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The role of aspirin in cancer treatment

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Abstract. Aspirin has attracted attention for its potential to prevent cancer, especially for the treatment of colorectal cancer. Historically, aspirin can be used for the prevention of cardiovascular disease because of its ability to irreversibly convert acetylcyclooxygenase (COX)-1, which inhibits platelet aggregation. In addition, aspirin can be also used to reduce cancer incidence and mortality, showing a good application for cancer treatment. The evolution of the role of aspirin is explored here, with a focus on the epidemiological and clinical evidence supporting its anticancer effects, where low-dose aspirin can reduce overall cancer incidence and mortality by 20-30%. Potential mechanisms of aspirin, including inhibition of platelet activation and inhibition of tumor-promoting pathways, are also discussed. Despite these findings, the use of aspirin must balance benefits with bleeding risk, especially in average-risk populations. Future studies should focus on determining the optimal dosing regimen and identifying the population that would benefit most from the cancer-preventive effects of aspirin.

Keywords: Aspirin; Cancer prevention; Cyclooxygenase inhibition; Antiplatelet effects; Cardiovascular benefits.

1. Introduction

Aspirin is widely used, and its role has evolved from its origins as a pain reliever and anti-inflammatory agent to its present-day role as a possible preventive and therapeutic agent for cancer. This shift in its utility reflects a broader trend in pharmacology to revisit new applications of historical drugs in light of emerging scientific evidence [1]. The literature about aspirin is vast, as known as a large number of studies examining the mechanisms, applications, and effects of its long-term use, particularly in chronic diseases such as cancer.

In the history of medicine, the development of aspirin began more than a century ago, and it remains a major part of the treatment regimen as scientists demonstrated its efficacy in reducing pain, fever, and inflammation [2]. The discovery of its antiplatelet effect has further expanded its use for cardiovascular disease prevention. In the past decades, the potential anti-cancer properties of aspirin have attracted much attention and new studies have been initiated to understand the underlying mechanisms and clinical implications of its cancer applications.

The pharmacological basis of action of aspirin is its inhibition of cyclooxygenase (COX) enzymes, such as COX-1 and COX-2. These enzymes play an important role in the biosynthesis of prostaglandins [2]. Aspirin not only reduces pain and inflammation, but also prevents thrombotic events and reducing the risk of heart attack and stroke. This anti-thrombotic property has made aspirin a leading agent in cardiovascular disease treatment.

The role of aspirin for cancer treatment has been explored. The regular aspirin use is associated with a reduced risk for cancer, where the mechanism behind this protective effect is related to aspirin's ability to inhibit COX-2 [3], which is frequently overexpressed in tumors and promotes carcinogenesis by promoting angiogenesis, inhibiting apoptosis, and suppressing immune responses. Advances in the molecular biology of aspirin have shed new light on its anticancer effects. Aspirin can modulate various signaling pathways related to cell proliferation, apoptosis, immune responses, and the discovery of aspirin as a potential adjuvant therapy in cancer treatment has opened up new

avenues, especially in enhancing the efficacy of other therapeutic agents and in the management of cancer-related inflammation.

The effect of aspirin on cancer progression and metastasis can be also investigated. For example, aspirin can inhibit the spread of cancer cells by regulating the tumor microenvironment, reducing inflammation, and preventing the formation of new blood vessels. These findings are supported by observational studies showing that the use of aspirin can be used to improve the survival rate of cancer patients. Despite this prior evidence, there is still controversy regarding the use of aspirin in cancer prevention and treatment, such as potential adverse effects [3]. Therefore, it needs to understand the role of aspirin in oncology, such as designed randomized controlled trials, is needed to provide clearer answers. This article explores potential of aspirin to prevent cancer, particularly colorectal cancer, as well as its well-known cardiovascular benefits. It reviewed evidence from clinical trials that regular use of low-dose aspirin may reduce cancer incidence and mortality over time. The proposed mechanisms include the inhibition of COX enzymes and inhibition of platelet activation, both of which have been implicated progression.

2. Application of aspirin for cancer treatment

2.1. Early theories

The use of aspirin-like substances dates back thousands of years, with early use involving willow bark containing salicylate. In 1897, Felix Hoffman, a chemist at Bayer, synthesized acetylsalicylic acid. Despite the widespread use of aspirin at the time, the precise mechanisms by which aspirin alleviates pain and inflammation remained unclear for decades. Early theories focused on various biochemical effects, such as dehydrogenase inhibition and interference with oxidative phosphorylation [4]. However, these theories were inadequate because the concentrations of aspirin required to produce these effects were much higher than those typically achieved during treatment. There was a lack of correlation between these biochemical effects and the clinical efficacy of aspirin.

Despite the continuous development of new anti-inflammatory drugs, aspirin is still widely used because of its unique combined effects. Its role in cardiovascular disease prevention, particularly at low doses, is well established. The ability of aspirin to inhibit platelet aggregation has made it a cornerstone in the prevention of secondary heart attacks and strokes. The ongoing research suggests that aspirin may have additional benefits, such as reducing the risk of certain cancers, particularly colorectal cancer. This potential chemopreventive effect is thought to be related to its COX inhibition, but other mechanisms may also be involved [5].

2.2. Clinical implications and management

The main mechanism of aspirin is inhibition of COX, which reduces the production of prostaglandins involved in inflammation and platelet aggregation. These effects are relevant to cancer, in which chronic inflammation and platelet-driven tumor progression play a role [6, 7]. In addition to COX inhibition, aspirin has been shown to affect energy metabolism, cancer-related inflammation, and DNA repair pathways, especially in colorectal cancer. This COX-independent effect is of interest in cancers characterized by genetic instability, such as Lynch syndrome [8]. The effect of aspirin on DNA repair pathways and epigenetic mechanisms highlights its potential to target cancer cells, alter the tumor microenvironment, and reduce metastatic spread.

Ensuring patient adherence to aspirin therapy is critical to mitigating marked resistance. Non-adherence is an important cause of treatment failure. Clinical strategies should include patient education, regular follow-up, and use of technology to improve medication adherence, such as electronic reminders or pill organizer. Poor adherence leads to increased cardiovascular events, underscoring the need for rigorous adherence monitoring. For patients with a high platelet turnover rate or other risk factors for aspirin resistance, alternative dosing regimens are needed. For example, twice-daily dosing has been shown to be more effective in maintaining adequate COX-1 inhibition in

patients with high platelet turnover. This approach ensures a more consistent antiplatelet effect throughout the day.

Managing patients receiving aspirin requires careful consideration of the benefits and risks. Low-dose aspirin is commonly used for long-term prevention of cardiovascular events. The higher dose does not provide additional benefit in terms of efficacy but does increase the risk of bleeding. Strategies such as enteric-coated aspirin or aspirin plus a PPI can be used in patients who are considered to be at high risk for gastrointestinal complications [7] and monitoring for signs of aspirin resistance is also important, particularly in high-risk patients who have persistent thrombotic events despite treatment. Genetic testing and personalized treatment strategies can help identify patients with aspirin resistance. Clinicians can tailor treatment to improve efficacy. For example, patients with polymorphisms in COX-1 or platelet receptor genes may benefit from other antiplatelet agents or dosing strategies. Clinicians should be aware of potential drug interactions that could impair compromise the efficacy of aspirin. It is critical to avoid concomitant use of NSAIDs such as ibuprofen, which competes with aspirin for COX-1 binding. If the use of NSAID is necessary, alternative medications that do not interfere with aspirin, such as acetaminophen, should be considered.

2.3. Cardiovascular benefits and cancer prevention

Traditionally, the antithrombotic properties of aspirin have helped to prevent heart attacks and strokes by inhibiting the aggregation of platelets. This effect is achieved through the irreversible inhibition of COX-1 in platelets, thereby reducing the thromboxane A2 production, a promoter of platelet activation and aggregation. The ability of aspirin to reduce the risk of cancer has gained attention. Early studies focused on the reduction of adenomatous polyps, precursors to colorectal cancer, and showing that regular aspirin significantly reduced the rate of recurrence of these polyps. This finding is supported by randomized clinical trials that have shown that aspirin can reduce the incidence and mortality of colorectal cancer. Despite these promising results, the potential harms associated with aspirin, particularly gastrointestinal bleeding, have made it difficult to justify its use solely for cancer prevention in average-risk populations.

2.4. Meta-analysis

Recent meta-analysis of cardiovascular trials has provided compelling evidence that the benefits of aspirin extend beyond heart disease prevention. These studies suggest that low-dose aspirin is not only reduces the incidence of colorectal cancer but may also decrease the overall risk of developing and dying from all types of cancers combined. A 20% reduction in overall cancer incidence was observed between 3 to 5 years of aspirin initiation, and a 30% reduction in cancer mortality was observed after more than 5 years of continuous use [5]. Interestingly, the benefits of aspirin in cancer prevention were not dose-dependent, as higher doses did not confer additional protection. The hypothesis is supported by this finding that the antiplatelet effect of low-dose aspirin may play a key role in its cancer-preventive properties through the inhibition of platelet activation.

2.5. Mechanism

The most detailed mechanism is COX inhibition. COX-1 is constitutively expressed in most tissues and is involved in the maintenance of normal physiological functions, and COX-2 promotes inflammation and is frequently over-expressed in various cancers [4, 5]. It is an inducible enzyme, expressed primarily during inflammatory responses and is responsible for the production of prostaglandins that mediate inflammation and pain, and these enzymes have shown similar protective effects. The mechanism is further supported.

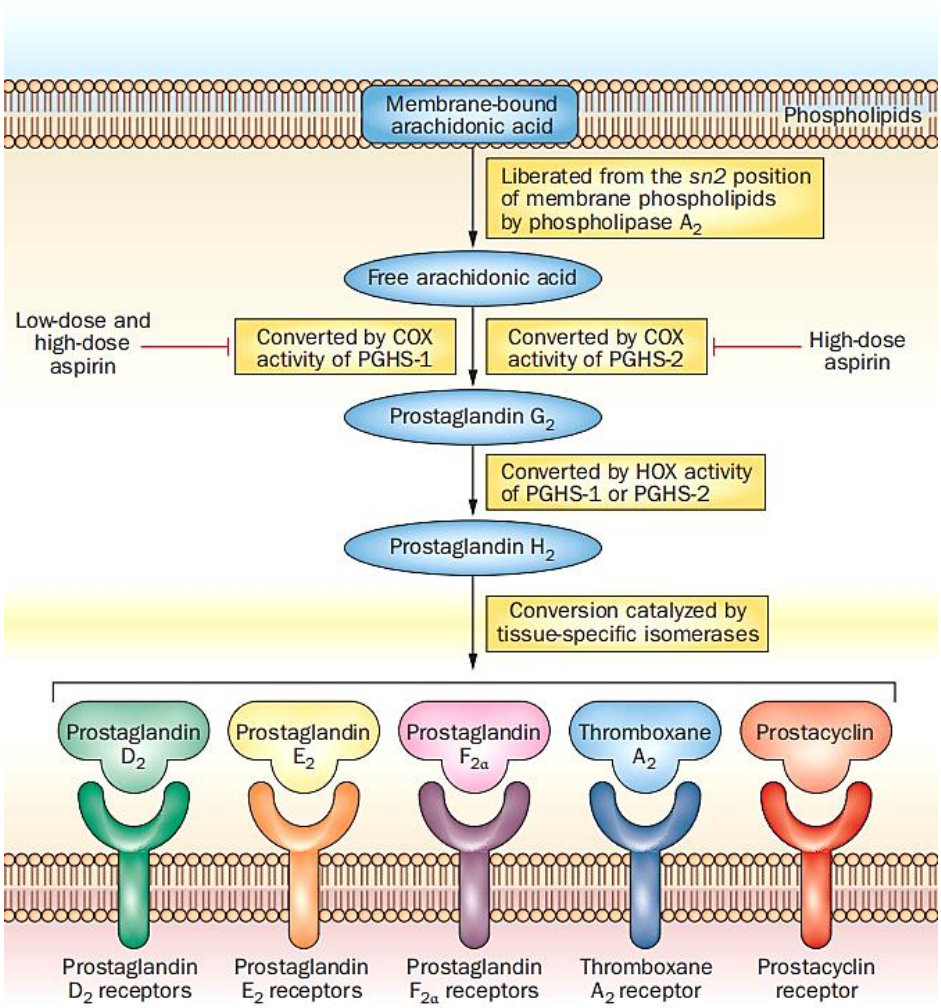

Figure 1. Mechanism of action of aspirin in the cyclooxygenase pathway [5].

Figure 1 explains how aspirin inhibits COX activity, which results in decreased production of prostaglandins that play a role in inflammation and cancer progression. Aspirin exerts its effects by irreversibly acetylating serine residues. This acetylation blocks the ability of enzyme to convert arachidonic acid to prostaglandin G2 (PGG2) and subsequently to prostaglandin H2 (PGH2), the precursor of other prostaglandins and thromboxanes. The irreversible nature of this inhibition is particularly significant in platelets, which are anucleate cells. Because platelets cannot synthesize new COX enzymes, the effects of aspirin last for the duration of the lifespan of platelet [6]. This property underlies anti-thrombotic effects of aspirin, which making it an important agent for the prevention of heart attacks and strokes.

According to anti-platelet of aspirin, its activity is not without limitations. Approximately 50-60% of patients exhibit aspirin resistance, which means their platelets respond poorly to the antiplatelet effects of aspirin. Multiple factors, including increased production of isoprostanes, which can activate platelets independent of TXA2 genetic polymorphisms. And drug interactions, can contribute to this resistance. This variability in aspirin response may reduce its overall effectiveness in preventing cardiovascular events [7].

Low-dose aspirin primarily inhibits COX-1, raising questions about how it protects against cancer if COX-2 inhibition is the key. One proposed explanation is that the antiplatelet effect of aspirin prevents the release of pro-inflammatory and pro-tumor factors, thereby indirectly reducing cancer risk. Platelets can interact with tumor cells to promote the growth of tumor cell and metastasis. By inhibiting platelet activation, aspirin may disrupt this process, thereby reducing cancer development and spread.

The discovery of two COX isoforms in the late 1980s and early 1990s led to a deeper understanding of the actions and side effects of aspirin. Although the inhibition of COX-2 is responsible for the anti-inflammatory and analgesic effects of aspirin, the inhibition of COX-1 is associated with gastrointestinal side effects of aspirin, due to a decrease in protective prostaglandins in the gastric lining. This understanding has facilitated the development of selective COX-2 inhibitors, which aimed to reduce inflammation without the gastrointestinal side effects associated with non-selective COX inhibition. However, these selective inhibitors also raised cardiovascular safety concerns and led to a reevaluation of their use.

2.6. Risk-benefit considerations

When considering the use of aspirin for cancer prevention, it is crucial to weigh the benefits against the risks, particularly the increased likelihood of gastrointestinal bleeding. Although the use of aspirin can reduce the incidence rate and mortality of cancer, the potential harm of aspirin induced bleeding cannot be ignored, especially in populations at low or average risk of cardiovascular disease. Despite these concerns, even a modest reduction in cancer incidence might justify aspirin use, especially for individuals with a higher risk of cancer or cardiovascular disease. The potential for aspirin to prevent multiple types of cancer, including colorectal, esophageal, and gastric cancers, further strengthens the case for its use in specific populations.

2.7. Pharmacokinetic factors

Aspirin is converted to salicylate by esterase water in the gastrointestinal tract and systemic circulation. This enzymatic conversion affects its bioavailability and effectiveness. Aspirin absorption is affected by these esterase activities. These esterase activities may vary between individuals and contribute to differences in drug efficacy. For example, concomitant coadministration of a proton-pump inhibitor (PPIs) or prolonged absorption with enteric-coated aspirin may enhance esterase activity, thereby reducing the bioavailability of active aspirin [6].

The pharmacokinetics of aspirin are influenced by several factors, including dose, route of administration, and the presence of food. Enteric-coated aspirin tablets are intended to reduce gastrointestinal irritation, but they may also delay absorption of the drug and reduce bioavailability. In addition, genetic polymorphism of enzymes involved in aspirin metabolism can affect an individual's response to treatment. For example, changes in plasma esterase activity can affect the rate at which aspirin is deacetylated to salicylic acid, potentially affecting its efficacy [7]. An important pharmacokinetic factor which affecting aspirin resistance is multidrug resistance protein 4 (MRP4). MRP4 expels aspirin from platelets, thereby reducing its intracellular concentration and availability. It has been shown that inhibition of MRP4 can improve the inhibitory effect of aspirin on COX-1. Excess aspirin resistance due to increased MRP4 activity in patients after coronary-artery bypass grafting (CABG) can be mitigated by MRP4 inhibitors such as dipyridamole.

2.8. Biological factors

In conditions of high platelet turnover, such as atherosclerosis or inflammation, the functional COX-1 enzyme generates new platelets and allows them to enter the circulation more rapidly. This rate of regeneration may exceed that with a once-daily aspirin regimen, resulting in a period of platelet free inhibition that attenuates the antiplatelet effect of aspirin. Twice-daily aspirin is more effective in patients with essential thrombocythemia, a disorder with a high platelet turnover rate. Platelets can synthesize new COX-1 in response to external stimuli. This denovo synthesis could counteract the irreversible inhibition caused by aspirin, thereby leading to a restoration of platelet function and continued TXA2 production. This phenomenon highlights the importance of considering the dynamic biology of platelets when managing aspirin therapy. Platelets and other cells will produce TXA2 y bypassing the inhibitory pathway of aspirin, endothelial cells and vascular smooth muscle cells can also utilize platelet-derived intermediates to produce TXA2, this alternative synthetic pathway could promote aspirin resistance by maintaining platelet aggregation in the presence of COX-1 inhibition.

3. Conclusions

All in all, because of recognized antiplatelet effects of aspirin and ability to inhibit COX, scientists have focused on aspirin potential to prevent cancer, especially colorectal cancer. Low-dose aspirin reduces cancer incidence and mortality and has significant long-term benefits. In terms of the mechanism of aspirin, in addition to its anti-inflammatory properties, it also inhibits platelet activation. Platelet activation plays a role in tumor progression and metastasis. The risks which in gastrointestinal bleeding, are associated with aspirin need to be weighed against the benefits. Despite its potential for cancer prevention, aspirin has not been widely used because of concerns about adverse effects in average-risk populations. Scientists need to continue to conduct research, including long-term clinical trials, to determine the optimal dose of aspirin and to find populations in which aspirin would benefit most as a cancer preventive agent. Until more definitive data are available, aspirin use for cancer prevention should be targeted and cautious.

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