Published in final edited form as:

Lancet. 2012 April 28; 379(9826): 1569–1571. doi:10.1016/S0140-6736(11)61654-1.

Are we ready to recommend aspirin for the prevention of cancer?

Andrew T Chan and Nancy R Cook*

Division of Gastroenterology, Massachusetts General Hospital and Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (ATC); and Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA (NRC)

Rothwell and colleagues report additional data supporting the hope that daily aspirin can ward off a panoply of cancers (1). Aspirin's role in reducing risk of vascular events is well-established, although which risk factor profiles derive net benefit remain controversial (2). The strongest proof of aspirin's anti-neoplastic effect has been in colorectal tumors. Several epidemiological studies (3), randomised controlled trials (RCTs) of colon polyp recurrence (4), and RCTs in patients with hereditary colorectal cancer (CRC) syndromes (5, 6), have shown that aspirin reduces incidence of colorectal neoplasia. By long-term follow-up of participants in five cardiovascular-prevention RCTs, Rothwell and colleagues previously observed that daily aspirin at any dose reduced risk of CRC by 24% and of CRC-associated mortality by 35% after a delay of 8–10 years (7).

A chemopreventive benefit of aspirin for other cancer sites was far less certain until Rothwell and colleagues' earlier pooled analysis of individual patient data from 8 cardiovascular-prevention RCTs. Daily aspirin use at any dose was associated with a 21% lower risk of cancer death during the in-trial period, with benefit only apparent after 5 years (8), and reduced mortality due to several cancers on post-trial follow-up to 20-years. This finding was the first convincing evidence that aspirin might prevent death from several cancers, thereby widening its potential population-wide impact.

In their new report, Rothwell and colleagues have expanded their study to include an additional 43 RCTs of daily aspirin of any treatment duration for the primary or secondary prevention of vascular disease. Aspirin, irrespective of dose, significantly reduced risk of non-vascular death by 12% and of cancer death by 15%, with benefit observed within 3 years for high-dose (≥ 300 mg/day) and after 5 years for low-dose (<300 mg/day). Benefit on fatal plus non-fatal cancers emerged after 3 years across several body sites. Second, in 12 primary prevention trials aspirin again reduced non-vascular death by 12%, but not vascular death, leading to a non-significant effect on all-cause mortality. Third, among 6 primary prevention trials, low-dose aspirin reduced risk of incident cancer by 12%. In contrast, aspirin reduced risk of major vascular events and increased risk of major extracranial bleeds, but only within the first 3 years of follow-up.

© 2012 Elsevier Ltd. All rights reserved.

ncook@rics.bwh.harvard.edu.

Conflict of interest statement: ATC has served as a consultant to Bayer HealthCare and Millennium Pharmaceuticals. NRC declares she has no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Although these results are compelling, they have some limitations. First, these analyses do not include the largest primary prevention aspirin RCTs: the Women's Health Study (WHS) of 39,876 women treated with alternate-day 100 mg aspirin over 10 years and the Physicians' Health Study (PHS) of 22,071 men treated with alternate-day 325 mg aspirin over 5 years. After 10–12 years of follow-up, aspirin was not associated with lower risk of CRC (9, 10) or overall cancer incidence or mortality (9). In the present report, these RCTs were excluded due to possible differences in the biological effect of alternate-day rather than daily aspirin. Such differences, although plausible, are far from conclusively established. Second, analyses of cancer incidence were confined to 6 low-dose aspirin primary prevention RCTs, although including the available secondary prevention trials of cardiovascular disease would be less selective. Third, because these studies were originally designed to examine cardiovascular endpoints, information was not collected on cancer screening or surveillance. Thus, the potential for earlier diagnosis and removal of either precancerous precursors (e.g. polyps) or cancers due to aspirin-associated bleeding or anemia remains a conceivable explanation for some results. Last, certain analyses were limited by the quality of available data. Some estimates pooled individual-level data with published results. Moreover, in analyses of cancer incidence, fatal outcome data for some RCTs were combined with incidence data from others.

These caveats notwithstanding, Rothwell and colleagues' show quite convincingly that aspirin seems to reduce cancer incidence and death across different subgroups and cancer sites, with an apparent delayed effect. Perhaps most strikingly, aspirin's known benefits in vascular disease and known toxicities in causing major bleeding emerged in the short-term, but diminished over time. Thus, for most individuals, the risk-benefit calculus of aspirin appears decidedly weighted in favor of aspirin's long-term anti-cancer benefit. These findings are consistent with prior observational findings and our understanding of the slower, stepwise progression of carcinogenesis (11, 12).

Does this additional data now allow a definitive conclusion about population-based recommendations regarding routine use of aspirin for cancer prevention? Perhaps not, since the WHS and PHS remain significant counterbalancing RCTs which have not shown a cancer benefit with alternate-day aspirin. The lower propensity for bias in the WHS and PHS as RCTs with cancer as a pre-specified endpoint should be weighed against their possible limitations regarding the dose or frequency of aspirin used. Second, despite a convincing case that the vascular and anti-cancer benefits of aspirin outweigh the harms of major extracranial bleeding, these analyses do not account for less serious adverse effects on quality of life, such as less severe bleed. Third, although it appears that doses as low as 75 mg/day are sufficient for cancer prevention across several included RCTs, data directly comparing doses within a single trial are inadequate. In fact, the limited data presented here suggest an earlier reduction in cancer deaths with higher doses (potentially related to an effect on prevalent tumors). Nonetheless, as we await data from additional trials (NCT01038583 and NCT00501059) and longer-term follow-up of the WHS and PHS, Rothwell and colleagues' impressive collection of data do move us another step closer to broadening recommendations for aspirin use. Moreover, future evidence-based guidelines for aspirin prophylaxis can no longer consider the use of aspirin for the prevention of vascular disease in isolation from the prevention of cancer (2, 3).

References

1. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognon G, et al. Short-term effects of daily aspirin on cancer incidence, mortality and non-vascular death: analysis of the time-course of risks and benefits in randomised controlled trials. *Lancet*. 2011

2. Aspirin for the prevention of cardiovascular disease: U S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2009 Mar 17; 150(6):396–404. [PubMed: 19293072]
3. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U. S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2007 Mar 6; 146(5):361–4. [PubMed: 17339621]
4. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Natl Cancer Inst.* 2009 Feb 18; 101(4):256–66. [PubMed: 19211452]
5. Burn J, Bishop DT, Chapman PD, Elliott F, Bertario L, Dunlop MG, 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 May; 4(5):655–65. [PubMed: 21543343]
6. Burn J, Gerdes A, Macrae F, Mecklin J, Moslein G, Olschwang S, et al. The long term impact of aspirin on cancer risk in carriers of hereditary colorectal cancer: the CAPP2 randomized controlled trial. *Lancet.* 2011
7. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet.* 2010 Nov 20; 376(9754):1741–50. [PubMed: 20970847]
8. Rothwell PM, Fowkes FG, Belch JF, 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 Jan 1; 377(9759):31–41. [PubMed: 21144578]
9. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *Jama.* 2005 Jul 6; 294(1):47–55. [PubMed: 15998890]
10. Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med.* 1998 May 1; 128(9):713–20. [PubMed: 9556464]
11. Chan AT, Manson JE, Feskanich D, Stampfer MJ, Colditz GA, Fuchs CS. Long-term aspirin use and mortality in women. *Arch Intern Med.* 2007 Mar 26; 167(6):562–72. [PubMed: 17389287]
12. Huang ES, Strate LL, Ho WW, Lee SS, Chan AT. Long-term use of aspirin and the risk of gastrointestinal bleeding. *Am J Med.* 2011 May; 124(5):426–33. [PubMed: 21531232]