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ORIGINAL ARTICLE

Aspirin use improves the biochemical control of prostate cancer in Chinese men

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Summary

Purpose: *Aspirin may improve treatment outcomes and increase the survival of patients with prostate cancer, but the results remain controversial.*

Methods: *This study consisted of 483 patients who underwent radical prostatectomy for localized prostate cancer, 231 of whom were in the aspirin group. The associations between aspirin use and freedom from biochemical failure (FFBF), overall survival (OS) and relative factors were evaluated.*

Results: *Multivariate analysis showed that aspirin therapy, T classification, Gleason score (GS), and prostate-specific antigen (PSA) were associated with biochemical failure. The aspirin group had a significantly better FFBF rate (91.1%) at 5 years than the control group (82.3%, p=0.000). Among patients with high-risk disease, the FFBF rate for patients in the aspirin group was 79.1% at 5 years compared to 52.2% in the control group (p=0.000).*

Conclusions: *We demonstrate that the use of aspirin may be beneficial for the biochemical control of prostate cancer. The mechanism of the antineoplastic effect of aspirin is not fully understood. Further clinical trials and large-scale studies will be necessary to confirm the relationship between aspirin use and prostate cancer risk.*

Key words: *aspirin, biochemical control, prostate cancer, radical prostatectomy*

Introduction

Prostate cancer is the most commonly diagnosed malignancy among men [1], and its prevention is becoming a demanding public health issue worldwide. In the United States in 2018, an estimated 164,690 new cases of prostate cancer and 29,430 deaths from this disease will occur [2]. It is estimated that the costs for prostate cancer were 11.9 billion in the United States in 2011 [3], and the projected incidence will reach 228,000 patients in 2030 [4]. The reasons for prostate cancer development are multifactorial, including healthcare and intrinsic factors related to ancestry [5-7].

The mechanism of prostate cancer remains largely unknown. Inflammation was shown to have beneficial effects on prostate cancer by inhibiting cyclooxygenase (COX) [8,9]. As one of the most common anti-inflammatory drugs, aspirin's anti-cancer effect was first reported in animals in 1972 [10]. Previous studies have suggested that aspirin is associated with cancers, including colorectal cancer [11], breast cancer [12], and lung cancer [13]. Increasing evidence suggests that aspirin may reduce the metastatic spread and increase the survival of patients with prostate cancer. However, the results

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remain controversial. A meta-analysis based on 15 relevant studies found no significant association between aspirin and prostate cancer [14]. Recently, a large-scale study found that aspirin was associated with a reduced risk of prostate cancer [15], and the effect of aspirin on prostate cancer appeared to vary with geographic regions [16]. Thus, the aim of this retrospective case-control study was to examine the relationship between aspirin use and prostate cancer in Chinese populations.

Methods

Study populations

The current study included patients with prostate cancer who were subjected to radical prostatectomy or radical prostatectomy with androgen deprivation therapy (ADT) and were followed-up for at least 2 years at Beijing Tian Tan Hospital and Beijing Hospital. The sample was restricted to a cohort of men treated between 2007 and 2010, and these subjects provided signed informed consent to participate in the study. Patients with no documented list of medications were excluded (n=73). Patients were assigned to the aspirin group if they had listed aspirin use at the time of the initial consultation. Overall, 483 patients were included, of whom 231were in the aspirin group.

Clinical data

Age, risk category, GS, PSA values and T classification were collected from patient medical records. The patients were categorized as having low-risk, intermediate-risk or high-risk disease according to the National Comprehensive Cancer Network classification [17]. Low-risk disease was defined as a pretreatment PSA level ≤10 ng/mL, GS ≤6, and T classification T1-T2a. Intermediate-risk disease was defined as any of the following risk factors: a pretreatment PSA level between 10 and 20 ng/mL, a GS up to 7, or T classification of T2b-T2c. High-risk disease was defined as any of the following risk factors: PSA level ≥20 ng/mL, GS ≥8, or T classification ≥T3. The majority of patients had intermediate-risk disease (46.8%) or low-risk disease (42.7%). Fifty-one patients (10.6%) had high-risk disease, 273 patients (56.5%) had GS ≤6,

Table 1. Patient characteristics (n=483)

Characteristics	*No. of patients (%)*		*p value*
	Cases n=231 n (%)	*Controls n=252 n (%)*	
Age, years			0.054
Median	65	69	
Range	46-81	43-85	
Risk category			0.230
High	30 (13.0)	21 (8.3)	
Intermediate	103 (44.6)	123 (48.8)	
Low	98 (42.4)	108 (42.9)	
Gleason score			0.567
2-6	131 (56.7)	142 (56.3)	
7	82 (35.5)	96 (38.1)	
8-10	18 (7.8)	14 (5.6)	
Initial PSA, ng/mL			0.062
Median	23.5	22.1	
Range	4.3-578.1	4.1-623.8	
T classification			0.478
T1	123 (53.2)	145 (57.9)	
T2	91 (39.4)	94 (37.3)	
T3	17 (7.4)	13 (5.2)	
PSA follow-up, mo			0.081
Median	58.1	60.2	
Range	0.5-328.4	0.7-423.8	
Radical prostatectomy (laparoscopic radical prostatectomy)			0.462
Radical prostatectomy only	128 (55.4)	148 (58.7)	
Radical prostatectomy with ADT	103 (44.6)	104 (41.3)	

PSA: prostate-specific antigen

178 patients (36.9%) had GS of 7, and 32 patients (7.0%) had GS 8-10. Thirty patients (6.2%) had T3 disease, while no patient had T4 disease. Two hundred seventy-six patients (57.1%) were subjected to radical prostatectomy as their sole therapy, and 207 underwent radical prostatectomy with ADT. ADT consisted of administration of a LHRH analogue for a median of 4 months. Of 190 patients with available records, 152 (80%) received ADT for <6 months, 15 (8%) received ADT for 6 to 12 months, and 23 (12%) received ADT for >12 months.

Patients who received only100 mg of aspirin once a day were included in the study [18]. Meanwhile, patients who used other anticoagulants (e.g.,warfarin or clopidogrel) were excluded. Patients typically had indications for daily use of aspirin (e.g., secondary prevention of coronary heart disease). The duration or onset of aspirin therapy was not controlled in this study. Generally, once aspirin therapy was initiated, it was continued indefinitely.

Patients generally were examined at 3-6 month intervals for 5 years after the completion of radical prostatectomy. The median follow-up period was 59.3 (range 12-74) months from the date of radical prostatectomy until the last PSA measurement.

The study involved the administration of a survey at the time of enrollment given by a trained interviewer and the collection of peripheral blood monocytes and urine from all study subjects. Biochemical failure was defined as two consecutive PSA values of >0.2 ng/mL and increasing values following radical prostatectomy measured during follow-up [19].

Statistics

The statistical analyses were performed using SPSS (19.0) software. Comparisons between the aspirin group and the control group were performed using chi-square test, t-test or Wilcoxon two-sample tests, with exposures assessed as categorical or continuous metrics. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-free survival (DFS).

Results

Patient characteristics

The patient characteristics are described in Table 1. The study population comprised 231 patients who used aspirin and 252 controls. The patients who did or did not receive aspirin had similar demographic characteristics. The median age of the cases and controls were 65 (range 46-81) and 69 (range 43-85) years, respectively. The median initial PSA levels were 23.5 (range 4.3-578.1) and 22.1 (range 4.1-623.8) ng/mL in the aspirin and control

Table 2. Univariate and multivariate analyses of freedom from biochemical failure (n=483)

	5-year FFBF, %	*p value*
Univariate analysis		
Aspirin therapy: yes vs no	91.1 vs 82.3	0.001
T classification:≤T2a vs ≥T2b	74.2 vs 59.6	0.032
Gleason score: ≤6 vs ≥7	81.2vs 73.2	0.004
PSA:<median vs ≥median	90.2 vs 76.4	0.021
Radical prostatectomy (laparoscopic radical prostatectomy): radical prostatectomy with ADT vs radical prostatectomy only	84.6 vs 79.7	0.038
Multivariate analysis	*RR(95% CI)*	*p value*
Aspirin therapy: yes vs no	0.32(0.28,0.76)	0.001
T classification: ≤T2a vs ≥T2b	0.53(0.3,0.89)	0.015
Gleason score: ≤6 vs ≥7	0.48(0.42,0.79)	0.042
PSA:<median vs ≥median	0.41(0.21,0.84)	0.027
Radical prostatectomy (laparoscopic radical prostatectomy): radical prostatectomy with ADT vs radical prostatectomy only	0.66(0.43,0.91)	0.321

FFBF: freedom from biochemical failure, ADT: androgen deprivation therapy, PSA: prostate specific antigen

Table 3. The effect of aspirin therapy on freedom from biochemical failure stratified by disease risk

Risk category (n=483)	*Aspirin group (n=231)*	*Control group (n=252)*	*p value*
Low, n=206	91.3[1] (98)[2]	89.2[1] (108)[2]	0.241
Intermediate, n=226	88.3[1] (103)[2]	80.4[1] (123)[2]	0.084
High, n=51	79.1[1] (30)[2]	52.2[1] (21)[2]	0.000

[1]The rate of freedom from biochemical failture for low risk patients in the aspirin group; [2]The number of patients with freedom from biochemical failture for low risk patients in the control group.

groups, respectively. No significant differences were observed in the length of PSA follow-up, disease risk category, distribution of T classification, GS or comorbidities.

Univariate and multivariate analyses of biochemical failure

The univariate analysis included aspirin use, T classification, GS, and PSA values. All variables were tested as binary variables, with continuous variables dichotomized by the median value. Variables with p values ≤0.05 were considered in the multivariate analysis, the results of which showed that aspirin therapy, T classification, GS and PSA values were associated with biochemical failure (Table 2).

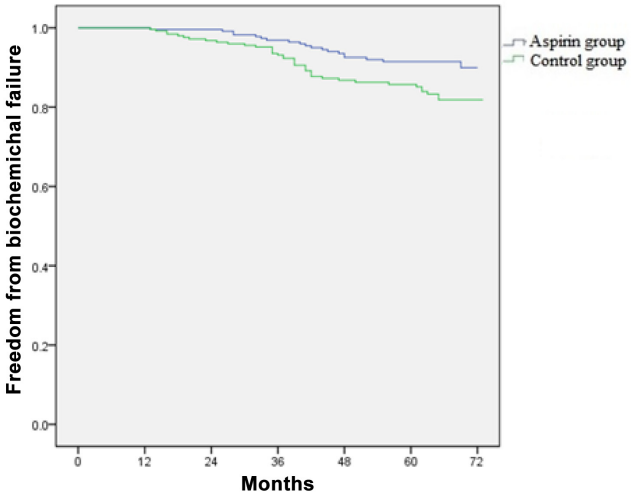

Figure 1. The rate of freedom from biochemical failure for patients in the aspirin group was 91.1% at 5 years compared to 82.3% in the control group (p=0.000).

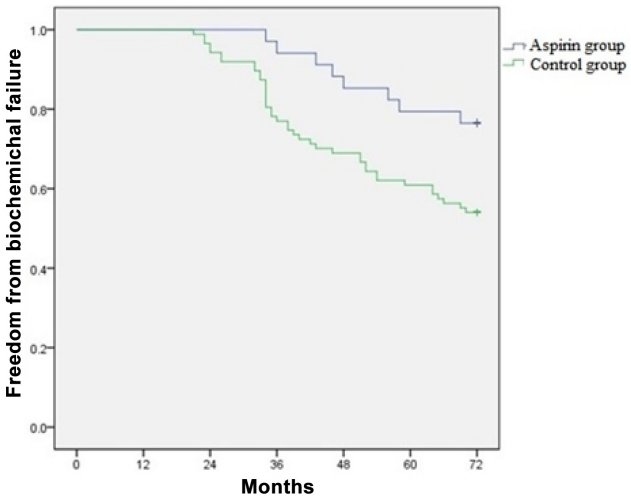

Figure 2. Among the patients with high-risk disease, the rate of freedom from biochemical failure for patients in the aspirin group was 79.1% at 5 years compared to 52.2% in the control group (p=0.000).

Comparison of outcomes between the aspirin and control groups

The biochemical control rate for the entire group was 87.3% at 5 years. When the rate of FFBF was compared between the two groups, the aspirin group had a significantly better FFBF rate of 91.1% at 5 years than the control group (82.3%, p=0.000). The Kaplan-Meier curves for FFBF are shown in Figure 1, and display that the rate of FBFF for patients in the aspirin group was 91.1% at 5 years compared to 82.3% in the control group (p=0.000).

Subgroup analyses

Several subgroup analyses were performed to characterize patients who may benefit most from aspirin therapy. When the entire group was divided by risk category, the difference in biochemical control between the aspirin group and the control group was most prominent for patients in the high-risk group (Figure 2), and the difference was significant only for this group (Table 3).

Discussion

In this study we observed that biochemical control improved significantly for patients who used aspirin compared to the control group. The use of aspirin was independently associated with better biochemical control in the multivariate analysis.

Aspirin is a nonsteroidal anti-inflammatory drug that has been shown to play an important role in the chemoprevention of carcinogenesis. The anti-inflammatory activity of aspirin has been proposed to be mediated through inhibition COX enzymes and iNOS [20,21]. Studies have shown that aspirin may reduce the risk of prostate cancer [22], but the potential mechanisms of the action of aspirin on prostate cancer are diverse and remain controversial. Several mechanisms have been proposed to explain these effects. One is that aspirin could inhibit COX enzymes, which play important roles in cell invasion, carcinogenesis, and metastasis through the synthesis of prostanoids, such as prostaglandin E2 [23]. Animal and laboratory studies have demonstrated the preventive effect of aspirin on prostate cancer [16].

Another possible mechanism involves the antineoplastic effect of aspirin in prostate cancer patients. It has been suggested that antineoplastics may influence tumor growth and dissemination. Aspirin inhibits the generation of serine proteases involved in coagulation by altering the expression of genes that are involved in tumor proliferation

[24]. Additionally, investigators have inferred that the use of anticoagulants may reverse a hypercoagulable state necessary for cancer growth or metastasis [25]. Furthermore, aspirin likely decreases radiation-induced reactive oxygen species and promotes cell killing to increase blood flow to hypoxic cancer cells [26].

All patients in this study were treated with radical prostatectomy, and aspirin therapy may lead to decreased PSA outcomes by inhibiting prostate cancer cell growth and metastasis. However, in our current study, no difference in 5-year FFBF was observed when aspirin therapy was initiated before or after ADT, suggesting that the antineoplastic effect of aspirin therapy on prostate cancer may be independent of ADT. Our data appear consistent with those of Kevin et al. [18], who studied 622 patients with localized prostate cancer. Investigations including more patients receiving radiotherapy may be necessary to further test the hypothesis that the antineoplastic effect of aspirin therapy on prostate cancer may be independent of ADT.

We found no significant difference in biochemical control between the low-risk and the intermediate-risk group of patients. The difference was significant only for the high-risk group, suggesting a complex relationship among aspirin use, extent of disease, and FFBF in prostate cancer patients.

The use of anticoagulants, such as aspirin, is associated with an increased risk of bleeding complications [27], which may be even more substantial in cancer patients. In prostate cancer patients who undergo radical prostatectomy, the risk of serious bleeding must be weighed against the potential benefit. With the use of newer classes of anticoagulants, such as low-molecular-weight heparin (LMWH), the bleeding risk may be decreased [28].

This study postulated that the use of aspirin can reduce the biochemical recurrence of prostate cancer, especially in the high-risk group. Some studies have shown significant implications with respect to the dose, frequency and duration of aspirin use, and a significant inverse dose-effect relationship was shown for patients who took more than one aspirin per day (100mg/day) [29,30]. Nevertheless, other studies found no evidence of a dose-effect relationship [31,32]. Pooled results, consistent with the results of our study, demonstrated a negative trend of prostate cancer risk with more than four years of aspirin use [16].

Considering the widespread use of aspirin and the high incidence of prostate cancer in the general population, physicians should be aware of patients at high risk of prostate cancer, the optimal dosage of aspirin, and its side effects. It appears that the use of aspirin for the prevention of prostate cancer still requires further investigations; however, a study implied that it has beneficial effects on the risk of prostate cancer [16].

To the best of our knowledge, this is the first report to study the effect of anticoagulant therapy on prostate cancer treated with radical prostatectomy with or without ADT. The conclusions are limited by the nature of the analysis. Moreover, the duration and onset of anticoagulant therapy were not controlled. The patients were treated at two institutions during a period that spanned many years. It would be interesting to study prostate cancer patients who undergo radical prostatectomy because the greatest benefit from anticoagulants may be observed in patients who have maximal disease burden.

Conclusions

In this study, we demonstrated that the use of aspirin may be beneficial for the biochemical control of prostate cancer. The mechanisms of the antineoplastic effect are not understood, and the suppression of metastasis might play an important role. Further clinical trials and large-scale studies will be necessary to confirm the causal relationship between aspirin use and prostate cancer risk.

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Conflict of interests

The authors declare no conflict of interests.

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