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Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review

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Abstract

Background: Prostate cancer constitutes fifteen percent of all cancers diagnosed in males, it ranks fifth in terms of cancer-related fatalities; and it contributes to 6.6% of all male mortality.

Aim and objectives: To assess the impact of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, on the incidence and mortality of prostate cancer.

Patients and methods: This systematic review was performed in April 2021 and chose the related study from PubMed, Web of Science databases, Embase with the following keywords: ("prostate cancer" or "prostate tumor"), ("aspirin" or "acetylsalicylic acid") 'anti-inflammatory agents', 'NSAID', and 'NSAID*.

Results: The current study documented that Regular current aspirin use was found to be correlated with a reduced risk of fatal PC in all participants. The correlation between current post-diagnostic use and increased survival after diagnosis is consistent with the possibility that aspirin inhibits the development of PC. The use of aspirin was not correlated with the incidence of prostate cancer. In contrast, the use of aspirin was inversely correlated with mortality from prostate cancer. Consistent among both white and black men, this association appeared to be limited to men who took aspirin every day or for the prevention of cardiovascular disease. The use of NA-NSAIDs did not correlate with these endpoints.

Conclusion: Potential benefits of aspirin use, as long-term use, include a decreased incidence &mortality rate associated with prostate cancer. Advanced prostate cancer exhibited a significantly increased inverse correlation in comparison to total prostate cancer.

Key words: Aspirin, Non-steroidal anti-inflammatory drugs, Incidence Mortality

Introduction

Male prostate cancer is a significant contributor to both morbidity and mortality. Globally, an estimated 1.6 million males had recently been diagnosed with prostate cancer, & the disease caused the deaths of 366,000 males in 2015. Prostate cancer constitutes fifteen percent of all cancers diagnosed in males, ranks fifth in terms of cancer-related fatalities, and causes 6.6% of the overall mortality rate among males **(1).** Age, race, & family history are significant risk factors for the total incidence of prostate cancer **(2).** Furthermore, genetic epidemiology researches have detected over 140 independent genetic risk loci **(3).**

Despite a 25-year raising in the five-year relative survival rate, prostate cancer continues to be the primary cause of cancer-related mortality among older males **(4).**

There is an immediate need for a greater comprehension of the factors that influence the prognosis and progression of prostate cancer.

Utilizing aspirin to combat inflammation is effective, and its potent anti-inflammatory properties may inhibit the growth of tumor cells and the progression of tumors. Preclinical researchers have identified potential antitumor mechanisms of aspirin in prostate cancer (PC) **(5).**

Cyclooxygenase-2 (COX-2), an inducible enzyme, is significantly upregulated in prostate cancer tissue and plays a role in the proliferation of PC cells. Aberrant or great COX-2 expression has been implicated in carcinogenesis and worse prognosis. So, NSAIDs, which inhibit the COX pathway, have thus been hypothesized to offer a potential mechanistic approach for chemoprevention and therapy of PC **(6).**

The aspirin's primary mechanism is inhibition of COX-1/2. COX-1/2 was highly expressed in PC cells. Thus, the growth of tumor cells and distant metastasis were both inhibited by aspirin. Numerous epidemiologic RESERCHES have been conducted to examine the correlation among NSAIDs & the risk of PC However, the research findings presented inconclusive results: while the majority of studies reported no effects, a minority reported statistically significant inverse associations, & a minority found NSAID or non-aspirin NSAID (NA-NSAID) use to be associated with a significantly increased risk of prostate cancer **(7), (8).**

According to Downer et al. consistent aspirin usage was linked to a reduced likelihood of developing lethal PC **(9).** While Assayag et al. found no association between post-diagnostic aspirin use and an increased risk of PC outcomes **(10).**

Conversely, since substantial evidence suggests that aspirin use may reduce the risk of prostate cancer, it is essential and necessary to gain a better understanding of whether such therapy can affect disease outcome. Numerous researches have investigated the relationship among NSAID (aspirin) usage & mortality specific to PC, with conflicting results **(11), (12).**

As a result of the ongoing discussion among researchers, we conducted this exhaustive review to examine the impact of NSAIDs, including aspirin, on the incidence & mortality of PC. A well understanding of the correlation may also highlight the significance of considering additional prevention methods in this area.

Methods

Data sources and searches strategy

In April 2021, a comprehensive literature search was conducted & the relevant research was selected from PubMed, Web of Science databases, Embase with the following keywords: ("prostate cancer" or "prostate tumor"), ("aspirin" or "acetylsalicylic acid") 'anti-inflammatory agents', 'NSAID', and 'NSAID*

Inclusion criteria

Studies were included if studied participants were exposed to any NSAID, including aspirin, NA-NSAIDs, any other single NSAID (not including acetaminophen) or a mixture of NSAIDs or selective COX-2 inhibitors and reference participants had not used these drugs; the study assessed the incidence of PCa or PCa-specific mortality; and the study reported the multivariate-adjusted relative risks (RRs), including study-specific odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs), study design was prospective/retrospective cohort study or randomized controlled trial. No language restrictions were imposed. Additional studies were searched for manually through the reference lists of retrieved articles and using PubMed's related articles option.

Data extraction

For each trial, the study and participant characteristics, sample size, number of cases and controls, geographic region (USA vs others), drug types, exposure period and outcomes were extracted and transferred to specially designed forms.

Results

Table (1): Baseline characteristics of the included studies

Study	Country	Study design	Sample size (intervention / control)	Exposure period	Age
Jacobs et al., (13)	USA	Cohort Study	86,402	1993-2009	65-85 years
Veitonmäki et al., (14)	Finland	Case Control Study	31,866 / 48,278	1996–2009	63–71 years
Downer et al., (9)	USA	Randomized, placebo-controlled trial	12,454 / 9496	1981/82 to 2009	40–84 years
Ma et al., (15)	Sweden	Swedish nationwide population-based cohort study	643,368	2005-2012	≥18 years
Lauren et al., (16)	USA	Prospective cohort study	15,792	1987–2017	45-64 years

Table (2): The main findings of the included studies

Study	Drugs	Outcomes
Jacobs et al., (13)	Aspirin	Compared with no aspirin use, neither pre-diagnosis nor postdiagnosis daily aspirin use were statistically significantly associated with prostate cancer–specific mortality. However, among men diagnosed with high-risk cancers (T3 and/or Gleason score 8), postdiagnosis daily aspirin use was associated with lower PCSM (HR 0.60; 95% CI, 0.37 to 0.97), with no clear difference by dose (low-dose, typically 81 mg per day, HR 0.50; 95% CI, 0.27 to 0.92, higher dose, HR 0.73; 95% CI, 0.40 to 1.34).
Veitonmäki et al., (14)	Aspirin/NSAID	Increased risk of prostate cancer death associated with both pre- and post-diagnostic NSAID usage (HR 1.30, 95%CI 1.07–1.58 and HR 2.09, 95%CI 1.75–2.50, respectively). An increasing risk trend was observed by cumulative dose and intensity of NSAID use. When the last three years were excluded from the analysis, the death risk diminished to a protective level (HR 0.42, 95%CI 0.34–0.51 and HR 0.30 95%CI 0.24–0.39). Aspirin use was not significantly associated with prostate cancer survival.

Downer et al., (9)	Aspirin/ Placebo	Current regular aspirin use was associated with a lower risk of lethal PC among all participants. Current post diagnostic use was associated with improved survival after diagnosis, consistent with a potential inhibitory effect of aspirin on PC progression.
Ma et al., (15)	Aspirin / non-aspirin NSAIDs	The overall SIR suggests that maintenance use of aspirin decreases the risk of prostate cancer, in particular if used ≥5 years. The overall risk was decreased among other NSAIDs users, and again in particular among longer-term users (≥3 years). When statins users were excluded from all aspirin users, there was no remaining association with prostate cancer, only if taken ≥5 years. For non-aspirin NSAIDs users, the protective effect remained after exclusion of statins users . They concluded that their study provides evidence for a protective effect of aspirin and other NSAIDs against prostate cancer, in particular for longer durations of use, yet concomitant use of statins strongly influences the risk among aspirin users.
Hurwitz et al., (16)	Aspirin/NSAID	Aspirin use was not associated with prostate cancer incidence. However, aspirin use was inversely associated with prostate cancer mortality. This association was consistent among white and black men and appeared restricted to men using aspirin daily and/or for cardiovascular disease prevention. NA-NSAID use was not associated with these endpoints.

Discussion

Chronic inflammation contributes to about 20% of all human cancers in adults. For prostate cancer specifically, there is evidence that chronic or recurrent inflammation plays an important role in prostate cancer initiation, development, progression, and metastasis. Biopsies in several carcinogenic and non-carcinogenic prostate diseases show signs of inflammation, including prostatitis, benign prostatic hyperplasia (BPH), prostate cancer "risk lesions" (proliferative inflammatory atrophy (PIA), prostatic intraepithelial neoplasia (PIN)), and prostate cancer **(17).**

Recent original publications and meta-analysis which included 18 case-control and 13 cohort studies tried to assess the association between aspirin and non-aspirin NSAIDs **(18), (19).** Results suggested that aspirin could decrease the risk of prostate cancer, especially after long-term use (≥4 years). In terms of non-aspirin NSAIDs, their meta-analysis found no protective effects against prostate cancer and authors claimed that the results were less consistent and need further investigation. The major problems of observational studies were (1) Insufficient power because of limited sample sizes and follow-up time, in particularly for non-aspirin NSAIDs which are less commonly used than aspirin; (2) different definitions of exposure which often based on e.g., questionnaires, interviews or medical notes, with a high risk of recall bias and incomplete/incorrect information on exposure in particular dose and duration. Statins are also considered promising chemo-preventive agents commonly prescribed in

particular among aspirin users, although there is currently insufficient evidence supporting a protective effect against prostate cancer **(20), (21).**

In 2017, **Downer et al.,** demonstrated that regular use of aspirin reduced the risk of advanced PC (defined as tumor metastases to bones or other organs or death if the cause of death was PC) **(9).** These studies supported the protective influence of aspirin on PC patients and delayed the progression of PC. **Hurwitz et al**., recently discovered that aspirin use was inversely associated with the risk of PCSM **(16)**. However, they found that aspirin did not effectively reduce the incidence of PC. **Assayag et al.,** in 2015 reported post-diagnostic aspirin use was linked to an increased risk of PCSM **(10)**. **Veitonmäki et al.,** observed that the risk of PC death was associated with NSAID (non-steroidal anti-inflammatory drugs) usage regarding whether diagnosis of PC **(22)**. However, according to their report, we discovered that aspirin was not significantly associated with the risk of PCSM. Their results could also give a clinical indication that aspirin might not improve the prognosis of PC patients, but other NSAIDs might affect the growth of PC cells from a mechanism different from aspirin. Other NSAIDs might promote tumor progression and increase the risk of PC death.

Cumulative use of NSAID and medication intensity may increase risk PC death proposed by **Veitonmäki et al., (22). Downer et al.,** suggested there was no association between pro -diagnostic aspirin use and the risk of PCSM for localized PC, but current high doses (> 75 mg) of aspirin could reduce PCSM. From their study, treatment of PC combined with high-dose aspirin may decrease the risk of PCSM. However, it should be pointed out that high doses of aspirin use can cause spontaneous bleeding **(9)**.

Jacobs et al., also thought neither pre-diagnosis nor post-diagnosis daily aspirin use was significantly associated with the risk of PCSM **(13).**

Conclusion

This systemic review concluded that aspirin use, including long-term use, provides potential benefits in the reduction of prostate cancer incidence and mortality. The inverse association was slightly stronger for advanced prostate cancer than for total prostate cancer, but the effect estimates varied by geographic region. Also unclear is the influence of dose and the frequency of aspirin use on PCa incidence and outcomes. Thus, caution needs to be exercised to ensure that the associated prevention benefits of aspirin outweigh the potential side effects.

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