Relationship between aspirin use of esophageal, gastric and colorectal cancer patient survival: a meta-analysis

Juli Lin  
Xiehe Affiliated Hospital of Fujian Medical University

Jian-xian Lin  
Xiehe Affiliated Hospital of Fujian Medical University

Chao-hui Zheng  
Xiehe Affiliated Hospital of Fujian Medical University

Ping Li  
Xiehe Affiliated Hospital of Fujian Medical University

Jian-wei Xie  
Xiehe Affiliated Hospital of Fujian Medical University

Jia-bin Wang  
Xiehe Affiliated Hospital of Fujian Medical University

Jun Lu  
Xiehe Affiliated Hospital of Fujian Medical University

Qi-yue Chen  
Xiehe Affiliated Hospital of Fujian Medical University

Long-Long Cao  
Xiehe Affiliated Hospital of Fujian Medical University

Mi Lin  
Xiehe Affiliated Hospital of Fujian Medical University

Chang-ming Huang (hcmlr2002@163.com)  
Fujian Medical University Union Hospital  
https://orcid.org/0000-0002-0019-885X

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Abstract

Background: Many studies have found that use of aspirin can lengthen survival in patients with gastrointestinal cancer. The aim of this study was to assess the survival benefit of aspirin use compared with non-aspirin use for patients with esophageal, gastric or colorectal cancer.

Methods: We searched online databases, including PubMed, the Cochrane Library, Embase and www.clinicaltrials.gov for studies that were conducted, before April 30th, 2020, to identify relevant studies. Overall survival and cancer-specific survival of esophageal, gastric and colorectal cancers among aspirin users were compared with those among non-aspirin users. Data extraction and quality evaluation were independently conducted by 2 investigators. A meta-analysis was performed to calculate the pooled risk ratios (RRs) for overall survival and cancer-specific survival by using either a fixed-effects model or a random-effects model.

Results: A total of 18 studies were included in this meta-analysis, with more than 74,936 patients. There were no significant differences between postdiagnosis aspirin use and overall survival for esophageal and gastric cancers. For colorectal cancer, a benefit that was associated with postdiagnosis aspirin use was observed for overall survival and cancer-specific survival [HR= 0.83, 95%CI(0.75, 0.9)];[HR= 0.78, 95%CI(0.66, 0.92)], respectively. However, a prediagnosis of aspirin use did not provide a benefit for overall or cancer-specific survival in colorectal cancer. HR values for overall and cancer-specific survival benefits for colorectal cancer associated with both prediagnosis and postdiagnosis aspirin were as follows: HR=0.75%95%CI(0.61, 0.92) and HR=0.78, 95%CI(0.73, 0.85), respectively. In addition, the survival benefit of postdiagnosis aspirin use appeared to be confined to patients with mutated PIK3CA tumors [HR= 0.78, 95%CI(0.50, 0.99)] and was positive for PTGS2 (COX-2) expression [HR= 0.75, 95%CI(0.43, 1.30)].

Conclusions: These findings provide further indications that postdiagnosis aspirin use improves overall survival and cancer-specific survival in colorectal cancer, especially for patients who are positive for PTGS2 (COX-2) expression and PIK3CA-mutated tumors. However, aspirin therapy does not improve overall survival in esophageal and gastric cancers, although the meta-analysis was mainly limited to retrospective studies.

Background

Esophageal, gastric and colorectal cancers are the most common cancers of the digestive tract1. Many factors, including old age and poor living habits, are risk factors for gastrointestinal malignancies. Although the incidence and mortality of gastrointestinal malignancies have been reduced in recent years, the comprehensive treatment of gastrointestinal malignancies has progressed slowly in recent decades. Therefore, it is urgent to discover a more effective comprehensive treatment for gastrointestinal malignancies. Aspirin is a nonselective cyclooxygenase inhibitor with strong antipyretic and analgesic effects and is widely used for its anti-inflammatory and anti-rheumatic properties. For example, small doses of aspirin are used to prevent the onset of cardiovascular disease, cerebrovascular disease and transient ischemic attacks. In recent years, many studies2-7 have found that aspirin also has anticancer effects. However, as there are still some controversy about these studies, the aim of this study was to assess the survival benefits of aspirin use (compared with non-aspirin use) for esophageal, gastric and colorectal cancer patients through the use of a meta-analysis.

Methods

All of the search results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) statement8.
Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) RCTs or observational studies including cohort and case-control studies; (2) the outcomes of interest being defined as OS (overall survival) and CSS (cancer-specific survival) of esophageal, gastric, colorectal, colon or rectal cancer; (3) the study addressing aspirin usage at the times of prediagnosis and/or postdiagnosis of esophageal, gastric, colorectal, colon or rectal cancer; (4) HR or OR estimates with 95% CIs were available. The exclusion criteria were as follows: (1) duplicate articles; (2) inadequate data; and (3) sample sizes less than 20; (4) NOS $\leq 5$

Literature Search

We conducted a comprehensive systematic literature search of online databases, including PubMed, the Cochrane Library, Embase and www.clinicaltrials.gov for studies that were conducted before April 30th, 2020, to identify all RCTs and observational studies. The following key words were used in these literature searches: ('colorectal cancer' or 'colon cancer' or 'rectal cancer' or 'colorectal adenocarcinoma' or 'colon adenocarcinoma' or 'rectal adenocarcinoma') AND ('aspirin' or 'non-steroidal anti-inflammatory drugs' or 'NSAIDS') ('gastric cancer' or 'gastric adenocarcinoma') AND ('aspirin' or 'non-steroidal anti-inflammatory drugs' or 'NSAIDS') ('esophageal cancer' or 'esophageal adenocarcinoma' or 'esophageal squamous cell carcinoma') AND ('aspirin' or 'non-steroidal anti-inflammatory drugs' or 'NSAIDS'). There were no language restrictions. We also reviewed the references of the included articles and the related systematic reviews, in order to identify additional studies.

Study Selection and Quality Assessment

The qualities of the included non-RCTs were assessed by using the Newcastle–Ottawa Scale (NOS)$^9$. The scale utilizes a score system ranging from 0 to 9, and the quality of the observational studies were considered to be high-quality with a score of 5 or higher.

Data Extraction

Data extraction and the evaluation of the quality of the literature were independently conducted by 2 investigators (Ju-li Lin and Jian-xian Lin). At time when there was any uncertainty about the inclusion of a study, the issue was discussed between the two investigators to achieve a resolution. A Microsoft Excel database was employed to record all of the available information, including the baseline details, title, first author's name, year of publication, study design, region, journal, sample size, period of patient recruitment, follow-up time, and HRs.

Statistical Analysis

The Cochran’s Q statistic and $I^2$ statistics were applied to assess the heterogeneity among all of the studies.$^{10}$ For the Q statistic, a $p$ value of less than 0.1 was considered to be statistically significant. When statistical heterogeneity was
detected, the sources of the heterogeneity were explored, and sensitivity analyses were performed. A random-effects model was used if heterogeneity existed; otherwise, the fixed-effect model was used. When possible, subgroup analyses were conducted to assess the potential impacts of the mutation statuses. The cut-off point for quality among observational studies (NOS ≤ 5 vs. NOS >5) was arbitrarily defined. Publication bias was assessed using the Begg and Egger regression asymmetry test, together with funnel plots. All of the statistical analyses were conducted by using STATA, version 13.0 (Stata Corporation, College Station, TX).

Results

1. Retrieved studies and characteristics

According to the previously described search strategy, 3612 citations were obtained from the online database up until April 30th, 2020. A total of 3569 articles were excluded by viewing the titles and abstracts. The full texts of 36 records were read. Ultimately, 18 full-text studies4-7,11-24 were obtained and assessed according to the eligibility criteria, including 1 case-control study and 17 cohort studies, with the studies comprised of more than 74,936 patients. The detailed literature search and screening process are shown in Supplement Figure 1. The characteristics included in the study are shown in Table 1, including the first author's name, year of publication, study design, region, journal, sample size, period of patient recruitment patients, follow-up time and definition of aspirin use.

The qualities of 18 studies was assessed by using NOS; four studies achieved a score of 6, six studies achieved a score of 7 and eight studies achieved a score of 8 (Table 2). Thirteen studies stated a clear follow-up time. The longest median follow-up period was 10.8 years. Six studies reported a clear definition of the use of PPIs. Seven studies compared the risk of gastric cancer between PPI users and non-PPI users. Thirteen studies evaluated the association between prediagnosis aspirin use and colorectal cancer survival. Thirteen studies evaluated the association between postdiagnosis aspirin use and colorectal cancer survival.

2. Association between postdiagnosis aspirin use and survival (OS and CSS) in esophageal and gastric cancers

Three studies (involving 6,797 patients) compared the overall survival of esophageal cancer among aspirin users compared with non-aspirin users. The estimated pooled HRs showed no significant differences between the two groups [HR= 1.00995%CI(0.847, 1.202)] (figure 1A).

Two studies (involving 4,589 patients) compared the overall survival of gastric cancer among aspirin users compared with non-aspirin users, and the estimated pooled HRs indicated no significant differences between the groups [HR= 0.87095%CI(0.470, 1.610)] (figure 1A).

Three studies (involving 11,380 patients) compared the overall survival of upper digestive cancer among aspirin users compared with non-aspirin users, with no significant differences between the two groups based on estimated pooled HRs [HR= 0.83195%CI(0.679, 1.016)] (figure 1A).

One study (involving 946 patients) compared the cancer-specific survival of esophageal cancer among aspirin users with non-aspirin users; based on HRs, the use of aspirin postdiagnosis was associated with longer cancer-specific survival [HR= 0.3495%CI(0.14 , 0.69)] (figure 1B). One study involving 750 patients compared the cancer-specific survival of gastric cancer among aspirin users with non-aspirin users, and the HRs revealed no significant differences between the groups [HR= 0.70, 95% CI (0.29, 1.69)] (figure 1B).

3. Association between postdiagnosis aspirin use and survival (OS and CSS) in colorectal cancer
Ten studies (involving 67,552 patients) compared the overall survival of colorectal cancer among aspirin users compared with non-aspirin users. According to the estimated pooled HRs, the use of aspirin postdiagnosis was associated with longer overall survival [HR = 0.83, 95% CI (0.75, 0.93)] (figure 2A).

The result of cumulative meta-analysis showed that the significant difference supporting PPI use was first found in the latest study in Joseph et al. [HR = 0.89, 95% CI (0.86 – 0.93)], with the CI narrowing and the effect size becoming stable (Figure 2B).

Eight studies (involving 52,662 patients) compared cancer-specific survival in colorectal cancer among aspirin users and non-aspirin users. The estimated pooled HRs showed that the use of aspirin postdiagnosis was associated with longer overall survival [HR = 0.78, 95% CI (0.66, 0.92)] (figure 2C).

The result of cumulative meta-analysis indicated that the significant difference supporting PPI use was first found in the latest study by Joseph et al. [HR = 0.85, 95% CI (0.80 - 0.89], with the CI narrowing and the effect size becoming stable (Figure 2D).

4. Association between prediagnosis aspirin use and survival (OS and CSS) in colorectal cancer

With regard to overall survival in colorectal cancer, five studies involving 6,202 patients compared among aspirin users compared with non-aspirin users. The estimated pooled HRs demonstrated no significant differences between the two groups [HR = 1.01, 95% CI (0.96, 1.06)] (figure 3A).

Five studies (involving 45,101 patients) compared the cancer-specific survival of colorectal cancer among aspirin users compared with non-aspirin users, and according to the estimated pooled HRs, there were no significant differences between the groups [HR = 0.93, 95% CI (0.84, 1.03)] (figure 3B).

5. Association between both prediagnosis and postdiagnosis aspirin use and survival (OS and CSS) in colorectal cancer

Four studies (involving 2,350 patients) compared the overall survival of colorectal cancer among aspirin users compared with non-aspirin users. The estimated pooled HRs revealed that the use of aspirin both prediagnosis and postdiagnosis was associated with longer overall survival [HR = 0.75, 95% CI (0.61, 0.92)] (figure 4A).

Three studies (involving 1,849 patients) compared cancer-specific survival in colorectal cancer among aspirin users compared with non-aspirin users, and the estimated pooled HRs indicated that the use of aspirin both prediagnosis and postdiagnosis was associated with longer overall survival [HR = 0.78, 95% CI (0.73, 0.85)] (figure 4B).

6. Subgroup analysis according to the PIK3CA gene status

Four studies (involving 4,346 patients) compared the overall survival of colorectal cancer among aspirin users compared with non-aspirin users among those with PIK3CA gene mutation. Based on the estimated pooled HRs, the use of aspirin postdiagnosis was associated with longer overall survival [HR = 0.70, 95% CI (0.50, 0.99)] (figure 5A).

For overall survival in colorectal cancer, three studies involving 8,490 patients compared among aspirin users compared with non-aspirin users among patients with a wild-type PIK3CA gene, and the estimated pooled HRs showed no significant differences between the groups [HR = 0.79, 95% CI (0.53, 1.13)] (figure 5A).

Two studies involving 2,451 patients compared the cancer-specific survival in colorectal cancer among aspirin users compared with non-aspirin users among patients with a mutated PIK3CA gene. The estimated pooled HRs showed
that the use of aspirin postdiagnosis was associated with longer overall survival [HR= 0.27\%CI(0.08, 0.91)] (figure 5B).

7. **Subgroup analysis according to the PTGS2 (COX-2) expression status**

Two studies involving 560 patients compared overall survival in colorectal cancer among aspirin users compared with non-aspirin users in patients with strong PTGS2 (COX-2) expression. According to the estimated pooled HRs, the use of aspirin postdiagnosis was associated with longer overall survival [HR= 0.65\%CI(0.54, 0.83)] (figure 5C).

Regarding the overall survival of colorectal cancer, two studies involving 4,328 patients compared aspirin users with non-aspirin users among patients with weak PTGS2 (COX-2) expression. The estimated pooled HRs showed no significant differences between the two groups [HR= 0.75\%CI(0.43, 1.30)] (figure 5C).

8. **Subgroup analysis according tumor stage**

Four studies involving 28032 patients compared overall survival in colorectal cancer among aspirin users compared with non-aspirin users among patients. The estimated pooled HRs showed no significant differences between the groups (Supplement Figure 3A).

Five studies involving 32826 patients compared cancer specific survival in colorectal cancer among aspirin users compared with non-aspirin users. The estimated pooled HRs showed no significant differences between the groups in stage I, stage III and stage IV patients. While the use of aspirin was associated with longer cancer specific survival in stage II patients [HR= 0.65\%CI(0.54, 0.83)] (Supplement Figure 3B).

**Sensitivity analysis**

Sensitivity analysis was performed to test the stability of the results by excluding each study successively. The results were not affected by sequential exclusion of any particular trial, except for one study (Bains et al, 2016). The detailed sensitivity analysis results are depicted in figure 6.

**Publication bias**

In a meta-analysis with few studies (less than 10), the power of asymmetrical tests is too low to distinguish chance from real asymmetry. Because of the limited number of included studies, it was difficult to confirm the existence of publication bias in the current meta-analysis.

**Discussion**

Aspirin is a nonselective cyclooxygenase inhibitor. Many studies\textsuperscript{2-7} have observed that aspirin can improve the prognosis of digestive malignant tumors. However, there were some controversial issues in these studies, especially among those studies that focused on esophageal, gastric, and colorectal cancers with different gene mutation types, such as PIK3CA, that have survival benefits. This meta-analysis included 17 recent clinical studies with large sample sizes to investigate the effects of aspirin on the long-term survival of esophageal, gastric and colorectal cancers. Although the studies included were retrospective studies, they were of high quality and had large sample sizes. The results indicated that postdiagnosis aspirin use may improve OS and CSS in patients with colorectal cancer but not in patients with esophageal cancer or gastric cancer. Subgroup analysis indicated that postdiagnosis aspirin use could prolong the long-term survival of patients with PIK3CA gene mutations and high expression of PTGS2 (COX-2).
A Dutch cohort study\textsuperscript{7} that involved 946 patients with esophageal cancer and 750 patients with gastric cancer demonstrated that postdiagnosis aspirin use significantly reduced mortality in esophageal cancer [HR = 0.42, 95% CI (0.30-0.57)] but failed to observe reduced mortality in gastric cancer [HR = 0.87, 95% CI 0.47-1.61]. Additionally, a British study\textsuperscript{11} that included 4654 patients with esophageal cancer and 3833 patients with gastric cancer observed that low-dose aspirin use did not reduce mortality in these patients. The present study also found that aspirin did not improve the overall survival rate of patients with esophageal and gastric cancer. Although the original studies had high quality and large sample sizes, more RCTs and evidence-based studies are needed because there are few studies that have focused on the long-term survival of patients with esophageal or gastric cancer.

Previous prospective studies\textsuperscript{25,26} have observed that aspirin can reduce colorectal adenomas and reduce the risk of colorectal adenomas recurrence. Most studies have found that aspirin should be used at least one year. The optimal dosage and duration is not consistent and large-scale prospective studies are still needed. This meta-analysis further supports that postdiagnosis aspirin use can improve the long-term survival of patients with colorectal cancer; however, prediagnosis aspirin use cannot improve the long-term survival of patients with colorectal cancer. Aspirin can lead to gastrointestinal bleeding and other side effects, it remains unclear whether low-dose aspirin can achieve adequate antitumor effects. Therefore, the long-term survival of patients with colorectal cancer needs to be evaluated with aspirin in the optimal dose and the best course of treatment. Moreover, side effects on the survival benefit of patients need to be investigated in the future. The daily dose of aspirin in the included observational studies was 75 mg-325 mg, and studies\textsuperscript{27,28} have shown that 81 mg aspirin is sufficient to inhibit rectal mucosal PGE2 production. The US Preventive Services Working Group\textsuperscript{29} recommends 81 mg as a prescription dose for aspirin for the primary prevention of cardiovascular diseases and colorectal cancer. However, due to data limitations, a dose-response analysis between aspirin use and the long-term survival of patients with colorectal cancer was difficult to ascertain in the present study, and the optimal course of aspirin treatment needs to be investigated. We perform stratified analysis according to tumor stages. In patients with I-IV, aspirin may increase the overall survival (HR [0.88 (0.79, 0.98)]) and cancer-specific survival (HR [0.85 (0.74, 0.98)]) as shown in supplement Figure 3. We found that aspirin may increase CSS HR [0.73 (0.63, 0.85)] in stage II patients, but there was no survival benefit in other stages. Due to the limited literatures and high heterogeneity, more literatures need to be included for further analysis. Because the inclusion studies did not provide detailed information, it was impossible to conduct a subgroup analysis based on whether surgery or chemotherapy.

The mechanism of action of aspirin in the treatment of colorectal cancer is unclear. Some biomarkers can be used to predict the survival benefit of aspirin in colorectal cancer, including PTGS2 (COX-2) expression and the effects of the PIK3CA gene. The anti-inflammatory effects of aspirin are mediated through direct inhibition of COX-1 and COX-2\textsuperscript{30-32}. PTGS2 (COX-2) promotes the inflammatory response and cell proliferation, and high expression of PTGS2 (COX-2) is associated with poor survival in patients with colorectal cancer\textsuperscript{33,34}. The up-regulation of PI3K enhances PTGS2 (COX-2) activity and prostaglandin synthesis and plays an important role in the signal transduction pathway of tumorigenesis\textsuperscript{35,36}. According to the subgroup analysis in our study, the effects of aspirin use on PIK3CA gene mutation and survival of patients with high expression of PTGS2 (COX-2) was different from that of patients with wildtype PIK3CA and PTGS2 (COX-2)-negative colorectal cancer. These findings provide a basis for the use of aspirin in patients with different types of mutations in colorectal cancer and the result can be used as a preliminary basis for further research.

Due to the bias of retrospective articles, it is necessary to perform randomised prospective studies to validate these data. At present, many clinical trials about aspirin and GI malignancies have not been completed. The ASAC trial (NCT03326791) are the first clinical interventional trial to assess the beneficial role of ASA in recurrence of CRC liver...
metastases and survival. Add-Aspirin (NCT02804815) aims to assess whether regular aspirin use after standard curative therapy can prevent recurrence and improve survival in individuals with non-metastatic common tumours. ASPIK French trial (NCT02945033) investigate Aspirin Versus Placebo in Resected Colon Cancer With PI3K Mutation Stage III or II High Risk. We also look forward to more prospective studies supporting the impact of aspirin on the prognosis of GI malignancies.

There were some limitations in this study. First, because the original studies were retrospective, there was some publication bias and selection bias. Second, due to the different definitions of aspirin use in the literature, the inclusion and exclusion criteria of the original studies were inconsistent; such differences may lead to deviations in the results. In addition, the number of studies involved was relatively small. Other potential confounding factors include the staging of tumors, whether surgery was performed, whether chemotherapy was performed, and the location of colorectal tumors. Because the included studies did not provide detailed information, it was impossible to conduct a subgroup analysis according to whether surgery, whether chemotherapy, the dosage, duration and reason for taking aspirin.

**Conclusion**

In conclusion, based on the results of this study, aspirin can improve OS and CSS in patients with colorectal cancer after diagnosis, especially in those with PIK3CA gene mutations and high PTGS2 (COX-2) gene expression, but it cannot improve OS in patients with esophageal cancer and gastric cancer. The results provide a theoretical basis for the conductance of future RCTs. If RCTs can further confirm that aspirin can improve the long-term survival of patients with colorectal cancer, such therapies will have important clinical significance and socioeconomic value for patients with colorectal cancer because aspirin is inexpensive.

**Abbreviations**

Proton Pump Inhibitor (PPI) pooled risk ratios (RRs) OS (Overall survival) CSS (Cancer-specific survival) Newcastle–Ottawa Scale (NOS) random control trials (RCTs)

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

The data that support the findings of this study are available from the corresponding author upon reasonable request

**Competing Interests**

The authors have no conflicts of interest associated with the publication of this manuscript to declare. The authors report no relevant financial disclosures related to this current work.
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**Author contributions**

All authors have read and approved the manuscript. CMH, JLL and JXL conceptualized and designed the study, acquired and analysed data, interpreted the study results, drafted the manuscript and critically revised the manuscript for important intellectual content. CHZ and PL acquired and analysed data, interpreted the study results and critically revised the manuscript for important intellectual content. JWX and JBW designed the study, interpreted the study results and critically revised the manuscript for important intellectual content. JL and QYC designed the study, interpreted the study results and critically revised the manuscript for important intellectual content. LLC and ML conceptualized and designed the study, interpreted the study results and critically revised the manuscript for important intellectual content.

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**Supplementary File Legends**

Supplementary file 1:

Supplement Figure 1A flow diagram of the selection process of gastric cancer

Supplement Figure 1B flow diagram of the selection process of esophageal cancer

Supplement Figure 1C flow diagram of the selection process of colorectal cancer

Supplementary file 2:

Supplement Figure 2 post-diagnosis aspirin use and overall survival for esophageal cancer according to pathologic type

A subgroup analysis was conducted according to the pathologic type of esophageal cancer.

The estimated pooled HRs showed no significant differences were seen between the two groups HR= 1.05
95%CI(0.92, 1.20) of esophageal adenocarcinoma.

The estimated pooled HRs showed no significant differences were seen between the two groups HR= 0.89
95%CI(0.74, 1.07) of esophageal squamous cell carcinoma.
Tables

Table 1 Characteristics of the included trials and participants
| Included Trials | Design | Region | database | Journal | Sample size | Period | aspirin use | Follow-up time | Surgery* | Chemotherapy† |
|-----------------|--------|--------|----------|---------|-------------|--------|-------------|----------------|----------|--------------|
| **gastric cancer** |        |        |          |         |             |        |             |                |          |              |
| Spence et al.¹¹ 2018 | Cohort study | United Kingdom | cancer registries in England | Gastroenterology | 2391 | 1998-2012 | post-diagnosis use | until September 2015 | 947 (50.0%) / 273 (55.0%) | 720 (38.0%) / 146 (29.4%) |
| Spence et al.¹¹ 2018 | Cohort study | United Kingdom | the Scottish Cancer Registry | Gastroenterology | 1442 | 2009-2012 | post-diagnosis use | until January 2015 | 376 (33.3%) / 124 (39.7%) | 587 (51.9%) / 145 (46.5%) |
| Frouws et al.⁷ 2017 | Cohort study | Netherlands | Eindhoven Cancer Registry | British Journal of Cancer | 750 | Jan 1998-Dec 2011 | Pre- and post-diagnosis use | NA | Unknown | Unknown |
| **esophageal cancer** |        |        |          |         |             |        |             |                |          |              |
| Macfarlane et al.¹³ 2015 | Cohort study | United Kingdom | PCCIU database IN Scotland | Cancer Epidemiology | 1197 | 1996-2010 | Pre- and post-diagnosis use | 9 | Unknown | Unknown |
| Spence et al.¹¹ 2018 | Cohort study | United Kingdom | cancer registries in England | Gastroenterology | 2733 | 1998-2012 | post-diagnosis use | until September 2015 | 879 (40.4%) / 215 (38.5%) | 108 (50.0%) / 235 (42.0%) |
| Spence et al.¹¹ 2018 | Cohort study | United Kingdom | the Scottish Cancer Registry | Gastroenterology | 1921 | 2009-2012 | post-diagnosis use | until January 2015 | 266 (18.5%) / 883 (61.5%) | 256 (52.8%) |
| Frouws et al.⁷ 2017 | Cohort study | Netherlands | Eindhoven Cancer Registry | British Journal of Cancer | 946 | Jan 1998-Dec 2011 | Pre- and post-diagnosis use | NA | Unknown | Unknown |
| **Colorectal cancer** |        |        |          |         |             |        |             |                |          |              |
| Chan et al.¹⁷ 2009 | Cohort study | USA | Nurses’ Health Study and the Health Professionals Follow-up Study | JAMA | 1279 | 1980-2002 | Pre- and post-diagnosis use | 11.8 years | Unknown | Unknown |
| Liao et al.²⁰ 2012 | Cohort study | USA | Nurses’ Health Study and Health Professionals Follow-up Study | NEJM | 964 | 1976-July 1st2006 | Pre- and post-diagnosis use | until death or January 2011 | Unknown | Unknown |
| Walker et al.²⁰ 2012 | Cohort study | UK | General Practice Research Database | British Journal of Cancer | 13994 | 1987-2010 | Pre- and post-diagnosis use | 1.7-3.1 years | Unknown | Unknown |
| Domingo et al.¹⁸ 2013 | Cohort study | UK | VICTOR trial | J Clin Oncol | 896 | Apr 2002-Sep 2004 | post-diagnosis use | NA | All patients | 430 (63.1%) / 62 (55.9%) / 59 (65.6 %)/7 (50 %) |
| McCowan et al.¹⁹ 2013 | Cohort study | Tayside, United Kingdom | Health Informatics Centre | European Journal of Cancer | 2990 | 1st January 1997-30th December 2006 | Pre- and post-diagnosis use | 2.8 years | Unknown | Unknown |
| Kothari et al.²¹ 2015 | Cohort study | Australia and USA | Moffitt Cancer Center and Royal Melbourne Hospital | Acta Oncol | 1487 | 1996-2010 | post-diagnosis use | 4.5 years | All patients | Unknown |
| Reimers et al.⁵ 2014 | Cohort study | Netherlands | Eindhoven Cancer Registry | JAMA Intern Med. | 999 | 2002-2008 | post-diagnosis use | until January 1, | All patients | Unknown |
| Researcher et al. | Type of study | Country | Database | Journal | Study period | Use of aspirin before and after CRC diagnosis | Pre- and post-diagnosis duration | Treatment use | Notes |
|------------------|---------------|---------|-----------|----------|--------------|-----------------------------------------------|---------------------------------|---------------|-------|
| Cardwell et al. | Case-control  | Study | UK        | National Cancer Data Repository | Gastroenterology | 4794 | 1998-2007 | Pre- and post-diagnosis use | 7.2 years | Unknown | Unknown |
| Bains et al.     | Cohort Study  | Norway  | Cancer Registry of Norway | J Clin Oncol | 23162 | Jan 2004-Dec 2011 | Pre- and post-diagnosis use | median 3.0 years after CRC diagnosis | 88.9% of the patients | Unknown | Unknown |
| Frouws et al.    | Cohort Study  | Netherlands | Eindhoven Cancer Registry | British Journal of Cancer | 6335 | Jan 1998-Dec 2011 | Pre- and post-diagnosis use | NA | Unknown | Unknown |
| Newcomb et al.   | Cohort Study  | USA, Canada, Australia | Four database | J Clin Oncol | 2419 | 1997-2008 | Pre- and post-diagnosis use | 10.8 years | Unknown | Unknown |
| Gray et al.      | Cohort Study  | UK      | Scottish Cancer Registry | BMC Cancer | 8391 | Jan 2009 - Jan 2015 | Pre- and post-diagnosis use | 3.6 years | 2167 (34.7%) | 5008 (94.7%) |
| Joseph et al.    | Cohort Study  | Hong Kong | Hong Kong Hospital | J Gastroenterol Hepatol | 3292 | 2004 - 2015 | post-diagnosis use | 10 years | All received surgery | Unknown |
| Zell et al.      | Cohort Study  | USA      | California Teachers Study cohort | Cancer | 621 | Date of diagnosis to death or to December 31, 2005 | Pre-diagnosis use | 2.8 years | 26 (7%) | 361 (91%) |
| Din et al.       | Case-control  | UK       | Study of Colorectal Cancer in Scotland | Gut | 4080 to 30 April 2008 | Pre-diagnosis use | NA | Unknown | Unknown |
| Coghill et al.   | Cohort Study  | USA      | Hutchinson Cancer Research Center AND SEER | Gut | 1737 | 1997-2002 | Pre-diagnosis use | 8 years | Unknown | Unknown |

* 947 (50.0%) / 273 (55.0%) means 947 (50.0%) receive surgery in aspirin non-user patients and 273 (55.0%) receive surgery in aspirin user patients.

† 720 (38.0%) / 146 (29.4%) means 720 (38.0%) receive chemotherapy in aspirin non-user patients and 146 (29.4%) receive chemotherapy in aspirin user patients.
| Included Trials | Stage# | Dosage | Duration | Reason | Outcomes |
|----------------|--------|--------|----------|--------|----------|
| **gastric cancer** | | | | | |
| Spence et al.\textsuperscript{11} 2018 | I 28 (1.5%) 12 (2.4%) | Low-dose aspirin (75 mg) use | 182, 365, 548 and 730 tablets | Unknown | not associated with increased survival in esophageal or gastric cancer |
| | II 43 (2.3%) 20 (4.0%) | | | | |
| | III 59 (3.1%) 16 (3.2%) | | | | |
| | IV 119 (6.3%) 16 (3.2%) | | | | |
| | Missing 1,646 (86.9%) 432 (87.1%) | | | | |
| Spence et al.\textsuperscript{11} 2018 | Unknown | Low-dose aspirin (75 mg) use | 182, 365, 548 and 730 tablets | Unknown | not associated with increased survival in esophageal or gastric cancer |
| Frouws et al.\textsuperscript{7} 2017 | Unknown | Nonusers were defined as patients who received for less than 30 days or never used aspirin. | Unknown | Unknown | increased survival in cancers |
| **esophageal cancer** | | | | | |
| Macfarlane et al.\textsuperscript{13} 2015 | Unknown | Unknown | Unknown | Unknown | improved survival was observed |
| Spence et al.\textsuperscript{11} 2018 | I 34 (1.6%) 10 (1.8%) | Low-dose aspirin (75 mg) use | 182, 365, 548 and 730 tablets | Unknown | not associated with increased survival in esophageal or gastric cancer |
| | II 69 (3.2%) 28 (5.0%) | | | | |
| | III 183 (8.4%) 47 (8.4%) | | | | |
| | IV 132 (6.1%) 23 (4.1%) | | | | |
| | Unknown 1,756 (80.8%) 451 (80.7%) | | | | |
| Spence et al.\textsuperscript{11} 2018 | Unknown | Low-dose aspirin (75 mg) use | 182, 365, 548 and 730 tablets | Unknown | not associated with increased survival in esophageal or gastric cancer |
| Frouws et al.\textsuperscript{7} 2017 | Unknown | Nonusers were defined as patients who received for less than 30 days or never used aspirin. | Unknown | Unknown | increased survival in cancers |
| **Colorectal cancer** | | | | | |
| Chan et al.\textsuperscript{17} 2009 | I 228 (32%) 193 (35%) | used aspirin 2 or more times per week | Unknown | Headache/arthritis and other musculoskeletal pain/ cardiovascular disease | associated with lower risk of colorectal cancer-specific and overall mortality |
| Study               | Stage | Aspirin Use | Other | Related Findings                                                                 |
|--------------------|-------|-------------|-------|----------------------------------------------------------------------------------|
| Liao et al. 2012   | I 112 (24%) | as regular use of aspirin during most weeks | Unknown | associated with longer survival among patients with mutated-PIK3CA colorectal cancer |
|                    | II 159 (34%) |                       | Unknown |                                                                       |
|                    | III 128 (27%) |                       | Unknown |                                                                       |
|                    | IV 31 (7%) |                       | Unknown |                                                                       |
|                    | Unknown 36 (8%) |                       | Unknown |                                                                       |
|                    | I 19 (20%) |                       | Unknown |                                                                       |
|                    | II 36 (38%) |                       | Unknown |                                                                       |
|                    | III 23 (24%) |                       | Unknown |                                                                       |
|                    | IV 12 (13%) |                       | Unknown |                                                                       |
|                    | Unknown 5 (5%) |                       | Unknown |                                                                       |
| Walker et al. 2012 | Unknown | a repeat prescription (>2) within the period | Unknown | have a potential as anti-neoplastics in diagnosed colorectal cancer          |
| Domingo et al. 2013 | II 332 (48.7%) | taking regular low-dose aspirin at random assignment or who started during follow-up | Unknown | support the prospective evaluation of adjuvant low-dose aspirin in patients with tumor PIK3CA mutation |
|                    | III 349 (51.2%) |                       | Unknown |                                                                       |
|                    | II 46 (51.1%) |                       | Unknown |                                                                       |
|                    | III 44 (48.9%) |                       | Unknown |                                                                       |
| McCowan et al. 2013 | Unknown | 28 tablets at one per day gave coverage for that prescription of 28 days. | Unknown | use post-diagnosis of colorectal cancer may reduce both all cause and colorectal cancer specific mortality |
| Kothari et al. 2015 | I 6(4%) | at least 75 mg of aspirin daily at the time of CRC diagnosis | Unknown | significant improvements in survival in PIK3CA-mutated CRC patients    |
| Study | Group | Count (Percentage) | Data Description | Action Taken | Outcome |
|-------|-------|-------------------|------------------|--------------|---------|
| Reimers et al. | Unknown | 3 | Increased PTGS2 expression or the presence of mutated PIK3CA did not predict benefit from aspirin |
| Cardwell et al. | Unknown | 3 | low-dose aspirin usage after diagnosis of colorectal cancer did not increase survival time. |
| Bains et al. | Unknown | 3 | Aspirin use after the diagnosis of CRC is independently associated with improved CSS and OS. |
| Frouws et al. | Unknown | 3 | Increased survival in cancers |
| Newcomb et al. | Unknown | 3 | regular use of NSAIDs after CRC diagnosis was significantly associated with improved survival in individuals with KRAS wild-type tumors |
| Authors          | Year | Low-dose (75 mg) aspirin exposure | Users after a lag of 6 months after their first aspirin prescription | Unknown | Either before or after diagnosis, did not prolong survival in this population-based CRC cohort. |
|------------------|------|----------------------------------|-------------------------------------------------|---------|-------------------------------------------------|
| Gray et al.      | 2018 | Low-dose (75 mg) aspirin exposure was identified from dispensing records within this database | Unknown | Unknown | Low-dose (75 mg) aspirin exposure was identified from dispensing records within this database | Unknown | Either before or after diagnosis, did not prolong survival in this population-based CRC cohort. |
| Joseph et al.    | 2019 | No less than 80mg per day        | At least a month                                 | Unknown | Lowers risk of both CRC-related mortality and overall mortality |
| Zell et al.      | 2009 | Taken aspirin regularly at least once a week | The total duration of use in number of years (<1, 1, 2, 3-4, 5-9, or 10). | Unknown | NSAIDs are associated with decreased mortality among female CRC patients |
| Din et al.       | 2010 | Reported intake of aspirin       | Unknown                                         | Unknown | NSAID use prior to CRC diagnosis does not influence survival of colorectal cancer |
| Coghill et al.   | 2011 | At least twice per week for 1 month | First, 0-6 months; second, 6 months; third, 2.5-7 years; fourth, >7 years | Unknown | NSAIDs prior to diagnosis is associated with improved colorectal cancer survival |

# stage I 28 (1.5%) 12 (2.4%) means 28 (1.5%) are stage I aspirin non-user patients and 12 (2.4%) are stage I aspirin user patients.

Table 2: Quality assessment of the observational studies using the Newcastle-Ottawa Scale (NOS)

Table 2.1 Assessment of the cohort studies
| Author | Year | Is the case definition adequate | Representativeness of the cases | Selection of Controls | Definition of Controls | Comparability of cohorts | Ascertainment of exposure to implants | Demonstration that outcome of interest was not present at start of study | Assessment of outcome | Follow up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total score |
|--------|------|-------------------------------|-------------------------------|----------------------|----------------------|------------------------|-------------------------------------|----------------------------------------|-----------------------|---------------------------------|-----------------------|------------|
| et     | 2009 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| ill et | 2011 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| i et   | 2016 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| et     | 2012 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| er et  | 2012 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 6          |
| ngo   | 2013 | +                             | +                             | -                    | +                    | +                      | +                                   | -                                     | +                     | +                               | +                     | 7          |
| as et  | 2017 | +                             | +                             | -                    | +                    | +                      | +                                   | -                                     | +                     | +                               | +                     | 7          |
| et     | 2018 | +                             | +                             | -                    | -                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 6          |
| ari et | 2014 | +                             | +                             | -                    | -                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 6          |
| swan  | 2013 | +                             | +                             | -                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 7          |
| arlane| 2015 | +                             | +                             | -                    | -                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 6          |
| comb  | 2017 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| ers et | 2014 | +                             | +                             | -                    | +                    | +                      | +                                   | -                                     | +                     | +                               | +                     | 7          |
| ce et  | 2017 | +                             | +                             | +                    | +                    | +                      | -                                   | +                                     | +                     | +                               | +                     | 8          |
| it    | 2009 | +                             | +                             | -                    | +                    | +                      | +                                   | +                                     | -                     | +                               | +                     | 7          |
| nh et  | 2019 | +                             | +                             | -                    | +                    | +                      | +                                   | +                                     | -                     | +                               | +                     | 7          |

Table 2.2 Assessment of the case–control study

**Figures**
Figure 1

Figure 1A post-diagnosis aspirin use and overall survival for upper digestive cancer. Figure 1B post-diagnosis aspirin use and cancer-specific survival for upper digestive cancer.
Figure 2

Figure 2A post-diagnosis aspirin use and overall survival for colorectal cancer Figure 2B cumulative meta-analysis of the HR for the gastric cancer according to time Figure 2C post-diagnosis aspirin use and cancer specific survival for colorectal cancer Figure 2D cumulative meta-analysis of the HR for the gastric cancer according to time
Figure 3

Figure 3A pre-diagnosis aspirin use and overall survival for colorectal cancer Figure 3B pre-diagnosis aspirin use and cancer specific survival for colorectal cancer
Figure 4

Figure 4A both pre and post-diagnosis aspirin use and overall survival for colorectal cancer Figure 4B both pre and post-diagnosis aspirin use and cancer specific survival for colorectal cancer
Figure 5

Figure 5A post-diagnosis aspirin use and overall survival for colorectal cancer according to PIK3CA mutation
Figure 5B post-diagnosis aspirin use and cancer specific survival for colorectal cancer according to PIK3CA mutation
Figure 5C post-diagnosis aspirin use and overall survival for colorectal cancer according to PTGS2(COX-2) mutation
Figure 6

Figure 6A Sensitivity analysis post-diagnosis aspirin use and overall survival for colorectal cancer Figure 6B Sensitivity analysis post-diagnosis aspirin use and cancer specific survival for colorectal cancer Figure 6C Sensitivity analysis both pre and post-diagnosis aspirin use and overall survival for colorectal cancer

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementFigure2.pdf
