EDITORIAL

Aspirin and Chemoprevention—Have We Arrived?

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We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
T.S. Elliot, *Little Gidding*, 1942[1]

Aspirin (acetylsalicylic acid) is one of the oldest and most widely used medications worldwide. In 400 BC, Hippocrates described the ability of salicylic tea to relieve fever; by the 19th century, pharmacists were widely prescribing salicylic acid derivatives. Today in the United States alone, almost half of adults ages 45 to 75 years take aspirin on a regular basis.[2] For those who take aspirin regularly, there is a widespread belief in aspirin's anticancer potential; in a 2015 study[2] (prior to any formal cancer prevention guidelines), 18% of Americans who took aspirin regularly said they were doing so to prevent cancer.

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The belief in aspirin's ability to prevent cancer has deep roots in our popular culture, medical practice, and scientific literature. It is well known that aspirin reduces inflammation; the concept that inflammation promotes cancer is nothing new. As far back as 1863, Virchow hypothesized that cancer occurred at the site of inflammation. In 1986, Dvorak built on Virchow's hypothesis, writing that "tumors are wounds that do not heal."[3(p1650)] It has been well documented that human tumors are generally infiltrated by inflammatory cells.[4] However, it has only been during the past decade that the molecular and cellular mechanism(s) by which inflammatory cells and the inflammatory microenvironment may drive cancer initiation and progression have begun to be defined. Today, immune cells and the inflammatory microenvironment provide new strategies for cancer treatment. While these new strategies hold promise, the majority are too toxic and/or expensive for primary chemoprevention. Less toxic and less expensive strategies for primary chemoprevention are needed.

Several decades of research provide strong evidence that the anti-inflammatory properties of aspirin may reduce cancer risk, particularly for colorectal cancer. The first evidence that regular aspirin use was associated with cancer risk reduction was observed incidentally during cardiovascular prevention trials. These early studies showed that prolonged aspirin use at doses of 81 to 325 mg per day were associated with a decreased incidence and mortality associated with colorectal cancer. Since then, key prospective studies have demonstrated the power of aspirin uses to prevent colorectal cancer.[5] Analysis of 2 large prospective cohort studies, the Nurses' Health Study (1980-2010) and Health Professionals Follow-up Study (1986-2012), linked the use of aspirin for 6 years or longer with a 19% decreased risk of colorectal cancer and a 15% decreased risk of any type of gastrointestinal cancer.[5]

In 2015, given the strength of the association between aspirin use and colorectal cancer risk reduction, the US Preventive Services Task Force (USPSTF) recommended that in individuals aged between 50 and 69 years with specific cardiovascular risk profiles, colorectal cancer prevention be included in the rationale for regular aspirin prophylaxis.[6] The USPSTF recommendations make aspirin the first pharmacological agent recommended for cancer chemoprevention in a population not characterized as having a high risk of developing cancer. Despite the USPSTF recommendations, many questions remain. Key remaining questions include (1) the dose, duration, and timing of aspirin chemoprevention, (2) the molecular mechanisms underlying aspirin's chemoprevention effects, and (3) most importantly, the ability of aspirin to prevent other malignant neoplasms.

In this issue of *JAMA Oncology*, 2 separate articles by Barnard et al[7] and Simon et al[8] provide key evidence that supports the ability of regular aspirin use to prevent ovarian cancer and hepatocellular cancer (HCC), respectively. Both ovarian cancer and HCC are deadly cancers in need of new prevention strategies. The findings from these 2 studies provide important information that can guide chemoprevention.

Despite much research, ovarian cancer remains a lethal disease. This poor prognosis is compounded by advanced presentation, genetic instability, and chemotherapy resistance. Current early detection strategies lack efficacy, and chemoprevention is limited to birth control pills.[9] There is increasing evidence that aspirin use is associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin. In 2014, Trabert et al[10] showed in a population-based case-control study of more than 10 000 case subjects that low-dose aspirin use may reduce the risk of ovarian cancer. In this issue of *JAMA Oncology*, Barnard et al[7] show, in 2 prospective cohorts, the Nurses' Health Study and Nurses' Health Study II, that regular use of low-dose aspirin (≤100 mg) is associated with a reduced risk of ovarian cancer (hazard ratio [HR], 0.77; 95% CI, 0.61-0.96). As in other studies, there was no risk reduction association for standard-dose aspirin (HR, 1.17; 95% CI, 0.92-1.49). Importantly, current use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) was positively associated with an increased risk of ovarian cancer compared with nonuse (HR, 1.19; 95% CI, 1.00-1.41). These findings suggest that the same low-dose, long-term aspirin regimens that are recommended for cardiovascular prophylaxis and colorectal cancer risk reduction can also reduce ovarian cancer risk.

Hepatocellular cancer is a leading cause of cancer death in the United States and worldwide,[11,12] and it arises almost exclusively in the setting of chronic inflammation.[13] Driven by the spread of hepatitis B and hepatitis C virus infection, the incidence of HCC in the United States has almost tripled since the early 1980s.[11] While the rate of increase of HCC has slowed,[12] HCC continues to increase in men ages 55 to 64 years old; recently, the rates of HCC in Hispanics have surpassed those in Asian Americans.[12] In a second article appearing in this issue of *JAMA Oncology*, Simon et al[8] show that regular, long-term aspirin use is associated with a dose-dependent reduction in the risk of HCC. The authors examined the dose- and duration-dependent associations between aspirin use and HCC risk in 2 prospective, nationwide cohorts, the Nurses' Health Study and Health Professionals Follow-up Study. With more than 26 years of follow-up encompassing 4 232 188 person-years, compared with non-regular use, regular moderate-dose aspirin use (≥2 standard 325-mg tablets/wk) was associated with reduced HCC risk (adjusted HR, 0.51; 95% CI, 0.34-0.77). Hepatocellular cancer risk reduction was apparent only after at least 5 years of use. Similar associations were not found with use of nonaspirin NSAIDs. This is the strongest evidence to date that aspirin use can reduce the risk of HCC.

The 2 studies by Barnard et al[7] and Simon et al[8] have the power to start to change clinical practice; however, there is still much to be learned about the mechanism underlying dose and duration of aspirin use. Furthermore, as both articles caution, the potential benefits of aspirin must be weighed against the risk of bleeding, particularly in individuals with chronic liver disease. To reach the full promise of aspirin's ability to prevent cancer, there needs to be better understanding of dose, duration, and mechanism.

The pharmacologic characteristics and pharmacodynamics of aspirin are well understood. Aspirin is prescribed at a range of doses from 75 mg (antiplatelet) to 325 to 600 mg (analgesic) to 1.2 g (anti-inflammatory) per day.[14,15] Following oral administration, low-dose aspirin gives a peak plasma acetylsalicylic acid concentration of approximately 7 μM; analgesic and anti-inflammatory doses yield acetylsalicylic acid plasma concentrations of 30 to 150 μM.[14] The primary metabolite of aspirin is salicylic acid. The plasma salicylate concentration from low-dose aspirin is approximately 15 μM; the analgesic and anti-inflammatory doses of aspirin result in plasma salicylate concentrations of 500 to 2500 μM.[14]

The study by Barnard et al[7] provides evidence that regular use aspirin at 100 mg or less (antiplatelet) doses, but not 325 to 600 mg (analgesic) or 1.2 g (anti-inflammatory) doses per day, are associated with a reduced incidence of ovarian cancer.[15] Furthermore, current use of nonaspirin NSAIDs was positively associated with an increased (not decreased) risk of ovarian cancer. Simon et al[8] show that regular moderate-dose aspirin use (≥2 standard 325-mg tablets/wk; analgesic dose) was associated with reduced HCC risk.[15] Hepatocellular cancer risk reduction was observed only after 5 years of use. There was no risk reduction associated with nonaspirin NSAID use. The dose of aspirin associated with ovarian cancer risk reduction results in an antiplatelet effect; the dose associated with HCC risk reduction is associated with an antiplatelet and/or analgesic effect; neither dose is associated with an anti-inflammatory effect. Unfortunately, the paradigm that cancer is associated with inflammation and that aspirin prevents cancer by reducing inflammation does not hold. The doses associated with these 2 important studies raise fundamental questions as to the molecular and cellular mechanism(s) of aspirin's ability to reduce cancer risk.

So, have we arrived? The 2 studies by Barnard et al[7] and Simon et al[8] are a critical step in realizing a broader population-wide use of aspirin for cancer chemoprevention. However, to realize the full potential of aspirin in precision chemoprevention, the molecular underpinnings of these important risk reduction effects also need to be defined.

ARTICLE INFORMATION

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