Inflammation on Prostate Needle Biopsy is Associated with Lower Prostate Cancer Risk: A Meta-Analysis

Shaleen R. Vasavada, Ryan W. Dobbs, André A. Kajdacsy-Balla, Michael R. Abern and Daniel M. Moreira*

From the Departments of Urology and Pathology (AAK-B), University of Illinois at Chicago, Chicago, Illinois

Abbreviations and Acronyms

PCa = prostate cancer

PNB = prostate needle biopsy

PSA = prostate specific antigen

Accepted for publication November 30, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence: Department of Urology, University of Illinois at Chicago, 820 South Wood St., Suite 515 (MC 955), Chicago, Illinois 60612 (e-mail: moreira@uic.edu).

Purpose: We performed a comprehensive literature review and meta-analysis to evaluate the association of inflammation on prostate needle biopsies and prostate cancer risk.

Materials and Methods: We searched Embase®, PubMed® and Web of Science™ from January 1, 1990 to October 1, 2016 for abstracts containing the key words prostate cancer, inflammation and biopsy. Study inclusion criteria were original research, adult human subjects, cohort or case-control study design, histological inflammation on prostate needle biopsy and prostate cancer on histology. Two independent teams reviewed abstracts and extracted data from the selected manuscripts. Combined ORs and 95% CIs of any, acute and chronic inflammation were calculated using the random effects method.

Results: Of the 1,030 retrieved abstracts 46 underwent full text review and 25 were included in the final analysis, comprising a total of 20,585 subjects and 6,641 patients with prostate cancer. There was significant heterogeneity among studies (I^2 = 84.4%, p <0.001). The presence of any inflammation was significantly associated with a lower prostate cancer risk in 25 studies (OR 0.455, 95% CI 0.337–0.573). There was no evidence of publication bias (p >0.05). When subanalyzed by inflammation type, acute inflammation in 4 studies and chronic inflammation in 15 were each associated with a lower prostate cancer risk (OR 0.681, 95% CI 0.450–0.913 and OR 0.499, 95% CI 0.334–0.665, respectively).

Conclusions: In a meta-analysis of 25 studies inflammation on prostate needle biopsy was associated with a lower prostate cancer risk. Clinically the presence of inflammation on prostate needle biopsy may lower the risk of a subsequent prostate cancer diagnosis.

Key Words: prostatic neoplasms, biopsy, inflammation, prostate-specific antigen, risk factors

Inflammation is a critical step in the development of many types of cancer. Cervical, hepatocellular, esophageal and gastric carcinomas have well established models of inflammation leading to neoplasia. However, the role of inflammation in the development of PCa remains controversial. Although inflammatory infiltrate is a common histological finding on PNB, varying from 68% to 82%, its association with PCa has been the subject of multiple studies with mixed results.[1] For example, Gurel et al found that prostate inflammation was associated with a higher incidence of PCa[1] while Moreira et al used data from a large clinical trial and

0022-5347/18/1995-1174/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.11.120
Vol. 199, 1174-1181, May 2018
Printed in U.S.A.

reported that baseline acute and chronic inflammation were independently associated with a lower risk of subsequent PCa diagnosis.[2] Moreover, several studies showed no association between inflammation and PCa.[3–6]

Given the multitude of studies showing mixed results, we performed a systematic review and meta-analysis of studies evaluating the association of prostate inflammation in PNB and the diagnosis of PCa among adult males. We hypothesized that any inflammation (chronic or acute) on PNB is associated with an increased risk of PCa diagnosis. Secondarily, we examined the association of chronic and acute inflammation separately with PCa diagnosis.

MATERIAL AND METHODS

Evidence Acquisition

To determine the relationship between inflammation on PNB and PCa diagnosis we performed a comprehensive literature search on the Embase, PubMed and Web of Science databases for articles published between January 1, 1990 and October 1, 2016 with the relevant terms PCa, biopsy and inflammation. We retrieved 1,458 abstracts, including 260 from Embase, 704 from PubMed and 494 from Web of Science. After removing duplicates the final abstract count was 1,030.

Two independent teams (SRV and MRA, and RWD and DMM) reviewed the abstracts to select those for full manuscript review based on certain criteria, including English language, original research, adult human subjects, cohort or case-control study design, evaluation of histological inflammation on PNB and PCa demonstrated on histology. Discrepancies between the reviewing teams were reconciled by consensus. Unpublished studies and abstracts without full text publications were not considered for analysis.

A total of 46 abstracts met study inclusion criteria and were selected for full text review. Of these studies an additional 21 were excluded due to lack of calculated or calculable measure of association between inflammation and PCa (RR, OR or HR) for a final study sample of 25 (fig. 1). The final analysis study sample consisted of 20,585 subjects and 6,641 PCa cases.

Data Abstraction

Data were abstracted from full text articles by 2 independent reviewers (SRV and RWD) and discrepancies were reconciled by a third reviewer (DMM). For each study the number of cases, defined as patients with confirmed PCa, and the total cohort size, defined as patients who underwent PNB, were recorded. Study interval, mean PSA, mean patient age, percent of African American men and percent of family history positive for PCa were also included when reported. Articles that did not distinguish between acute or chronic cases were labeled as any type of inflammation. For articles showing acute and chronic separately and no overall or any inflammation we considered chronic inflammation data to be any inflammation since the prevalence of chronic inflammation is far greater than that of acute inflammation.[2] Publications were evaluated for quality and risk of bias using NOS (Newcastle-Ottawa Scale).[7]

Statistical Analysis

The primary objective of the study was the association of any histological prostate inflammation and the diagnosis of pathology proven PCa as dichotomous variables. The 2 secondary objectives of the study were the association of acute and chronic histological prostate inflammation with the diagnosis of pathology proven PCa with all treated as dichotomous variables.

The summary of effects of the outcomes was calculated as the OR and 95% CI. Multivariate ORs were used when available and otherwise univariate ORs were used. The presence of heterogeneity across studies was evaluated by the chi-square test for homogeneity and the I^2 statistic with I^2 greater than 50% indicating at least moderate statistical heterogeneity. Because the chi-square statistic has low sensitivity to detect heterogeneity, $p \leq 0.1$ was considered to indicate significant heterogeneity. Given the significant heterogeneity across studies, data were pooled using the DerSimonian-Laird random effects method. Publication bias was assessed using a funnel plot as well as the Begg and Egger tests. We performed sensitivity analysis stratifying studies based on the specimen in which prostate cancer was determined (the same specimen as inflammation vs a subsequent specimen). All statistical analyses were 2-tailed and done using Stata®, version 12.0 with $p < 0.05$ considered statistically significant.

RESULTS

A total of 20,585 subjects and 6,641 PCa cases were included in the final analysis. Of the 25 studies evaluated 15 measured chronic inflammation only, 4 recorded acute and chronic inflammation, and 10 only recorded any inflammation. A total of 12 studies did not adjust for covariates while the remaining 13 adjusted for variables including age, PSA, race and prostate volume. Median study quality based on NOS was 6.5 (range 5 to 9) (supplementary table, http://jurology.com/).[1–6,8–26]

Among the 25 studies included in the meta-analysis there was significant heterogeneity ($I^2 = 84.4\%$, $p < 0.001$). Thus, a random effects model was used. The presence of any inflammation in PNB was significantly associated with a lower PCa risk (OR 0.455, 95% CI 0.337–0.573). Figure 2 shows a forest plot of individual studies. There was no evidence of publication bias in the Begg and Egger tests (each $p > 0.05$) or in the funnel plot (fig. 3). A cumulative forest plot showed that there were no significant effects of time/year of publication (supplementary figure, http://jurology.com/).

A total of 13 studies measured inflammation and prostate cancer in the same specimen (ie the same PNB) while 12 measured inflammation prior to prostate cancer (ie different specimens).