

*Point/Counterpoint***Aspirin Should Not Be Promoted for Colon Cancer Prevention: Counterpoint****Robert S. Sandler**

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There is little question that aspirin can decrease the risk of large bowel cancer. A large number of observational studies in humans, both case-control and cohort, consistently show a strong protective effect of aspirin (1). Importantly, three randomized controlled trials show that aspirin decreases the risk of new adenomas in humans (2-4). Because most colorectal cancers arise from adenomas, the results from the adenoma prevention trials are presumptive evidence that aspirin can prevent cancer as well. There are few examples in epidemiology where the body of evidence is so consistent.

The decision to recommend aspirin to prevent colorectal cancer cannot be based exclusively on the effect of aspirin on the colon. Aspirin is a systemic agent that has both beneficial and adverse effects throughout the body. It is the balance of these effects that should drive the decision. In contrast to cancer chemotherapy, given to patients with life-threatening disease for short intervals with major toxicity, agents for cancer chemoprevention are given to healthy people for years. Whereas toxicity may be acceptable in the case of chemotherapy, we can accept minimal or no toxicity when treating healthy individuals. The term healthy, in the context of colon cancer chemoprevention, refers to individuals who have no colon disease that causes symptoms or requires treatment. People who have had an adenoma are at higher risk of colorectal cancer, but are not suffering from a disease, particularly after their adenomas are removed. Whereas some have advocated aspirin chemoprevention for higher-risk individuals with prior adenomas, others have proposed more indiscriminate use irrespective of adenoma status.

Despite its widespread availability without a prescription, aspirin is not completely safe, even in low dose. Aspirin can cause potentially fatal gastrointestinal bleeding and hemorrhagic strokes. The U.S. Preventive Services Task Force calculated that there would be 2 to 4 major gastrointestinal bleeds and 0 to 2 hemorrhagic strokes per 1,000 individuals followed for 5 years among individuals taking low-dose aspirin (5).

The toxicity of aspirin might be acceptable if the benefits clearly outweighed the risk. What are the true

benefits of aspirin in a colorectal cancer chemoprevention program? Whereas it is true that aspirin can lower the risk for adenomas, ~40% of individuals with prior adenomas still develop new adenomas on aspirin therapy (3). That level of prevention would probably not provide much reassurance to patients and their providers. As a consequence of imperfect protection, aspirin chemoprevention would have to be recommended as part of a program that also included colonoscopy. Most of the benefits in the combined program would come from colonoscopy, which would remove most of the adenomas— aspirin would confer risk with little benefit.

Furthermore, it is recognized that colonoscopy, even in the best hands, misses lesions. A recent systematic review suggests that 22% (95% confidence interval, 19-26%) of lesions of any size are missed (6). The miss rate is lower for larger and potentially more dangerous polyps. Because colonoscopy is not completely reliable, aspirin could be of benefit to reduce the malignant potential of any adenomas missed by colonoscopy. Aspirin might limit the growth of adenomas, so any adenomas that are detected would be smaller and thereby easier and safer to remove. In theory, it might be possible to lengthen the interval between colonoscopies in aspirin takers, but that has not been studied. Overall, however, formal cost-effectiveness analyses have not shown aspirin to be cost-effective in a program including colonoscopy (7, 8). In such a program, colonoscopy provides most of the benefit, and adding aspirin simply contributes to risk. Because of the unfavorable risk-benefit ratio, the authoritative U.S. Preventive Services Task Force has recommended against the routine use of aspirin and nonsteroidal anti-inflammatory drugs to prevent colorectal cancer in individuals at average risk for colorectal cancer (9, 10).

There are some people who should be taking aspirin, but not to prevent colorectal cancer. High-quality evidence has shown that aspirin can decrease serious adverse events in patients with previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation (11). In these individuals, the benefits are thought to exceed the risk. Individuals at high risk for cardiovascular disease by virtue of age, gender, elevated lipids, and hypertension could also benefit from it. The U.S. Preventive Services Task Force has recommended aspirin for individuals estimated to have a 5% risk for coronary heart disease events over 5 years (5).

The number of individuals who are at cardiovascular risk is substantial and many of them are not

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taking aspirin as they should. If we could identify these individuals and motivate them to take aspirin, they would have fewer adverse cardiovascular outcomes and they would enjoy the added benefit of fewer colon adenomas and cancers. It is equally important to understand that giving aspirin to individuals at low risk for cardiovascular disease would have an unfavorable cost-benefit ratio. Finally, it would be unfortunate if individuals at higher risk for colorectal cancer because of prior adenomas or cancer or positive family history of colorectal neoplasia were falsely reassured by taking aspirin and failed to have regular surveillance colonoscopies.

Aspirin should not be promoted for colorectal cancer prevention in average-risk individuals and should probably not be promoted in those with modestly increased risk such as those with prior adenomas. It might be promoted to individuals with substantial risk of colon cancer such as those with prior colon cancer and those with large numbers of adenomas. It should be promoted to prevent adverse cardiovascular events that dwarf colorectal cancer as a cause of morbidity and death in the United States. We can recommend aspirin to those at increased risk for cardiovascular disease, taking comfort in the fact that doing so will also be protecting their colons.

Disclosure of Potential Conflicts of Interest

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