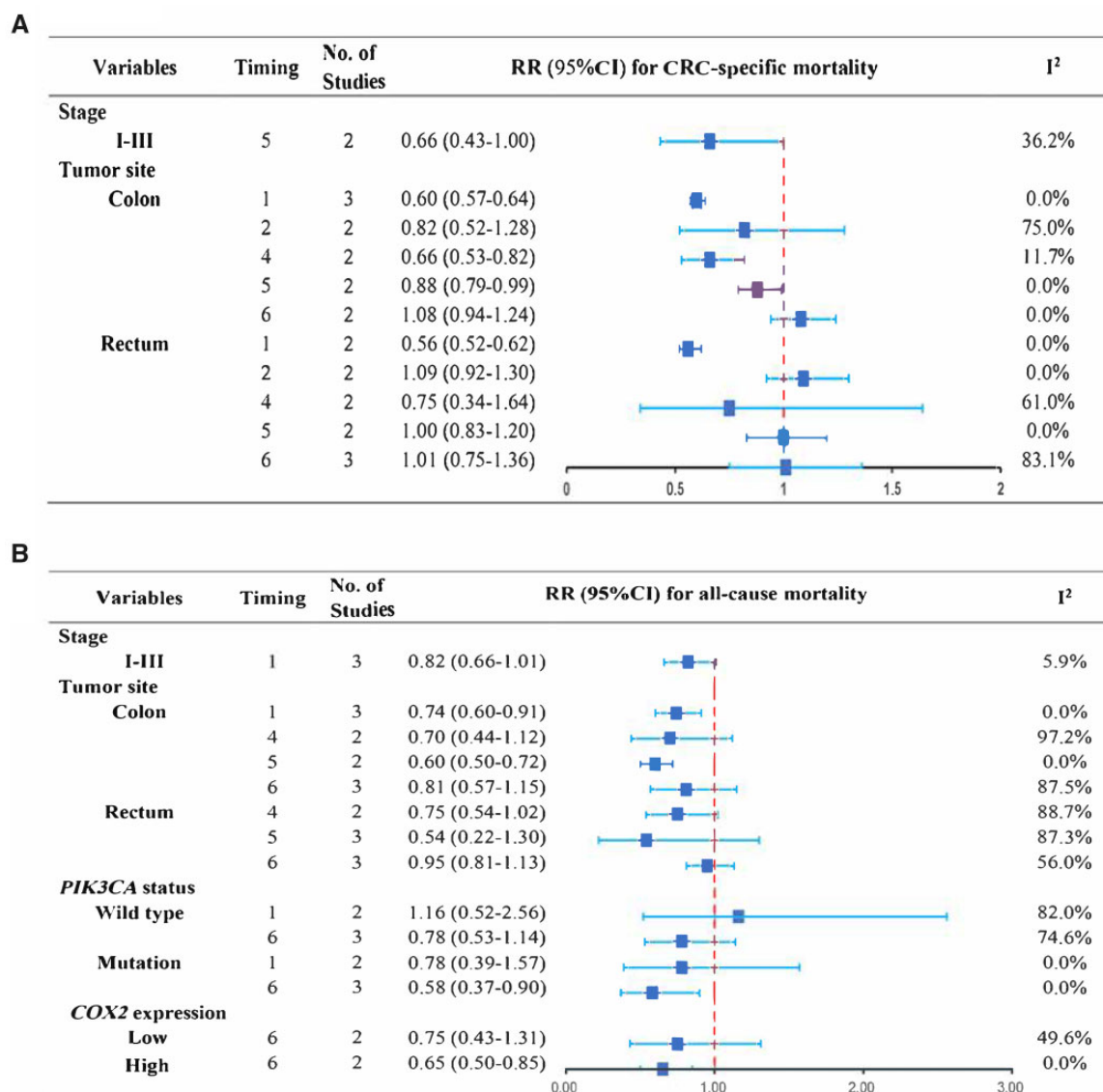
A

Variables	Timing	No. of Studies	RR (95%CI) for CRC-specific mortality	I²
Stage				
I-III	5	2	0.66 (0.43-1.00)	36.2%
Tumor site				
Colon	1	3	0.60 (0.57-0.64)	0.0%
	2	2	0.82 (0.52-1.28)	75.0%
	4	2	0.66 (0.53-0.82)	11.7%
	5	2	0.88 (0.79-0.99)	0.0%
	6	2	1.08 (0.94-1.24)	0.0%
Rectum	1	2	0.56 (0.52-0.62)	0.0%
	2	2	1.09 (0.92-1.30)	0.0%
	4	2	0.75 (0.34-1.64)	61.0%
	5	2	1.00 (0.83-1.20)	0.0%
	6	3	1.01 (0.75-1.36)	83.1%

B

Variables	Timing	No. of Studies	RR (95%CI) for all-cause mortality	I²
Stage				
I-III	1	3	0.82 (0.66-1.01)	5.9%
Tumor site				
Colon	1	3	0.74 (0.60-0.91)	0.0%
	4	2	0.70 (0.44-1.12)	97.2%
	5	2	0.60 (0.50-0.72)	0.0%
	6	3	0.81 (0.57-1.15)	87.5%
Rectum	4	2	0.75 (0.54-1.02)	88.7%
	5	3	0.54 (0.22-1.30)	87.3%
	6	3	0.95 (0.81-1.13)	56.0%
PIK3CA status				
Wild type	1	2	1.16 (0.52-2.56)	82.0%
	6	3	0.78 (0.53-1.14)	74.6%
Mutation	1	2	0.78 (0.39-1.57)	0.0%
	6	3	0.58 (0.37-0.90)	0.0%
COX2 expression				
Low	6	2	0.75 (0.43-1.31)	49.6%
High	6	2	0.65 (0.50-0.85)	0.0%

Figure 2. Subgroup analysis of aspirin use in relation to CRC mortality. **A)** Different timing of aspirin use in relation to CRC-specific mortality regarding clinical stage and tumor site. **B)** Different timing of aspirin use in relation to all-cause mortality with regard to tumor stage, tumor site, and molecular markers (*PIK3CA* status and *COX2* expression). Timing definitions: 1 = ever-use; 2 = prediagnosis use; 3 = aspirin use only before diagnosis; 4 = continued use; 5 = postdiagnosis use; 6 = aspirin use after diagnosis regardless of its use before diagnosis. The error bars represent the 95% CI of pooled effect. CI = confidence interval; CRC = colorectal cancer; RR = risk ratio.

3 years, postdiagnosis or continued use for more than 3 years had lower mortality (all-cause mortality: 0.71, 95% CI = 0.52 to 0.94; CRC-specific mortality: 0.26, 95% CI = 0.11 to 0.61), whereas Walker et al. (33) suggested aspirin might be beneficial in reducing CRC mortality during the first 5 years. This might be one of the reasons that most of the current ongoing trials adopt 3 years or 5 years as the duration of adjunctive aspirin therapy (Supplementary Table 1, available online). On the other hand, CRC often recurs in the first 3 years after surgery, so there is likely to be diminishing benefit after 3 years, and at some point (maybe 5 years), the risks might exceed the benefits from aspirin. Based on this available evidence, it is insufficient to make a speculation that the adjuvant effect of aspirin use in relation to CRC mortality would be a dose- or duration-dependent manner.

In addition to the factors we discussed above, some important factors that were closely associated with CRC mortality should be considered when interpreting the results. CRC screening is considered a primary way to control this disease; numerous studies have demonstrated the significant effect of fecal occult blood test or coloscopy screening on reducing CRC mortality (62). But few observational studies considered these variables in multivariate analysis, although 1 study considering this issue showed that the reduction of CRC mortality was not attributable to a higher CRC screening participation in aspirin users (49). Moreover, regular aspirin use may increase the risk of bleeding events especially among elderly patients, which might prompt more frequent interactions with the medical system. Thus, individuals with incident CRC might be detected earlier resulting in a better prognosis. Additionally, lifestyle (such as diet preference, physical activity) and other modifiable factors (such as smoking, body mass index) during aspirin use should be taken into account, although some studies adjusted certain factors in multivariable Cox analysis as we summarized in Supplementary Table 2 (available online). Taken together, for

Table 3. Sensitivity analysis of different timing of aspirin use in relation to CRC mortality

Timing[a]	Study	RR (95% CI)
Timing 1		
CRC-specific mortality	Gray RT et al. 2017 (21)	0.61 (0.53 to 0.69)
	Tsoi KK et al. 2018 (48)	0.70 (0.56 to 0.89)
	Ventura L et al. 2018 (49)	0.59 (0.56 to 0.62)
All-cause mortality	Chae YK et al. 2013 (51)	1.08 (0.92 to 1.28)
	Ng K et al. 2015 (37)	1.14 (0.97 to 1.35)
	Zanders MM et al. 2015 (39)	1.13 (0.95 to 1.35)
	Gray RT et al. 2017 (21)	1.18 (1.00 to 1.39)
	Tsoi KK et al. 2018 (48)	0.97 (0.76 to 1.24)
	Ventura L et al. 2018 (49)	1.00 (0.71 to 1.42)
Timing 2		
CRC-specific mortality	Zell JA et al. 2009 (30)	0.95 (0.84 to 1.07)
	Din FV et al. 2010 (31)	0.88 (0.74 to 1.05)
	Coghill AE et al. 2011 (14)	0.96 (0.84 to 1.10)
	McCowan C et al. 2013 (34)	0.88 (0.72 to 1.08)
	Cardwell CR et al. 2014 (16)	0.86 (0.72 to 1.04)
All-cause mortality	Zell JA et al. 2009 (30)	0.89 (0.54 to 1.45)
	Din FV et al. 2010 (31)	0.81 (0.49 to 1.33)
	McCowan C et al. 2013 (34)	0.83 (0.49 to 1.43)
	Frouws MA et al. 2017 (43)	0.99 (0.87 to 1.13)
	Murphy C et al. 2017 (46)	0.81 (0.51 to 1.28)
	Rouette J et al. 2018 (53)	0.83 (0.53 to 1.31)
Timing 4		
CRC-specific mortality	Chan AT et al. 2009 (29)	0.75 (0.70 to 0.81)
	Cardwell CR et al. 2014 (16)	0.76 (0.70 to 0.81)
	Bains SJ et al. 2016 (41)	0.72 (0.64 to 0.82)
	Hua XW et al. 2017 (17)	0.76 (0.70 to 0.81)
	Gray RT et al. 2018 (47)	0.75 (0.70 to 0.81)
	Sung JJY et al. 2019 (50)	0.77 (0.71 to 0.84)
All-cause mortality	Chan AT et al. 2009 (29)	0.81 (0.72 to 0.92)
	Bastiaannet E et al. 2012 (15)	0.82 (0.70 to 0.95)
	Walker AJ et al. 2012 (33)	0.82 (0.72 to 0.94)
	Bains SJ et al. 2016 (41)	0.82 (0.70 to 0.97)
	Hua XW et al. 2017 (17)	0.82 (0.73 to 0.93)
	Gray RT et al. 2018 (47)	0.82 (0.72 to 0.93)
	Sung JJY et al. 2019 (50)	0.87 (0.83 to 0.91)
Timing 5		
CRC-specific mortality	Chan AT et al. 2009 (29)	0.95 (0.78 to 1.14)
	Cardwell CR et al. 2014 (16)	0.88 (0.70 to 1.09)
	Goh CH et al. 2014 (35)	0.90 (0.73 to 1.11)
	Bains SJ et al. 2016 (41)	0.84 (0.63 to 1.11)
	Hua XW et al. 2017 (17)	0.94 (0.79 to 1.13)
	Gray RT et al. 2018 (47)	0.84 (0.71 to 0.99)
	Sung JJY et al. 2019 (50)	0.86 (0.65 to 1.15)
All-cause mortality	Chan AT et al. 2009 (29)	0.82 (0.69 to 0.96)
	Bastiaannet E et al. 2012 (15)	0.80 (0.68 to 0.96)
	Reimers MS et al. 2012 (32)	0.83 (0.71 to 0.97)
	Walker AJ et al. 2012 (33)	0.78 (0.65 to 0.93)
	Restivo A et al. 2015 (38)	0.82 (0.70 to 0.95)
	Bains SJ et al. 2016 (41)	0.77 (0.64 to 0.92)
	Frouws MA et al. 2017 (44)	0.82 (0.70 to 0.97)
	Giampieri R et al. 2017 (45)	0.84 (0.72 to 0.98)
	Hua XW et al. 2017 (17)	0.82 (0.70 to 0.97)
	Gray RT et al. 2018 (47)	0.76 (0.65 to 0.88)
	Sung JJY et al. 2019 (50)	0.77 (0.63 to 0.95)
Timing 6		
CRC-specific mortality	Chan AT et al. 2009 (29)	0.82 (0.66 to 1.01)
	McCowan C et al. 2013 (34)	0.86 (0.71 to 1.04)
	Cardwell CR et al. 2014 (16)	0.75 (0.60 to 0.94)
	Bains SJ et al. 2016 (41)	0.77 (0.58 to 1.02)
	Hamada T et al. 2017 (22)	0.82 (0.66 to 1.00)
	Hua XW et al. 2017 (17)	0.84 (0.70 to 1.02)

(continued)

Table 3. (continued)

Timing[a]	Study	RR (95% CI)
All-cause mortality	Gray RT et al. 2018 (47)	0.74 (0.61 to 0.91)
	Chan AT et al. 2009 (29)	0.87 (0.77 to 0.99)
	Walker AJ et al. 2012 (33)	0.85 (0.74 to 0.99)
	McCowan C et al. 2013 (34)	0.90 (0.80 to 1.01)
	Cardwell CR et al. 2014 (16)	0.84 (0.73 to 0.96)
	Reimers MS et al. 2014 (20)	0.89 (0.79 to 1.00)
	Bains SJ et al. 2016 (41)	0.84 (0.72 to 0.99)
	Hamada T et al. 2017 (22)	0.87 (0.77 to 0.99)
	Hua XW et al. 2017 (17)	0.88 (0.77 to 1.00)
	Gray RT et al. 2018 (47)	0.82 (0.74 to 0.93)

[a]Timing 1 = ever-use; timing 2 = prediagnosis use; timing 4 = continued use; timing 5 = postdiagnosis use; timing 6 = aspirin use after diagnosis regardless of its usage before diagnosis. CI = confidence interval; CRC = colorectal cancer; RR = risk ratio.

future studies, screening and preventive health behaviors of individuals should not be neglectable in study design.

The molecular mechanisms underlying the synergistic anticancer effect of aspirin are still incompletely understood. Biologically, this might be attributed to the induction of apoptosis via COX-dependent or COX-independent pathway (8), reduction of metastatic risk through disrupting platelet-circulating cancer cell interaction (54,63,64) or modulation of antitumor immune response (65). Eventually, aspirin may have more than 1 target and probably acts in different ways as an adjunctive agent.

The strength of our study lies in the comprehensive inclusion of all observational studies concerning the relationship between different timing of aspirin use and the mortality of CRC patients. We also present all available evidence in a systematic and unbiased fashion; however, limitations may exist when the findings are interpreted. First, for many of the pooled estimates, there was substantial between-study heterogeneity. It was likely because of differences in study population, distribution of tumor stages at entry, aspirin dose and duration, other medications (mainly including nonaspirin NSAIDs, metformin, statin), and the adjusted covariates across individual studies (Supplementary Table 2, available online). Second, inherent biases of observational studies cannot be ignored, such as selection bias and information bias which could lead to exaggeration or underestimation of survival benefit estimates. Meanwhile, causal interpretations of the estimates measures of association cannot be made, because findings from this study are based on observational data. Third, most of the studies were conducted in the United States or in European countries. This may make generalization of the findings to the patients in other ethnicities and geographical regions uncertain. Moreover, it is noteworthy that some estimates in subgroup analysis should be cautiously interpreted, because certain subgroup analysis is based on a limited number of studies. In addition, cancer-specific mortality was lacking in certain subgroup analyses, which may weaken the conclusion, because overall survival is less sensitive regarding antitumor effect and may be subject to dilution of any real effect.

In conclusion, based on best available evidence, the updated comprehensive systematic review and meta-analysis suggests that persistent aspirin use prior to and after CRC diagnosis has the most advantage with respect to cancer-specific mortality and overall mortality. Stratifying by tumor site and certain molecular markers further demonstrates that patients with colon cancer or CRC with *PIK3CA* mutation and *COX2* expression might be candidates for aspirin use as an adjuvant therapy. Therefore, the current ongoing randomized clinical trials are highly warranted to determine the clinical efficacy of this findings. In addition, adequately powered mechanistic research is also needed to help elucidate the mechanism underlying this correlation.

Funding

Notes

Data Availability

The data supporting the findings of this study are available in the article and in its online supplementary materials .

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