

## Original Article

# Prostate calculi in cancer and BPH in a cohort of Korean men: presence of calculi did not correlate with cancer risk

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### Abstract

Prostatic calculi are common and are associated with inflammation of the prostate. Recently, it has been suggested that this inflammation may be associated with prostate carcinogenesis. The aim of this study was to investigate the relationship between prostatic calculi and prostate cancer (PCa) in prostate biopsy specimens. We retrospectively analyzed 417 consecutive patients who underwent transrectal ultrasonography (TRUS) and prostate biopsies between January 2005 and January 2008. Based on the biopsy findings, patients were divided into benign prostatic hyperplasia and PCa groups. TRUS was used to detect prostatic calculi and to measure prostate volume. The correlations between PCa risk and age, serum total PSA levels, prostate volume, and prostatic calculi were analyzed. Patient age and PSA, as well as the frequency of prostatic calculi in the biopsy specimens, differed significantly between both the groups ( $P < 0.05$ ). In the PCa group, the Gleason scores (GSs) were higher in patients with prostatic calculi than in patients without prostatic calculi ( $P = 0.023$ ). Using multivariate logistic regression analysis, we found that patient age, serum total PSA and prostate volume were risk factors for PCa ( $P = 0.001$ ), but that the presence of prostatic calculi was not associated with an increased risk of PCa ( $P = 0.13$ ). In conclusion, although the presence of prostatic calculi was not shown to be a risk factor for PCa, prostatic calculi were more common in patients with PCa and were associated with a higher GS among these men.

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**Keywords:** calculi, prostate, prostatic neoplasms, risk factors

## 1 Introduction

It has been suggested that immunological and inflammatory reactions contribute to the process of carcinogenesis [1]. Inflammation is thought to be involved in carcinogenesis via multiple mechanisms,

such as by inducing genomic damage and damage to cellular structures, acceleration of cell substitution, cell cloning, dispersed angiogenesis, and by the generation of a microenvironment that facilitates tissue regeneration [2]. Moreover, one study found that infection may be a main factor that predisposes individuals to liver cancer, and that many bacteria, such as *Helicobacter pylori*, can cause chronic inflammation that is related to carcinogenesis [3]. In fact, approximately 20% of all cancers in adults result from chronic inflammation due to infection or exposure to other environmental factors [1, 4]. Recently, epidemiological, histopathological and molecular

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biological studies have reported that inflammation of the prostate gland may contribute to the development of prostate cancer (PCa) [5, 6].

Prostatic calculi are very common and consist of calcified corpora amyloacea. They are associated with chronic inflammation, epithelial damage and obstruction of the glandular tissue on histological examination [7]. However, the clinical significance of prostatic calculi is not known. Prostatic calculi are asymptomatic in most cases, but large calculi may lead to urinary retention, prostatitis or chronic pelvic pain syndrome [8, 9] via unclear mechanisms.

It has been reported that a prostatic calculus is actually a cluster of bacteria and that these calculi may be the cause of prolonged bacteriosis in patients with recurrent urinary tract infections [10]. We therefore sought to determine the relationship between PCa and prostatic calculi detected by transrectal ultrasonography (TRUS) in patients with benign prostatic hyperplasia (BPH) and PCa.

## 2 Materials and methods

### 2.1 Patients

A total of 417 patients who underwent a TRUS-guided prostate biopsy between January 2005 and January 2008 were retrospectively analyzed. Patients who had a history of any of the following were excluded from the study: PCa, prostatitis, prostate or lower urinary tract surgery, radiotherapy, acute urinary retention, pyuria, or bacteriuria, as well as patients who had been previously prescribed medications for BPH.

A serum PSA level was obtained for all patients before a digital rectal examination (DRE) was performed. A biopsy was recommended when there was an abnormal finding on DRE or TRUS, or when the serum PSA was  $> 4 \text{ ng mL}^{-1}$ . Patients were divided into two groups (BPH and PCa) based on the results of prostate biopsy. Multiple parameters, including patient age, PSA, prostate volume, and the presence or absence of prostatic calculi, were recorded.

### 2.2 Prostate volume and calculi measurement

A single radiologist retrospectively analyzed the results of the prostate ultrasonography for all 417 patients. The radiologist's report included the prostate volume, the presence or absence of prostatic calculi, and the position of any prostatic calculi that were present. TRUS was performed with a 7-MHz Logicq



Figure 1. Prostatic calculi was determined by transrectal ultrasonography.

700 (GE, Cincinnati, OH, USA) linear transducer (Figure 1).

### 2.3 Histopathological analysis

A single pathologist examined all tissue specimens obtained from the prostate biopsies and classified each specimen as BPH or PCa. The pathologist also determined the Gleason score (GS) of the biopsies of men in the PCa group.

### 2.4 Statistical analysis

The age, PSA and prostate volume of patients in the BPH and PCa groups were compared using paired *t*-test. Rates of prostatic calculi in the two groups were compared using Pearson's chi-square test. Multivariate logistic regression analysis was performed to determine the correlation between PCa and age, total PSA, prostatic volume, and prostatic calculi. Pearson's Chi-square test was used to compare the GS of patients in the PCa group with and without prostatic calculi. *P*-values less than 0.05 were considered statistically significant. A statistical software package (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

## 3 Results

### 3.1 Patient characteristics

Of the 417 patients (mean age: 68.4 years) we included in this study, 291 had a pathological diagnosis

Table 1. Characteristics of patient.

Patient's characteristics	
Age (years), mean (95% CI)	68.4 (67.5–69.4)
BPH, <i>n</i> (%)	291 (69.8)
Prostate cancer, <i>n</i> (%)	126 (30.2)
Prostatic calculi, <i>n</i> (%)	182 (43.6)
BPH with calculi, <i>n</i>	113
Central zone calculi, <i>n</i> (%)	52 (46.02)
Peripheral zone calculi, <i>n</i> (%)	61 (53.98)
Prostate cancer with calculi, <i>n</i>	69
Central zone calculi, <i>n</i> (%)	28 (40.58)
Peripheral zone calculi, <i>n</i> (%)	41 (59.42)
PSA (ng mL <sup>-1</sup> ), mean (95% CI)	12.0 (10.5–13.8)
Prostate volume (mL), mean (95% CI)	38.4 (36.5–40.5)
Gleason score in PCa group, mean (95% CI)	7.6 (7.3–7.8)

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; PSA, prostate-specific antigen.

Table 2. Comparison of clinical variables between men in the prostate cancer and BPH groups.

	PCa ( <i>n</i> = 126)	BPH ( <i>n</i> = 291)	<i>P</i> -value
Age (years)	72.6 ± 7.5	66.6 ± 10.3	< 0.001 <sup>a</sup>
PSA (ng mL <sup>-1</sup> ) <sup>b</sup>	3.7 ± 1.6	2.0 ± 1.0	< 0.001 <sup>a</sup>
Prostate volume (mL) <sup>b</sup>	3.6 ± 0.5	3.7 ± 0.6	0.15 <sup>a</sup>
Prostate calculi, <i>n</i> (%)	69 (54.8%)	113 (38.8%)	0.003 <sup>c</sup>

Abbreviations: BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen. <sup>a</sup>Paired *t*-test; <sup>b</sup>Logarithmically adjusted; <sup>c</sup>Pearson's Chi-square test. Values are presented as mean ± SD.

Table 3. Results of multiple logistic regression analysis examining the correlation between clinicopathological variables and prostate cancer risk.

	Adjusted odds ratio	95% CI	<i>P</i> -value
Age	1.09	(1.05–1.12)	< 0.001
PSA <sup>a</sup>	3.29	(2.53–4.28)	< 0.001
Prostate volume <sup>a</sup>	0.22	(0.12–0.40)	< 0.001
Prostate calculi	1.54	(0.89–2.68)	0.13

Abbreviation: PSA, prostate-specific antigen; CI, confidence interval.

<sup>a</sup>Logarithmically adjusted.

Table 4. Association between prostatic calculi and Gleason score in men with prostate cancer.

	GS ≤ 6 ( <i>n</i> = 32)	GS ≥ 7 ( <i>n</i> = 94)				
		3 + 4	4 + 3	8	9	10
No. of patients with calculi	12	6	8	15	22	6
Percentage	37.50%	60.60% <sup>a</sup>				

Abbreviations: CI, confidence interval; GS, Gleason score; No., number.

<sup>a</sup>*P* = 0.023, compared with those with GS ≤ 6. Adjusted odds ratio, 2.56 (1.12–5.86) (95% CI), Pearson's Chi-square test.

of BPH and 126 had a pathological diagnosis of PCa. Prostatic calculi were noted in 182 patients. Of these 182 patients, 80 had calculi in the central zone and 102 had calculi in the peripheral zone. In the included 417 patients, the mean PSA was 12.0 ng mL<sup>-1</sup> and the mean prostate volume was 38.4 mL. The mean GS was 7.6 in the PCa group (Table 1).

### 3.2 Comparison of clinical variables of patients in the PCa and BPH groups

The mean age of patients in the PCa and BPH groups differed (72.6 and 66.6 years, respectively; *P* < 0.001). The mean PSA was 3.7 and 2.0 ng mL<sup>-1</sup> for the PCa and BPH groups, respectively (*P* < 0.001, PSA was logarithmically adjusted for analysis). However, logarithmically adjusted prostate volume did not differ between the two groups (3.6 and 3.7 mL, respectively; *P* = 0.15). Prostatic calculi were detected more frequently in the PCa group (54.8%) than in the BPH group (38.8%; *P* = 0.003) (Table 2).

### 3.3 Correlation between PCa and each variable

The frequency of PCa increased as patient age increased. In addition, men with PCa had higher PSA levels and smaller prostates than men without PCa (*P* < 0.001). However, there was no correlation observed between PCa and the presence of prostatic calculi (*P* = 0.13) (Table 3).

### 3.4 Relationship between GS and prostatic calculi

Among men in the PCa group, the percentage of patients with calculi was higher in the group with GS ≥ 7 than in the group with GS ≤ 6 (*P* = 0.023) (Table 4).

## 4 Discussion

In this study, prostatic calculi were identified more often among men in the PCa group than among men in the BPH group. The presence of prostatic calculi was correlated with a higher GS when PCa



was present, but it was not found to be associated with the presence of PCa. Previous studies regarding the relationship between PCa and prostatic calculi have found that bacteria were present in prostatic calculi. The authors were able to culture *Escherichia coli* and *Pseudomonas* species from prostatic calculi in PCa patients and postulated that inflammation resulting from the presence of these bacteria could influence prostate carcinogenesis [10, 11]. Moreover, there is a report that states that the risk of PCa is reduced as ejaculation frequency increases, thus indirectly demonstrating that prostatic calculi have a relationship with PCa, as the frequency of prostatic calculi is inversely correlated with ejaculatory frequency [12]. On the other hand, according to a report by Christian *et al.* [13], the precursor of prostatic calculi based on the prostate biopsies of 19 men (out of a total of 5 130 cases), and corpora amylacea were found to be uncommon in men with PCa. Therefore, the influence of prostatic calculi on PCa carcinogenesis has not been clearly established.

Recently, it has been shown that chronic inflammation of the prostate contributes to carcinogenesis. Researchers have postulated that inflammation is a cause of PCa because acute or chronic inflammatory infiltrates are frequently observed in PCa precursor lesions [14–16].

The causes of prostatic inflammation include sexually transmitted diseases, other infections, and exposure to chemicals, as well as physical stimulation. Many epidemiological studies have been conducted in order to examine the hypothesis that chronic or recurrent prostatitis results from the aforementioned causes and is involved in the induction or acceleration of PCa.

Dennis *et al.* [17] reported that a medical history of prostatitis was positively correlated with PCa (OR = 1.6), in a meta-analysis that included 11 case-control studies. Moreover, Roberts *et al.* [18] examined the correlation of acute, chronic and non-bacterial prostatitis with PCa. They found that acute prostatitis was significantly positively correlated with PCa, whereas chronic bacterial prostatitis was positively, but insignificantly correlated with PCa. No association was found between non-bacterial prostatitis and PCa.

In another study, Rosenblatt *et al.* [19] found that an insignificant positive correlation existed between prostatitis and PCa if the prostatitis was diagnosed  $\leq 2$  years before the diagnosis of PCa was made. This finding suggests the possibility of detection bias. Therefore, there is insufficient evidence available to

conclude that PCa is correlated with clinical prostatitis due to the discordance between the available research on this topic and the possibility of detection bias. Moreover, because research regarding the correlation between prostatitis and PCa has mostly been based on retrospective studies, detection bias, as a result of which the diagnosis rate of PCa is increased because of frequent urological examinations of patients with prostatitis, likely exists. In addition, recall bias exists regarding the difference in the ability of patients to remember a personal medical history of prostatitis based on their existing medical conditions. One study compared men with PCa and men with BPH patients, and found a recall bias regarding their recollection of having prostatitis based on whether or not they had PCa [6]. This type of bias can generate significant statistical errors.

The formative mechanism of prostatic calculi is not well understood, but is generally observed more often in normal prostate tissue than in the prostates of patients with PCa. Prostatic calculi are usually subclinical, but if inflammation is present along with the calculi, various symptoms of prostatism can be present. Shoskes *et al.* [20] found that prostatic calculi were generally identified in patients with chronic prostatitis and postulated that because prostatic calculi were present, there was more inflammation in the prostates of these men and that these men had to strain more to urinate than men without prostatic calculi. Therefore, it is possible that more inflammation is present in patients with a history of prostatitis or patients who have co-existing prostatitis and prostatic calculi as compared with patients who do not have prostatic calculi, and that this inflammation may therefore influence the development of PCa.

In another study regarding the association between prostatic calculi and prostatitis that was performed in 1961, Joachim [21] presented the hypothesis that prostatic calculi contributed to PCa carcinogenesis because they are related to chronic inflammation of the prostate and to intermittent bacterial infection. This was based on the finding that many more calculi were identified in the prostate tissue of PCa patients than in that of men with BPH. However, the overall frequency of prostatic calculi did not differ between the PCa and BPH groups in this study, based on histological examination and an X-ray that was performed before or after research [22, 23].

Moreover, in an epidemiological study comparing

the X-ray evidence of prostatic calculi with self-report of a history of prostatic calculi, the authors found no relationship between the presence of prostatic calculi and PCa [24, 25]. Of note, there is a large difference in the detection rate of prostatic calculi using X-rays and that using ultrasonography. Harada *et al.* [26] reported that 80% of calculi are identified with TRUS, but that X-ray only identifies 28% of the calculi. In addition, Peeling *et al.* [27] found that > 70% of prostate calculi images were identified with TRUS, which were not visualized with X-rays. Therefore, we used TRUS to image the prostate in order to analyze the correlation between the presence of prostatic calculus and PCa.

Limitations of this study included the retrospective nature of the analysis, and the significant difference in age that existed between men in the PCa group and those in the BPH group. It is possible that the incidence of prostatic calculi increases with age. However, a prospective study would be necessary to verify this postulate. Because the presence of prostatic calculi in men in the PCa group was associated with a significantly higher GS, it can be concluded that prostatic calculi have a relationship with PCa, excluding the effect of age. Besides this, one possible bias of this study is the method of calculi detection that favors the detection of only large calculi. However, we only included prostatic calculi that were more than 3 mm in diameter on ultrasonography, because when the size was less than 3 mm, it was difficult to discriminate between calculi and artifacts.

An additional purpose of our study was to enhance the evidence provided by epidemiological studies regarding the relationship between PCa and inflammation by investigating the correlation between prostatitis and PCa, because prostatic calculi are frequently associated with prostatitis. We sought to do so because the pre-existing research on this topic had several limitations, including recall and detection bias, the lack of inclusion of patients with subclinical prostatitis (because patients could be excluded only when clinical prostatitis was considered), and the fact that prostatitis was diagnosed histologically in all patients. When reviewing evidence regarding the molecular pathogenesis, genetics and epidemiology of PCa, several authors have inferred that inflammation or infection of the prostate can cause PCa. Our study provides further evidence to support such hypotheses.

## 5 Conclusion

Inflammation of the prostate has recently been postulated to be causally related to PCa, but definitive evidence supporting this hypothesis is not available. In this study, prostatic calculi were observed more often in patients with PCa than in BPH patients, although there was no statistical difference in the overall risk of carcinogenesis between these two groups based on the presence of prostatic calculi. In conclusion, prostate calculi have no effect on the development of PCa. However, because PCa patients with prostatic calculi had higher GS than PCa patients without prostatic calculi, we hypothesize that prostatic inflammation is correlated with PCa differentiation. Further studies on this subject are necessary to more fully elucidate the relationship between inflammation, prostatic calculi, and prostate carcinogenesis.

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