Comment re: "Sporadic Aberrant Crypt Foci Are Not a Surrogate Endpoint for Colorectal Adenoma Prevention" and "Aberrant Crypt Foci in the Adenoma Prevention with Celecoxib Trial"

To the Editor: We believe that the enthusiasm of Lance and Hamilton (1) in embracing the study by Cho et al. (2) as "seminal" and their finality in dismissing aberrant crypt foci (ACF) as a surrogate end point for chemoprevention trials are misplaced. We are concerned that the Perspective of Lance and Hamilton (1) may have overlooked important evidence in arriving at these conclusions, which the authors state were based on their "diverse perspectives of gastroenterology and clinical chemoprevention and of gastrointestinal and molecular pathology."

ACF in the colon have been the focus of many mechanistic and preclinical, and a few epidemiologic, studies (3) since their initial description (4). Given the potential value of ACF as an early and readily identifiable change that might indicate colorectal cancer risk or response to preventive measures, the specifics of the Lance and Hamilton Perspective require close scrutiny.

The authors' statement (regarding the first description of ACF in humans) that "at least one ACF was found in each left colon of the 13 autopsy patients without colorectal cancer" (1) is factually incorrect. Table 1 of the original article (5) clearly states that 13 patients had "left colon from autopsy," only 1 of whom had ACF (one in this case). More important, two key references that very strongly link human ACF to colon tumorigenesis (6, 7) were omitted from the Perspective. In the first, all human ACF were monoclonal proliferations (i.e., the earliest identified neoplastic lesions in the colon; ref. 6). In the second, it seems that Wnt signaling was constitutively active in more than 90% of human ACF through promoter methylation of the genes for secreted frizzled-related protein 1 or 2 (7). In addition, a number of recent molecular and genetic analyses have shown that ACF of each histologic subtype have characteristic aberrations found in colorectal cancer (e.g., ref. 8).

There is a long, impressive history of preclinical animal studies showing that ACF suppression by a wide variety of dietary factors is associated with reduced cancer incidence (9).[1] In rodent studies, larger ACF and/or crypt multiplicity often correlates with tumors better than does the number of ACF (10).

The clinical evidence is provocative but limited (10) and the Cho et al. study (2) is the first and only prospective randomized trial. Although innovative, it alone cannot be taken as strong evidence against human ACF as a suitable surrogate end point. The study was based on only 45 patients (of whom 10 were regular aspirin users), who were evaluated at five different sites with five different investigators. These investigators found that "the mean number of ACF at baseline was… not different between those with and without advanced adenomas," in contrast to several other reports (10). Most important, the 45 patients in the Cho et al. study did not provide evidence that celecoxib reduced the incidence of adenomas: Adenoma detection was 37.5% in the placebo group and 45.7% in the celecoxib group at "year 1 and/or year 3." If this study did not have the statistical power to detect a protective effect of celecoxib, it certainly did not have the power to make any definitive conclusion about ACF as a surrogate end point.

We view the Perspective by Lance and Hamilton (1) as an example of "jury nullification." They present the evidence with clarity and scholarship, but then render a verdict that is strikingly inconsistent with that evidence. Our position is not that ACF should now be accepted as a surrogate end point for human chemoprevention trials, but rather that the existing direct evidence is woefully inadequate to render a verdict at this time. In other words, more research is needed.

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Disclosure of Potential Conflicts of Interest

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