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COX-2 expression in adenoma: an imperfect marker for chemoprevention

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Four randomized, placebo-controlled studies have each shown that daily aspirin use reduces the occurrence of colorectal adenomatous polyps among individuals with a history of prior colorectal adenomas or cancer [1,2,3,4]. In one of these trials, conducted by the Association pour la Prevention par l' Aspirine du Cancer Colorectal (APACC), 272 patients were randomized to two doses of a soluble aspirin salt (lysine acetylsalicylate) at 160 mg or 300 mg or placebo after removal of at least 3 adenomas or one adenoma at least 6mm in diameter in a clearing colonoscopy. Compared with placebo, aspirin treatment at either dose was associated with a 37% reduction in risk of any recurrent adenoma and 70% reduction in risk of recurrent adenoma greater than 5 mm at the Year 1 surveillance colonoscopy [3]. In this issue of Gut, Benamouzig and colleagues now present a secondary analysis of a subset of 136 participants in the APACC trial [5]. The authors examined immunohistochemical expression of cyclooxygenase-2 (COX-2) in the adenomas resected at the baseline clearing colonoscopy in relation to aspirin use and risk of adenoma recurrence at the Year 1 or 4 surveillance colonoscopy. Aspirin is likely, at least in part, to prevent colorectal neoplasia through inhibition of COX-2, the rate-limiting step for the conversion of arachidonic acid to prostaglandins and related eicosanoids. COX-2 promotes inflammation and cell proliferation, and colorectal cancers often overexpress this enzyme [6]. Thus, Benamouzig *et al's* study is a unique opportunity to examine if likelihood of overall adenoma recurrence as well as the effect of aspirin on recurrence varies according to tumoral expression of COX-2 in the baseline adenoma.

As a caveat, a formal presentation of the final main results of the APACC trial incorporating the outcomes at the Year 4 colonoscopy has not yet been published except as part of a larger meta-analysis [7]. Surprisingly, it appears that aspirin at either dose did not reduce adenoma recurrence at Year 4 (relative risk 0.95; 95% CI, 0.75–1.21), in contrast to the positive findings reported at Year 1. These data could reflect a true biological difference in the effect of aspirin with 1 year compared with 4 years of treatment. However, this is unlikely since the APACC results at 4 years of treatment are also inconsistent with the findings of the other three larger randomized trials of aspirin that examined 3 years of treatment. Thus, methodological issues, including the high dropout rate (>30%) and poor adherence to the surveillance interval, could

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account for the unexpected findings at Year 4. As a result, interpretation of Benamouzig *et al's* secondary analysis based on the Year 4 endpoint should be tempered by these potential concerns.

Setting aside these issues, Benamouzig *et al* observed several interesting findings with important potential implications. First, deep stromal expression of COX-2 in baseline adenoma predicted adenoma recurrence: 65% of individuals with high deep stromal expression of COX-2 developed recurrent adenoma compared with of 47% of individuals with low deep stromal expression (p=.04). This result provides additional compelling evidence that the COX-2 pathway is highly relevant to human colorectal carcinogenesis. The association observed with deep stromal expression rather than epithelial expression of COX-2 and risk of recurrent adenoma also highlights the potential importance of tumor-stromal interactions at the adenoma stage of neoplasia. Specifically, neoplastic factors may first stimulate stromal cells, such as fibroblasts and immune cells, to express COX-2 in adenoma. This subsequently leads to stromal induction of increasing levels of tumor epithelial COX-2 expression over the course of progression from early to advanced adenoma to cancer. This correlation between level of epithelial COX-2 expression and increasing lesion size and degree of dysplasia was confirmed in the present study and has been observed previously [8].

In contrast, Benamouzig *et al* found that overall or epithelial, rather than deep stromal expression of COX-2 predicted responsiveness to chemopreventative benefit of aspirin. Among those with low overall COX-2 expression, patients randomized to either dose of aspirin had a significant 41% lower risk of adenoma recurrence compared to those randomized to placebo (p=.02). In contrast, among those with high overall COX-2 expression, patients treated with aspirin had no significant reduction in risk of adenoma recurrence. In two large population-based cohorts, we have also previously showed that the association between aspirin use and incident colorectal cancers or survival from the disease varied according to expression of COX-2 in the cancer epithelium. However, in our studies, high COX-2 expression, rather than low COX-2 expression, was preferentially associated with the effect of aspirin on risk of incident cancer and survival [9,10].

Why do these data presented by Benamouzig *et al* appear to differ from our studies? First, the potential aforementioned methodological issues with the overall APACC trial that may have led to the unexpected overall Year 4 results could also have influenced these findings. Second, as already described by this study, deep stromal expression of COX-2 in a baseline adenoma appears to more strongly associated with recurrent neoplasia than epithelial expression of COX-2. As a result, epithelial expression of COX-2 in adenoma may not have the same relevance in predicting aspirin's influence as we have seen for epithelial expression in a mature cancer or metastatic lesion. The significance of COX-2 expression in an adenoma in either stroma or epithelium is also not likely directly translatable to expression in a cancer. Although the proportion of adenomas expressing high levels of COX-2 is considerably lower than the proportion of cancers [8], aspirin is generally associated with a similar magnitude of risk reduction (25–30%) for adenoma, cancer or death from the disease. Thus, COX-2 expression in an adenoma is an insensitive marker for aspirin-susceptibility.

Finally, trials of adenoma recurrence likely interrogate different steps in the carcinogenesis pathway compared with studies conducted within population-based cohorts. In the APACC trial, patients were treated with aspirin after polypectomy and followed for recurrent adenoma. It is likely that many of the recurrent adenomas which developed were attributable to either missed synchronous adenoma, residual adenoma from inadequate polypectomy of the baseline lesion, or adenoma that arose from tissue harboring a field change. A field change is broadly defined as macroscopically normal tissue in an at-risk individual that may have accumulated many of the alterations (including COX-2 RNA expression) routinely found in adenoma or

cancer [11,12]. Thus, the results of APACC may reflect the effect of aspirin in interrupting the growth and progression of residual adenoma or tissue harboring field changes. By the time a baseline adenoma is induced to express COX-2, the remaining colonic mucosa at-risk may have already developed alterations associated with aspirin resistance. In contrast, we examined the influence of early aspirin exposure in a cohort of individuals without a prior history of neoplasia. Aspirin was inversely associated with the development of colorectal cancers with high COX-2 expression (RR 0.64; 95% CI, 0.52–0.78) but not cancers with low COX-2 expression (RR 0.96, 95% CI, 0.73–1.26) [9]. This likely reflects the effect of aspirin on the earliest steps of tumor initiation, prior to the development of neoplasia or field changes. More recently, we also reported that among patients with Stage I, II, III colorectal cancer who underwent a curative resection, aspirin use was associated with a significant 39% reduction in colorectal cancer-specific mortality, with the strongest reduction in risk observed among those with primary tumors with high COX-2 expression. This data suggest that the COX-2 status of the primary tumor may predict the susceptibility of micrometastases to aspirin. Taken together, our studies along with the present study of Benamouzig *et al*, may reflect not only differences in the significance of COX-2 expression according to stage of neoplasia (adenoma vs. carcinoma), but also according to the timing of aspirin treatment within the various steps in carcinogenesis.

Nonetheless, the results presented here provide additional proof-of-principle that knowledge of the molecular underpinnings of carcinogenesis has the potential to be exploited to predict responsiveness to chemoprevention. However, these findings also highlight the relative challenges of using COX-2 expression in adenoma for this purpose. The comparatively low proportion of adenomas that express COX-2 compared with cancers suggests that COX-2 is a relatively late molecular event that cannot be routinely utilized as a chemoprevention susceptibility marker in the precancerous state. Moreover, given the potential importance of tumor-stromal cross-talk early in the development of neoplasia, the relative significance of expression in stroma compared with adenoma epithelium remains unclear. Thus, further research is needed to identify alternative markers or panels of markers relevant to COX-2-related pathways that are more widely expressed in early stage disease. Such molecular markers could be based on DNA alterations or their associated influences on RNA and protein expression. Moreover, detection of such changes could focus not only on assays of adenoma, but also on assays of histologically normal mucosa with field changes. For example, in a recent secondary analysis of separate chemoprevention trial, the level of 15-prostaglandin dehydrogenase (15-PGDH) RNA transcripts within endoscopically normal colonic tissue predicted resistance to a COX-2 selective inhibitor [13]. This finding is consistent with our emerging understanding of 15-PGDH as a critical physiologic COX-2 antagonist. Thus, as our insight into the biology of carcinogenesis evolves, we will likely identify more specific molecular markers that can be translated directly into successful strategies to tailor cancer prevention.

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