REVIEW ARTICLE

Relationship between aspirin, radiation therapy, and hormone deprivation in prostate cancer

Santiago Vilar-González*

Combined Hematology/Oncology, Level B, Queen Alexandra Hospital, Cosham, Hampshire, UK

Received for publication: 24 June 2016; accepted for publication: 25 February 2017
Available online: 6 November 2017

Abstract Systematic review of studies published in PubMed about the relationship between prostate cancer and anticoagulants, especially aspirin. We analyze the role that their association with radiation and hormone deprivation and his possible synergistic effect in treatment. We describe bibliographic evidence of possible association between aspirin use and the onset, development and mortality by prostate cancer. Continue delving into the pathophysiological mechanisms involved. Finally, we describe and discuss the works related to the association between anticoagulants, radiation and hormone deprivation. Randomized trials are guaranteed, taking into account disease-related, patients and therapies factors, in order to obtain unbiased evidence of their likely relationship. Once confirmed the hypothesis of its synergistic effect, in prevention and/or in adjuvant treatment setting of prostate cancer, it opens up a whole range of future possibilities of great impact in the management of this prevalent disease. (creativecommons.org/licenses/by-nc-nd/4.0/).

KEY WORDS
Prostate cancer; Prostatic cancer; Aspirin; Anticoagulants; Nonsteroidal anti-inflammatory drugs; Antiaggregant drugs; Radiotherapy; Brachytherapy, irradiation, hormone deprivation; Androgen deprivation

*E-mail for correspondence: santiagov06@gmail.com (S. Vilar-González)
OBJECTIVE, MATERIALS AND METHODS

The purpose of this work is double: On the one hand, to review existing evidence on the possible epidemiologic relationship of anticoagulants (AC), especially aspirin with prostate cancer (PC), and on the other, the role they might play, together with radiation therapy and hormone deprivation (HD), in the treatment of PC. A selective search was conducted in PubMed using the terms “cancer of prostate” or “prostatic cancer” together with the terms “aspirin,” “AC,” “nonsteroidal anti-inflammatory drugs (NSAIDs),” “antiaggregants,” “radiotherapy,” “brachytherapy,” “irradiation,” “hormonal deprivation,” and “androgen deprivation.” After their review, those articles of the highest relevance due to their methodology or outcomes were selected without any retrospective limitation and up to March 2016. Through them, other articles of interest for the present work were accessed. After briefly reviewing epidemiological evidence on the use of aspirin or ACs to prevent cancer, the pathophysiological mechanisms involved in the possible beneficial effect of ACs on PC will be described. Then, those studies associating ACs, radiation therapy, and HD to each other will be shown. Finally, those aspects that beforehand may be of higher interest such as the hypothesis of a possible synergistic interaction, where the addition of these factors may play an important role with regard to cancer treatment, will be discussed.

DEVELOPMENT

There is evidence that drugs that alter hemostasis, such as aspirin and other AC, may play an important role with regard to PC. This evidence suggests that ACs might prevent its onset, development, and dissemination. Nevertheless, clinical data examining such an association shows results that are not entirely conclusive. There is also evidence of a positive association between neoplastic conditions and the coagulation system. Increased risk for thromboembolism in cancer patients is a known fact as well as the higher risk for the development of cancer in patients with a history of blood dyscrasias.

Studies carried out with aspirin in primary prevention of cardiovascular disease (CVD) have also demonstrated a reduction in long-term cancer-related mortality. There is evidence available on the possible effect of aspirin on a number of particular cancers. We know that it can prevent their onset and decrease their mortality. Different studies, including a meta-analysis, confirm the efficacy of aspirin in the reduction of adenocarcinoma-related mortality risk, especially in colorectal adenocarcinoma, hence, the interest to verify a possible relationship with prostate carcinoma. There are multiple epidemiological studies that refer an association between the use of ACs and a reduced risk of PC onset, PC-related mortality, and PC diagnoses with less aggressive initial clinical factors. Even when there are also studies against this relationship, some of them show important biases. Recently, some meta-analyses that appear to confirm this positive relationship have become available. Prolonged intake of the drug appears to be necessary for its positive effects with regard to cancer prevention to be obtained. On the other hand, the pathophysiological processes involved in cancer prevention and mortality are mediated by several cyclooxygenases (COXs)-dependent and independent mechanisms of action. COX-dependent mechanisms are those mediated by the COX enzyme. COX is an enzyme that converts arachidonic acid into eicosanoids including leukotrienes, thromboxanes, and prostaglandins. The latter are potent mediators of inflammation and other physiological processes. Aspirin inhibits in a nonselective form both COX isoforms: COX-1 and COX-2. COX-1 pathway inhibition is irreversible, even at aspirin low daily doses. This is the main pathway involved in the control of platelet aggregation, although it is also responsible for gastrointestinal (GI) mucosa integrity preservation. Higher aspirin doses are required to inhibit the COX-2 pathway. COX-2 is inducible by the action of mitogens, growth factors, oncogenes, cytokines, and carcinogens. After induced activation of this pathway, a whole range of mechanisms such as angiogenesis promotion, apoptosis inhibition, cell proliferation stimulation, and immunosuppression reduction all of them factors clearly associated with carcinogenesis are set in motion. All these observations prompted an interest on looking into the role of COX-2 selective inhibitors, both in the prevention and treatment of cancer. Such interest decreased when their toxic profile was demonstrated. COX-2 is responsible for the synthesis of prostaglandin I2 (PGI2), which is a vasodilator and platelet aggregation inhibitor agent. Therefore, by selectively inhibiting COX-2, the balance between the antithrombotic effect and the prothrombotic effect mediated by COX-1-generated thromboxane A2 (TxA2) is broken, which generates the possibility of cardiovascular thrombosis. This is the mechanism that would explain its toxicity. Increased expression of COX-2 has been substantiated in certain cancers, such as prostate, bladder, and colon cancer, as well as a possible relationship between this overexpression inhibition by aspirin and lower risk of PC development and aggressiveness.

The role of COX-2 in the genesis of cancer is reaffirmed when a higher possibility for developing PC in certain polymorphisms such as rs2745557, rs20415, and rs20417 is verified.

To conclude this section, apoptosis and angiogenesis can be activated by COX-independent mechanisms that are also affected by ACs. These mechanisms are multiple, and daily there are new ones described, but an exhaustive description of them is beyond the scope of the present work (Table 1). In addition, aspirin might act on chronic inflammatory processes involved in the development of PC. Specifically, it might act by inhibiting prostaglandin E2 (PGE2) formation, which is involved in carcinogenesis through the activation of mediators. Recently, PGE2 has been described to silence tumor-suppressor and DNA-repair genes through DNA methylation, a mechanism that helps to clarify its mechanism of action.

Association of ACs with radiation therapy and HD

The use of aspirin or ACs is correlated with the use of radiation and/or HD in different works. Thus, in the study by Chloe et al., the effect of ACs on survival was tried to be assessed in a prospective cohort of 662 patients with PC who received radiation therapy with curative intent. About 37% of them (243 patients) were on medical treatment with warfarin, clopidogrel, and/or aspirin. All of them received external beam radiation therapy (EBRT), permanent seed implants, or both procedures. Prostate-specific antigen
(PSA) was monitored for biochemical control of the disease. With a median follow-up of 49 months, 4-year biochemical control was significantly higher in those patients using ACs, specifically, 91% versus 78% (p = 0.0002). Furthermore, 4-year metastatic disease-free survival (MDFS) was higher (99% vs. 95%; p = 0.0248). In the subgroup analysis, significant improvement of biochemical control was recorded only in high-risk patients. Together with the Gleason score, the significant improvement of biochemical control was significantly higher in those patients using statins with the risk for PC and survival improvement in a retrospective cohort of 7042 patients, since 35% of patients had T2, 63% T3, and 2% T4, in addition to, 57% of them having positive margins. After 50-month median follow-up, the univariate analysis showed a relationship with 5-year biochemical relapse-free survival (BRFS), with overall survival (OS), and with MDFS, whereas the multivariate analysis only showed BRFS improvement (HR: 0.35; 95% confidence interval [CI]: 0.155-0.786).

Caon et al.41 studied the association of ACs/statins and comorbidity with survival in a prospective cohort of 3898 patients treated with EBRT. The mean age was 70.3 years, with 23% of patients using statins and 29% ACs. Charlson comorbidity index was 0 in 65%, 1 in 25%, and ≥2 in 10%, with 39% at intermediate risk and 44% at high risk. HD was received by 67%, and EBRT median dose used was 70 Gy; mean follow-up was 5.3 years. In the multivariate analysis, statins intake was associated with better cancer-specific survival (p = 0.049). Better OS was associated with statins and HD treatment (both p < 0.01), with a deleterious trend for the use of ACs (p = 0.04).

Finally, Katz et al.42 reviewed the relationship of ACs and statins with the risk for PC and survival improvement in a retrospective cohort of 7042 patients, 4611 of them treated with RP, and 2431 with EBRT. After a median follow-up of 4 years, the multivariate study showed an association between lower all-cause mortality after RP (HR: 0.47; 95% CI: 0.30-0.75) or EBRT (HR: 0.39; 95% CI: 0.25-0.59) and the use of ACs. This association was also demonstrated for the use of statins (HR after RP: 0.35; 95% CI: 0.21-0.58; and HR after EBRT: 0.59; 95% CI: 0.37-0.94). This study evidence the need for data collection to be as extensive as possible to obtain the most information with regard to existing interrelations.

**DISCUSSION**

From the observations exposed in the review, it can be inferred that AC may contribute to prevent tumor development, growth, and dissemination in patients with prostate carcinoma. Specifically, patients at higher risk of dissemination can derive the most benefit. Nevertheless, there is still no clear information based on adequate clinical trials.

In addition, there are data endorsing lower aggressiveness in PC presentation with the use of ACs43, which can

---

**Table 1. COX-independent cancer prevention mechanisms**

- Akt (antiapoptotic protein kinase) activation inhibition by Celecoxib23
- Antiaproliferative effect of Meloxicam on prostate cancer PC3 cell line24
- Cyclic guanosine monophosphate inhibition26
- Generation of free radicals26
- Suppression of apoptosis-inhibitor protein “survivin”29,30
- Aspirin-triggered lipoxin activation31
- NF-KappaB inhibition, which prevents uPA secretion in PC3 cells32
- Direct action on the uPA-uPA receptor complex32
- Ibuprofen stimulates p75 (NTR) expression in PC cells, a member of the tumor necrosis factor receptors family with proapoptotic activity33
- Leukotriene B4 (LTB4) expression inhibition in PC3 cells by celeboxib34
- NAG-1 expression induction, a gene associated with prostate cancer better differentiation35
- Regulation of the PKB/Akt pathway, especially of its isoform Akt2, by indomethacin36
- Celecoxib is a potent inhibitor of the androgen receptor through c-Jun induction/phosphorylation37
- Aspirin-triggered lipoxin activation31
- Suppression of apoptosis-inhibitor protein "survivin"29,30
- Akt (antiapoptotic protein kinase) activation inhibition by Celecoxib23
- Antiaproliferative effect of Meloxicam on prostate cancer PC3 cell line24
- Cyclic guanosine monophosphate inhibition26
- Generation of free radicals26
- Suppression of apoptosis-inhibitor protein “survivin”29,30
- Aspirin-triggered lipoxin activation31
- NF-KappaB inhibition, which prevents uPA secretion in PC3 cells32
- Direct action on the uPA-uPA receptor complex32
- Ibuprofen stimulates p75 (NTR) expression in PC cells, a member of the tumor necrosis factor receptors family with proapoptotic activity33
- Leukotriene B4 (LTB4) expression inhibition in PC3 cells by celeboxib34
- NAG-1 expression induction, a gene associated with prostate cancer better differentiation35
- Regulation of the PKB/Akt pathway, especially of its isoform Akt2, by indomethacin36
- Celecoxib is a potent inhibitor of the androgen receptor through c-Jun induction/phosphorylation37

---
also be highly important to decrease PC-associated mortality, which is a condition of high incidence and prevalence in developed countries. However, there is also information against this correlation with PC presentation profile. At present, radiotherapy with HD addition is the standard of care in high-risk PC. A clear benefit has been corroborated in cancer-specific survival, OS, and in clinical relapse-free survival, BRFS, and MDFS. HD can be neoadjuvantly, concomitantly, or adjuvantly administered. In high-risk patients, it is common to start it in the neoadjuvant setting to continue concomitantly and adjuvantly for a prolonged period (for a total of 1.5-3 years). The rationale to combine HD with radiation therapy in the neoadjuvant setting lies in several factors: Prostatic volume debulking, which allows for doses to be increased without so much toxicity, tumor hypoxia reduction, which increases radiosensitivity, cell cycle slowing, which would result in decreased cell repopulation during radiation therapy, and finally, an apoptosis direct effect on tumor cells through an immunomodulation phenomenon. Based on this, it has been speculated that HD neoadjuvant administration and radiation might have an additive (confirmed in animal models) and even supra-additive effect. Finally, HD would act by sterilizing occult metastases, whereas radiation would kill tumor cells regardless of hormone sensitivity in a spatial cooperation phenomenon similar to that of chemoradiation. 

As a result of all this, ACs addition to radiation might be thought of as possibly playing a similar role than that of HD, in this case by preventing metastatic dissemination throughout the development of cancer. This hypothesis seems to be reaffirmed by the work of Rothwell et al., where after aspirin prolonged intake, fewer cancers had metastasis at diagnosis, the risk for the development of metastasis was decreased, and finally, cancer-related mortality risk was reduced, particularly in those patients with no metastasis at diagnosis. This suggests that aspirin would generate both tumor growth delay and decreased metastatic dissemination, hence, the importance to exclude patients with metastasis at diagnosis from all clinical trials assessing cancer-specific mortality with the use of ACs. On the other hand, Woodward et al. propose that HD increases tumor oxygenation by radiosensitizing them. The implicated mechanism would be through vascular endothelial growth factor inhibition, which would prevent neo-proliferation of a fragile and inefficient vascular network around the tumor that would limit oxygen supply. The same anti-angiogenesis mechanism could be generated by addition of ACs in an additive mechanism together with radiation and even a synergistic one together with HD.

With regard to other interrelations between ACs and radiation, in the study by Anai et al., COX-2 overexpression was observed to increase PC cells chemoresistance. With escalating doses of celecoxib added to radiotherapy, an increase in radiation cytotoxic effect is observed. Other studies show COX-2-overexpressing PC cells increased resistance to radiation as well. As in the study by Anai et al., other works with COX-2 selective inhibitors have shown their radiosensitizing effect, even in situations of hormone refractoriness, although there is also some work available with opposing information. As for the relationship between ACs and HD, a recent work demonstrated both in vitro and in vivo that after complete blockade using flutamide as an androgen antagonist, the COX-2 expression is increased, with this mechanism likely being involved in the development of HD resistance. This information opens the door to the study of PC adjuvant treatment with HD combined with COX-2 inhibitors in a cooperative mechanism. The role of adjuvant with HD and ACs is prospectively and comparatively studied as well with the use of intermittent HD (IHD) at biochemical relapse after RP, using bicalutamide 150 mg/day at “on” periods in both comparative groups and etoricoxib at “off” periods in the intervention group. A higher percentage of responses to IHD and longer “off” periods are observed with the use of the COX-2 inhibitor. Moreover, finally, a synergistic effect can also be obtained from ACs and HD, since some ACs have been found to exert a potent inhibitory effect of the androgen receptor function. In any case, caution should be exercised with the concurrent use of ACs and HD due to the potential risk for liver toxicity, which might limit the alleged benefit owing to the need for HD early discontinuation.

The influence of COX-2 overexpression and its relationship with survival in patients treated with radiation and HD was also substantiated in a sub-study of the RTOG 92-02 trial. After assessing the 586 patients with sufficient immunohistochemical information on the individual, the multivariate analysis demonstrated that COX-2 overexpression status as a continuous variable is an independent predictive factor of distant metastasis, biochemical failure (according to ASTRO and Phoenix criteria) and of any failure. As a dichotomous covariable, COX-2 overexpression appears to better discriminate survival of patients receiving HD short sequence versus those receiving the extended sequence. This study supports the possible association between COX-2 expression and the response to HD. This reaffirms the need to stratify our PC patients according to COX-2 expression as an independent prognostic factor of both hormone and radioresistance and worse survival. Depending on this information, we can assess reinforcing the treatment by prolonging HD time or by adding COX inhibitors, with the latter point yet to be studied.

When assessing the possible cooperation in the PC adjuvant setting, it can be claimed that the effect of COX-2 inhibitors has shown to be independent of the response to HD in PC cell lines in vitro, even with regard to apoptosis generation. Its radiation-independent effect has also been demonstrated since no differences with regard to its efficacy in biochemical relapse rates decrease were observed when its use was initiated prior or after radiation therapy.

Another role to be played by ACs would be in delaying the need for treatment after biochemical relapse. In a Phase II trial in recurrent disease after RP or EBRT, Pruthi et al. showed celecoxib efficacy in the decrease of PSA concentration, thus delaying the need for treatment.

With regard to higher relative efficacy between different ACs, there is evidence that aspirin, versus other ACs, is the main responsible in PC prevention as well as in its decreased mortality. Although there are also studies that do not find a clear relationship with aspirin or its dose or length of administration, there are also data on PC prevention and lower aggressiveness with acetaminophen (paracetamol). In experimental in vitro studies with androgen-dependent and androgen-independent PC cells, ibu-
profen was considerably superior versus other ACs with regard to apoptosis induction and survival reduction\(^5\). These diverging data between different NSAIDs may be related to the degree of inhibition of the COX pathway as well as to its reversible or irreversible nature. We know that studies in vivo showed that 95% suppression of COX-1 activity is required to block TxA2-induced platelet aggregation. This degree of suppression, being also of an irreversible nature, is only achieved by aspirin. The remaining NSAIDs exert a reversible and less intense inhibition (between 50% and 95%)\(^6\). Therefore, it can be deducted that high doses of NSAIDs are required to obtain a beneficial effect, which was confirmed by one study of colorectal adenocarcinoma\(^3\). Somehow, this could be extrapolated to the effect of different ACs on cancer.

Some of the negative results in the presented epidemiological studies, or even the conclusions, should be assessed with caution due to the possibility of biases. In many of them, confounding factors may be involved including the use of statins, the type of diet, body mass index (BMI), smoking, physical activity, administered treatments, comorbidities, sample size, doses, and intervals of ACs used, or even the use of different PC screening and follow-up protocols\(^16,17,67\). It should be pointed out that most studies contemplating ACs positive effect do not report statins intake and vice versa. Another interesting observation arises from the work by Salinas et al., where a positive effect is demonstrated in cancer prevention in one of the COX expression phenotypes, specifically r12042763, which opens the door to research in those cases with COX overexpression caused by single-nucleotide polymorphisms\(^10\).

In retrospective studies, the use of statins has also been observed to be associated with lower risk for PC, with less aggressive presentations, lower rates of biochemical relapse, and longer survival\(^14,41,67-69\). Similar effects have been observed in breast\(^6\) but not in colon cancer\(^7\). The use of statins could also be related to clinical factors of disease presentation such as PSA level, stage, or Gleason score\(^57,68\). Their possible action might be related to the type of statin, the dose used and length of use, since a decrease in the risk of biochemical relapse has been observed in relation to dose increase\(^6\). Based on preclinical studies, statins anti-cancer potential would be based on their antiproliferative, proapoptotic, radiosensitizing, and lipid profile regulating capacity\(^57,68\).

Going back to the ACs role, long duration therapy (between 5 and 7.5 years) is required to obtain chemoprevention benefits in PC and other cancers such as colorectal cancer. In addition, there is a latency period to obtain benefits in terms of cancer onset and mortality, which in the case of PC will be longer than 5 years, probably between 8 and 15 years\(^6,9,12,71\). Such latency period has also been proven necessary with acetyaminophen (paracetamol)\(^63\). On the other hand, intake interruptions would make for all obtained prevention benefit to be lost.\(^1\) These data suggest the possibility of starting aspirin intake at low doses at 40-50 years of age to prevent PC onset, aggressiveness, and mortality\(^10,73\). The dose and duration to obtain the maximum benefit would remain to be elucidated. All this should be counterbalanced with possible related toxicity. There is certain evidence in favor and against a dose-response relationship with the use of aspirin and its beneficial effect, although a recent consensus statement considers benefits to be superior\(^7,21\). The use of low doses (75-300 mg/day) versus high doses (≥500 mg), continues to prevent cancer incidence and mortality, with a more adequate toxicity profile\(^1,7,12,72\). In spite of the use of low-dose aspirin, the incidence of peptic ulcer disease is still 11%\(^13\). The risk factors associated with the development of GI bleeding would be the existence of an ulcer or previous GI bleeding, aspirin higher doses, age older than 70 years, NSAIDs and corticosteroids concomitant use and Helicobacter pylori infection\(^74\). Therefore, it is necessary bearing in mind GI toxicity prevention by adding proton-pump inhibitors, which have shown efficacy at this point\(^74\). On the other hand, a decrease in the risk for intracranial bleeding has been shown with aspirin prolonged use, which contributes with data on long-term safety\(^75\).

Its toxic profile, in particular, the risk of severe hemorrhage has limited the use of aspirin in cancer prevention\(^3,10\). This could be counterbalanced by those epidemiological studies that demonstrate that aspirin regular use has protective effects against CVD\(^76\).

To conclude, recent findings associate androgen deprivation with an increased risk for the development of colorectal cancer\(^76\). The benefit obtained by continued aspirin intake in terms of PC-related mortality prevention, the fact of counterbalancing the higher risk to develop colorectal cancer would be added in HD-treated patients\(^77,78\). Furthermore, according to some preclinical and clinical studies, it might prevent radio-induced rectitis\(^77\), although there are works that refer an increase in seriousness with its use\(^79\).

**CONCLUSION**

Positive effects of AC, especially of aspirin, have been demonstrated in PC, in terms of incidence, presentation profile, progression velocity, and metastasis development. All this can considerably impact on PC survival, especially considering its high incidence and prevalence as well as aspirin greater effect on high-risk patients. All the above exposed suggests that aspirin might play an important role in PC chemoprevention and treatment, provided the risk/benefit balance of its use would suggest so. Its effect would be added to the therapies established today for high-risk prostate cancer, such as radiaLon and hormonal deprivation. It would consist of a exercise of temporop-paLal cooperaLon, has not yet evaluated, and which if confirmed, has great potential." mejor que lo que pone " Its effect would this way add to that of high-risk PC currently established therapies such as radiotherapy and HD. It would constitute a time-spatial cooperation exercise hitherto not assessed that holds if so confirmed great potential. Therefore, randomized trials are warranted to give an answer to these questions. This would require for future investigations to include patients on treatment with radiation and HD to record a series of items related to PC onset, evolution, and mortality such as ACs and/or statins intake, usage time, type, and doses as well other factors that may confound the results such as the diet, daily activity, weight, BMI, smoking, and frequency and type of PC screening.
REFERENCES


