Response

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We thank Drs. Lee and Gibbs for their comments. CALGB 89803 began enrollment in 1999, when data on the potential of aspirin to decrease the risk of colorectal adenomas and cancer was just beginning to emerge (1–3). At that time, there were no prospective studies on the role of aspirin after cancer diagnosis, much less within molecular subgroups that predict greater benefit from aspirin. Fortunately, investigators involved in CALGB 89803 did consider the possibility that aspirin may have a role in patients with established colon cancer. Consequently, questions on aspirin use, including dosage and frequency, were incorporated into the two diet and lifestyle questionnaires administered during and after completion of adjuvant chemotherapy. With rapidly mounting data on the importance of the COX-2 pathway, the second questionnaire was also expanded to include questions on selective COX-2 inhibitors. Thus, contrary to Drs. Lee and Gibbs’ contention, our exposures were not defined arbitrarily. Because of the availability of aspirin data on both questionnaires, we were able to determine consistent aspirin use as a proxy for longer duration of use. However, we could examine COX-2 inhibitor use on the second questionnaire only.

We first presented our results at the Annual Meeting of the American Society of Clinical Oncology in 2005 (4). At the time, those initial results provided the first prospective evidence of a statistically significant association between postdiagnostic aspirin and COX-2 inhibitor use and improved survival in stage III colon cancer patients with a median 2.7 years of follow-up. We subsequently confirmed our findings in a larger cohort of 1279 patients with stages I-III colorectal cancer (CRC) in the Nurses’ Health Study and Health Professionals’ Follow-Up Study (5). Our work collectively led to the development of two ongoing phase III trials of aspirin (ASCOLT) and celecoxib (CALGB 80702) as adjuvant therapy in patients with stage III colon cancer. The VICTOR trial also attempted to evaluate the impact of adjuvant rofecoxib in patients with stages II and III colon cancer, but was terminated early because of withdrawal of the medication for cardiovascular toxicity (6). Because enrolled patients had been treated with rofecoxib for only a median of eight months, no meaningful conclusions can be drawn.

Our current publication extends our initial results with mature follow-up of a median of six and a half years. The multivariable-adjusted hazard ratios were largely unchanged, particularly after censoring non–cancer related deaths at five years to minimize misclassification. We acknowledge that some of the 95% confidence intervals cross 1.0 because of the small number of patients with self-reported medication use. However, given the consistency and directionality of the hazard ratios, all results were reported in the abstract. Ultimately, definitive conclusions on the benefit of aspirin and COX-2 inhibitors in patients with stage III colon cancer, and associated biomarkers of efficacy, will require the results of the ongoing phase III trials. Until such data become available, though, it remains important to continue to build an evidence base for patients, clinicians, and researchers through leveraging the high-quality data provided by patients enrolled in already completed clinical trials.

References


Received: April 27, 2015; Accepted: May 5, 2015

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