

resolution and NBI. The large number of patients enrolled also adds merit to the study results.

However, it is important to keep in mind some of the limitations of this study. First and foremost, the authors of this study make an overreaching conclusion in stating that NBI seems to be an equally effective alternative to CE. This study was not powered to detect such differences. Per their own power calculations, the study's ability to detect any differences was quite low at 39%. The high miss rate with NBI, as pointed out by the authors, certainly makes NBI not advisable as the standard technique to detect dysplasia in patients with long-standing IBD. However, this was the first study to compare these techniques and subsequent investigators may use these data to help power future trials. Tandem design with documentation of lesions on first examination and intraprocedure unblinding on second examination may have allowed for a larger numbers of lesions to be studied; tandem design may also have higher acceptance rates in patients.

The authors provide a useful starting point in the investigation of newer NBI technologies as a possible tool for surveillance practices in IBD patients. Further investigation in the form of larger, appropriately powered studies to detect differences is warranted to fully understand the possible promise and limitations of NBI compared with CE. Although the data for CE seem promising, there are limitations, including the time and training required and the associated expense. Optical coherence tomography, confocal microscopy, and autofluorescence are additional endoscopic tools that should be evaluated in long-standing IBD patients (*Gastroenterology* 2004;127:706–713; *Inflammatory Bowel Dis* 2007;13:640–641). As is often the case with technology outpacing our ability to fully interpret its value, we may find that neither NBI nor CE fully penetrate our practices before being supplanted by other more beneficial tools.

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ASPIRIN AND CHEMOPREVENTION OF CANCER: REACHING BEYOND THE COLON

Rothwell PM, Price JF, Fowkes GR, 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 51 randomised controlled trials. Lancet 2012;379:1602–1612.

There is little disagreement that aspirin reduces the risk of colorectal neoplasia (*Cancer Prev Res (Phila)* 2012;5:164–178). Beyond compelling experimental data, the vast majority of cohort and case-control studies have observed inverse associations between aspirin use and colorectal

cancer (CRC). Four placebo-controlled, randomized, controlled trials (RCTs) have shown that aspirin reduced the risk of colorectal adenomas among patients with a prior adenoma or CRC (*J Natl Cancer Inst* 2009;101:256–266). An RCT in patients with familial adenomatous polyposis found a trend of aspirin in protecting against adenoma development (*Cancer Prev Res (Phila)* 2011;4:655–665). Most recently, long-term results from the Colorectal Adenoma/Carcinoma Prevention Programme 2 RCT of aspirin in carriers of the Lynch syndrome demonstrated that aspirin significantly reduced CRC risk in a prespecified per-protocol analysis (hazard ratio, 0.41; 95% confidence interval, 0.19–0.86; $P = .02$) and in intention-to-treat analyses accounting for multiple primary CRCs in some individuals (incidence rate ratio, 0.56; 95% confidence interval, 0.32–0.99; $P = .05$; *Lancet* 2011;378:2081–2087). Last, a recent pooled analysis of a long-term post-trial follow-up of nearly 14,000 patients from 4 randomized, cardiovascular disease prevention trials showed that daily aspirin treatment for about 5 years was associated with a 34% reduction in 20-year CRC mortality (*Lancet* 2010;376:1741–1750).

Although mechanistically it might be expected that aspirin's chemopreventive effect on CRC should extend to adenocarcinomas of other body sites, convincing data in humans were lacking until Rothwell et al's earlier pooled analysis of individual-level data from 8 randomized trials of cardiovascular prevention linked to cancer outcomes (*Lancet* 2011;377:31–41). Daily aspirin use, irrespective of dose, was associated with a 21% reduced risk of cancer death during the trials, with benefit only apparent after 5 years. A reduction in cancer mortality was also observed during post-trial follow-up to 20 years.

Rothwell et al have now extended these findings with analyses including an additional 43 randomized trials of daily aspirin of any treatment duration for the primary or secondary prevention of vascular disease (*Lancet* 2012;379:1602–1612). Aspirin (at any dose) significantly reduced risk of nonvascular death by 12% and of cancer death by 15%, with benefit accrued within 3 years for high doses (≥ 300 mg/d) and after 5 years for low doses (< 300 mg/d). Across several body sites, a lower risk of fatal and nonfatal cancers emerged after 3 years. In an analysis of 12 primary prevention trials, aspirin also reduced nonvascular death by 12%, but not vascular death, leading to a nonsignificant effect on all-cause mortality. Finally, in 6 primary prevention trials, low-dose aspirin reduced risk of incident cancer by 12%. In contrast, aspirin reduced the risk of major vascular events and increased risk of major extracranial bleeds, but only within the first 3 years of follow-up.

Comment. This study is an impressive tour-de-force. Through rigorous systematic reviews of RCTs of aspirin compared with controls in the Antithrombotic Trialists' (ATT Collaboration) and detailed searches of the literature, the investigators managed to assemble nearly all available RCT data on aspirin in relation to cancer end-

points. In so doing, the study was able to examine the effect of randomized aspirin across 51 trials that encompassed a total of 40,269 participants. This permitted detailed and well-powered analyses of the effect of aspirin allocation on deaths from cancer, deaths from nonvascular causes, deaths from vascular causes, and deaths from all causes. Within trials of low-dose aspirin for primary prevention, the investigators were also able to examine the impact of aspirin on incident cancer, major vascular events, and major extracranial bleeds, thereby permitting an assessment of the overall balance of aspirin's risk and benefits in primary prevention. Moreover, by including all trials, irrespective of treatment duration or follow-up, the investigators were well positioned to shed light on the time course of aspirin's effects on these various endpoints.

Nonetheless, the study should be viewed within the context of several limitations. First, data were collected from RCTs that were originally designed to examine cardiovascular endpoints and not cancer. Thus, the methods of ascertaining cancer endpoints across studies varied and information was not uniformly obtained about cancer screening or surveillance. This suggests that diagnosis and removal of either precancerous precursors (eg, polyps) or cancers due to aspirin-associated bleeding or anemia remains an alternative explanation for the findings. Second, these analyses do not include the largest primary prevention RCTs: The Women's Health Study (WHS) of 39,876 women assigned alternate-day 100 mg aspirin over 10 years (JAMA 2005;294:47-55) and the Physicians' Health Study (PHS) of 22,071 men assigned alternate-day 325 mg aspirin over 5 years (Ann Intern Med 1998;128:713-720). In these studies, aspirin was not associated with reduced risk of CRC or overall cancer incidence or mortality after 10-12 years of follow-up. The investigators excluded these RCTs owing to potential differences in the biological effect of administering aspirin on every other day rather than daily. Such differences, although plausible, are largely speculative and not conclusively established. Third, the investigators' analyses of cancer incidence were confined to 6 randomized trials of low-dose aspirin in primary prevention. It would have been informative (and less selective) to evaluate the effect of aspirin on cancer incidence in the secondary prevention trials of cardiovascular disease as well. Last, the quality of available data across the included trials varied, with some estimates based on pooling of published results as well as individual-level data. Moreover, in analyses of cancer incidence, fatal outcome data for some trials were combined with incidence data from others.

Despite these caveats, this study is an important contribution to the field of cancer prevention. First, these data provide mechanistic insight into aspirin's effect on various stages of carcinogenesis. Although prior adenoma prevention studies suggested that aspirin has an early effect on the initial development of neoplasia, treatment with high-dose aspirin reduced cancer death within only 2-3 years after randomization in some of the included trials in the present analysis. This supports an effect for aspirin on the growth and spread of established tumors as

well as their initiation. The investigators' more detailed analysis of the clinical presentation and outcome of patients diagnosed with cancers in five of the included vascular prevention trials actually showed that the benefit of aspirin was primarily confined to adenocarcinomas that were metastatic at initial presentation (Lancet 2012; 379:1591-1601). Furthermore, among patients who presented with localized cancer, particularly of the colorectum, individuals allocated to aspirin therapy had a lower risk of developing metastases over follow-up, particularly if they continued aspirin treatment after diagnosis. This finding is consistent with previous observational studies demonstrating a lower risk of CRC-specific mortality associated with postdiagnosis aspirin use (JAMA 2009;302: 649-658). This collection of data suggests the strong possibility that aspirin may influence cancer progression in addition to preventing its occurrence. From a clinical standpoint, this raises the exciting prospect of a role for aspirin as an adjuvant treatment for cancer patients.

Second, by convincingly demonstrating that aspirin reduces cancer incidence and death across different subgroups and cancer sites, these results have significant implications for the estimates of aspirin's risk-benefit that are central to public health decision making. At present, recommendations for aspirin in chronic disease prevention focus almost entirely on vascular outcomes (Ann Intern Med 2009;150:396-404), and the few guidelines for aspirin in cancer prevention have considered only its effects on CRC (Ann Intern Med 2007;146:361-364). Although CRC is a leading cause of cancer death, the disease ultimately impacts only 5%-6% of the US population in their lifetime (CA Cancer J Clin 2010;60:277-300). Thus, concerns about toxicity continue to dominate the risk-benefit equation, as well as continued uncertainty regarding the optimal dose, duration of use, and age of initiation. These new data regarding the potential benefit of aspirin in prevention of cancer incidence at multiple sites, vascular disease, total cancer death, and vascular death may at last tip the balance in favor of aspirin for broader population-based chronic disease prevention. It is likely that the benefits of such disease prevention in terms of morbidity and mortality will outweigh concerns about gastrointestinal bleeding, which is rarely life threatening, and cerebral bleeding, which is extremely rare. Indeed, in Rothwell et al's analysis, aspirin's benefits on vascular disease and toxicities emerged in the short term, but diminished over time.

Are we ready yet for population-based recommendations regarding routine use of aspirin for cancer prevention? Perhaps not, because the results of the WHS and PHS linger as significant contrary RCTs that have not shown a cancer benefit with alternate-day aspirin with follow-up to 10-12 years. As RCTs designed with cancer as a prespecified endpoint, the lower propensity for bias in the WHS and PHS should be weighed against potential limitations regarding the dose of aspirin or frequency of administration. Second, although doses as low as 75 mg/d seemed to be sufficient for cancer prevention across sev-

eral RCTs, data directly comparing doses within a single trial are inadequate. In fact, the limited data presented in the present study suggest an earlier reduction in cancer deaths with higher doses than with lower doses. Finally, although the investigators provide convincing data that the vascular and anticancer benefits of aspirin outweigh the harms of major bleeding, it remains unclear how we should weigh the impact of aspirin's less serious toxicities, including minor bleeding, on quality of life. Nonetheless, as we await data from additional trials (NCT01038583 and NCT00501059), longer term follow-up of the WHS and PHS, as well as additional studies that incorporate aspirin's effect on cancer in risk-benefit estimates, this study moves us one step closer to broader recommendations for aspirin in chronic disease prevention.

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COLONOSCOPY WITH POLYPECTOMY REDUCES COLORECTAL CANCER MORTALITY IN PATIENTS WITH ADENOMAS

Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687–696.

In this long-term follow-up study of patients from the National Polyp Study (NPS) cohort, Zauber et al sought to quantify the efficacy of polypectomy in reducing the risk of colorectal cancer (CRC) death (*N Engl J Med* 2012;366:687–696). The NPS cohort consisted of 3,778 patients who underwent polypectomy. Of these patients, 2632 were found to have ≥ 1 adenomatous polyps, and 776 had only nonadenomatous polyps. After exclusions, 2602 patients with adenomas and 773 patients without adenomas remained. Of the 2,602 patients with adenomas, 1418 were randomized to surveillance colonoscopy at varying intervals (*N Engl J Med* 1993;328:901–906).

The authors examined the long-term risk of CRC mortality in 3 groups of patients from NPS: (1) Patients enrolled in NPS who had adenomas ($n = 2602$); (2) patients enrolled in NPS who did not have adenomas (serving as an internal comparator, with $n = 773$); and (3) the general US population, estimated using data from the Surveillance, Epidemiology, and End Results (SEER) registry. For the adenoma and nonadenoma groups, authors used the National Death Index (NDI), a mortality database maintained by the Centers for Disease Control and Prevention, to measure mortality and cause of mortality. Although the NDI is imperfect (*Ann Epidemiol* 2002;12:462–468), the authors validated the accuracy of the NDI for the subset of randomized NPS patients in this study

(for whom additional follow-up data were available from the original NPS randomized, controlled trial), finding NDI data to be highly sensitive and specific in this group. The authors compared CRC mortality in each of the study groups (adenoma and nonadenoma) with that expected from the SEER registry, expressing the reduction in CRC mortality with polypectomy as a standardized incidence ratio.

The median follow-up period was 16 years (maximum, 23). In the adenoma cohort, CRC death occurred in 12 patients compared with an expected 25.4 CRC deaths based on SEER registry data, reflecting a 53% reduction in CRC mortality (standardized incidence ratio, 0.47; 95% confidence interval, 0.26–0.80). In terms of cumulative mortality, 0.8% of patients in the adenoma cohort had died of CRC at 20 years of follow-up, versus an expected 1.5% based on SEER data. In the nonadenoma cohort, only 1 CRC death occurred over the follow-up period (7.7 years after the index colonoscopy).

Comment. Recent data have suggested that patients who undergo colonoscopy are at decreased risk for developing and dying from CRC (*Ann Intern Med* 2009;150:1–8; *Ann Intern Med* 2011;154:22–30). However, these studies have been retrospective, and only a minority of patients in these studies underwent polypectomy (~25%, indicating a population at average-risk for CRC). The impact of high-quality colonoscopy and polypectomy in patients at increased risk for CRC is less clear. This study demonstrates that high-quality colonoscopy with polypectomy can markedly reduce CRC mortality in patients with adenomas. Because the patients enrolled in NPS were at higher than average risk (nearly 60% of patients with adenomas had advanced adenomas), these data also provide a reasonable estimate of how colonoscopy might be expected to perform in high-risk adenoma patients. Furthermore, the very low risk of CRC mortality in patients with no adenomas is consistent with data from the recent “UK Flex Sig” study, where patients were randomized to sigmoidoscopy and only offered colonoscopy if high-risk adenomas were identified (*Lancet* 2010;375:1624–1633). Overall, these data suggest that colonoscopy is an effective tool in reducing mortality owing to CRC, but the absolute benefit is greatest in individuals at increased risk for CRC. Patients who are found to have no adenomas seem to be at very low risk for CRC death.

Although the study was well designed, several limitations should also be highlighted. First, the investigators had no way of quantifying additional exposures to colonoscopy after the index examination or after NPS follow-up was completed. It is possible and perhaps likely that additional colonoscopies were performed in the no adenoma group, for instance, meaning that readers should be cautious in drawing the conclusion that 1-time negative colonoscopy portends such a low risk of CRC death. Furthermore, the number of overall CRC deaths was small (13 total), making it difficult to perform meaningful subgroup analyses. As a result, we cannot be sure of the true effect of polypectomy in high-risk patients (ie,