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Review

Aspirin in the Management of Patients with Prostate Cancer Undergoing Radiotherapy: Friend or Foe?

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Abstract. *Aspirin has cyclooxygenase-2 (COX2)-mediated anti-inflammatory and anti-coagulant properties that may confer a positive effect in preventing and limiting the progression of prostate cancer. Prostate cancer has been shown to have poor treatment outcomes due to therapeutic resistance; therefore, COX2 inhibition caused by aspirin could represent an opportunity to augment current therapies. This is particularly of interest to patients undergoing radiation therapy (RT) where inflammation is a common side-effect. This review discusses the evidence for the potential role of aspirin in the management of patients with prostate cancer undergoing RT.*

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related deaths among males (1). It is a significant health concern that may become increasingly prevalent in the coming years due to the gradual aging of the population (1). In spite of increasing survival rates and improved treatment outcomes (2, 3) , there is a need to further boost current therapies.

The association between carcinogenesis, inflammation and the coagulatory system is widely recognised (4, 5). There are substantial experimental data to suggest that the coagulatory system may modulate many multiple cancer pathways such as those controlling tumour proliferation, angiogenesis and metastasis (6).

The role of inflammation in prostate disease is suggested by the presence of inflammatory cells in benign prostatic hyperplasia and PCa (5). The prostate has a fully active immunological response which involves a broad spectrum of intra-epithelial endogenous inflammatory cells such as T-lymphocytes. T-Cells increase with age, which correlates with the incidence of prostate inflammation during the aging process (5, 7). T-Cells are known to release factors that stimulate matrix formation and secretion of potent epithelial and stromal mitogens which could promote prostate stromal and epithelial proliferation/hyperplasia (5).

Although a causative link has not been unequivocally established, evidence suggests that recurrent or persistent inflammation may influence susceptibility to, or initiate or promote carcinogenesis (4). Since increased inflammation can increase coagulation, which in turn can enhance inflammation, not using an anticoagulant such as aspirin to control the clotting process would naturally increase the inflammatory process (4).

Non-steroidal anti-inflammatory drugs, including aspirin, have been available for many years and are widely used throughout the world (8). Aspirin as a treatment for cancer is currently of interest (9, 10). Randomised trials assessing the effect of aspirin on the cardiovascular system and disease have also collected data on cancer incidence. Rothwell *et al*. found that aspirin reduced the risk of a cancer diagnosis with a hazard ratio (HR) of 0.88 (11). It has also been reported that aspirin reduced the risk of cancer with metastasis (12). The long-term effect of aspirin on cancer incidence and mortality has been shown to be beneficial in colorectal cancer (12-14), however, not in PCa specifically. As aspirin is commonly used in the PCa population, its potential effect on treatment outcomes is promising (15).

Subsequent research established cyclooxygenase-2 (COX2) as a candidate protein that might explain the effect of aspirin on cancer (16, 17). COX2 is an inducible form of the enzyme that catalyses the synthesis of prostanoids, including prostaglandin E2, a major mediator of inflammation and angiogenesis (18, 19). COX2 increases the carcinogenic potential of cells through oxidation of pro-carcinogens to carcinogens, increased cell growth, reduced apoptosis, as well as reduced immune response to abnormal

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or cancer cells. Although the mechanism of COX2 action in carcinogenesis or progression is not well established, COX2 inhibitors have been shown to be chemopreventive in cancer, specifically in colorectal cancer (20).

COX2 overexpression was also reported in prostate tumours (21). Its overexpression correlated with a decrease in apoptosis and an increase in angiogenesis (16). Overexpression of COX2 is also suggested to be a significant prognostic factor for patients with PCa (20, 22).

Thus, aspirin and its anti-inflammatory, anti-coagulant properties may confer a positive effect in preventing and limiting the progression of PCa (23).

It is believed that *COX2* is a survival gene (24) since it renders cells more resistant to apoptotic stresses, *e.g.* radiation therapy (RT) (25, 26). COX2 inhibitors are potent enhancers of tumour response to radiation. RT plays a key role in the management of patients with PCa (2, 27). The anti-inflammatory and anti-coagulant characteristics of aspirin may be particularly important for patients undergoing RT as inflammation is a common side-effect of such treatment (28). RT is delivered in fractions to allow the recovery of normal tissues between treatments. However, surviving cancer cells also proliferate during treatment intervals, leading to repopulation of the tumour and limiting the effectiveness of the treatment. Tumour cell repopulation is a major cause of treatment failure. There is compelling evidence of an active proliferative response, driven by increased COX2 expression, which contributes to the repopulation of tumours and poor patient outcome (18).

At the ages when PCa is usually diagnosed, cardiovascular morbidity is usually already high. Aspirin is one of the most frequently used drugs in cardiovascular disease, and it has been shown to be implicated in prostate carcinogenesis (29, 30). Although PCa can be cured at early stages, the disease in most patients is at a more advanced stage when diagnosed. Endocrinology is used for these patients. Androgen deprivation therapy can induce a series of metabolic changes such as hypertension, atherosclerosis and obesity, in which the perniciousness of cardiovascular disease is serious (31). This further provides encouraging reasons for aspirin use in patients undergoing RT.

Currently, there are no clear, effective treatment options for patients with increasing prostate-specific antigen (PSA) level after definitive RT. The use of chemotherapy in PCa has been uniformly disappointing in both a primary and adjuvant roles (32). It has been reported that aspirin use is associated with significantly lower baseline PSA level in men with PCa who opted for active surveillance for their disease (33), especially those with PSA level <20 ng/ml. Aspirin may therefore also have an effect on cancer aggressiveness (8, 34).

Several investigations have demonstrated that increased COX2 expression is predictive of poor clinical outcomes following primary treatment for PCa (20, 22, 35, 36). Most of these studies evaluated patient outcomes after radical prostatectomy, while the most convincing evidence has resulted from the RTOG 92-02 trial (22), which included patients with locally advanced PCa who were treated with RT plus either short- or long-term androgen deprivation. More specifically, the associations of increased COX2 expression with distant metastasis, biochemical failure, and any failure was demonstrated. Motivated by these findings, this review evaluated the ability of aspirin to augment RT in order to improve biochemical control and PCa-specific mortality (Figure 1).

COX2 has been shown to be involved in PCa, several other types of human cancer, and inflammatory diseases (37). Therefore, the potential use of aspirin, a well-known COX inhibitor, as chemopreventive or therapeutic agent for PCa, is worth being investigated. This review evaluates whether aspirin should be administered to all patients with PCa undergoing RT.

Aspirin is associated with improved biochemical control in patients with PCa undergoing RT. A number of studies have investigated the association between aspirin and its potential to improve biochemical control in PCa (38-41), with some reporting statistically significant associations (38-40), while one study showed conflicting results, finding null effects (41).

Zaorsky *et al.* found that aspirin use was associated with a two-fold decreased risk of an interval to biochemical failure (IBF) of less than 18 months in RT PCa patients (38). IBF has been shown to be the strongest predictor of distant metastasis, PCa-specific survival and overall survival (42). The authors associated their findings with aspirin's antineoplastic effects. These effects were also found by Choe *et al.*, who retrospectively looked at aspirin use in combination with RT. They found that the 4-year rates of both biochemical failure and distant metastasis were significantly improved with aspirin use. The difference in biochemical control was most prominent for patients in the high-risk group (39). The reported anti-angiogenic properties of aspirin in ovarian cancer may represent an underlying mechanism for the increase in the tumoricidal effect of RT (43). It is possible that blood flow to potentially hypoxic cancer cells is increased, thereby enhancing radiation-induced reactive oxygen species and improving cell kill.

Jacobs *et al.* found that aspirin was associated with a delayed biochemical relapse benefit in high-risk patients with PCa undergoing RT, which would in turn translate into improved overall survival. However, a major limitation to this study was the small number of patients (n=27) (40).

In contradiction to the above findings, null results were found by Dhillon *et al.* in regards to metastatic or fatal PCa (41), suggesting that aspirin does not have an impact on biochemical control for patients undergoing RT.

The findings with regards to the effect of aspirin on disease severity and biochemical control require further confirmation in larger studies. Considering the high incidence of PCa and the widespread of aspirin use in the general population (44), confirmation of these findings could have a major impact on public health.

Aspirin improves PCa-specific mortality in patients with PCa undergoing RT. A number of studies have investigated the association between aspirin and improved PCa-specific mortality (45-51) but have shown conflicting results, with the majority finding null effects (48-51), while some reported statistically significant associations (45-47).

A systematic review and meta-analysis by Liu *et al.* provides additional support for the hypothesis that aspirin should be administered to all patients with PCa undergoing RT (45).

In the Cancer of the Prostate Strategic Urologic Research Endeavor database, patients with localised PCa treated with RT, after a follow up of 70 months, aspirin use was independently associated with a lower risk of PCa-specific mortality with a *p*-value of 0.02. Ten-year mortality was also found to be significantly different at 3% for those taking aspirin compared to 8% for those who did not (46).

Although studies have reported mixed results regarding aspirin use and PCa mortality rates, the study by Jacobs *et al.* (47) included a larger cohort (7118 patients) than previous articles, as well as data regarding aspirin dose, which, according to the authors, is lacking in other studies.

As to be expected, most aspirin users had cardiovascular disease or diabetes in this study, as the primary indication for aspirin is the prevention of cardiovascular disease. However, analysis using Cox proportional hazard models adjusting for age, tumour extent, lymph node involvement *etc.*, aspirin use and decreased mortality rates were not found to be statistically significantly associated.

In a subset analysis of high-risk patients, aspirin was found to be associated with a lower PCa-specific mortality rate, with a HR of 0.60 (47). The results of this study indicate that daily aspirin use was associated with a 40% lower mortality rate in high-risk patients. This is closely related to the importance of biochemical control, adding to the controversy on this topic.

Contradictory to the findings of the above studies, Cardwell *et al.* found no association between aspirin use and PCa-specific mortality after potential confounders such as Gleason score were accounted for (48). This study, therefore, did not provide any evidence of a reduction in mortality risk.

Similar to these latter studies, Caon *et al.* (49) found that aspirin did not have an impact on survival, therefore nor on mortality.

Flahavan *et al.* reported a small, non-significant reduced risk of prostate cancer specific mortality on multivariate analysis (50). This was also supported by Assayag *et al.*, who found that aspirin use was not associated with a decreased risk of PCa outcomes such as death (51). Interestingly, this study found that aspirin use was associated with an increased risk of PCa mortality (HR=1.37, 95% confidence interval=1.26-1.50). The authors highlighted that

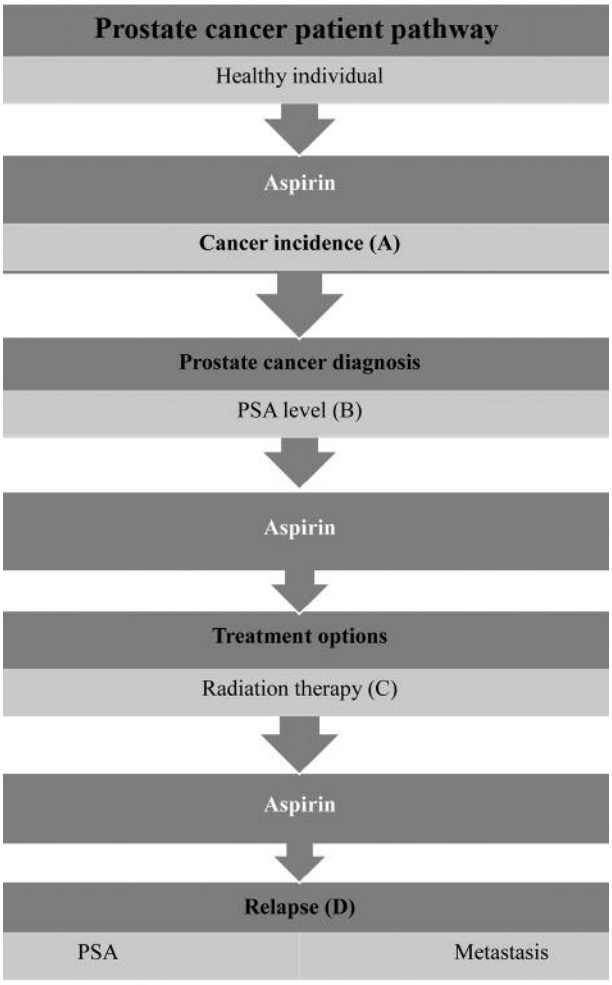

Figure 1. *Schematic representation of the potential impact of aspirin throughout the prostate cancer patient management pathway. A: Cancer incidence. Aspirin, a known cyclooxygenase-2 (COX2) inhibitor has been found to reduce the risk of cancer incidence. A chemopreventive role has also been reported in colorectal cancer. COX2 increases the carcinogenic potential of cells through the oxidation of pro-carcinogens to carcinogens, increased cell growth, reduced apoptosis, as well as reduced immune response to abnormal or cancer cells. B: Prostate Specific Antigen (PSA) level. Aspirin was found to be associated with significantly lower baseline PSA levels in men with PCa who opted for active surveillance. C: Radiation therapy. COX2 was found to be involved in tumour resistance to radiation. Aspirin may be a potent enhancer of tumour response to radiation. D: Relapse. Aspirin was reported to reduce the risk of metastasis. It may also possibly have an effect on cancer aggressiveness. COX2 inhibition caused by aspirin has been reported to reduce distant metastasis risk and biochemical relapse.*

the increase in mortality risk may be related to PCa progression. This is inconsistent once again with what was found in the previous argument on biochemical control and disease progression. Taken together, these results argue against a protective association between the use of aspirin and the risk of PCa mortality.

It is important to note that, for example, none of the patients included by Choe *et al*. had node-positive or metastatic disease, 72% had T1 disease and virtually all patients had intracapsular disease (46). Thus, it seems unlikely that aspirin could reduce the risk of recurrence and progression and not the risk of PCa mortality.

Caution needs to be exercised to ensure the associated benefits outweigh the potential side-effects, for example, gastrointestinal bleeding. Although data are limited, it is logical to assume that aspirin can significantly influence the risk of bleeding (52). Bleeding is a common complication of anticoagulant therapy (53), and for patients undergoing RT, bleeding toxicity is expected to be even greater, especially with dose-escalating techniques such as Intensity Moderated Radiation Therapy (IMRT) (54). Grade 3 rectal bleeding was reported in a prospective study of 57 men undergoing RT for PCa and taking high-dose aspirin (55). Aspirin, even at low doses, can double the incidence of gastric bleeding (56).

Conclusion

Despite the overwhelmingly large number of patients examined across the 11 studies reviewed here, the evidence for the effects of aspirin on biochemical control and PCa mortality remain difficult to interpret. This is firstly because of the heterogeneity in the patient population studies, associated with differences in the definition of exposure, statistical analysis, information collection methods (for example medical records), age, lifestyle, race, sample size, duration of study follow-up, *etc*. Second, this is because of the retrospective, observational nature of the included studies.

Prospective, randomised studies are needed to confirm these findings and determine the optimal dosage and duration of aspirin administration, as well as the risks and benefits associated with its use. Such randomized control trials are difficult to conduct, firstly because PCa mainly occurs in older men, and secondly because too many people in the general population take aspirin for various important medical reasons.

The proposed Add-Aspirin trial (57) has the potential to close this debate. The authors are aiming to recruit 10,000 patients who have had radical treatment for cancer, including PCa. Participants will receive standard adjuvant therapy according to local protocols, and then be randomised to receive aspirin or placebo daily for 5 years with a primary outcome measure based on survival. Outcomes of this work may clarify the clinical potential of aspirin as an adjuvant therapy for patients with PCa undergoing RT.

Conflicts of Interest

Both Authors have no conflict of interest to declare.

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