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

Shaleen R. Vasavada¹, Ryan W. Dobbs¹, André A. Kajdacsy-Balla², Michael R. Abern¹, Daniel M. Moreira¹

¹Department of Urology, University of Illinois at Chicago
²Department of Pathology, University of Illinois at Chicago

Word count: 2,235
Abstract count: 248
References: 30
Tables: 0
Figures: 4
Supplemental materials: 3

Source of Funding: None

Key Words: Humans; Incidence, Inflammation; Male; Meta-analysis; Prostate Cancer; Prostatic Neoplasm; Prostate-Specific Antigen; Prostatitis; Risk Factors.

Corresponding author:
Daniel M. Moreira, MD MHS
Assistant Professor of Urology
University of Illinois at Chicago (UIC)
820 S. Wood street, Suite 515 (MC 955)
Chicago, IL 60612
moreira@uic.edu
Purpose:
We performed a comprehensive literature review and meta-analysis evaluating the association of inflammation on prostate needle biopsies (PNB) and prostate cancer (PCa) risk.

Materials and Methods:
We searched EMBASE, PubMed, and Web of Science from January 1, 1990 to October 1, 2016 for abstracts containing PCa, inflammation, and biopsy keywords. Inclusion criteria were original research, adult human subjects, cohort or case-control study design, histologic inflammation on PNB, and PCa demonstrated on histology. Two independent teams reviewed abstracts and extracted data from the selected manuscripts. Combined odds ratio (OR) and 95% confidence intervals (CI) for any, acute and chronic inflammation were calculated using random effects method.

Results:
Of the 1030 abstracts retrieved, 46 underwent full text review and 25 studies were included in the final analysis, comprising 20,585 subjects and 6,641 PCa cases. There was significant heterogeneity among studies ($I^2 = 84.4\%$, $P<0.001$). The presence of any inflammation was significantly associated with a lower PCa risk ($OR = 0.455$, 95% CI = 0.337 - 0.573, 25 studies). There was no evidence of publication bias ($P>0.05$). When sub-analyzed by type of inflammation, the presence of acute ($OR = 0.681$, 95% CI = 0.450 - 0.913, 4 studies) and chronic inflammation ($OR = 0.499$, 95% CI = 0.334 - 0.665, 15 studies) were each associated with lower PCa risk.

Conclusion:
In a meta-analysis of 25 studies, inflammation on PNB was associated with lower PCa risk. Clinically, the presence of inflammation on PNB may lower the risk of subsequent PCa diagnosis.
Introduction:

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 prostate cancer (PCa) remains controversial. Although inflammatory infiltrate is a common histological finding on prostate needle biopsies (PNB), varying from 68% and 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 while Moreira et al., using data from a large clinical trial, reported that baseline acute and chronic inflammation were independently associated with lower risk of subsequent PCa diagnosis.¹,² Moreover, several studies found no association between inflammation and PCa.³–⁶ Given the multitude of studies showing mixed results, we sought to perform 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 hypothesize that any inflammation (chronic or acute) on PNB is associated with an increased risk of PCa diagnosis. Secondarily, we sought to examine 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 diagnosis of PCa, we performed a comprehensive literature search on 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 (full search strings available in the supplemental materials). We retrieved a total of 1,458 abstracts: 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; RWD and DMM) reviewed the abstracts to select those for full manuscript review based on the following criteria: English language, original research, adult human subjects, cohort or case-control study design, evaluation of histologic inflammation on PNB, and PCa demonstrated on histology. Discrepancies between reviewing teams were
reconciled by consensus. Unpublished studies and abstracts without full-text publications were not considered. A total of 46 abstracts met the inclusion criteria and were selected for full text review. Of these, 21 additional studies were excluded due to lack of calculated or calculable measure of association between inflammation and PCa (either relative risk, odds ratio or hazard ratio) for a final study sample of 25 studies (Figure 1). The final analysis study sample consisted of 20,585 subjects and 6,641 PCa cases.

Data Abstraction:
Data abstraction from full text articles was performed by two 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 total cohort size (defined as patients undergoing PNB) were recorded. Study interval, mean prostate-specific antigen (PSA), mean patient age, percentage of African American men, and percentage of positive family history for PCa were also included when reported. Articles that did not distinguish between acute or chronic were labeled as “any” type of inflammation. For articles reporting acute and chronic separately and no overall or “any” inflammation, chronic inflammation data was considered “any” inflammation given the prevalence of chronic inflammation is far greater than acute.\textsuperscript{2} Publications were evaluated for quality and risk of bias using the Newcastle-Ottawa scale (NOS).\textsuperscript{7}

Statistical Analysis:
The primary objective of the study was the association of any histological prostate inflammation and the diagnosis of pathology-proven PCa, both as dichotomous variables. The two secondary objectives of the study were the association of acute and chronic histological prostate inflammation with the diagnosis of pathology-proven PCa, all treated as dichotomous variables. Summary of effects for the outcomes were calculated as odds ratio (OR) and 95% confidence intervals (CI). Multivariate odds ratios were used when available; otherwise, univariate odds ratios were used. The presence of heterogeneity across studies was evaluated using the $\chi^2$ test for homogeneity and the $I^2$ statistic, with $I^2 > 50\%$ indicating at least moderate
statistical heterogeneity. Given the $\chi^2$ statistic has a low sensitivity for detecting heterogeneity, a $P$ value $\leq 0.1$ was considered to indicate significant heterogeneity. Given the significant heterogeneity across studies, data was pooled using the DerSimonian–Laird random effects method. Publication bias was assessed using funnel plot as well as the Begg's and Egger's tests. We performed sensitivity analysis stratifying studies based on the specimen in which prostate cancer was determined (same specimen as inflammation versus subsequent specimen). All statistical analyses were two-tailed and done using Stata 12.0 (StataCorp LP, TX). A $P$ value $< 0.05$ was considered to indicate statistical significance.
Results:

A total of 20,585 subjects and 6,641 PCa cases were included in the final analysis. Of the 25 studies evaluated, 15 studies measured chronic inflammation only, 4 studies recorded acute and chronic inflammations, and 10 studies only recorded “any” inflammation. A total of 12 studies did not adjust for co-variates; the remaining 13 adjusted for variables including age, PSA, race, and prostate volume. The median study quality based on NOS was 6.5 (range: 5-9, Supplemental Table 1). 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). The Forest plot for individual studies is shown in Figure 2. There was no evidence of publication bias in the Begg’s and Egger’s tests (both $P > 0.05$) and in the funnel plot (Figure 3). A cumulative forest plot showed that there were no significant effects of time/year of publication (Supplemental Figure 1). A total of 13 studies measured inflammation and prostate cancer in the same specimen (i.e. same PNB) while 12 measured inflammation prior to prostate cancer (i.e. different specimens). Comparable results were found in stratified analysis based on the timing of inflammation and prostate cancer diagnosis (same specimen OR = 0.363, 95% CI = 0.245 - 0.480; different specimens OR = 0.560, 95% CI = 0.329 - 0.791).

Of the 4 studies evaluating the association of acute inflammation and PCa, there was no significant heterogeneity ($I^2 = 31.6\%, P = 0.223$). The presence of acute inflammation was also associated with lower PCa risk (OR = 0.681, 95% CI = 0.450 - 0.913, Figure 4a). Finally, significant heterogeneity ($I^2 = 88\%, P < 0.001$) was also verified in the 15 studies evaluating the association of chronic inflammation and PCa. Similar to any and acute inflammation, chronic inflammation was associated with lower PCa risk (OR = 0.499, 95% CI = 0.334 - 0.665, Figure 4b). No evidence of publication bias was observed in the analysis of acute and chronic inflammations (both $P > 0.05$, data not shown).
Discussion:

Inflammation is a common histological finding in the prostate of men undergoing PNB. However, its clinical significance is still the matter of much debate. Multiple previous studies have evaluated the relationship between inflammation and the subsequent diagnosis of PCa and have reached differing conclusions. To better assess this association, we performed a comprehensive literature review and meta-analysis evaluating the association of inflammation on PNB and PCa risk. We found that overall inflammation on PNB was associated with lower PCa risk. We also found that acute and chronic inflammations on PNB evaluated separately were also associated with lower PCa risk.

Previous studies have sought to evaluate the association between prostate inflammation and PCa. Meta-analyses by Dennis et al.\textsuperscript{8} and Jiang et al.\textsuperscript{9} both found a positive association between clinical prostatitis and PCa with similar pooled odds ratios of 1.65 (95% CI = 1.32 - 2.06) and 1.50 (95% CI = 1.39 - 1.62) respectively for fixed effects models.\textsuperscript{8,9} These studies were comprised of pooled analyses of either cohort or case-control studies and the presence or absence of prostatitis was determined by chart review or personal interview. While these studies provide an important clinical link between clinical prostatitis and PCa, they rely on patient definitions and recall of prior prostatitis which may be vulnerable to recall bias. Moreover, clinical prostatitis is not always accompanied by histological signs of inflammation and vice versa. Thus, these studies are not well-suited to determine the associated of histological inflammation and PCa. Prior studies have shown that rates of asymptomatic histological inflammation and latent infection are common findings in men, particularly those with BPH and concomitant urologic conditions. Given that subclinical inflammation may be present in many men, our study utilizes histology to better determine the association between histological inflammation and the subsequent development of PCa. The high prevalence of inflammation in pathological samples of prostate tissue from surgery or biopsy has suggested a possible link between inflammation and PCa. While the molecular pathogenesis of PCa has been characterized by genes and proteins involved in pro-inflammatory pathways, most scientific literature has shown inflammation having a protective role for PCa incidence.\textsuperscript{2} The ability for pre-malignant cells to evade and downregulate the host’s immune defenses
determines their survival and neoplastic potential. Inflammatory response can prevent this carcinogenesis by recognizing and eliminating tumor-specific antigens, a process known as immunosurveillance. Therefore, in PCa’s tumor milieu, a balance between the immune system upregulation and downregulation exists. Inflammation is a hallmark of immune system upregulation and thus it is plausible that it favors the host’s defense mechanisms with a lower risk of PCa in the current study. Our results implicate inflammation and immunomodulation as candidate targets for pharmacologic intervention to prevent and potentially treat PCa.

Confounding factors could play a role in the association between inflammation and lower PCa risk. Histological prostate inflammation has been shown to elevate PSA levels and prostates are biopsied based on patients’ PSA levels; therefore, for a given PSA level those with inflammation would seem to have lower risk of PCa because the elevation in PSA is related to inflammation as opposed to PCa. Alternatively, given that inflammation-related PSA elevation can lead to more PNB, men with inflammation are more likely to undergo PNB and thus more likely to be diagnosed with indolent PCa that would not be detected in the absence of inflammation. This phenomenon could increase the incidence of cancers among men with inflammation. To minimize these potential biases, we calculated odds ratios using multivariate analysis when available which, in most cases, were adjusted for PSA levels. Moreover, studies like Moreira et al., where PNBs were performed regardless of PSA levels, showed an association of inflammation and lower PCa risk. Thus, the association between inflammation and lower risk of PCa appears to be independent of PSA levels. Reviewer selection bias can also occur if reviewers select favorable participant data that is not representative of the entire evidence base. We avoided this by forming two independent review teams for evidence acquisition and strictly applying exclusion criteria to the studies. Although these exclusions increase the homogeneity of the results, they limit the generalizability of our study. Another potential confounding factor is that patients with inflammation may have had more opportunities to be diagnosed with PCa since they were selected for re-biopsy more frequently. Nickel et al. found evidence of a relationship between the degree of lower urinary tract symptoms and the degree of chronic inflammation.10 Due to their urinary symptoms, patients are more likely to visit a urologist, have their PSA levels monitored, and undergo PNB. Additionally, acute inflammation
on PNB is usually associated with chronic inflammation and infrequently an isolated finding. Of the 25 studies evaluated, only 4 analyzed acute inflammation separately. Thus, our findings related to acute inflammation are limited by lower statistical power and the co-occurrence of chronic inflammation. Finally, by only including articles published in English, our meta-analysis is subject to language bias, where non-English language articles are more likely to be written in English if they report significant results.

Determining causal relationship based on observational studies is a difficult endeavor. However, there are established criteria to indicate potential causality. Our systematic review suggests that some elements of this criteria applies to the association of histological prostate inflammation and PCa risk. For example, the strength of the association is relatively large (nearly 50% reduction in PCa odds) and it seems to be consistent across multiple studies with only a few exceptions. Moreover, multiple studies showed temporal association, where inflammation preceded PCa, and others found a biologic gradient, where more extensive inflammation was associated with lower PCa risk. While the mechanisms linking inflammation to lower prostate carcinogenesis could not be established in our study, it is likely that a combination of biological and confounding factors may explain the association between inflammation and lower PCa risk.

There are several potential implications of our study. Since we found histological prostate inflammation is associated with lower PCa risk, the follow-up guidelines for these patients might be adjusted for their reduced PCa risk. As such, our results encourage pathologists to systematically evaluate and report the presence of prostate inflammation on biopsies as it may have implications for repeat prostate biopsy strategy. Furthermore, studies evaluating the biology of inflammation and how it relates to carcinogenesis are needed since they may identify areas for PCa prevention therapies.

In conclusion, in a meta-analysis of 25 studies evaluating the association of prostate inflammation on PNB and PCa, histological prostate inflammation was associated with lower PCa risk. From a clinical standpoint, the presence of inflammation on PNB may lower the risk of subsequent PCa diagnosis.
References:


Supplemental Material:

Search strings:

**PUBMED:**


**Web of Science:**

(TI="prostatic neoplasms" OR "prostate cancer" OR "prostate neoplasm" OR "prostatic neoplasm" OR "prostatic cancer" OR "neoplasm of the prostate" OR "cancer of the prostate" OR "neoplasm of prostate" OR "cancer of prostate" OR "prostate malignancy" OR "prostatic malignancy" OR "prostate tumor") OR TO="prostatic neoplasms" OR "prostate cancer" OR "prostate neoplasm" OR "prostatic neoplasm" OR "prostatic cancer" OR "neoplasm of the prostate" OR "cancer of the prostate" OR "neoplasm of prostate" OR "cancer of prostate" OR "prostate malignancy" OR "prostatic malignancy" OR "prostate tumor") AND (TI="prostatitis" OR "inflammatory" OR "inflammation" OR "inflammed" OR "macrophage" OR "neutrophil" OR "lymphocyte" OR "stromal reaction") OR TO="prostatitis" OR "inflammatory" OR "inflammation" OR "inflammed" OR "macrophage" OR "neutrophil" OR "lymphocyte" OR "stromal reaction") AND (TI="biopsy" OR "histology") OR TO="biopsy" OR "histology")

**EMBASE:**
'prostatic neoplasms'/exp/mj OR 'prostatic neoplasms'/mj OR 'prostate cancer'/exp/mj OR 'prostate cancer' OR 'prostate neoplasm'/exp/mj OR 'prostate neoplasm'/mj OR 'prostatic neoplasm'/exp/mj OR 'prostatic neoplasm'/mj OR 'prostatic cancer'/exp/mj OR 'prostatic cancer'/mj OR 'neoplasm of the prostate' OR 'cancer of the prostate' OR 'neoplasm of prostate' OR 'cancer of prostate' OR 'prostate malignancy' OR 'prostatic malignancy' OR 'prostate tumor'/exp/mj OR 'prostate tumor'/mj AND ('prostatitis'/exp/mj OR 'prostatitis'/mj OR 'inflammatory' OR 'inflammation'/exp/mj OR 'inflammation'/mj OR 'macrophage'/exp/mj OR 'macrophage'/mj OR 'neutrophil'/exp/mj OR 'neutrophil'/mj OR 'lymphocyte'/exp/mj OR 'lymphocyte'/mj OR 'stromal reaction') AND ('biopsy'/exp OR 'biopsy' OR 'histology'/exp OR 'histology') AND ([young adult]/lim [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [1990-2016]/py NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Country</th>
<th>No of subjects / PCa cases</th>
<th>Inflammation type</th>
<th>OR (95% CI)</th>
<th>Multivariable adjustments</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu12, 1998</td>
<td>USA</td>
<td>388/129</td>
<td>Chronic</td>
<td>0.58 (0.35, 0.96)</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>Chan3, 1999</td>
<td>USA</td>
<td>92/45</td>
<td>Any</td>
<td>1.83 (0.41, 8.17)</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>MacLennan13, 2006</td>
<td>USA</td>
<td>177/39</td>
<td>Chronic</td>
<td>0.58 (0.25, 1.35)</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>Karakiewicz14, 2007</td>
<td>Canada</td>
<td>4526/1633</td>
<td>Chronic</td>
<td>0.19 (0.13, 0.27)</td>
<td>Age, PV, PSA</td>
<td>6</td>
</tr>
<tr>
<td>Wolters3, 2007</td>
<td>Multiple</td>
<td>98/44</td>
<td>Both</td>
<td>1.24 (0.48, 3.19)</td>
<td>n/a</td>
<td>6</td>
</tr>
<tr>
<td>Abouassaly15, 2008</td>
<td>USA</td>
<td>57/23</td>
<td>Chronic</td>
<td>0.28 (0.08, 0.92)</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>Terakawa16, 2008</td>
<td>Japan</td>
<td>143/86</td>
<td>Any</td>
<td>0.25 (0.12, 0.51)</td>
<td>n/a</td>
<td>8</td>
</tr>
<tr>
<td>Abdel-Meguid17, 2009</td>
<td>Saudi Arabia</td>
<td>214/76</td>
<td>Chronic</td>
<td>1.18 (0.67, 2.08)</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>Bassett18, 2009</td>
<td>USA</td>
<td>655/159</td>
<td>Chronic</td>
<td>0.06 (0.01, 0.23)</td>
<td>n/a</td>
<td>6</td>
</tr>
<tr>
<td>Kopp19, 2011</td>
<td>USA</td>
<td>139/41</td>
<td>Any</td>
<td>0.15 (0.04, 0.57)</td>
<td>Age, race, FMH, PSA</td>
<td>8</td>
</tr>
<tr>
<td>Pepe20, 2011</td>
<td>Italy</td>
<td>320/66</td>
<td>Chronic</td>
<td>4.79 (2.7, 8.49)</td>
<td>n/a</td>
<td>4</td>
</tr>
<tr>
<td>Kryvenko21, 2012</td>
<td>USA</td>
<td>1148/574</td>
<td>Any</td>
<td>0.59 (0.45, 0.77)</td>
<td>PSA</td>
<td>8</td>
</tr>
<tr>
<td>van Vuuren22, 2012</td>
<td>South Africa</td>
<td>201/405</td>
<td>Any</td>
<td>0.37 (0.24-0.56)</td>
<td>n/a</td>
<td>7</td>
</tr>
<tr>
<td>Yli-Hemminki23, 2013</td>
<td>Finland</td>
<td>85/293</td>
<td>Any, Acute</td>
<td>0.71 (0.46-1.10)</td>
<td>Age, FMH, PV, PSA</td>
<td>9</td>
</tr>
<tr>
<td>Gurel1, 2014</td>
<td>USA</td>
<td>400/191</td>
<td>Chronic</td>
<td>2.19 (1.18, 4.09)</td>
<td>Age, race, FMH</td>
<td>9</td>
</tr>
<tr>
<td>Moreira3, 2014</td>
<td>Multiple</td>
<td>6238/900</td>
<td>Both</td>
<td>0.65 (0.55, 0.77)</td>
<td>Age, race, BMI, FMH, PV, PSA</td>
<td>8</td>
</tr>
<tr>
<td>Amini4, 2015</td>
<td>Iran</td>
<td>2207/920</td>
<td>Chronic</td>
<td>0.40 (0.31, 0.53)</td>
<td>Age, PSA</td>
<td>6</td>
</tr>
<tr>
<td>Murtola5, 2015</td>
<td>USA</td>
<td>445/197</td>
<td>Any</td>
<td>0.85 (0.41, 1.76)</td>
<td>n/a</td>
<td>7</td>
</tr>
<tr>
<td>Porcaro25, 2015</td>
<td>Italy</td>
<td>441/203</td>
<td>Chronic</td>
<td>0.19 (0.10, 0.37)</td>
<td>Age, PV, PSA</td>
<td>7</td>
</tr>
<tr>
<td>Porcaro26, 2015</td>
<td>Italy</td>
<td>251/103</td>
<td>Chronic</td>
<td>0.57 (0.32, 1.01)</td>
<td>Age, BMI, PSAD, PV, TZV, PZV, PVI</td>
<td>7</td>
</tr>
<tr>
<td>Servian26, 2015</td>
<td>Spain</td>
<td>528/201</td>
<td>Any</td>
<td>0.51 (0.34, 0.76)</td>
<td>Age, PV, PSA</td>
<td>6</td>
</tr>
<tr>
<td>Yun6, 2015</td>
<td>Korea</td>
<td>171/45</td>
<td>Any</td>
<td>1.03 (0.36, 2.94)</td>
<td>Age, PV, PSA</td>
<td>8</td>
</tr>
<tr>
<td>Benedetti27, 2016</td>
<td>Columbia</td>
<td>203/90</td>
<td>Chronic</td>
<td>0.95 (0.39, 2.32)</td>
<td>Presence, intensity and location of chronic inflammation, HGPIN, PIA</td>
<td>5</td>
</tr>
<tr>
<td>Kato28, 2016</td>
<td>Japan</td>
<td>78/16</td>
<td>Any</td>
<td>0.05 n/a</td>
<td>n/a</td>
<td>7</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Cases</td>
<td>Comparison</td>
<td>Odds Ratio (CI)</td>
<td>Test</td>
<td>Blinded</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>-------</td>
<td>------------</td>
<td>----------------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Rybicki\textsuperscript{29}, 2016</td>
<td>USA</td>
<td>968/574</td>
<td>Both</td>
<td>0.82 (0.58, 1.15)</td>
<td>PSA</td>
<td>8</td>
</tr>
</tbody>
</table>

BMI: body mass index, CI: confidence interval, FMH: family history, HGPIN: high-grade prostatic intraepithelial neoplasm, n/a: not available, NOS: Newcastle-Ottawa scale, OR: odds ratio, PIA: proliferative inflammatory atrophy, PSA: prostate-specific antigen, PSAD: PSA density, PV: prostate volume, PVI: prostate volume index, PZV: peripheral zone volume, TZV: transition zone volume
Supplemental Figure 1: Forest plot for individual studies sorted by publication year

CI: confidence interval
Figure 1: Evidence acquisition flowchart

Abstracts identified from EMBASE (N = 260)

Abstracts identified from Web of Science (N = 494)

Abstracts identified from PUBMED (N = 704)

Abstracts identified by initial search (N = 1458)

Duplicates removed (N = 428)

Abstracts excluded after applying inclusion criteria (N = 984)

Manuscripts selected for full-text review (N = 46)

Studies excluded due to lack of measure of association (N = 21)

Studies included in the meta-analysis (N = 25)
Figure 2: Forest plot for individual studies

CI: confidence interval
Figure 3: Funnel plot

Funnel plot with pseudo 95% confidence limits
**Figure 4a: Forest plot for acute inflammation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolters*, 2007</td>
<td>1.24 (0.48, 3.19)</td>
<td>2.82</td>
</tr>
<tr>
<td>Yli-Hemminni², 2013</td>
<td>0.41 (0.20, 0.86)</td>
<td>30.07</td>
</tr>
<tr>
<td>Moreira², 2014</td>
<td>0.75 (0.59, 0.94)</td>
<td>53.89</td>
</tr>
<tr>
<td>Rybicki²⁹, 2016</td>
<td>0.92 (0.51, 1.67)</td>
<td>13.22</td>
</tr>
<tr>
<td>Overall (I-squared = 31.6%, p = 0.223)</td>
<td>0.68 (0.45, 0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*NOTE: Weights are from random effects analysis*

CI: confidence interval
Figure 4b: Forest plot for chronic inflammation

CI: confidence interval
Abbreviations:

BMI: body mass index
CI: confidence interval
NOS: Newcastle-Ottawa scale
OR: odds ratio
PCa: prostate cancer
PNB: prostate needle biopsy
PSA: prostate-specific antigen