Point/Counterpoint

Cyclooxygenase-2 Inhibitors in Colorectal Cancer Prevention: Counterpoint

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Abstract

Aspirin is the best chemoprevention agent for colorectal cancer risk reduction despite the fact that the evidence for a decrease in mortality is weak. The cyclooxygenase-2 selective agents (COXIBS) have an efficacy similar to that of aspirin for most gastrointestinal (GI) lesions but not esophagus. Specifically, there are beneficial short term effects of COXIBs on the risk of colorectal adenoma as shown in the Approve, PreSAP, and APC studies. However, there is still an increased risk of upper GI complications with COXIBs when compared with placebo, and this risk may increase further in some people when aspirin is also consumed. Whereas aspirin reduces the risk of cardiovascular events, COXIBs and most traditional nonsteroidal anti-inflammatory drugs (but not all) are both associated with an increased risk of thrombotic cardiovascular events compared with placebo.

In conclusion, COXIBs have a niche role for patients with familial adenomatous polyposis. The value of aspirin remains with respect for efficacy, mainly in the esophagus, and the side effect profile, especially in the elderly if given with acid suppression therapy. COXIBs should be used in younger populations, but if they are considered in the elderly because of increased GI risks, and the cardiovascular risk is also increased, then combination treatment with aspirin and a proton-pump inhibitor should also be considered instead, such as in the ASPECT trial. (Cancer Epidemiol Biomarkers Prev 2008;17(8):1858–61)

Background

The risk of colon cancer in the general population is ~5%, and therefore, a generalizable intervention that can prevent this common cancer pharmacologically is important—chemoprevention. The data from trials in patients with spontaneous adenomatous polyps and with familial adenomatous polyposis (FAP) indicate that aspirin and cyclooxygenase-2 selective agents (COXIBS) may both have a role to play as chemopreventive agents.

Aspirin is a synthetic analogue of a naturally occurring phytochemical class, the salicylates, which are commonly found in fruits and vegetables. The interest in exogenous salicylates began when Rosenburg et al. (1) published their prospective cohort study of 662,424 adults and showed that the mortality rate from colon cancer decreased with more frequent aspirin use in both men and women. The decreased relative risk of colon cancer among frequent aspirin users (16 or more times per month for at least 1 year; ≥160 mg) was 0.60 in men (95% confidence interval, 0.4-0.89) and 0.58 in women (95% confidence interval, 0.37-0.9). Furthermore, the data from the National Health and Nutrition Examination Survey I (2) and National Health and Nutrition Examination Survey I Epidemiologic Follow-up Studies in 12,668 subjects, followed for an average of 12.4 years, showed that the cancer preventive effects of aspirin were greatest in the colon, followed by the esophagus, lung, and breast (hazard ratio, 0.35, 0.60, 0.68, and 0.70, respectively; ref. 2). However, there are two randomized controlled trials that have shown nonsignificant trends in favor of aspirin use (3, 4). Although aspirin does reduce adenoma recurrence (and perhaps also downstream both the incidence of colorectal cancer and mortality), the exact formulation, dose, frequency, and duration of aspirin use that are needed to produce these effects optimally is not yet elucidated (3, 5-8). There is some evidence that aspirin can also decrease the recurrence of colorectal adenomas in patients with previously treated colorectal cancer (relative risk, 0.65; 95% confidence interval, 0.46-0.91, at 325 mg per day) or with a recent history of colorectal adenomas (relative risk, 0.81; 95% confidence interval, 0.69-0.96 at 81 mg per day; refs. 7, 8). However, 325 mg per day of aspirin in this latter study did not significantly decrease colorectal adenoma recurrence in patients with a recent history of colorectal adenomas (7) or colorectal cancer incidence in the Physicians Health study (3), thus providing contradictory data. Part of the explanation may be that the effect may only be observed after a decade of aspirin use and that excessive smoking, alcohol consumption, and obesity may offset the benefits of aspirin (9, 10). Aspirin may also have a use in adjuvant colon cancer therapy as Fuchs et al. (6) have shown in a retrospective analysis of 830 patients in the CALGB study who were treated with 5-fluorouracil ± irinotecan. Seventy-two regular users of aspirin and 35 regular users of COXIBs had a hazard ratio for disease

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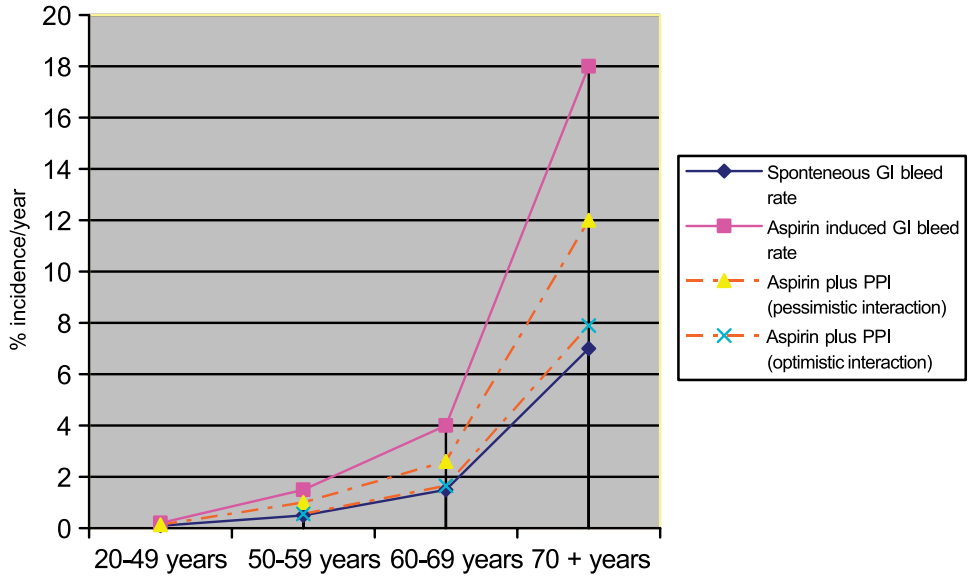

Figure 1. Spontaneous, aspirin-induced, and aspirin with PPI prophylaxis GI bleed rates (Adapted from Hernandez-Diaz S et al., 2002 and Pilotto A et al., 2004, Serebruany VL et al., 2004, Tramer MR et al., 2000). The expected aspirin-induced GI bleed rates on PPI therapy lies somewhere between the brown dashed lines.

recurrence or death of 0.45 and 0.56, respectively. Unfortunately, the chemopreventive effects of aspirin may not act universally in everyone, which means that a proportion of patients might not benefit from taking aspirin (11). There are many possible mechanisms of aspirin resistance including increased aspirin metabolizing enzymes [prostaglandin H synthase 2 (Val511Ala) polymorphism and the uridine diphosphatidyl glucotransferase UGT1A6 polymorphism], which decrease the chemopreventive effectiveness of aspirin by ~50% (12, 13). Furthermore, nonsmokers have a better chemopreventive benefit than smokers (14). Thus, colonoscopy surveillance of patients using aspirin could still be an important clinical requirement (15). The optimal dose of aspirin (75, 81, 150, or 300 mg/day) is still unelucidated.

Aspirin, as secondary prevention, also decreases fatal cardiovascular events in patients with known vascular disease by one-sixth and vascular death by 25% (Antithrombotic Trialist's Collaboration, 2002; ref. 16). In those without known vascular disease (Primary Prevention), aspirin decreases the risk of cardiovascular events by one-third, but there is no evidence of a beneficial effect on cerebrovascular accidents (CVAs) or death (17). The risk of myocardial infraction in the general population is ~2 of 1,000, between the ages of 20 and 59 years, and this risk increases to 5 of 1,000 above age 60 years. Therefore, aspirin has considerable cardiac protective properties as well as chemoprevention effects in those ages above 60 years. The evidence suggests that in women at any rate, low to moderate doses of aspirin are associated with significantly lower risk of all cause mortality, particularly in older women and in those with cardiac risk factors. A significant benefit is evident with 5 years for cardiovascular disease, whereas a modest benefit for cancer is not apparent until 10 years of use and perhaps then mainly a subset of cancers expressing cyclooxygenase-2 (18).

Although aspirin has proven efficacy in decreasing the risks of colorectal cancer, cardiac disease, and perhaps also dementia (19), aspirin use is associated with significant morbidity due, in part, to gastric mucosal injury and particularly gastrointestinal (GI) bleeding regardless of preparation (20). This is one important reason why aspirin cannot be given to everyone because of the increased risk of GI bleeding of 2- to 4-fold, especially in patients over the age of 70 years (21-25). There is also a dose-dependent increased in risk of both haemorrhagic stroke and GI bleeding in doses

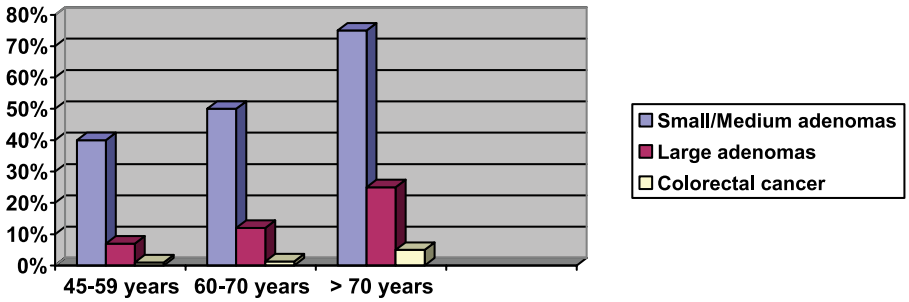

Figure 2. Risk of detecting small/medium adenomas, large adenomas, and colorectal cancer in aging cohorts (Adapted from Bertagnolli MM, Eagle CJ, Zauber AG et al.; APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006;355:873-84.). The most important age group are those >70 y.

Table 1. The risk benefit of aspirin, tNSAIDs, and COXIBs

	Chemoprevention efficacy	Cardiovascular Risk or benefit —relative risk	UGI complications/y—relative risk (absolute risk)	Cost—US$/y
Aspirin*	~ 20-30% (40% for esophageal and colon cancer)	0.75	~1.05 (2.5-4%/y)	~5
tNSAIDs †	~15-25%	0.90-1.40	~1.04 (1.4%/y)	~50
COXIBs †	~20-25% (66% for colorectal adenomas)	1.4-3.4	~1.02 (0.6-1%/y)	~500

Abbreviation: UGI, upper gastrointestinal.
*If aspirin is given with an acid suppressing drug the UGI complication rate decreases from 4% per year to 1.5% per year.
† If tNSAIDS and COXIBs are given with low dose aspirin they may have similar UGI complications per year of 2-3%.

>100 mg/day [hemorrhagic stroke, <100 mg/day (0.3%); cf, >325 mg/day (1.1%); GI bleeding, <100 mg/day (1.1%); cf >325 mg/day (2.5%)]. When aspirin is given with a proton-pump inhibitor (PPI), however, especially after *Helicobacter pylori* eradication, the risk of bleeding complications after aspirin or traditional nonsteroidal anti-inflammatory drug (tNSAID) use is decreased by 50% to 90% (Fig. 1; refs. 26, 27). In this regard, the aspirin-esomeprazole chemoprevention trial (ASPECT) is assessing the role of a PPI with or without aspirin in decreasing the risk of all causes of mortality as well as gastro-esophageal adenocarcinoma, colorectal cancer, and cardiac disease in patients with Barrett's esophagus (28).

After the original report that sulindac decreased polyp progression in patients with FAP (29), several groups have tried to prove this in large randomized controlled trials and the results have been disappointing (30). Unfortunately, although tNSAIDs have a promising efficacy comparable with the ASA profile (although in the esophagus, ASA has twice the benefit of tNSAID) for cancer chemoprevention, they have serious side effects, and this has tempered enthusiasm for their use in long-term randomized controlled trials (31-33). In addition, side effects of tNSAIDs is heterogeneous as they may either weakly decrease (naproxen by 13%) or increase (diclofenac by 38%) the risk of myocardial infraction in the general population (34). Several large trials, including the APPROVe, APC ADAPT, PreSAP trials, and VICTOR have studied COXIBs for secondary prevention in patients successfully cured of colorectal cancer (35-42). The overall trend in these studies is to a greater but differential risk reduction in advanced adenomas depending on the COXIB used. These trials have recently shown an increased risk of vascular events, of relatively low frequency but significant magnitude to cause serious concern for the use of these drugs on a population basis (38). There is an associated 2-fold increase in mortality from a background of 0.12% to 0.25% in patients using COXIBS (38). In the VICTOR trial, the cardiovascular thrombotic end points were significant at even a median duration of active treatment of 7.4 months, and this was maintained for 2 years after therapy stopped (unadjusted relative risk of 1.6 and 1.5, respectively; refs. 41, 43). This information has lead to some arguing that cyclooxygenase-2 agents should be used in people most likely to get cancer especially those ages >65/70 years (Fig. 2). Although the available evidence suggests there may be a slightly improved efficacy of adenoma reduction in those ages >65 years, it is this age group that has a higher cardiovascular risk (37). Thus, the COXIBS have now been excluded in their current formulation as viable candidates for unselected use in chemoprevention trials (35). There is intriguing data from colon cancer models that indicate that in the long term, cyclooxygenase-2 and PGE2 levels may paradoxically ''rebound,'' further minimizing long term efficacy (44). Furthermore, these agents have an increased risk for GI bleeding twice to thrice that of placebo ~ 0.5% per year, although 30% less than that of tNSAIDs (relative risk, 2.6 versus 3.7; ref. 23). Furthermore, when a COXIB is combined with aspirin, the risk of GI bleeding may be further increased in several but not all studies (Table 1; ref. 23).

Polypectomy is now being offered for colorectal cancer prevention in many westernized countries and reduces the colorectal cancer risk in the elderly from 5% to 1%. Therefore, the elderly, if fit, should receive endotherapy as a first choice. Chemoprevention should be used in the younger patients before 70 years and probably only in high-risk individuals. In this scenario, aspirin may produce serious GI complications 3-fold, but most cases would respond to medical management well. On the otherhand, the 2- to 3-fold serious cardiac complications will still have the same prognosis regardless of age. COXIBS specifically might be useful in a subset of patients for whom the efficacy/risk ratio is more favorable, such as FAP patients. Giardiello et al. (29) showed in a small randomized controlled trial of 22 patients that there was a 44% decrease in the number of polyps and a 35% decrease in the size of polyps from baseline with the tNSAID, sulindac. This was followed by a report from Steinbach et al. (45) in a larger randomized controlled trial of 77 patients with FAP using celebrex, which showed a 30% reduction in polyp burden, and this evidence led to the Food and Drug Administration approving celebrex for use in FAP.

In conclusion, aspirin may have a place for the secondary chemoprevention of GI cancer(s) in patients with no antecedent risk of GI bleeding. COXIBs or, to a lesser extent, tNSAID, however, should be reserved for younger patients with no cardiac risk with FAP. Aspirin has a unique role in that it can prevent cardiovascular disease as well. Our aim should be to design large scale chemoprevention trials for the community.

Disclosure of Potential Conflicts of Interest

J. Jankowski consultant to A7 and CI of aspirin-esomeprazole chemoprevention trial (using aspirin and PPI chemoprevention). R. Hunt: sometime consultant, investigator, or speaker for Astrazeneca, Aryx, Axcan, Merck, Negma, Novartis, Nycomed, Pfizer, Santarus, and TAP.

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