

## CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 47

**Does the long-term use of aspirin decrease the risk of death due to cancer?**

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The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”<sup>1</sup> The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS). The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

**Reference**

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

**SELECTED ARTICLE**

Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily ASA on long-term risk of death due to cancer: analysis of individual patient data from randomized trials. *Lancet* 2011;377:31-41.

## ABSTRACT

**Question:** Does the long-term use of acetylsalicylic acid (ASA) decrease the risk of death due to cancer? **Design:** Pooled analysis. **Data source:** Cochrane Collaboration, Database of Systematic reviews, PubMed and Embase. **Study selection:** Individual patient data from all randomized trials of daily ASA versus no ASA with a mean duration of scheduled trial treatment of 4 years or longer were used to determine the effect of allocation to ASA on risk of cancer death in relation to scheduled duration of trial treatment for gastrointestinal (GI) and non-GI cancers. **Results:** In 8 eligible trials (25 570 patients, 674 cancer-related deaths), allocation to ASA reduced the risk of death due to cancer (pooled odds ratio [OR] 0.79, 95% confidence interval [CI] 0.68–0.92,  $p = 0.003$ ). On analysis of individual patient data, which were available from 7 trials (23 535 patients, 657 cancer-related deaths), the benefit was apparent only after 5 years' follow-up (all cancers, hazard ratio [HR] 0.66, 95% CI 0.50–0.87; GI cancers, 0.46, 95% CI 0.27–0.77; both  $p = 0.003$ ). The 20-year risk of cancer death (deaths in 12 659 patients in 3 trials) remained lower in the ASA groups than in the control groups (all solid organ cancers, HR 0.80, 95% CI 0.72–0.88,  $p < 0.001$ ; GI cancers, HR 0.65, 95% CI 0.54–0.78,  $p < 0.001$ ), and benefit increased (interaction  $p = 0.01$ ) with scheduled duration of trial treatment ( $\geq 7.5$  years: all solid cancers, HR 0.69, 95% CI 0.54–0.88,  $p = 0.003$ ; GI cancers, HR 0.41, 95% CI 0.26–0.66,  $p < 0.001$ ). The latent period before an effect on deaths could be observed was about 5 years for esophageal, pancreatic, brain and lung cancer, but was longer for stomach, colorectal and prostate cancer. For lung or esophageal cancer, the benefit was confined to adenocarcinomas, and the overall effect on 20-year risk of cancer-related death was greatest for adenocarcinomas (HR 0.66, 95% CI 0.56–0.77,  $p < 0.001$ ). The benefit was unrelated to ASA dose (75 mg or higher), sex or smoking, but was increased with age; the absolute reduction in 20-year risk of cancer-related death reached 7.08% at age 65 years and older. **Conclusion:** Daily ASA reduced deaths due to several common cancers during and after the trials. The benefit increased with duration of treatment and was consistent across the different study populations. These findings have implications for guidelines on use of ASA and for understanding carcinogenesis and its susceptibility to drug intervention.

## COMMENTARY

Cancer is one of the leading causes of death in the developed world, with the lifetime risk approaching 40%. Although great strides have been made in cancer treatment, there has been relatively little progress in terms of primary cancer prevention. There is some evidence, both from observational trials and animal models, suggesting that long-term ASA use may reduce the risk of cancer, par-

ticularly cancers of the GI tract. The effect of ASA is hypothesized to be due to cyclo-oxygenase inhibition and to decreased production of prostaglandins and inflammatory mediators. Although the mechanism of action is not yet clear, data from several trials support the role of daily ASA use in reducing the incidence of colorectal cancers.

Rothwell and colleagues performed a pooled analysis of randomized controlled trials of ASA versus control with a mean treatment duration of at least 4 years. The study design was a variant of a systematic review and meta-analysis. This study design is a variant of a systematic review and meta-analysis called a “pooled analysis,” whereby individual patient data from multiple studies are combined and analyzed. Individual patient-level data are required, thus it is usually not possible to perform with standard aggregated data available in published trials. Instead, patient-level data usually have to be requested from the original investigators

Pooled analyses are usually considered more rigorous than meta-analyses. First the researcher has the raw data and is not relying on the assumptions written in a previously published paper (some of which may not be apparent in the paper). Second, the researcher can impose common inclusion and exclusion criteria, statistical methods and other methods across all data. For example, rather than including patients 25 years and older from one study and patients 18 years and older from a second study, if the researcher has the raw data, he/she can exclude the 18- to 24-year-olds from the first study to make the data consistent. Third, when working with raw data, the statistic may be more accurate because in a meta-analysis, means are rounded and sometimes the data must be approximated by looking at graphs. Finally, the researcher often can control for publication bias if the data were not chosen based on publications, but rather based on knowledge of existing trials.

On the other hand, one cannot just pool all data together and use standard statistics. Because the patients from the different studies were not accrued from the same sampling frame, it is best to use a random-effects model in which “the study” is modelled/controlled for as a random effect. This method is akin to the issue of clustering of centres in randomized controlled trials.

The major advantage to meta-analysis is that the author can use data from many studies for which one would not necessarily have access to the data. Finally, not all pooled analyses are performed rigorously. “Sample pooling” of data where there is no adjustment for the fact that the data come from different trials (i.e., sampling frames) should not be performed.

The pooled analysis of the 8 studies included in the study by Rothwell and colleagues demonstrated that in the patients receiving ASA, cancer-related deaths were significantly reduced (OR 0.79, 95% CI 0.68–0.92,  $p = 0.003$ ). On analysis of individual patient data, the benefit became

apparent only after 5 years of follow-up. A significantly decreased HR was observed for all solid organ cancers.

The findings of Rothwell and colleagues are consistent with those of many previous studies assessing the effect of ASA on cancer prevention, particularly the prevention of colorectal cancer. Unique in this study was the long follow-up and the finding of risk reduction for several cancers not previously shown to be impacted by ASA use. Although this pooled analysis supports the cancer reduction effects of daily ASA, conflicting results have been reported: the Women's Health Study, a large 10-year trial of 100 mg of ASA taken every other day, reported no reduction in cancer incidence or mortality.<sup>1</sup>

There were some methodological problems with the study by Rothwell and colleagues. From the point of view of reporting, the authors did not adhere strictly to the preferred reporting items for systematic reviews and meta-analysis guidelines.<sup>2</sup> The authors did not clearly present their search strategy or their assessment of the quality of the included trials. The primary outcome of the included trials was the primary or secondary prevention of cardiovascular events. Most patients included were men who were at risk for or who were known to have vascular disease. The population studied was therefore not representative of the population at large. Cancers that are sex-specific and those impacted by local environmental factors may be prone to bias in any analysis that does not control for these factors. In addition, because our knowledge of genetic versus environmental factors is not well known in cancer pathogenesis, controlling for yet unknown factors also limits the generalizability of any results.

In addition, the authors did not have information on baseline risk for the various cancers or on what screening or other follow-up patients had during the study. Also missing from their study is clear information on the com-

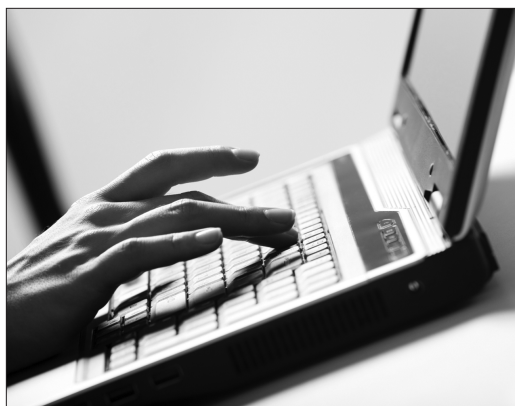
plications, such as bleeding GI issues and renal failure, associated with treatment. The authors do mention that there was no excess of nonfatal vascular events in the treatment group, but these data were not shown. This is particularly relevant, as GI side effects of bleeding and ulcerations may have biased the enrolled patients to receiving more GI investigations. With increased endoscopies, premalignancies or early malignancies may have been identified to account for the decreased mortality. However, at least 1 trial included in the paper by Rothwell and colleagues studied patients taking warfarin, and these patients did not experience the same rate of cancer reduction as other groups, suggesting that GI bleeding was not prompting investigations that led to the earlier detection of malignancy.

Rothwell and colleagues conclude, "Daily aspirin reduced deaths due to several common cancers during and after the trials. The benefit increased with duration of treatment and was consistent across the different study populations. These findings have implications for guidelines on use of aspirin and for understanding of carcinogenesis and its susceptibility to drug intervention."

Although the data presented cannot be considered strong enough to make a broad recommendation on the use of ASA in the chemoprophylaxis of cancer, there consistently seems to be a signal that ASA use decreases cancer-related mortality, and it is time that this be investigated directly.

#### References

1. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294:47-55.
2. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.



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