

# Prevalence of histological prostatitis in men with benign prostatic hyperplasia or adenocarcinoma of the prostate presenting without urinary retention

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**Objective.** To determine the prevalence of prostatitis on histopathological evaluation of prostatic tissue in men without urinary retention.

**Design, setting and subjects.** The clinical data and histopathology reports of men seen from January 1999 through March 2009 at our institution were analysed using Student's *t*-test, the Mann-Whitney test and Fisher's exact test where appropriate. Values were expressed as means, medians and ranges ( $p < 0.05$  accepted as statistically significant).

**Outcome measures.** Data collected included patient age, duration of lower urinary tract symptoms and hospitalisation, findings on digital rectal examination, prostate volume, haemoglobin concentration, serum creatinine and prostate-specific antigen (PSA) levels, and histological findings.

**Results.** Prostatic tissue of 385 men without urinary retention at presentation was obtained via biopsy (48.3% of cases), transurethral prostatectomy (62.9%), retropubic prostatectomy (6.8%) or radical prostatectomy (28.3%). On histological examination, benign prostatic hyperplasia (BPH) was found to be present in 213 patients (55.3%) and adenocarcinoma of the prostate (ACP) in 172 (44.7%). Histological prostatitis was present in 130 patients (61.0%) with BPH and 51 (29.7%) with ACP ( $p < 0.001$ ). A previous study of 405 men presenting with urinary retention at our institution showed histological prostatitis in 98/204 (48.0%) with BPH and in 51/201 (25.4%) with ACP. The group of men with BPH alone had a significantly lower mean serum PSA at presentation (4.5 ng/ml, range 0.3 - 20.8 ng/ml) compared with the group with BPH and prostatitis (11.2 ng/ml, range 0.2 - 145 ng/ml,  $p = 0.011$ ). The mean PSA level at presentation did not differ significantly between the group with ACP only (40.9 ng/ml, range 0 - 255 ng/ml) and the group with ACP plus prostatitis (1 672 ng/ml, range 0.3 - 38 169 ng/ml,  $p = 0.076$ ).

**Conclusions.** Among men presenting without urinary retention, histological prostatitis was significantly more prevalent in those with BPH than in those with ACP (61% v. 30%), similar to the previous study of men presenting with retention at our institution, in which histological prostatitis was significantly more prevalent in BPH than in ACP (48% v. 25%). This finding suggests that histological prostatitis is not significantly associated with the causation of ACP or urinary retention. Serum PSA at presentation was significantly higher in the group with BPH plus prostatitis compared with BPH alone, but not in the group with ACP plus prostatitis compared with ACP alone.

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Prostatic disease causes enormous morbidity worldwide. Currently adenocarcinoma of the prostate (ACP) is the most common form of cancer in men in the USA, with a predicted cost of US \$8.8 billion for continuing care of these patients by 2020.<sup>1</sup> Moreover, benign prostatic hyperplasia (BPH) affects an estimated 70% of men aged 61 - 70 years and 90% of those aged 81 - 90. By 2025, BPH is likely to affect 20% of the total male population.<sup>2</sup> Improved understanding of these diseases could have a significant impact on male health.

ACP and BPH are chronic diseases with a long period of development and progression. Interestingly, a self-reported history of prostatitis is associated with ACP and BPH.<sup>3</sup> The role of inflammation in prostatic disease is currently yet to be fully

elucidated, although there is emerging evidence that prostatic inflammation may contribute to prostate growth in terms of hyperplastic or neoplastic changes.<sup>4</sup> Histological evidence of inflammation has been reported in approximately 40% of cases of BPH and is associated with a significantly increased risk of acute urinary retention.<sup>5</sup> About 20% of all human cancers are caused by chronic inflammation, perhaps including ACP.<sup>6</sup> A better understanding of the relationship between prostatic inflammation and BPH or ACP may provide an opportunity to influence the diagnosis or treatment of prostatic disease.

In a previous study, we analysed 405 men presenting with urinary retention and found histological evidence of prostatitis in 98/204 men (48.0%) with BPH and in 51/201 (25.4%) with

ACP, suggesting that histological prostatitis is not significantly associated with causation of ACP in patients presenting with urinary retention.<sup>7</sup>

The aims of this study were to determine the prevalence of prostatic inflammation in men with histologically proven BPH or ACP without urinary retention and to compare their clinical features.

## Patients and methods

We performed a retrospective analysis of the clinical data on patients without urinary retention who underwent prostatic biopsy or prostatectomy between January 1999 and March 2009 in the Urology Department of our institution, a tertiary-level academic teaching hospital. The results of special investigations were obtained from the Chemical Pathology, Microbiology and Radiology departments. Histopathology reports on prostatic tissue specimens obtained by transrectal biopsy, transurethral prostatectomy, or open prostatectomy were provided by the Department of Anatomical Pathology at our institution.

The data were entered on an Excel database for statistical analysis with Student's *t*-test, the Mann-Whitney test and Fisher's exact test where appropriate, using GraphPad InStat software. All values are expressed as means or medians (ranges). A two-tailed *p*-value <0.05 was accepted as statistically significant.

## Results

Prostatic tissue was examined in a total of 385 men who did not have urinary retention at presentation (mean age 67.2 years,

median 67.1 years, range 47.4 - 97.0 years). Tissue was obtained by biopsy of the prostate in 48.3%, transurethral prostatectomy in 62.9%, retropubic prostatectomy in 6.8% and radical prostatectomy in 28.3% (more than one procedure was performed in some patients). On microscopic examination BPH was present in 213 patients (55.3%) and ACP in 172 (44.7%). Histological prostatitis was recorded by the pathologist in 130 of 213 men with BPH (61.0%) and in 51 of 172 (29.7%) of those with ACP (*p*<0.001).

Compared with the group with ACP, the men with BPH had a statistically significantly higher mean serum prostate-specific antigen (PSA) level at presentation and a greater proportion of them had a clinically benign prostate on digital rectal examination (DRE) (Table 1). However, there were no significant differences regarding age, duration of lower urinary tract symptoms (LUTS), length of hospitalisation, prostate volume, haemoglobin concentration or creatinine level (Table 1).

The group of men with BPH alone had a significantly lower mean serum PSA level at presentation compared with the group with BPH and histological prostatitis. The groups were otherwise statistically equivalent (Table 2).

Similarly, the group of men with ACP alone was statistically equivalent when compared with the group with ACP and histological prostatitis (Table 3).

## Discussion

There is emerging evidence suggesting a role of intraprostatic inflammation in prostatic disease, although its precise role in the pathogenesis or progression of disease has yet

**Table 1. Comparison of men with histological benign prostatic hyperplasia v. adenocarcinoma of the prostate**

	BPH	ACP	<i>p</i> -value
Number, <i>N</i>	213	172	
Age (years), mean (range)	67.6 (48.9 - 97.0)	66.7 (47.4 - 83.4)	0.4614
Histological prostatitis, <i>n</i> (%)	130/213 (61.0)	51/172 (29.7)	<0.001
LUTS duration (months), mean (range)	27.1 (0.5 - 180.0)	15.8 (1.0 - 60.0)	0.5397
DRE: BPH, <i>n</i> (%)	92/98 (93.9)	40/77 (51.9)	<0.0001
Hospitalisation (d), mean (range)	7.7 (1.0 - 38.0)	10.3 (2.0 - 181.0)	0.1228
Prostate volume (ml), mean (range)	45.6 (5.0 - 174.0)	46.1 (15.0 - 190.0)	0.9308
Haemoglobin (g/dl), mean (range)	13.6 (4.50 - 17.1)	13.6 (9.00 - 17.0)	0.9738
Creatinine (µmol/l), mean (range)	156.6 (10.0 - 1 636.0)	123.9 (72.0 - 834.0)	0.6946
PSA (ng/ml), mean (median; range)	8.8 (3.5; 0.2 - 145.0)	504.1 (10.4; 0 - 38 169)	<0.0001

**Table 2. Comparison of men with histological benign prostatic hyperplasia only v. BPH plus prostatitis**

	BPH only	BPH + prostatitis	<i>p</i> -value
Number, <i>N</i>	83	130	
Age (years), mean (range)	66.5 (48.9 - 88.3)	68.2 (51.1 - 97.0)	0.1855
Prostate volume (ml), mean (range)	39.4 (20.0 - 100.0)	49.7 (5.0 - 174.0)	0.5245
Haemoglobin (g/dl), mean (range)	14.0 (10.0 - 17.1)	13.4 (4.5 - 16.9)	0.0860
Creatinine (µmol/l), mean (range)	141.6 (10.0 - 1 265.0)	166.6 (32.0 - 1 636.0)	0.5386
PSA (ng/ml), mean (median; range)	4.5 (3.0; 0.3 - 20.8)	11.2 (6.0; 0.2 - 145.0)	0.0105

**Table 3. Comparison of men with histological adenocarcinoma of the prostate only v. ACP plus prostatitis**

	ACP only	ACP plus prostatitis	p-value
Number, N	121	51	
Age (years), mean (range)	67.2 (52.8 - 82.9)	65.4 (47.4 - 83.4)	0.3517
Prostate volume (ml), mean (range)	46.3 (15.0 - 190.0)	45.8 (20.0 - 86.0)	0.9685
Haemoglobin (g/dl), mean (range)	13.5 (9.0 - 17.0)	13.9 (11.5 - 17.0)	0.3615
Creatinine (µmol/l), mean (range)	130.0 (72.0 - 834.0)	106.8 (81.0 - 183.0)	0.3371
PSA (ng/ml), mean (median; range)	40.9 (13.2; 0 - 255.0)	1 672 (9.1; 0.3 - 38 169)	0.0759

to be determined. Dennis *et al.* conducted a meta-analysis examining the reported associations between prostatitis and ACP and found an increased risk of ACP among men with a history of prostatitis (odds ratio 1.7, 95% confidence interval 1.3 - 2.1).<sup>8</sup>

There are several potential causes of prostatic inflammation, including, though not limited to, infectious agents, hormonal changes, physical trauma, urine reflux and dietary habits.<sup>6</sup> Molecular pathological studies have suggested that inflammation generates free radicals, which cause severe oxidative and nitrosative damage to DNA and prostatic epithelial cells as well as inducing permanent genomic alterations, which may result in carcinogenesis.<sup>4,8</sup>

Moreover, genetic studies suggest that repeated bouts of injury – possibly due to damage from inflammatory cells – cause focal atrophy or proliferative inflammatory atrophy, leading to an increase in proliferation.<sup>6,9,10</sup> A small subset of the resultant cells may contain somatic genome alterations such as cytosine methylation within GSTP1 and telomere shortening, creating an increase in genetic instability that might initiate high-grade prostatic intraepithelial neoplasia and early ACP. Further insults activate further oncogenic transcription factors and deactivate tumour-suppressor genes, driving tumour progression.

Considering this evidence, our study sought to evaluate the prevalence of histological inflammation in men with ACP. A previous study of 405 men presenting with urinary retention found histological evidence of prostatitis in 48% of men with BPH and 25% with ACP ( $p < 0.0001$ ).<sup>7</sup> Data from the current study are similar; among 385 men who did not have urinary retention at presentation, 61% of those with BPH and 30% of those with ACP were found to have histological evidence of prostatitis ( $p < 0.001$ ). This suggests that histological prostatitis is more significantly associated with the causation of BPH than with that of ACP. Of note, other groups have also failed to demonstrate compelling evidence for a role of chronic inflammation with ACP.<sup>11,12</sup>

Regarding BPH, Mishra *et al.* found an increased incidence of acute and/or chronic intraprostatic inflammation (ACI) in more advanced BPH by utilising urinary retention as an endpoint in the natural history of BPH.<sup>2</sup> Asgari *et al.* also demonstrated a significant association between ACI and acute urinary retention.<sup>13</sup> Importantly, the MTOPS study demonstrated that men with BPH and prostatic inflammation showed an increased percentage of disease progression. At 4-year follow-up, only BPH patients with inflammation

developed acute urinary retention.<sup>14</sup> In the present study, prostatitis was present histologically in 61% of men with BPH. While this finding corresponds to the hypothesis that inflammation and BPH may be related, this study does not address BPH progression.

Several studies have evaluated the effect of inflammation and BPH on serum PSA levels. Irani *et al.* analysed 66 patients with exclusively benign prostatic tissue on prostate biopsies and found a significant correlation between the aggressiveness grading of the inflammatory reaction and serum PSA.<sup>15</sup> Nadler *et al.* found that acute and chronic inflammation was significantly more prevalent in patients with an elevated serum PSA level ( $>4.0$  ng/ml) (63% v. 27% and 99% v. 77%, respectively).<sup>16</sup> Recently a prospective study of 51 patients without evidence of ACP demonstrated extension of the inflammatory process directly related to elevations of serum PSA levels.<sup>17</sup> Correlating with these conclusions, the present data demonstrate a significantly elevated serum PSA in men with BPH plus prostatitis versus BPH alone (504.1 v. 8.8 ng/ml,  $p > 0.001$ ). Approaching significance, serum PSA was also increased in men with ACP plus prostatitis versus ACP alone (1 672 v. 41 ng/ml,  $p = 0.076$ ).

The limitations of this study include the facts that it was retrospective and some study parameters were incompletely recorded. Histological examination of prostatic tissue was not performed by a single pathologist, and data analysis was based on the written reports of various pathologists, so there may be under-reporting of inflammatory changes. Also, the extent or grade of inflammation was not quantified. However, there is no reason to suspect that the assessment of histological prostatitis would be biased by the presence of underlying BPH or ACP. Only men who had undergone procedures providing prostatic tissue were included in this study, so those with less severe prostatic disease may have been excluded. Finally, the study may be underpowered to demonstrate significance in all variables, such as PSA in the ACP versus ACP plus prostatitis cohorts.

While accumulating experimental evidence suggests a role for inflammation in both BPH progression and the causation of ACP, our clinical data do not entirely support this. Further clinical studies are needed to develop a more comprehensive understanding of the relationship between inflammation and prostatic disease.

## Conclusion

In men without urinary retention, histological prostatitis was significantly more prevalent in those with BPH than ACP. Serum

PSA at presentation was significantly higher in the group with BPH plus prostatitis than in the group with BPH alone, and approached significance in the group with ACP plus prostatitis compared with the group with ACP alone. The results of this study suggest that histological prostatitis is not significantly associated with the causation of ACP or with urinary retention.

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