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Aspirin for prevention of colorectal cancer in the elderly: friend or foe?

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Abstract

Cancer is the leading cause of death among men and women aged 60-79 years. Colorectal cancer is the third most common cancer in males and the second most common in females, with about 0.8 million deaths worldwide per year. Individuals older than 50 years account for 20-50% of colonic adenomas. Several measures have been proposed to decrease colorectal cancer risks, such as an increase in dietary fiber, use of aspirin, and physical activity. Nonsteroidal anti-inflammatory drugs have been proposed as protective agents against the development of colorectal cancer and colorectal adenomas. Aspirin was the first pharmacological agent endorsed by the United States Preventive Services Task Force screening for colorectal cancer chemoprevention. Although studies have shown up to 40% colorectal cancer risk reduction in individuals at average risk, data regarding this benefit are inconsistent. Several recent studies show that prophylactic use of aspirin in elderly subjects may not be beneficial in preventing the occurrence of colorectal cancers. Given the risks associated with aspirin, such as non-fatal and fatal bleeding events, aspirin's role should be redefined, especially in individuals at risk of bleeding. This review provides a discussion of the recent studies on the role of aspirin use in elderly individuals at risk of colorectal cancer.

Keywords Aspirin, colorectal cancer, elderly, cancer prevention, chemoprophylaxis

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Introduction

Colorectal cancer (CRC) is a neoplasm developing from the colon or/and rectum. It is a global health problem, with more than 1.84 million new cases per year and 0.8 million deaths per year worldwide [1]. The incidence of and mortality from CRC is high in developed regions such as Australia, New Zealand, Europe, Eastern Asia, and North America [1]. This may be partially attributable to better screening practices and better access to health care. A low-fiber diet, low levels of physical activity, and environmental factors may play a role in the high incidence of CRC. The role of various diets and physical activity and the use of non-steroidal anti-inflammatory drugs has been discussed [2,3].

Aspirin use in CRC prevention has been reported in multiple studies in the recent past. Among the general population with an average risk of CRC, the United States Preventive Services Task Force (USPSTF) in 2015 recommended low-dose aspirin for subjects 50-59 years of age, regardless of sex [4]. It is a grade "B" recommendation for individuals with a 10-year atherosclerotic cardiovascular disease risk of 10% or higher, a life expectancy of at least 10 years, and no risk of bleeding (Table 1) [4,5]. For subjects 60-69 years of age with a 10% or higher risk of atherosclerotic cardiovascular disease, the USPSTF recommends an individualized decision (level of recommendation grade C). Potential difficulties associated with identifying candidacy include lack of predetermined endpoints (other than polyp recurrence), a relatively healthy population, drug-related adverse effects and drug-drug interaction, and relationship with comorbidities, which hampers the ability to identify the chemopreventive agents accurately. Recent studies show that the routine use of aspirin for primary prevention of atherosclerotic cardiovascular disease may be associated with a high risk of bleeding. Incidentally, aspirin use did not decrease the risk of cancer or all-cause mortality among

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Table 1 Society guidelines for aspirin and primary prevention of colorectal cancer

Society	Dose	Age	Ref
USPSTF	81 mg daily	50-59 years: Recommend low-dose aspirin* 60-69 years: Individual-based decision# Less than 50 or greater than 70 years of age: Insufficient evidence^	USPSTF [4]
Cancer Council Australia	100-300 mg daily	50-75 years	Council [85]

* ASCVD= 10% or higher who are not at increased risk of bleeding, average life expectancy at least 10 years; Grade A

ASCVD= 10% or higher who are not at increased risk of bleeding, average life expectancy at least 10 years; Grade C

^ Grade. No society guidelines available for Europe, China and Canada

USPSTF, United States Preventive Screening Task Force; ASCVD, atherosclerotic cardiovascular disease risk

patients with cancers (including CRC), especially in the elderly, in recent large trials [6,7].

Why focus on the elderly?

There are only limited data on the use of aspirin use for CRC prevention in the elderly. Elderly patients are a subset of the population who need special consideration for multiple reasons: they often have many comorbidities, a high risk of cancers, polypharmacy, often a discrepancy between physiological and chronological age, frailty, complex psychological issues, and a high risk of bleeding and thrombotic episodes [8-10]. The elderly are also at increased risk of gastrointestinal bleeding because of a higher prevalence of diverticula, intake of multiple drugs that affect the coagulation system, and advanced age *per se* [11]. The dose of antithrombotic agents, including aspirin, is also an important factor in the elderly because of their low glomerular filtration, low body weight and frequent drug-drug interactions [12]. Thus, the use of aspirin could increase gastrointestinal bleeding, interfere with chemotherapy, and potentially increase the risk of non-CRC-related *in situ* cancers [11,13,14].

This review presents the historical basis of the use of aspirin in the prevention of CRC, the theoretical basis of aspirin's benefit in the prevention of CRC, and lastly, current data on the efficacy and safety of routine use of aspirin in light of recent studies in the elderly population.

History of aspirin use in cancer prevention

Aspirin (or acetylsalicylic acid) was obtained initially from willow bark. Its use dates back to 400 BC when salicylic tea was used by Hippocrates and was part of the western pharmacopoeia. Willow bark was proposed for the treatment of inflammatory pain and to relieve the pain of childbirth in the 5th century BC [15]. In 1820, salicin was extracted from willow bark, and renamed as salicylic acid. Felix Hoffman, a German scientist in 1897, acetylated the hydroxyl groups of salicylic acid, resulting in acetylsalicylic acid. Two years later, in 1899, Bayer marketed its new drug, ASPIRin ("A" Acetyl, "SPIR" spireae flower) [16]. In 1971 the effect of aspirin in inhibiting the cyclooxygenase (COX) enzyme was described, and this knowledge led to the use of aspirin as a potential chemotherapeutic agent for cancer prevention [17].

Chemoprevention is the use of a chemical agent for the prevention or interruption of events early in the course of a disease. Aspirin has long been proposed as a chemopreventive agent for cardiovascular disease. Predetermined cardiovascular disease endpoints used to determine the efficacy of aspirin have generally been myocardial infarction, cerebrovascular events, and death from cardiovascular disease. However, determining a "surrogate endpoint" for cancer prevention has been a matter of debate. The reduction in polyp or adenoma burden has been considered a significant endpoint in the prevention of CRC. This endpoint led clinicians and investigators to identify chemopreventive therapies such as aspirin and COX inhibitors. However, the challenge in defining the role of these strategies involves a relatively short duration of 10 years and the potential risk of crossover to other studies [18,19].

Mechanism of aspirin anti-cancer effects

The anti-cancer effects of aspirin are thought to be mediated by its COX-dependent and independent mechanisms [20-23]. The cellular effects of aspirin in the prevention of CRC are noted in Table 2.

COX-dependent mechanisms

A- COX-1-mediated effects: Aspirin is rapidly absorbed in the stomach and upper intestine. It is hydrolyzed by esterases in the gastrointestinal mucosa and liver to form salicylic acid [24]. It enters the portal circulation and comes in contact with platelets for the first time. Levels of aspirin are significantly higher in the portal circulation than in the systemic circulation, because of its rapid clearance and half-life of 15-20 min [25]. While platelets express only COX-1, epithelial cells express both COX-1 and COX-2 enzymes [25]. Since non-nucleated platelets are unable to resynthesize the COX enzymes, exposure of platelets to aspirin, even for a short time, can have an effect that lasts their entire life in the circulation (Fig. 1, Table 2).

High levels of the drug are needed to inhibit COX-2 in epithelial cells compared to COX-1 in platelets [26]. COX-1 inhibition leads to decreased thromboxane (TXA2)

Table 2 Mechanism of actions of aspirin in colorectal cancer

Type of cell	Mechanism [20-23]	Role in colorectal cancer
COX-dependent pathway • COX-1 in platelets • COX-2 effects in epithelial cells	Aspirin inhibits COX-1, which leads to decreased production of thromboxane A2 required for platelet activation and recruitment Aspirin inhibits COX-2, decreases PGE2, which affects epithelial cells in paracrine fashion by binding to PGE2 receptor	In colorectal cancer inflammation, associated tumorigenesis is noted which is targeted by aspirin In colorectal cancer prostaglandin-endoperoxidase synthase-2 is upregulated, but is inhibited by aspirin
COX-independent pathway • β-catenin pathway • Angiogenesis inhibition • Apoptosis	Aspirin inactivates PP2A to stabilize cytosolic β-catenin	In colorectal cancer, β-catenin is upregulated, but is inhibited by aspirin.
Others • Host immune system	Affects MIC 1 and soluble TNF receptor	Reduces tumor-related inflammation

COX, cyclooxygenase; PGE2, prostaglandin E2; PP2A, protein phosphatase 2A; MIC 1, macrophage inhibitory cytokine 1; TNF, tumor necrosis factor

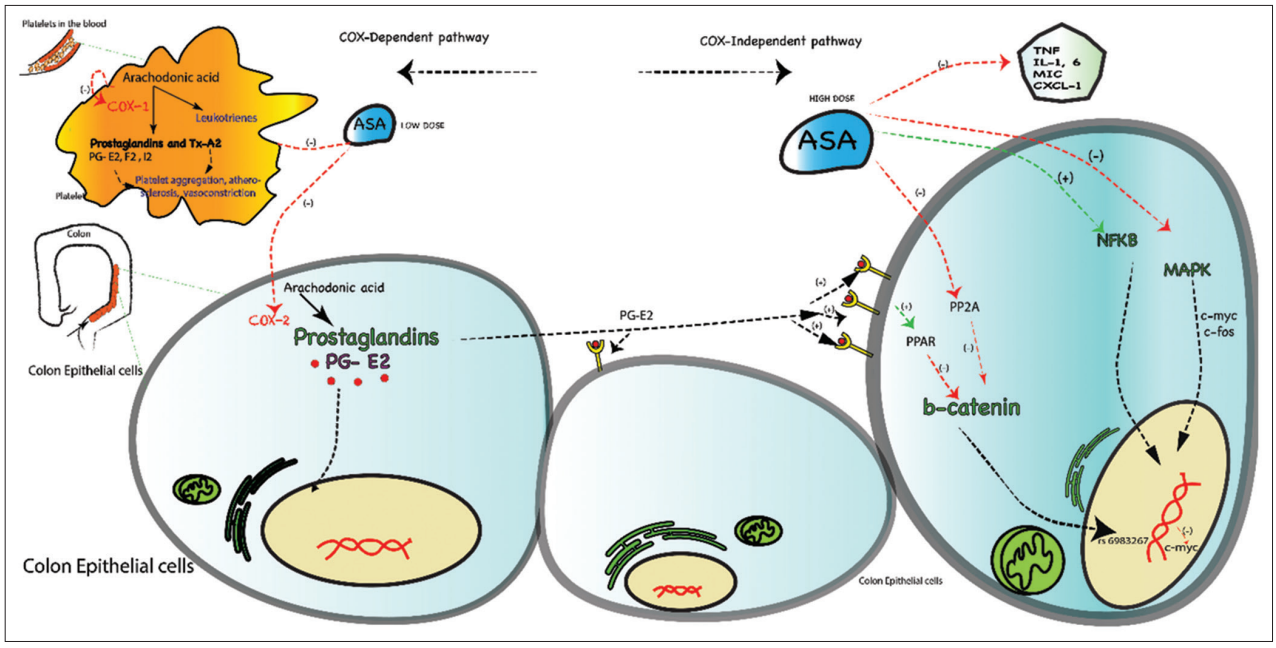

Figure 1 Schematic illustration of aspirin's role in colorectal cancer prevention *Cyclooxygenase (COX) dependent pathway* (Left panel): Inhibition of COX-1 in platelets and COX-2 in epithelial cells. Prostaglandins (PGs) are important derivatives of arachidonic acid. Prostaglandins and thromboxane A2 (TXA2) play a role in platelet aggregation, atherosclerosis, and vasoconstriction. Prostaglandin E2 *(PGE2) receptor* is involved in cell growth, survival, and proliferation. It is an essential target for hydroxyprostaglandin dehydrogenase (HPDG). COX metabolism also involves gene by environment (GxE), single nucleotide polymorphisms (SNP) rs2920421 and rs2965667, and prostaglandin M (PG-M). *COX independent pathway* (Right panel): WNT β-catenin is an important target for aspirin by inhibition of protein phosphatase 2A (PP2A). It is also inhibited by the peroxisome proliferator activated receptor (PPAR) induced by the paracrine effect of PGE2. Chromosome 8q24 has an important SNP, rs6983267, which lowers the expression of MYC proto-oncogene via WNT signaling. Furthermore, aspirin mediates its effects via a mitogenic activated protein kinase (MAPK) signaling cascade, nuclear factor kappa beta (NF-κB) and resulting apoptosis (via c-myc and c-fos). Aspirin exerts its anti-inflammatory effects by targeting soluble tumor necrosis factor (TNF) receptor 2 and macrophage inhibitory cytokine (MIC). These actions induce a reduction in the generation of cytokines interleukin (IL) -1 and -6, TNF and chemokines

formation, involved in platelet aggregation, atherogenesis and vasoconstriction. Aspirin also inhibits the formation of platelet aggregation inhibitor and vasodilator prostaglandin I2 (PGI2) in the vessel wall. While aspirin inhibits both TXA2 and PGI2, the TXA2 inhibitory effects predominate [27]. COX-1 inhibition by aspirin also inhibits the formation of prostaglandin E2 (PGE2). Suppression of PGE2 also contributes to aspirin's anti-neoplastic effects in the colon. PGE2 inhibition has been implicated in the aspirin role in colorectal chemoprevention [28].

B- COX-2-mediated effects: In addition to COX-1 inhibition, COX-2 inhibition also contributes to a reduction in colorectal carcinogenesis, especially in humans [29-32]. COX-2-dependent generation of lipoxins and polycyclic aromatic hydrocarbons is responsible for cell proliferation

and carcinogenesis [29,32]. COX-2 is induced at sites of inflammation in response to cytokines such as interleukin 1 (IL-1, α and β), IL-6, tumor necrosis factor (TNF), interferon-y and chemokines (CXCL1). These proinflammatory cytokines are elevated in CRC patients. Aspirin-mediated inhibition of C inhibitory cytokine-1, whose levels are elevated in the plasma of CRC OX-2, results in the reduction in these inflammatory cytokines [31].

Similarly, levels of macrophages are reduced by aspirin, conferring a theoretically protective effect against CRC [32]. Aspirin has also been shown to reduce the risk of CRC among individuals with certain single-nucleotide polymorphisms. An example of such polymorphisms includes the rs2965667-AA phenotype located on chromosome 12 [33]. Further, by inhibiting COX-2, aspirin reduces the expression of a wide variety of angiogenic factors, such as vascular endothelial growth factor, endothelin-1, nitric oxide synthase, and fibroblast growth factors. These antiangiogenic effects of aspirin may contribute to its salutary effects against the development of gastrointestinal cancers [34].

Aspirin also exerts its antineoplastic influence via indirect pathways that affect COX metabolism, acting on targets such as hydroxy PG dehydrogenase (HPGD), *SLC02A1* (the gene responsible for PG transporter), gene by environment (GxE), single nucleotide polymorphisms (SNP) rs2920421 and rs2965667, and PG-M, all of which are associated with the development of CRC [33,35,36].

COX-independent pathways

Aspirin's mechanism of action has been elucidated in multiple studies, and inhibition of platelet function and formation of PGs remain the most important among its anti-cancer effects [20]. However, COX-independent effects of aspirin, noted at high concentrations achieved with the intake of doses >300 mg per day, may also contribute to its cancer-limiting effect.

A- Aspirin-induced apoptosis: Apoptosis is critical for the control of colon epithelial cell number. Aspirin induces apoptosis via various mechanisms (Fig. 1) [37]. It modulates the mitogen-activated protein kinase (MAPK) signaling cascade involved in proto-oncogene BRAF mutations. It has been shown to lower the risk of BRAF wild type CRC through epigenetic dysregulation affecting the serrated cancer pathway [38,39]. Aspirin is known to induce nuclear translocation of the transcription factor NF-κB. The repression of NF-κB-driven transcription, irrespective of p53, induces DNA mismatch and halts the repair status [40]. Further, aspirin also induces caspase-dependent externalization of phosphatidylserine in colon cancer cell lines, even before nuclear condensation. These mechanisms, in part or in combination with its COX inhibitory effects, could explain aspirin's role in cell death by apoptosis.

B- Role of WNT β-catenin signaling axis: WNT β-catenin is a pathway dysregulated in a number of CRCs [41]. This pathway is activated by an extracellular ligand (WNT) on the cell surface receptors, which causes the stabilization of β-catenin and translocation of β-catenin to the nucleus. In the nucleus, it binds to transcriptional factors to form an activated complex responsible for gene expression, cell proliferation, and migration [42]. Reduced levels of β-catenin inhibit cell proliferation and CRC progression. A loss of function of the adenomatous polyposis coli gene leads to abnormal activation of WNT signaling, leading to cytosolic and nuclear accumulation of β-catenin, observed in the majority of CRC cases [43]. Aspirin reduces the pool of cytoplasmic β-catenin in CRC cell lines through its inhibitory effect on protein phosphatase 2A (PP2A) and the resulting ubiquitylation of β-catenin (Fig. 1). PGE-2 also effects β-catenin, in part via the EP2 receptor. PGE2 also increases transcription of peroxisome proliferator-activated receptor (PPAR), which combines with β-catenin to form a complex. This has been associated with the apoptotic resistance of CRC cell lines. Aspirin affects the PPAR pathway by targeting β-catenin and its downstream effects [44,45]. Chromosome 8q24 has an important SNP named rs 6983267, which lowers the expression of MYC proto-oncogene via WNT signaling and reduction in CRC by 17% [46]. Regular use of aspirin altered the risk of CRC expression in individuals with this SNP rs6983267; however, the details differed according to the genotype. Compared to non-users, regular use of aspirin was associated with reduced odds of CRC in GT genotype (odds ratio [OR] 0.61, 95% confidence interval [CI] 0.47-0.79) and in TT genotype (OR 0.52, 95%CI 0.35-0.78), whereas no benefit was noted in GG genotype (OR 0.99, 95%CI 0.70-1.40) [35].

C- Paracrine upregulation of COX enzymes: Paracrine upregulation of PGs is noted in CRC tissue. This is mediated by increased activity of the COX enzyme. Epithelial cells and macrophages in CRC have high COX-2 activity with increased dysplasia and submucosal invasion [47]. It is hypothesized that this increase in COX activity is probably from additional recruitment of platelets from excess inflammation and mucosal injury noted in the tumor tissue [48]. Some of these epithelial cells communicate with platelets in a paracrine fashion. Low-dose aspirin can irreversibly inhibit the COX activity in platelets, interfering with tumorigenesis. In addition, this combined antiplatelet and anti-inflammatory action of aspirin induces inhibition of the tumor growth [47].

D- Modulation of host immune response: Chronic inflammation, combined with modulation of the host immune response, plays a role in CRC progression. As PG synthesis increases at these sites, aspirin reduces the levels of cytokines and overall inflammation [49]. These effects are exerted by targeting multiple cytokines, such as soluble TNF receptor 2, macrophage inhibitory cytokine (MIC), IL-1 and 6, TNF, and chemokines [50]. Among these, aspirin use with high plasma levels of soluble TNF receptor 2 was associated with a lower risk of CRC (relative risk [RR] 0.39, 95%CI 0.41-1.79) [31]. Similarly, higher levels of macrophage inhibitory cytokine 1 were associated

with a 93% increased risk of CRC (hazard ratio [HR] 1.93, 95%CI 1.27-2.94), while the use of aspirin reduced the risk in PG-synthase-2-positive patients (RR 0.60, 95%CI 0.41-0.88) [51]. These anti-inflammatory effects may be another mechanism through which aspirin reduces tumor-related inflammation and tumor growth [52].

E- Inhibition of proto-oncogene: CRC in adults is mostly sporadic, and the majority of cases go through classic pathways of adenoma-carcinoma sequence [53]. An alternate pathway involves serrated polyp progression to serrated CRC in the last 5-10 years. This process involves the development of colonic mucosal cell mutations, and epigenetic alterations contributed by tumor-promoting factors from adjacent tissue (gut microbiome) [39]. The time required for this accumulation of mutations and the development of cancer is about 10-15 years. BRAF, a proto-oncogene in the MAPK signaling cascade, is strongly associated with the serrated CRC pathway [36]. Aspirin use was associated with a lower risk of BRAF wild type CRC (HR 0.73, 95%CI 0.64-0.83) [54]. By inhibiting this proto-oncogene, aspirin could potentially interrupt the serrated-carcinoma sequence.

Aspirin chemoprevention trials

In 1988, the Melbourne CRC study first identified that patients with CRC had a decreased use of aspirin-containing medications [55]. This was followed by multiple randomized controlled trials (RCTs) to evaluate the protective role of aspirin. Many subsequent RCTs studied the role of aspirin for CRC prevention. Important questions, however, remain regarding the dose of aspirin, duration of its use, population specificity, follow-up duration and type of aspirin (enteric-coated or not) in relation to its protective value against CRC, particularly in patients aged more than 60 years [19,56].

RCTs involving aspirin for CRC for chemoprevention

The results of some major RCTs on the role of aspirin in CRC prevention are shown in Table 3 [19,57-64]. As shown in Table 4, data related to the efficacy of aspirin for the prevention of CRC in subjects over the age of >60 years appear less robust [6,62,65] (Tables 3,4).

A- In-favor trials (protective role) of aspirin in CRC: Studies conducted until 2014 showed a protective effect of aspirin against CRC adenomas and cancer incidence and mortality [66,67]. The aspirin doses in the studies ranged from 81-325 mg [68]. Few studies were conducted in patients at high risk of developing CRC (with the history of multiple polyps diagnosed on prior colonoscopy or adenocarcinoma restricted to the mucosa). In 2007, the British Doctor Aspirin Trial and the UK-TIA Aspirin Trial showed that aspirin reduced the incidence of CRC if it was given for 5 years or more in patients with a mean age of 60 years or higher [69]. However, this effect was only seen after a latency of 10 years and was most pronounced 10-14 years after randomization. Analyses of multiple RCTs to assess revealed a chemoprotective effect after 3 years of exposure of aspirin [63]. In multiple RCTs performed to evaluate the protective role of aspirin in cardiovascular disease (Table 5), gastrointestinal and overall cancer risk was noted along with a higher incidence of bleeding [70-76]. In 2017, the incidence of CRC in individuals free of cardiovascular disease was assessed in cohorts with and without low-dose aspirin. It was noted that individuals aged 40-79 years taking low-dose aspirin for a mean period of 5 years had a lower incidence of CRC compared to non-aspirin users. However, this protective effect was not observed in subjects 80-89 years of age [77] (Table 5).

B- Not-in-favor trials (non-protective role) of aspirin in CRC: A recently published RCT (ASPREE) showed that the use of 81-100 mg of aspirin in adults 70 years or higher (age 65 years and more blacks and Hispanics in the USA cohort) with a mean follow up of 4.7 years showed an increased risk of CRC-related mortality (HR 1.77, 95%CI 1.02-3.06; P<0.05) [6]. The study population in this trial was predominantly Australian (16,703 patients) and had no previous exposure to aspirin. In addition to CRC, non-CRC-related deaths (breast, lung, lung, esophageal, and stomach) were higher in subjects given aspirin. In addition, the risk of death from any cause was 12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group (HR 1.14, 95%CI 1.01-1.29). Bleeding was not the primary cause of death in these patients (28 patients died from major hemorrhage among 558 deaths [0.3%]). A systematic review, published in 2019, of multiple published RCTs involving 165,502 participants showed that, compared with control, aspirin was associated with similar rates of cancer and cancer-related deaths, even on secondary analysis restricted to long-term follow-up trials (>5 years). Use of aspirin was associated with a higher risk of major bleeding (RR 1.5, 95%CI 1.33-1.69), intracranial bleeding (RR 1.32, 95%CI 1.12-1.55), and major bleeding (RR 1.52, 95%CI 1.34-1.73) [7].

On the other hand, a study in late 2019 that reported a prostate, lung, colorectal and ovarian cancer screening trial in elderly patients (aged 65 years or above) showed a protective effect, since the use of aspirin 3 times or more per week reduced the risk of CRC (HR 0.71, 95%CI 0.61-0.84; P<0.001) [78]. A similar trend was observed with all-cause mortality, any cancer, and gastrointestinal cancer (HR 0.75, 95%CI 0.66-0.84; P<0.001). The authors performed a subgroup analysis based on body mass index and frequency of aspirin intake (1-3 times intake per month, 1-2 times per week, or more than 3 times per week). Participants who were underweight (body mass index less than 20) did not benefit from aspirin use, while those with higher body mass index (20 kg/m^2 or higher) had reduced overall mortality, including CRC mortality [78]. Further, the authors noted the use of ibuprofen (<3 times per week) in the participants. This concomitant use of a non-steroidal anti-inflammatory agent could be a potential confounder in reducing the risk

Table 3 Trials of aspirin in colorectal cancer chemoprevention regardless of age

Study	Characteristics	Endpoints & Conclusions	Strengths & Weakness
Cook *et al* [60]	N=33,682 Follow up 10 years Dose 100 mg every other day Population: USA	*Primary endpoint*- Overall incidence of cancer *Conclusion*- Incidence of colorectal cancer was lower in aspirin group (HR 0.80, 95%CI 0.67-0.90; P=0.02)	*Strengths*- Large sample size. Extended duration of follow up (>10 years). Data on multiple confounders and variables available *Weakness*- Study restricted to females. Colorectal cancer was a secondary endpoint
Baron *et al* [57]	N=1121 Follow up 4 years Aspirin 81 mg and 325 mg Population: USA	*Primary endpoint*- Adenoma detection *Conclusion*- Long-term aspirin use associated with lower incidence of colorectal adenoma in 81 mg group (RR 0.81, 95%CI 0.69-0.96) and 325 mg group (RR 0.96, 95%CI 0.81-1.13)	*Strengths*- Comparison of different doses (81 & 325 mg) of aspirin and effect on adenoma and advanced adenomas *Weakness*- Wide age range from 21-80 years, inclusion of patients with a moderately elevated risk of colorectal cancer
Rothwell *et al* [19]	N=14,033 Follow up 18.3 years Aspirin 75 mg daily, 283 mg vs. 30 mg daily, 300 mg vs. 1200 mg daily, 500 mg daily. Population: British, Swedish and Dutch	*Primary endpoint*- Colorectal cancer incidence and mortality *Conclusion*- Long-term aspirin use associated with lower incidence of 20-year risk of colon cancer (HR 0.76, 95%CI 0.60-0.96) and mortality (HR 0.65, 95%CI 0.48-0.88)	*Strengths*- Follow up of 20 years to predict the effects of aspirin. Large sample size. Data availability on different dosing of aspirin *Weakness*- Aspirin group probably had higher rates of investigations due to side effects
Sandler *et al* [64]	N=517 Follow up 1 year Aspirin 325 mg daily Population: USA	*Primary endpoint*- Colorectal adenoma detection *Conclusion*- The adjusted relative risk of recurrent adenoma in the aspirin group was lower than placebo (RR 0.65, 95%CI 0.46-0.91)	*Strengths*- Risk of adenoma reduction after curative resection of colorectal cancer *Weakness*- Wide age limit from 30-80 years. Only one dose of aspirin used.
Benamouzig *et al* [58]	N=272 Follow up 4 years Dose of aspirin 160 or 300 mg daily Population: France	*Primary endpoint*- Colorectal adenoma detection *Conclusion*- Adenoma detection in aspirin group was lower than placebo (RR 0.73, 95%CI 0.52-1.04)	*Strengths*- Data available on the size of adenoma's and its relation with aspirin. Confounders such as smoking, body mass index, family history were accounted for *Weakness*- Wide age limit from 18-75 years. Limited power to show the protective effect of aspirin
Logan *et al* [62]	N=945 Follow up 4 years Dose of aspirin 300 mg daily Population UK and Denmark	*Primary endpoint*- Colorectal adenoma detection *Conclusion*- Adenoma detection in aspirin group was lower than placebo (RR 0.79, 95%CI 0.63-0.99)	*Strengths* Data available on aspirin alone and combined with folic acid. Data on adverse events, including GI bleeding, dyspepsia and mortality presented *Weakness*- Wide age limit from 18-75 years. Confounders such as body mass index, smoking not available

ASA, aspirin; CRC, colorectal cancer; CI, confidence interval; WHS, world health study; APACC, Association pour la Prevention par l'Aspirine du colorectal cancer Study Group; RR, relative risk; BMI, body mass index; UK, United Kingdom; USA, United States of America, CI, confidence interval; HR, hazard ratio

of CRC [78]. This highlights the importance of the duration and dosing of aspirin, frequency of administration, prior exposure to aspirin, and patient characteristics (body mass index and bleeding risks).

These findings suggest a need to explore the role of aspirin in elderly individuals, especially in those above 70 years. Due to advancing age, the incidence of age-adjusted cancer has risen significantly. Whether the initiation of aspirin in these individuals without prior exposure would theoretically increase the risk of cancer needs further study. Recent studies showing a lack of benefit of aspirin in primary prevention suggest a close evaluation of patients' cardiovascular disease status, age, and risk of overall cancer. Given the trend towards primary prevention with the use of statins, aggressive blood pressure control, decreasing trends of smoking, the risk of cardiovascular diseases in the individuals enrolled in these RCTs have decreased to <10%. In addition, there is also the risk of overestimating the atherosclerotic cardiovascular disease risk in a "real-world" population [79]. This might decrease the protective effects of aspirin in these populations, which could probably explain the results. Furthermore, the risk of bias (survivor, type of indication for aspirin use, reverse causation) needs to be assessed when the results of these studies are interpreted [80]. Lastly, older age and male sex may increase the aspirin-induced risks of bleeding and might affect the results of these RCTs. Some of the ongoing clinical trials

Table 4 Aspirin in colorectal cancer chemoprevention in elderly

Study	Characteristics	Endpoints and Conclusions	Strengths and Weaknesses
McNeil *et al* [6]	N=19114 Mean follow up 4.7 years Dose of aspirin 100 mg/ day Population: Australia (85%) & USA (15%) Name: ASPREE	*Primary endpoint*- disability free survival *Conclusion*- Aspirin use in healthy elderly did not prolong survival (HR 1.01, 95%CI 0.92-1.11; P=0.79) but led to a higher rate of major hemorrhage.	*Strengths*- Community-dwelling elderly included. Large sample size, confounders like smoking, hypertension, diabetes frailty were accounted *Weakness*- Short follow up duration for aspirin to exert its protective effects
Ishikawa *et al* [61]	N=389 Follow up 2 years Dose of aspirin 100 mg/ day Population: Japan	*Primary endpoint*- Adenoma or adenocarcinoma recurrence *Conclusion*- Low-dose aspirin reduced colorectal cancer and tumor recurrence in Asian population. Adjusted OR 0.60 (95%CI 0.36-0.98)	*Strengths*- All patients underwent colonoscopy prior to participation. Confounders like smoking, body mass index, alcohol were accounted for *Weakness*- Study restricted to the Asian (Japanese) population
Jacobs *et al* [65]	N=10931 men & 7196 women Follow up 11 years Dose of aspirin 325 mg or higher Population: USA	*Primary endpoint*- Overall incidence of cancer *Conclusion*- Long-term aspirin use associated with lower incidence of colorectal cancer (RR 0.68, 95%CI 0.52-0.90)	*Strengths*- Large sample size. Extended duration of follow up (>10 years). Data on multiple cancers *Weakness*- Colorectal cancer was a secondary endpoint. Indication for aspirin use not available

RCT, randomized controlled trial; ASA, aspirin, ASPREE (Aspirin in Reducing Events in the Elderly); CPS II, Cancer Prevention Study II

designed to determine the chemopreventive role of aspirin in elderly individuals are shown in Table 6 [59,81-83]. As more data emerge from these studies, some of the effects of reduced atherosclerotic cardiovascular disease risks and the role of age in aspirin-induced CRC chemoprevention may become clearer.

Ongoing trials of aspirin in CRC chemoprevention among the elderly

In response to the ongoing concerns about the effects of aspirin in the elderly population, various clinical trials have been initiated and are currently in different phases. Table 6 provides a list of clinical trials, completion date and dosing of aspirin used in these trials. For instance, aspirin intervention for the reduction in CRC risk (ASPIRED) is a prospective, double-blind, placebo-controlled randomized trial involving 180 participants, which is comparing the effects of low-dose (81 mg) and standard-dose (325 mg) aspirin on CRC [59]. Similarly, an observational study involving 1005 participants in Italy was initiated in 2019 to evaluate patients' preferences and their perspectives on the benefits and risks of low-dose aspirin for CRC prevention [81]. A randomized clinical trial in Spain of 60 participants is underway to assess the dosing and mechanisms of aspirin-induced chemoprevention in CRC. This study is currently in phase 2. Also in phase 2 is a clinical trial in the United States involving 90 participants to evaluate the role of intermittent dosing of aspirin for CRC prevention. It is estimated that this study could be completed by July 1, 2021 [83]. These clinical trials might shed light on the mechanism of aspirin-induced chemoprotection against colorectal carcinogenesis, especially in the elderly.

Clinical message

Aspirin is one of the most commonly prescribed pharmacological agent in the United States and beyond for a number of indications. Prophylactic use of aspirin for chemoprevention of CRC has been recommended by preventive task force for non-elderly average-risk individuals. However, data in elderly individuals have been inconsistent, with recent trials showing aspirin may not be beneficial, and the possibility of harm has been noted, with an increased risk of fatal and non-fatal bleeding events. Given these findings, prescribers should actively participate in educating their patients about the results of these recent studies. Furthermore, as our understanding of aspirin-induced chemoprevention in the elderly evolves, indications for this agent could potentially change in the future.

Concluding remarks

Chemoprevention of CRC with aspirin is dependent on age, risk factors for CRC, and the presence of comorbidities. Inhibition of the COX pathway is probably the most important mechanism by which aspirin exerts its preventative effect against CRC. Though there is some evidence of a protective effect of aspirin in chemoprevention against CRC from earlier studies, recent studies show little if any benefit, suggesting that the age and cardiovascular disease risk profile of the enrolled population play a role [6,7]. Although aspirin has been widely studied as a chemopreventive agent against CRC, gastrointestinal and renal toxicity in the long term preclude its widespread use [14]. Identifying the risk status of an individual (age, sex, mutations, environmental factors, baseline cardiovascular

Table 5 The role of aspirin in cardiovascular disease prevention with reduction of GI cancer and bleeding risks

Study	Characteristics	Incidence of cancer in aspirin group vs. placebo	Incidence of bleeding
ARRIVE (2018) [70]	N=6270 aspirin/ 6276 placebo Mean age 55 (men) 60 (woman) or older Start year 2007 End year 2016 Follow up 5 years Dose of aspirin 100 mg daily Population: 7 countries (Germany, Italy, Ireland, Poland, UK, USA, Spain)	*Colon cancer*- 14/6270 (0.22%) vs. 6/6270 (0.10%) *Overall cancer*- 73/6270 (1.16%) vs. 50/6270 (0.78%)	*Any GI bleeding*- 61/6270 (0.97%) vs. 29/6276 (0.46%) *Severe GI bleeding*- 4/ 6270 (0.06%) vs. 2/6270 (0.03%)
ASCEND (2018) [71]	N=7740 aspirin/ 7740 placebo Mean age 40 or older Start year 2005 End year 2011 Follow up 7.4 years Dose of aspirin 100 mg daily Population: UK	*GI cancer*- 157/7740 (2%) vs. 158/7740 (2%) *Overall cancer*- 896/7740 (11.6%) vs. 887 (11.5%)	*Any major bleeding*- 314/7740 (4.1%) vs. 245/7740 (3.2%) *Serious GI bleeding*- 137/7740 (1.8%) vs. 101 (1.3%)
AAA (2010) [72]	N=7740 aspirin/ 7740 placebo Mean age 50-75 years Start year 1998 End year 2008 Follow up 8.2 years Dose of aspirin 100 mg daily Population: Scotland	GI cancer- N/A Overall cancer-166/1635 (10.1%) vs. 194/1675 (11.5%)	*Any major bleeding*- 34/1675 (0.20%) vs. 20/1675 (1.1%) *Serious GI bleeding*- 9/1675 (0.54%) vs. 8/1675 (0.48%)
POPADAD (2008) [73]	N=638 aspirin/ 638 placebo Mean age 40 or above Start year 1997 End year 2001 Follow up 8.6 years Dose of aspirin 100 mg daily Population: Scotland	*GI cancer*- N/A *Overall cancer*- 53/638 (8.3%) vs. 68/638 (10.6%)	*Any major bleeding*- N/A *Serious GI bleeding*- 28/638 (4.4%) vs. 31/638 (4.9%)
PPP (2001) [74]	N=2226 aspirin/ 2269 placebo Mean age 50-65 years Start year 1994 End year 1998 Follow up 3.6 years Dose of aspirin 100 mg daily Population: Italy	*GI cancer*- N/A *Overall cancer*- 86/2226 (3.8%) vs. 80/2226 (3.5%)	*Any major bleeding*- N/A *Serious GI bleeding*- 17/2226 (0.77%) vs. 5/2226 (0.23%)
HOT (1998) [75]	N=2226 aspirin/ 2269 placebo Mean age 50-80 years Start year 1992 End year 1997 Follow up 3.8 years Dose of aspirin 75 mg daily Population: 26 countries	*GI cancer*- N/A *Overall cancer*- 294/9399 (3.1%) vs. 311/9399 (3.3%)	*Any major bleeding*: 136/9399 (1.5%) vs. 78/9399 (0.83%) *Serious GI bleeding*- 77/9399 (0.82%) vs. 37/9399 (0.40%)
BMD (1988) [76]	N=2226 aspirin/ 2269 placebo Mean age 50 to 80 years Start year 1978 End year 1997 Follow up 3.8 years Dose of aspirin 300 to 500 mg daily Population: UK	*GI cancer*- N/A *Overall cancer*- 119/3429 (3.5%) vs. 58/1710 (3.4%)	*Any major bleeding*- 29/3429 (0.85%) vs. 9/1710 (0.50%) *Serious GI bleeding*- 3/3429 (0.08%) vs. 3/1710 (0.02%)

AAA, aspirin for asymptomatic; ARRIVE, aspirin to reduce risk of initial vascular events; ASCEND, a study of cardiovascular events in diabetes; BMD, British male doctors; HOT, hypertension optimal treatment; POPADAD, prevention of progression of arterial disease and diabetes; PPP, primary prevention project; GI, gastrointestinal; N/A, not available, GI, gastrointestinal; N/A, not applicable

risks, risks of major gastrointestinal bleeding) [84] with an assessment of cumulative benefits (cardiovascular disease prevention) provides the best strategy for the use of aspirin to prevent CRC. As data emerge from ongoing trials, the CRC-preventing effect of aspirin may become evident, especially in the elderly population.

Table 6 Clinical trials investigating the role of aspirin in chemoprevention of colorectal cancer in the elderly as of December 31, 2019

Study	Phase, completion data, Location	Aspirin dose
ASPIRED: Aspirin Intervention for the Reduction of Colorectal Cancer [NCT02394769] [59]	N/A, July 2029 USA	81 mg aspirin vs. 325 mg aspirin
Patient-centered Benefit-risk Observational Study of Low-dose Aspirin for Cardiovascular Diseases and colorectal cancer Prevention [NCT03603366] [81]	Oct 31, 2019 Italy	Low-dose aspirin
Assessment of Direct Biomarkers of Aspirin Action to Develop a Precision Chemoprevention Therapy of colorectal cancer [NCT03957902] [82]	Phase II. May 2020 Spain	100 mg aspirin vs. 300 mg aspirin
Evaluating Intermittent Dosing of Aspirin for colorectal Cancer Chemoprevention NCT02965703 [83]	Phase II, July 2021	Aspirin less than 12 weeks vs. more than 12 weeks

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