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Review

Aspirin and NSAIDs as Cancer Preventive Agents: A Review

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ABSTRACT

Aspirin and non-steroidal anti-inflammatory drugs are widely utilized pharmaceuticals globally for their analgesic, anti-inflammatory, and antipyretic properties. These compounds are known to inhibit the enzyme cyclooxygenase, whose upregulation is implicated in various cancers, thereby suppressing the synthesis of prostaglandin, prostacyclin, and thromboxane in cancer cell lines, thereby manifesting anticancer attributes. This review aims to investigate the potential utility of aspirin as a neoadjuvant in several cancer types, particularly colorectal cancer, based on its anticancer efficacy, elucidate its mechanistic roles across diverse cancer types, and ascertain whether the risk of cancer escalation or mitigation varies depending on drug dosages across different cancer entities.

Keywords: Aspirin, cancer, COX gene, inflammation, NSAIDs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are compounds that are widely used due to their anti-inflammatory and antipyretic effects.[1] However, the use of NSAIDs (celecoxib, diclofenac, ibuprofen, naproxen), which are also preferably used as analgesics, has been deemed risky by medical regulatory authorities, including the Food and Drug Administration and the European Medicines Agency. Despite its results, its effective use continues today despite its side effects in terms of cardiovascular disorders.[2]

Lethal drug causes toxicity in children due to misuse of the drug.[3] Additionally, Manso et al.[4] revealed that people using sodium salicylate between the ages of 13 and 23 had higher blood transaminase levels in their research. The liver damage caused by aspirin has been reported to be triggered by an increase in glutamic pyruvic transaminase and glutamic oxaloacetic transaminase levels, which have been detected in over 50% of children with rheumatic fever.

According to reports, NSAIDs block the cyclooxygenase (COX-2) enzyme, which inhibits prostaglandin, prostacyclin, and thromboxane from producing. It has been thought that NSAIDs' ability to suppress COX-2 and limit prostaglandin synthesis has anticancer properties.[5]

ASPIRIN AND CANCER: A STATISTICAL ANALYSIS

Aspirin, a molecule containing a reactive acetyl group and a salicylate metabolite, is one of the most widely used drugs worldwide, first produced and offered for sale by Bayer in 1897 and serving as an antipyretic, analgesic, and anti-inflammatory.[6,7] Studies have demonstrated its anticancer capabilities, and its association with cancer was first reported in 1971. Preclinical studies focused on its relationship with the cardiovascular system, and it was observed that the resulting analyses reduced the risk of inflammation-related cancers.[8] This conclusion has been reached as a result of the chemopreventive action of NSAIDs and aspirin via the inhibition of COX enzymes, which are overexpressed in many cancer cell lines and are responsible for the synthesis of prostaglandins. In addition, the induction of apoptosis, which are characteristics of aspirin and NSAIDs, the inhibition of nuclear factor kappa B (NF-κB) factor,

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which regulates immunity and inflammation and prevents cellular stress-induced apoptosis, and the regulation of tumor suppressor genes, prove their anticancer effects.[9,10]

Research has indicated that aspirin exhibits anticancer effects in several cancer types, particularly colorectal cancer (CRC).

Aspirin and Colorectal Cancer

Colorectal cancer is the fourth most common cause of cancer-related deaths in the world, with 1.4 million new cases and approximately 700,000 deaths estimated in 2012.[11] Incidence and mortality rates are decreasing with advanced screening measures and molecular studies.[12] According to CRC promising information on aspirin's anticancer effects has been collected through the outcomes of clinical and molecular research done over the past ten years. The recommendation for the use of aspirin in the treatment of CRC was made by the United States Preventive Services Task Force (USPSTF) in 2007. Thus, aspirin was presented as the first pharmacological agent that did not increase the risk of cancer. The USPSTF warned about the possible harms associated with regular aspirin use and emphasized that more studies should be conducted on this anticancer property and that the relevant mechanisms to prevent the development of neoplasia in CRCs should be elucidated.[13]

Regular aspirin usage has been demonstrated to reduce the risk of CRC compared to irregular use.[14] Based on this result, it may be concluded that long-term, low-dose aspirin use lowers the risk of CRC and adenoma, but it shouldn't be the main method of prevention. Additionally, aspirin is beneficial when used after CRC diagnosis. Additionally, it may improve survival in tumors with PIK3CA mutations and prevent metastasis in localized CRCs.[15]

Aspirin and Breast Cancer

Compared to American women, African-American women have greater incidence and mortality in breast cancer subgroups with worse prognosis, such as estrogen receptor (ER)-negative cancers and also it could contribute to inflammation in breast cancer that is ER-negative. Epidemiological studies for this kind of cancer have produced new information, even though the chemopreventive effects of NSAIDs and aspirin, which have anti-inflammatory qualities, are well recognized. In 2008, Takkouche et al.[16] conducted a study aiming to see whether breast cancer reduces the risk due to NSAID usage. A decrease due to NSAID use was observed in the analysis of a total of 38 studies, including 16 case-control, 18 cohorts, three case-control studies, and one clinical study.

Bertrand et al.[17] In one study, a cohort study of 59,000 African-American women was conducted to obtain concrete data on the relationship between aspirin and breast cancer. 1919 patients had invasive breast cancer; of them, 284 were triple-negative (TN) patients, 569 were ER-negative, and 1112 were ER-positive. In conclusion, ER-negative and TN breast cancer is associated with hypothesized inflammatory mechanisms, thus aspirin seems to be a potential anticancer drug for ER-negative and TN.

In their study, Kwan et al.[18] found that in individuals with invasive or ductal carcinoma *in situ*, it dramatically decreased the risk of recurrence. Aspirin has been shown in studies to lower the risk, but no results have been seen to alter this circumstance. Zhou et al.[19] in another study conducted to learn the effect of aspirin on breast cancer, out of 1227 patients, 32 used high-dose aspirin (325 mg), 121 used low-dose aspirin (81 mg), and the remaining 1074 individuals did not use aspirin before or after diagnosis. According to the results, patients who took aspirin regularly and at a high dose (325 mg) fared better than those who took it at a low dose (81 mg). A slight benefit has been observed in patients with PIK3CA mutation who use low-dose and long-term aspirin, and it has been reported that high-dose will provide survival benefits in people who use aspirin after diagnosis.

Aspirin and Gastric Cancer

Gastric cancer (GC), one of the most common cancers worldwide, is associated with *Helicobacter pylori* infection. Aspirin has a role in the prevention of gastrointestinal cancers by stimulating apoptosis, inhibition of angiogenesis, and anti-inflammatory and antiplatelet effects. When the studies are evaluated, there are very few studies on the incidence of GC due to aspirin use.[20]

It causes acute gastric mucosal damage, which is evaluated based on endoscopy or measurement of gastrointestinal blood loss. However, the occurrence of many side effects is related to the dose used. In studies involving endoscopy or measurement of gastrointestinal blood loss with acute aspirin use, the effect of dose-related response affects chronic gastric ulcer formation.[21]

Aspirin or other NSAIDs, which have an anti-inflammatory effect by inhibiting prostaglandins

synthesized from arachidonic acid, have an anticancer effect for GC. In addition, long-term use of high doses has been shown to reduce the risk of GC.[22]

Aspirin and Liver Cancer

Primary liver cancers rank fifth among the cancers seen worldwide; It ranks third in terms of cancer mortality. Hepatocellular carcinomas (HCC) constitute 85%-90% of primary liver cancers. The development of HCC is at risk due to epidemiological factors such as geographic region features, racial and ethnic groups, gender, and rate of environmental exposure.[23] Additionally, genetic factors, hepatitis B (HBV) hepatitis C viruses (HCV), and alcoholism can also induce. HCC prognosis; It progresses negatively due to the low rate of early diagnosis and the high risk of metastasis and recurrence.[24]

Yuan et al.[24] in a study they conducted; aspirin inhibited the proliferation of HepG2 cells depending on time and concentration differences, and a significant decrease in the number of colonies was observed compared to the control group. The concentration-dependent rate of apoptosis also increased in aspirin-treated HCC cells. In a study, involving patients with chronic HBV and HCV, over a follow-up period of approximately 8 years, patients using low-dose aspirin had a lower incidence of HCC than non-users, 8.3% versus 4% has been seen.[25] Wang et al.[26] conducted for the analysis of aspirin dose-dependent HCC risk, eight studies were conducted with 2,604,319 participants, and as a result of the meta-analysis, an inverse relationship between dose and HCC was observed and a decrease was recorded in individuals using aspirin in their study.

Apart from this, the relationship of Aspirin with HCC risk in patients with alcoholic cirrhosis is unknown. HCC and gastrointestinal bleeding were observed in a study of 949 patients with alcoholic cirrhosis who did not consume alcohol. Subsequently, 224 people who used aspirin and 725 people who did not use aspirin were included in the study, and HCC was observed in 133 (13.6%) patients within an average of 3.1 years. Medication with aspirin was associated with a reduction in HCC risk and did not appear to increase bleeding risk when used in conjunction with other treatments for bleeding. As a result, it has been reported that patients with alcoholic cirrhosis have lower HCC during treatment with aspirin.[27]

Aspirin and Kidney Cancer

Renal cell carcinoma (RCC) is a heterogeneous cancer type that exhibits a range of histological and molecular subgroups along with distinct clinical outcomes. Mutation of *VHL*, *FLCN*, *TFE3*, *FH,* or *SDHB* genes, which are associated with RCC, disrupts the regulation of oxygen, iron, nutrients, and oxygen levels of the tumor.[28] Most of the data obtained from the studies were obtained from patients with clear cell renal cell carcinoma (ccRCC), which includes 70% of RCC. The mutation of *VHL* associated with cellular oxygen sensing is linked to ccRCC. The *VHL* is rendered inactive by a mutation in 52% of RCC cases.[29]

A study conducted in Italy between 1992 and 2004 aimed to understand the relationship between RCC and aspirin. It included 755 patients diagnosed histologically with RCC and 1297 non-neoplastic control subjects. Upon analysis of the dataset, it was found that regular aspirin use did not increase the risk of RCC.[30] In a study by Karami et al.[31], conducted to understand the relationship between analgesics and RCC, data analysis was performed on a large population. The study included 1,217 RCC patients and 1,235 control subjects from the American kidney cancer study, as well as 98,807 individuals participating in the US prostate, lung, colorectal, and ovarian cancer screening trial. Upon examination of the findings, it was reported that the use of over-the-counter acetaminophen (paracetamol), a type of analgesic, was associated with RCC, with usage for ≥10 years doubling the risk. However, in both studies, no association was found between the use of aspirin and NSAIDs and the risk of RCC.

THE COX GENE AND ITS FUNCTION

The cyclooxygenase isoenzymes, COX-1 and COX-2, stimulate prostaglandins, thromboxanes, and levuloglandins. They are important in human physiology, including cardiovascular, neuronal, renal, immune, gastrointestinal, and reproductive systems.[32]

Data obtained from molecular, animal experiments, and human research indicate that abnormal COX-2 induction and upregulation of the prostaglandin cascade play a role in cancer mechanisms. Inhibition of these compounds is considered appropriate for cancer prevention.[33]

Non-steroidal anti-inflammatory drugs inhibit the synthesis of prostaglandins by blocking the activation of the COX enzyme. Findings suggesting that NSAIDs regress the formation of rectal polyps in patients with Gardner syndrome have also raised the possibility of their use in cancer treatment.[34]

The COX-2 enzyme plays a role in many cancer types. Abnormal expression of COX-2, observed in BRCA, occurring in 40% of all cases, and seen in pre-invasive ductal carcinoma in situ tissue lesions, could suggest its involvement in carcinogenesis. Despite significant reductions in cancer risk associated with regular NSAID use, the mechanisms demonstrating the anti-cancer properties of NSAIDs remain unknown. Experimental studies using BRCA-mutant rats have associated the use of COX-2 inhibitors, as well as NSAIDs including aspirin and ibuprofen, with a decrease in cancer risk.[35]

THE ROLE OF INFLAMMATION IN CANCER DEVELOPMENT

Cellular and molecular responses occur in response to harmful components due to infection and tissue damage in the body. Inflammation is observed due to the formation of chronic infections, type 2 diabetes, cardiovascular diseases, and autoimmune diseases. Little is known about the mechanism of action of diseases that cause inflammation.[36]

Cancer, which develops due to genomic instability, genetic factors, and environmental stress, can occur in any tissue or organ. The occurrence of these factors leads to the formation of malignancy and neoplastic tissues. Features such as evasion of apoptosis, irregular proliferation, angiogenesis, and metastasis in cells contribute to malignant growth. Chronic inflammation is associated with many conditions. Continuous tissue damage, increased cell proliferation with damage, and tissue regeneration are examples of this condition.[37] Inflammation associated with cancer occurs through certain reactions present in the tumor tissue region, contributing to the development of malignancy. The development of inflammation varies depending on the stage of the disease and the prognosis. Tumor necrosis, observed in many cancer types such as kidney, breast, colorectal, and lung cancers, indicates a worsening prognosis in malignant tissues. Furthermore, the combination of necrosis and inflammation plays a significant role in the progression of the tumor.[38]

In conclusion, aspirin and/or NSAIDs, commonly used as analgesics, anti-inflammatory, and antipyretic agents, have been reported to have a relationship with cancer, with studies indicating their chemopreventive effects. This conclusion is attributed to the inhibition of prostaglandin synthesis by blocking the activation of cyclooxygenase isoenzymes, COX-1, and COX-2, which are observed to have increased expression in many cancer types. Abnormal expression of COX enzymes, which are present in human physiology, including cardiovascular, neuronal, renal, immune, gastrointestinal, and reproductive systems, has been noted in various tumor types such as breast, prostate, pancreas, skin, lungs, bladder, and head-neck. Furthermore, the inhibition of the NF-κB factor by aspirin and NSAIDs is suggestive of their anticancer effects, as they are responsible for the regulation of tumor suppressor genes. Due to the lack of definitive results regarding the mechanism of NSAIDs and aspirin in preventing malignancy, numerous studies and meta-analyses have been conducted. Although regular use of NSAIDs has been reported to reduce the risk of cancer compared to aspirin, studies on this matter are insufficient. Moreover, information regarding the anticancer mechanisms of NSAIDs on human cancers is limited. Despite reports of their anticancer effects, it is not known how they induce apoptosis or halt cell proliferation. Research on elucidating the biological mechanisms of aspirin and NSAIDs in humans, as well as investigating their beneficial and toxic effects, could potentially pave the way for their future use as neoadjuvants.

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