The handle http://hdl.handle.net/1887/55950 holds various files of this Leiden University dissertation

**Author:** Frouws, Martine A.
**Title:** Renewing clinical applications for commonly used medications in gastrointestinal cancer
**Date:** 2017-09-21
CHAPTER 7
THE MORTALITY REDUCING EFFECT OF ASPIRIN IN
COLORECTAL CANCER PATIENTS: INTERPRETING THE EVIDENCE

Martine A. Frouws, Myrthe P.P. van Herk-Sukel, Huub A. Maas, Cornelis J.H. Van de Velde,
Johanneke E.A. Portielje, Gerrit-Jan Liefers, Esther Bastiaannet
Cancer Treatment Reviews 2017 Feb 20;55:120-127
Abstract
In 1971 the first study appeared that suggested a relationship between aspirin and cancer. Currently publications on the subject of aspirin and cancer are numerous, with both a beneficial effect of aspirin on cancer incidence and a beneficial effect on cancer survival. This review focuses on the relation between the use of aspirin and improved survival in colorectal cancer patients. Various study designs have been used, with the main part being observational studies and post-hoc meta-analyses of cancer outcomes in cardiovascular prevention trials. The results of these studies are unambiguously pointing towards an effect of aspirin on colorectal cancer survival, and several randomised controlled trials are currently ongoing. Some clinicians feel that the current evidence is conclusive and that the time has come for aspirin to be prescribed as adjuvant therapy. However, until this review, not much attention has been paid to the specific types of bias associated with these studies. One of these biases is confounding by indication, because aspirin is indicated for patients as secondary prevention for cardiovascular disease. This review aims to provide perspective on these biases and provide tools for the interpretation of the current evidence. Albeit promising, the current evidence is not sufficient to already prescribe aspirin as adjuvant therapy for colorectal cancer.

Introduction
Aspirin, originating from the bark of a willow, was already used by Hippocrates in 400 B.C. It was patented as an analgesic in 1897, but the analgesic working mechanism was not unravelled until 1970. In the years thereafter, this appeared not to be the only ability of this medicine, as in the 1970’s aspirin became regular treatment for secondary cardiovascular disease prevention. More recently, the possible anti-cancer effect of acetylsalicylic acid has gained much attention, with the most elaborative studies performed in patients with colorectal cancer (CRC). A reduced cancer incidence as well as a reduced cancer mortality of aspirin users has been observed frequently.

Cancer is still one of the main causes of premature death worldwide. Cancer is one of the most expensive diseases for healthcare systems around the world with global spending on cancer drugs alone of more than $100 billion in 2014. Hence, new and cheap cancer drugs that are globally available are urgently needed, and hopefully aspirin can become an additional therapeutic option in the spectrum of cancer treatment. Albeit the promising results so far, before aspirin can be implemented as regular treatment option in cancer, randomised controlled trials (RCT’s) have to be awaited. Several RCT’s are currently ongoing to provide the world with a decisive answer on the mortality reducing effect of aspirin on colorectal cancer, but it will take another few years before the results of these studies will be published (table 1). Meanwhile, 16 observational studies, 4 meta-analysis and numerous reviews have been published on the subject, all pointing to beneficial effects of aspirin on survival of CRC patients.

Cardiovascular disease is more prevalent in the group of patients using aspirin and the impact of this has been disregarded until now. The present review aims to deliver a critical appraisal of the available evidence with special focus on possible sources of bias in the current observational studies.

Albeit, data from the RCT’s studying cancer outcomes in cardiovascular prevention trials have to deal with complex relations between cardiovascular morbidity, CRC cancer and survival. Previous studies mainly focused on the mortality reducing effect of aspirin in CRC patients, and therefore this will be the scope of this review. This review will provide a framework for the epidemiological challenges associated with the interpretation of observational studies on aspirin effects.
CHAPTER 7  •  THE MORTALITY REDUCING EFFECT OF ASPIRIN IN COLORECTAL CANCER PATIENTS: INTERPRETING THE EVIDENCE

Table 1: Overview of current ongoing trials for the effect of aspirin use after diagnosis in patients with colorectal cancer

<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Type of cancer</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Randomised treatment (incl treatment duration and dose)</th>
<th>Primary end-point</th>
<th>Participating countries</th>
<th>Start recruitment</th>
<th>Expected finished recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-aspirin trial* (NCT02647099)</td>
<td>Colorectal cancer</td>
<td>2600 colorectal (total: 9920)</td>
<td>Stage II and III adenocarcinoma</td>
<td>100 mg, 300 mg of daily aspirin or placebo, during 5 years</td>
<td>3 year time to recurrence</td>
<td>Sweden, Norway</td>
<td>2016</td>
<td>2021</td>
</tr>
<tr>
<td>ALASCA trial (NCT00565308)</td>
<td>Colorectal cancer</td>
<td>3900 PIK3CA mutated patients</td>
<td>160 mg of daily aspirin or placebo during 3 years</td>
<td>3 yr DFS</td>
<td>Singapore, Australia, India, China, Hong-Kong, South-Korea, Malaysia, Taiwan, Saudi-Arabia, Indonesia and the Philippines</td>
<td>2012</td>
<td>2022</td>
<td></td>
</tr>
<tr>
<td>ASCOLT trial (NCT02647099)</td>
<td>Colorectal cancer</td>
<td>1200 Dukes B or C</td>
<td>300 mg of daily aspirin or placebo during 3 years</td>
<td>3 yr DFS</td>
<td>Switzerland, Hungary</td>
<td>2015</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>ASPIRIN trial (NCT0231286)</td>
<td>Colon cancer</td>
<td>1588 Stage II or III adenocarcinoma</td>
<td>100 mg of daily aspirin or placebo during 5 years</td>
<td>5 yr OS</td>
<td>Netherland, Belgium, Portugal</td>
<td>2015</td>
<td>2018</td>
<td></td>
</tr>
<tr>
<td>SAKK 4/11 (NCT0267782)</td>
<td>Colorectal cancer</td>
<td>896 Stage II and III adenocarcinoma</td>
<td>300 mg of daily aspirin or placebo during 3 years</td>
<td>3 yr DFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only the specifications of the colorectal arm of the Add-aspirin trial are provided in this overview

Abbreviations:
DFS: Disease-Free Survival
OS: Overall Survival
PIK3CA: phosphatidylinositol 3-kinase

Current evidence from observational studies

Four meta-analyses have addressed the effect of aspirin on survival in CRC. The most recent and comprehensive meta-analysis of Ewolof et al provides a complete overview of all relevant studies. In this meta-analysis, sixteen CRC specific studies of approximately 20,000 colorectal cancer patients were included. A reduction in all-cause mortality of 25% and a reduction in CRC specific mortality of 35% was demonstrated. The authors also noted several limitations of the included studies, such as the risk of bias and the use of self-reported aspirin use. In addition, the authors highlighted the need for further research to better understand the underlying mechanisms of the effects of aspirin on CRC survival.

The review also included a section on the role of aspirin in the prevention of CRC. Several population-based studies have shown a reduced risk of CRC in individuals who use aspirin. In a review of observational studies, a pooled analysis of fourteen studies found a 25% reduction in CRC incidence among users of aspirin. Another meta-analysis of ten studies found a 30% reduction in CRC incidence among long-term aspirin users. These findings support the use of aspirin as a preventive measure for CRC.

The review also discussed the role of aspirin in the treatment of CRC. Several studies have shown a survival benefit for patients who use aspirin as adjuvant therapy. A review of three randomized controlled trials found a 20% reduction in mortality among CRC patients who used aspirin as adjuvant therapy. Another study found a 30% reduction in mortality among CRC patients who used aspirin for more than five years. These findings support the use of aspirin as adjuvant therapy for CRC.

The review also considered the potential adverse effects of aspirin. Several studies have shown an increased risk of gastrointestinal bleeding among aspirin users. However, the review noted that the risk of bleeding was low and that the benefits of aspirin outweighed the risks in most cases. The review also noted the importance of individualizing aspirin use based on the risk of bleeding and the risk of CRC.

The review concluded that aspirin is a promising agent for the prevention and treatment of CRC. However, further research is needed to better understand the underlying mechanisms of the effects of aspirin on CRC and to develop personalized strategies for the use of aspirin.
### Table 2: Overview of observational studies assessing the effect of aspirin on survival in patients with colorectal cancer, adapted from Elwood et al.7

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Analysis of drug exposure (time-varying yes/no)</th>
<th>Moment of assessment of use</th>
<th>Results</th>
<th>Overall survival (OS)</th>
<th>CRC-spec survival</th>
<th>Source</th>
<th>Design</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bains et al.6</td>
<td>2016</td>
<td>Yes</td>
<td>Postdiagnosis</td>
<td>HR CRC-spec: 1.00 (0.87-1.14) HR OS: 1.06 (0.96-1.18)</td>
<td>Deaths/nonusers</td>
<td>Cancer Registry of Norway, The Norwegian Prescription Database</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 3 years</td>
<td></td>
</tr>
<tr>
<td>Bastiaannet et al.14</td>
<td>2012</td>
<td>Yes</td>
<td>At diagnosis and postdiagnosis</td>
<td>RR OS: 0.77 (0.63-0.95)*</td>
<td>No information</td>
<td>Eindhoven Cancer Registry-PHARMO Drug Cohort</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 3.5 years</td>
<td>(0–12)</td>
</tr>
<tr>
<td>Cardwell et al.11</td>
<td>2014</td>
<td>Yes</td>
<td>Postdiagnosis</td>
<td>HR CRC-spec: 0.99 (0.88-1.15) HR OS: 1.06 (0.94-1.19)</td>
<td>No information</td>
<td>Linkages between the National Cancer Data Repository, UK Clinical Practice</td>
<td>Nested case-control analysis from a cohort of 4794 cancer patients</td>
<td>Mean FU: 7.2 years</td>
<td>(range 1-13.6)</td>
</tr>
<tr>
<td>Chan et al.12</td>
<td>2009</td>
<td>No</td>
<td>Pre- and postdiagnosis</td>
<td>HR CRC-spec: 0.53 (0.30-0.86) HR OS: 0.89 (0.53-0.92)</td>
<td>72/17/60 250/711</td>
<td>No information</td>
<td>US Nurses and Health Professionals Cohorts</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 11.8 years</td>
</tr>
<tr>
<td>Coghill et al.13</td>
<td>2011</td>
<td>No</td>
<td>Only prediagnosis use</td>
<td>HR CRC-spec: 0.76 (0.61-0.94)</td>
<td>No information</td>
<td>Seattle Colon Cancer Family Registry</td>
<td>Cohort of cancer patients</td>
<td>Mean FU: 8 years</td>
<td></td>
</tr>
<tr>
<td>Din et al.15</td>
<td>2010</td>
<td>No information</td>
<td>Only prediagnosis use</td>
<td>HR CRC-spec:1.03 (0.88-1.31) HR OS: 1.12 (0.93-1.38)</td>
<td>69/158 124/350</td>
<td>Study of Colorectal Cancer Scotland, SRC/OES</td>
<td>Population-based case-control study in cancer patients</td>
<td>Median FU: 4.7 years</td>
<td>(IQR 2.37-5.74)</td>
</tr>
<tr>
<td>Domingo et al.16</td>
<td>2013</td>
<td>No</td>
<td>At diagnosis and postdiagnosis</td>
<td>HR DFS: 0.85 (0.55–1.35) HR OS: 0.89 (0.53-1.47)</td>
<td>14/1527 81/349</td>
<td>Series of patients from the VICTOR trial</td>
<td>Cohort study in trial cohort of cancer patients</td>
<td>Median FU: 6.15 months</td>
<td>(IQR 49.9-69.9)</td>
</tr>
<tr>
<td>Goh et al.16</td>
<td>2014</td>
<td>No information</td>
<td>Pre- and postdiagnosis</td>
<td>HR DFS: 0.38 (0.17-0.84)* HR CRCspec: 0.71 (0.43-1.16)*</td>
<td>160/634 21/92</td>
<td>Series of patients</td>
<td>Cohort study of cancer patients</td>
<td>FU ‘long term’</td>
<td></td>
</tr>
<tr>
<td>Jacobs et al.17</td>
<td>2012</td>
<td>No information</td>
<td>No information</td>
<td>HR CRC-spec: 0.63 (0.46-0.88)</td>
<td>116 deaths 67 deaths</td>
<td>CPS-II Nutrition Cohort</td>
<td>Cohort study of cancer patients</td>
<td>FU 6 years (1997-2003)</td>
<td></td>
</tr>
<tr>
<td>Liao et al.18</td>
<td>2012</td>
<td>No</td>
<td>Pre- and postdiagnosis</td>
<td>HR CRC-spec: 0.83 (0.61–1.23) HR OS: 0.87 (0.71-1.06)</td>
<td>240/561 192/403</td>
<td>Nurses Health Study and Health Professionals Cohorts</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 153 months</td>
<td>(IQR 104-195)</td>
</tr>
<tr>
<td>McCowan et al.19</td>
<td>2012</td>
<td>Yes</td>
<td>Pre- and postdiagnosis</td>
<td>HR CRC-spec: 0.58 (0.45-0.75) HR OS: HR 6.07 (0.57-0.79)</td>
<td>1101/1650 153/350</td>
<td>Cancer Registry records in Tayside region, Scotland</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 2.80 years</td>
<td>(IQR 0.63-6.21)</td>
</tr>
<tr>
<td>Ng et al.20 (same cohort and results as Fuchs et al.21)</td>
<td>2015</td>
<td>No information</td>
<td>Postdiagnosis</td>
<td>HR DFS: 0.68 (0.42-1.11) HR OS: 0.63 (0.35-1.12)</td>
<td>156/724 14/75</td>
<td>Series of trial patients from CALGB 89803</td>
<td>Cohort study in trial cohort</td>
<td>Median FU: 6.5 years</td>
<td></td>
</tr>
<tr>
<td>Reimers et al.22</td>
<td>2014</td>
<td>Yes</td>
<td>At diagnosis and postdiagnosis</td>
<td>HR OS: 0.64 (0.49-0.83)</td>
<td>396/917 69/182</td>
<td>Eindhoven Cancer Registry-PHARMO Drug Cohort</td>
<td>Cohort study</td>
<td>No information</td>
<td></td>
</tr>
<tr>
<td>Sun et al.23</td>
<td>2013</td>
<td>No information</td>
<td>No information</td>
<td>HR CRC-spec: 0.77 (0.52-1.14)</td>
<td>931 events total</td>
<td>US Nurses and Health Professionals Cohorts</td>
<td>Cohort study of cancer patients</td>
<td>Total FU: 28 years</td>
<td></td>
</tr>
<tr>
<td>Walker et al.24</td>
<td>2012</td>
<td>Yes</td>
<td>Pre- and postdiagnosis</td>
<td>HR OS: 0.99 (0.84-1.16)</td>
<td>No information</td>
<td>UK General Practice Research Database</td>
<td>Cohort study of cancer patients</td>
<td>Median FU: 1.7 years</td>
<td></td>
</tr>
<tr>
<td>Zanders et al.25</td>
<td>2015</td>
<td>Yes</td>
<td>Postdiagnosis</td>
<td>HR OS: 0.98 (0.93–1.03)</td>
<td>No information</td>
<td>Eindhoven Cancer Registry-PHARMO Drug Cohort</td>
<td>Cohort study of cancer patients</td>
<td>Median FI: 1.5 years</td>
<td>(IQR 2–3.4)</td>
</tr>
</tbody>
</table>

**IQR:** Interquartile range; **DFS:** Disease Free Survival; **CRC-spec:** Colorectal Cancer Specific; **CRC:** Colorectal Cancer

*HR for postdiagnosis use
CHAPTER 7
THE MORTALITY REDUCING EFFECT OF ASPIRIN IN COLORECTAL CANCER PATIENTS: INTERPRETING THE EVIDENCE

Methodology and bias

The overall goal of an epidemiological study is accuracy and precision in estimating the value of the parameter of interest, i.e. a measurement without bias. With the increased availability of population-based drug use information, the methods of analysis are increasingly important as are the consequences of biased analysis.

Nearly all types of bias can be categorised as either selection bias, misclassification bias or confounding:
1) Selection bias entails the selective recruitment into the study of subjects that are not representative of the exposure or outcome pattern in the source population.
2) Misclassification bias arises by incorrect information about either exposure or outcome or covariates for the study participants.
3) Confounding is a bias in estimating an epidemiologic measure of effect resulting from an imbalance of other determinants of disease (or their proxies) in the compared groups.

Immortal time bias

One important pitfall for observational studies is immortal time bias.11-12 Immortal time bias (also called survivor bias) has been described as a span of time in the follow-up period of a cohort during which the outcome under study could not have occurred, because subjects should be alive for the event to have occurred.21 Immortal time bias is a form of information bias.23

First, immortal time bias could have occurred in the method of how the use of aspirin was analysed. Person-time prior to the prescription should be analysed as unexposed (by the use of a time-varying covariate) and this will result in valid and precise risk estimates.25 Not using a time-varying covariate results in misclassification of drug exposure time. In studies where large prescription databases are used, immortal time bias is usually avoidable, but the risk of immortal time bias should be taken into account early in the designing of the study.22 This will be more problematic in studies where patients are defined as users by means of questionnaires at one (or several) time-points. When not accounting for this type of bias, this can cause an illusory strengthening of the protective effect of medication.21,23,24 Several publications found that when time-varying covariates are used properly they can even result in no effects of exposure.26 The study of Assayag et al found no association between aspirin mortality in patients with prostate cancer when using proper analysis techniques.25,26 In contrast, a large US cohort found only significant results when aspirin use was analysed as a time-varying covariate.17 The impact of these differences of analyses have been displayed in figure 1, where the hazard ratios of the observational studies of table 2 are plotted and grouped according to whether or not a time-varying analysis was used. Van Walraven et al demonstrated that appropriate time-dependent methods were used in only 40% of cohort studies published in prominent medical journals.27 Subsequently, Austin et al quantified the impact of immortal time bias in drug exposure studies and found that the estimated treatment effect varied from 4% to 27% mortality reduction in these studies when the time-varying nature of the treatment was ignored, when there was no actual treatment effect.24

Protopathic bias

Another form of bias that is likely to occur in drug exposure studies is reverse causation, also referred to as protopathic bias.28 This type of bias appears when the outcome leads to changes in exposure, e.g. if cancer recurrence causes early symptoms. As a result, patients may use pain medication for early symptoms of disease and therefore, pain medication may appear to be associated with increased cancer recurrence.28,40 It is unlikely that this type of bias may have influenced the results of the observational studies of aspirin and CRC mortality because aspirin is hardly used as an analgesic these days. Even more, the use of aspirin as analgesic would dilute the association between improved survival and the use of aspirin and not cause reverse causation. Lastly, aspirin in low-dose is not indicated as an analgesic.

Confounding by indication

Confounding by indication (indication bias), is an important cause of bias in non-randomised studies, and present in several forms in the observational studies assessing the association between aspirin use and cancer survival.41 Confounding by indication occurs when the clinical indication for selecting specific treatment is also related to the outcome. When studying the effect of aspirin specific colorectal cancer survival, this is not applicable, but when studying aspirin use and the relation with overall survival this is could have influenced results.42,43

Several studies have suggested a difference in the association with survival with regard to the moment of starting aspirin. In general, most studies distinguish two groups of users; patients that use aspirin at the moment of diagnosis and continue after diagnosis (pre-and...
postdiagnosis use), and patients starting aspirin after being diagnosed with cancer (solely postdiagnosis use). In studies that assessed both pre- and postdiagnosis use and also solely postdiagnosis use, the effect was more pronounced in patients using aspirin only after diagnosis, which was confirmed by the meta-analysis of Ye et al.6

The moment of selection of users may introduce bias. Bias arises when patients are selected to be users only in the period after diagnosis of colorectal cancer. Commencing the use of aspirin after diagnosis implies that patients are considered fit enough for the prevention of cardiovascular disease according to their (cancer) prognosis (healthy user bias). As a result, the patients with the worst prognosis will end up in the group of nonusers and the survival benefit will appear to be (falsely) larger. An additional factor complicating factor here is that patients with worse cardiovascular disease warrant treatment with oral anticoagulation therapy (mostly coumarine derivatives). Aspirin is not supposed to be prescribed in combination with oral anticoagulation therapy because of the high bleeding risk, this has only been found appropriate in patients with mechanical heart valves.44-46 On the contrary, one advantage for the assessment of aspirin use commenced after diagnosis, is the ‘new-user design’. Because patients are not yet differentiated into groups of users and nonusers at the moment of CRC diagnosis, this implies that the groups of users and nonusers are equally comparable at the moment of diagnosis with a similar prognosis.

Regarding this observation, a study with data from the Swedish Cancer Register demonstrated that aspirin use in the year prior to diagnosis had a beneficial effect on tumor stage in patients with CRC with lower invasion depth of the primary tumor (T-stage) and less distant metastasis (M-stage) but not on nodal status.47 According to the authors this could partially account for the survival benefit found in patients using aspirin. As tumours are diagnosed in a lower stage, it could be that this can partially explain the observed survival benefit for patients that use aspirin both pre- and postdiagnosis. No difference was found between users of aspirin and non-users with regard to nodal status. This is an intriguing observation which the authors attribute to the antiplatelet properties of aspirin. Because platelets are not existent in the lymphatic systemic and therefore no effect of aspirin can be found in the nodal status.

Another hypothetical type of confounding by indication may result from earlier detection of tumours due to aspirin use, when aspirin induces early symptoms such as rectal bleeding or bleeding from polyps. This could however not been demonstrated by Rothwell, who studied time from randomisation to cancer incidence.48

Lastly, it could also be possible that patients who develop a tumour and already use aspirin are less sensitive for aspirin treatment, because the tumour developed in an environment where aspirin was already present. This was not found confirmed by the observations in an in vivo study, where mice were treated prediagnosis with aspirin and after tumour growth exposed to additionally postdiagnosis aspirin, versus mouse that were only postdiagnosis exposed. Both tumours were reduced in size with the use of aspirin after tumor diagnosis.48 Additionally, the meta-analysis of Elwood et al. did not detect a difference between the use of aspirin pre- and postdiagnosis and the use of aspirin solely postdiagnosis.7 Table 2 shows the timing of assessment of use of all current observational studies.

The effect of cardiovascular morbidity on cancer survival

The second form in which confounding by indication is also related to the indication for which aspirin has been prescribed to these patients. In the current guidelines, aspirin is solely indicated as medication for secondary prevention of CVD.52.53 Up until this point in time, the net value of aspirin as primary prevention for CVD could not be proven.52.53 This makes it reasonable to assume that all patients taking low-dose aspirin in observational studies should have a history of CVD.25,52 Despite (at least) one additional comorbidity (CVD) compared to other patients with cancer, patients taking aspirin seem to have a survival benefit over patients not taking aspirin. This paragraph will enlighten on the magnitude of the effect of CVD in patients with cancer on survival.

There are several mutual risk factors for both CVD and cancer, suggesting a shared biology: inflammation, oxidative stress, reactive oxygen species, hormones, and other metabolic reactions.53 Obesity, diabetes mellitus, hypertension, hyperlipidaemia, diet, and physical activity are further overlapping, lifestyle-related risk factors in CVD and cancer development.

The effect of CVD and the effect on the outcome of patients with cancer has been studied extensively. Patients with both CVD and cancer have a higher chance of overall and cancer specific mortality; 1.2 to 4.8 fold higher five-year mortality rates have been observed in patients with both cancer and CVD compared to cancer patients without comorbidity.25,54 In patients with cardiovascular diseases survival rates are comparable to patients with cancer within the age-cohort of 10 years older without cardiovascular disease.23 One study found that patients with previous cardiovascular condition have a HR of 1.66 (95% CI 1.20-2.31) for cancer specific mortality and this risk increases when patients have both previous CVD and another comorbidity.55 Patients with serious comorbid conditions and stage I cancer have similar survival rates compared to patients with no comorbidity and stage II cancer.26 Thirty-four percent of the mortality in the first year of follow-up for patients with a Charlson Comorbidity Index of four has been observed to be accountable for the interaction between comorbidity and cancer.28

That at least some part of the observed survival benefit can be attributed to confounding by indication is further supported by both short-term and long-term observed survival benefits of aspirin use. A study by van Erning et al. has provided insight in the long-term causes of death in patients with CRC in a Dutch population-based cohort.56 This study showed that the risk of dying from cancer diminishes with each additional survived year after diagnosis. The risk even decreases below 5% risk of dying from CRC five years after diagnosis.23 After these five years, there are still several studies showing a survival benefit for patients taking aspirin, suggesting that this benefit can hardly be from dying of CRC.52,56,60

Cancer specific mortality may be less likely when subjects are at risk of dying from another cause first, in this case cardiovascular disease.29 Additionally, if patients have very serious cardiovascular disease they are likely to die before they are able to develop a malignancy.24 On the contrary, patients with cardiovascular disease also experience more risk to die from colorectal cancer itself because of overall worse condition.24

The risk profile and unfavourable prognosis in patients with CVD is more emphasized in older patients. Colorectal cancer is associated with an increased comorbidity burden in
older patients when compared to the general population of elderly, severe comorbidity is subsequently associated with an increased overall mortality, HR 1.41 (95% CI 1.14-1.73).63 Older patients have an average of three comorbidities in addition to cancer.62 The proportion of patients with comorbidities increases with age; in an unslected cancer population in the Netherlands, 53% of patients aged 60-74 years have at least one comorbidity, up to 63% for patients 75 years and older with CVD being the most common comorbidity.65 Treatment of cancer patients with comorbidity tends to be different compared to patients with no comorbidity. Patients with comorbidity are less likely to receive surgery, chemotherapy and radiotherapy compared to patients without comorbidity.55 The underlying reason for the apparent under treatment is not clear from literature, but greater toxicity risk, poorer clinical quality, patient preferences, or poor adherence have been suggested as optional causes.56,66 Lastly, older patients and patients with comorbidity seem to receive less adjuvant chemotherapy which, at baseline, also worsens their prognosis.66 Additional to the increased risk of (cancer specific) mortality and reduced likelihood to receive treatment in patients with cardiovascular disease, complications of cancer treatment form an extra risk. Risk factors for CVD also predict cardiotoxicity from cancer therapy, e.g. for patients treated with trastuzumab, and this can consequently cause reduced treatment adherence leading to an additional worse survival.55

**Current evidence from Randomised Controlled Trials**

Rothwell et al. published a series of meta-analyses assessing the effect of aspirin from individual patient data from RCT’s, originally designed for primary or secondary prevention of vascular events.48,60,65,66 Additional data were collected with information on cancer incidence, cancer metastasis and cancer specific death for these meta-analyses. The first meta-analysis (n=14,033) in 2010 showed a 40-50% reduction in 20-year risk of death due to CRC in patients using low-dose aspirin.60 The effect of aspirin on cancer-specific mortality increased with treatment duration, with the largest effect observed in patients with gastrointestinal tumours, more specific in CRC.66 In several subgroups an even greater mortality reduction was found, such as patients with a tumour of the proximal colon and in patients taking aspirin in low dose.60,65

Despite the fact that the effect on cancer death was greater after additional years of follow-up, there was also a reduction in mortality in some cancer types already after 2-3 years since randomisation. This appeared to be too fast to effect carcinogenesis or early cancer growth and therefore the risk of metastasis was assessed in a next study.66 In this study, the risk of metastasis in patients diagnosed with CRC appeared to be lower when patients took aspirin (HR 0.26 (95% CI 0.11-0.57). The reduced risk of death in patients with CRC was greatest in patients without metastasis at diagnosis, compared to patients with metastasis at diagnosis.66 Additionally, it was observed that patients who continued aspirin after diagnosis of (localized) cancer have a lower chance of developing metastasis.64 The authors concluded that the early effects on cancer death can probably be contributed to reductions in cancer metastasis.66

The United States Preventive Services Task Force (USPSTF) has carried out a meta-analysis of the RCT’s for primary cardiovascular prevention, analysing the effect on (colorectal) cancer outcomes. The study found a RR of 0.67 (95% CI 0.52-0.86) on CRC cancer death for patients using long-term aspirin.67

One additional study with randomised data is the Women’s Health Study. This study randomised between alternate-day use of aspirin 100 mg versus placebo in healthy women, with a median treatment duration of 9 years. When the trial period was finished, post-trial aspirin use was additionally registered by means of annual questionnaires. After a follow-up of 12 years, a difference was found in the number of patients diagnosed with a metastatic adenocarcinoma (in favour of patients taking aspirin) but only in the group of patients who took additional aspirin in the period after the randomised treatment was finished. This effect could have been also the result of immortal time bias. No difference in cancer death was observed.68 In the Women’s Health Study no reduction in incidence of major CVD or CVD death was observed, correlating with the results of the study of Rothwell et al.65,66

The studies of Rothwell and his colleagues have made a valuable contribution in addition to the field of observational studies. What might have influenced the results of the above described observational studies, is confounding by indication, and this is largely avoided with the design of these meta-analyses. Some limitations remain, since most patients in the studies that were included in the meta-analysis (even in the primary prevention trials) have at least some risk factors for CVD and these risk factors overlap with the risk factors for cancer.65 The trials were not designed to assess cancer outcomes, and it could be possible that not all death causes were recorded thoroughly, compared to when this was planned prior to the study, and the registration of cancer specific details may be less accurate. Time from randomisation in the original trials was analysed until date of death, which is different from most observational studies, where time from diagnosis until date of death was analysed. This complicates the comparison between the observational studies and the RCT’s, because it is unknown if the actual time from diagnosis to death in the RCT’s is also improved for patients using aspirin.

One last study of the group of Rothwell et al. analysed if the post-hoc analysis of the cardiovascular prevention trials were comparable to observational studies. This study showed that the effects found in observational studies with a rigorous definition of exposure are consistent with the results in RCT’s. Sensitivity was particularly dependent on the appropriate and detailed recording and analysis of the use of aspirin.69

Despite the fact that the research group of Rothwell et al. concluded that the results of the observational studies are comparable with the results of the post-hoc results of the RCT’s, several important biases could have influenced the results of the observational studies. By raising the awareness about these biases, the interpretation of the current evidence may improve.

**RCT’s of aspirin and CRC**

In the field of CRC, there have been two RCT’s specifically designed to assess the effect of aspirin on cancer outcome which have been already completed. The first RCT, performed in 1982, assessed the effect of aspirin in patients with CRC, although with a very small number of patients (n=68) and the treatment period was only two years.70 The results did not show a significant difference between patients taking aspirin and placebo.
The CAPP2 trial assessed the effectiveness of 600 mg aspirin on cancer incidence in patients with Lynch syndrome and showed a significant reduction in time to first colorectal cancer. A significant association was observed only in patients who had taken the intervention for more than two years analysed in the per-protocol analysis, HR 0.41 (0.18-0.78). At present, the CAPP3 trial is ongoing to assess the most optimal dosage of aspirin as chemoprevention for patients diagnosed with Lynch syndrome. Rates of death were similar in any-dose aspirin versus the placebo groups.

Currently, several RCT’s are ongoing, designed to study the effect of adjuvant aspirin treatment on (cancer) survival in patients with colorectal cancer. An overview of these studies is provided in Table 1. Two trials recruit only patients with a phosphatidylinositol 3-kinase (PIK3CA) mutation and randomise between aspirin and placebo, ALASCCA in Sweden (NCT02647099) and the SAKK 41/13 trial in Switzerland (NCT02467582). These trials have been designed mainly based on the results of the study of Liao et al. where a hazard ratio of 0.18 (95% CI 0.06-0.61) was found in patients with a PIK3CA mutation.

After this first publication several other studies have been published on this topic, suggesting a relation between the effect of aspirin and a PIK3CA mutation on cancer survival.

All trials are united in the Aspirin Trialist Collaborative Group and have plans for elaborative meta-analysis once all trials have been published individually. This will provide answers for urgent questions regarding dose, tumour location, treatment duration and racial differences.

Future perspectives

Future observational studies should focus on proper methodology. Therefore we plead for (pharmaco)-epidemiologists to always be involved in studies analysing population based prescription data. Furthermore, an evolving and promising topic is Molecular Pathological Epidemiology (MPE). MPE is an integrative transdisciplinary science. Because molecular pathology tests are increasingly becoming routine clinical practice, pathology tests may be utilized in population-based studies. Therefore this could provide a solid base for future studies, and MPE should be used to expand current knowledge on the aetiology of the effect of aspirin.

Discussion

With this review we point out that the results of the current studies are promising, especially considering the results of the observational studies complemented with the results of the randomised data of Rothwell et al. and the USPSTF meta-analysis.

The hypothesis that death from multiple causes is prevented in a population with a high-risk of several causes of death, combined with the more favourable mortality estimates that tend to be found by routinely collected health data compared to RCT’s, indicate that the effect that the results from the ongoing randomised trials shall be lower than the results of the observational studies so far. As described in this review, the risk of (cancer) mortality in patients with cardiovascular disease is higher than in patients without cardiovascular disease. This implies that the potential benefit from aspirin in the overall cancer population will also be lower. The combination of the increased risk of (cancer-specific) death and the demonstration of the more marked effect of aspirin in older patients, suggests that the observed survival benefit of cancer patients taking aspirin is because multiple death causes are prevented. Aspirin has also been shown to be associated with a reduced cancer risk in patients with Lynch syndrome and it has been suggested that patients at highest risk of CRC are most likely to gain from chemoprevention. This has also been observed by the United States Preventive Services Task Force (USPSTF); the higher the risk for CRC, the higher the mortality benefit. Because of this expectation, the ongoing Aspirin trial is powered conservatively (HR of 0.75), allowing to still detect a significant difference between the group of patients using aspirin versus patients randomised to a placebo.

Some clinicians in current practice plead already for the regular use of aspirin based on the results of the current studies. However, with this review we aimed to demonstrate that with the many caveats left, this is a bridge too far. In the past decade there has been many media attention for aspirin as possible anti-cancer therapy. Patients and clinicians lean towards settling for the current evidence. Recruitment of the current RCT’s is lacking behind since some patients find the evidence too convincing and use aspirin regardless of the RCT’s. The meta-analysis of Elwood et al. endorses this statement. Despite the current existing limitations, the present evidence is promising, since multiple meta-analysis and pre-clinical studies show an effect of aspirin on cancer.

The results of the ongoing randomised trials will determine the effect of aspirin on survival in cancer patients. Before these trials have been finished, studies should focus on the working mechanism of aspirin in relation to cancer.

Conclusion

Current observational studies assessing the association between the use of aspirin and survival show mutually comparable results, but could have been subject to multiple forms of bias. The present, abundant number of observational studies and pooled trial data from the RCT’s of Rothwell et al. combined with the numerous and promising pre-clinical studies make it highly likely that the ongoing RCT’s will result in a survival benefit for colorectal cancer patients.
Conflicts of interest
Myrthe P.P. van Herk-Sukel is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. However, this study was not financially supported by a pharmaceutical company.

The remaining authors declare no competing financial interests.

All authors approved the final version of this manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements
The authors would like to thank M. Swets (Leiden University Medical Center) for preliminary data analysis and R.E. Langley (University College London) for reviewing an early draft of the manuscript.

Reference list