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Synergistic interaction of benign prostatic hyperplasia and prostatitis on prostate cancer risk

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Background: The incidence of prostate cancer is much lower in Asian men than in Western men. This study investigated whether prostate cancer is associated with prostatitis, benign prostatic hyperplasia (BPH), and other medical conditions in the low-incidence population.

Methods: From the claims data obtained from the universal National Health Insurance of Taiwan, we identified 1184 patients with prostate cancer diagnosed from 1997 to 2008. Controls comprised 4736 men randomly selected from a cancer-free population. Both groups were 50 years of age or above. Medical histories between the two groups were compared.

Results: Multivariate logistic regression analysis showed that prostatitis and BPH had stronger association with prostate cancer than the other medical conditions tested. Compared with men without prostatitis and BPH, a higher odds ratio (OR) for prostate cancer was associated with BPH (26.2, 95% confidence interval (CI) 20.8–33.0) than with prostatitis (10.5, 95% CI = 3.36–32.7). Men with both conditions had an OR of 49.2 (95% CI = 34.7–69.9).

Conclusion: Men with prostate cancer have strong association with prostatitis and/or BPH. Prostatitis interacts with BPH, resulting in higher estimated relative risk of prostate cancer in men suffering from both conditions.

Prostate cancer is the most common cancer that affects men in Western countries, particularly in the United States (Klein *et al*, 2007; Jemal *et al*, 2009, 2010). The incidence and prevalence of prostate cancer in the United States have continuously increased since the introduction of prostate-specific antigen (PSA) screen test in 1992. Among the 217 730 new cases estimated in 2010, prostate cancer accounted for 28% of all cancers in American men. This cancer was also responsible for 22.2% ($n = 382\,000$) of cancers that affected men in 40 European countries in 2008 (Ferlay *et al*, 2010) and 31.2% ($n = 19\,403$) of cancers in Australian men in 2007 (Australian Institute of Health and Welfare and; Australasian Association of Cancer Registries (2010)). Although the incidence is

much lower in Asian men than in Western men, the incidence rate of prostate cancer has continuously increased in recent decades (Pu *et al*, 2004). According to the Taiwan Cancer Registry Report, the incidence of prostate cancer increased from 7.5/100 000 in 1992 to 23.5/100 000 in 2007 (Taiwan Cancer Registry, 2010). Furthermore, the clinical outcome of localised prostate cancer post-radical prostatectomy has been unsatisfactory, and mortality due to prostate cancer is increasing in Taiwan (Huang *et al*, 2010; Tseng, 2011).

Relatively little is known about the risk factors associated with the increasing trend of prostate cancer in Asian men, other than the fact that prostate cancer is highly related to aging, ethnicity,

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and family history of prostate cancer (Hsing and Chokkalingam, 2006; Klein *et al*, 2007). Much attention has recently been given to the roles of chronic inflammation and infection in the pathogenesis and progression of prostate cancer (Kramer *et al*, 2007; Drake, 2010; De Nunzio *et al*, 2011). The literature has suggested the association between prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer. van Vuuren *et al* (2012) considered prostatitis as an early sign of cancer for men with adenocarcinoma of the prostate. Components of metabolic syndromes and BPH are also strongly related to aging (Klein *et al*, 2007). These metabolic syndromes may contribute to the development of BPH and clinical prostate cancer (Hammarsten and Hogstedt, 2002). Prostate cancer screening in symptomatic BPH patients is, therefore, of great concern for men, particularly when the alternative therapies used do not involve tissue pathological analysis (Hall *et al*, 1996).

The results of studies on the risk of prostate cancer associated with prostatitis and BPH using population-based data remain inconclusive. In particular, studies on this association are limited for Asian men. We suspect that the mechanism through which prostatitis and BPH contribute to prostate cancer in Asian men is different from Western men, primarily because the incidence of the said cancer type is much rarer in Asian men (Pu *et al*, 2004; Taiwan Cancer Registry, 2010). Using a population-based data set with information on the medical conditions available for men with low cancer incidence to investigate the said mechanisms can aid in clarifying the association between prostate cancer and prostatitis and BPH. We, therefore, used the data from universal insurance claims to investigate whether prostatitis and BPH contribute in the risk of prostate cancer in Taiwanese men. In addition to BPH and prostatitis, this study also explored comorbidities that may be associated with the risk of prostate cancer.

MATERIALS AND METHODS

Data sources. This study used the 1996–2008 reimbursement claims submitted to the National Health Insurance programme, a

universal insurance system established by the Bureau of National Health Insurance of the Department of Health in Taiwan. This insurance programme has covered >99% of the population since 1999 (Cheng, 2003). The data set consisted of claims from 1 000 000 people randomly selected from a total of 23 million insured individuals based on the year 2000 population. In these claims, information on socio-demographic status was available, in addition to health care visits of in-patients and out-patients, from 1996 to 2008. The electronic data files were obtained from the National Health Research Institutes. The identification numbers of all the patients were scrambled to ensure patient confidentiality. This study was, therefore, exempted from full institutional review. We used the International Codes of Diseases 9th Revision, Clinical Modification (ICD-9-CM) to identify diseases.

Study subjects. We identified men aged 50 years and above with primary prostate cancer (ICD-9-CM 185 or A-code A124) diagnosed during the period of 1997–2008 as the sample population. For each prostate cancer patient, four controls comprising cancer-free men at the age of 50 and above were randomly selected from the same data set within the same time period. The age of a study subject was defined according to the date when the patient was diagnosed with prostate cancer or when the control was selected. To explore the potential comorbidities associated with increased risk of prostate cancer, we screened the medical history to search for comorbidities that existed before the identification of the study subjects. Metabolism syndrome and infection have been previously studied as risk factors associated with prostate cancer (Hammarsten and Hogstedt, 2002; Kramer *et al*, 2007; Drake, 2010; De Nunzio *et al*, 2011; Taylor *et al*, 2005). Comorbidities including diabetes mellitus (ICD-9-CM 250 or A-code A181), hypertension (ICD-9-CM 401-405 or A-code A260, A269), hyperlipidemia (ICD-9-CM 272 or A-code A182), prostatitis (ICD-9-CM 601.X), testitis and epididymitis (604.X), gonorrhoea and chlamydia infection (ICD-9-CM 098.X, 099.X), BPH (ICD-9-CM 600 or A-code A360), and obesity (ICD-9-CM 278.00, 278.01 or A-code A183) were included as covariates in this study.

Table 1. Comparison of baseline characteristics between prostate cancer cases and cancer-free controls

	Prostate cancer						P-value*
	Total, N = 5920		No, N = 4736		Yes, N = 1184		
	N	%	N	%	N	%	
Age group (years)							<0.0001
50–64	2765	46.7	2611	55.1	154	13.0	
65–74	1610	27.2	1162	24.5	448	37.8	
≥75	1545	26.1	963	20.3	582	49.2	
Mean (s.d.)	66.9	(11.4)	65.0	(11.4)	74.4	(8.1)	<0.0001
Comorbidity and medication^a							
Diabetes mellitus	704	11.9	530	11.2	174	14.7	0.0009
Hypertension	2739	46.3	1951	41.2	788	66.6	<0.0001
Hyperlipidemia	1217	20.6	869	18.4	348	29.4	<0.0001
Prostatitis	236	3.99	99	2.09	137	11.6	<0.0001
Testitis and epididymitis	48	0.81	31	0.65	17	1.44	0.007
Gonorrhoea and chlamydia infection	16	0.27	11	0.23	5	0.42	0.26
Benign prostatic hyperplasia	2155	36.4	1071	22.6	1084	91.6	<0.0001
Obesity	17	0.29	11	0.23	6	0.51	0.11

* χ^2 -test comparing patients with and without prostate cancer.

^aComorbidities: enrolled diagnosis criterion for hypertension and hyperlipidemia is visited the clinic at least three times; for diabetes mellitus (DM), at least twice per year with anti-DM medication; for other comorbidities, at least two times.

Table 2. Logistic regression model measured ORs and 95% CIs of prostate cancer associated with prostatitis, BPH, and other covariates

Variable	Crude		Adjusted ^a	
	OR	(95% CI)	OR	(95% CI)
Age group (years)				
50–64	1.00	(reference)	1.00	(reference)
65–74	6.54	(5.38–7.95)	3.05	(2.43–3.83)
≥ 75	10.2	(8.45–12.4)	3.97	(3.16–4.98)
Diabetes mellitus				
Yes	1.37	(1.14–1.64)	0.70	(0.56–0.88)
Hypertension				
Yes	2.84	(2.49–3.25)	1.03	(0.97–1.24)
Hyperlipidemia				
Yes	1.85	(1.60–2.14)	1.24	(1.02–1.50)
Prostatitis				
Yes	6.13	(4.69–8.00)	9.77	(3.09–30.9)
Testitis and epididymitis				
Yes	2.21	(1.22–4.01)	0.66	(0.34–1.29)
BPH				
Yes	37.1	(29.9–46.0)	24.9	(19.8–31.4)
Prostatitis × BPH	7.09	(5.35–9.41)	5.17	(1.58–17.0)

Abbreviations: BPH = benign prostatic hyperplasia; CI = confidence interval; OR = odds ratio.
^aMultivariate analysis including age, diabetes mellitus, hypertension, hyperlipidemia, prostatitis, testitis and epididymitis and BPH.

Statistical analysis. In the data analysis, we first compared the distributions of age and comorbidities between cases and controls. χ^2 -test and *t*-test were used to compare differences between cases and controls for categorical variables and continuous variables, respectively. The significant variables were further included in the multivariate logistic regression analysis to measure the odds ratio (OR) at 95% confidence interval (CI) for the prostate cancer-associated covariates. Data analysis further verified the role of the interaction between prostatitis and BPH in the development of prostate cancer. All tests were two-tailed, and a *P*-value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using the statistical package SAS for Windows (version 9.1 SAS Institute Inc., Cary, NC, USA).

RESULTS

This study consisted of 1184 prostate cancer cases and 4736 cancer-free controls. Cases were ~10 years older than controls, as suggested by the mean age (*P* < 0.0001) (Table 1). Compared with the controls, cases were more prone to diabetes (14.7% vs 11.2%), hypertension (66.6% vs 41.2%), hyperlipidemia (29.4% vs 18.4%), prostatitis (11.6% vs 2.09%), testitis and epididymitis (1.44% vs 0.65%), and BPH (91.6% vs 22.6%).

In the multivariate logistic regression model, compared with the 50- to 64-year-old age group, older patients were at higher odds of prostate cancer, with an OR of 3.05 (95% CI = 2.43–3.83) for the 65- 74-year-old age group, and 3.97 (95% CI = 3.16–4.98)

Table 3. Interaction between prostatitis and benign prostatic hyperplasia (BPH) in predicting prostate cancer risk

Prostatitis	BPH	Case (N)	Control (N)	Crude OR (95% CI)	Adjusted OR (95% CI)
No	No	96	3649	1.00 (reference)	1.00 (reference)
No	Yes	951	988	36.6 (29.3–45.7)	26.2 (20.8–33.0)
Yes	No	4	16	9.50 (3.12–29.0)	10.5 (3.36–32.7)
Yes	Yes	133	83	60.9 (43.3–85.7)	49.2 (34.7–69.9)

Abbreviations: CI = confidence interval; OR = odds ratio. Adjusted for age, DM, hypertension, hyperlipidemia, and testitis and epididymitis.

for the ≥75-year-old age group (Table 2). Among comorbidities, a high estimated relative risk for prostate cancer was observed in men with prostatitis (OR = 9.77, 95% CI = 3.09–30.9) and BPH (OR = 24.9, 95% CI = 19.8–31.4). The interaction term of prostatitis × BPH was also significant with an OR of 5.17 (95% CI = 1.58–17.0).

Table 3 shows the results of the stratified analysis for the demonstration of the interaction between prostatitis and BPH in predicting prostate cancer. Compared with patients without both prostatitis and BPH, patients with history of both diseases were at the highest odds for prostate cancer development, with adjusted OR of 49.2 (95% CI = 34.7–69.9). BPH (OR = 26.2, 95% CI = 20.8–33.0) was also found to have a much stronger association with prostate cancer than prostatitis (OR = 10.5, 95% CI = 3.36–32.7).

DISCUSSION

Based on the data set in this study, the calculated average incidence of prostate cancer was around 19.7/100 000 for men aged 50 years and above from 1997 to 2008 in Taiwan (data not shown), which was in agreement with the incidence trend officially reported by the Taiwan Cancer Registry, namely, 7.5–23.5/100 000 in 1992–2007 (Taiwan Cancer Registry, 2010). A decline of prostate cancer incidence was noted in the United States and in some European countries, but not in Taiwan (Bray *et al*, 2010). Some studies have suggested that the trend of prostate cancer incidence is mainly affected by the availability of PSA testing and screening programs. No regular extensive PSA screening programme existed in Taiwan before the reformation of the universal health insurance programme. This test has become easily available for men as part of the national health insurance routine checkup since 1996, particularly for men who complain about low urinary track symptoms. The persisting elevated incidence of prostate cancer and the possible risk associated with it should not be ignored.

In this study, age was found to be highly related to the incidence of prostate cancer. The prevalence of metabolic syndromes is also related to age. To determine the relationship between prostate cancer and other comorbidities, we investigated the metabolic syndromes available in the data of the reimbursement claims. The relationships between prostate cancer, obesity, and metabolic syndromes remain inconclusive (Hsing *et al*, 2007; Gorbachinsky *et al*, 2010). We failed to identify a significant relationship between prostate cancer and the components of metabolic syndromes, including hypertension, hyperlipidemia, and obesity.

One interesting observation is that diabetes mellitus may have a protective relationship with prostate cancer. The association of diabetes mellitus with cancers has been widely discussed, and most studies found negative relationship or non-specific relationship between diabetes mellitus and prostate cancer. Recent cohort

studies using the same claim data of the National Health Insurance in Taiwan found weak linkages between diabetes mellitus and prostate cancer (Tseng, 2011), possibly because the follow-up period is not sufficient. The carcinogenesis process is complicated and taking a long latent period. Thus, a short follow-up period may not be sufficient to observe the interaction between diabetes mellitus and various anti-diabetic drugs as oncogenes (Feng *et al*, 2011; Pettaway *et al*, 2011).

This study found that prostate cancer is associated with prostatitis and BPH. The human prostate has four zones: peripheral, central, transitional, and fibromuscular stroma. Normally, BPH appears in the central part of the prostate and may induce low urinary tract syndrome earlier than prostate cancer development. However, this incident is unusual because most prostate cancers occur in the peripheral zone (McNeal *et al*, 1988; Pavelic and Zeljko, 2002). The causal relationship among BPH, prostatitis, and prostate cancer has been a point of controversy because they are strongly associated with similar risk factors, in addition to age (Dennis *et al*, 2002; Roberts *et al*, 2004; De Nunzio *et al*, 2011; Schenk *et al*, 2011; Chang and Kirby, 2012). Moreover, patients with BPH symptoms may have a greater urge to visit urologists, and thus, have a higher chance to detect whether they are afflicted with prostate cancer. The relationship appears in this study is much greater than that reported for Western men. An 11-year follow-up study from a single health system has recently reported that the incidences of prostate cancer are 9% in men with BPH, including 14.3% in African-American and 7.3% in Caucasian men (Pettaway *et al*, 2011). In the present study, BPH was found to be strongly associated with prostate cancer in the logistic regression model after normalising the age and other covariates. However, we were unable to identify the site at which the prostate cancer developed from the claims data. Selection bias might also exist, especially in patients who received transurethral retrograde prosectomy (TURP) for BPH. Prostate cancers can be found in 4–15% of the surgical histology samples, with or without previous clinical suspicion (Dellavedova *et al*, 2010). However, the strong association between BPH and prostate cancer may diminish little even if the cases identified by TURP are excluded.

Inflammation is another important factor contributing to cancer progression. Chronic inflammatory conditions are associated with cancer development, such as reflux esophagitis with oesophageal cancer and virus hepatitis with hepatocellular carcinoma. The hypothesis about chronic inflammation inducing carcinogenesis is based on the local irritation associated with the regulation of the inflammatory cells and cytokine (Coussens and Werb, 2002). Both bacteria- and non-bacteria-related prostatitis are, but not sexually transmitted diseases (STDs), significant factors associated with prostate cancer. However, the causality remains unclear (Dennis *et al*, 2002; Roberts *et al*, 2004).

Based on six population-based case-control studies and five hospital-based case-control studies, an earlier meta-analysis found a 1.6-fold increased risk of prostate cancer for men with a prostatitis history (Dennis *et al*, 2002). Studies also found that STDs are potentially associated with increased risk of prostate cancer (Dennis *et al*, 2002; Taylor *et al*, 2005). However, the selecting bias and recall bias about the history of prostatitis are concerned in epidemiological studies. Prostatitis could be categorised into four groups: category I comprising acute bacteria prostatitis, category II comprising chronic bacterial prostatitis, category III comprising chronic prostatitis/chronic pelvic pain syndrome, and category IV comprising asymptomatic inflammation prostatitis (Krieger *et al*, 1999). Category III prostatitis may account for 90% of diagnosed cases (Krieger *et al*, 1999), and patients with category IV prostatitis are usually cases that are accidentally diagnosed (Habermacher *et al*, 2006). Delongchamps *et al* (2008) evaluated 167 autopsied prostates and found that chronic inflammation is commonly associated with BPH, but not

the cancer. However, the sample size was probably too small to identify a significant relationship. They found that chronic inflammatory infiltrations are mostly located in the transitional zones instead of the peripheral zone where prostate cancer is usually diagnosed (McNeal *et al*, 1988; Pavelic and Zeljko, 2002). These pathological findings are valuable for further studies. However, the autopsied findings may not truly reflect the entire past exposure history of prostatitis.

In the present study, patients with prostatitis history may have increased risk of prostate cancer, but not patients with testitis and epididymitis, as well as those with gonorrhoea and chlamydia infection. This result suggests that the localised inflammation effect may have a more important role in carcinogenesis. Compared with previous self-report case-control studies, the high-coverage claims data set may be more reliable in exploring the history of prostatitis and STDs.

Studies have focused on the contribution of inflammation to both BPH and prostate cancer (Alcaraz *et al*, 2009; De Nunzio *et al*, 2011). Case-control studies have linked BPH to the risk of prostate cancer for Saudi Arabian men who also have low incidence of the disease (Mosli, 2003; Abdel-Meguid *et al*, 2009; Alcaraz *et al*, 2009). Chronic inflammation is associated with BPH and prostate cancer based on medical records and needle biopsy findings (Mosli, 2003; Abdel-Meguid *et al*, 2009). However, the magnitude of the relationship among these three disorders was not well clarified (Abdel-Meguid *et al*, 2009).

Our population-based study proved that prostate cancer is associated with prostatitis and BPH. Benign prostatic hyperplasia is a much stronger risk factor than prostatitis in terms of cancer association. Overlap in BPH and prostatitis exists in our study. Patients with prostatitis are more likely to overlap with BPH in cancer cases than in controls (97.1% vs 16.2%), indicating high linearity between prostatitis and BPH. A strong interaction between prostatitis and BPH for predicting prostate cancer thus appeared in this study, which culminated with an adjusted OR of 49.2 for men with the history of both prostatitis and BPH. To the best of our knowledge, no previous study has reported such a strong synergistic interaction. The causal association of prostate cancer involving prostatitis and BPH is inconclusive in studies done on Western men. This association in Asian men is rather different from that in Western men. With a relatively low incidence of prostate cancer, the pattern observed in this research is worthy of further study. In this study, cases are 6.2-fold more likely to have a history of both BPH and prostatitis than controls (11.9% vs 1.92%). The irritation and stimulation from BPH and prostatitis combined may increase the risk of prostate cancer.

Some medications have been discussed as risk factors for prostate cancer. We also analysed the association with medications that were mostly studied in relation with prostate cancer (Jacobs *et al*, 2005). Our results showed that only aspirin exhibited a protective association in reducing the risk of prostate cancer (data not shown). This result is consistent with a large cohort study done on the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) conducted in the United States. Jacobs *et al* (2005) found that men with long-term regular use of aspirin have reduced risk of prostate cancer (RR = 0.85, 95% CI = 0.73 to 0.99). Their recent study showed long-term regular acetaminophen use may also reduce the overall prostate cancer risk to a relative risk of 0.62 (Jacobs *et al*, 2011). Although acetaminophen shares the same pathway as NSAID, the anti-inflammation effect is weak. This result may provide information for further explorations on prostate carcinogenesis.

Limitations. This study was limited by the use of data from insurance claims because some information on lifestyle and physical examination status are not available. Thus, we were

unable to ascertain whether prostate cancer is associated with smoking, drinking, waist measurement, and so on. Data on family history, molecular factors, and pathophysiology examinations were not available as well. However, we found that obesity is not a significant factor associated with the cancer. Patients with prostatitis and/or BPH may have higher odds to be diagnosed with prostate cancer than the controls, primarily because the former group may visit physicians more frequently. Therefore, the risk estimation for prostate cancer might be overestimated. However, the high accessibility and inexpensive national health system make our analysis more reliable. Some concerns may exist regarding the miscoding and over diagnosis of BPH and prostatitis using the claims data set. The causality of prostate cancer was not established in this study, although BPH and prostatitis were diagnosed before the diagnosis of prostate cancer. Therefore, the mechanism remains unclear.

CONCLUSIONS

Although the incidence of prostate cancer is much lower in Taiwanese men than in men from Western countries, the incidence in Taiwan is steadily increasing. Diabetes and taking aspirin may have a protective effect against prostate cancer, but their beneficial effect may be compromised by overall impairment, leading to the development of BPH and/or prostatitis. Patients with the history of BPH and/or prostatitis could have significantly increased risk of prostate cancer, which is stronger for those with BPH than those with prostatitis. The odds is much higher for patients with both BPH and prostatitis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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