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REVIEW TOPIC OF THE WEEK

Aspirin and Cancer

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ABSTRACT

The place of aspirin in primary prevention remains controversial, with North American and European organizations issuing contradictory treatment guidelines. More recently, the U.S. Preventive Services Task Force recommended "initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years." This recommendation reflects increasing evidence for a chemopreventive effect of low-dose aspirin against colorectal (and other) cancer. The intent of this paper is to review the evidence supporting a chemopreventive effect of aspirin, discuss its potential mechanism(s) of action, and provide a conceptual framework for assessing current guidelines in the light of ongoing studies.
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Although first marketed in 1899, aspirin remains the cornerstone of antiplatelet therapy for the treatment of patients with acute coronary syndromes (1,2) and for the secondary prevention of atherothrombotic complications in high-risk patients (3,4). However, the place of aspirin in primary prevention remains controversial (5), with North American (6) and European (7) organizations issuing contradictory treatment guidelines. More recently, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation stating, "The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years" (8). This recommendation reflects increasing evidence for a chemopreventive effect of low-dose aspirin against colorectal (and other) cancer (4,9).

The intent of this paper is to review the evidence supporting a chemopreventive effect of aspirin, discuss its potential mechanism(s) of action (**Central Illustration**), and provide a conceptual framework for assessing current guidelines in the light of ongoing studies.

SOURCES OF EVIDENCE FOR A CHEMOPREVENTIVE EFFECT OF ASPIRIN

At least 4 independent lines of evidence suggest that regular use of aspirin has a protective effect against the development of CRC: 1) a large number of observational case-control studies and a meta-analysis thereof (10,11); 2) 4 randomized controlled trials (RCTs) in subjects with sporadic colorectal adenomas and a meta-analysis thereof (12); 3) an RCT of Lynch syndrome with post-trial follow-up (13,14); and

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ABBREVIATIONS AND ACRONYMS

ASA = acetylsalicylic acid

CI = confidence interval

COX = cyclooxygenase

CRC = colorectal cancer

CV = cardiovascular

CVD = cardiovascular disease

GI = gastrointestinal

IPD = individual patient data

OR = odds ratio

PGE_2 = prostaglandin E_2

RCT = randomized controlled trial

USPSTF = U.S. Preventive Services Task Force

4) an individual patient data (IPD) meta-analysis of 51 RCTs in the prevention of vascular events (15).

In 1988, Kune et al. (10) described the association between CRC risk and several chronic illnesses, operations, and various medications among 715 patients with CRC and 727 age- and sex-matched control subjects using data from a large population-based study of this cancer, the Melbourne Colorectal Cancer Study. There was a statistically significant deficit among cases in the use of aspirin-containing medications, and this was consistent for both colon and rectal cancer and for both men and women (10). This interesting finding, without an apparent mechanistic explanation, was confirmed by many subsequent epidemiological studies and a meta-analysis thereof (11). In case-control studies, regular use of aspirin was associated with reduced risk for CRC (pooled odds ratio [OR]: 0.62; 95% confidence interval [CI]: 0.58 to 0.67; $p < 0.0001$; 17 studies), with little heterogeneity in the effect among studies (11). Similarly, consistent reductions were observed in risks for esophageal, gastric, biliary, and breast cancer. Overall, the largest effects seen in case-control studies were on the risk for gastrointestinal (GI) cancers (OR: 0.62; 95% CI: 0.55 to 0.70; $p < 0.0001$; 41 studies) (11).

By the end of the past century, a large body of evidence had accumulated from both basic science, suggesting an important role of cyclooxygenase (COX) isozymes, particularly COX-2, in GI carcinogenesis, and from epidemiology, suggesting an association between the regular use of COX inhibitors (both aspirin and other traditional nonsteroidal anti-inflammatory drugs) and reduced risk for GI (particularly colorectal) cancer (16). This evidence was considered sufficiently convincing by the drug companies developing celecoxib and rofecoxib to initiate long-term RCTs to test the chemopreventive effect of selective COX-2 inhibitors in patients with sporadic colorectal adenomas. This evidence also prompted independent investigators to probe the chemopreventive effect of relatively low doses of aspirin (81 to 325 mg once daily) in the same clinical setting (i.e., the prevention of recurrence of a sporadic colorectal adenoma). The results of these RCTs were remarkably consistent in showing a 20% to 40% relative risk reduction in any adenoma recurrence (17) associated with 3-year treatment with a COX inhibitor, regardless of COX isozyme selectivity. However, the coxib RCTs also unequivocally established the cardiovascular (CV) hazard associated with these agents (18) and led to the halting of other ongoing cancer trials. In contrast, the results of the aspirin trials provided further impetus to basic and clinical research in the field of COX inhibition and cancer. An IPD meta-analysis of the 4 aspirin RCTs in approximately 3,000 participants with recent histories of sporadic colorectal adenoma (3 RCTs) or large-bowel cancer (1 RCT) demonstrated a 17% relative risk reduction in any adenoma recurrence, and a 28% relative risk reduction in the recurrence of advanced lesions (12), with no apparent dose dependence of the chemopreventive effect within the 4-fold range of daily doses used in these trials. In fact, a direct comparison of higher dose (300 or 325 mg/day) versus lower dose (81 or 160 mg/day) aspirin showed significantly greater risk reduction for any adenoma recurrence (the primary endpoint of these analyses) with lower dose aspirin. A similar comparison for advanced lesions yielded inconsistent and highly variable results (12). These findings provided convincing evidence that low-dose aspirin interferes with an early event in the transformation of an apparently normal intestinal mucosa into an adenoma, the precursor to most CRCs (**Central Illustration**).

A third piece of evidence for a chemopreventive effect of aspirin against CRC comes from CAPP2 (Colorectal Adenoma/Carcinoma Prevention Programme 2) (13,14), an RCT of aspirin 600 mg/day versus placebo in patients with Lynch syndrome, the major form of hereditary CRC. Up to 5% of CRCs result from Lynch syndrome, which is characterized by a mismatch repair gene defect (13). Although there was no detectable clinical benefit during the scheduled treatment period among carriers of a mutation for Lynch syndrome who received aspirin for up to 4 years (13), a statistically significant reduction in cancer incidence was found after a mean follow-up period of 56 months for participants completing 2 years of intervention (14), consistent with aspirin preventing early events in colorectal carcinogenesis. On the basis of these results, CAPP3 will explore the optimal dose of aspirin for people with Lynch syndrome by randomizing 3,000 subjects to 100, 300, and 600 mg/day (19).

Fourth, Flossmann and Rothwell (20) reported longer-term effects of aspirin on the incidence of cancer among British subjects in 2 early trials of aspirin for the prevention of CVD and cerebrovascular disease. There were significantly fewer CRC among subjects who received aspirin; however, this did not become apparent until 10 years after randomization, even though aspirin was given for only 4 years during the trial (20). Additional post hoc analyses of RCTs for CV prevention revealed that daily aspirin for about 5 years reduced incidence and mortality due to CRC by

30% to 40% after 20 years of follow-up and reduced the 20-year risk for all-cause cancer mortality by about 20% (21). Benefit increased with duration of treatment and was consistent across different study populations (21). Rothwell et al. (15) also performed IPD analyses of aspirin RCTs to assess the time course of the chemopreventive effect of aspirin. In 6 primary prevention trials of daily aspirin 75 to 100 mg (n = 35,535), overall cancer incidence was reduced from 3 years onward (324 vs. 421 cases; OR: 0.76; 95% CI: 0.66 to 0.88; p = 0.0003) in women (132 vs. 176; OR: 0.75; 95% CI: 0.59 to 0.94; p = 0.01) and in men (192 vs. 245; OR: 0.77; 95% CI: 0.63 to 0.93, p = 0.008), suggesting a potential effect in reducing the progression of pre-existing cancer and/or metastasis (15) (**Central Illustration**). In fact, the possibility that aspirin prevents distant metastasis could account for the early reduction in cancer deaths in these trials (22).

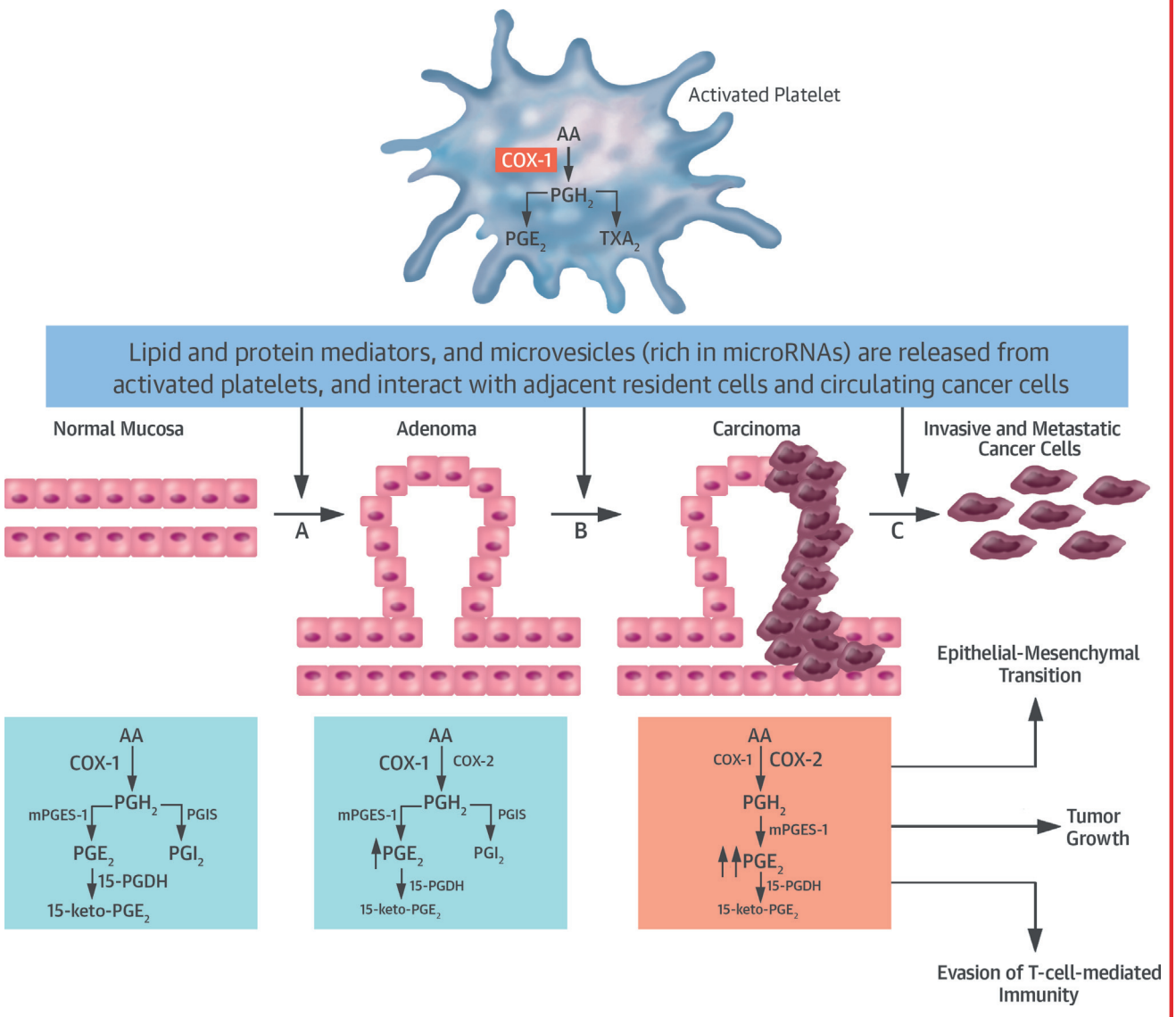
Within the limitations of post hoc analyses of cancer events that were not pre-specified endpoints of the aspirin trials for CV prevention, the results of these follow-up studies (15,20–22) indicate the following: 1) detectable benefits were seen at daily doses as low as 75 mg; 2) the apparent chemopreventive effect of aspirin was saturable at low doses (i.e., 10- to 20-fold higher doses were not more effective than lower doses); and 3) chemoprevention was apparent in men at high CV risk treated with a 75-mg controlled-release aspirin formulation developed to maximize cumulative inhibition of platelet COX-1 in the pre-hepatic circulation and minimize inhibition of COX-2 in the systemic compartment (23). Moreover, in the long-term observational follow-up of the Women's Health Study, reduced risk for CRC (a pre-specified secondary endpoint) was reported in association with alternate-day 100-mg aspirin versus placebo (24). Thus, the main characteristics of the chemopreventive effect of aspirin appear to recapitulate the unique features of its antiplatelet effect, that is, its long-lasting duration (25) and, most importantly, its saturability at low doses (25–27) (**Figure 1**). Strengths of these analyses include consistency of the evidence from many different trials, as well as the fact that 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; weaknesses include the largely retrospective nature of the analyses. Additional prospective data on the effects of low-dose aspirin on cancer incidence and mortality are currently being collected in at least 4 primary prevention RCTs in more than 50,000 asymptomatic participants recruited because of diabetes mellitus, advanced age, or an expected 10-year CVD risk >15% (4). Both the size and duration (5.0 to 7.5 years) of these RCTs should enable recording approximately 3,000 new cancer cases during follow-up (4), thus providing adequate statistical power to detect a moderate treatment effect of aspirin therapy.

IS THERE A BIOLOGICALLY PLAUSIBLE MECHANISM OF ACTION?

Structurally unrelated nonsteroidal anti-inflammatory drugs can inhibit proliferation and induce apoptosis of cancer cells in vitro, independently of their inhibitory effect on prostanoid biosynthesis (reviewed by Dovizio et al. [28]). These off-target effects were detected mainly at very high concentrations of aspirin, often in the millimolar range, that are not reached in vivo in the systemic circulation, even when aspirin is administered at anti-inflammatory doses (28). In fact, after long-term dosing with low-dose aspirin (100 mg/day), acetylsalicylic acid (ASA) and salicylic acid are detected in the systemic circulation with peak plasma concentrations of 4.0 and 40 μM, respectively (26); the plasma half-life of ASA is only 20 min, whereas that of salicylic acid is 2 to 4 h. Poor systemic bioavailability of aspirin is due to the rapid hydrolysis of ASA to salicylic acid by intestinal, plasma, and hepatic esterases. On the basis of these pharmacokinetic features of aspirin, the putative molecular pathways involved in its anticancer effect (Online Table 1) should be affected by micromolar concentrations of ASA, and the inhibitory effect should persist for 24 h, despite the short half-life of the drug. These requirements would be fulfilled by irreversible inactivation of a drug target or targets in cells with low rate of de novo protein synthesis. These assumptions, as well as the lack of dose dependence of its chemopreventive effect (16), led us to hypothesize that low-dose aspirin causes an anticancer effect by inhibiting platelet function through its capacity to irreversibly inactivate platelet COX-1 by acetylation of a critical serine residue (Ser529) near the catalytic site of the enzyme (9,28,29). Although aspirin can acetylate a number of plasma proteins, enzymes, and deoxyribonucleic acid in vitro (30), this usually requires millimolar concentrations that are approximately 100 to 1,000 times higher than those achievable after a low-dose regimen (26).

The protective effects of low-dose aspirin against cancer appear to reflect the prevention of early neoplastic transformation throughout the alimentary tract, as well as an antimetastatic action. Both effects may be explained by the antiplatelet effect of low-dose

CENTRAL ILLUSTRATION **Platelet-Induced Phenotypic Switching of Cells Involved in Colorectal Carcinogenesis: A Potential Mechanism of Action of Low-Dose Aspirin as a Chemopreventive Agent**



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aspirin (9,28,29) (**Central Illustration**). Platelet-derived lipid mediators that are inhibited by low-dose aspirin, such as the prostanoids thromboxane A_2 and prostaglandin E_2 (PGE_2) (31), prostaglandin-containing oxidized phospholipids (32), and sphingosine-1-phosphate (33) may contribute to the crosstalk among platelets, cancer cells, and other cells of the tumor microenvironment. In this context, one should consider the release of platelet α-granule content (34), which comprises a plethora of proteins, including angiogenic autacoids and growth factors that may induce COX-2 expression in adjacent cells of the GI mucosa (31). Activated platelets may also release different types of vesicles, including exosomes (35), which contain abundant microribonucleic acids (36).

An important event that takes place in tumorigenesis is the enhanced biosynthesis of PGE_2; this prostanoid binds to and activates G protein-coupled EP1-4 receptors, whose signaling can influence the adhesive, migratory, and invasive behavior of cells during the development and progression of cancer (37) and generate a microenvironment that facilitates

tumor formation and progression through successful evasion of type I interferon and/or T cell-dependent tumor elimination (38). PGE_2 can be produced by both COX isozymes, and deletion of either the COX-1 or the COX-2 gene leads to reduced intestinal tumorigenesis (39). Increased COX-1-dependent PGE_2 levels may also reflect the suppression of the prostaglandin-catabolizing enzyme 15-prostaglandin dehydrogenase, which has been proposed to play a role in the early stages of intestinal tumorigenesis (40). In contrast, COX-2 expression is detectable in a subset of adenomas but is markedly elevated in most human CRCs (41). However, the anticancer effect of low-dose aspirin cannot be explained by a direct inhibitory effect on COX-2 (**Table 1**), because circulating levels of the drug are inadequate to cause full acetylation of COX-2, and transient acetylation of COX-2 can be rapidly reversed by new protein synthesis in proliferating cells. Low-dose aspirin may also acetylate COX-1 in nucleated cells of the intestinal mucosa, thereby reducing local PGE_2 production (42). However, the time and dose dependence of this effect remains to be investigated.

Altogether, the experimental evidence is consistent with the hypothesis that the anticancer effect of low-dose aspirin involves primarily the inhibition of platelet activation triggered by GI mucosal lesions, thus restraining stromal cell activation and the interaction with epithelial cells. Platelet inhibition will also down-regulate signaling pathways involved in the aberrant expression of COX-2 in neoplastic lesions (28,29). The sequential involvement of platelet COX-1 and epithelial COX-2 in colorectal tumorigenesis would explain the apparently similar chemopreventive effects of low-dose aspirin and other nonsteroidal anti-inflammatory drugs, the former acting upstream to inactivate platelet COX-1 and the latter acting downstream to inhibit COX-2 activity. Furthermore, the inhibition of platelet function may interfere with tumor metastasis (43), inasmuch as the formation of platelet aggregates surrounding circulating tumor cells protects them from immune elimination and promotes their arrest at the endothelium and extravasation (43). The crosstalk between platelets and cancer cells induces a mesenchymal-like phenotype, endowing cancer cells with high metastatic capacity (31,44). Interestingly, mesenchymal-like cancer cells have a proaggregatory action on mouse platelets in vivo (45); this acquired property of cancer cells may contribute to the formation of platelet aggregates surrounding tumor cells, thus facilitating the spreading of cancer metastases (43). In fact, the administration of low-dose aspirin to mice inhibited platelet prostanoid biosynthesis and function and was associated with reduced formation of metastases (45).

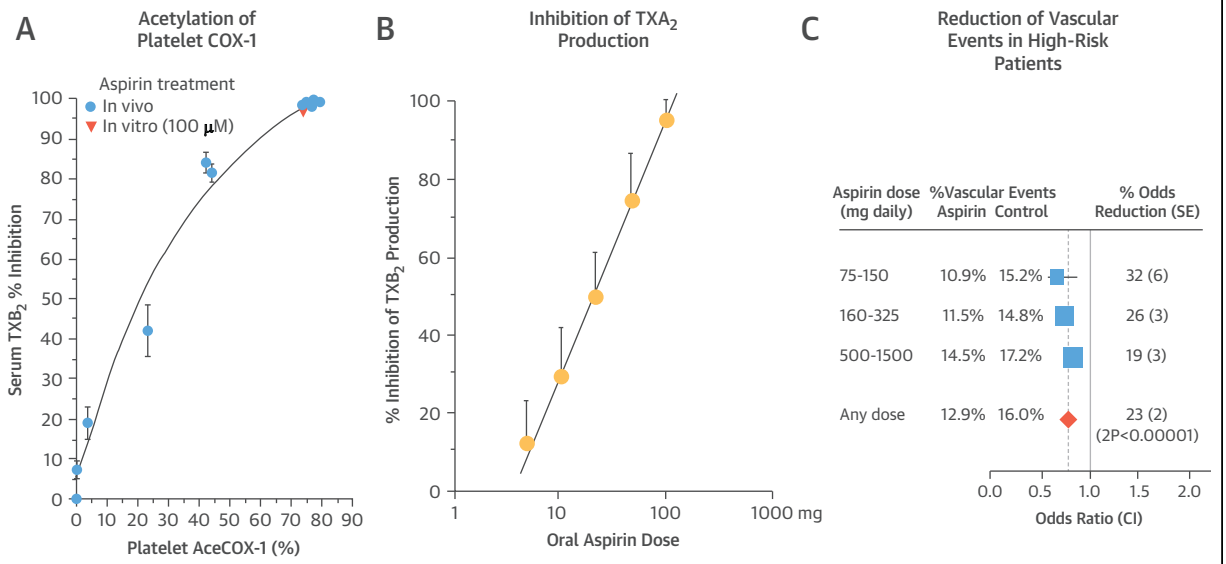
WHAT IS THE SIZE OF THE APPARENT CHEMOPREVENTIVE EFFECT, AND CAN IT POSSIBLY CHANGE THE BENEFIT/RISK PROFILE OF ASPIRIN IN PRIMARY PREVENTION?

Any attempt to integrate the potential chemopreventive effects of aspirin therapy into existing

CENTRAL ILLUSTRATION Continued

Platelets are activated in response to environmental factors, atherosclerotic plaque rupture or fissuring, and intestinal mucosa damage. Activated platelets release several lipid mediators, including the prostanoids thromboxane A_2 (TXA_2) and prostaglandin E_2 (PGE_2), α-granule proteins (such as angiogenic factors [e.g., angiogenin, vascular endothelial growth factor], antiangiogenic factors [e.g., angiostatin, platelet factor-4], growth factors [e.g., platelet-derived growth factor, basic fibroblast growth factor, stromal cell-derived factor 1α], proteases [e.g., matrix metalloproteinase-2, matrix metalloproteinase-9], and many cytokines) and different types of vesicles, including exosomes rich in micro-ribonucleic acids (microRNAs). Thus, activated platelets release a wide repertoire of mediators that may evoke numerous signaling pathways associated with phenotypic switch of the cellular compartment of the stromal environment. These events alter epithelial and stromal cell interactions and create a tissue microenvironment that promotes intestinal neoplasia. A key event is represented by enhanced biosynthesis of PGE_2 in intestinal mucosa, which occurs in the early stages of tumor development through cyclooxygenase (COX)-1 activity, in association with the suppression of the prostaglandin-degrading enzyme 15-prostaglandin dehydrogenase (15-PGDH). Later, COX-2 is induced and further increases PGE_2 production, thus promoting colorectal adenoma to adenocarcinoma progression. Elevated levels of microsomal PGE_2 synthase-1 (mPGES-1; a major terminal PGE_2 synthase) are often observed concomitantly with COX-2 overexpression. Enhanced PGE_2 production by transformed intestinal epithelial cells disrupts the normal apoptotic processes, allows the affected cells to accumulate genetic mutations, and leads ultimately to loss of proliferative control. Moreover, it may suppress immune functions and facilitate tumor immune escape. In contrast, prostacyclin (PGI_2), produced via COX-1/COX-2 and PGI_2 synthase (PGIS), exerts anticarcinogenic effects. However, its biosynthesis appears to be reduced in tumors because of diminished PGIS gene expression caused by hypermethylation of its promoter. Platelet-derived mediators also lead to the activation of epithelial-mesenchymal transition (EMT) programs. EMT is a process in which epithelial cells lose their polarity and are converted to a mesenchymal phenotype, a critical event during tumor metastasis. In cancer cells, this event disrupts the intercellular junctions and enhances migration, but it also promotes stem cell–like properties that facilitate metastatic colonization. Down-regulation of platelet function by low-dose aspirin restrains the induction of the cascade of molecular and biological events associated with tumorigenesis and metastasis occurring in the stromal compartment and in epithelial cells. The participation of a COX-dependent mechanism in the transition from normal colorectal mucosa to adenoma (step A in the illustration) is proved by low-dose aspirin randomized controlled trials (RCTs) (12). The participation of COX-dependent mechanisms in the transition from adenoma to carcinoma (step B) and from carcinoma to metastasis (step C) is supported by observational studies (10,11) and retrospective analyses of aspirin RCTs for cardiovascular disease prevention (15,20–22) and is being tested prospectively in ongoing RCTs. AA = arachidonic acid; PGH_2 = prostaglandin H_2.

FIGURE 1 Acetylation of Platelet Cyclooxygenase-1, Inhibition of Platelet Thromboxane Production, and Cardioprotection by Aspirin Are Saturable at Low Doses



(A) The relationship between the percentage of platelet cyclooxygenase (COX)-1 acetylation (AceCOX-1) and the percentage inhibition of serum thromboxane B_2 (TXB_2) by high concentrations of aspirin added in vitro **(orange triangles)** and following oral dosing with 100 mg/day in healthy subjects **(blue dots)**. Reprinted with permission from Patrignani et al. (26). **(B)** The log-linear relationship between the single aspirin dose given orally to healthy subjects and the percentage inhibition of platelet TXB_2 production during whole-blood clotting, an index of COX-1 activity. Reprinted with permission from Patrignani et al. (25). **(C)** Indirect comparisons of the proportional effects of different aspirin regimens on major vascular events in high-risk patients. The stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials **(blue squares)**, along with its 99% confidence interval (CI) **(horizontal line)**. Meta-analysis of results for all trials (and 95% CI) is represented by a **diamond** (redrawn from Antithrombotic Trialists' Collaboration [27]). The figure illustrates that acetylation of the platelet drug target (COX-1), inhibition of its main product (thromboxane A_2 [TXA_2]), and reduction of atherothrombotic events by aspirin are all processes that reach a ceiling effect (i.e., are saturable) at low doses.

algorithms that compare the CV benefits with the increased risk for major bleeding must rely on certain assumptions (9). A main consideration is related to the effect size of the alleged benefit and the time frame over which it develops. Thun et al. (9) based their calculations on a conservative 10% reduction in overall cancer incidence during 5 years of aspirin therapy. Moreover, they based estimates of absolute reductions in major vascular events and absolute excess of major bleeding on an IPD meta-analysis of 6 primary prevention trials (46). The probabilities of developing such events in subjects allocated to aspirin or placebo during 5 years are depicted in **Figures 2 and 3** for participants in 4 strata of age and sex. If only the CV benefits and GI bleeding were considered, the balance between the 2 would be substantially uncertain (ratio of number needed to harm to number needed to treat = 2:1) (4). However, if aspirin also causes a hypothetical 10% reduction in overall cancer incidence, then the absolute benefit of cancer prevention would be at least as large as the CV benefit both in younger and older men and women, and the combined beneficial effects would outnumber the potential harm by a factor of 3 to 5 (9). Similar conclusions were reached by independent estimates of benefits and harms of prophylactic use of aspirin in the general population (47).

TABLE 1 Effects of Aspirin on Cyclooxygenase-2-Dependent Clinical Read-Outs

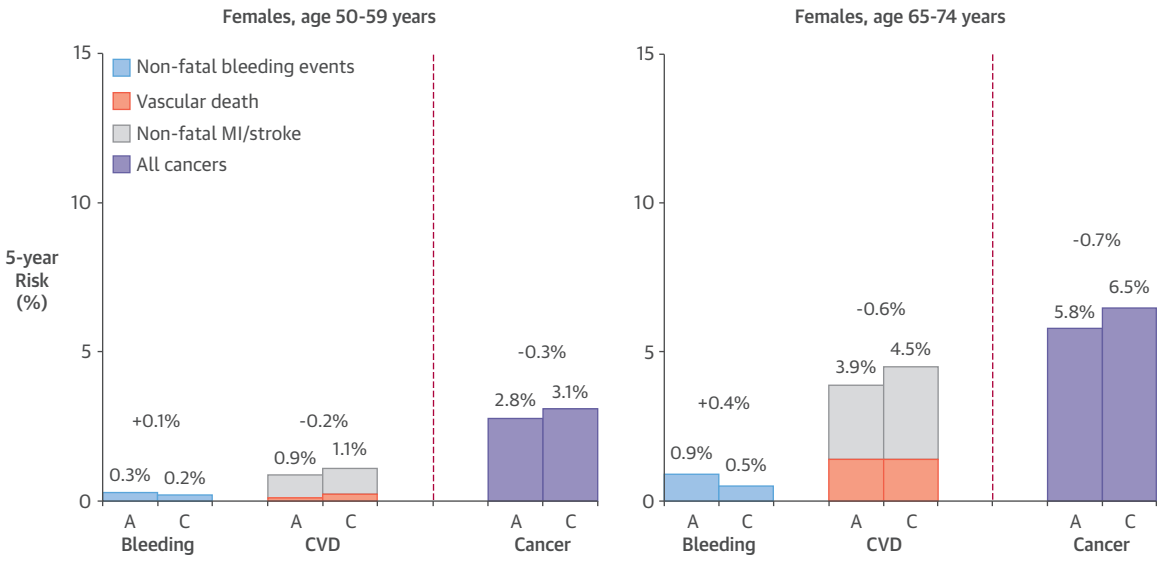
Clinical Read-Out	Effect of 75-100 mg	Effect of 300-325 mg	Effect of 650-1,300 mg
PGI_2 biosynthesis	→ ←	↓	↓↓
PD interaction with ACE inhibitors	→ ←	+	++
Pain and inflammation in OA/RA	NT	↓	↓↓

ACE = angiotensin-converting enzyme; NT = not tested; OA = osteoarthritis; PD = pharmacodynamic; PGI_2 = prostaglandin I_2; RA = rheumatoid arthritis.

IS THE CURRENT EVIDENCE SUFFICIENT TO ISSUE CHEMOPREVENTIVE TREATMENT GUIDELINES?

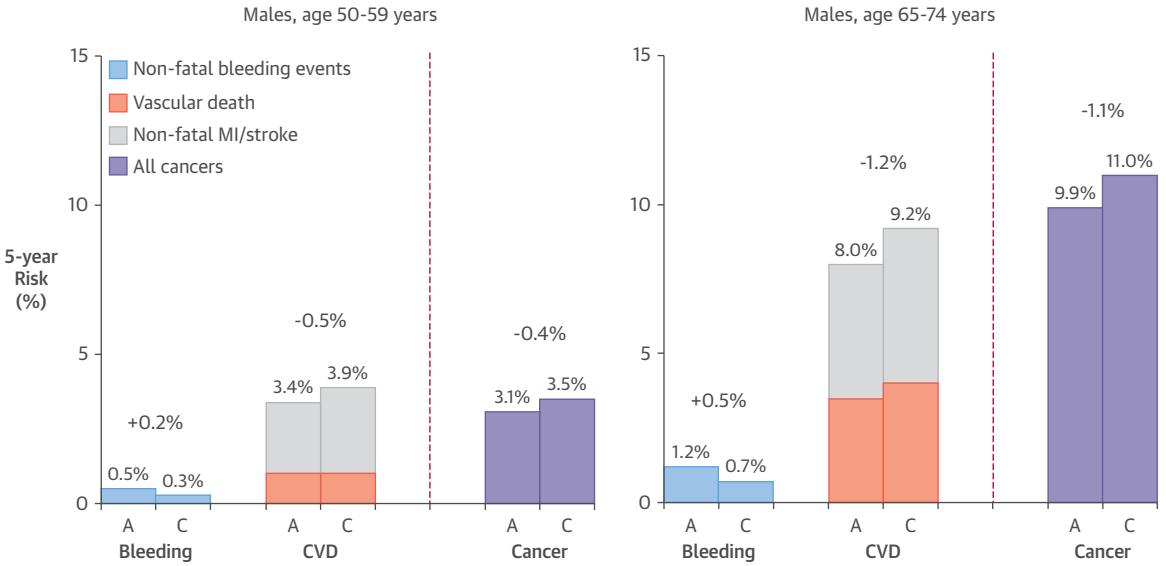
In 2007, the USPSTF recommended against the routine use of aspirin for the prevention of CRC (48).

FIGURE 2 **Balance of Benefits and Risks of Low-Dose Aspirin for Primary Prevention in Women**



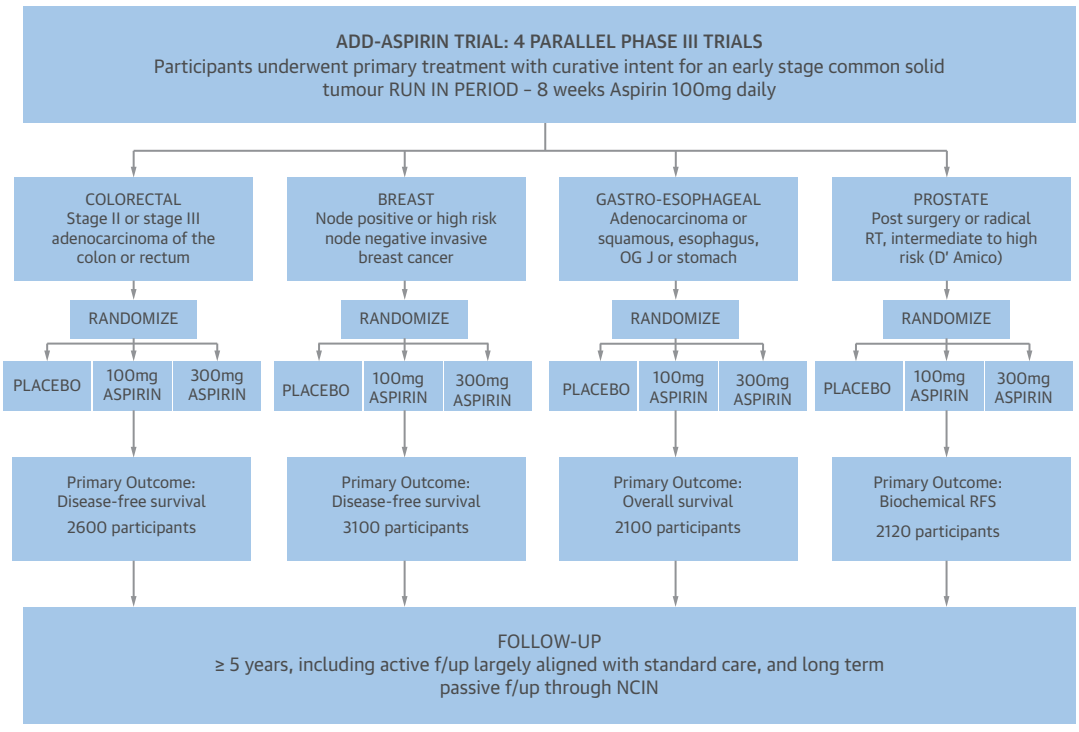
The figure depicts 5-year risk for vascular events and major extracranial bleeding on the basis of primary prevention trials of aspirin (A) and placebo and hypothetical 10% reduction in cancer incidence by age. Risks for vascular and bleeding events are on the basis of the Antithrombotic Trialists' Collaboration's analysis of 6 primary prevention trials (46). Cancer risks are on the basis of an assumed 10% reduction in Surveillance, Epidemiology, and End Results probabilities as reported by Thun et al. (9). **(Left)** Women, 50 to 59 years of age; **(right)** women, 65 to 74 years of age. Modified with permission from Thun et al. (9). C = control; CVD = cardiovascular disease.

FIGURE 3 **Balance of Benefits and Risks of Low-Dose Aspirin for Primary Prevention in Men**



The figure depicts 5-year risk for vascular events and major extracranial bleeding on the basis of primary prevention trials of aspirin (A) and placebo and hypothetical 10% reduction in cancer incidence by age. Risks for vascular and bleeding events are on the basis of the Antithrombotic Trialists' Collaboration's analysis of 6 primary prevention trials (46). Cancer risks are on the basis of an assumed 10% reduction in Surveillance, Epidemiology, and End Results probabilities as reported by Thun et al. (9). **(Left)** Men, 50 to 59 years of age; **(right)** men, 65 to 74 years of age. Modified with permission from Thun et al. (9). Abbreviations as in Figure 2.

FIGURE 4 Design of the Add-Aspirin Trial



Add-Aspirin is a large, randomized clinical trial currently taking place in the United Kingdom and India. It will recruit approximately 10,000 participants to help determine whether regular aspirin use after treatment for an early-stage cancer (colon/rectum, breast, stomach/esophagus, prostate) can prevent cancer recurrence and death. Cancer Research UK, the National Institute for Health Research Health Technology Assessment Programme, and the Medical Research Council Clinical Trials Unit at University College London are jointly funding the trial. Courtesy of Prof. Ruth Langley, University College London. f/up = follow-up; NCIN = National Cancer Intelligence Network; OG J = esophagogastric junction; RFS = relapse-free survival; RT = radiation therapy.

Nine years later, the USPSTF issued a grade B recommendation for the use of low-dose aspirin (75 to 100 mg/day) "for the primary prevention of CVD and CRC in adults 50 to 59 years of age who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years" (8). Furthermore, the USPSTF recommended that "the decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults age 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one" (grade C) (8). Before the USPSTF recommendation, no major organization had explicitly considered a potential reduction in CRC among the long-term goals of primary prevention with low-dose aspirin. However, in drafting its 2012 evidence-based clinical practice guidelines for antithrombotic therapy and prevention of thrombosis, the American College of Chest Physicians did review the anticipated absolute effect of aspirin therapy on cancer mortality and issued the following recommendation (6): "For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B)." In striking contrast, the 2012 version of the European guidelines on CVD prevention stated that "aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding (IIIB)," with no mention of a potential protective effect of aspirin against CRC (7). Interestingly, 2 years later, a position paper on aspirin in primary prevention from the European Society of Cardiology Working Group on Thrombosis suggested including family history of GI cancer (especially colon cancer) in a case-by-case discussion with asymptomatic subjects at an estimated 10-year CVD risk between 10% and 20% (49).

When considering the wording of the recent USPSTF recommendation, it should be emphasized

that it does not represent an endorsement of low-dose aspirin for the chemoprevention of CRC but rather suggests that lowering the long-term risk for developing CRC may represent an additional benefit of antiplatelet prophylaxis for primary CV prevention (50). Although simulations suggest that the population impact of aspirin prophylaxis could be comparable with that of CRC screening (9,50), aspirin should not be considered a substitute for but rather a potential complement to screening (50).

Although discussing the currently available knowledge on aspirin and cancer may well help physicians and patients work together to reach a personalized decision on primary prevention (5), we suggest that treatment guidelines be informed by a regulatory review of the totality of the evidence, including the substantial prospective component that will become available over the next 2 to 3 years.

WHERE DO WE GO FROM HERE?

Additional evidence for the chemopreventive effects of aspirin is being sought prospectively in 4 ongoing primary prevention trials that are due to be completed by 2018 (4). Moreover, several adjuvant trials of various low-dose aspirin regimens have been initiated recently in patients with newly diagnosed cancers, including colorectal, gastroesophageal, breast, and prostate cancer (e.g., the Add-Aspirin trial) (**Figure 4**).

Additional mechanistic studies to test the "platelet hypothesis" should be performed in animal models of intestinal cancer and, ideally, in different stages of the human disease. These could help address the current uncertainty concerning the optimal chemopreventive dose and dosing regimen of aspirin. Should this hypothesis be confirmed by ongoing studies, this would provide a rationale for targeting other pathways of platelet activation and assessing the efficacy and safety of combined antiplatelet strategies for cancer prevention.

An important field of clinical research is focused on the discovery of biomarkers to identify those subjects who will respond to the antineoplastic effect of aspirin. These include plasma markers, such as soluble tumor necrosis factor receptor-2, as well as tumor expression levels of genes involved in prostanoid biosynthesis or signaling pathways activated by the aberrant expression of COX-2, such as phosphatidylinositol 3-kinase (51,52). Most of these studies suffer from the limitation of investigating large cohorts of nonrandomized participants who provided data on aspirin use in a questionnaire. Thus, these findings should be confirmed by large RCTs, such as the Add-Aspirin trial. A systems biology approach to the analysis of heterogeneous datasets (genomics, epigenomics, proteomics, lipidomics, and clinical) would allow performing dynamic systems modeling of candidate pathways involved in the antineoplastic effect of aspirin. This strategy would also allow the identification of susceptibility profiles for CRC and their use to develop new biomarkers to predict its occurrence and recurrence.

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APPENDIX For a supplemental table, please see the online version of this article.