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Editorial

The ASPREE Trial: An Unanticipated Stimulus for Greater Precision in Prevention?

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The Aspirin in Reducing Events in the Elderly (ASPREE) trial, a large (n = 19 114) multi-center, randomized, double-blind, placebo-controlled study examining the effects of low-dose aspirin (100 mg/d) on disability-free survival, cardiovascular disease (CVD), and major hemorrhage in the elderly (1), originally reported its results in 3 separate articles published in 2018 (2-4). In this aged population, aspirin use did not prolong disability-free survival over 5 years (2), nor did it confer cardiovascular protection, but it statistically significantly increased the rate of major hemorrhage (3). These results are in line with results from both the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) and A Study of Cardiovascular Events in Diabetes (ASCEND) trials, conducted and reported concomitantly with ASPREE (5,6). But unlike ARRIVE, ASCEND, and nearly all prior primary prevention CVD trials of aspirin (7), ASPREE surprisingly demonstrated increased all-cause mortality in the aspirin group, which appeared to be driven largely by an increase in cancer-related deaths (4). These findings have raised important concerns regarding the use of aspirin among the elderly.

In this issue of the Journal, McNeil et al. (8) now follow up with a more in-depth analysis of cancer incidence and mortality by site and stage in ASPREE. In brief, overall and site-specific cancer incidence did not differ between the treatment groups; however, there were differences by stage. Aspirin increased the risk of metastatic cancer (hazard ratio [HR] = 1.19, 95% confidence interval [CI] = 1.00 to 1.43) and stage IV cancer at diagnosis (HR = 1.22, 95% CI = 1.02 to 1.45). Regarding mortality, aspirin conferred a statistically significant increased risk of death from all cancers (HR = 1.35, 95% CI = 1.13 to 1.61), both localized (HR = 1.47, 95% CI = 1.07 to 2.02) and metastatic cancers (HR = 1.30, 95% CI = 1.03 to 1.70), cancers presenting at stage III (HR = 2.11, 95% CI = 1.03 to 4.33) or stage IV (HR = 1.31, 95% CI = 1.04 to 1.64), and colorectal cancer (HR = 1.77, 95% CI = 1.02 to 3.06). Unfortunately, these new findings neither explain nor alleviate the concerns raised by the initial ASPREE report with regard to increased all-cause and cancer-related mortality.

These results and their potential implications are in opposition to the large body of evidence from preclinical, observational, and clinical studies supporting the potential use of aspirin for cancer prevention (9). As the authors discuss in more detail, potential sources of bias in the ASPREE results, such as from multiple testing or in the ascertainment of outcomes, are unlikely to explain their findings. Nevertheless, such unexpected and contrary findings compel us to seek confirmation as well as potential biologically plausible explanations for why aspirin use would result in a cancer-promoting effect in the elderly compared with its cancer-protective or -inhibiting effects reported in earlier studies of more heterogeneous populations. Confirmation, however, may prove difficult, because it is unlikely that another such primary prevention trial will be conducted given the clinically significant harms (eg, bleeding) and lack of benefit from aspirin use that have been consistently documented across ASPREE, ASCEND, and ARRIVE. The ASCEND trial, with a longer follow-up period but younger cohort, did not detect a difference in cancer mortality between its treatment groups. The ARRIVE trial, which recruited men aged 55 years and older and women aged 60 years and older, has yet to report on cancer outcomes but may represent the best chance for confirmation. McNeil et al. (10) point towards several ongoing randomized controlled trials that are examining aspirin prescribed following a cancer diagnosis as potential sources of confirmation, but these trials are considerably smaller than ASPREE and do not focus on elderly patients (one, NCT02927249, specifically excludes them) so are therefore unlikely to either confirm or refute ASPREE's unexpected findings. Long-term follow-up of ASPREE participants is ongoing and will be critical in assessing any delayed benefits or harms of aspirin in this population, particularly as they relate to cancer incidence and mortality. Until any of these data become available, we must consider ASPREE's findings solely on their own merit.

Potential biologically plausible explanations for the apparent differential effect of aspirin in aged vs younger populations

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include a relatively different molecular (eg, a different spectrum of mutations or methylation) and/or immunological (eg, immunosuppression or less immune surveillance) pathogenesis of cancer in the elderly. As mentioned by the authors, an intriguing possibility is that aspirin may suppress immune functions critical to control malignant cell growth and metastasis among the elderly. Because the McNeil et al. study is unable to provide insight into this or other potential biological mechanisms underlying its findings, it will be important to follow-up this work with detailed mechanistic studies. Substudies of ASPREE that incorporate participants' biospecimens will be particularly important in clarifying the role of aspirin in cancer evolution and mortality in healthy older adults.

Implications of the ASPREE findings are clinically noteworthy. First is the implication for the clinical use of aspirin by the elderly. Given these most recent data, aspirin should not be recommended as a preventive in those 70 years and older because of its well-established increased risk of causing serious gastrointestinal bleeding and the unexplained, statistically significant increase in cancer deaths and late-stage cancers at presentation reported in ASPREE, the best and largest study in this population to date. Second, there are broader implications for the use of aspirin as a low-cost, widespread primary prevention strategy in the general population. Not only have data from recent trials established that aspirin's cardioprotective benefit is marginal in contemporary populations without CVD (11), but these latest findings from ASPREE cast doubt on its cancer prevention benefits as well, at least in healthy older adults.

Together, these findings alter the calculus of aspirin's risks and benefits such that its use as a cancer chemo-preventive agent in the general population looks less likely. Lifestyle modifications (12,13) combined with age- and risk-based screening will continue to be the mainstay for cancer prevention among the healthy, unselected general public. Aspirin use is best reserved for individuals with specific molecularly driven cancer risks, such as those with Lynch syndrome, in whom it has been shown to halve the risk of colorectal cancer, without serious bleeding risk, on extended follow-up (14). Finally, the unexpected and unexplained results of ASPREE suggest that we may still be missing a critical piece of the puzzle in our understanding of aspirin's biologic effects on cancer development and evolution within and across individuals of differing ages. Careful posttrial follow-up of the ASPREE participants is warranted, as are mechanistic studies to better understand how aspirin's effects on cancer development could differ so profoundly by age.

In sum, results of the ASPREE trial to date underscore the growing importance of more precise preventive strategies that better align an individual's molecular risks with specific interventions that mitigate them (15).

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