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Aspirin in the Prevention of Colorectal Cancer: Efficacy and Mechanisms

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Abstract. Colorectal cancer is one of the most common cancers worldwide, and in China, both its incidence and mortality remain relatively high. Although screening and treatment strategies have continued to improve, a high rate of late-stage diagnosis, along with postoperative recurrence and metastasis, still significantly affects patient outcomes. Therefore, exploring effective, safe, and broadly applicable chemopreventive strategies is of great clinical importance. This review summarized the existing evidence supporting the role of aspirin in the primary prevention of colorectal cancer and in the control of postoperative recurrence, and to outline its potential molecular mechanisms and the characteristics of populations most likely to benefit, thereby providing a reference for clinical decision-making and future research. The epidemiological studies indicates that long-term, low-dose aspirin use can reduce the risk of colorectal cancer in both the general population and genetically high-risk individuals, with some studies also showing a trend toward reduced mortality. Postoperative studies have further shown that aspirin can reduce recurrence rates, prolong disease-free survival, and may also improve tolerance to chemotherapy. Mechanistically, aspirin irreversibly inhibits COX-1 and COX-2, leading to reduced production of the pro-tumorigenic prostaglandin PGE2, thereby suppressing tumor cell proliferation, invasion, and immune evasion. Although long-term use of aspirin carries potential risks such as gastrointestinal bleeding, careful selection of appropriate populations and the implementation of standardized dosing regimens may allow it to serve as an important adjunct for chemoprevention of colorectal cancer. Further large-scale prospective studies are still needed to determine the optimal dose, treatment duration, and target populations most likely to benefit.

Keywords: colorectal cancer, aspirin, COX-2 pathway

1. Introduction

Colorectal cancer (CRC) is at the moment among the largest cancer types globally. The most recent data on cancer incidence published by the National Cancer Center of China indicates that colorectal cancer is the second most commonly identified malignancy in the country with almost 520,000 new cases. The deaths caused by colorectal cancer in the same year stood at 240,000 and this is the fourth most common death due cancer, making it easy to deduce that traditional method of cancer

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treatment that uses radiotherapy and chemotherapy is not always optimal [1]. Such a high mortality rate indicates that conventional cancer treatments, such as radiotherapy and chemotherapy, are often suboptimal. Many patients are already diagnosed at intermediate or advanced stages, making postoperative recurrence and distant metastasis almost inevitable.Although radiotherapy and chemotherapy can prolong patient survival, resistance is common, and these treatments are often accompanied by significant adverse effects, such as gastrointestinal toxicity and myelosuppression, which severely impact quality of life. Given the high incidence of colorectal cancer, preventive strategies are therefore crucial, and aspirin has shown certain efficacy in the prevention of this disease.Multiple large cohort studies and randomized controlled trials have shown that long-term, low-dose aspirin use can reduce the incidence of colorectal cancer by approximately 20%–40%, with some studies even reporting a reduction in mortality of 18%–30% [2-6].

Aspirin or acetylsalicylic acid (Aspirin) is a nonsteroidal anti-inflammatory drug (nonsteroidal anti-inflammatory drug or NSAID) that is widely used in terms of pain and fever treatment. As there is growing evidence, it also helps in prevention of colorectal cancer by delaying the growth of tumor cells through several signaling pathways. There are studies that suggest aspirin can be particularly effective with patients having PIK3CA gene mutations and the potential of targeted preventive measure. Colorectal cancer is a slow-growing cancer that usually takes 10-15 years before polyps become adenoma which develops into adenocarcinoma thus creating a period of early intervention [7]. Since aspirin has been shown to act on inflammation, platelet activity, and some of the most important pathways of cancer-related signaling, researchers have suggested it could be used to prevent the development of polyp formation and tumors (advertisements) to the cancerous stage. The potential of its prevention is promising but the mechanisms are still not completely summarized. The purpose of the present review, then, will be to find out how aspirin cancer prevents colorectal cancer, and the biological processes that underlie it, which may assist in reducing the rates of the disease and enhance the health of the general population.

2. The preventive effect of aspirin on colorectal cancer

2.1. The preventive effect of aspirin on the onset of colorectal cancer

Those whose genes can lead to hereditary colorectal cancer are regarded as high-risk incidences and 5%-6% will ultimately develop the cancer. In a study by Jone that used 861 respondents, the subjects were randomly selected into aspirin group and placebo group. Incidences of colorectal cancer were found to be 4.2% (18/427) in the aspirin group against 6.9% (30/434) in placebo group in a period of more than four years which indicated a significant reduction in the risk. Notably, the effect was more pronounced among individuals who used aspirin over two years (HR = 0.41) [3]. This is primarily associated with the fact that aspirin has the capacity to suppress cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). DNA mismatch repair defects make the gut of patients with hereditary colorectal cancer, including Lynch syndrome, to be in a persistent, low-level, inflammatory state. The continuous presence of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a causes COX-2 to be overexpressed, leading to production of more PGE 2. The principal pro-tumor lipid mediator, PGE2, stimulates several cancer-promoting pathways through EP2/EP4 receptor that promote the proliferation of intestinal stem cells, inhibit apoptosis and enhance the formation of adenoma. It further compromises the repair of DNA and amplifies oxidative stress exposing one to mutations. Aspirin decreases the PGE2 level by an irreversible inactivation of COX, and reduces the development of a pro-tumor environment. Its antiplatelet action can further decrease the signal of inflammation and proliferation and the protective effect can be quite strong in the case

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of high-risk groups. The protective effect of aspirin is also temporal and has been noted to be found in the general population. Peter studied approximately 14,000 participants in 20 years and discovered that long-term use of aspirin (long-term) reduced incidences and mortality of colorectal cancer significantly over controls. The risk of proximal colorectal cancer was as much as 70% reduced in participants who used aspirin, over a period of over five years [4]. According to the recent studies, it has also been found that aspirin may affect the most important signaling pathways, including Wnt/ β-catenin, PI3K/AKT, and Hippo/ YAP, which further decreases the appearance of early adenomas. It seems as though these mechanisms act more synergistically with long-term administration, which can be used to explain their tendency to give better protection when aspirin is taken over five years. In general, these are large-scale, long-term studies that offer some convincing evidence on the use of aspirin as a primary preventive agent against colorectal cancer.

Aspirin in its side effects and risks are to be taken seriously, although it exhibits evidence of having antitumor effects in some patients. Aspirin can also cause gastrointestinal mucosa injury, gastrointestinal bleeding, long-term/high-dose use, which is dose-dependent (high rather than low-dose groups show slightly higher risk, but significantly different to control groups). Clinical findings include melena, hematemesis, and intracranial hemorrhage and mucocutaneous hemorrhage (e.g., bruising, gum bleeding) but overall cases of severe bleeding happen rather uncommonly. The side effects of aspirin are time-varying as well, bleeding risk is comparatively more significant during the initial 5 years of administering the drug, yet gradually declines after that, whereas the ability of aspirin to prevent colorectal cancer will be more evident after a long-term use. Thus, clinical practice should rely on a holistic evaluation of genetic mutation status of a patient, risk factors of cardiovascular as well as bleeding risks and postoperative treatment plan to decide on using aspirin.

2.2. The preventive effect of aspirin on the recurrence of colorectal cancer

AAspirin being a nonsteroidal anti-inflammatory drug does not specifically target tumor cells to die. Nevertheless, more research studies have indicated that aspirin is capable of reducing relapse of colorectal cancer. As to a case study carried out in the Baoan people hospital in Shenzhen, patients that continued taking aspirin at the end of colorectal cancer surgical procedures had a recurrence rate of only 7.7 percent (4/52) compared against the 23.1 percent(12/52) in the patients who did not take the aspirin [5]. These findings give provisional support that aspirin can inhibit microscopic lesfus postoperative, and in the way curb initial recurrence.

This was followed by the research by Lin Xiaoping on a group of elderly patients with postoperative colorectal cancer customers who showed a similar effect of aspirin. The researchers concluded that recurrence was reduced much in the patients on aspirin post-operative treatment (18.33% vs. 36.92, $p = 0.007$), and disease-free survival during 3, 4, and 5 years was longer in patients who received aspirin [6]. These results imply that the positive effect of aspirin does not serve the population in general but could also apply to the older population. This effect can be linked with the generally hyperactive inflammatory microenvironment of old age. Complex processes are involved in age-related inflammation, such as the changes of bone marrow derived- cells, and especially the prostaglandin E2 (PGE2) is rather significant. The homeostatic conditions increase PGE2, a significant pro-inflammatory mediator, which further increases in the occurrence of tissue injury and repair, which may contribute to tumor formation; aspirin seems to prevent this phenomenon. Nevertheless, it might be possible that the preventative effect of aspirin will be less effective when it is used with late-onset inflammatory load [6].

An example report of Zhengzhou People hospital showed the preventive effect of aspirin on recurrence. Daily low-dose aspirin was given to patients (with oxaliplatin-based chemotherapy) and

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three years later, the survival rate was found to be 92% (n = 50) as opposed to 70% (n = 50) in the control group (no aspirin). In addition, the level of adverse reactions was considerably reduced in the group using aspirin (42 vs. 64, $p < 0.05$) [8]. These and other results not only support the future development of aspirin as a postoperative maintenance therapy but also imply that aspirin could be effective during chemotherapy by adjusting the condition of inflammation, increasing the level of patient tolerance, or regulating the microenvironment of the immune system and other serious complications were not detected during the follow-up period, including upper gastrointestinal bleeding, heart failure, and stones in the urinary tract. However, there are still some risks associated with the long-term usage of aspirin as they include gastrointestinal bleeding, peptic ulcers, anemia, and, though the risk is low, severe intracranial bleeding. Thus, aspirin therapy in the postoperative period requires a thorough evaluation of the patient concerning their age, comorbid manifestations, the risk of bleeding and concomitant drugs.

3. Mechanisms of aspirin in colorectal cancer prevention and postoperative recurrence

3.1. Prevention of colorectal cancer

The antitumor effect of aspirin has been widely regarded to focus on dual control of the COX-2-associated signaling events and platelet activity in the prevention of colorectal cancer. Mutations in DNA mismatch repair genes in patients with hereditary colorectal cancer, including Lynch syndrome, predispose intestinal epithelial cells to progressive damage to their DNA and mutation accretion leading to a long-term inflammatory condition of low grade. This is coupled with perpetual upregulation of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-a that directly cause inappropriate overexpression of COX-2 [9]. COX-2, which is expressed in vascular endothelium, brain, kidney, and other tissues, catalyzes the conversion of arachidonic acid to prostaglandin E2 (PGE2). PGE2 is considered an important pro-tumorigenic lipid signaling molecule in the tumor microenvironment. It stimulates several downstream oncogenic pathways EP2/EP4 receptors, including MAPK, PI3K/AKT, ERK, and cAMP/PKA, resulting in the inhibition of apoptosis, the inhibition of excessive proliferation of intestinal stem cells and an accelerated progression to adenoma, and the production of prostaglandin E2 (PGE2), a mediator of excessive proliferation action [9]. PGE2 also disrupts DNA repair and exacerbates oxidative stress, which adds to the accumulation of mutations and increases the risk of the development of cancer [10]. Aspirin reduces the number of PGE2 promotes COX-2/PGE2-based pro-tumor signaling, which reduces the provider inflammatory environment, especially in the high-roof sectors as patients with hereditary colorectal cancer. Although it is also yet unknown whether aspirin directly suppresses the expression of COX-2 in epithelial cells of the intestinal tract, the antiplatelet action exerts a significant indirect regulatory effect. Aspirin inhibits platelet activation and, therefore, the release of platelet-derived factors such as PDGF, TGF-b, and VEGF, which decreases the development of the tumor-promoting microenvironment and, eventually, tumor cell proliferation, survival, and local inflammation [11].

Aspirin is also the drug that irreversibly inhibits cox-1 that is very sensitive to the drug. COX -1 plays a role in the synthesis of thromboxane A2 (TXA2), which is one of the critical agents of platelet aggregation. Platelet aggregation can be used by tumor cells as a defense against immune clearance and this process is referred to as tumor cell-induced platelet aggregation (TCIPA). It is a mechanism which enables circulating tumor cells to avoid being checked by the immune system, spend more time in the blood flow, and locate to other locations. Aspirin may disrupt this process by inhibiting platelet activity and permanently inactivating COX-1, which decreases the dissemination of tumor cells [11]. Also, PTGS-2 may be inhibited directly by aspirin, which reduces downstreams

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prostaglandins, including PGE2. Because PGE2 is a key driver of inflammatory signals, cell proliferation, and tumor growth, lowering its concentrations can have an impact on essential oncogenic pathways such as Wnt, cAMP-PKA, and 2-catenin, and infertilize tumor development [6]. It is also mentioned in the recent literature that there are additional molecular mechanisms that might also cause the effect of aspirin as an anticancer agent [9].

Other major promoters of colorectal tumorigenesis are the PI3K pathway. Approximately 1215 per cent of patients are carriers of PIK3CA mutations that cause persistent AKT / PKB signaling. This sustained activation stimulates proliferative signaling, suppresses apoptosis, stimulates epithelial-mesenchymal transition, and primed cell migration, which all lead normal intestinal epithelial cells to a tumor phenotype [12].

Laboratory research suggests that aspirin has the ability of suppressing COX-2 transcription, decreasing PGE2, a possible upstream mediator of PI3K/AKT. Aspirin inhibits PI3K pathway operation, decelerates the progression of cancer cells, revives the apoptotic reaction, and inhibits migration and invasion by dampening PGE2-mediated survive and grow signals [12]. In clinical setting, aspirin is still seen to have a beneficial effect in patients with PIK3CA-mutated colorectal cancer with minimal or no effect in PIK3CA wild-type and COX-2 overexpressing tumor [9]. It confirms the concept of precision prevention and emphasizes on the fact that tumor genetic background is important in deciding on the efficacy of aspirin.

3.2. Prevention of postoperative recurrence

Recurrence of colorectal cancer occurring after surgery does not typically result due to the growth of de novo tumor, but instead the proliferation of remnant microscopic tumor cells in an optimum microclimate of inflammatory and immunosuppressive environment. Recurrence is directly linked with the viability of tumor cells, local inflammation and immune monitoring effectiveness. Not only has aspirin been shown to show potential primary preventive effects on colorectal cancer, it also reduces the recurrence and risk of metastasis in patients undergoing curative resection of the disease in early stages [13]. Extensive in vitro and in vivo research establish that COX-2 activity persists in cancer tissue of the colon rectum and promotes the production of the PGE2. PGE2 does not only promote tumor cell growth, invasion and resistance to apoptosis, but also inhibits the maturation of dendritic cells, invalidates the function of effector T-cells, and attracts immunosuppressive cells, which play a role in immune evasion. In this way, the COX-2/PGE2 is viewed as a major molecular foundation of residual cell survival in operations and ongoing activation is largely related to higher recurrence and susceptibility to metastasis [14]. Aspirin suppresses the expression of aberrant COX-2 and decreases the COX activity, lowering the production of PGE2 [6]. The local activity of the COX-2/PGE2 pathway in tumor tissue could also be a useful biomarker to predict the anti-recidivism effect of aspirin.

Recent studies also indicate that the anti-recurrence effect of aspirin may also be associated with tumor immune microenvironment modulation. A retrospective study has observed that only patients with low CD274 expression had their survival extended significantly by aspirin, regardless of the presence or absence of microsatellite loss, PIK3CA mutation, or COX-2 expression [9]. Aspirin can help partially restore the antitumor immune monitoring during the postoperative period by inhibiting the effect of COX-2/PGE2 on immunosuppressive communication, which helps eliminate remaining tumor cells. Yet, tumors may use immune checkpoint pathways as an evolutionary reaction, and restore antitumor immunosuppressive microenvironment which can partially reverse antitumor effects of aspirin. This gives a reason as to why there are inter-individual differences in the efficacy

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of aspirin, and it can be proposed that aspirin could be a combination therapy in use with immunotherapy in post-operative setting.

Beyond COX-dependent mechanisms, aspirin influences residual tumor cell survival through multiple COX-independent pathways. It inhibits NF-κB signaling, downregulates anti-apoptotic proteins such as Bcl-2, and interferes with Wnt/β-catenin and other pathways related to cell self-renewal and survival, increasing tumor cell sensitivity to apoptosis. NF-κB regulates numerous molecules involved in immunity, inflammation, and apoptosis. Both in vitro and in vivo studies demonstrate that aspirin and its derivatives (e.g., nitric oxide–aspirin) reduce NF-κB protein levels and inhibit the growth of HT-29 human colorectal cancer cells [11]. According to the recurrence point of view, such inhibition of anti-apoptotic signaling can lead to the decreased survivability of postoperative remnant tumor cells to delay or inhibit recurrence.

4. Conclusion

To conclude, aspirin which is a nonsteroidal anti-inflammatory medication demonstrates great potential in primary and secondary prevention as well as recurrence upon surgery in colorectal cancer. Clinical research shows that frequent and prolonged use of aspirin has great benefits in terms of incidence and mortality rates of colorectal cancer as well as in terms of delaying recurrences in postoperative patients and high-risk groups, and therefore it has the strongest protective effect among the high-risk populations and in patients with chronic use. Its primary action involves; COX-2, tumor-promoting PGE2, and repression of key pathways, PI3K/AKT, that result in tumor cell proliferation and survival [11].

There are however limitations in the current studies. Majority are observational studies, and there is deficiency in the large scale, long-term randomized controlled trials in order to determine causality. Comparison and generalizability are low because of the difference in the dose of aspirin, periods of treatment, and sample populations. Aspirin is associated with risks, such as gastrointestinal bleeding, and the ratio between risks and benefits should be accurately assessed in the long-term perspective. Additionally, individually tailored preventative interventions that are informed by the biomarkers, including PIK3CA mutation status, are still in the preliminary stages of the exploration phase. Altogether, the long-term, low dose, and non-expensive characteristics of aspirin predetermine its high potential as a chemoprevention approach, yet additional, high-quality research is required to determine the most effective dosage, target group, and risk-benefit ratio.

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