Aspirin and Cancer: Trials and Observational Studies

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Aspirin recently celebrated its commercial centenary, but the exciting news has been a series of articles by Rothwell et al. (1–6) that report on the follow-up of cardiovascular trials begun in the late 1970s and afterward. Those data suggest striking efficacy of aspirin in reducing cancer mortality. One of the recent reports (2) analyzed short-term, in-trial incidence and mortality data from 51 trials. It showed that aspirin conferred a 31% reduction in cancer mortality 5–10 years after subjects were randomized to study treatment, though there was essentially no reduction during the first 5 years.

Motivated by these striking findings, in this issue of the Journal, Jacobs et al. (7) report on the association of aspirin use with cancer mortality in the large American Cancer Society (ACS) cohort. Taking advantage of the study’s repeated assessment of aspirin use, they attempted to replicate the trial findings by evaluating the association of 5 or more years of reported daily aspirin use with subsequent cancer mortality. Unfortunately, they found only 8% or 16% lower cancer mortality, depending on the analytic approach used. In apparent contrast to the trials, associations were similar among those using daily aspirin for less than 5 years and for those using for 5 or more years.

An observational study such as the ACS cohort describes the association of aspirin use with cancer mortality in real life. Did the trials lead us to an overoptimistic assessment, or is the report by Jacobs et al. off the mark? The answer is important, as it clearly will affect an important clinical decision: whether to recommend aspirin for primary prevention of cancer.

An earlier analysis from the ACS cohort assessed cancer incidence in relation to aspirin use (8). As in the report from Jacobs et al., it showed more modest associations than the corresponding ones in the trials’ meta-analysis (2), though the differences were less marked than those reported for mortality. The ACS analysis of cancer incidence (8)—like the trials’ meta-analysis (2,3), but unlike the ACS mortality analysis (7)—saw reduced cancer risks only with longer aspirin use and follow-up. Two other sizeable cohort studies have reported on aspirin use and cancer mortality (9,10). Both report stronger associations for ever users of aspirin than Jacobs et al. report, suggesting that the ACS estimates may be conservative.

Several factors probably do not explain the difference between the short-term trials’ meta-analysis (2) and the ACS mortality study (7). In both reports, age and sex were not related to the observed effects of aspirin on cancer mortality. Primary prevention studies dominated the clinical trials’ analysis, but in the ACS cohort the findings were similar in subjects with, and without, cardiovascular disease. There was no material impact of dose on the aspirin effects in either analysis. Differences in the assignment of causes of death seem unlikely to account for the studies’ findings. Rothwell et al. have argued persuasively that various biases in disease ascertainment are not likely explanations for their findings (2,6), and many of their arguments apply equally as well to the study by Jacobs et al.

It has to be acknowledged that there are fundamental differences between the observational ACS data and those from the randomized trials. The trials’ intention-to-treat analysis isolates the study factor but ignores compliance: individuals who stop using aspirin (or placebo subjects who use it on their own) are retained in the originally assigned treatment groups for the analysis, even though they have become former users (or new users, in the placebo group). Because there was a high rate of treatment dropout in the trials (1,3), there is a corresponding disconnect between the trials’ analysis and the reality of the actual aspirin use. In contrast, as in all observational studies, the ACS investigators simply recorded whether or not a subject used aspirin. This is potentially important, because most observational analyses (11) [including the ACS study (7,8)] have found little association with cancer mortality or incidence in former users of aspirin. How all this relates to the ACS and trials’ analyses is not clear: neither report considered continued vs discontinued use after the time of the study baseline (or updated baseline for the ACS updated analysis). Nonetheless, the ACS analysis is likely less affected by former users than the trials, and so it would be expected to show more pronounced effects, not less.

Neither the trials nor the ACS study analyzed the actual duration of aspirin use. Subjects in either analysis may have used aspirin before study baseline; clearly a proportion of the longer-term daily aspirin users in the ACS cohort did so. A true comparison of the findings about duration of use is therefore difficult. Nonetheless, primary prevention trials dominated the trials’ data, and these were conducted largely in Europe in the 1980s and 1990s when use of cardioprotective aspirin was less common than more recently in the United States. It is likely that the ACS aspirin users had been taking the drug longer than the trial subjects who were randomly assigned to aspirin. Thus, a shorter duration of use is also unlikely to contribute to the lower efficacy of aspirin in the ACS cohort.

Details of the ACS analysis do provide some possible clues about the differences with the aspirin trials. The ACS “updated” analysis suggested stronger aspirin effects than the baseline analysis, entirely because of the findings for the years 2004 through 2008, when there were marked reductions among aspirin users in mortality from luminal gastrointestinal cancers and borderline statistically significant reductions for other malignancies. In that subanalysis, cancer deaths were included only if the malignancy was diagnosed after January 1, 2004: the only cancers included were those that were fatal within 5 years of diagnosis. This resembles the trials’ analysis because individuals with a cancer diagnosis are unlikely to enter trials and so accounted for only 3% of the cancer deaths in the short-term cancer mortality analysis (2). Thus, the sort
of endpoint included in the ACS and trials’ analyses might explain some of the differences between the findings of the two reports.

A noticeable difference between the trials’ results and those reported by Jacobs et al. involves cigarette smoking. Whereas smoking did not alter the aspirin mortality benefit in the trials, it did so in the ACS analysis, in which there was no association between aspirin use and cancer mortality among current or former smokers but substantial mortality reductions in never smokers. Given this, naturally there was no hint of a reduction in lung cancer mortality associated with aspirin use. Both of the other cohort studies of aspirin and cancer mortality also found no aspirin benefit for cancer mortality in current smokers (9,10). Cigarette smoking may confer resistance to the cardioprotective effects of aspirin (12,13). Whether this applies to the cancer chemopreventative effects is not clear. The observational data (but not the trials’ data) suggest that this may be true.

Though duration of aspirin use is unlikely to explain the differences between the ACS and the trials’ analyses (7,8), it remains an important point of comparison. The ACS study stands out in its suggestion that duration of aspirin use does not affect cancer mortality. One of the other large aspirin-mortality cohorts did not address this issue (9). The other found substantial associations of aspirin with cancer mortality that began only among subjects who reported taking aspirin regularly for 10 or more years; for breast and lung cancer mortality, even longer use was required (10). Despite the null findings from the current ACS article, these findings, together with those from the trials’ analyses (1–3,6) support the idea that the duration of continued use is important for aspirin’s effects on cancer mortality. Both randomized and observational studies of cancer incidence have generally come to a similar conclusion, ie, that aspirin reduces risk and that the duration of use matters (6).

It is not clear how long-term use might affect cancer mortality. It could be through decreased case fatality or through decreased cancer incidence and unchanged case fatality. For colorectal cancer, it appears that prediagnostic use of aspirin reduces cancer incidence but not mortality after diagnosis, whereas postdiagnostic use reduces case fatality among patients who did not previously use aspirin (14,15). Total duration of aspirin use may be crucial for the former but less so for the latter. Clearly more research on this topic is needed, ideally in randomized adjuvant treatment trials.

Cancer mortality data on aspirin track with those on incidence in more ways than in the impact of duration of use. In the trials’ analyses, the strongest reductions in cancer incidence were shown for luminal gastrointestinal cancer (2,3,5). Previous observational research has also suggested that aspirin’s preventive effects on cancer incidence are most pronounced in the luminal gastrointestinal tract (6,16), and the current ACS mortality findings are in agreement.

Overall, the well-conducted ACS study is an echo of other data on aspirin and cancer mortality, not a resounding confirmation. There are no ready explanations for some of the differences between its findings and those of the trials and other observational studies. Nonetheless, the big picture on aspirin use and cancer is very positive. The drug clearly reduces the incidence and mortality from luminal gastrointestinal cancers, and it may similarly affect other cancers. This is exciting: simply taking a pill can prevent cancer incidence and cancer death. However, just because aspirin is effective does not mean it necessarily should be used. Aspirin is a real drug, with definite toxicity. As for any preventative intervention, the benefits must be balanced against the risks, particularly when the benefits are delayed whereas the risks are not. The ACS data have the potential to help us assess the risk–benefit balance by providing a unique window on aspirin’s effects.

References

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The author is a consultant to Bayer and in studies of the side effects of aspirin use. He also holds a use patent for the chemopreventative use of aspirin, currently not licensed.

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