Review

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Review

The Association Between Colorectal Cancer and Pharmaceuticals with Emphasis on Low-Dose Aspirin and Anticoagulants

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Abstract: Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death. Chemoprevention has been widely explored due to its potential cost-effectiveness, availability, and scalability. Aspirin is the most researched chemopreventive medication, with a substantial body of evidence supporting its survival benefits, particularly with regular long-term use and in genetically susceptible individuals with COX-2 overexpression or PIK3CA mutations. The evidence suggesting that oral anticoagulation could facilitate early CRC detection is quickly accumulating. Metformin has demonstrated improved CRC survival, most likely by reducing the diabetes-mediated risk, but it could also potentially confer direct anti-tumor effects. Corticosteroids, statins, and beta-blockers have shown mixed results, highlighting the need for further exploration. Chemoprevention remains an active research field with the potential to deliver significant clinical benefits for CRC patients, optimizing care and providing personalized prevention strategies.

Keywords: colorectal cancer; aspirin; oral anticoagulation; metformin; chemoprevention; pharmacoepidemiology

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with approximately 2 million new cases diagnosed annually, and it remains the second leading cause of cancer-related death globally [1]. CRC incidence mirrors socioeconomic development: while incidence rates have stabilized or decreased in developed nations, developing countries are facing rapid increase in CRC burden [1]. As CRC continues to pose a growing global health challenge, particularly in low- and middle-income countries, there is increasing interest in preventive strategies that are accessible, cost-effective, and scalable. One such measure has been chemoprevention, as certain medications could serve as a cost-effective and accessible strategy to reduce CRC incidence or mortality. This is of importance given both the rising incidence of CRC in developing countries and the increasing use of common medications, especially aspirin and OACs [2,3].

However, studies examining medication use and cancer-related survival face notable methodological challenges, including immortal time bias, lead-time bias, the healthy user effect, and confounding by indication. Accurate assessment of medication exposure and disentangling mechanisms—whether affecting cancer progression, underlying risk factors, or detection—remains an ongoing challenge. Despite these complexities, high-quality pharmacoepidemiologic research that employs rigorous study designs and advanced statistical methods continues to provide valuable insights. In this review, we summarize current evidence on the association between CRC outcomes and the use of aspirin, OACs, metformin, and corticosteroids, and briefly discuss emerging data on beta-blockers and statins.

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2. Results

2.1. Aspirin and Colorectal Cancer

Aspirin (or acetylsalicylic acid) is an irreversible cyclooxygenase (COX) enzyme inhibitor widely used for the secondary prevention of myocardial infarction or stroke [4]. In an original publication from 1988 in Cancer Research, aspirin users had less often CRC compared to non-users, suggesting that aspirin could affect the incidence CRC [5].

Aspirin's inhibition of COX-2 likely reduces prostaglandin-mediated tumor progression, supporting its role as a chemopreventive agent. Inspired by this finding, numerous studies have since been conducted on the effects of aspirin on CRC-specific survival, including large, long-term observational cohort studies, randomized controlled trials (RCTs), and meta-analyses. Table 1 summarises the estimated effects of aspirin on CRC-specific survival and aspirin dose for notable and highly cited studies. This scientific body demonstrated that aspirin use might greatly reduce CRC-specific mortality by around 20-30%.

Table 1. Overview of notable and highly cited studies conducted on aspirin and colorectal cancer (CRC) specific survival.

Observational Studies	**Aspirin dose**	**CRC-specific survival* (Hazard Ratio (95% CI), p) (Relative Risk (95% CI), p)**
Lam et.al. 2025 [6]	Low dose**	sHR = 0.78 (0.76 – 0.81)
Skriver et.al. 2023 [7]	75-150 mg	HR = 0.90 (0.84 - 0.95)
Shahrivar et.al. 2023 [8]	75 or 160mg	HR = 0.99 (0.91 – 1.07)
Shami et.al. 2022 [9]	75-300mg	HR = 0.83 (0.76 - 0.91)
Sung et.al. 2019	Low dose**	sHR = 0.69 (0.59 – 0.81)
Tsoi et.al. 2018 [10]	Low dose**	sHR = 0.59 (0.56 - 0.62)
Cao et.al. 2016 [11]	81 or 325mg	RR = 0.81 (0.75 - 0.88)
Cook et.al. 2013 [12] - 8 year follow-up post-trial	100mg	HR = 0.80 (0.67 - 0.97), $p = 0.021$
Liao et.al. 2012 [13] **PIK3CA-mutated patients	81 or 325mg post-diagnosis	HR = 0.18 (0.06 - 0.61), p<0.001
Rothwell et.al. 2011 [14]	75mg	HR = 0.60 (0.45 – 0.81), p = 0·0007
Rothwell et.al. 2010 [15]	75mg	HR = 0.65 (0.48 – 0.88), p = 0·005
Chan et.al. 2009 [16]	81 or 325mg	HR = 0.71 (0.53 - 0.95)
Thun Michael et.al. 1991 [17]	Low dose**	Men: RR = 0.60 (0.40 – 0.89), p<0.001 Women: RR = 0.58 (0.37 – 0.90), p<0.001
Randomized controlled studies	**Aspirin dose**	**CRC-specific survival* (Hazard Ratio (95% CI), p) (Relative Risk (95% CI), p)**
McNeil et.al. 2018 [18]	100mg	HR = 1.77 (1.02 – 3.06)
Cook et.al. 2005 [19]	100mg	RR = 0.94 (0.79 - 1.11), p = 0.45
Meta-analysis	**Aspirin dose**	**CRC-specific survival* (Hazard Ratio (95% CI), p) (Relative Risk (95% CI), p)**

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Mädge et.al. 2022 [20]	Variable, most often low-dose**	HR = 0.74 (0.62 – 0.89)
Wang et.al. 2021 [21]	Variable, most often low-dose*	Cohort studies: RR = 0.85 (0.78 - 0.92) RCTs: RR = 0.74 (0.56 - 0.97)
Bosetti et.al. 2020 [22]	Variable, most often low-dose**	RR = 0.73 (0.69–0.78), p<0.001
Lin et.al. 2020 [23]	Variable, most often low-dose**	HR = 0.78 (0.73 - 0.85)
Algra et.al. 2012 [24]	Variable, most often low-dose**	OR = 0.58 (0.44 – 0.78), p=0·0002
Rothwell et.al. 2012 [25]	Low dose**	OR = 0.58 (0.38 – 0.89), p=0·008

*HR = Hazard ratio, RR = Relative Risk, OR = Odds ratio, 95% CI = 95% confidence interval, sHR = Subdistribution Hazard ratio. **Low-dose: usually between 75-100mg, some studies did not state a specific dose but stated low-dose aspirin.

In 2016, the U.S. Preventive Services Task Force (USPSTF) recommended the use of low dose aspirin for primary prevention of CRC in patients aged 50-59 years old, given that they would be willing to take low dose aspirin daily for at least 10 years and were not at increased risk of bleeding events [26]. They also recommended that patients 60-69 years old should make an individualised decision of taking daily low-dose aspirin for primary CRC prevention, granted they were not at increased risk of bleeding [26]. However, no recommendation was given for 70-79 year old patients, primarily due to lack of evidence, and that primary prevention occurred after consistent long-term use of aspirin, which is less applicable in the older cohort.

Unexpectedly, when examining mortality in the elderly, aspirin use was associated with increased CRC incidence and CRC-specific mortality (HR: 1.77 (1.02–3.06)) [18]. Subsequently, this was studied in more detail, and increased mortality was found for all solid cancers [27]. This contrasts with the evidence presented in Table 1, which includes patients over 70, so these results should be interpreted carefully. Additionally, a recent study found that patients over 70 had protective effects only if they had initiated aspirin therapy before age 70 [28]. Thus, different studies have shown conflicting results. There fore there is a need for future studies on aspirin use and its association with both CRC incidence and CRC mortality in the group aged over 70, to determine whether aspirin use could be beneficial or harmful.

The beneficial effects of aspirin on CRC-survival have consistently been shown to take a few years to develop. This was most prominently observed in the Women's Health Study conducted by Cook et al., a randomized controlled study (RCT) published in 2005, which did not find survival benefits when comparing aspirin use to placebo over a 10-year follow-up period [19]. However, in the 8-year post-trial follow-up, protective effects of aspirin use emerged with a sharp post-trial reduction of CRCs of 42% (HR, 0.58 [CI, 0.42 to 0.80]; P < 0.001) [12]. This finding of delayed effects has been consistently demonstrated in multiple large studies, finding that>5 years of aspirin therapy effectively improves CRC survival [7,14,15,29,30].

However, studies examining aspirin use initiated after CRC diagnosis have also shown CRC-specific survival benefits in aspirin-naïve patients at CRC diagnosis [16,31–33], with some studies suggesting no survival benefits [34,35]. Additionally, in a study by Rothwell et.al., aspirin use was associated with lower risk of metastatic disease compared to non-users, especially in CRC (HR 0·26, 95% CI 0·11-0·57, p=0·0008) [36]. These results could indicate that aspirin could delay or hinder the metastatic development of CRC. This is further supported by studies finding that the COX-2 enzyme playes a key role in promoting tumor metastasis [37–42]. Therefore, this could be a crucial mechanism by which aspirin lowers CRC mortality, both in overall patients, as a second prevention for current CRC patients, and in aspirin-naïve patients. This is most likely just one key mechanism by which aspirin could mediate its beneficial effects, as significant differences in stage IV diseases between aspirin users and non-users have not been observed.

This discovery of aspirin's chemopreventive effects on CRC mortality has led to numerous studies being conducted on the potential mechanism. Two mechanisms have been proposed: direct anti-tumor activity of aspirin or early detection through increased bleeding events.

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Aspirin's inhibition of the COX enzymes is often believed to be the primary mediator of the CRC survival benefits. COX-2 enzyme expression in CRC is involved in apoptosis, angiogenesis and invasiveness of the cancer [43]. Several studies have demonstrated that the COX-2 enzyme is overexpressed in most CRCs [44–47]. Furthermore, studies have shown explicit survival benefits in patients using aspirin and having CRCs with COX-2 overexpression or having a mutation in the PI3K pathway (PIK3CA mutation), causing increased COX-2 signaling [13,16,47]. This was demonstrated by Liao et.al., finding aspirin use after CRC-diagnosis in PIK3CA-mutated CRCs having improved CRC-specific survival (0.18; 95% CI, 0.06 to 0.61; P<0.001). This is important as it suggest that aspirin might affect only a part of the population diagnosed with CRC and might explain why some studies have found no effect (see Table 1). In the study by Liao et.al., only 17% of CRCs had PIK3CA mutations [13], while a study by Chan et.al. found 67% of tumors had COX-2 overexpression [47].

Aspirin's effects on CRCs with the PIK3CA mutation is a hot research topic [48], with results from a randomized controlled trial (RCT) that examined disease-free survival in CRC patients diagnosed at stages II-III, finding a clear trend towards improved survival in aspirin users [49]. Additionally, the preliminary results from the ALASCCA trial, a multicenter Nordic RCT, demonstrated an over 50% reduction in CRC recurrence in aspirin users when examining patients with PIK3CA-mutated CRCs [50]. Further results from the ALASCCA trial and future RCTs examining the PIK3CA mutations in CRCs will illuminate the effects of aspirin use and, with further risk/benefit studies on aspirin use, could lead to aspirin being used as a component of adjuvant therapy in CRCs.

Further supporting aspirin´s anti-tumor effects, several studies have demonstrated a reduction in colonic polyps among high-risk individuals. Regular long-term use of aspirin has been shown to reduce the incidence of CRC [51–54]. The RCTs examining aspirin and colonic polyps have demonstrated aspirin´s protective effects, particularly in patients with prior CRCs or colonic polyps [55,56], but not in men with average risk of CRC [57]. This suggests that aspirin's effects are not evenly distributed, as they may not carry overall protective effects for the population but may carry protective effects for individuals at high risk or with certain mutations.

One of the most important adverse effects of aspirin is the increased risk of bleeding, especially gastrointestinal bleeding (GIB) [58–60]. Since lower GIB events are the most common presentation of CRC [61–63], this could cause aspirin users to have increased detection through increased bleeding events. However, it would be expected that, on average, aspirin users would have been diagnosed at earlier stages compared to non-users in the observational studies in Table 1. To address this gap in the literature, further studies are required to assess the relationship between aspirin use, GIB events, and CRC, as it is unlikely that there would be a consistent survival benefit due to early diagnosis without staging being different in aspirin users compared to non-users.

Lastly, aspirin use has been associated with protective effects in patients with Lynch syndrome [64,65]. Lynch syndrome, caused by germline mutations of DNA mismatch-repair mutations (MMR), accounts for approximately 5% of all CRC, but carriers of these mutations have a lifetime risk of around 50% of CRC [66]. The CAPP2 study was a multicenter RCT that compared 600mg of aspirin to placebo in patients with Lynch syndrome, and aspirin reduced CRC risk substantially (HR = 0.65 (95% CI 0·43–0·97; p=0·035)) [67].

2.2. Oral Anticoagulation and Colorectal Cancer

The use of oral anticoagulation (OAC), including vitamin-K antagonists (VKA) or direct oral anticoagulants (DOACS; including rivaroxaban, apixaban, dabigatran, and edoxaban), has been increasing in recent decades [68,69]. Their most common serious adverse effects are the occurrence of GIB events and that has led to the hypothesis that their use might lead to early detection of tumors in the gastrointestinal tract. Since GIB events are the most common presentation of CRC [61,62], there has been great interest if OAC use could cause early detection of CRC. Additionally, OAC use has also been shown to disproportionally increase CRC-caused GIB events, further suggesting a potential early detection effect [70].

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In fact, a number of observational cohort studies have shown higher incidence of CRC detection in OAC users compared to non-users [71–74]. A Danish population-based and primary care study on GIB events, found that patients on OACs had more GIB events caused by CRC than non-users with GIB events, irrespective of age [74]. Similarly, a study from the UK found a significant association between OAC use and CRC incidence but no association between OAC use and any other cancer [75]. Therefore, both of the above mentioned studies indicated that patients taking OACs had more bleeding events from cancer, potentially facilitating early detection in the OAC users. However, none of these studies examined CRC staging or CRC survival, two key end-points that could further support the hypothesis of OAC use causing early CRC detection. Future studies would also need to evaluate how OAC use could affect CRC survival, as there have been hypothesis on the anti-tumor effects of warfarin but without clear evidence to support it [76,77]. With the increasing use of OACs, and particularly DOACs, there is a clear need to determine if their use could lead to early CRC detection with improved survival, which could suggest OAC users should undergo systematic follow-up and potentially justify earlier screening or shorter time intervals between screening.

2.3. Metformin and Colorectal Cancer

Most studies have indicated that metformin use is associated with lower CRC-risk. Metformin use has been associated with decreased CRC-risk, finding metformin to both lower the incidence of CRC (RR 0.76, CI 0.69–0.84, $p < 0.001$) and increase the CRC-specific survival (HR 0.66, CI 0.59–0.74, $p < 0.001$) [78]. Three meta-analyses suggest the same CRC-indicence lowering effects in metformin users compared to non-users [79–81] and a meta-analysis from Mei et.al. found a 34% decrease in CRC-specific mortality (0.66 (95% CI, 0.50 to 0.87)) [82] . Meanwhile, two quality large observational studies have not demonstrated metformin use to lower the CRC-incidene [83] or CRC-mortality [84].

Another added complexity to the metformin literature is the proposed effects of metformin. Metformin is used to treat type 2 diabetes (T2D) and two meta-analyses have demonstrated that patients with T2D had higher risk of CRC incidence [85,86] and CRC-mortality [85]. This has been further demonstrated that elevated hemoglobin A1c (HbA1c) is associated with worse short term outcomes, such as more aggressive cancer and higher rate of post-operative complications perhaps due to impaired metabolic control in these patients [87,88]. Additionally, in a meta-analysis, elevated HbA1c was associated with higher incidence and mortality from CRC [89]. In contrast, a large, well-conducted population-based study from Sweden found no association with increased CRC risk [90]. However, other studies have found that patients with T2D and CRC have increased risk of CRC-mortality compared to CRC patients without T2D [91,92]. This inconsistency underlines the further need for large studies assessing HbA1c levels and the CRC risk.

Some studies have indicated that the potential mechanism of metformin's beneficial effects are due to a reduction in tumor cell growth by the AMPK pathway [93–95]. This suggests that metformins' effects are not directly connected to its effects on patients with T2D. However, no studies have been conducted on metformin use without patients with T2D and those studies are unlikely as the potential benefit is unclear and metformin use has potential adverse effects. Additionally, separating the potential beneficial effects on metformin from the increased risk in patients T2D is challenging. Even though hypothesis of potential direct anti-tumor effects of metformin are intriguing, its clinical benefit may largely reflect mitigation of diabetes-related oncogenic risk. Large studies of high quality examining patients with T2D and assessing the severity of T2D using end-organ damage or Hb1Ac and the metformin dose would shed further light on the association of T2D, metformin use and CRC indicence and CRC-mortality.

2.4. Corticosteroids and Colorectal Cancer

As chronic inflammation plays a critical role in cancer development, it is unsurprising to see Ulcerative Colitis (UC) and Crohn's disease (CD) have increased risk of CRC [96,97]. Corticosteroids have been demonstrated to reduce CRC risk in UC and CD [98] and prolonged corticosteroid use has

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been associated with increased skin and bladder cancers [99–102]. Two population-based cohort studies have been conducted on the effects of prior corticosteroid use and CRC-incidence without finding any clear association [103,104]. However, to our knowledge, no study has been conducted on corticosteroids and CRC-survival and with the potentially complex and multifactorial effects of corticosteroids on CRC progression, this remains an exciting area for future research.

2.4. Statins, Beta-Blockers and Colorectal Cancer

Evidence on the potential beneficial effects on CRC risk of statins (or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase) have been debated. Statin's inhibition of cholesterole synthesis could cause a decrease in tumor growth, a basis for their potential anti-tumor effects [105]. A RCT demonstrated protective effects against recurrence of CRC in patients with prior CRC diagnosis [106]. Two meta-analyses have demonstrated a modest reduction in CRC risk in cohort studies, but not in RCTs [107,108]. Another meta-analysis demonstrated CRC risk benefits, both for overall and CRC-specific mortality, and both for pre-diagnosis and post-diagnosis statin use [109]. The CRC-specific mortality reduction of statins was demonstrated again in two meta-analyses [110,111]. This inconsistent data, heterogenetic studies suggests that future studies are needed to examine the association of statins and CRC risk, and to assess if this is mediated by direct anti-tumor effects or by mitigating the risk from hyperlipidemia.

There is growing evidence to suggests that beta-adrenergic pathways could play important role in cancer-mediaded cell proliferation, apoptosis and angiogenesis [112]. This has generated interest in the effects of beta-blockers on CRC risk, potentially identifying chemopreventive effects. The results from two population-based studies from the Netherlands did not suggest any potential benefits of beta-blockers compared to non-users [113,114]. However, when examining beta-blocker use by stage, stage IV CRC patients had improved survival rate compared to non-users [115,116]. These results was further seen in a recent meta-analysis, beta-blockers had marginally improved CRC-specific survival but stage IV CRC patients on immunotherapy had a significantly improved progression-free survival (HR 0.76; 95%CI, 0.62–0.92; P = 0.005) [117]. It is very interesting that the combination of immunotherapy and beta-blockers signal a significant improvement in survival for stage IV CRC patients. Assessing the survival benefit for the entire CRC cohort is difficult since the benefits found are either not significant or marginal.

3. Conclusions

Colorectal cancer is a growing challenge when considering the rising incidence rate in the world and the high mortality rate. Chemoprevention through widely used medications is exciting and holds promise for cost-effective and available strategies even in developing countries. Low-dose aspirin has been the most extensively studied medication, with consistent, clear beneficial effects on CRC survival, particularly among patients with COX-2 overexpression or PIK3CA mutations. Future research should aim to refine risk-benefit analyses in these genetically defined patient populations.

OAC use is increasingly hypothesized to facilitate early CRC detection via induction of GIB events, but robust studies are needed to identify hard end points such as tumor stage and survival outcomes. Metformin is associated with a survival benefit, most likely due to lowering of an increased risk factor in type 2 diabetes patients. Interestingly, these drugs all have either strong and consistent or emerging evidence of survival benefits for CRC patients, with very variable potential mechanisms. While corticosteroids, statins and beta-blockers have shown mixed results, their possible roles in CRC prevention and survival warrant further exploration. Future studies conducted on chemoprevention for CRC are likely to improve and deliver meaningful clinical benefits for CRC patients, including personalized preventive strategies and optimized care.

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Abbreviations

The following abbreviations are used in this manuscript:

CRC	Colorectal cancer
GIB	Gastrointestinal bleeding
OAC	Oral anticoagulation
COX	Cyclooxygenase

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