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Aspirin for Cancer Prevention

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The United States Preventive Services Task Force (USPSTF) recently released a draft statement recommending the use of low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in some adults aged 50 to 69 (published on-line September 15, 2015). Individuals considering use should have a 10% or greater 10-year risk of cardiovascular disease, not be at increased risk of bleeding, have a life expectancy of at least 10 years, and be willing to take aspirin for at least 10 years. The purpose of the draft statement was to get public input, with a final recommendation to be developed after the feedback is considered. The draft statement attracted attention since it is the first time that a major medical organization in the US suggested the use of aspirin for the primary prevention of colorectal cancer in average risk adults. Since aspirin has been around for a very long time, as described below, why is a new recommendation coming out now?

A Brief History of Aspirin

Aspirin, or acetylsalicylic acid, is one of the most intensively studied, most frequently used, and cheapest drugs in the world. Salicylic acid originally was purified as the fever-reducing ingredient from the bark of the willow tree. The acetyl component later was added during chemical synthesis in order to improve its efficacy and reduce side effects, including stomach irritation with nausea and vomiting. Aspirin originally was patented by the German pharmaceutical company Bayer in 1900 and quickly became a common household remedy against fever, pain and inflammation, although its mechanisms of action were not known.

It wasn't until the late 1960s that the first studies were performed that shed light on how aspirin works. Initially, there were reports of a bleeding tendency after surgical interventions if aspirin was used for treatment of pain. However, early experiments indicated that aspirin had no direct effects on the soluble factors involved in blood clotting reactions but instead inhibited the activity of platelets. Platelets are small blood cells that, when activated, initiate blood clotting by aggregating into clumps and releasing stored clotting factors into the blood. In 1971, John Vane and colleagues first discovered that aspirin inhibits prostaglandin biosynthesis (Vane, 1971), which led to his sharing the Nobel Prize for medicine in 1982. Prostaglandins, and other signaling lipids called eicosanoids, are synthesized from arachidonic acid by enzymes called cyclooxygenases. Eicosanoids have numerous functions: some cause fever, others cause inflammation, and one of them, called thromboxane A2, causes platelet activation and aggregation. In 1975, Philip Majerus and colleagues first reported that aspirin acetylates and irreversibly inhibits the activity of a cyclooxygenase (COX-1) in platelets, thereby blocking thromboxane A2 synthesis and platelet activation (Roth et al., 1975). Importantly, aspirin permanently inactivates platelets for their entire life span (about 10 days), since these cells don't have a nucleus and therefore can't synthesize new proteins, including cyclooxygenase.

Aspirin and Cardiovascular Disease

Following those early findings on aspirin's antiplatelet effects, numerous clinical studies were conducted to evaluate the use of aspirin in preventing heart attacks, strokes, and other disorders related to blood clotting. In a combined analysis of results from many different studies including many thousands of individuals, the Antithrombotic Trialists' Collaboration found that low dose aspirin (75-100 mg/day) reduced the risk of a serious vascular event among high-risk patients with vascular disease (Antithrombotic Trialists Collaboration, 2002). Although aspirin treatment also increases the risk of potentially serious bleeding, primarily gastrointestinal, it is still recommended for patients whose risk for coronary heart disease is at least 1% per year and who do not have increased susceptibility to bleeding, because the number of vascular events avoided should be significantly greater than the number of bleeding events caused by treatment (Patrono et al., 2005). It is less clear whether individuals at lower risk for vascular disease should take aspirin, since there are inconsistent results from primary prevention trials and harms may outweigh benefits.

Aspirin and Cancer

In addition to preventing cardiovascular disease, there is now considerable evidence that regular use of aspirin also may be useful for preventing colorectal cancer (Chan et al., 2012). First, in numerous epidemiologic studies, it has been observed that aspirin use is associated with a reduction in colorectal cancer risk. Second, in several randomized placebo-controlled trials, aspirin treatment decreased risk of colorectal adenomas, which are precursors to the majority of colorectal cancers (Cole et al., 2009). Third, there is compelling evidence from a series of recent analyses combining long-term follow-up data on cancer outcomes from randomized controlled trials designed to study cardiovascular disease prevention. In these secondary analyses, low-dose aspirin treatment reduced colorectal cancer incidence and mortality and also overall cancer metastasis and mortality (Rothwell et al., 2011; Rothwell et al., 2010; Rothwell et al., 2012).

Perhaps surprisingly, the mechanism for aspirin's anti-cancer effect is still unclear. One possibility is that inhibition of a second type of cyclooxygenase, called COX-2, is involved. Acetylation of COX-2 prevents synthesis of prostaglandin E2 (PGE2), and both COX-2 and PGE2 have been implicated in the development of colorectal cancer (Chan et al., 2007). Another possibility is the involvement of novel inflammation resolving lipids mediators that are synthesized by acetylated COX-2 (Serhan and Chiang, 2013). Additionally, numerous cyclooxygenase-independent effects of aspirin have been identified whose role in aspirin's anti-cancer effects are uncertain. For example, it appears to modify the activity of transcription factors, cellular signaling and mitochondrial function. There are potentially many more molecular targets of aspirin and of its primary metabolite, salicylate, which have yet to be discovered. Nonetheless, the recent evidence that the low dose of aspirin used in cardiovascular disease prevention trials also prevents colorectal cancer has been suggested to imply an important role for the inhibition of COX-1 in platelets (Thun et al., 2012). The reason is that higher doses of aspirin appear to be required for acetylation of COX-2 and for many of the other cyclooxygenase-independent effects identified to date.

What's Next?

Recent analyses by the USPSTF, incorporating all currently available evidence, was used to update prior recommendations and create a decision analysis tool that formed the basis of the new draft recommendations that just were released (Dehmer et al., 2015). However, uncertainties remain about the magnitudes of the estimates used to calculate some of the risks and benefits of aspirin treatment. Additional research will be valuable in updating these calculations. Also, future research may identify further benefits (such as protective effects against other cancer types) or harms that could be incorporated into an improved decision analysis tool at a later date.

Reduction in the risk of colorectal cancer in average risk adults now represents an additional benefit for individuals considering use of low-dose aspirin to reduce their risk of cardiovascular disease. Results in these individuals could help to better define the risks and benefits, regarding colorectal and other cancers, of use of low-dose aspirin regardless of an individual's risk of cardiovascular disease.

Further investigation into aspirin's mechanisms of action against cancer remains a high research priority. An improved understanding of the mechanism(s) involved would help to clarify existing uncertainties regarding the optimal aspirin dose and frequency of administration and the potential use of combination therapy with other drugs. This work may also identify novel biological pathways and targets for cancer prevention that could be pursued with new drugs designed to reduce toxicities while maximizing efficacy.

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