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Review Article

Oncology Section

Can Aspirin and Cancer Prevention be Ageless Companions?

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ABSTRACT

Over the past few decades, the rate of cancer diagnosis has increased worldwide due to the increase in population and average life expectancy, and also, due to the advances in diagnostic medical technology that facilitate early cancer detection and recognition. Nonetheless, the treatment options have not been developed proportional to this increase, with a huge number of patients frequently being diagnosed with different types of fatal cancer. This has prompted different health organizations to search for novel strategies to prevent cancer, or even halt its progression. Having failed to provide optimum vascular protection benefits, especially with the introduction of relatively superior antiplatelets, such as adenosine diphosphate (ADP) receptor inhibitors; clopidogrel and ticagrelor, regular aspirin use was proposed to reduce the risk of common cancers like colorectal cancer, gastric cancer, breast cancer, lung cancer, prostate cancer and haematological malignancies, as suggested by epidemiological studies. However, it is difficult to draw any firm conclusions on such weak data, as this could raise false hopes among patients and physicians and could potentially mislead scientific research. Clearly, current evidence highlights a gap in medical research and emphasizes the need to carry out interventional studies in high risk for cancer patients using specific aspirin doses in order to validate the data. This should also shed some light on the risk-benefit profile in view of the potential for bleeding complications, especially with the higher doses.

Keywords: Aspirin, Cancer, NSAID

INTRODUCTION

According to the World Health Organization (WHO), the rate of cancer has been increasing worldwide due to the increase in population and average life expectancy. This has prompted health organizations to search for effective and inexpensive strategies to prevent cancer. Over the past two decades epidemiological studies suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may provide some promise for the prevention of several cancers. Accumulating evidence supports an effect of aspirin in reducing overall cancer incidence and mortality in the general population. Aspirin is considered a cheap, widely accessible and easily administered drug. It is widely used as a preventive measure against vascular occlusive diseases, yet with no sufficient evidence to support its use [1]. The anti-cancer effects of aspirin were first identified in animal models four decades ago. Although, there is a growing body of evidence to indicate that aspirin causes a reduction in the incidence of cancer and its associated mortality, a clear role of the drug has not yet been established in human [2]. The results from observational studies remain controversial as NSAIDs are the most frequently used over-the-counter medicines. Another confounding factor was the lack of data on total number of agents. In the case of aspirin use, there is inconsistency in its dose, duration and frequency. Inference from most studies favors that high dose and long-term use of aspirin may reduce the risk of common cancers like colorectal cancer, gastric cancer, breast cancer, lung cancer and prostate cancer [3]. Evidence is most compelling for the potential benefit in the primary prevention. However, it is still unclear whether aspirin can reduce the recurrence of cancers (i.e. secondary prevention). Current evidence highlights a gap in medical research and emphasizes the need to carry out intervention studies using specific aspirin doses in order to validate the data, as currently, there are no direct comparisons between doses. The design of these studies remains an ethical challenge, as the randomization of aging participants to the non-aspirin arm may increase their risk for vascular events [4]. Moreover, whether long-term use of aspirin in higher doses will be associated with worse risk-benefit profile given the potential bleeding adverse effects, is unknown.

MECHANISM OF ACTION OF ASPIRIN

Rothwell and colleagues concluded that long-term daily aspirin lowers mortality from several common cancers in eight randomized trials originally looking at its effects on vascular diseases [5]. However, the mechanisms underlying this beneficial effect are not clearly understood. Aspirin irreversibly inactivates cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, as opposed to the mechanism of action of the rest of NSAIDs, which is a reversible inhibition. COX-2 enzyme synthesizes prostaglandin E2 (PGE2), which inhibits apoptosis and stimulates tumor angiogenesis, proliferation and migration. Moreover, many of the downstream mediators of this pathway are thought to be involved in the development and spread of cancer [6]. Furthermore, it has been suggested recently that inhibition of COX-2 is mediated by downregulation of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PI3KCA), which results in inhibition of apoptosis [7]. Aspirin has also an additional advantage of inhibiting tumour cell induced platelets aggregation, which is thought to contribute to the haematogenous metastasis of cancers in experimental models [8].

Role of Aspirin in Colorectal Cancer

It is known for a long time that aspirin, as well as other NSAIDs, has a protective effect against colorectal cancer and adenoma recurrence through unknown exact mechanisms. Din and colleagues suggested that the aspirin effect on regulators of signalling pathways, which regulate cancer cell proliferation, might contribute to its protective effects against the development of colorectal cancer [9]. Two recent meta-analyses of observational studies reported a big reduction of the risk of colorectal cancer with long-term (>5 y), low-dose (75-325 mg per day) and regular aspirin use [10,11]. In diabetes, high frequency and long-term aspirin use was suggested to reduce the risk of colorectal cancer in a large cohort of patients [12]. CAPP2 study also suggested that daily aspirin use in people with Lynch syndrome reduces the incidence of colorectal cancer [13]. Moreover, it was suggested that aspirin use after a diagnosis of colorectal cancer may reduce both all-cause and colorectal cancer-specific mortality rates [14,15]. In a recent molecular epidemiologic study in

patients with a diagnosis of colorectal cancer, regular use of aspirin resulted in longer survival only in patients with mutated-PIK3CA and not in patients with wild-PIK3CA (i.e. don't have the PIK3CA gene) [7]. This significant finding has opened doors for adjuvant colorectal studies with aspirin using mutated-PIK3CA as a biomarker.

Another exciting area with emerging evidence is the B-Raf proto-oncogene, serine/threonine kinase (BRAF) pathways. It is known that in about 10% to 15% of colon cancers, there is a BRAF gene mutation. A recent study found that individuals who take aspirin have a lower risk of developing colon cancer that was BRAF wild-type (i.e. don't have the BRAF gene mutation) [16]. However, on the other hand, aspirin didn't seem to have a significant effect on cancers that had a BRAF gene mutation. In a recent randomised trial, it was suggested that low-dose aspirin may reduce colorectal tumour recurrence in a cohort of Asian population [17].

The current evidence highlights the fact that the aspirin doses needed to prevent colorectal cancer are substantially higher than those needed for cardiovascular disease prophylaxis. Therefore, an associated higher gastrointestinal bleeding risk should be taken into consideration before justifying aspirin use in the prevention of colorectal cancer.

Role of Aspirin in Gastric Cancer

Unlike colorectal cancer, the current evidence for the role of aspirin in reducing the risk of gastric cancer is scant. Aspirin ingestion has always been associated with gastrointestinal bleeding due to the occurrence of erosions and ulcerations. However, there have been few studies suggesting that it may reduce the risk of gastric cancer. Two recent meta-analyses found that regular use of aspirin may be associated with reduced risk of gastric cancer, especially among Caucasians [18,19]. There is also another suggestion that even after the diagnosis of gastric cancer, aspirin use may have favorable effects in reducing the progression of the tumour [20]. Several mechanisms of action were described in the literature, but the main mechanism suggested was that aspirin induces apoptosis and inhibits the growth of gastric cancer cells.

Role of Aspirin in Breast Cancer

Breast cancer is one of the most common cancers in the UK accounting for a high mortality every year. The number of cases worldwide has significantly increased over the past few decades. A recent meta-analysis of studies in vitro concluded that regular use of aspirin may be associated with a reduction of the risk of breast cancer [21]. A cohort study showed that aspirin use after the diagnosis of breast cancer may reduce both all-cause and breast cancer-specific mortality [22]. One large study showed some positive effects on breast cancer incidence among patients of African-American origin [23]. Witton and colleagues found a significant association between COX-2 expression and poor outcome in estrogen receptor negative breast cancer highlighting the benefit from aspirin use in those patients [24]. Fewer studies hypothesized that aspirin, by inhibiting COX-2, may prevent breast cancer metastasis to the brain and can potentially increase the efficacy of anticancer agents [25,26]. Another mechanism was thought to be mediated through interference with estrogen synthesis via reduction in inflammation, which is increased in the adipose tissues of the breast. A recent randomized trial showed that a single daily administration of 325 mg of aspirin for six months had no effect on serum estrogens or sex hormone binding globulin in postmenopausal women, suggesting that aspirin may influence breast cancer risk through pathways other than estrogens [27].

Role of Aspirin in Lung Cancer

Lung cancer is the most common cancer worldwide and the second most common cancer diagnosed in the UK after breast cancer. Also, it is considered the most common cause of cancer death in the UK. Although there is evidence that aspirin and NSAIDs have anti-carcinogenic properties, their effect on lung cancer remains unclear. Results from observational studies showed inconsistent results. A recent meta-analysis suggested that aspirin use in men may provide some protection for lung cancer, especially among smokers [28]. In contrast, another meta-analysis reported no association between aspirin use and lung cancer risk [29]. Additional high quality studies are needed to verify the effect if it exists at all. Also, these studies should ideally provide data on dose, duration and relation to sex and smoking status.

Role of Aspirin in Prostate Cancer

Prostate cancer is the most common cancer in men in the UK and the second most common cause of cancer death after lung cancer. The results from epidemiological studies that evaluated the role of aspirin in prostate cancer have been limited and inconsistent. However, many studies reported that aspirin may reduce the risk of prostate cancer. The mechanism of this effect is still unclear. A recent meta-analysis of epidemiological studies showed that long-time regular aspirin use may reduce the risk of overall and advanced prostate cancer [30]. Kashiwagi and colleagues proposed that aspirin down-regulates androgen receptors and prostate specific antigen (PSA) in prostate cancer cells [31]. No sufficient data exists about whether aspirin influences the progression or survival after prostate cancer diagnosis. Recently, Dhillon and colleagues found no association between aspirin use and progressive disease in a cohort of prostate cancer survivors [32].

Role of Aspirin in Haematological Malignancies

Haematological malignancies are cancers that affect bone marrow, blood and lymph nodes. Few observational studies evaluated the association between aspirin and the risk of leukaemias [33,34]. Results showed that long-term and regular aspirin use may be associated with a modest decrease in the risk and recurrence of acute leukaemias. In chronic leukaemias, no sufficient evidence exists to evaluate the association between aspirin and risk assessment. However, Bellosillo and colleagues found that aspirin induced apoptosis in B-cell chronic lymphocytic leukaemia cells in vitro [35]. Several epidemiological studies looked at the potential association between aspirin use and lymphoid malignancies. However, the data from these studies are controversial. Chang and colleagues reported a significant lower risk of Hodgkin's lymphoma associated with regular aspirin use [36]. As regard to non-Hodgkin's lymphoma (NHL), Holly and colleagues found that aspirin use was associated with a decreased risk [37]. In contrast, Kato and colleagues found an increased risk associated with long-term use of aspirin in NHL [38]. As for multiple myeloma (MM), Moysich and colleagues reported no chemoprotective effect of aspirin on MM risk [39].

CONCLUSION

A huge number of patients are diagnosed with different types of cancer in the UK and worldwide with around seven million deaths every year. Several strategies have been promoted and developed for effective screening and prevention of cancer. Epidemiological studies suggested that regular aspirin use may be associated with reduced risk of some types of cancers. However, the data are inconsistent. Indeed, no definitive recommendations can be made at present due to the lack of high quality data. Further research is needed to validate the data. In conclusion, aspirin may be a promising chemopreventive agent and it deserves further exploration with interventional studies, yet the bleeding adverse effects profile should be taken into consideration especially with higher doses. In the meanwhile, aspirin use may be justified only in patients with cardiovascular disease.

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