More than a century after aspirin was first synthesized, its benefits continue to be discovered and now include everything from relief of headaches to cardiovascular disease prevention. Evidence pointing to an association between aspirin and reduced cancer risk is largely derived from epidemiologic studies, although laboratory experiments and a few clinical trials have provided support for this idea. The apparent anticancer effect of aspirin has been seen most consistently for gastrointestinal tract cancers and especially for colorectal cancer (1); it is thought to occur through the drug’s ability to inhibit cyclooxygenase enzymes, which are produced by the body when there is inflammation, although alternate hypotheses have been suggested (2).

Prior epidemiologic studies of aspirin and cancer prevention have often lacked detailed information on the dosage and duration of aspirin use, and this fact may account for some of the reported inconsistencies in their results. In this issue of the Journal, Jacobs et al. (3) report on long-term use of adult-strength aspirin and risk of cancer using data from the American Cancer Society’s Cancer Prevention Study II (CPS II) Nutrition Cohort. The investigators collected information on aspirin use at the beginning of the study in 1982, with more detailed information collected between 1992 and 2001. They found a modest 15% relative reduction in risk of developing any cancer associated with daily use of adult-strength aspirin for 5 years or longer. The strongest inverse association was shown for colorectal cancer, but a weaker, although statistically significant, inverse association for prostate cancer was also observed. Breast cancer occurrence also seemed to be decreased, but this result was not statistically significant. There was no clear evidence of reduced risk for cancer associated with use of lower dose aspirin or for use that was less than daily or of less than 5-year duration.

The detailed information on aspirin use in the CPS II from Jacobs et al. (3) permits a sharper view of the possible role of aspirin dose and duration in cancer prevention, and the results strongly point to an association that is confined to individuals who use adult-strength aspirin (360 mg) at least daily for 5 or more years. However, only about 2% of men and 1% of women who were surveyed in 1992 fell into this category, and they appear to include a group that differs from other study participants in important ways besides aspirin usage. The investigators report that this group was, on average, older and had more chronic medical conditions than the overall cohort; thus, they were likely to be under closer medical surveillance. The investigators adjusted in their statistical analyses for a number of potential confounding variables and for measures of cancer screening behavior, but this process may not have fully accounted for confounding or for possible biases in cancer ascertainment. Nevertheless, it is unclear whether unrecognized confounding and bias in this study would magnify or diminish the associations found in the analyses.

Two randomized controlled trials of aspirin and cardiovascular disease in men (4) and in women (5) tested low-dose aspirin against placebo; the duration of aspirin treatment in the men was 5 years, whereas in women, the intervention lasted 10 years. Both trials showed no reduction in cancer occurrence, findings that are consistent with those from the report by Jacobs et al. (3). The results of clinical trials have not been entirely consistent, however, and one trial of colorectal adenoma prevention reported a reduction in...
adenoma associated with 80 mg, but not 360 mg, of aspirin per day (6). On balance, however, the results from epidemiologic studies and clinical trials do suggest that low-dose aspirin, as currently recommended for cardiovascular protection, may not be enough to prevent cancer.

Despite its beneficial effects, aspirin also has toxic side effects, which include gastrointestinal bleeding and hemorrhagic stroke (7). Data from randomized controlled trials of aspirin and cardiovascular disease have shown that aspirin use reduces risk of cardiovascular events and stroke but increases risk of bleeding (8). Cost benefit analyses (9) have indicated that low-dose aspirin is worth prescribing to men with a moderate risk of cardiovascular disease (>1% per year), but the drug’s benefits relative to cost or risk are less certain at lower levels of individual risk. Furthermore, low-dose aspirin is less clearly indicated for women due to the more limited effect on cardiovascular disease and the imprecision of the data on benefits and risks in women (10). Prophylactic aspirin use at higher doses would be less favorable for both women and men because of increased toxicity (11).

Ironically, the strongest support for an anticancer effect of aspirin relates to colorectal cancer (7,12), but a highly effective method of preventing this cancer already exists (i.e., screening colonoscopy). Based on a systematic review of the literature, the US Preventive Services Task Force noted that the potential benefit of aspirin chemoprevention needs to be carefully weighed against its harms and further recommends that cost-effectiveness data are needed to compare aspirin and screening, as well as the combination of the two strategies (7). In fact, the results of one such study (13) indicated that the addition of aspirin to a screening regimen would offer no benefit; furthermore, the authors did not recommend the use of aspirin as a substitute for colorectal cancer screening. Thus, even if one were to accept the existence of an anticancer effect of aspirin, this alone would not be sufficient to support recommending aspirin for cancer prevention. The toxicity of aspirin appears to be dose related (11), so a recommendation to take adult-strength aspirin for cancer prevention would entail greater toxicity than the strategy for using low-dose aspirin for preventing cardiovascular disease. Under most scenarios, the potential cardiovascular disease consequences, gastrointestinal toxicity, and hemorrhage risks would overshadow considerations of potential anticancer effects.

However, if aspirin were shown to truly prevent a multitude of common cancers, there might be clinical situations in which daily adult-strength aspirin would be indicated, e.g., among individuals at elevated cancer risk whose cardiovascular risk profile already made them candidates for low-dose aspirin. The report by Jacobs et al. (3) supports an association between taking adult-strength aspirin and reduced risk for colon and prostate cancers, and their data also suggest a similar association for breast cancer and possibly for other cancers. It will be important to verify whether the findings from this study, and especially those for breast and prostate cancer incidence, represent a real benefit or an artifact due to detection biases or confounding. Data on cancer mortality and all-cause mortality from the cohort might eventually shed further light on this topic. The authors also note that a trial of high-dose aspirin to confirm their results would need to last at least 10 years. Although such a trial merits careful consideration, it might be difficult to conduct it among average-risk individuals, given the toxicity of aspirin at doses greater than 80 mg/day. Thus, the authors appear justified in concluding that their results do not have immediate clinical implications, but they clearly illustrate the potential future importance of aspirin and other anti-inflammatory interventions as cancer control strategies.

References