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# Relationship between aspirin use after diagnosis of colorectal cancer and patient survival: a meta-analysis of observational studies

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**Background:** Epidemiological evidence suggests that use of aspirin after the diagnosis of colorectal cancer can lengthen survival. However, the supporting data vary between studies, and this hypothesis remains controversial. We conducted a meta-analysis to provide a quantitative assessment of the association between use of aspirin after diagnosis of colorectal cancer and patient survival.

**Methods:** We searched the Medline and Embase databases up to April 2014 to identify studies related to aspirin use after diagnosis and all-cause mortality or colorectal cancer-specific mortality. Summary effect estimates with 95% confidence intervals (CIs) were derived using a fixed or random effects model, depending on the heterogeneity between the included studies.

**Results:** Seven epidemiologic studies that consisted of six cohort studies and one nested case–control study were included in this meta-analysis. The hazard ratio (HR) of the association between aspirin use after colorectal cancer diagnosis and overall mortality, which was reported in five studies, was 0.74 (95% CI, 0.62–0.89) using a random model (heterogeneity test $P = 0.003$, $I^2 = 75.3\%$), and for colorectal cancer-specific mortality (four studies), it was 0.75 (95% CI, 0.51–1.10) using a random model (heterogeneity test $P = 0.001$, $I^2 = 84.1\%$). In addition, we analysed postdiagnosis aspirin use according to whether aspirin was also used before diagnosis. The HR for the overall mortality of patients who did not use aspirin before diagnosis, which was reported in four studies, was 0.84 (95% CI, 0.70–1.00), and for colorectal cancer-specific mortality (three studies), it was 0.79 (95% CI, 0.61–1.02). For those who did use aspirin before diagnosis, the HR for overall mortality (four studies) was 0.88 (95% CI, 0.83–0.93), and for colorectal cancer-specific mortality (three studies), it was 0.80 (95% CI, 0.59–1.09). Subgroup analysis showed that use of aspirin after diagnosis was associated with longer overall survival among patients with the variant *PIK3CA* gene but not for those with wild-type *PIK3CA*.

**Conclusions:** Based on current evidence, the use of aspirin after diagnosis does not reduce colorectal cancer-specific mortality, but it does reduce all-cause mortality for colorectal cancer patients.

Colorectal cancer originates in the colon or the rectum, and its incidence is currently increasing. It has been reported to be the third most common cancer and the fourth leading cause of cancer-related death worldwide (Ferlay *et al*, 2010). Several factors, including lifestyle and age, are risk factors for colorectal cancer. However, the prognosis of individuals with colorectal cancer has improved since the introduction of adjuvant chemotherapy. Recent studies have revealed that regular aspirin use after the diagnosis of

colorectal cancer is associated with a lower risk of both colorectal cancer-specific and overall mortality (Chan *et al*, 2009; Bastiaannet *et al*, 2012).

Aspirin, a non-steroidal anti-inflammatory drug, is usually indicated for the treatment of pain and inflammation and for the prevention of stroke at low dosage. In addition to its intrinsic clinical effect, it has also been shown to reduce the risk of cardiovascular disease and cancer (Baigent *et al*, 2009; Rothwell *et al*, 2011, 2012a, b; Algra & Rothwell, 2012), including colorectal cancer (Hollestein *et al*, 2014). Aspirin has also been reported to reduce both the long-term incidence of colorectal cancer and mortality owing to this malignancy (Din *et al*, 2010; Rothwell *et al*, 2010). However, most of these studies only considered the use of aspirin before the diagnosis of colorectal cancer.

One of the main mechanisms of action of aspirin is the inhibition of cyclo-oxygenase (COX), the enzyme responsible for biosynthesing the prostaglandins, which increase cellular proliferation, migration, and invasiveness, and promotes angiogenesis. Aspirin inhibits both COX-1 and COX-2. COX-2 is expressed in 70% of colorectal tumours and has an important role in colorectal carcinogenesis, invasion, and metastasis (Chan *et al*, 2009, 2012; Midgley *et al*, 2010; Bacchi *et al*, 2012; Wang & DuBois, 2013).

Recently, a number of studies have been conducted to assess the use of aspirin after diagnosis and the survival of colorectal cancer patients, with varying results. Although some of these studies suggested that postdiagnosis use of aspirin could lengthen colorectal cancer survival, others found no effect, resulting in uncertainty and controversy regarding these findings. McCowan *et al* (2012) reported postdiagnosis aspirin use was associated with a 30% reduction in all-cause mortality. Walker *et al* (2012) reported a 10% reduction in all-cause mortality in patients treated with postdiagnosis aspirin. Moreover, to date, no meta-analysis has been performed to analyse and summarise the evidence for survival benefit of postdiagnosis use of aspirin. Hence, we performed a meta-analysis of relevant epidemiological studies to obtain an overview of the association between the use of aspirin after diagnosis and the survival of colorectal cancer patients, for both all-cause mortality and colorectal cancer-specific mortality.

## MATERIALS AND METHODS

This review was conducted and reported following the Meta-analysis Of Observational Studies in Epidemiology guidelines (Stroup *et al*, 2000).

**Search strategy.** Any observational study that examined the relationship between the use of aspirin after colorectal cancer diagnosis and patient survival was eligible for inclusion in our study. We searched PubMed and Embase for articles published until April 2014 and used 'aspirin' and 'colorectal cancer' or 'rectal cancer' or 'colon cancer' as the search terms. We also conducted manual searches of reference lists from all the relevant original and review articles to identify any additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies.

The literature search was independently undertaken by two authors (SWT and WJ) with a standardised approach. Any inconsistencies between the findings of these two authors were reviewed by the primary author (HJ), and a consensus was reached.

**Criteria for inclusion.** The study was eligible for inclusion if the following criteria were met: (1) the study was a prospective cohort or a prospective nested case–control study; (2) the study investigated the association between the postdiagnosis use of aspirin among colorectal cancer patients and their survival; and (3) effect estimates (hazard ratio (HR)) and 95% confidence intervals

(CIs) were used. All English-language literature was eligible for inclusion in our analysis. Studies investigating only the use of aspirin before the diagnosis of colorectal cancer and survival were excluded.

**Data extraction.** The data were collected using a standardised data collection form and included the first author's name, publication year, country, database, study design, sample size, age at baseline, follow-up duration, dose, duration, effect estimates and 95% CIs, and covariates in the fully adjusted model.

**Quality assessment.** The Newcastle–Ottawa scale (NOS), which is widely used and has been partially validated for evaluating the quality of observational studies in a meta-analysis, was used to evaluate the methodological quality (Wells *et al*, 2009).The NOS consists of three aspects: selection, comparability, and exposure. Each satisfactory answer scores one point. A 'star system' (range, 0–9) is used for assessment.

The quality assessment was independently conducted by two authors (YXF and WJ). Information was examined and adjudicated independently by an additional author (HJ) after referring to the original studies.

**Statistical analysis.** The study-specific adjusted HRs and corresponding 95% CIs were used as the common measure of association across studies. Heterogeneity was assessed using the Cochran Q and $I^2$ statistics (Higgins *et al*, 2003). For the Q statistic, a $P$-value $>0.10$ for the $\chi^2$-test, and for the $I^2$ statistic, an $I^2$ value $<25\%$ was interpreted as low-level heterogeneity. A pooled effect was calculated with a fixed-effect model if there was no statistically significant heterogeneity; otherwise, a random effect model was employed.

Publication bias was assessed using the Begg and Egger regression asymmetry test, together with the funnel plot. All reported $P$-values are two-sided, and $P$-values $<0.05$ were considered statistically significant for all the included studies. Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

## RESULTS

**Description of the selected studies.** A total of 1267 potentially relevant articles were retrieved using our search strategy, of which 1230 were excluded because they were irrelevant (1158 articles), duplications (16 articles), or concerned diseases other than colorectal cancer (56 articles). This left 37 studies, all of which were evaluated based on the full text. Thirteen irrelevant articles, 11 articles reporting no desirable outcomes, 5 articles (review or letter to editor), and 1 duplicate article were excluded. Finally, seven studies were included in this meta-analysis, including one nested case–control study and six cohort studies (Chan *et al*, 2009; Bastiaannet *et al*, 2012; Liao *et al*, 2012; McCowan *et al*, 2012; Walker *et al*, 2012; Cardwell *et al*, 2014; Reimers *et al*, 2014). The detailed literature screening process is shown in Figure 1, and the exclusion reasons for duplicate and irrelevant are listed in Supplementary Table S1. All of these studies were published after 2009. Two studies were conducted in the United States, two in the Netherlands, and three in the United Kingdom. In prospective studies, participants entered the studies after they were diagnosed with colorectal cancers in different studies. Then those who were prescribed aspirin were classified as aspirin users and others were classified as aspirin non-users. In the nested case–control study, cases were ascertained by cancer registries, and each case was matched to five controls.

Among the included studies, six studies reported the association between postdiagnosis use of aspirin and all-cause mortality, and four studies reported the colorectal cancer-specific mortality. Four

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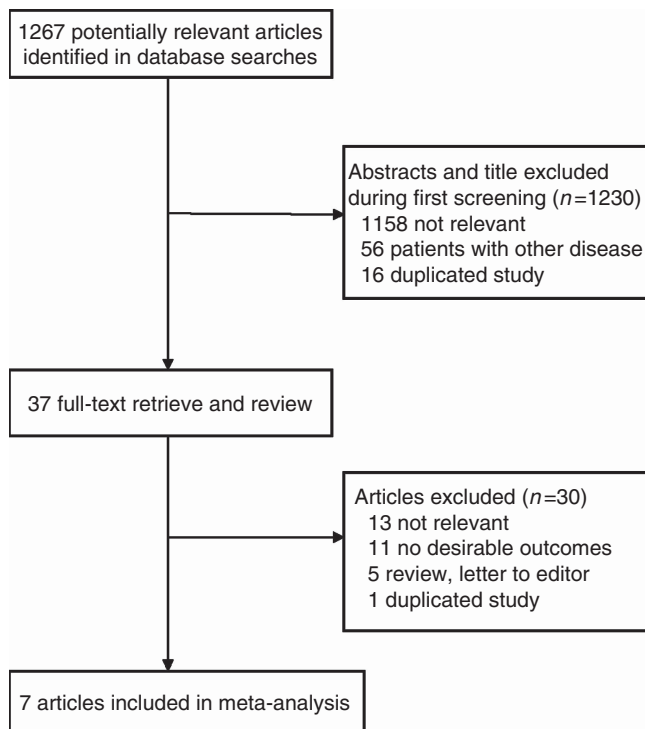
Figure 1. Flow diagram of the search and selection process of the studies.

studies analysed the use of aspirin prior to colorectal cancer diagnosis with respect to all-cause mortality, and three studies reported colorectal cancer-specific mortality. According to the nine-point NOS, three studies had NOS scores of eight; two studies had NOS scores of seven, whereas two studies had scores of six. The general characteristics of each study are listed in Table 1.

**Aspirin use after colorectal cancer diagnosis and survival.** The estimated pooled HRs showed a statistical significantly association between the use of aspirin after diagnosis and all-cause mortality, compared with aspirin non-users (pooled HR = 0.74; 95% CI, 0.62–0.89; Figure 2) using a random model (heterogeneity test $P = 0.003$, $I^2 = 75.3\%$) without publication bias (Egger test $P = 0.091$). However, no association was found between the use of aspirin after diagnosis and colorectal cancer-specific mortality, compared with aspirin non-users (pooled HR = 0.75; 95% CI, 0.51–1.10; Figure 2) using a random model (heterogeneity test $P = 0.001$, $I^2 = 84.1\%$) without publication bias (Egger test $P = 0.397$). Funnel plot for publication bias assessment is illustrated in Supplementary Figure S1.

In order to compare the outcome of patients who regularly used aspirin before diagnosis but then discontinued after diagnosis, we analysed postdiagnosis aspirin use according to whether aspirin was used before diagnosis.

**Prediagnosis aspirin use.** Prediagnosis aspirin non-users were defined as those who did not use aspirin prior to diagnosis of colorectal cancer but started to use aspirin after diagnosis. There was a statistical significantly association between aspirin use and all-cause mortality, compared with aspirin non-users (pooled HR = 0.84; 95% CI, 0.70–1.00; Figure 3), but not colorectal cancer-specific mortality (pooled HR = 0.79; 95% CI, 0.61–1.02; Figure 3) in this group. Prediagnosis aspirin users were defined as those who regularly used aspirin most weeks prior to the diagnosis of colorectal cancer and continued to use aspirin after diagnosis. For this group, there was also a statistically significant association between aspirin use and all-cause mortality, compared with aspirin

non-users (pooled HR = 0.88; 95% CI, 0.83–0.93; Figure 4), but not for colorectal cancer-specific mortality (pooled HR = 0.80; 95% CI, 0.59–1.09; Figure 4). Funnel plot for publication bias assessment is illustrated in Supplementary Figure S1.

We found no evidence of an interaction between prediagnosis aspirin non-users and prediagnosis aspirin users. The interaction $P$ for all-cause mortality and colorectal cancer specific mortality was 0.6262 and 0.9509, respectively.

**Subgroup analysis.** A subgroup analysis was conducted according to the status of the *PIK3CA* gene. The results suggest that, among patients with a mutated *PIK3CA* gene, use of aspirin after diagnosis was associated with longer overall survival, compared with aspirin non-users (pooled HR = 0.60; 95% CI, 0.38–0.94; Figure 5). However, among patients with the wild-type *PIK3CA* gene, use of aspirin after diagnosis was not associated with longer overall survival, compared with aspirin non-users (pooled HR = 0.73; 95% CI, 0.43–1.23; Figure 5). No significant interactions were found between mutated *PIK3CA* gene and wild-type *PIK3CA* gene (interaction $P = 0.5795$).

**Sensitivity analysis.** Sensitivity analysis was performed to test the stability of the results by excluding each study iteratively. This showed that the results were not affected by sequential exclusion of any particular trial except for one study (Cardwell *et al*, 2014). The detailed sensitivity analysis results are listed in Table 2.

## DISCUSSION

There was uncertainty and controversy regarding the association between postdiagnosis use of aspirin and survival of colorectal cancer patients in the previous studies. In addition, whether patients with a mutant form of the *PIK3CA* gene might benefit from the prescription of aspirin was reported with different results. In this study, we investigated the association between the postdiagnosis use of aspirin and survival of colorectal cancer patients. We carried a broad search of manually reviewed databases, which yielded seven studies that met out inclusion criteria. Statistical analysis of these studies showed that post-diagnosis use of aspirin did not improve colorectal cancer-specific mortality but improved all-cause mortality for colorectal cancer patients. In addition, subgroup analysis suggested that the use of aspirin after diagnosis was associated with longer overall survival among patients with a mutated form of the *PIK3CA* gene but not for those with the wild-type *PIK3CA* gene.

The results suggest that the use of aspirin after diagnosis does not reduce colorectal cancer-specific mortality, but it does reduce all-cause mortality for colorectal cancer patients. The mechanism by which the use of aspirin prior to colorectal cancer diagnosis reduced all-cause mortality remains unknown. However, high levels of prostaglandin endoperoxide synthase 2, which is inhibited by aspirin, are associated with a poor prognosis in colorectal cancer. In addition, aspirin has been reported to prevent a number of diseases, including cardiovascular disease. This mechanism might also contribute to the longer survival of colorectal patients.

The analysis of prediagnosis aspirin might be a confounder for the relationship between aspirin use after diagnosis of colorectal cancer and patient survival. But, in the clinical settings, some colorectal patients were prescribed aspirin to prevent cardiovascular diseases and so on and continued to use aspirin after colorectal diagnosis. The result could give some information for those patients.

The included studies have different characteristics. Both of the study by Walker *et al* (2012) and Cardwell *et al* (2014) used the CPRD database in United Kingdom. We included both studies because they reported different outcomes. Walker *et al* (2012) conducted a cohort study and compared aspirin users with

| Table 1. Characteristic of the included studies | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author (year) | Country/region | Database | Median follow-up | Study type | Sample size | No. of aspirin users | No. of aspirin non-users | Median age | Adjusted variable | NOS score |
| Cardwell et al, 2014 | Northern Ireland | National Cancer Data Repository | NR | Nested case–control study | 9089 | 2387 | 6711 | NR | Including surgery, chemotherapy, radiotherapy, statin use, metformin use, and comorbidities, including myocardial infarction, cerebrovascular disease, congestive heart disease, chronic pulmonary disease, peripheral vascular disease, peptic ulcer disease, renal disease and rheumatological disease, and diabetes | 7 |
| Liao et al, 2012 | US | Nurses' Health Study and the Health Professionals Follow-up Study | 14.75 | Cohort study | 964 | 561 | 403 | 68 | Disease stage, initially included age, sex, year of diagnosis, aspirin use after diagnosis, tumour location, tumour differentiation, body mass index, microsatellite instability status, sex | 8 |
| Reimers et al, 2014 | Netherlands | PHARMO | NR | Cohort study | 999 | 180 | 794 | NR | Sex, age, comorbidity, year of incidence, histological grade, stage, and chemotherapy | 7 |
| McCowan et al, 2012 | UK | The Health Informatics Centre | 4.22 | Cohort study | 2990 | 1340 | 1650 | 73 | Age, sex, social class, stage of disease diagnosis | 8 |
| Bastiaannet et al, 2012 | Netherlands | PHARMO | 3.5 | Cohort study | 4481 | 3305 | 1176 | 69 | Sex, age, comorbidity, year of incidence, grade, stage and treatment | 6 |
| Walker et al, 2012 | UK | General Practice Research Database | NR | Cohort study | 13 994 | 2619 | 1365 | NR | Age, gender, smoking, BMI, alcohol use and comorbidity | 8 |
| Chan et al, 2009 | US | Mailed questionnaire | 11.8 | Cohort study | 1279 | 549 | 730 | 60.7 | Age, sex, date of diagnosis, stage of cancer, site of primary cancer, histological grade of cancer, aspirin use, smoking, BMI, cancer in a parent or sibling | 6 |

Abbreviations: BMI = body mass index; NR = not reported.

non-users based upon use in the first year after diagnosis in individuals surviving 1 year. They adjusted gender, age, smoking status, alcohol use, body mass index, and comorbidity as potential confounders. However, they did not adjust tumour stage and cancer treatments as Cardwell et al (2014) did. Cardwell et al (2014) conducted a nested case–control analysis and included 1559 colorectal cancer-specific deaths. One case was matched to five controls, and conditional logistic regression was performed. Cardwell et al (2014) focussed solely on low-dose aspirin usage while Walker et al (2012) analysed both the low-dose aspirin usage

and high-dose aspirin usage. In addition, the analysis in the studies by Walker et al (2012) and Cardwell et al (2014) was all restricted to individuals with at least 1 year of follow-up (Walker et al, 2012; Cardwell et al, 2014). Bastiaannet et al (2012) and McCowan et al (2012) used a time-varying covariate model to compare aspirin users with non-users. In the study by Bastiaannet et al (2012), they excluded patients who died within 30 days from diagnosis. In all, 45% of the populations in the study by McCowan et al (2012) were prescribed aspirin, which was higher than other studies. The study by McCowan et al (2012) did not adjust some important variables,
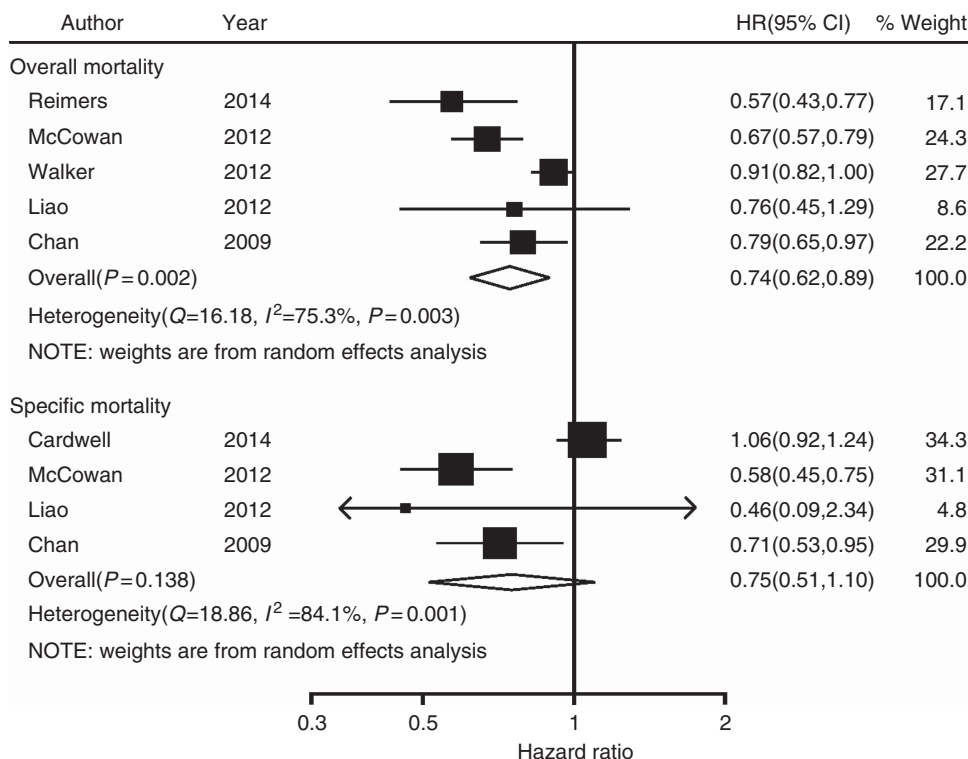
Figure 2. Forest plot of aspirin use after diagnosis of colorectal cancer and patient survival.
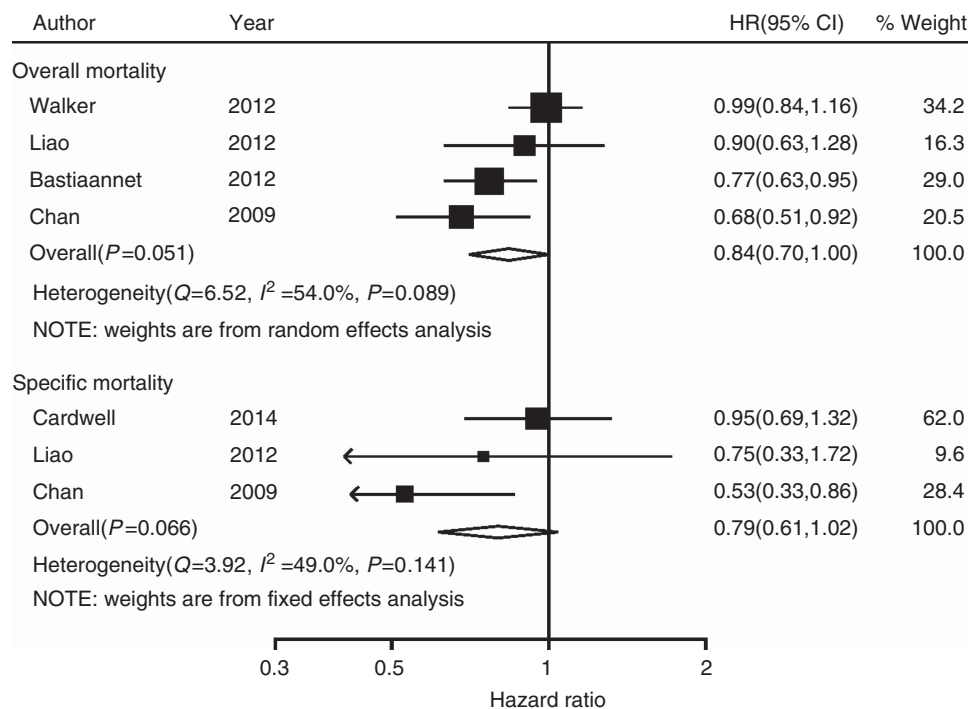


Figure 3. Forest plot of aspirin use after diagnosis of colorectal cancer (prediagnosis aspirin non-users) and patient survival.

such as comorbidity, smoking status, body mass index, and so on. The study by Chan et al (2009) excluded stage IV colorectal cancer patients. In the analysis, they excluded deaths that occurred within 12 months of completing aspirin assessment. Both of the study by Liao et al (2012) and Reimers et al (2014) focussed on the effect of aspirin on survival based on the mutation of some biomarkers, such as PIK3CA. Studies included were conducted under different

settings as discussed, such as different aspirin dosage, patients characteristic, statistical analysis method, and so onn, which would lead to the heterogeneity between studies.

Liao et al (2012) and Reimers et al (2014) conducted cohort studies to explore the relationship between aspirin use after diagnosis of colorectal cancer and patient survival according to the status of the PIK3CA gene. The two studies reported completely
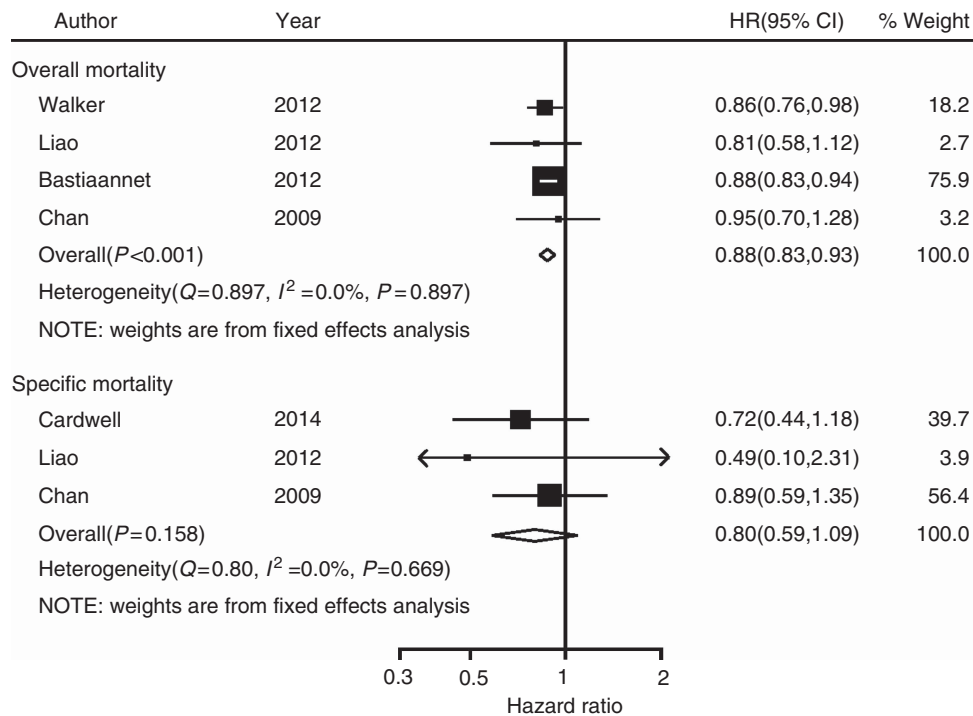
Figure 4. Forest plot of aspirin use after diagnosis of colorectal cancer (prediagnosis aspirin users) and patient survival.
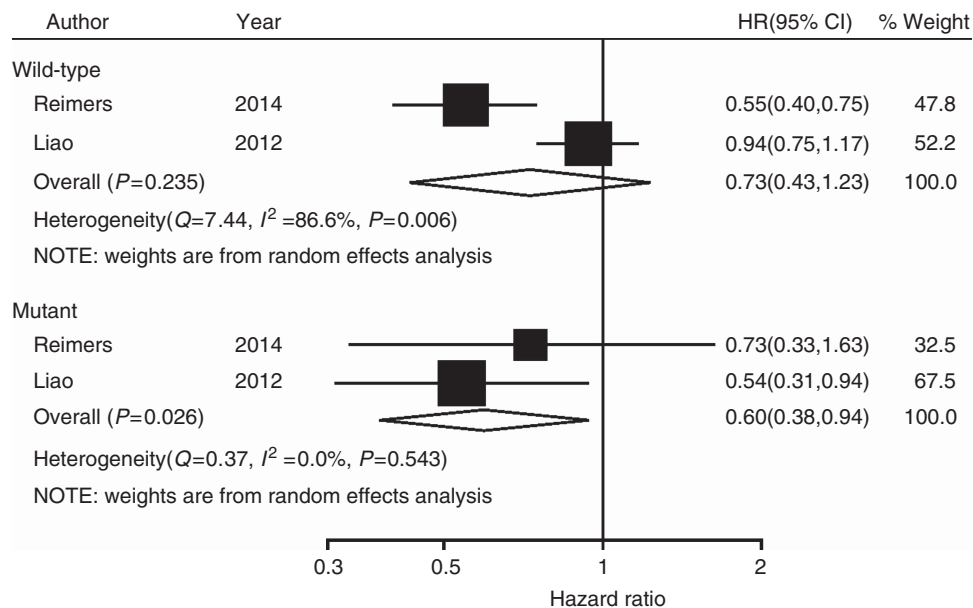


Figure5. Forest plot of the risk of aspirin use and overall mortality after diagnosis of colorectal cancer according to tumour PIK3CA mutation status.

opposite results. Liao *et al* (2012) reported that use of aspirin after diagnosis was associated with longer overall survival among patients with the mutant *PIK3CA* gene but not for those with wild-type *PIK3CA*. Although Reimers *et al* (2014) reported a benefit for those with wild-type *PIK3CA*, Liao *et al* (2012) postulated that by blocking the *PIK3CA* pathway PTGS2 activity decreases, which leads to apoptosis of colon cancer cells. The result echoes with a previous randomised clinical trial by Domingo *et al* (2013). In addition, one drawback of both the two studies is the limited sample sizes, especially in the mutant *PIK3CA* gene group, with 100 and 161 patients, respectively. The small sample size could not have had an enough power to detect the difference

between aspirin users and non-users. After combining the two separate studies together, a subgroup analysis showed that use of aspirin after diagnosis was associated with longer overall survival among patients with the variant *PIK3CA* gene but not for those with wild-type *PIK3CA*.

The strength of our study lies in the inclusion of all the observational studies concerning postdiagnosis use of aspirin and the survival of colorectal cancer patients. We present all available evidence in a systematic, quantitative, and unbiased fashion. However, our study also has some limitations that deserve further discussion. First, and most importantly, this meta-analysis used data from epidemiological studies, which were unable to control

| Design/effect | Study (year) | HR | LL | UL |
|---|---|---|---|---|
| **Table 2.** Sensitivity analysis | | | | |
| **Aspirin postdiagnosis** | | | | |
| All-cause mortality | | 0.74 | 0.62 | 0.89 |
| | Reimers et al, 2014 | 0.79 | 0.66 | 0.94 |
| | McCowan et al, 2012 | 0.77 | 0.63 | 0.95 |
| | Walker et al, 2012 | 0.69 | 0.61 | 0.79 |
| | Liao et al, 2012 | 0.74 | 0.61 | 0.91 |
| | Chan et al, 2009 | 0.73 | 0.57 | 0.93 |
| Colorectal cancer-specific mortality | | 0.75 | 0.51 | 1.10 |
| | Cardwell et al, 2014 | 0.63 | 0.52 | 0.76 |
| | McCowan et al, 2012 | 0.86 | 0.59 | 1.24 |
| | Liao et al, 2012 | 0.77 | 0.52 | 1.14 |
| | Chan et al, 2009 | 0.75 | 0.43 | 1.31 |
| **Users prediagnosis** | | | | |
| All-cause mortality | | 0.88 | 0.83 | 0.93 |
| | Walker et al, 2012 | 0.88 | 0.83 | 0.93 |
| | Liao et al, 2012 | 0.88 | 0.83 | 0.93 |
| | Chan et al, 2009 | 0.87 | 0.83 | 0.92 |
| | Bastiaannet et al, 2012 | 0.87 | 0.78 | 0.97 |
| Colorectal cancer-specific mortality | | 0.80 | 0.59 | 1.09 |
| | Cardwell et al, 2014 | 0.86 | 0.57 | 1.28 |
| | Liao et al, 2012 | 0.82 | 0.59 | 1.12 |
| | Chan et al, 2009 | 0.70 | 0.43 | 1.11 |
| **Nonusers prediagnosis** | | | | |
| All-cause mortality | | 0.84 | 0.70 | 1.00 |
| | Walker et al, 2012 | 0.77 | 0.66 | 0.89 |
| | Liao et al, 2012 | 0.82 | 0.66 | 1.03 |
| | Chan et al, 2009 | 0.89 | 0.75 | 1.05 |
| | Bastiaannet et al, 2012 | 0.86 | 0.68 | 1.09 |
| Colorectal cancer-specific mortality | | 0.79 | 0.61 | 1.02 |
| | Cardwell et al, 2014 | 0.58 | 0.38 | 0.88 |
| | Liao et al, 2012 | 0.79 | 0.60 | 1.03 |
| | Chan et al, 2009 | 0.92 | 0.68 | 1.24 |

Abbreviations: HR = hazard ratio; LL = lower limit; UL = upper limit.

the same important potential confounders. The demographics of a study population may lead to valid differences in the magnitude and direction of association. Second, we did not analyse the effect of drug dosage and duration in the subgroup analysis. Dosage and duration are important factors to support the relationship between postdiagnosis use of aspirin and the survival of colorectal cancer patients. Few of the included studies provided information on the effect of dosage and duration. Third, we only included English language studies, which could lead to an incomplete search of relevant studies. Fourth, some bias lying in the included observational studies could not be ignored, such as immortal time bias and confounding by indication. Immortal time in epidemiology refers to a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur (Shariff et al, 2008). Confounding by indication refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention (Grobbee & Hoes, 1997). Becuse of the limitation of this meta-analysis, further studies are required to determine the clinical importance of our findings.

In summary, this comprehensive meta-analysis reveals that postdiagnosis use of aspirin does not reduce colorectal cancer-specific mortality but does reduce all-cause mortality among colorectal cancer patients. In addition, patients with a mutant form of the *PIK3CA* gene might benefit from the prescription of aspirin.

## ACKNOWLEDGEMENTS

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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