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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