

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”

In Response: Our article (Cho et al.; ref. 1) was a substudy of 45 participants from a larger clinical trial of 2,035 participants. The purpose of the substudy was to assess whether ACF were effective early surrogate biomarkers in a chemoprevention trial assessing adenoma recurrence over 3 years of treatment and surveillance. The larger study, which was designed with high power (96%) to detect whether celecoxib reduced the risk of adenoma recurrence over 3 years, found a 33% reduction for 200 mg twice daily users and a 45% reduction for 400 mg twice daily users (2). The 45 substudy patients were similar to the overall cohort in baseline characteristics and adenoma recurrence at 1 year: Adenoma recurrence rates of placebo groups were 45% (large trial) and 37.5% (substudy); recurrence rates of celecoxib groups were 26.6% (large trial) and 18.5% (substudy). If ACF were an early intermediate biomarker, they surely would have responded early (at 8-12 months) because adenoma response was very pronounced at 1 year. With a small sample size ($n = 17$), the substudy placebo group had 6 patients with an adenoma recurrence in year 1 but none subsequently. Consequently, the cumulative adenoma recurrence rate over 3 years for the placebo group in the substudy was lower than that in the larger study (61%). On the other hand, the cumulative adenoma recurrence rate of the substudy treatment group (45.7%) was comparable to that of the trial's entire treatment group (40.4%).

We agree with the statement in the letter of Stevens and colleagues that our study (i.e., the substudy in 45 patients) “did not have the statistical power to detect a protective effect of celecoxib” against an adenoma end point. However, it does not therefore follow that “it certainly did not have the power to make any definitive conclusion about ACF as a surrogate end point.” The requirements of a surrogate end point are dif-

ferent from those of a chemopreventive agent. For ACF determination to be a valid surrogate end point, this marker must (a) correlate in incidence with the target disease; (b) be modulated by treatments that alter the target disease; and (c) show changes in response to treatment consistent with those observed for the target disease (3). As we described in detail (1), these conditions were not met, even though 655 ACF were identified in the 45 patients.

Given the wealth of data available from animal and human studies, we conclude that dysplastic ACF, which are common in rodents and very uncommon in humans, most likely meet the conditions required for a valid surrogate end point. Unfortunately, their very small incidence in the population at risk for sporadic colorectal cancer makes them unsuitable for use in chemoprevention drug development.

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Disclosure of Potential Conflicts of Interest

M.M. Bertagnolli, commercial research grant, Pfizer, Inc.; honorarium, Meta-mark, Inc. No other potential conflicts of interest were disclosed.

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