The role of aspirin in cancer prevention

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Abstract | Clinical guidelines for prophylactic aspirin use currently only consider the cardiovascular benefits of aspirin, weighed against the potential harm from aspirin-induced bleeding. Daily aspirin use has been convincingly shown to reduce the risk of colorectal cancer and recurrence of adenomatous polyps, but in average-risk populations, these benefits alone do not outweigh harms from aspirin-induced bleeding. Recently published secondary analyses of cardiovascular trials provide the first randomized evidence that daily aspirin use may also reduce the incidence of all cancers combined, even at low doses (75–100 mg daily). This Review considers the general mechanism of action that defines aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) as a class, the specific advantages of aspirin over other NSAIDs for prophylactic use, the current evidence concerning the main health outcomes affected by aspirin use, and the hypothesis that inhibition of platelet activation may mediate both the cardioprotective and cancer-preventive effects of low-dose aspirin. It also considers how even a 10% reduction in overall cancer incidence beginning during the first 10 years of treatment could tip the balance of benefits and risks favourably in average-risk populations.

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Introduction

Despite optimism about the potential role of aspirin in cancer prevention, clinical guidelines for prophylactic use[1,2] currently only consider the cardiovascular benefits of treatment and whether these outweigh the potential harm from aspirin-induced bleeding. Protection against colorectal cancer has been considered, but the absolute benefit from reducing the risk of cancer at this site alone was considered insufficient to justify treatment in average-risk individuals, given the risk of bleeding, particularly serious gastrointestinal bleeding.[3] Until recently, there has been no evidence from randomized clinical trials to indicate that regular aspirin use protects against other forms of cancer and no attempt to integrate cancer prevention with the well-established cardiovascular benefits of aspirin treatment. There have also been unresolved questions about the dose and treatment regimen needed for cancer prevention. In particular, it has seemed implausible that the low-dose treatment (75–100 mg aspirin daily) recommended for cardioprotection[4] could effectively inhibit carcinogenesis through the mechanisms that had been proposed.

Recently published meta-analyses of results from randomized trials of daily aspirin treatment to prevent vascular events, summarized in Table 1, have provided provocative evidence that daily aspirin at doses of 75 mg and above might lower both overall cancer incidence[5] and overall cancer mortality.[5,6] In six primary prevention trials of daily low-dose aspirin, randomization to aspirin treatment was associated with an approximately 20% reduction in overall cancer incidence between 3 years and 5 years after initiation of the intervention (meta-odds ratio [OR] = 0.81; 95% CI 0.67–0.98) and a 30% reduction during follow up >5 years after randomization (meta-OR = 0.71; 95% CI 0.57–0.89).[5] Cancer mortality was also reduced during the >5 years of follow up after randomization (meta-OR = 0.63; 95% CI 0.49–0.82) in analyses that included 34 trials of daily aspirin at various doses.[5] Surprisingly, the size of the observed benefit did not increase with daily doses of aspirin above 75–100 mg. The risk of cancer with distant metastases was also reduced (meta-hazard ratio [HR] for all cancers 0.64; 95% CI 0.48–0.84), in a separate analysis of five randomized trials in the UK of daily aspirin use at ≥75 mg to prevent vascular events.[7] These meta-analyses excluded results from the Women's Health Study (WHS), a large 10-year-long trial of 100 mg of aspirin taken every other day, which reported no reduction in cancer incidence or mortality.[8]

The accumulating data from randomized clinical trials provide an exciting opportunity to reconsider the potential role of aspirin in cancer prevention. This Review first considers the general mechanism of action that defines aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) as a class and the specific advantages of low-dose aspirin over other NSAIDs in protecting against arterial thrombosis. It then summarizes the current status of evidence on the major health outcomes affected by prophylactic aspirin use, specifically cardiovascular conditions, bleeding complications, and cancer. We then consider the various mechanisms that have been proposed to account for the chemopreventive effects of aspirin and discuss the hypothesis that inhibition of

Competing interests
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Key points

- Clinical guidelines for prophylactic aspirin use currently only consider the cardiovascular benefits of aspirin, weighed against the potential harm from aspirin-induced bleeding
- Daily aspirin use has been convincingly shown to reduce the risk of colorectal cancer but in average-risk populations this benefit alone does not outweigh harm from aspirin-induced bleeding
- Secondary analyses of cardiovascular trials showed that daily low-dose aspirin use may also reduce the incidence of all cancers combined, although uncertainty remains about the magnitude of the potential benefit.
- Even a 10% reduction in overall cancer incidence could substantially broaden the indications for prophylactic daily treatment with low-dose aspirin
- As daily treatment with low-dose aspirin was as effective as treatment with higher doses, inhibition of platelet activation may mediate both the cardioprotective and cancer preventive effects of low-dose aspirin

platelet activation may mediate both the cardioprotective and cancer preventive effects of low-dose aspirin. Finally, we consider how even a 10% reduction in the incidence of all cancers combined might tip the balance of benefits and risks in average-risk populations in favour of prophylactic treatment.

Background—general mechanism of action

The molecular mechanism that defines aspirin and other NSAIDs as a class is their ability to block the metabolism of arachidonic acid through the prostaglandin H (PGH) synthase or cyclooxygenase (COX) pathway.[9] Inhibition of COX activity decreases the formation of downstream tissue-specific signalling lipids known as prostanoids (Figure 1).[4] These prostanoids include prostaglandin (PG)D_2, PGE_2 and $PGF_{2\alpha}$, prostacyclin (PGI_2) and thromboxane A (TXA_2). TXA_2 is the major metabolite in platelets that promotes the activation and aggregation of platelets, vasoconstriction, and the proliferation of vascular smooth muscle cells. Two distinct isoforms of PGH synthase, derived from different genes, have been identified and designated COX-1 and COX-2.[9] COX-1 is constitutively expressed in most tissues and has a central role in platelet aggregation and gastric cytoprotection. COX-1 is the only isoform present in mature platelets where it is the source of TXA_2; COX-2 is constitutively expressed in several tissues (vascular endothelium, kidney and brain) and expression is induced in other tissues during inflammation, wound healing, and neoplasia. COX-2 is the main source of PGI_2 in the vascular endothelium.[4,9] A splicing variant of COX-1 mRNA has been identified that is occasionally referred to as COX-3;[10,11] however, there is little evidence of a functional COX-3 enzyme in humans.[12,13]

Although aspirin shares the same molecular targets as other NSAIDs, it differs importantly in how it inhibits the COX isozymes.[4] Whereas aspirin irreversibly inactivates COX-1 and COX-2 through selective acetylation of a critical serine residue within the 'COX-channel' (Ser529 and Ser516, respectively), NSAIDs compete with arachidonic acid for reversible binding to a common docking site (Arg120) within the COX-channel.[9] Thus, recovery of COX activity after treatment with aspirin requires *de novo* synthesis of the enzyme(s), whereas inhibition by other NSAIDs is reversible. Mature platelets, which contain only COX-1, are particularly susceptible to the long-lasting effects of low-dose aspirin treatment, because they lack a nucleus. Other nucleated cells can resynthesize COX isozymes within a few hours. Platelets also encounter a higher concentration of aspirin during their passage through the portal circulation than the concentration that reaches systemic tissues.[9,14] The systemic concentration of aspirin is 50% lower than in the portal circulation and decreases rapidly (half-life, 15–20 min) because of metabolism by liver and plasma esterases.[15] Thus, the typical aspirin regimen for cardioprotection (once daily administration of 75–100 mg) has negligible and transient effects on extra-platelet targets. Anti-inflammatory doses of aspirin (that is, >2,000 mg daily) do achieve sufficient systemic concentrations to inhibit COX-2 as well as COX-1 activity, but this inhibition can only be maintained in nucleated cells by repeated dosing three or four times daily.[9,4]

Direct inhibition of COX-2 activity is the main mechanism by which aspirin and other NSAIDs have been proposed to inhibit the development of certain cancers,[16,17] although other mechanisms have been hypothesized, as discussed below.[16–18] The hypothesis that the effect of aspirin on colorectal cancer is mediated by COX-2 inhibition is also supported by results from an epidemiologic study that found aspirin use was associated with lower risk of colorectal cancers that overexpressed COX-2, but was not associated with lower risk of colorectal cancers that showed weak or absent COX-2 expression.[19] Because low-dose aspirin selectively inhibits COX-1 in platelets, and only marginally and transiently inhibits COX-2, it has been considered implausible that the daily low-dose regimen used to inhibit arterial thrombosis could also effectively inhibit the development and/or progression of certain cancers. To address this inconsistency, we hypothesize that the antiplatelet effect of low-dose aspirin might mediate both its cardioprotective and cancer preventive effects.

Health effects of aspirin treatment

Cardiovascular disease

More than 50 randomized clinical trials have been conducted to assess aspirin for the prevention or treatment of cardiovascular conditions.[20–22] Meta-analyses and pooled analyses of these trials established that aspirin, even at low doses (30–100 mg daily), has substantial net benefit in patients who are at high risk of arterial thrombotic complications due to pre-existing occlusive vascular disease.[20–22] In contrast to low-dose aspirin, traditional NSAIDs and selective COX-2 inhibitors (coxibs) do not reduce the risk of atherothrombotic complications and might actually increase it, because of inadequate suppression of platelet COX-1 in conjunction with inhibition of COX-2 dependent biosynthesis of prostacyclin.[9] There is broad scientific consensus that prophylactic treatment with aspirin is beneficial for most patients who are at high risk of arterial thrombosis (such as, patients with evolving acute myocardial infarction, recovery from myocardial infarction, stable or unstable angina, bypass grafting

Table 1 | Overall cancer incidence and mortality results from randomized trials of aspirin versus control

Study	Outcomes (participants)	Regimen	Intervention and follow-up period	Results: RR or OR (95% CI)
Cancer incidence				
Women's Health Study[8]	2,865 (39,876)	100 mg every other day	Mean 10-year intervention and follow-up period	1.01 (0.94–1.08) during full follow-up period 0.98 (0.89–1.09) during follow-up >5 years
Pooled analysis of 2 UK trials with long-term follow-up[29,*]	1,572 (7,588)	300–1,200 mg per day	Median 23 years follow-up including mean 5-year intervention period	1.01 (0.88–1.16) for all cancers except colorectal 0.74 (0.56–0.97) for colorectal cancer
Pooled analysis of 6 trials of low-dose aspirin for primary prevention of vascular events[5]	1,632 (35,535)	75–100 mg per day	Mean intervention and follow-up period 4–8 years, depending on individual trial	0.88 (0.80–0.98) during full follow-up period 1.00 (0.88–1.15) during follow-up from 0 to <3 years 0.81 (0.67–0.98) during follow-up from 3 to <5 years 0.71 (0.57–0.89) during follow-up >5 years
Cancer mortality				
Women's Health Study[8]	583 (39,876)	100 mg every other day	Mean 10-year intervention and follow-up period	0.95 (0.81–1.11) during full follow-up period 0.96 (0.78–1.18) during following up >5 years
Pooled analysis of 3 UK trials of aspirin for prevention of vascular events with 20 years of follow up[6,‡]	1,634 (12,659)	75–1,200 mg per day	20 years of follow up, including a median intervention period of 4–7 years, depending on individual trial	0.80 (0.72–0.88) for all solid cancers 1.03 (0.74–1.43) for haematologic cancers Overall cancer mortality results below limited to participants scheduled for treatment for >5 years (1,378 deaths, 10,502 patients): 0.78 (0.70–0.87) during full 20-year follow up 0.79 (0.66–0.93) during follow up 0–10 years 0.77 (0.67–0.89) during follow up 10–20 years
Pooled analysis of 34 trials of daily aspirin for prevention of vascular events[5]	1,226 (69,224)	40–1,500 mg per day	Mean intervention and follow-up periods 1–8 years depending on individual trial	All 34 trials of daily aspirin at any dose: 0.85 (0.76–0.96) during full follow-up period 0.90 (0.76–1.06) during follow up 0 to <3 years 0.93 (0.75–1.16) during follow up 3 to <5 years 0.63 (0.49–0.82) during follow up >5 years Subset of 15 trials with doses ≤200 mg per day: 0.86 (0.75–0.99) during full follow-up period 1.01 (0.83–1.23) during follow up 0 to <3 years 0.87 (0.66–1.15) during follow up 3 to <5 years 0.63 (0.46–0.86) during follow up >5 years

*Overall cancer incidence not reported. Results specifically during intervention period not reported. ‡These analyses of cancer mortality include overlapping person time. Abbreviations: OR, odds ratio; RR, relative risk.

or angioplasty of coronary or peripheral arteries, acute ischemic stroke, history of ischemic stroke or transient ischemic attack, and lower limb arterial insufficiency).[1,22] The situation is less clear with respect to primary prevention. In a 2009 report, the Antithrombotic Trialists' (ATT) Collaboration concluded that aspirin therapy is beneficial in persons with existing occlusive vascular disease, but that "in primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds."[22]

Prophylactic aspirin use is more-broadly recommended in North America than in Europe. The US Preventive Services Task Force (USPSTF) recommends that men aged 45 years to 79 years and women aged 55 years to 79 years be encouraged to use aspirin when the benefits of aspirin for the primary prevention of myocardial infarction (for men) and ischemic strokes (for women) outweigh the potential harm of an increase in gastrointestinal haemorrhage.[1] Unlike the ATT, the USPSTF recommends the routine use of aspirin for many apparently healthy individuals with a moderate coronary risk (10-year risk 5–19%). The USPSTF calculations assume a gender difference in the cardiovascular benefits of low-dose aspirin and weigh the estimated reduction in 10-year risk of coronary heart disease (in men) or stroke (in women), against the estimated risk of bleeding.[1] A more-extensive analysis of primary and secondary cardiovascular trials by ATT has not substantiated either the gender difference or the net benefit of treatment for individuals at moderate levels of coronary risk.[22] A recent position paper of the Working Group on Thrombosis of the European Society of Cardiology[23] does not endorse a general recommendation for routine aspirin use in apparently healthy individuals at moderate level of coronary risk, unless additional long-term benefits of antiplatelet therapy become established.

Bleeding complications

The most-important side effect of aspirin is bleeding, predominantly in the upper gastrointestinal tract and rarely involving intracranial haemorrhage.[9] Doses above 30 mg per day increase this risk by inhibiting COX-1 activity and TXA_2 production in platelets, thereby reducing platelet aggregation and interfering with primary haemostasis.[9] Dosage levels of 75–325 mg per day approximately double the risk of major gastrointestinal bleeding from aspirin treatment, and the risk of bleeding increases with age.[4] NSAID-associated bleeding can occur throughout the entire gastrointestinal tract as measured in the CONDOR trial;[24] however, data on lower gastrointestinal tract bleeding are missing in most trials.

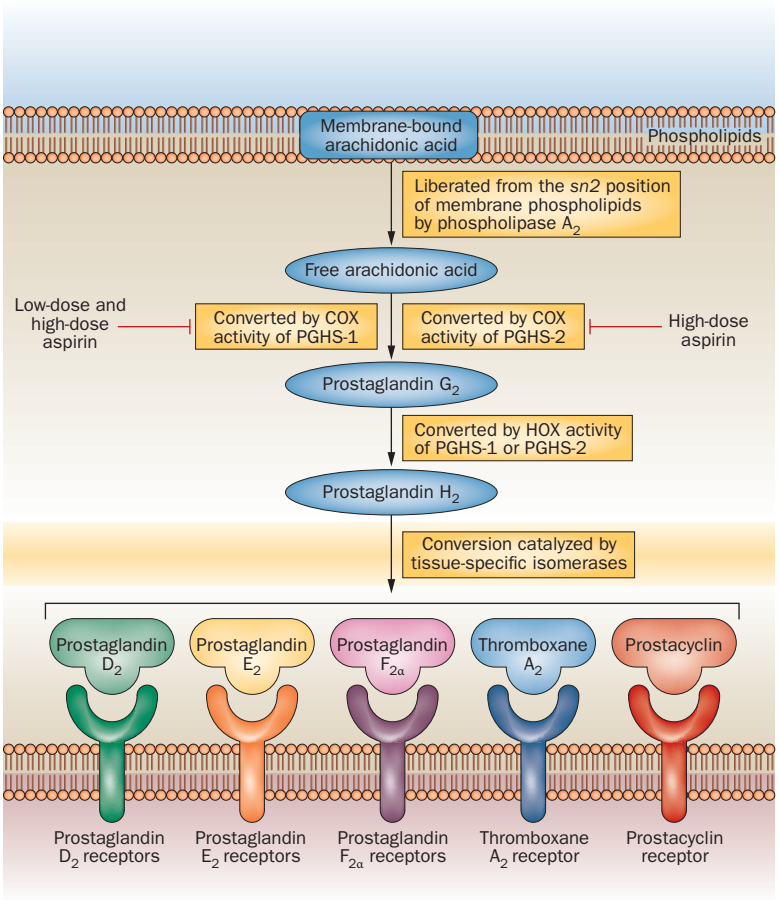

Figure 1 | Mechanism of action of high-dose and low-dose aspirin depicted on a simplified schematic of the cyclooxygenase pathway. The 20-carbon fatty acid arachidonic acid is released from the membrane phospholipids by several forms of phospholipase A_2, which have previously been activated by one of a range of stimuli. The free arachidonic acid is converted to the cyclic endoperoxides prostaglandin G_2 and prostaglandin H_2 by the sequential COX and HOX actions of PGHS-1 or PGHS-2; these isoforms both have dual COX and HOX activity. Aspirin acts to inhibit the conversion of free arachidonic acid to prostaglandin G_2 by inhibiting the COX activity of PGHS-1 (low-dose and high-dose aspirin) or PGHS-2 (high-dose aspirin). Prostaglandin H_2 is converted into a range of prostanoids by tissue-specific isomerases; therefore, the inhibition of this pathway prevents (or reduces) the downstream activation of a superfamily of G-protein-coupled receptors by these prostanoids. Abbreviations: COX, cyclooxygenase; HOX, hydroperoxidase; PGHS, prostaglandin H synthase.

At higher doses of aspirin, commonly used for analgesia (for example, 650 mg three times daily), sufficient concentrations are achieved to inhibit COX-1 in the gastrointestinal mucosa, thereby impairing PGE_2 and PGI_2 mediated cytoprotection of the gastrointestinal mucosa.[4] In contrast to the antiplatelet effect, which is independent of dose in excess of 30 mg daily, the gastrointestinal effects are dose dependent. Analgesic doses of aspirin amplify the risk of gastrointestinal bleeding and perforation by fourfold to 10-fold compared with no aspirin use.[4] Fortunately, these doses are substantially higher than those under consideration in most of the trials that report chemoprevention from regular aspirin use.

Cancer

The chemopreventive effect of aspirin has been convincingly established for colorectal cancer. Randomized clinical trials of daily aspirin treatment demonstrate that regular aspirin use reduces recurrence of colorectal adenomas,[25–28] incidence of colorectal cancer,[29–31] and mortality from colorectal cancer.[6,29,30] These trial results are also supported by numerous observational studies.[32] Recently published results from the CAPP2 trial demonstrate that allocation to 600 mg daily aspirin for a mean of 25 months reduces the incidence of colorectal cancer by about 40% in patients with high hereditary risk due to Lynch syndrome.[31] Prognosis after diagnosis of colorectal cancer has also been reported to be improved in patients who took aspirin in one observational study.[33]

As noted above, not all randomized clinical trials have observed lower risk of colorectal cancer in patients allocated to aspirin treatment. Neither the Physicians' Health Study (PHS),[34,35] nor the WHS[8] observed any reduction in colorectal cancer following alternate day treatment with 325 mg or 100 mg aspirin for 5 years or 10 years, respectively. Results were reported at the end of randomized treatment in the WHS[8] and at both the end of randomized treatment[34] and after 12 years of follow up (seven of these post-trial completion) in the PHS.[35] These null findings are plausibly attributable to the relatively short follow-up period, possibly in combination with alternate day dosing. A delayed effect of aspirin treatment on colorectal cancer was observed in a secondary analysis of three trials of daily aspirin use[6] in which no statistically significant reduction in mortality from colorectal cancer was observed until post-intervention follow up 10–20 years after initiation of the trials.

Meta-analyses of randomized clinical trials also suggest that daily aspirin use might protect against cancers of the esophagus and stomach as well as colorectal cancer,[6] although the effect on upper gastrointestinal tract cancers may also depend on the duration of treatment or length of follow up. No statistically significant reduction in the risk of either cancer was observed during the intervention period of seven trials of daily aspirin use.[6] However, in analyses of 20 years of follow up (including post-intervention follow up) from three of these trials, death rates from cancers of the oesophagus (HR = 0.36; 95% CI 0.18–0.71) and stomach (HR = 0.42; 95% CI 0.23–0.79) were reduced during the second 10 years of follow up.[6] Only for oesophageal cancer was the reduction in the mortality risk statistically significant during the full 20 year follow-up period (HR = 0.42; 95% CI 0.25–0.71; $P = 0.001$). Observational studies have generally reported lower incidence and/or death rates from cancers of the oesophagus[36–39] and stomach[36,39–42] among people who regularly use aspirin.

The evidence that aspirin protects against cancers outside the gastrointestinal tract remains provocative rather than conclusive for any single site. Analyses of the intervention period of seven trials of daily aspirin use observed a statistically significant reduction in cancer of the pancreas (HR = 0.25; 95% CI 0.07–0.92) during follow up occurring >5 years after randomization.[6] However, no association between aspirin use and cancer prevention was observed in analyses of 20 years of follow up (including post-intervention follow up) from three of these trials.[6] Associations between aspirin use and the

prevention of pancreatic cancer have not generally been reported in observational studies.[43]

Lung cancer mortality was not significantly decreased in analyses of the intervention period of seven trials of daily aspirin use,[6] but was significantly decreased (HR = 0.71; 95% CI 0.58–0.89) in analyses of 20 years of follow up (including post-intervention follow up) from three of these trials.[6] In the WHS, at 10-year follow up there was a statistically borderline reduction in the incidence of lung cancer (HR = 0.78; 95% CI 0.59–1.03).[8] A recent meta-analysis of observational studies found no association between aspirin use and lung cancer risk.[44] For breast cancer, the WHS—with a total of almost 40,000 participants—found no difference in incidence between women randomized to aspirin and those treated with placebo during 10 years of intervention and follow up (HR = 0.98; 95% CI 0.87–1.09).[8] A pooled analysis of randomized trials of daily aspirin use by Rothwell *et al.*[6] showed fewer cancers of the breast (27 versus 42) among women treated with aspirin than with placebo, although the difference was not statistically significant ($P = 0.07$).[5] Several reviews[45–47] and meta-analyses[48] of observational studies on this issue have concluded that aspirin use might reduce breast cancer risk by 10–20%, but that the evidence is limited by the lack of randomized clinical trials with long-term follow up. One observational study has reported improved survival in women who used aspirin after diagnosis of breast cancer.[49]

Prostate cancer mortality seemed to be lower among participants treated with aspirin than with placebo during a follow-up period >5 years after randomization in seven trials of daily aspirin use (HR = 0.52; 95% CI 0.20–1.34), although this reduction was not statistically significant.[6] Some suggestion of a reduction in prostate cancer mortality was also observed in analyses of 20 years of follow up (including post-intervention follow up) from three of these trials (HR = 0.81; 95% CI 0.61–1.06).[6] The evidence from observational studies was reviewed up to 2007 and judged to be inconclusive.[50,51]

Possible inverse associations have also been observed between aspirin use and several other cancers including ovary,[47,50,52] Hodgkin lymphoma,[53,54] non-Hodgkin lymphoma[55] and multiple myeloma.[51] Decreased risk of bladder cancer has been observed with other NSAIDs but not with aspirin.[56] Studies of kidney cancer produced inconsistent results.[50,57]

The evidence regarding the effect of daily aspirin treatment on all cancers combined comes principally from the secondary analyses of cardiovascular trials (Table 1).[5] While this outcome lacks specificity as a disease end point and its association with aspirin might depend on the mix of cancers in a particular population, it provides an aggregated estimate of the effect of aspirin treatment across multiple sites. As noted above, a 30% reduction in cancer incidence and a nearly 40% reduction in cancer mortality was observed during follow up occurring after 5 or more years of randomized treatment with daily low-dose aspirin.[5] These results conflict with the findings of the WHS, which found no association between alternate day low-dose aspirin use and either total cancer incidence (HR = 0.98; 95% CI 0.89–1.09) or mortality (HR = 0.96; 95% CI 0.78–1.18), even during the second 5 years of the 10-year intervention and follow-up period (Table 1).[8] Whether the difference in findings results from different dosing schedules (alternate day versus daily treatment), differences in study populations, or chance remains unclear. The 95% CI ranges overlap between the association with overall cancer mortality after 5 years of aspirin treatment in the negative WHS trial (HR = 0.96; 95% CI 0.78–1.18)[8] and those of low-dose aspirin in the positive secondary analyses by Rothwell *et al.*[5] (OR = 0.63; 95% CI 0.46–0.86; Table 1).

Cancer prevention mechanisms of action

Several features of the chemopreventive effects of aspirin against cancer might provide important clues about potential mechanisms of action. First, the chemopreventive effects occur at low doses (75–160 mg), as observed in secondary analyses of the cardiovascular trials[5,6,30] and in two randomized trials (AFPPS and APACC) with sporadic adenoma recurrence as the primary end point,[25,58] and higher doses do not seem to provide greater protection. Second, dosing at 24-h intervals seems to be adequate, despite the short half-life of aspirin and the ability of cells other than platelets to regenerate COX-1 and COX-2 within a few hours. Third, a clear reduction in mortality from gastrointestinal adenocarcinoma was observed in long-term follow up of the Thrombosis Prevention Trial (TPT),[30] which used a controlled-release formulation of 75 mg aspirin with negligible systemic bioavailability.[59]

None of these features are compatible with a direct inhibitory effect of low-dose aspirin on COX-2 or with various COX-independent mechanisms that have been proposed. Despite the strong clinical and preclinical evidence that implicates COX-2 expression in the promotion and progression of colorectal and other cancers,[16,19] treatment with low-dose aspirin once daily cannot achieve sustained inhibition of COX-2 in nucleated cells. As noted above, higher doses of aspirin (for example, 650 mg of aspirin administered three or four times daily) are needed to achieve sustained inhibition of COX-2. Other proposed mechanisms that are independent of COX include inhibition of NF-κB[19] and induction of polyamine catabolism.[60] However, the potential relevance of these alternative mechanisms is unclear because these effects were largely characterized at millimolar concentrations of aspirin in protein-free media at least two orders of magnitude above the peak concentration of acetylsalicylic acid in plasma (50 uM, largely protein-bound) achieved by oral dosing of 300 mg aspirin.[9]

Although all of the important features of the chemopreventive effect of aspirin noted above are inconsistent with either a direct inhibitory effect of low-dose aspirin on COX-2 or with the proposed COX-independent mechanism, they are consistent with a different hypothesis concerning how aspirin might inhibit colorectal carcinogenesis, namely that permanent inactivation of platelet COX-1 has a key role in preventing colorectal adenoma formation.[61] This working hypothesis is seemingly at odds

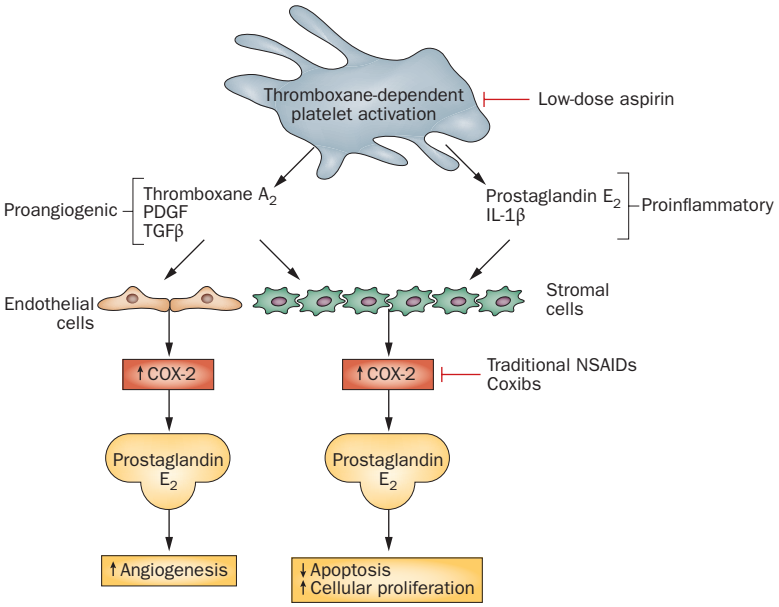

Figure 2 | Hypothesized mechanism by which the inhibition of COX-1 in platelets by low-dose aspirin may suppress the induction of COX-2 in adjacent nucleated cells of the intestinal mucosa in early stage neoplasia. Platelet activation at sites of intestinal mucosal injury might trigger downstream signalling events leading to reduced apoptosis, enhanced cellular proliferation and angiogenesis. The hypothesized mechanism by which the inhibition of COX-1 in platelets by low-dose aspirin may suppress the induction of COX-2 in adjacent nucleated cells of the intestinal mucosa in early stage neoplasia is depicted. The sequential involvement of COX-1 and COX-2 would explain the similar inhibitory effects of deletion of either gene on murine intestinal tumorigenesis, as well as the similar effects of low-dose aspirin and coxibs in preventing sporadic colorectal adenoma recurrence in man. Abbreviations: COX, cyclooxygenase; IL, interleukin.

with the proposed COX-2-dependence of early intestinal carcinogenesis. However, the two models could be reconciled if it was shown that activated platelets signal COX-2 upregulation in one or more adjacent cell types (for example, stromal cells) of the intestinal mucosa at sites of mucosal injury, where platelets are likely to be recruited and activated (Figure 2). Such a platelet-dependent effect might work through paracrine lipid (for example, TXA_2) or protein (such as interleukin-1β and PDGF) mediators. Indeed, Dixon *et al.*[62] demonstrated that activated platelets induce COX-2 expression in monocytes by combinatorial signalling to transcriptional and post-transcriptional checkpoints involving adhesion and cytokine signalling. The finding that deletion of either the *COX1* or the *COX2* gene reduces intestinal polyp formation in the Min mouse[63] is compatible with such a sequential paradigm. Also, the generally similar effects of low-dose aspirin[25,26,58] and conventionally used doses of coxibs[64–66] in preventing sporadic adenoma recurrence are consistent with the hypothesis that the early transformation of a normal intestinal epithelium into an adenomatous lesion might be blocked, at least in part, either by interfering with platelet activation upstream or inhibiting COX-2 activity downstream (Figure 2). Platelet inhibition might also be important in later stages of carcinogenesis, as extensive experimental evidence shows that platelets are important, if not essential, in the development of tumour metastases from the bloodstream.[67,68] Analogous platelet mediated mechanisms could also be relevant for inhibition of cancers other than colorectal cancer, but evidence is currently more limited.

Risk–benefit issues

Any attempt to integrate the potential cancer preventive benefits of aspirin use into existing algorithms that compare the cardiovascular benefits with the harmful effects on bleeding must rely on certain assumptions. Chief among these is the magnitude of the assumed benefit and the time period over which it accrues. The most conservative approach would be to consider only those cancer sites for which there is now strong evidence for chemoprevention and to delay any calculations of benefit until at least 10 years after the initiation of treatment. Under these assumptions, the additional benefits from cancer prevention would be small, because cancers of the colon, rectum and esophagus collectively contribute only 10–12% of all cancer cases and deaths,[69] and a 30–40% reduction in these will have a relatively minor impact on the overall benefit of treatment. By contrast, even a 10% reduction in the incidence of all cancers combined beginning during the first 10 years of treatment would have substantial impact on the overall balance of benefits and risks. We base our calculations on a hypothetical 10% reduction in overall cancer incidence. This assumed reduction might slightly overestimate benefits during the first 5 years of use, based on data from the pooled trial analyses showing no apparent reduction in cancer incidence during the first 3 years of use, and an estimated 20% reduction in risk during the fourth and fifth year of use. However, it may underestimate benefits after 5 years of use, based on data from the pooled trial analyses showing an estimated 30% reduction in incidence during this period.[5]

In comparing the risks and benefits of aspirin therapy, we based our estimates of cardiovascular benefits and risks from bleeding on the ATT meta-analysis of individual patient data from six primary prevention trials.[22] The probabilities of developing a serious cardiovascular event or extra-cerebral bleed in patients allocated to aspirin or placebo during 5 years of aspirin therapy are shown in Figure 3 for participants in four strata of age and sex. If only cardiovascular benefits and harm from aspirin-induced bleeding were considered, the reduction in cardiovascular events would be at least partially offset by the increase in major bleeds. As the ATT concluded, it is uncertain whether aspirin prophylaxis produces a net benefit in the context of primary prevention if only these end points are considered. However, if low-dose aspirin treatment also causes a hypothetical 10% reduction in overall cancer incidence, then the net effect of therapy becomes clearly favourable for a much larger population.

Caveats about the risk–benefit analysis

We present our analysis of risks and benefits as hypothetical rather than definite owing to several important uncertainties. First among these is that while some reduction in the risk of all cancers combined seems reasonably certain based on the available data, there is still considerable

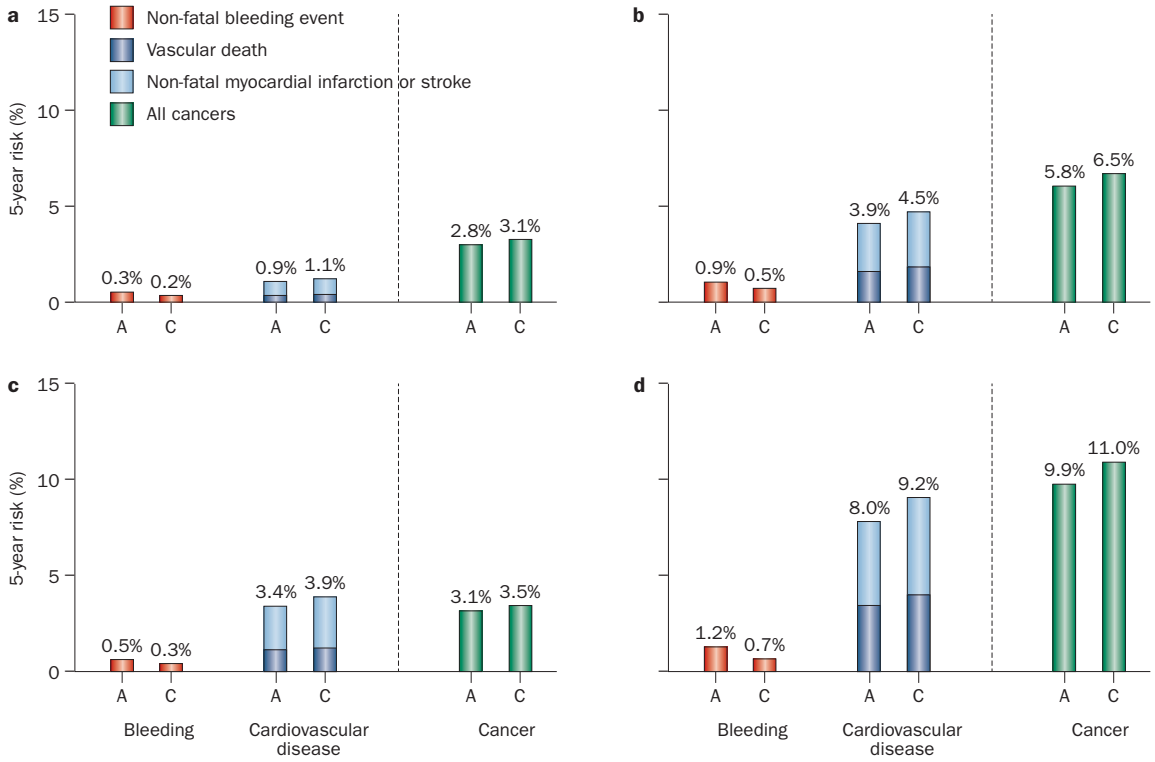

Figure 3 | 5-year risk of vascular events and major bleeding based on primary prevention trials of aspirin and placebo and hypothetical 10% reduction in cancer incidence by age and sex. Risk of vascular and bleeding events based on Antithrombotic Trialists' analysis of the six primary prevention trials.[22] Cancer risks based on an assumed 10% reduction in Surveillance, Epidemiology and End Results probabilities for sex and age.[68] **a** | Females, age 50–59 years. **b** | Females, age 65–74 years. **c** | Males, age 50–59 years. **d** | Males, age 65–74 years. Abbreviations: A, aspirin; C, placebo.

uncertainty about the magnitude and timing of the preventive effect of aspirin on cancer. The analyses by Rothwell and colleagues exclude the two large null clinical trials[8,35] in which aspirin was taken on alternate days. As yet no formal analysis has been presented that documents statistical heterogeneity between the results of trials of daily and alternate day aspirin use. The generalizability of these trials of daily aspirin use to broader and more-diverse populations in terms of race, ethnicity, socioeconomic status and comorbidities may be questioned. The size of the benefit will likely differ depending on the mix of cancers in different populations. Notwithstanding these uncertainties, the analyses of Rothwell *et al.*[5,6] were also conservative in many respects in estimating the effect on cancer. First, they were assessed as intention-to-treat cohorts, comparing aspirin groups in which not all patients took the drug and control groups in which crossover likely occurred after a few years.[5,6] Second, they examined the effect of taking aspirin daily for less than 10 years. The 10% reduction on cancer incidence used in our presentation of risks and benefits is hypothetical, rather than based on empirical data, and may substantially underestimate reductions in cancer incidence that would occur with continued aspirin use beyond 10 years.

Conclusions

An advantage of aspirin over other candidate chemopreventive agents is the availability of large randomized clinical trials that were originally conducted to study the cardioprotective effects of aspirin, but that can now be combined to study cancer end points. Results from secondary analyses of these trials have recently provided the first randomized evidence that prophylactic daily treatment with aspirin reduces incidence and death rates from all cancers combined, even at doses as low as 75 mg. An important limitation of the current evidence is uncertainty about the size of the chemopreventive benefit. However, even a 10% reduction in overall cancer incidence from aspirin treatment would substantially broaden the indication for treatment in populations at average risk. With respect to biological mechanisms, the fact that daily treatment with low-dose aspirin was as effective as higher doses raises the possibility that the inhibitory effect of aspirin on platelet activation may mediate both the cardioprotective and cancer preventive effects. Several important questions remain unanswered, such as the exact magnitude of the overall cancer benefit and which individual cancer sites contribute to this benefit. However, these new data bring us considerably closer to the time when cancer prevention can be integrated into the clinical guidelines for prophylactic treatment following regulatory review by the FDA and the European Medicines Agency.

An important first step in future research on this issue is for independent analysts to formally assess the heterogeneity of results between the trials of daily aspirin use and the two large null trials of alternate-day aspirin use.[8,35] These analyses should include both cancer incidence and

cancer mortality outcomes, and should stratify analyses by follow-up time. If compelling statistical evidence of heterogeneity is not present, analyses that combine results from trials of daily and alternate-day aspirin would be informative. Other recommendations for future research include: first, amend the protocols of ongoing primary prevention trials (ASCEND, ACCEPT-D, ARRIVE and ASPREE)[70] to collect prospective information about cancer during and after the scheduled randomized treatment; second, where possible, extend the follow-up period of completed randomized clinical trials of daily aspirin in order to measure the effect of aspirin therapy on individual cancer sites more precisely; third, assess the results from 20-year follow up of the Physicians Health Study and (when available) the WHS to clarify whether a protective effect appears with a longer follow-up period; fourth, conduct mechanistic studies to test the hypothesis that the effects of low-dose aspirin on early stage neoplasia are mediated through inhibition of COX-1 in platelets and the resultant decrease in the release of substances that induce COX-2 expression or directly promote tumour development; finally, use these mechanistic studies to develop novel biomarkers to more-precisely define the potential optimal dose and dosing regimen for long-term aspirin treatment.

Review criteria

This is not a comprehensive review of the literature, which is available in other reports.[1–3,9,16,17,22,32] The paper is a focused discussion of the key outstanding issues. Studies published since the release of recent comprehensive reviews were identified through periodic searches of PubMed using the search term "aspirin" and through the authors' ongoing personal involvement in research on these issues.

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