Asian Journal of Urology (2015) 2, 224–232

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ORIGINAL ARTICLE

Prostate chronic inflammation type IV and prostate cancer risk in patients undergoing first biopsy set: Results of a large cohort study

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Received 2 May 2015; received in revised form 2 July 2015; accepted 18 August 2015
Available online 25 September 2015

KEYWORDS
Prostate;
Prostate cancer;
Prostate specific antigen;
Prostate biopsy;
Chronic inflammation;
Prostate volume;
Biopsy Gleason score

Abstract *Objective:* In prostate specimens, chronic inflammatory infiltrate (CII) type IV has been detected, but its association with prostate cancer (PCa) is controversial. The aim of the present study is to investigate on associations of CII with PCa detection in patients undergoing prostate first biopsy set.
Methods: Ultrasound transrectal-guided biopsies by the transperineal approach were retrospectively evaluated in 441 consecutive patients. The study excluded patients who were in active surveillance, prostate specific antigen (PSA) $\geq$30 ng/mL, re-biopsies, incidental PCa after transurethral resection of the prostate (TURP), less than 14 cores or metastatic. Analysis of population and subpopulations (with or without PCa) was performed by statistical methods which included Mann–Whitney (*U* test), Kruskal–Wallis test, Chi-squared statistic, logistic regression. Multivariate logistic regression models predicting mean probability of PCa detection were established.
Results: PCa detection rate was 46.03%. Age, PSA, prostate volume (PV), prostate intraepithelial neoplasia (PIN) and CII were the significant independent predictors of PCa detection. PV (OR = 0.934) and CII (OR = 0.192) were both negative independent predictors. CII was a significant negative independent predictor in multivariate logistic regression models predicting the mean probability of PCa detection by age, PSA and PV. The inverse association of CII with PCa does not necessary mean protection because of PSA confounding.

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Peer review under responsibility of Shanghai Medical Association and SMMU.

http://dx.doi.org/10.1016/j.ajur.2015.08.007

Conclusion: In a population of patients undergoing prostate first biopsy set, CII was a strong negative independent predictor of PCa detection. CII type IV should be considered as an adjunctive parameter in re-biopsy or active surveillance protocols.

1. Introduction

The concept of zonal anatomy is used to indicate origin and location of growing processes within the prostate [1]. The two major diseases affecting the human prostate are benign prostate hyperplasia (BPH) and prostate cancer (PCa), and the former predominantly develops within the transition zone while the latter in the peripheral part of the gland.

The prostate gland may also undergo chronic inflammatory processes. The prostate is considered an immunocompetent organ and its environment is populated by inflammatory cells including T and B lymphocytes, macrophages and mast cells [2,3]. The histology of proliferative inflammatory atrophy (PIA), which appears as simple atrophy or postatrophic hyperplasia, includes proliferative glandular epithelium and associates with inflammation [3]. It has been suggested that infiltrates and mediators of chronic inflammation might be involved in PCa carcinogenesis [4—12]. Basic science has shown that chronic inflammation plays an important role in human carcinogenesis [2,3]; indeed, development and progression of cancer might be related to reactive oxygen and nitrogen species developing in tissue microenvironment after related damage and regeneration [13—21]. Experimental and epidemiologic studies show that estrogens might also have an independent role in chronic inflammation and PCa carcinogenesis [22—26]. There are studies showing that chronic inflammation is the link between BPH and PCa [27,28]. Because of the association of chronic inflammation with oxidative stress which is mediated by the cyclo-oxygenase (COX) gene pathway, it has been proposed that aspirin, which is a nonsteroidal anti-inflammatory drug, might prevent PCa carcinogenesis by inhibiting COXs [29—31]. However, the inflammatory infiltrate includes cells of both the innate (e.g., monocytes and macrophages) and adaptive (B and T lymphocytes) immune system which is currently used for PCa immunotherapy strategies [5,32].

Clinically, the prostatitis syndromes have been classified in four categories by the National Institutes of Health (NIH) [33]. The last category is named type IV and is diagnosed in patients who have no history of genitourinary tract pain complaints, but undergo prostate biopsy for evaluation of possible PCa because of increased serum prostate specific antigen (PSA) level, abnormal digital rectal exam (DRE) or both. The presence of chronic inflammatory infiltrate (CII) has been detected in prostate specimens and might be involved in the growing processes involving both PCa and BPH [34—37]. However, the nature of the association of CII with PCa is a matter of controversy and still holds unsettled.

The aim of the present study was to investigate on associations, if any, of CII with PCa detection in a population of patients who were referred to our institution for a first set biopsy because of suspected PCa.

2. Materials and methods

We retrospectively reviewed the records of 1260 patients who underwent transrectal ultrasound biopsy (TRUSB) at our institution from September 2010 to September 2014. Excluding criteria were as follows: (i) prostate re-biopsy, (ii) patients in active surveillance, (iii) PSA $\geq$ 30 mg/dL, (iv) metastatic patients, (v) number of biopsy cores less than 14, (vi) incidental PCa after transurethral resection of the prostate (TURP) and (vii) painful rectal exam. After excluding criteria, indications of TRUSB included increased serum PSA levels, abnormal DRE with normal PSA, increased PSA and abnormal DRE (DRE + PSA), abnormal ultrasound imaging of the prostate with normal PSA. Abnormal DRE findings were as follows: diffusely hard prostate, discrete firm area, irregular contours or prominent lobe asymmetry. Family history of PCa (Fam PCa) and treatment with inhibitors of the enzyme 5-α reductase (5-ARI) were also investigated. Age (years) and body mass index (BMI, kg/m^2) were calculated in each patient. PSA was measured by immuno-radiometric test (normal range: 2—4 mg/dL). The volume of the prostate (PV) was measured by TRUS before performing biopsies. PV was determined by using the formula for an ellipsoid when viewed 3-dimensionally and the formula was transformed into volume (mL). The density of PSA (PSAD) was also computed.

In each biopsy core, the dedicated pathologists systematically assessed the following issues: (i) length, (ii) detection and grade of PCa according to the Gleason score system (biopsy Gleason score: BGS), (iii) length of biopsy core involved by PCa, (iv) prostatic intraepithelial neoplasia (PIN), (v) chronic inflammatory infiltrate (CII), (vi) glandular atrophy (GA) and (vii) atypical small acinar cell proliferation (ASAP). Chronic inflammation criteria, which have already been reported [9,10], included inflammatory cell infiltrate composed predominantly of lymphocytes associated with admixed plasma cells showing a periglandular distribution pattern. Sheets of neutrophils around and within the glands as well as aspects granulomatous prostatitis were the histopathology criteria which excluded a diagnosis of CII of the prostate.

According to biopsy outcome, the patient population was clustered in subpopulations with or without PCa. Summary statistics of population and subpopulations (with or without PCa) were calculated, and included means (SD) for continues variables as well as proportions (rates) for