

Aspirin and colorectal cancer prevention in Lynch syndrome

More than 600 000 people worldwide die of colorectal cancer annually,¹ making development of effective preventive agents for this disease a high priority. One of the most promising such agents, aspirin, is the subject of a major report in *The Lancet* by John Burn and colleagues.² In previous work, four placebo-controlled randomised trials showed that aspirin reduced risk of colorectal adenomas, precursor of almost all colorectal cancers, in patients with a history of adenoma or colorectal cancer.³ A randomised trial in familial adenomatous polyposis suggested that aspirin may protect against adenoma development.⁴ In a meta-analysis of long-term data from five randomised trials of cardiovascular prevention, aspirin reduced the 20-year risk of colorectal cancer by 24% and of associated mortality by 35%.⁵

Although this collection of data is compelling, a definitive conclusion on aspirin's ability to prevent colorectal cancer requires a randomised trial of aspirin with colorectal cancer as the primary endpoint. The Colorectal Adenoma/carcinoma Prevention Programme 2 (CAPP2) study of aspirin in Lynch syndrome was designed as such a trial. Colorectal cancer associated with Lynch syndrome is the most common inherited colorectal cancer, and results from germline mutations in mismatch repair genes that confer a high lifetime risk of colorectal (70%) and other cancers, including those of the uterus, small intestine, and ovaries.⁶ In CAPP2, 937 carriers of Lynch syndrome were randomly assigned to four groups in a two-by-two factorial design: high-dose aspirin (600 mg/day) plus resistant starch placebo, resistant starch (30 g) plus aspirin placebo, aspirin plus resistant starch, or aspirin placebo plus starch placebo. The initially reported analysis (after a mean of 29 months on treatment) suggested that aspirin or resistant starch, or both, did not reduce the risk of colorectal neoplasia (adenomas plus colorectal cancer).⁷ A non-significant reduction in colorectal neoplasia, however, occurred in the aspirin group (8%) compared with the non-aspirin group (11%; $p=0.3$). Observational and clinical studies suggesting the need for extended follow-up to reveal a reduced risk of colorectal cancer^{5,8} led CAPP2 to prespecify a double-blind long-term follow-up in the postintervention period.

Burn and colleagues now report results of this long-term (mean 56 months) follow-up analysis in 861 individuals.² Contrasting strikingly with the

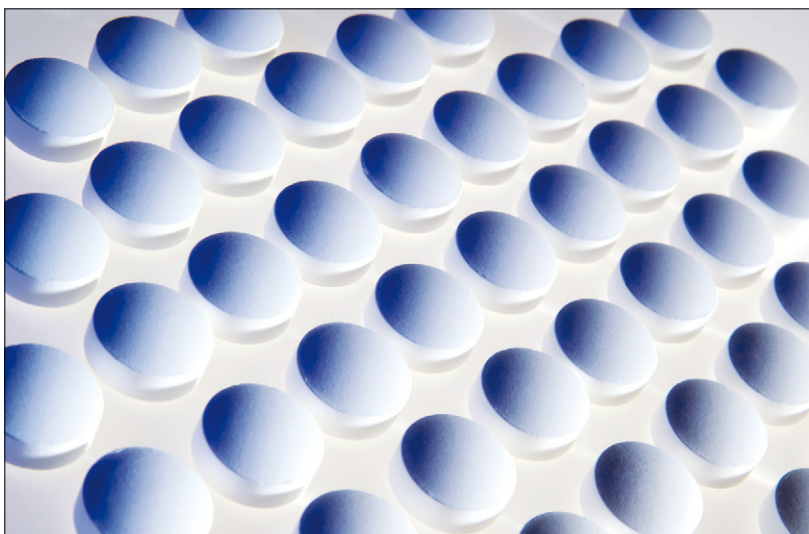
short-term findings, colorectal cancer (not combined with adenoma) developed in fewer patients on aspirin (4%) than in those not on aspirin (7%; hazard ratio [HR] 0.63, 95% CI 0.35–1.13, $p=0.12$) in an intention-to-treat (ITT) analysis, and significantly fewer (HR 0.41, 95% CI 0.19–0.86, $p=0.02$) in a prespecified per-protocol analysis (in about 60% of long-term patients; aspirin treatment for ≥ 2 years ascertained by extrapolated tablet counts). Aspirin was associated with a reduced risk of colorectal cancer (incidence rate ratio 0.56, 95% CI 0.32–0.99, $p=0.05$) in ITT analyses accounting for multiple primary colorectal cancers in some individuals.

These results are compelling and consistent with aspirin's preventive effect in sporadic neoplasia, although the study has limitations. For example, endpoint ascertainment was not standardised, and more intensive colonoscopic evaluation could have occurred in the aspirin group than in the non-aspirin group because of more frequent adverse effects after intervention. This is probably not the case, however, because gastrointestinal bleeding, ulcers, or anaemia did not differ between aspirin and non-aspirin groups even during intervention.

What are the implications of this study? First and foremost, the results provide a strong rationale for routine use of aspirin in individuals with Lynch syndrome. Colorectal cancer surveillance in carriers of Lynch syndrome necessitates frequent colonoscopies (every 1–2 years), beginning between age 20 and 25 years,⁶ which seem effective but have inherent risks and do not

Published Online
October 28, 2011
DOI:10.1016/S0140-6736(11)61216-6

See Online/Articles
DOI:10.1016/S0140-6736(11)61049-0



provide complete protection. Risk of colorectal cancer in these patients is up to 6% over 10 years⁹ and was even higher at 7% in CAPP2 (non-aspirin group) over 4-6 years, despite routine surveillance. Furthermore, aspirin non-significantly reduced extracolonic Lynch syndrome-associated cancers (eg, endometrial, small intestine) in CAPP2, giving hope that aspirin might also suppress these cancers, which have few screening options.

The long-term results of CAPP2 are also invaluable for the continued assessment of aspirin for prevention of sporadic colorectal cancer, which is not currently recommended mainly because of concerns about toxic effects and continuing uncertainty about dose and duration.¹⁰ With aspirin's well established vascular benefits and recent evidence of benefit for colorectal and other cancers in pooled cardiovascular randomised trials,¹¹ Burn and colleagues' findings might at last tip the scales in favour of aspirin as the chemopreventive agent of choice for many individuals.

Does this long-term follow-up analysis allow a definitive conclusion, say for standard regulatory approval, about aspirin's ability to prevent colorectal cancer? In isolation, no, since the results of the primary analysis were not significant for the ITT population. The data strongly support routine use of aspirin, however, for patients with Lynch syndrome as an adjunct to intensive cancer surveillance. As the first randomised trial of aspirin with colorectal cancer as the primary endpoint, CAPP2 also certainly moves us closer to a more definitive answer on aspirin's overall role in the prevention of colorectal cancer. Unfortunately, prohibitive logistics make a randomised trial of aspirin prevention with a colorectal cancer endpoint in a sporadic-risk population unlikely. Therefore, these results from CAPP2 and previous evidence arguably support more general

recommendations to consider aspirin for prevention of colorectal cancer in the context of individualised risk-benefit assessments.

Andrew T Chan, *Scott M Lippman

Division of Gastroenterology, Massachusetts General Hospital, and Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (ATC); and Departments of Thoracic/Head and Neck Medical Oncology and Clinical Cancer Prevention, University of Texas, MD Anderson Cancer Center, Houston, TX 77030, USA (SML)
slippman@mdanderson.org

ATC has consulted for Bayer HealthCare and Millennium Pharmaceuticals. SML declares that he has no conflicts of interest.

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2011; **127**: 2893-917.
- 2 Burn J, Gerdes A-M, Macrae F, et al, on behalf of the CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011; published online Oct 28. DOI:10.1016/S0140-6736(11)61049-0.
- 3 Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Natl Cancer Inst* 2009; **101**: 256-66.
- 4 Burn J, Bishop DT, Chapman PD, et al. A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. *Cancer Prev Res (Phila)* 2011; **4**: 655-65.
- 5 Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010; **376**: 1741-50.
- 6 Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* 2006; **296**: 1507-17.
- 7 Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *N Engl J Med* 2008; **359**: 2567-78.
- 8 Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005; **294**: 914-23.
- 9 Vasen HF, Abdirahman M, Brohet R, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology* 2010; **138**: 2300-06.
- 10 US Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007; **146**: 361-64.
- 11 Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; **377**: 31-41.