Aspirin and Colorectal Cancer: Back to the Future

David Tougeron1, Dan Sha3, Sashidhar Manthravadi1, and Frank A. Sinicrope1,2,3

Abstract

Abundant epidemiologic evidence indicates that regular and long-term use of aspirin is associated with a significant reduction in the incidence of colorectal cancer. The long duration of aspirin needed to prevent colorectal cancer is believed to be due to inhibition of precursor lesions known as adenomas, the recurrence of which is inhibited by aspirin in randomized trials. Aspirin intake has also been associated with a statistically significant improvement in patient survival after curative resection of colorectal cancer in large observational studies. In these cohorts, the survival benefit of aspirin was shown to depend upon the level of COX-2 expression in the primary colorectal cancer. More recent analysis of patient tumors from these observational cohorts suggests that the benefit of aspirin may be limited to specific molecular subtypes. Aspirin intake following colorectal cancer resection was associated with a significant improvement of survival in patients whose tumors carried mutant, but not wild-type, copies of the phosphoinositide 3-kinase (PI3KCA) gene, especially tumors that overexpressed COX-2. A mechanistic explanation is suggested by the finding that inhibition of COX-mediated prostaglandin E2 synthesis by aspirin attenuates PI3K signaling activity that is known to regulate cancer cell proliferation and survival. Aspirin has also been shown to reduce the incidence of colorectal cancers bearing wild-type, but not mutant alleles of the BRAFV600E oncogene. Although provocative, the potential utility of these molecular markers for predicting aspirin efficacy awaits prospective evaluation in clinical trials. If validated, these findings may support a personalized approach to using aspirin for the therapy of colorectal cancer.

Perspectives

Acetylsalicylic acid was first synthesized in 1853 and used for its analgesic and anti-inflammatory properties. Aspirin acts on COX enzymes that regulate the synthesis of prostaglandins (PG) and related eicosanoids from arachidonic acid (Fig. 1). It inhibits constitutively expressed COX-1 as well as the inducible COX-2 isofrom, which is upregulated at sites of inflammation (1). Selective COX-2 inhibitors were developed to reduce gastrointestinal injury but were later found to have cardiovascular toxicities (2). Large observational studies have demonstrated an association of regular and long-term aspirin intake with a significant reduction in the incidence (3–5) and mortality from colorectal cancer (3, 6). Cohorts from the Nurses’ Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) of 130,274 total participants provided data on aspirin use from a questionnaire administered every 2 years. Regular use of aspirin (≥two 325-mg tablets/wk) was shown to significantly reduce the incidence of colorectal cancers overexpressing COX-2 [relative risk (RR), 0.64; 95% confidence interval (CI), 0.52–0.78; \( P = 0.02 \)], but not those with weak or absent COX-2 expression in the primary tumor (Table 1). Importantly, the ability of aspirin to reduce colorectal cancer incidence became evident only after regular use for more than 10 years (multivariate RR, 0.59; 95% CI, 0.42–0.82; \( P_{\text{trend}} < 0.001 \)). The RR was further reduced as the number of aspirin tablets (325 mg) taken per week increased (0.5–1.5 vs. 2–5 vs. 6–14 vs. > 14; \( P_{\text{trend}} = 0.001 \)), indicating that the chemopreventive effect was dependent upon both the dose and duration of aspirin intake (7), suggesting the importance of cumulative dosage as a determinant of aspirin efficacy in these settings.

The explanation to why a prolonged duration of aspirin intake, varying between studies from 4 years to greater than 10 years (5, 8), is needed to reduce the incidence of colorectal cancer is likely due to a chemopreventive effect of aspirin on colorectal adenomas that are precursor lesions of colorectal cancer. In preclinical models, aspirin inhibits the development of colorectal adenomas and their progression to carcinoma (9). Using colorectal adenomas as a surrogate endpoint for colorectal cancer, earlier randomized and controlled trials of aspirin for the chemoprevention of colorectal cancer were negative (10, 11). However, more recent randomized trials have consistently demonstrated the ability of aspirin to decrease adenoma recurrence in patients with prior colorectal adenomas or cancer (12, 13) (Table 1), although the minimally effective dose remains unclear (14). The failure of earlier studies to detect a
chemopreventive effect of aspirin may be due, in part, to the need for prolonged follow-up as studies reporting no reduction in colorectal cancer incidence initially (11, 15, 16) often noticed an effect after a longer interval ranging from 56 months to around 17 years (8, 17). A recent study involving 39,876 women ages 45 years or older who were enrolled in the Women’s Health Study found that alternate day dosing of low-dose aspirin (100 mg) taken for 10 or more years significantly reduced the incidence of colorectal cancer in women (HR, 0.80; 95% CI, 0.67–0.97; \( P = 0.021 \)), especially in the proximal colon (17). After 18 years, the incidence of colorectal cancer was 20% lower in the aspirin group than in the placebo group and was accompanied by a significant increase in self-reported gastrointestinal toxicities (HR for gastrointestinal bleeding 1.14; 95% CI, 1.06–1.22; \( P < 0.001 \)). In a high-risk population, i.e., patients with prior colon cancer, a prospective study involving 635 participants found that treatment with 325 mg/d aspirin over a mean duration

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**Translational Relevance**

Aspirin has been shown to reduce the incidence of colorectal cancer, and accumulating evidence suggests that aspirin may improve the clinical outcome of patients with colorectal cancer following surgical resection. Recent data from large observational studies indicate that the survival benefit of aspirin may be confined to specific molecular subsets defined by phosphoinositide 3-kinase (PI3KCA) mutation status and COX-2 expression levels. Furthermore, regular aspirin intake was found to be associated with a reduced risk of developing colorectal cancers with wild-type BRAF alleles, but not tumors with activating V600E point mutations. Together, these data suggest that aspirin may selectively exert its antitumor effects in specific molecular subsets, thereby identifying potential predictive biomarkers for aspirin efficacy in patients with colorectal cancer.

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**Figure 1.** Molecular pathways regulated by PGE₂ that are inhibited by aspirin. PGE₂ promotes cancer cell growth by binding to its receptors (EP1–4) and modulating signaling pathways downstream of its receptors. In addition to binding Axin (57), the EP4 receptor activates PI3K, which phosphorylates GSK-3β to promote β-catenin–mediated transcription (40). PGE₂ signaling is also implicated in c-Src and β-arrestin–mediated transactivation of EGFR and upregulation of the RAS–RAF–MAPK pathway (58).
of 30.9 months was associated with a statistically significant reduction in the risk of recurrent colorectal adenomas (Table 1) (13). Similar to aspirin, the selective COX-2 inhibitor, celecoxib, has been shown to effectively reduce adenoma recurrence in patients with prior adenomas in randomized trials (18, 19). In a 20-year follow-up of five randomized trials, aspirin at doses of at least 75-mg daily taken for several years reduced the long-term incidence and mortality from colorectal cancer, with the benefit being greatest for cancers of the proximal colon (3). The tumor site–related efficacy of aspirin is clinically important in that colonoscopy has been shown to be less effective at preventing right-sided versus left-sided colon cancers (20). Data also exist for the chemopreventive efficacy of aspirin in patients with Lynch syndrome who have an 80% lifetime risk of colorectal cancer that develops via defective DNA mismatch repair (21). Long-term aspirin treatment (600 mg/d for >2 years) was shown to significantly reduce the incidence of colorectal cancers (N = 508; HR, 0.41; 95% CI, 0.19–0.86; P = 0.02) in patients with Lynch syndrome during prolonged follow-up (mean, 55.7 months; range 1–128; ref. 8).

In a recent report of patients within the NHS and HPFS who developed colorectal cancer, a potential predictive biomarker for aspirin efficacy was found. Regular aspirin intake was associated with a significant reduction in the incidence of colorectal cancers with wild-type (WT), but not mutant BRAFV600E (Table 2; ref. 22). Detailed analysis of the patients whose tumors carried WT–BRAF revealed that the preventive benefit of aspirin seemed to be concentrated in tumors overexpressing COX-2 proteins (multivariable HR, 0.67; 95% CI, 0.56–0.81; P = 0.018). In contrast, aspirin failed to lower the risk of BRAFV600E–mutated colorectal cancers irrespective of their level of COX-2 expression. Protection conferred by aspirin against the development of BRAF–WT colorectal cancers was not abrogated by mutations in PIK3CA exons 9 and 20 or KRAS exon 2 (22). Furthermore, aspirin benefit was unrelated to microsatellite instability status in incident colorectal cancers in the NHS and HPFS cohorts (A.T. Chan, Massachusetts General Hospital, personal communication). Of note, chemopreventive efficacy for aspirin was reported in colorectal cancers from patients with Lynch syndrome that almost uniformly carry WT copies of the mismatch repair gene (24, 25). In separate studies, COX-2 inhibition was unable to suppress proliferation in BRAFV600E–mutated colorectal cancer cells (26).

### Table 1. Efficacy of aspirin in the secondary prevention of colorectal cancer

<table>
<thead>
<tr>
<th>Name of the study group</th>
<th>Type</th>
<th>Study population (N)</th>
<th>Aspirin dose used</th>
<th>Result from aspirin use [multivariate HR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin/Folate Polyp Prevention Study (14)</td>
<td>Randomized controlled trial</td>
<td>1,121 patients with prior colorectal adenomas</td>
<td>81 mg or 325 mg/d</td>
<td>In the 81-mg patient group: Unadjusted RR, 0.81 (95% CI, 0.69–0.96) for developing any adenoma. Adjusted RR, 0.83 (95% CI, 0.70–0.98) for developing any adenoma.</td>
</tr>
<tr>
<td>The APACC Trial (59)</td>
<td>Randomized controlled trial</td>
<td>272 patients with prior colorectal adenomas</td>
<td>300 mg or 160 mg/d</td>
<td>In the 160-mg group: RR, 0.85 (95% CI, 0.57–1.26) for recurrent adenoma.</td>
</tr>
<tr>
<td>Colorectal Adenoma Prevention Study (13)</td>
<td>Randomized controlled trial</td>
<td>635 patients with prior colorectal cancer</td>
<td>325 mg/d</td>
<td>Adjusted RR 0.65 (95% CI, 0.46–0.91) for any recurrent adenoma.</td>
</tr>
</tbody>
</table>
agent in patients with resected colorectal cancer (Table 3). Compelling data were obtained from the NHS and HPFS studies (27) in which 1,279 patients with nonmetastatic colorectal cancers were identified retrospectively, and then categorized on the basis of aspirin usage after diagnosis. During a median follow-up of 11.8 years from diagnosis, aspirin use after diagnosis indicated no mortality reduction even when aspirin use was continued after diagnosis (n = 21; P\textsubscript{interaction} = 0.09; ref. 27), suggesting that exposure to aspirin prediagnosis may select for aspirin-resistant tumor cells. In an earlier study, the same investigators reported a post hoc analysis of a subgroup of patients with stage III colon cancer enrolled in an adjuvant chemotherapy trial (CALGB 89803) in which aspirin users had lower rates of colon cancer recurrence and death compared with nonusers (28). Among 2,916 patients with colorectal cancer identified from the Health Informatics Centre registry in Scotland, aspirin use (median of 1.53 years) after diagnosis was associated with improved colorectal cancer–specific survival (multivariate HR, 0.58; 95% CI, 0.45–0.75; P < 0.001; Table 3; ref. 29). Similarly, a cancer registry study conducted in the Netherlands identified 1,451 patients with colorectal cancer in whom aspirin use after diagnosis (defined as physician-prescribed aspirin for at least 14 days) conferred a statistically significant survival benefit in patients with colon cancer (HR, 0.62; 95% CI, 0.46–0.80; P < 0.001), but not rectal cancer (30).

Furthermore, in a study of 1,451 patients with colorectal cancer identified from the Health Informatics Centre registry in Scotland, aspirin use (median of 1.53 years) after diagnosis was associated with improved colorectal cancer–specific survival (multivariate HR, 0.58; 95% CI, 0.45–0.75; P < 0.001; Table 3; ref. 29). Similarly, a cancer registry study conducted in the Netherlands identified 1,451 patients with colorectal cancer in whom aspirin use after diagnosis (defined as physician-prescribed aspirin for at least 14 days) conferred a statistically significant survival benefit in patients with colon cancer (HR, 0.62; 95% CI, 0.46–0.80; P < 0.001), but not rectal cancer (30).

Table 2. Potential biomarkers indicating aspirin efficacy in colorectal cancer

<table>
<thead>
<tr>
<th>Name of the study group</th>
<th>Study population (N)</th>
<th>Biomarker used</th>
<th>Aspirin dose used</th>
<th>Results [multivariate HR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarkers predicting survival in established colorectal cancer</strong></td>
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<tr>
<td>Nurses’ Health Study, Health Professionals Follow-Up Study (7)</td>
<td>Stage I–III (N = 1,279) COX-2</td>
<td>325 mg</td>
<td>COX-2–overexpressing tumors: HR, 0.39 (95% CI, 0.20–0.76) for colorectal cancer–specific mortality COX-2–negative tumors: HR, 1.22 (0.36–4.18) for colorectal cancer–specific mortality</td>
<td></td>
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<tr>
<td>Nurses’ Health Study, Health Professionals Follow-Up Study (37)</td>
<td>Stage I–IV (N = 964) PIK3CA</td>
<td>325 mg</td>
<td>PIK3CA-mutant tumors: HR, 0.18 (95% CI, 0.05–0.60) for colorectal cancer–specific mortality PIK3CA–WT and COX-2–positive tumors: Stage-adjusted HR, 0.97 (95% CI, 0.73–1.29) for OS PIK3CA-mutant and COX-2–positive tumors(^a): Stage-adjusted HR, 0.34 (95% CI, 0.14–0.82) for OS</td>
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<tr>
<td><strong>Biomarkers predicting colorectal cancer incidence</strong></td>
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<tr>
<td>Nurses’ Health Study, Health Professionals Follow-Up Study (7)</td>
<td>NHS (N = 82,911) COX-2</td>
<td>325 mg</td>
<td>RR, 0.64 (95% CI, 0.52 to 0.78) for incidence of COX-2–overexpressing tumors RR, 0.96 (95% CI, 0.73 to 1.26) for incidence of COX-2–negative tumors</td>
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<tr>
<td>Nurses’ Health Study, Health Professionals Follow-Up Study (22)</td>
<td>NHS (N = 82,095) BRAF</td>
<td>325 mg</td>
<td>HR, 1.03 (95% CI, 0.76–1.38) for incidence of BRAF-mutant colorectal cancer HR, 0.73 (95% CI, 0.64–0.83) for incidence of BRAF–WT colorectal cancer Effect on BRAF–WT tumors based on COX-2 expression: HR, 0.67 (95% CI, 0.56–0.81) for incidence of COX-2–overexpressing colorectal cancer HR, 0.86 (95% CI, 0.67–1.09) for incidence of COX-2–negative colorectal cancer</td>
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\(^a\)The study recorded zero deaths in the cohort in which tumors were both PIK3CA-mutant and COX-2–expressing (n = 23).
the risk of subsequent metastasis at follow-up in patients who were initially metastasis-free (HR, 0.26; 95% CI, 0.11–0.57; \( P = 0.0008 \); ref. 31). As was seen for its chemopreventive effects, the presumed antimetastatic effects of aspirin also seem to be dose-dependent in that an increase in postdiagnosis aspirin dosage from 0.5 to \( \geq 6 \) tablets per week led to a modest improvement in survival benefit in the NHS and HPFS patient cohorts (Table 2; ref. 37). Among patient tumors with \( \text{PIK3CA} \) mutations, the survival benefit associated with aspirin carriers was associated with a statistically significant increase in survival (multivariate HR, 0.18; 95% CI, 0.06–0.61; \( P < 0.001 \)), whereas patients whose tumors had WT alleles (\( N = 803 \)) did not derive any benefit (Table 2; ref. 37). Among patient tumors with \( \text{PIK3CA} \) mutations, the survival benefit associated with aspirin was most evident in tumors with overexpression of \( \text{COX-2} \) (\( N = 55/161; 34\% \)). Similar findings were recently reported in a post hoc analysis of a clinical trial (VICTOR) evaluating rofecoxib as adjuvant therapy of stage II and III colon cancers (38). Patient tumors were categorized by

<table>
<thead>
<tr>
<th>Name of the study group</th>
<th>Study type</th>
<th>Study population (N)</th>
<th>Aspirin dose used</th>
<th>Result from aspirin use after diagnosis [multivariate HR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 89803 (28)</td>
<td>Subgroup analysis in a randomized controlled trial</td>
<td>Stage III colorectal cancer (N = 830)</td>
<td>325 mg</td>
<td>HR, 0.48 (95% CI, 0.24–0.99) for disease-free survival; HR, 0.52 (95% CI, 0.19–1.46) for death (OS)</td>
</tr>
<tr>
<td>Nurses’ Health Study and Health Professionals Follow-Up Study (27)</td>
<td>Prospective cohort study</td>
<td>Stage I–III colorectal cancer (N = 1279)</td>
<td>325 mg</td>
<td>HR, 0.71 (95% CI, 0.53–0.95) for colorectal cancer–specific mortality; HR, 0.79 (95% CI, 0.65–0.97) for overall mortality</td>
</tr>
<tr>
<td>Eindhoven cancer registry and PHARMO prescription registry (30)</td>
<td>Retrospective cohort study</td>
<td>Stage I–IV colorectal cancer (N = 4,481)</td>
<td>80 mg</td>
<td>RR, 0.77 (95% CI, 0.63–0.95) for colorectal cancer–specific mortality; RR, 0.65 (95% CI, 0.50–0.84) for colon cancer mortality; RR, 1.03 (95% CI, 0.75–1.40) for rectal cancer mortality</td>
</tr>
<tr>
<td>Health Informatics Centre Registry, Scotland (29)</td>
<td>Retrospective cohort study</td>
<td>Stage I–IV colorectal cancer (N = 2,916)</td>
<td>75 mg</td>
<td>HR, 0.67 (95% CI, 0.57–0.79) for colorectal cancer–specific mortality; HR, 0.72 (95% CI, 0.57–0.91) for colon cancer mortality; HR, 0.80 (95% CI, 0.58–1.11) for rectal cancer mortality</td>
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</table>
**PIK3CA** mutation status and aspirin usage was recorded at the time of study enrollment. Patients taking <100 mg of aspirin daily were not excluded and were allowed to continue this therapy during the clinical trial. In patients whose tumors carried **PIK3CA** mutations (N = 104), aspirin usage (n = 14) was associated with a statistically significant improvement in recurrence-free survival (RFS; multivariate HR, 0.11, 95% CI, 0.001–0.832; P = 0.027) at a median follow-up of 61.5 months (38). A modest improvement in overall survival (OS) was also found that did not reach statistical significance (multivariate HR, 0.29, 95% CI, 0.04–2.330; P = 0.260). In contrast to aspirin, rofecoxib treatment was not associated with a difference in RFS (multivariate HR, 1.22; 95% CI, 0.50–2.98; P = 0.473). Although the duration of aspirin use before study enrollment was not reported, the median duration of rofecoxib use was 7.4 months. Despite the pronounced survival benefit of aspirin in **PIK3Ca** mutation carriers observed in the VICTOR trial, these data derive from a very small number of patients who reported aspirin usage. The lack of efficacy of the selective COX-2 inhibitor rofecoxib suggests that inhibition of constitutive COX-1 is mechanistically important. Furthermore, the ability of aspirin to inhibit platelet aggregation that is mediated by COX-1 may be important in its antitumor effect (39).

Acting through its cell surface receptors EP1–EP4, PGE2 regulates cellular processes important in cancer development (Fig. 1). PGE2 acts through EP4 to activate Tcf/Lef signaling through a PI3K-dependent pathway (40). Inhibition of PGE2 signaling by aspirin may, therefore, attenuate PI3K activity in **PIK3CA** mutant cancers (41). In addition to inhibiting PGE2, aspirin has been shown to inhibit mTOR, a downstream effector of the PI3K pathway by activation of adenosine monophosphate-activated protein kinase (AMPK) in colorectal cancer cells (42). The mechanisms underlying the antitumor properties of aspirin include both COX-dependent and -independent effects (43). PGE2 stimulates angiogenesis by induction of VEGF and bFGF (basic fibroblast growth factor; ref. 44), and can modulate the WNT/β-catenin pathway to enable an epithelial-to-mesenchymal transition, a critical event for metastasis (45). COX-independent mechanisms contribute to the antitumor effects of aspirin by inhibiting PPARγ (46) and the NF-κB pathway (47–49). Aspirin can also exert immunomodulatory effects by altering chemokines (CCL2 and CXCL10) that lead to decreased numbers of myeloid-derived suppressor cells and an increase in cytotoxic CD8+ T cells (50). Both aspirin and selective COX-2 inhibitors can modulate apoptosis (51, 52) in tissues, including human colorectal epithelia (53), and cancer stem cells may be more sensitive to NSAID-induced apoptosis relative to differentiated cells that is relevant to eradicating micrometastases (54).

From a clinical perspective, identifying the lowest dose of aspirin that can achieve antitumor effects, whereas minimizing potential toxicities is critical. In a prior study, we reported that the 81-mg daily aspirin dose suppressed PGE2 levels equally as did the 650-mg daily dosage in the colorectal mucosa of patients with prior adenomas (55). The antitumor benefits of aspirin are achieved with a trade-off of increased toxicities, as described in a meta-analysis of 22 randomized trials of aspirin for vascular disease prevention. Most notable are the risks of gastrointestinal toxicities, mainly ulcers and gastrointestinal bleeding (RR, 1.62; 95% CI, 1.25–2.09), or intracranial bleeding (RR, 1.65; 95% CI, 1.06–5.99). In the meta-analysis, there was no difference in the rate of adverse events between patients receiving low-dose (75–162.5 mg/d) versus standard-dose (162.5–325 mg/d) aspirin (56). The risks versus potential benefits of aspirin must always be considered when advocating its use in patients. Although aspirin is currently not recommended for patients at average risk of developing colorectal cancer or in patients with removal of prior adenomatous polyps, its use in high-risk patients such as those with advanced adenomas or prior colorectal cancer may be warranted on an individualized basis. However, unresolved issues include the minimally effective dose, optimal duration, and the role of aspirin in patients already undergoing colonoscopic surveillance. For the adjuvant therapy of colorectal cancer, existing data justify the prospective evaluation of aspirin in this setting and a clinical trial (ASCOLT) is ongoing. Furthermore, the addition of celecoxib to standard chemotherapy with FOLFOX is being studied in an ongoing phase III adjuvant therapy trial (CALBG 80702).

More than a century after it was first synthesized, the therapeutic benefits of aspirin continue to emerge. Aspirin has been shown to protect against the recurrence of colorectal adenomas and carcinomas, and compelling evidence suggests its efficacy as an adjuvant agent in a molecular subset. Specifically, aspirin may selectively and potently inhibit colon cancer recurrence and improve survival in patient tumors with **PIK3CA** mutations. Although this finding is compelling, the modest number of patients whose tumors carried **PIK3CA** mutations and who also used aspirin in these studies necessitates caution in their interpretation and underscores the need for prospective validation. Aspirin is currently being studied as adjuvant therapy in an ongoing trial in patients with colorectal cancer (ASCOLT), and another adjuvant study evaluates the benefit of adding celecoxib to FOLFOX in patients with node-positive colon cancer (CALGB-80702). In both trials, a comparison of survival based on **PIK3CA** mutation status will be performed and will yield further efficacy data. Prospective evaluation will be challenging due to the relatively small number of patients whose tumors carry the **PIK3Ca** mutation, and studies will also need to address the issue of duration of aspirin therapy needed to achieve clinical benefit. Research into the mechanistic basis of the efficacy of aspirin in **PIK3CA**-mutated colorectal cancers is eagerly awaited. In an era of targeted therapy that is increasing health care costs, aspirin is an inexpensive and well-tolerated drug that may
prove to be an effective agent to prevent colon cancer recurrence.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: D. Tougeron, D. Sha, S. Manthravadi, F.A. Sinicrope
Development of methodology: D. Tougeron, D. Sha, F.A. Sinicrope
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Tougeron, D. Sha, F.A. Sinicrope
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Tougeron, D. Sha, F.A. Sinicrope

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1093
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