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Taking the starch out of hereditary colorectal cancer

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In *The Lancet Oncology*, John Mathers and colleagues[1] report additional results from the Colorectal cancer Adenoma/carcinoma Prevention Programme (CAPP)[2] randomised trial of interventions to reduce neoplasia in patients with Lynch syndrome, the hereditary cancer condition caused by germline mutations in DNA mismatch repair (MMR) genes.[2] In CAPP2, the investigators recruited 937 patients with Lynch syndrome from 43 international centres, and began a 4-year intervention study of two factors they proposed to reduce the risk of neoplasia in these individuals. They randomised participants into four groups, and administered 600 mg of aspirin and 30 g of a fermentable dietary fibre (resistant starch [Novelose]) every day to one group; aspirin and fibre-placebo to the second group; fermentable dietary fibre and aspirin-placebo to the third; and both placebos to the fourth group. The initial hypothesis was that aspirin, or fibre, or both, might reduce the incidence of colorectal adenomatous polyps, the precursors of colorectal cancer, over the period of administration. Unfortunately, neither intervention had any effect. The relative risk for subsequent colonic adenomas was 1·0.[3]

The CAPP2 investigators had the foresight to continue to gather masked data over a longer period of time, and later showed that participants who took 600 mg of aspirin for a mean of 25 months had a reduction in colorectal cancer compared with those who took placebo with a hazard ratio of 0·63 (95% CI 0·35–1·13; p=0·12).[4] Better yet, those participants who completed at least 2 years of the aspirin intervention had a hazard ratio of 0·41 (95% CI 0·19–0·86; p=0·02) for colorectal cancer. Furthermore, no difference in adverse events between the aspirin and placebo groups was identified, although the cohort of volunteers was relatively young, with a median age of 45 years. The effect of aspirin on incidence of colorectal cancer and mortality has extensive support in multiple studies of sporadic colorectal cancer.[5]

Dietary fibre has long been proposed to have a suppressive effect on the development of colorectal cancer. A study done 20 years ago noted a significant correlation between dietary fibre intake and stool weight, that mean stool weight correlated inversely with population risk for colorectal cancer, that adding fibre to the diet increases stool weights, and they predicted that the intake of about 18 g a day of dietary fibre would be associated with stool weights of about 150 g a day, which might reduce the risk of colorectal cancer.[6] Rational theoretical reasons exist as to why dietary fibre might affect the development of colorectal neoplasia. Many studies, both laboratory-based and clinical, have supported the concept that dietary fibre might reduce the risk of colorectal cancer, but this has remained an unsettled issue at a practical or clinical level.

In the current report, Mathers and colleagues reported no effect of fibre alone on cancer risk in patients with Lynch syndrome.[1] There were minor, non-significant increases in hazard

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ratios for colorectal cancer in participants randomised to the starch arms (ie, intention to treat), or for those who completed 2 years of intervention (ie, per protocol). A larger study might show a small beneficial effect, but it would never be clinically reasonable to recommend an intervention that reduces cancer risks by just 5–10% when colonoscopy is the standard of management, and has a substantial effect on colorectal cancer mortality in this disease.[7]

CAPP2 represents a huge contribution to the study of Lynch syndrome. No other study of any medical or dietary intervention in this disease exists. The finding that aspirin has a potentially substantial effect on cancer risk in this disease is important. The fact that aspirin can prevent colorectal cancer but not colorectal adenomas tells us something very important about the development of colorectal neoplasia, and where in the evolution of cancer the intervention with aspirin works. The patience of the CAPP2 investigators was rewarded after the disappointment that followed the null results for adenoma development. We now need to know what dose of aspirin is optimal for cancer prevention without causing adverse events. In fact, in view of the beneficial effects of aspirin and the absence of adverse effects in the treatment group, together with the knowledge of how long it took to complete this study, recommendation of its use in patients with Lynch syndrome is tempting—at least those who are young.

Importantly, dietary fibre seems not to be an intervention that needs revisiting in this disease. However good the concept might have seemed, the findings from the CAPP2 study offer little encouragement to continue study of the effects of fibre in this disease. Future studies in this area will involve an attempt to identify the optimum dose of aspirin, to determine how many years this intervention can be administered, and to determine whether the benefits of aspirin outweigh the risks in older individuals. The CAPP2 investigators deserve credit for their vision and perseverance in pushing the clinical boundaries in hereditary colorectal cancer.

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