

# CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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## Chemoprevention of Colorectal Cancer: Aspirin and Beyond



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### **H&O** What is the most effective approach to preventing colorectal cancer (CRC)?

**PL** As America's population reaching age 50 years expands, there is an urgent need to increase our stubbornly low CRC screening rates. This starts with patients and providers discussing all of the recommended CRC screening tests, including highly sensitive, noninvasive, more broadly scalable screening options. Increasing the screening rate through greater use of noninvasive options will offer the gastroenterology community a better opportunity to provide ready access for polyp resection for screen-positive patients, which should afford even greater ability to reduce CRC incidence and mortality.

### **H&O** Why are additional approaches to preventing CRC needed?

**PL** Screening continues to be suboptimally utilized. Not everyone is aware that screening has the potential to prevent CRC. Also, multiple screening options are available, with different recommended intervals between repeated tests. For colonoscopy, the interval can be up to 10 years. As a result, it makes good sense to have other ways to prevent CRC, like chemoprevention, that can complement screening.

### **H&O** Which patients are potential candidates for chemoprevention of CRC?

**PL** The decision comes down to the risk-benefit ratio. Chemoprevention has tremendous potential for people who have an inherited predisposition to CRC, such

as those with familial adenomatous polyposis (FAP) or Lynch syndrome, and is being explored in these populations. For example, retrospective and prospective studies have shown efficacy for cyclooxygenase 2 (COX-2) inhibitor agents and other nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing the risk for CRC among patients with FAP. NSAIDs are often used in patients with FAP, but less evidence is available in patients with Lynch syndrome, for whom the treatment may be less effective and the risk-benefit ratio remains incompletely defined.

Regarding the general population, the US Preventive Services Task Force stated in 2016 that low-dose aspirin is useful for the primary prevention of cardiovascular disease and CRC in certain individuals. They give a "B" rating to the use of this agent in adults aged 50 to 59 years who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. The decision should be individualized among adults aged 60 to 69 years who have a 10% or greater 10-year cardiovascular disease risk. However, these recommendations do not seem to be widely implemented on a population scale.

### **H&O** How common is it for people in the United States to take low-dose aspirin for the primary chemoprevention of CRC?

**PL** We do not have good statistics to answer that question directly, but it is common for people to take low-dose aspirin regularly. The wide use of low-dose aspirin across the population actually makes it difficult to do

studies of NSAIDs specifically to assess their true chemopreventive effects.

**H&O** What agents besides NSAIDs are being examined for use in the prevention of CRC?

**PL** Researchers have spent decades looking at various nutritional supplements, including calcium, selenium, folate, and curcumin. A newer line of investigation, immunoprevention, involves the use of vaccines against colon polyps or CRC. Another new approach involves the use of metformin and other oral diabetic agents. An additional agent that's being studied for use in patients with FAP is erlotinib (Tarceva, Genentech/Astellas; NCT02961374).

The major challenge with chemoprevention is that you're dealing with a generally healthy population.

**H&O** How is each of these agents believed to work to reduce the risk for CRC?

**PL** The current thinking is that NSAIDs work against CRC through modulation of the COX-2 pathway—that does seem to be at least part of the story. NSAIDs have the potential to lead to both benefit and toxicity, depending on the balance of arachidonic acid metabolism. The effectiveness of nutritional supplements is based on the hypothesis of sufficiency vs deficiency, which is fairly complicated to puzzle out. For example, how much selenium is enough and how much might be too much? It is possible for supplementation—with either macronutrients or micronutrients—to increase or decrease the risk for certain health conditions. As for curcumin, this may work through an anti-inflammatory effect.

Immunoprevention is typically based on a single target. For example, our group is currently studying the use of a mucin 1 (MUC1) vaccine to prevent CRC. The MUC1 glycoprotein is aberrantly expressed in many malignancies, including CRC. The idea behind our study is that we might be able to protect someone with a history of polyps against future polyps or even cancers by administering a vaccine against the MUC1 protein. Metformin is hypothesized to work by reducing cellular

proliferation and perhaps providing other beneficial effects.

**H&O** What are the potential long-term risks of treating somebody with one of these agents?

**PL** The primary risks of NSAIDs are gastrointestinal and cardiovascular. Epidemiologic data have suggested that calcium may be associated with an increased risk for prostate cancer in men, but the available data are inconsistent. Supplements also may have unanticipated side effects. In a famous example, a Finnish study that was published in 1994 found that giving  $\beta$ -carotene in an effort to prevent lung cancer actually seemed to increase the risk for lung cancer in current and former smokers.

The major challenge with chemoprevention is that you're dealing with a generally healthy population, and every agent has the potential for toxicity. Someone with a heritable cancer syndrome, such as FAP or Lynch syndrome, has a high-enough risk that considering chemopreventive interventions is warranted. The key is to optimize the benefit-risk ratio, which can be difficult because the degree of risk that we accept in a prevention setting is usually different from what we accept in a therapy setting. Another challenge is that studies need to be long when we are trying to prevent future disease—we don't have a tumor that we can watch to see if it shrinks, for example, so it is harder to measure the outcome over a reasonable period of time.

**H&O** Could you discuss your preliminary research on linaclotide (Linzess, Allergan)?

**PL** Linaclotide and the guanylate cyclase C (GUCY2C) pathway appear to play an important role in CRC. Drs David Weinberg and Scott Waldman, who are leading the investigation of this area for our group, have shown that a form of linaclotide approved by the US Food and Drug Administration, used to treat irritable bowel syndrome with constipation or chronic idiopathic constipation, does not reliably affect GUCY2C-mediated pathways in the colon and rectum. However, this approach is still intriguing for CRC chemoprevention if we can find a formulation that adequately delivers the active compound to the target organ, with an acceptable dosing regimen for CRC chemoprevention.

**H&O** What other important studies have been conducted that address the chemoprevention of CRC?

**PL** Dr Monica Bertagnolli was the lead author of a seminal study, published in the *New England Journal of*

*Medicine* in 2006, that showed a dramatic decrease in polyp recurrence associated with the use of celecoxib.

There's also a clinical trial by Dr Frank Meyskens and colleagues that randomly assigned patients with a history of resected polyps to a combination of difluoromethylornithine (DFMO) plus the NSAID sulindac vs placebo. The drug combination had a striking effect—the risk for recurrent polyps after 3 years was 41.1% with placebo and 12.3% with DFMO/sulindac. DFMO carries a risk for hearing loss that can be permanent in some cases, although the patients in this study did not experience any more hearing loss with DFMO than with placebo.

Other studies have been conducted with calcium, vitamin D, folate, and selenium, with mixed effects.

### **H&O** What approaches have been shown to be ineffective for CRC chemoprevention?

**PL** To date, clinical trials have not supported the use of a fiber-based intervention to prevent CRC or polyp recurrence. It is possible that something about the fiber intervention or its timing made it ineffective. But we do not have sufficient evidence from prospective, randomized trials that this approach works to reduce the risk for CRC, although fiber does have potential health benefits related to cardiovascular disease and diabetes prevention.

### **H&O** What questions should future studies address?

**PL** I like to think of this question as the ABCDs of chemoprevention, with *A* standing for agent, *B* standing for biomarkers, *C* standing for cohorts, and *D* standing for duration of the intervention or dosing. Regarding the agent, how can we best understand the potential chemopreventive benefit of some of these compounds? Which agents are more likely to work—those that are molecularly targeted, or those with anti-inflammatory properties? Regarding biomarkers, what should we measure in these trials to determine risk stratification and effects? Is there anything short of a polyp recurrence endpoint or a cancer incidence endpoint that we can measure and get meaningful sense of whether or not the agents are effective? This is where chemoprevention differs from chemotherapy. We typically don't have a lesion to monitor, so people have tried to measure proliferation or apoptosis in normal mucosa and extrapolate those findings.

Regarding cohorts, we need to learn which populations are at highest risk and how best to engage them. How can we enroll enough high-risk patients into studies that we obtain statistically meaningful data?

Regarding duration of the intervention or dosing, we want to find the right balance between reducing polyps and CRC and not causing harm.

### **H&O** Is there anything you would like to add?

**PL** The National Cancer Institute (NCI) is developing promising preventive agents through its Phase 0/I/II Cancer Prevention Clinical Trials Program, which funds research at 5 institutions, including our group at the Mayo Clinic. The NCI's commitment and investment have been considerable and extremely beneficial, and its continued support of those programs will help us realize the potential that chemoprevention offers.

I'd also like to point out that CRC is one of the most preventable yet least-prevented cancers. We know that screening is effective, yet screening rates for CRC are lower than those for breast cancer and cervical cancer. We need to work together to make sure that people understand that screening is effective, multiple screening options are available, and chemoprevention can be used as an adjunct to screening in higher-risk populations.

### **Disclosure**

*Mayo Clinic has a financial interest in Exact Sciences, which manufactures Cologuard. Dr Limburg serves as the co-Chief Medical Officer for Exact Sciences.*

### **Suggested Readings**

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