Role of Aspirin in Gastric Cancer Prevention

Asad Umar[1] and Holli A. Loomans-Kropp[1,2]

ABSTRACT

The role of aspirin in cancer prevention has been well described for multiple cancers, with strong data for gastrointestinal cancers. Studies, primarily conducted in colorectal cancer, suggest that aspirin exerts its cancer-preventive effects through the inhibition of gastrointestinal inflammation. Compared with colorectal cancer, the role of aspirin in gastric cancer prevention is less well described, however it stands to reason that aspirin and/or other nonsteroidal anti-inflammatory drugs may inhibit gastric cancer progression through the inhibition of COX-2. As discussed in this issue of *Cancer Prevention Research*, aspirin may prevent gastric cancer, albeit it appears to exert a disparate effect in men and women, the reason for which remain unclear. These results expand upon prior studies by prospectively examining aspirin use at a wider range of doses and durations in non-Asian participants and lend support to observations from previously conducted studies in Asian populations.

See related article, p. 265

The role of aspirin in cancer prevention has been well described, particularly for gastrointestinal cancers. The most extensive data has been accumulated in colorectal cancer, where preclinical studies and observational and randomized controlled clinical trials have consistently shown a reduction in incidence of adenoma, cancer or cancer-associated mortality (1). Other data from secondary analysis of large randomized clinical trials with cardiovascular endpoints have provided additional evidence for aspirin's generalized cancer-preventive benefit for incidence and mortality (2). These data indicate that aspirin use reduces cancer incidence, as well as cancer-associated mortality. The evidence for aspirin's role in preventing metastasis is somewhat equivocal, with most studies indicating the aspirin exerts a dose-independent cancer-preventive effect over a long duration of use (e.g., 5–10 years) and even following discontinuation (3–5). However, in a recent study, randomization to aspirin did not demonstrate cancer-preventive efficacy among individuals age 65 years or older, however, it reported a statistically significant 31% increase in cancer-associated mortality and an increased incidence of metastatic cancers and showed late-stages at presentation after a median 4.7 years of intervention and follow-up (6).

The role of aspirin in gastric cancer prevention is less well described as compared with colorectal cancer. Some reports have described gastric cancer-preventive efficacy with aspirin use. For example, a case–control study conducted in Russia showed a statistically significant decrease in risk for both men (OR, 0.48; 95% confidence interval (CI), 0.31–0.77) and women (OR, 0.52; 95% CI, 0.28–0.97) as well as those who were *Helicobacter pylori* (*H. pylori*) immunoglobulin G–positive (OR, 0.39; 95% CI, 0.19–0.77; ref. 7). Interestingly, analysis by anatomic subsite revealed that aspirin use did not affect the risk of cancer of the gastric cardia (non–*H. pylori*–related) but had a protective effect for non-cardia (*H. pylori*–related) gastric cancer (7). The other evidence evaluating gastric cancer and aspirin use has come from studies in Asian populations (8–10). Prospective data examining the association between aspirin use and long-term risk of gastric adenocarcinoma in non-Asian cohorts have also been recently collected (7, 11).

Gastric cancer remains a major public health issue, as it is the fifth most common cancer and fourth leading cause of cancer death worldwide (12); however, its incidence and mortality have fallen dramatically in the United States and elsewhere over the past several decades (13). Aspirin is usually not considered for gastric cancer prevention despite data implicating inflammation as a key driver of gastric carcinogenesis. This may be due to the downstream effects of *H. pylori* infection, which induces inflammation in response to cellular DNA damage and deficient DNA repair (14). Evidence suggests that indicators of inflammation, including COX-2, are present in the progression from atrophic gastritis to intestinal metaplasia and adenocarcinoma of the stomach. Other factors contributing to increased risk of gastric cancer, such as acidic conditions and exposure to cigarette smoke, have all been shown to induce COX-2 expression (14). Therefore, it stands to reason that aspirin and/or other nonsteroidal anti-inflammatory drugs may inhibit cancer progression through the inhibition of COX-2 in both genders; however, as discussed by Kwon and colleagues in this issue of *Cancer Prevention Research*, aspirin appears to exert a disparate effect in men and women, the cause of which is unclear (11).

In studies of colorectal cancer prevention, differences in the efficacy of aspirin by sex have not been noted, with few

[1]Gastrointestinal and Other Cancers Research Group, Division of Cancer Prevention, NCI, NIH, Rockville, Maryland. [2]Cancer Prevention Fellowship Program, Division of Cancer Prevention, NCI, NIH, Rockville, Maryland.

Corresponding Author: Asad Umar, Gastrointestinal and Other Cancers Research Group, Division of Cancer Prevention, NCI, NIH, 9609 Medical Center Dr., Rockville, MD 20850. Phone: 240-276-7070; E-mail: Asad.Umar@nih.gov

Cancer Prev Res 2022;15:213–6

doi: 10.1158/1940-6207.CAPR-22-0014

exceptions (15). For example, in the Multiethnic Cohort Study, a preventive effect was observed for colorectal cancer in men (HR, 0.77; 95% CI, 0.69–0.86), but not women (HR, 1.02; 95% CI, 0.89–1.17; ref. 16). Despite these new findings by Kwon and colleagues (11) demonstrating no association between aspirin use and gastric cancer risk for men but lower gastric cancer risk with regular aspirin use for women, there is not enough evidence supporting sex differences and aspirin efficacy, though inverse associations by other demographics have been reported. For example, Rothwell and colleagues found increased aspirin efficacy in the proximal colon (HR, 0.35; 95% CI, 0.20–0.63) but no association or a nonsignificant adverse association (increase in risk) in the distal colon (HR, 1.14; 95% CI, 0.69–1.86) colorectal cancer (2). In addition, Burn and colleagues recently showed that individuals with Lynch syndrome had delayed cancer onset after at least 6 years of use (17), suggesting that aspirin may exert differential effects based on etiology or genetic background. However, the association between aspirin and cancer risk may not be so clear-cut. In an analysis of clinical trials, Rothwell and colleagues showed a J-shaped relationship between colorectal cancer risk and bodyweight, with reduced risk of colorectal cancer for individuals with bodyweight 60 to 79 kg, but no association for individuals with bodyweight 40 to 59 kg or 80 to 100 kg (18).

Several plausible explanations might play into the association between aspirin and gastric cancer prevention. Inflammation is a characteristic of most gastrointestinal cancers, and it has been shown that inflammation promotes gastric carcinogenesis by inhibiting apoptosis, inducing angiogenesis and lymphatic metastasis, and assisting tumor invasion and immune response modulation (19). Aspirin inhibits inflammation by primarily inhibiting COX-1 and, to some extent, COX-2. For gastric cancer prevention, aspirin may also help through direct action on *H. pylori* as well (20). Kwon and colleagues (11) observed that regular aspirin use was significantly associated with reduced risk of *H. pylori* infection among women in a cross-sectional analysis. However, the American College of Gastroenterology suggests that patients taking long-term, low-dose aspirin consider *H. pylori* testing due to its association with increased ulcer risk (21). Clinically, those who test positive for *H. pylori* should be offered eradication therapy to reduce risk of ulcer bleeding eventually leading to reduction in gastric cancer risk due to *H. pylori* eradication. Another possibility may be that aspirin-induced ulcer and gastrointestinal symptoms in *H. pylori*–positive individuals lead to an increase in screening and surveillance, suggesting lead-time bias potentially disguised as a cancer-preventive effect. This is supported by recent data showing no benefit from aspirin use in those with metachronous gastric cancer regardless of *H. pylori* status (22).

Disparities by gender in cancer incidence and mortality have long been observed, for example, bladder cancer is more frequently observed in males, while thyroid cancer is more common among females. Similarly, death from liver cancer is more frequent in males compared with females (23). However, there are no current data suggesting how cancer prevention mechanisms of aspirin or similar anti-inflammatories might exert disparate effects by gender. There are several possible reasons for the observed associations in gastric cancer. First, in the current study, the size of the baseline cohort and length of follow-up was shorter for the men than women, which may have limited the ability to detect a significant association between aspirin use and gastric cancer incidence in men. Next, compared with women, a greater proportion of men reported low-dose aspirin use for cardiovascular disease prevention, which may be less effective in preventing cancer than the standard dose (325 mg). A study In Lynch syndrome carriers comparing the efficacy of 100 mg, 300 mg, and 600 mg aspirin for cancer prevention is currently ongoing (CaPP3 study; http://www.capp3.org) and may shed light on differential effects by dose. Finally, these results may point to biological differences in the effect of aspirin on the risk of gastric cancer between men and women, such as the potential heterogeneity in the association of aspirin with *H. pylori* infection.

Though the results of Kwon and colleagues (11) provide new insight into the potential role of aspirin for gastric cancer prevention, there were several notable limitations to the study. First, although *H. pylori* is a well-established risk factor for gastric cancer, the study team was not able to fully account for *H. pylori* infection within the entire cohort, with *H. pylori* status known for only 1% of the study population. However, because *H. pylori* infection is not routinely assessed in clinical practice, it would have not been feasible to capture this information comprehensively in a large, prospective cohort. Second, as this is an observational study, one cannot rule out the potential for residual confounding. However, definitive results through a randomized controlled trial also may not be feasible given the need for a large number of participants and long-term follow-up. Finally, more than 90% of participants in Kwon and colleagues (11) were white and the results thus cannot be generalized to other races and ethnicities. That said, a potential preventive effect of aspirin for gastric adenocarcinoma has been reported in cohort studies conducted in Asian countries (24). Hence, these results expand upon prior studies by prospectively examining aspirin use at a wider range of doses and durations in non-Asian participants and lend support to observations from previously conducted studies in Asian populations. Further data from additional cohorts that include both men and women will likely provide clarity toward a better understanding of the role of aspirin in gastric cancer prevention.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

A. Umar: Conceptualization, writing–original draft, writing–review and editing. **H.A. Loomans-Kropp:** Writing–review and editing.

Acknowledgments

The opinions expressed by the authors are their own and this material should not be interpreted as representing the official viewpoint of the US Department of Health and Human Services, the National Institutes of Health, or the National Cancer Institute.

Received January 7, 2022; revised January 19, 2022; accepted February 17, 2022; published first April 4, 2022.

References

1. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. Ann Oncol 2020;31:558–68.
2. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials. Lancet 2010; 376:1741–50.
3. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomized trials. Lancet Oncol 2012;13: 518–27.
4. Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;26:47–57.
5. Lin HD, Vora P, Soriano-Gabarro M, Chan KA. Association between low-dose aspirin use and colorectal cancer incidence in Taiwan. JAMA Netw Open 2020;3:e2026494.
6. McNeil JJ, Gibbs P, Orchard SG, Lockery JE, Bernstein WB, Cao Y, et al. Effect of aspirin on cancer incidence and mortality in older adults. J Natl Cancer Inst 2021;113:258–65.
7. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case–control study from Moscow, Russia. Int J Cancer 1999;82:473–6.
8. Tsoi KKF, Ho JMW, Chan FCH, Sung JJY. Long-term use of low-dose aspirin for cancer prevention: a 10-year population cohort study in Hong Kong. Int J Cancer 2019;145:267–73.
9. Li B, Cheung KS, Wong IY, Leung WK, Law S. Nonaspirin nonsteroidal anti-inflammatory drugs and gastric cancer risk after *Helicobacter pylori* eradication: a territory-wide study. Cancer 2021;127: 1805–15.
10. Cho MH, Yoo TG, Jeong SM, Shin DW. Association of aspirin, metformin, and statin use with gastric cancer incidence and mortality: a nationwide cohort study. Cancer Prev Res 2021;14:95–104.
11. Kwon S, Ma W, Drew DA, Klempner SJ, Leonardo BM, Flynn JJ, et al. Association between aspirin use and gastric adenocarcinoma: a prospective cohort study. Cancer Prev Res 2022.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
13. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
14. Sepulveda AR. *Helicobacter*, inflammation, and gastric cancer. Curr Pathobiol Rep 2013;1:9–18.
15. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;99:608–15.
16. Park SY, Wilkens LR, Kolonel LN, Monroe KR, Haiman CA, Marchand LL. Exploring differences in the aspirin-colorectal cancer association by sex and race/ethnicity: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev 2017;26:162–9.
17. Burn J, Sheth H, Elliott F, Reed L, Macrae F, Mecklin JP, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up, and registry-based 20-year data in the CAPP2 study: a double-blind, randomized, placebo-controlled trial. Lancet 2020;395:1855–63.
18. Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomized trials. Lancet 2018;392:387–99.
19. Cheng J, Fan XM. Role of cyclooxygenase-2 in gastric cancer development and progression. World J Gastroenterol 2013;19:7361–8.
20. Wang WH, Wong WM, Dailidiene D, Berg DE, Gu Q, Lai KC, et al. Aspirin inhibits the growth of *Helicobacter pylori* and enhances its susceptibility to antimicrobial agents. Gut 2003;52:490–5.
21. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212–39.
22. Kim JE, Kim TJ, Lee H, Lee YC, Chung HH, Min YW, et al. Aspirin use is not associated with the risk of metachronous gastric cancer in patients without *Helicobacter pylori* infection. Journal of Clinical Medicine 2022;11:193.
23. Zhu Y, Shao X, Wang X, Liu L, Liang H. Sex disparities in cancer. Cancer Lett 2019;466:35–8.
24. Wang Y, Shen C, Ge J, Duan H. Regular aspirin use and stomach cancer risk in China. Eur J Surg Oncol 2015;41:801–4.