Perceived Benefits and Risk of NSAIDs in Relation to Its Association with Cancer: A Comprehensive Review

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Authors’ contributions

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat fever and pain. Apart from its medicinal benefits, it is also well known for its numerous side effects, including myocardial infarction, gastrointestinal haemorrhage, renal failure, etc. Even beside these side effects NSAIDs are believed to play a major role in cancer. Though there are contrary of being inducing or preventive reason for cancer. Many studies shows NSAIDs are associated with the increasing risk of cancer. While as in various studies these drugs also have been investigated for their anti-cancer property as chronic inflammation has direct association with carcinogenesis. This review enlights the role of NSAIDs in cancer promotion and cancer prevention, connection between chronic inflammation and cancer, and some of the potentially lethal side effects of these drugs.

Keywords: NSAID; cancer; COX-2 inhibitors; chronic inflammation-associated cancer.
1. INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDs) are the commonly used medicine in the management/treatment of fever, pain, and inflammation condition. It is estimated that approximately 30 million people all around the world consume NSAIDs per day [1]. These drugs inhibit prostaglandin synthesis by blocking cyclooxygenase (COX) enzyme [2]. There are various reports revealed that NSAIDs are associated with decreased in a different type of cancer risk like prostate cancer [3,4], head and neck cancer [5], breast cancer [3,5], ovarian cancer [6] and colorectal cancer [7]. However, due to inconsistent and contradicting findings, the role of NSAIDs has still remained unclear. While according to some studies there is no relation between NSAIDs and cancer. For example, a study conducted on 20,000 women aged between 58–76 years was shown non-aspirin NSAIDs was not associated with neither ovarian nor uterine cancer risk [8]. Role of NSAIDs to prevent the formation of a spontaneous tumor are also investigated and linked with anti-inflammatory action. Therefore, a key point is to find the link of NSAIDs in the prevention of cancer and to investigate the role of anti-inflammatory effect in such effect [9]. At some point, it is logical to believe that NSAIDs can be used for the treatment or prevention of cancer as it acts against inflammation which is one of the main difficulty in cancer [10].

However, the relationship between NSAIDs and cancer is unclear as there is no solid proof to establish the mechanism observed by the different researchers. Few researchers also found that there was an increase in the rate of mortality in patient with certain types of cancer who used NSAIDs [11]. Also, the use of NSAIDs for a long period causes different side effects like renal, gastrointestinal or various cardiovascular complications [11]. There are conflicting findings on the association between NSAIDs and cancer. In this review, we have pointed towards the relationship between cancer and the use of NSAIDs in general and in a cancer patient in light of various scientific investigations. This review discusses in details about a various side effect, cancer-protective and cancer-promoting effects of NSAIDs.

2. INFLAMMATION INVOLVED WITH CANCER

It is very important to examine the role of NSAIDs in cancer and to find the link between carcinogenesis and chronic inflammation. The relationship was first hypothesized by R Virchow in 1863. It was observed that the main origin of cancer were the sites of chronic inflammation and tissue injury caused due to some irritants encouraged cell proliferation [12]. Till date, such observation is backed by many other epidemiologic and experimental studies. Many signalling pathways and molecular targets in cell proliferation, apoptosis, and angiogenesis are found similar in both carcinogenesis and inflammation [13–15]. Dysfunction of these signalling pathways in chronic inflammation leads to pro-inflammatory genes expression which can play a major role in malignant transformation [16].

Some cytokines involve in malignant development whether some other shows antitumor effecs. For example, IFN-α for the adjuvant therapy of Stage III melanoma and bolus IL-2 for renal cell carcinoma and metastatic melanoma have approved by FDA to use against tumors. The link between chronic inflammation and cancer can justify by the fact that some cancer expresses chemokines and cytokines, which are important in cell angiogenesis, proliferation, metastasis and cell migration [17]. Besides cytokines, other pro-inflammatory molecules like reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) are additionally downregulated in chronic inflammation [18]. It is now generally conventional that chronic inflammation is engaged in carcinogenesis. The fundamental aetiology for most cancers development can be infectious or sometime non-infectious nature.

2.1 NSAIDs in Cancer

Some of the well-known NSAIDs such as aspirin, ibuprofen, diclofenac, mefenamic acid and celecoxib etc have a common mechanism, i.e., they block prostaglandin endoperoxide H synthase (PGHS) or cyclooxygenase (COX) enzyme even they are very different by their chemical structure. However, the interrelationships between prostaglandin
synthesis, COX and inflammation define the role of NSAIDs drugs in cancer in the best way [17].

2.2 COX, Prostaglandin Synthesis, and Inflammation

Synthesis of prostaglandins (PGs) which are derived from the arachidonic acid pathway takes place due to COX Enzyme. These prostaglandins belong to eicosanoids which is a group of 20-carbon lipid compounds. They are easily available in the body consisting of various function and as known mediators of inflammation. The enzymatic action of phospholipase A2 (PLA$_2$) occurs on membrane phospholipids that begin the synthesis of prostaglandin which lead to the production of arachidonic acid (AA). These arachidonic acids then metabolised to prostaglandins by COX. PGE$_2$ augments increases microvascular permeability and also vasodilation during inflammation due to which classical signs of swelling and redness are occurring. It also increases pain by the act on neurons of the sensory nervous system during inflammation [19].

On the other hand, PGI$_2$ is a potent vasodilator which acts as an inhibitor of platelet aggregation [20]. It is involved in the regulation of cardiovascular homeostasis and it produced from endothelial, vascular, and smooth muscle cells. PGD$_2$ is the major synthesized eicosanoid in peripheral tissues and the central nervous system that play a similar role in both homeostasis and inflammation [21]. The research states that predominant prostanoid PGD$_2$ is produced by mast cell activation and which then initiates type I acute allergic responses which mediated by Immunoglobulin E (IGE) [22]. Another prostaglandin PGF2$_\alpha$ derived in the female reproductive system and plays important role in uterine contraction, ovulation, and parturition initiation. PGF2$_\alpha$ has been found at sites of inflammation like in collected synovial fluid from patients of psoriatic arthritis, rheumatoid arthritis, reactive arthritis and osteoarthritis [23]. However, it is important to mention that in the inflammatory process, platelets also act effectively as a result of COX’S effects on prostaglandin synthesis. Although in literature it was mentioned that platelets were the key player in haemostasis primarily, TXA$_2$, a substance derived from activated platelets, shows inflammation and also linked with the modulation of acquired immunity, allergic reactions, cancer cell metastasis and angiogenesis [24]. Increase in a tumor cell, tumor cell arrest and extravasation, production of lipid products are influenced by the effect of platelets‘ on tumorigenesis.

![Biosynthesis pathway of inflammatory mediators](image-url)

**Fig. 1. Biosynthesis pathway of inflammatory mediators**
3. NSAID ASSOCIATED WITH CANCER ELIMINATION

The basic mechanisms of the anticancer effects of NSAIDs were described either using animal models or cell lines. Various non-aspirin NSAIDs like loxoprofen [25] and celecoxib [26] have found to show their cancer-protective mechanism. For example, an experiment using a rat mammary model in an in vivo study, celecoxib displays a 90% tumor retreat and 25% depletion in the number of palpable tumors [27]. In an experiment, it is found that aspirin have synergic anticancer effects on HepG2 human hepatocellular carcinoma when it integrated with doxorubicin both in in vitro and in vivo. In that study, a high-level synergism was perceived in growth inhibition, cell-cycle arrest and apoptosis when both drugs were used in reciprocally (in vitro study), whereas a synergic antitumor effect was seen in nude mice with a HepG2 cell xenograft [27]. Interestingly it is found anticancer effects of NSAIDs are often independent of COX inhibition. An experiment disclosed in malignant melanomas, COX-2-independent NSAID-induced apoptosis [28].

Many epidemiologic studies reported the cancer protective effects of both nonaspirin NSAIDs and aspirin. Many of these studies have been carried out on targeting gastrointestinal tract cancers. A study investigated the relationship between digestive cancers other than colorectal cancer and use of NSAIDs (which included both aspirin and nonaspirin NSAIDs). It was reported that the risk for gastric cancer was decreased in regular NSAIDs consumer (OR 0.3; 95% CI: 0.1–0.6) [29].

In another study with 102,800 controls and 10,280 cases, the relationship between the use of aspirin and NSAIDs and colorectal cancer risk was investigated. A 27% less in colorectal cancer risk was found in case of using low-dose aspirin (OR = 0.73; 95% CI: 0.54 to 0.99). In case of nonaspirin NSAID consumers, a substantial depletion rate in risk was found especially for those who took agents with high COX-2 selectivity for a long term, high-intensity basis (OR = 0.57; 95% CI: 0.44 to 0.74) [7].

A study called sister study which investigated women with a sister who diagnosed with breast cancer. There was 2118 event of breast cancers from 50,884 women participated in the study. The study concluded that the use of noncoxb NSAIDs and nonaspirin was not related to the lower risk of breast cancer among postmenopausal women involve in the study [30].

Other than the life-threatening cancers arising from breast cancer and gastrointestinal tract, NSAIDs were also involved with a decreased cancer originating risk from the reproductive system in both man and women. In men, NSAIDs were found to be correlated with a depletion in prostate cancer risk in a study that investigated on 819 patients with prostate cancer and 879 controls. In the same study, use of aspirin was negatively correlated with the risk of prostate cancer (OR = 0.86, 95% CI: 0.65–1.14); however, such relation was not statistically significant (p > 0.05) [4].

3.1 NSAIDs Associated with Cancer Advancement

There are mostly epidemiologic studies that showed the role of NSAIDs in enhancing cancer risk, and the mechanisms underlying the developing risk are less explained. Several reports are available which established a link between the use of NSAIDs and the developing risk of renal cancer. A dose-response relation was found between renal cell carcinoma risk and duration of nonaspirin NSAIDs use. Users with less than 4 years, between 4–10 years, and for users with less than 10 years, the relative risks (RR) were 0.81 (95% CI: 0.59–1.11), 1.36 (95% CI: 0.98–1.89), and 2.92 (95% CI: 1.71–5.01), respectively (P_trend < 0.001) [31].

A meta-analysis of epidemiologic studies concerning analgesic use and kidney cancer risk revealed that there is an increased risk of kidney cancer with the use of acetaminophen (pooled RR, 1.28; 95% CI: 1.15 to 1.44) and nonaspirin NSAIDs (pooled RR, 1.25; 95% CI: 1.06 to 1.46). In another study, a meta-analysis of epidemiologic studies about the use of analgesic drug and the risk of kidney cancer reported a developing risk of kidney cancer with the use of nonaspirin NSAIDs (pooled RR, 1.25; 95% CI: 1.06 to 1.46) and acetaminophen (pooled RR, 1.28; 95% CI: 1.15 to 1.44). Overall, who used aspirin (pooled RR, 1.10; 95% CI: 0.96 to 1.28) was no risk found [11]. Although various previous studies reported, the use of NSAIDs decreases the endometrial cancer-causing risk [32,33]. Still, the link between endometrial cancer an NSAIDs remains unclear as there is no clear report or incomplete report on such association.
In the case of breast cancer, several studies have reported an inverse relationship between the risk of cancer and the use of NSAID [3,5]. It is important to report that such a connection depends only on the type of molecular subtype of breast cancer. A population-based case-control study held in Western New York (n = 1170) reported that an increased risk of HER2− (OR = 1.27, 95% CI: 1.05–1.53), ER+/PR+ (OR = 1.33, 95% CI: 1.09–1.62), and p53− breast cancers (OR = 1.28, 95% CI: 1.04–1.57) was connected with the use of ibuprofen [34]. Lastly, it is important to mention that NSAIDs and aspirin are effective painkillers and both drugs have properties to reduce prostate-specific antigen (PSA) levels [35]. This may refer to masking of various symptoms and a delay in the diagnosis process. Hence, various studies that reported a reduced risk in cancer, need to be evaluated carefully.

Apart from cancer, NSAIDs are also associated with various other noncancerous but major life-threatening side effects [36] like NSAIDs are generally exert an increased risk of acute myocardial infarction. Recently a study shows use of NSAID such as diclofenac (OR = 1.50; 95% CI: 1.06–2.04), rofecoxib (OR = 1.58; 95% CI: 1.07–2.17), naproxen (OR = 1.53; 95% CI: 1.07–2.33), ibuprofen (OR = 1.48; 95% credibility interval (CI):1.00–2.26) and celecoxib (OR = 1.24; 95% CI: 0.91–1.82) influence myocardial infarction risk [37].

### 3.2 Probable Molecular Mechanism

Propose mechanism associated with NSAID for its anti-tumor activity showed in Fig. 2. In COX independent mechanisms, COX-2 involvement in tumorigenesis and its overexpression in tumor was found beneficial as it responsible for chemopreventive efficacy. On the other side, Induction of claudin-4 and CHOP (a regimen of 4 drugs, which are cyclophosphamide, doxorubicin, vincristine, and prednisone) cause inhibition of invasion which induce apoptosis. These mechanisms are regulated by an increase in the intracellular Ca\(^{2+}\) concentration, the potent activity of NSAIDs to increase the intracellular Ca\(^{2+}\) concentration helps to lead anti-tumor activity. As ER-stress response is regulated by three different ER transmembrane proteins which are site-specific endoribonuclease, protein-kinase, R-like ER kinase and activating transcription factor 6. All have different pathways for induction of claudin-4, CHOP, ER chaperones and S100P and directly associated with potent anti-tumor activity [38].

![Fig. 2. Anti-tumor mechanism of non-steroidal anti-inflammatory drugs](image-url)
However, some pharmacological and clinical studies showed that the use of NSAID is inversely related to causing of some types of cancer. In case of Long-term NSAID users, the mortality rate is lower and it reduces the risk of colorectal cancer by 20% [39,40,41] and lung cancer by 69% [42]. The mechanism for the anticancer activity, related to NSAID belongs to various studies on inhibitory effects on cyclooxygenases are mostly overexpressed in various cancer types [43,44]. These kinds of mechanism observed in cultured HT-29 human colon cancer (colorectal cancer) cells, where apoptosis can be seen after incubation with salicylate, sulindac sulfide, sulindac and other NSAIDs by metalloproteinases and expression of vascular endothelial growth factor [45,46]. However, some studies showed that anti-neoplastic effects of NSAIDs are very difficult to understand by using only cyclooxygenase inhibition pathway [47].

3.3 Other Deadly Side Effects Associated with NSAIDs

A study on NSAID’s cardiovascular safety consisting of 116,429 patients in 31 trials, the cardiovascular risk of lumiracoxib, rofecoxib, etoricoxib, celecoxib, diclofenac, ibuprofen, and naproxen was examined and found highest risk was related with rofecoxib (rate ratio = 2.12, 95% credibility interval (CI): 1.26–3.56), followed by lumiracoxib (rate ratio = 2.00; 95% CI: 0.71–6.21). As for Stroke ibuprofen (rate ratio = 3.36, 95% CI: 1.00–11.6) and for 2nd highest risk diclofenac (rate ratio = 2.86, 95% CI: 1.09–8.36) was found. On the other side, two drugs, diclofenac (rate ratio = 3.98, 95% CI: 1.48–12.7) and etoricoxib (rate ratio = 4.07, 1.23–15.7) were found associated with highest risk of cardiovascular death. Hence, this study reported evidence that conclude amongst all drugs naproxen is the least harmful and investigated all drug were safe for use with respect to the cardiovascular system [48].

Many NSAID complaint about gastrointestinal side effects such as nausea, dyspeptic symptoms and mild discomfort and also some severe complications like bleeding, intestinal obstruction and peptic ulcer perforation (reviewed by Sostres et al.) [49]. In addition to serious gastrointestinal and cardiovascular side effects, NSAIDs are well known for renal side effects, which may cause renal failure in severe cases.

Lastly, as NSAIDs are related with other serious noncancerous side effects such as myocardial infarction, gastrointestinal bleeding and renal failure, the use of NSAIDs in cancer prevention or treatment should be assessed with various caution and there must be a balance between the benefits and side effects to avoid any other harmful or life risking event.

4. CONCLUSIONS

This study shows various aspects of NSAIDs use and the role of NSAIDs in cancer. In terms of the role of these drugs there are various inconsistent and contradicting reports drawn in this study. This study includes both aspirin and nonaspirin NSAIDs to study the risk of cancer involved with these drugs. Some of these studies indicates increasing risk of certain types of cancer with the use of these drugs and other indicates decreasing in risk and also various other studies shows no relation between the risk of cancer and use of these NSAIDs drugs. Whether this non-steroidal anti-inflammatory drug associated with lower or higher risk of cancer, it’s all depend on the type of the cancer it associated with. For example, in case of breast cancer even in the case of same type of cancer, the result of NSAIDs may differ between the various molecular subtypes. The above added studies are some of Experimental as well as Epidemiological In nature that determine the underlying mechanisms involved with cancer-protective effects of NSAID drugs. Therefore, those explained mechanisms are not well explained, especially studies that claimed and reported increase in the risk of cancer are not well appreciated. Generally Epidemiologic studies are not conclusive but suggestive, which indicates there are a lot more study needed to cover this area of research. Lastly, this non-steroidal anti-inflammatory drug are correlated with other life-threatening noncancerous complications such as gastrointestinal bleeding, renal failure and myocardial infarction. As a result, use of these drugs in cancer therapy and in cancer prevention is to be evaluate with a lot of care and warning and there is needed to be a balance between the benefits and the risks as there are still many reports to conclude.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and
producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

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