Cancer Epidemiology, Biomarkers & Prevention

Hypothesis/Commentary
Commentary on Setiawan et al. p. 1441

Aspirin and Cancer Prevention and Treatment: Are We There Yet?

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One of the great triumphs of 19th-century pathology was distinguishing inflammatory from neoplastic processes. It has become increasingly clear, however, that inflammatory processes are deeply entangled in carcinogenesis, thus provoking the search for possible anti-carcinogenic agents among those that are known to be anti-inflammatory.

Since the late 1980s (1), there have been multiple studies of inflammation and cancer and the possible preventive role of anti-inflammatory drugs, especially aspirin. The attention has largely been on colorectal cancer; the clearest initial evidence was for a reduction of adenomatous polyps (2, 3). Since 2007, Rothwell and colleagues have published a series of meta-analyses and found that: 300 mg aspirin/d for 5 years (2 studies; 12.8%women) resulted in a reduction of CRC incidence but only after a latency of 10 years (4); aspirin reduced incidence and mortality of proximal colon cancer (5 trials; 13.9%women) and showed increased benefit with longer duration but no further benefit above 75 mg/d (5); there was a reduction in mortality from several cancers, the benefit increasing with duration, but, again, no dose effects (8 trials; 29.4%women; ref. 6).

There are 2 recent papers from the same group (7, 8). The first is a meta-analysis of 5 trials (21.8% women), showing a reduced risk of cancer with distant metastases, including a reduced risk of an initial diagnosis of cancer with distant metastases and a reduced risk of fatal cancer (7). The second paper shows a modest reduction in cancer deaths (including in women) from 3 years onward (8). In this second paper, increased risk of bleeding balanced the benefit on vascular events but both diminished with further follow-up, a pattern suggestive of elimination of those who are susceptible both to the beneficial and the deleterious consequences of the agent.

The reports enhance the story and provide evidence of a reduction in mortality from cancer more generally, due in part to a reduction of metastases. One of the major issues in prevention is that it is not enough to lower incidence or mortality from the target disease; there must also be a reduced overall mortality (or at least, if that benefit is too small to detect, no increase in mortality or severe morbidity). It is of some importance, then, when it can be shown, as Rothwell and colleagues have done, that a preventive agent has both early and late effects.

Facing this body of evidence, one might conclude that aspirin is useful both as primary prevention and even as adjuvant therapy. However, some important questions remain: first, not all studies are concordant with Rothwell's findings. Seshasai and colleagues conducted a meta-analysis of 9 studies (a number of the studies overlap; ref. 9). They report that aspirin lowers risk of cardiovascular disease but results in no benefit for either cancer or cardiovascular mortality. Furthermore, they report an increase in nontrivial bleeding.

Second, do women and men benefit equally? As noted above, women are underrepresented in most of Rothwell's meta-analyses. It is not enough to adjust for sex; it is necessary to show that there is real benefit to women. There are other relevant data, including the long-term outcome of aspirin intervention in the Women's Health Study, where more than 40,000 women showed no benefit from aspirin after 12 years of follow-up (10). Furthermore, we found that there was no overall association between colorectal cancer survival and prediagnostic nonsteroidal anti-inflammatory drug (NSAID) use in women but that, paralleling the second Rothwell study (5), there was a reduction in mortality from proximal colon cancer (11). In today's CEBP, a paper from the Multi-Ethnic Cohort (12) shows no benefit of aspirin or nonaspirin NSAIDs to the incidence of either ovarian ($n = 275$) or endometrial ($n = 620$) cancer after follow-up of more than 13 years among approximately 64,000 women; there were no differences by ethnicity.

Third, in both Seshasai (9) and Rothwell (8), as well as elsewhere (13), GI bleeding and hemorrhagic stroke are elevated (14). One might want to argue that, if aspirin is successful as adjuvant cancer therapy, increased deleterious consequences are acceptable. Nonetheless, it remains a problem for any widespread long-term preventive agent. Furthermore, even the benefit as therapy, because of the data of Seshasai (9), remains unclear.

Finally, there is the problem of chemoprevention generally. There have been more deleterious than beneficial outcomes from single-agent chemoprevention (15). Although it seems to come as a surprise to many, evolution by natural selection is the norm for living creatures and no more visible anywhere than among cancer

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doi: 10.1158/1055-9965.EPI-12-0837

cells. For the same reason that we avoid single-agent chemotherapy (resistant cells grow out, even if the agent kills 99.99%), should we avoid single-agent chemoprevention (16)? It is intriguing that aspirin is different and, like just a few other therapies (e.g., tamoxifen), seems to be effective as a single-agent preventive. There are data to show that prevention strategies that mimic multiagent chemotherapy have modest but real benefit [e.g., exercise and low-fat diets (17)]. Does aspirin modify multiple pathways to cancer and thus act as a though it were a multiagent regimen? Could that pleiotropy also explain the sex and dose-regimen differences? One thing is clear: aspirin acts to inhibit prostaglandins, which have both cytoprotective and proinflammatory effects; those effects are widespread (18) and still being identified. The most recent and intriguing is evidence of growth promotion in GI tumors via effects on DNA methylation (19).

It is not yet time to identify aspirin as a chemotherapeutic agent and there seems to be yet no agreement on its use as a preventive for cancer (20, 21), even if it shows clear benefit for men at risk of heart disease (22).

Received July 16, 2012; accepted July 16, 2012; published online September 6, 2012.

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