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Impact of Benign Prostatic Hyperplasia and/or Prostatitis on the Risk of Prostate Cancer in Korean Patients

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Purpose: We evaluated the impact of benign prostatic hyperplasia (BPH) and prostatitis on the risk of prostate cancer (PCa) in patients using nationally representative data of the Korean population from the National Health Insurance Service.

Materials and Methods: A total of 5,580,495 Korean men, aged >20 years, who had undergone health screening in 2009 were followed-up for 9 years until 2017. Multivariate adjusted Cox regression analysis was conducted to determine the hazard ratio (HR) and 95% confidence interval (CI) for the association between BPH and/or prostatitis and PCa. The HR for PCa according to the presence of BPH and/or prostatitis was stratified by a combination of BPH and prostatitis in multivariable-adjusted models.

Results: The HR for PCa significantly increased in patients with BPH and prostatitis than in patients without BPH and prostatitis (adjusted HR, 1.626; 95% CI, 1.567–1.688 and adjusted HR, 1.557; 95% CI, 1.500–1.618, respectively). In particular, for the combination of BPH and prostatitis, the adjusted HR was 1.856 (95% CI, 1.743–1.976), which was the highest when a diagnosis of both BPH and prostatitis was made.

Conclusions: BPH and/or prostatitis are associated with an increased incidence for PCa in Korean patients, which is likely associated with similar effects to prostate-specific antigen (PSA) screening, so care must be taken in the interpretation. However, if follow-up survival studies demonstrate differences between the two groups (BPH and prostatitis *vs*. general), it could be one of the evidence for the introduction of PSA screening in Korea.

Keywords: Benign prostatic hyperplasia; Incidence; Prostate cancer; Prostatitis

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related death worldwide [1]. In Korea, the incidence of PCa is increasing rapidly [2]. Currently, there are established risk factors for diagnosing PCa [3]. Family history, increased age, and ethnicity are established risk factors for PCa diagnosis, while among many other potential risk factors, benign prostatic hyperplasia (BPH) and

prostatitis would be one cause [4].

BPH is a noncancerous increase in the prostate size caused by proliferation [5], a common aging disorder observed in 70% of men aged ≥70 years [6], and can be a cumbersome and potentially serious condition; it not only causes lower urinary tract symptoms and lowers the quality of life of patients, but is also associated with certain types of male urological cancers, such as PCa and bladder cancer [7,8]. The association between BPH and urological cancer is not fully understood, although metabolic syndrome, hormones, and inflammation may play a role in BPH and PCa [9].

Inflammation is thought to play a role in PCa by causing cell and gene damage, thereby causing increased cellular proliferation [10]. Prostatitis is defined as inflammation of the prostate gland, and the incidence of prostatitis is 8.2% (range, 2.2%–9.7%) [11]. The high prevalence of prostatitis might contribute to the onset of PCa. However, the association between prostatitis and PCa is controversial.

To date, although many epidemiologic studies have revealed a link among prostatitis, BPH, and PCa, these findings are contradictory [12,13]. One of the main issues is high prevalence of prostatitis, BPH, and urological cancer. So studies about the relevance of these diseases are of high public health and clinical importance. The link among BPH, prostatitis and PCa will help clinicians improve the effectiveness of cancer screening and treat cancer early by adopting general prevention strategies for BPH, prostatitis, and PCa [9,14].

Nonetheless, there were few studies dealt with the relationship of BPH, prostatitis, and PCa among Korean population. Therefore, we performed a related analysis of patients with prostatitis, BPH, and PCa using national data from the National Health Insurance Service (NHIS), representative of the Korean population.

MATERIALS AND METHODS

1. Ethics statement

This study was approved by the Myongji Hospital Bioethics Committee (No. 2019-06-004). Preliminary patient consent was not acquired because anonymized data were used for analysis. To protect patient's personal information, the subject and unique number were anonymized. The Institutional Review Board waived the written consents because of the anonymized data

from the NHIS.

2. Data sources

This study used data from the NHIS in Korea (www.nhis.co.kr), which provides comprehensive health insurance coverage for all Koreans citizens who paid Korean governmental taxes [15]. NHIS provided a time-limiting population-based cohort brought out by the NHIS in Korea during a certain period of time which was named the National Health Insurance Service-National Sample Cohort (NHIS-NSC) and used in this study with a total of 5,580,495 Korean screening men in 2009, aged over 20 years and followed-up for 9 years until 2017.

3. Study design

PCa was defined using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code C61. BPH and prostatitis were identified by searching for each code in the 10th edition International Classification of Diseases (ICD-10), *i.e.*, N40 and (EB451 or E7050 or EY521 or EY522) and N41, respectively. The definition of the measurement was also retrieved using ICD-10-CM.

Hypertension (HTN) (I10–13, I15) with a with a blood pressure (BP) of ≥140/90 mmHg or a history of taking antihypertensive drugs; diabetes mellitus (DM) (E11–14) with self-reporting of taking diabetes drugs with a fasting blood glucose level of ≥126 mg/dL; dyslipidemia (E78) with the use of a self-reported lipid-lowering agent or by a previous diagnostic code of E78 with a total cholesterol level of ≥240 mg/dL.

Body mass index (BMI) was defined as the body weight in kilograms divided by the height in square meters. The BMI range was according to the recommendations of the Obesity Society, as follows: normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obesity (>25 kg/m^2) [16]. BP was measured after the subject took rest for 5 minutes. The serum glucose, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were measured by taking a blood sample after overnight fasting. Smokers are classified into three groups: non-smokers; current smokers, those who smoked >100 cigarettes a day or more; and ex-smokers, those who smoked in the past but quit smoking. Drinking status was divided into three groups: people who did not drink, people who drank two or three times a month, and people who

drank weekly. Exercise status was divided into two groups: high intensity exercise: exercise for more than 3 days a week; and regular exercise: exercise for more than 5 days a week.

4. Statistical analysis

Statistical analysis was performed using SAS ver. 9.4 (SAS Institute, Carrie, NC, USA), and the data were expressed as mean±standard error and as percentages for continuous and categorical variables, respectively. The incidence between PCa risk and BPH and/or prostatitis was calculated per 1,000 people.

Multivariate adjusted Cox regression analysis was

performed, and the associated hazard ratio (HR) and 95% confidence interval (CI) for PCa and BPH and/or prostatitis were analyzed. Among the available variables (factors) in the database, clinical considerations were taken into consideration. Among them, a model without statistical multicollinearity problem was selected. Calculations were made after adjusting for age, income, BMI, smoking status, exercise status, DM, HTN, dyslipidemia, systolic and diastolic BP, cholesterol levels, and glucose levels. The chi-square test was used for category variables and one-way ANOVA test was used for continuous variables. The meaning of the corresponding p-value for each variable is "the distri-

Table 1. Baseline characteristics of the patients***

Characteristic	Without BPH or prostatitis (n=5,349,556)	With prostatitis but without BPH (n=146,964)	With BPH but without prostatitis (n=54,728)	With both BPH and prostatitis (n=29,247)
Age (y)	45.4±13.5	47.4±13.3	63.0±9.3	59.1±10.4
≤54	4,028,850 (75.31)	106,388 (72.39)	11,064 (20.22)	10,618 (36.31)
55–64	762,025 (14.24)	21,685 (14.76)	19,037 (34.78)	9,190 (31.42)
65–74	453,848 (8.48)	14,914 (10.15)	19,409 (35.46)	7,567 (25.87)
≥75	104,833 (1.96)	3,977 (2.71)	5,218 (9.53)	1,872 (6.40)
BMI (kg/m^2)	24.1±3.0	24.2±2.8	24.1±2.8	24.1±2.7
<18.5	124,750 (2.33)	2,518 (1.71)	1,223 (2.23)	521 (1.78)
18.5–23	1,829,496 (34.20)	47,880 (32.58)	17,179 (31.39)	9,264 (31.68)
23–25	1,439,841 (26.92)	42,293 (28.78)	16,203 (29.61)	8,724 (29.83)
25–30	1,763,828 (32.97)	50,119 (34.10)	18,845 (34.43)	10,106 (34.55)
>30	191,641 (3.58)	4,154 (2.83)	1,278 (2.34)	632 (2.16)
Smoking status				
Non-smoker	1,617,196 (30.23)	47,740 (32.48)	22,167 (40.50)	11,365 (38.86)
Ex-smoker	1,300,990 (24.32)	44,594 (30.34)	21,479 (39.25)	11,084 (37.90)
Current smoker	2,431,370 (45.45)	54,630 (37.17)	11,082 (20.25)	6,798 (23.24)
Drinking status				
Non-drinker	1,711,853 (32.00)	51,666 (35.16)	27,612 (50.45)	14,063 (48.08)
Mild drinker	2,906,755 (54.34)	76,778 (52.24)	22,897 (41.84)	12,664 (43.30)
Heavy drinker	730,948 (13.66)	18,520 (12.60)	4,219 (7.71)	2,520 (8.62)
Regular exercise	1,095,031 (20.47)	33,867 (23.04)	15,649 (28.59)	7,979 (27.28)
DM	517,136 (9.67)	14,624 (9.95)	10,448 (19.09)	4,592 (15.70)
HTN	1,454,206 (27.18)	42,654 (29.02)	28,460 (52.00)	12,998 (44.44)
DYS	888,666 (16.61)	27,784 (18.91)	14,996 (27.40)	7,210 (24.65)
SBP	124.6±14.0	123.5±13.4	125.9±14.6	124.6±14.1
DBP	78.0±9.6	77.3±9.4	77.3±9.7	77.3±9.4
Cholesterol	194.3±35.9	194.1±35.6	189.5±36.3	191.9±35.8
Glucose	98.8±24.6	98.4±22.7	103.1±25.6	101.9±24.5
PCa	38,946 (0.73)	1,882 (1.28)	2,052 (3.75)	1,002 (3.43)
Follow-up duration (y)	8.2±0.9	8.2±1.0	7.9±1.6	8.0±1.5

Values are presented as mean±standard deviation or number (%).
BPH: benign prostatic hyperplasia, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, DYS: dyslipidemia, SBP: systolic blood pressure, DBP: diastolic blood pressure, PCa: prostate cancer.
***The asterisk indicates a statistically significant difference (p<0.001).

Table 2. Risk of PCa according to the presence of prostatitis, BPH, or both

Variable	Subject (n)	Prostate cancer (n)	Duration (person-year)	Rate (1,000 person-year)	Crude HR	Adjusted HR
Prostatitis						
No	5,404,284	40,998	44,268,292.36	0.92613	1 (ref.)	1 (ref.)
Yes	176,211	2,884	1,434,401.21	2.0106	2.172 (2.091–2.255)	1.557 (1.500–1.618)
BPH						
No	5,496,520	40,828	45,039,001.83	0.9065	1 (ref.)	1 (ref.)
Yes	83,975	3,054	663,691.74	4.60153	5.084 (4.901–5.275)	1.626 (1.567–1.688)
Combination						
Without BPH or prostatitis	5,349,556	38,946	43,837,793.5	0.88841	1 (ref.)	1 (ref.)
With prostatitis but without BPH	146,964	1,882	1,201,208.33	1.56676	1.763 (1.683–1.846)	1.479 (1.412–1.549)
With BPH but without prostatitis	54,728	2,052	430,498.87	4.76656	5.382 (5.148–5.626)	1.570 (1.501–1.642)
With both BPH and prostatitis	29,247	1,002	233,192.87	4.29687	4.834 (4.540–5.147)	1.856 (1.743–1.976)

Adjusted for age, income, body mass index, smoking status, drinking status, exercise, diabetes mellitus, hypertension, dyslipidemia, systolic blood pressure, diastolic blood pressure, cholesterol, and glucose.
PCa: prostate cancer, BPH: benign prostatic hyperplasia, HR: hazard ratio, ref.: reference.

bution of variables (average in case of continuous type) is different in at least one stage among four stages (if significant)."

A p-value of <0.05 was considered statistically significant. The cumulative incidence probability analysis was performed using Kaplan–Meier curves with log-rank tests for patients with prostatitis but without BPH, those with BPH but without prostatitis, and those with both BPH and prostatitis.

RESULTS

1. Comparison of clinical characteristics according to the diagnosis of benign prostatic hyperplasia and prostatitis

Table 1 summarizes the general characteristics of the study population and subgroups. Among a total of 5,580,495 participants, 5,349,556 (95.86%) were diagnosed without BPH or prostatitis. A total of 2.63% (146,964/5,580,495), 0.52% (29,247/5,580,495), and 0.98% (54,728/5,580,495) patients were diagnosed with prostatitis but without BPH, with BPH but without prostatitis, and with both BPH and prostatitis. There were significant differences among the groups in all the variables including age.

2. Risk of prostate cancer according to the diagnosis of benign prostatic hyperplasia and prostatitis

Table 2 shows the HR for PCa according to the diagnosis of BPH and prostatitis. We performed the analysis after correction for age, income, BMI, smoking status, drinking status, exercise, DM, HTN, dyslipidemia, systolic and diastolic BP, cholesterol, and glucose. The patients with BPH had a higher risk of PCa than the patients without BPH did, among all the patients (HR, 1.626; 95% CI, 1.567–1.688). Furthermore, the patients with prostatitis had a higher risk of PCa than the patients without prostatitis did, among all the patients (HR, 1.557; 95% CI, 1.500–1.618). In the patients with BPH and prostatitis, the adjusted HR was 1.479 (95% CI, 1.412–1.549) when diagnosed without BPH or prostatitis, and the adjusted HR was 1.570 (95% CI, 1.501–1.642) when patients were diagnosed with BPH but without prostatitis. The adjusted HR was 1.856 (95% CI, 1.743–1.976), which was the highest when patients were diagnosed with both BPH and prostatitis. In addition, the risk of PCa of each other factors according to the presence of BPH and/or prostatitis are demonstrated (Supplement Table 1–3).

3. Incidence probability of prostate cancer according to the diagnosis of benign prostatic hyperplasia and prostatitis

The results of the cumulative incidence probability curves showed significant differences among patients with prostatitis but without BPH, those with BPH but without prostatitis, and those with both BPH and prostatitis (p<0.001; Fig. 1).

DISCUSSION

The controversial issue on the relationship between BPH, prostatitis and PCa has been dealt in many previous studies that some showed a positive relationship but others did not [10,12,13,17]. This population-based study supported the HR for PCa significantly increased in patients with BPH and prostatitis than in patients without BPH and prostatitis (HR, 1.626; 95% CI, 1.567–1.688 and HR, 1.557; 95% CI, 1.500–1.618, respectively). In particular, this study showed the combination of BPH and prostatitis had the highest adjusted HR of 1.856 (95% CI, 1.743–1.976) for the increased incidence of PCa.

A few years ago, an article published in the data obtained from the universal National Health Insurance of Taiwan found that men with PCa have strong association with prostatitis and/or BPH [18]. However, most of the past study has been mainly about the practice of single disease and PCa, but this study dealt with BPH and prostatitis at the same time, and the results are also remarkable. This study has great clinical significance because it is a large-population based study conducted on a single ethnic group in East Asia, especially in Korea, where the incidence of PCa is rapidly increasing [19].

A causal relationship between inflammatory disease and other tumor has been established in hepatocellular and hepatitis [20], cervical and cervicitis, anal and proctitis, genital carcinoma and sexually transmitted diseases [21], and gastric cancer and gastritis [22], similar to this study. Previous epidemiology and biology studies of prostatitis have already shown that inflammatory mediators could promote PCa through multiple signaling pathways, such as the suppression of apoptosis, cell growth promotion, and induction of the loss of
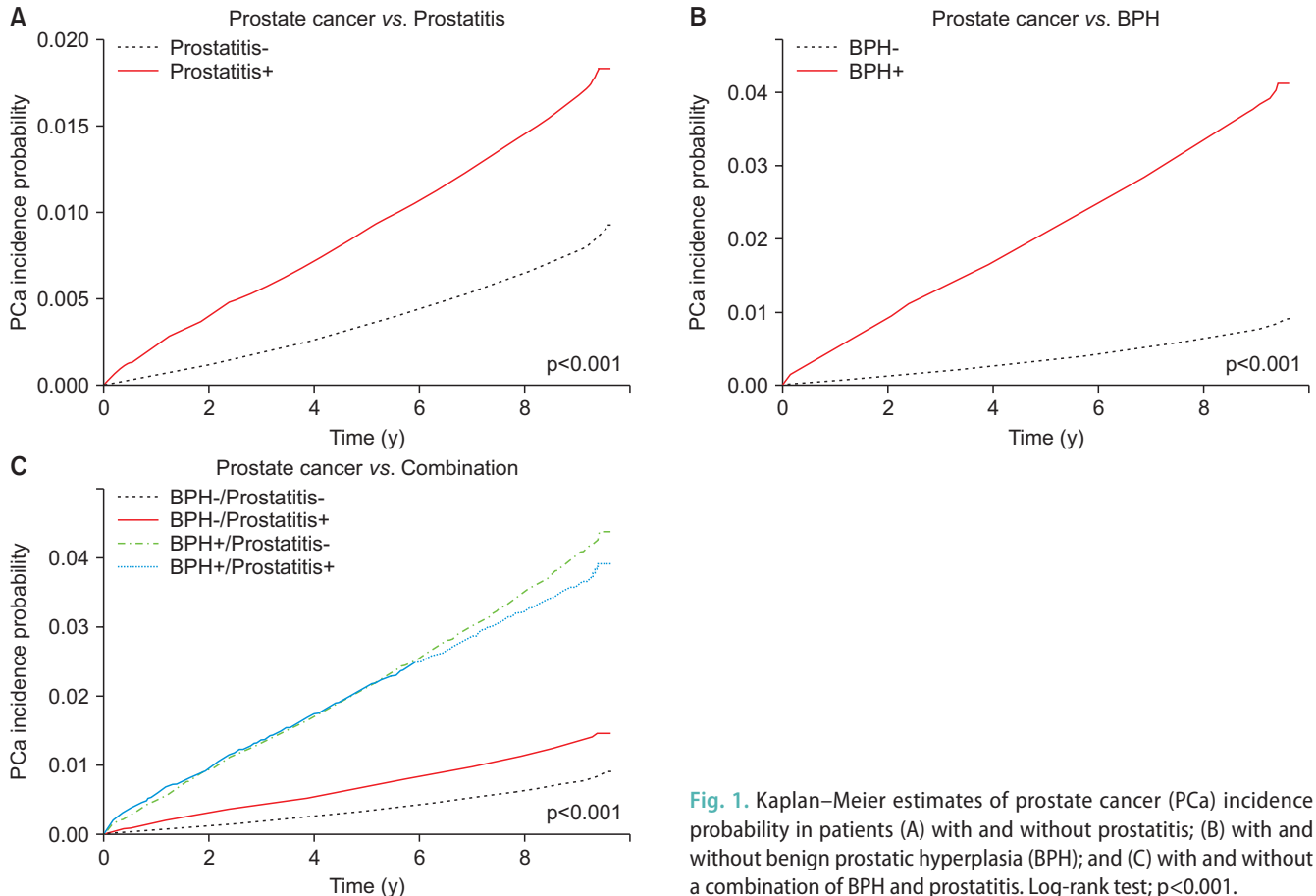

Fig. 1. Kaplan–Meier estimates of prostate cancer (PCa) incidence probability in patients (A) with and without prostatitis; (B) with and without benign prostatic hyperplasia (BPH); and (C) with and without a combination of BPH and prostatitis. Log-rank test; p<0.001.

tumor suppressor genes [23].

However, Schenk et al [13] found no significant association between BPH and the incidence of PCa. The Scheck's analysis was based on the low quality of generalized results owing to restrictions implemented in a highly selected population. Another study by Ørsted and Bojesen [14] found a contradictory finding with a positive association between BPH and PCa incidence as well as mortality in the largest population-based cohort study with a minimized potential influence of detection bias. Another study with meta-analysis study showing the association between BPH and PCa risk also with a considerable heterogeneity between studies partly owing to racial differences, and the risk of PCa was much greater in Caucasians than in Asians [24].

Hormones, inflammation, and metabolic syndrome played an important role in the development of BPH and PCa [9,25,26]. Homeostasis between prostate cell proliferation and apoptosis is often interrupted in patients with BPH, supported by the effects of dihydrotestosterone and estrogen [27]. Given the differences in the revalence, prognosis, and survival among Asian and Caucasian patients with PCa [6,28], it is reasonable to assume that the mechanisms by which BPH contributes to PCa can vary across ethnicities.

An important limitation of our study is the BPH and prostatitis detection bias in patients for PCa risk. This is related to the fact that unmeasured clinical practice might affect PCa detection in patients with BPH and prostatitis. For example, physicians may perform more intensive examinations, such as prostate-specific antigen (PSA) tests, Digital Rectal Examination, imaging procedures, and additional markers. It has been found that increased disease recognition in BPH patients might increase the likelihood of being diagnosed with PCa [29]. Second, because there is no information about not only pathological findings but also clinical stage or prognosis, it is not possible to coordinate disease assessments or arrange them hierarchically. Finally, the diagnosis of BPH and prostatitis was made with the NHIS diagnostic code, which would be different from the actual clinical diagnosis. For example, prostatitis is a combination of both acute and chronic prostatitis.

Despite the many limitations, the strength of the current study is that, to the best of our knowledge, it was the first and most comprehensive study about BPH, prostatitis, and the risk of PCa among Korean population. A thorough investigation of the latest literature was conducted to include the best observational studies. Moreover, the total number of participants who contributed to the analysis of the data is much higher than that used in previous studies on this subject. This allowed us to perform a stratified analysis to investigate potential influential factors.

CONCLUSIONS

BPH and/or prostatitis are associated with an increased incidence of PCa in Korean patients. In particular, it was highest in the combination of BPH and prostatitis, which is likely associated with similar effects to PSA screening, so care must be taken in the interpretation. However, if follow-up survival studies demonstrate differences between the two groups (BPH and prostatitis vs. general), it could be one of the evidence for the introduction of PSA screening in Korea.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: JYJ, WAK. Data curation: SHK, WAK. Formal analysis: SHK, WAK. Funding acquisition: JYJ. Investigation: JYJ, WAK. Methodology: JYJ, SHK. Project administration: JYJ, WAK. Resources: JYJ, SHK. Software: SHK, WAK. Supervision: all authors. Validation: all authors. Visualization: JYJ, SHK. Writing – original draft: SHK, WAK. Writing – review & editing: SHK, WAK.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.190135.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/9WRB5M.

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