Diabetes and Risk of Prostate Cancer

A study using the National Health Insurance

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OBJECTIVE—The link between diabetes and prostate cancer is rarely studied in Asians.

RESEARCH DESIGN AND METHODS—The trend of age-standardized prostate cancer incidence in 1995–2006 in the Taiwanese general population was calculated. A random sample of 1,000,000 subjects covered by the National Health Insurance in 2005 was recruited. A total of 494,630 men for all ages and 204,741 men ≥40 years old and without prostate cancer at the beginning of 2003 were followed to the end of 2005. Cumulative incidence and risk ratio between diabetic and nondiabetic men were calculated. Logistic regression estimated the adjusted odds ratios for risk factors.

RESULTS—The trend of prostate cancer incidence increased significantly ($P < 0.0001$). The cumulative incidence markedly increased with age in either the diabetic or nondiabetic men. The respective risk ratio (95% CI) for all ages and age 40–64, 65–74, and ≥75 years was 5.83 (5.10–6.66), 2.09 (1.60–2.74), 1.35 (1.07–1.71), and 1.39 (1.12–1.71). In logistic regression for all ages or for age ≥40 years, age, diabetes, nephropathy, ischemic heart disease, dyslipidemia, living region, and occupation were significantly associated with increased risk, but medications including insulin and oral antidiabetic agents were not.

CONCLUSIONS—Prostate cancer incidence is increasing in Taiwan. A positive link between diabetes and prostate cancer is observed, which is more remarkable in the youngest age of 40–64 years. The association between prostate cancer and comorbidities commonly seen in diabetic patients suggests a more complicated scenario in the link between prostate cancer and diabetes at different disease stages.

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The association between diabetes and prostate cancer has been inconsistently reported, even though two meta-analyses suggested that diabetic patients have a lower risk of prostate cancer of 9% (1) and 16% (2), respectively.

While the two meta-analyses were examined, many studies were case-control and only three focused on the follow-up of cohorts of diabetic patients (3–5). Among the three cohorts, the cases of prostate cancer were 9 (3), 498 (4), and 2,455 (5), respectively; and only the last (5) showed a significant 9% risk reduction in diabetic patients. Except for the first study being conducted in residents with diabetes in Rochester, Minnesota (3), the diabetic patients in the other two were from hospitalized patients in Denmark (4) and Sweden (5), respectively. The meta-analyses have limitations including a mixture of case-control and cohort designs, a mixture of incident and dead cases, a small number of prostate cancer in most studies, and different sources of subjects with potential selection bias. Although the contamination of type 1 diabetes is possibly minimal because >90% of overall patients have type 2 diabetes, residual confounding could not be excluded if the two types of diabetes are not differentiated.

Although some recent studies still suggested a lower risk of prostate cancer in diabetic patients including Caucasians (6,7), Iranians (8), Israelis (9), African Americans, Native Hawaiians, and Japanese Americans (6), the lower risk in African Americans and Native Hawaiians (6) was not significant. Two Japanese studies did not find any significant association (10,11). The Ohsaki Cohort Study suggested that diabetes was not predictive for total prostate cancer, but diabetic patients did show a higher risk of advanced cancer (11).

Because diabetic patients are prone to develop cancer involving pancreas, liver, breast, colorectum, bladder, and endometrium (12–15) and the protective effect of diabetes on prostate cancer requires confirmation, this study evaluated the possible link between diabetes and prostate cancer, and the potential risk factors, by using the reimbursement database of the National Health Insurance (NHI) in Taiwan.

RESEARCH DESIGN AND METHODS

Study population

According to the Ministry of Interior, >98.0% of the Taiwanese population in 2005 (22,770,383: 11,562,440 men and 11,207,943 women) were covered by the NHI (16). A random sample of 1,000,000 subjects covered by the NHI in 2005 was created by the National Health Research Institute. The reimbursement databases were available back to 1996. Identification number, sex, birth date, and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) were retrieved. Diabetes was coded 250.1–250.9, and prostate cancer was coded 185.

Because prostate cancer is rare in young men, we analyzed the data for all ages and for those aged ≥40 years in the following groups: 40–64, 65–74, and ≥75 years (case number of prostate cancer was too small for age <40 years). Figure 1 shows a flowchart for selecting cases for the study. After excluding women, type 1 diabetes (in Taiwan, patients with type 1 diabetes were issued a "Severe Morbidity Card" after certified diagnosis), living region unknown, and prostate cancer diagnosed before 2003, 494,630 men for all ages and 204,741 men ≥40 years old and without prostate cancer were

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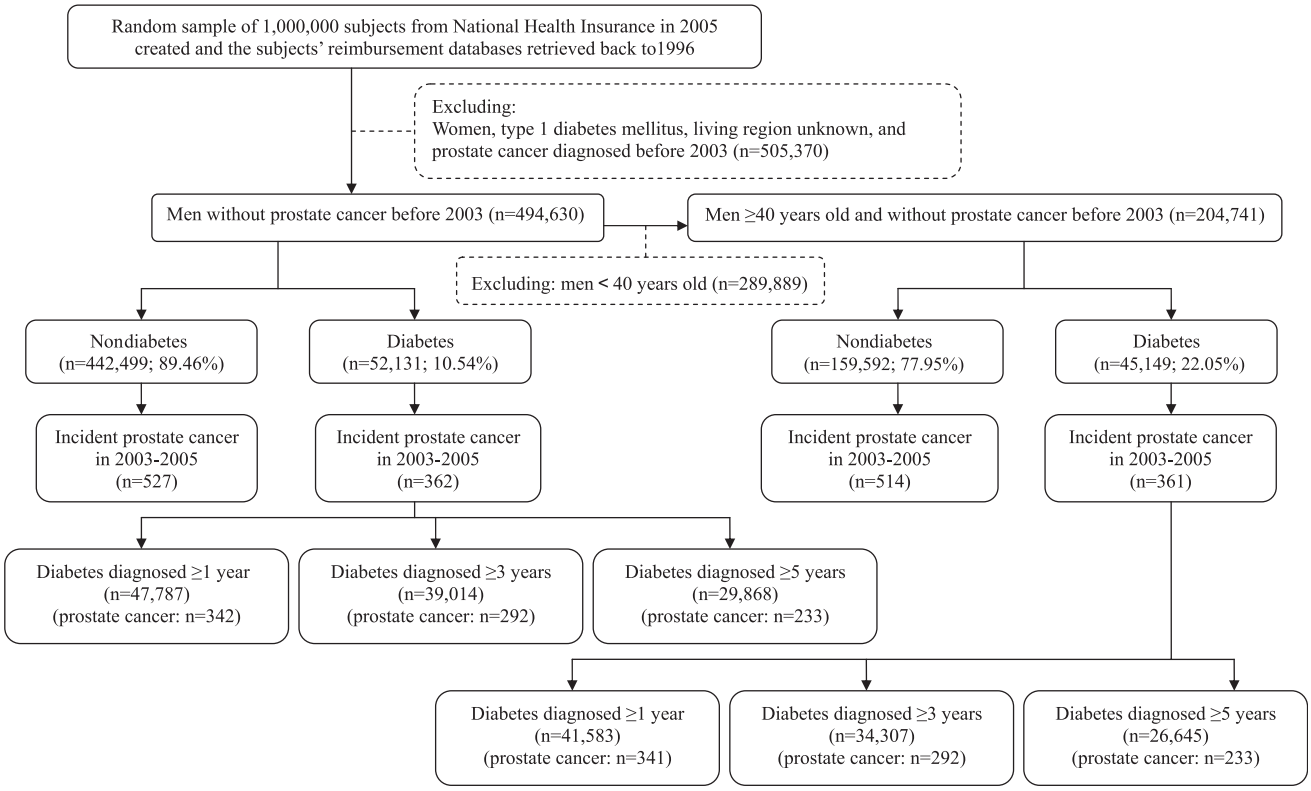

Figure 1—*Flowchart showing the procedures in the calculation of 3-year cumulative incidence of prostate cancer from 2003 to 2005.*

followed from the beginning of 2003 to the end of 2005.

Statistical analyses

The trends of crude and age-standardized (to the 2000 World Health Organization [WHO] population) incidence of prostate cancer in 1995–2006 in the general population were first calculated from the Taiwan Cancer Registry database (17). Linear regression evaluated whether the trends changed significantly, where the incidence was the dependent and the calendar year the independent variable.

The age-specific cumulative incidences from 2003 to 2005 in diabetic and nondiabetic men were calculated for all ages and age 40–64, 65–74, and ≥75 years. The numerator was the number of patients with a first diagnosis of prostate cancer within 2003–2005; and the denominator was the number of insurants in that specific age. The risk ratio between diabetic and nondiabetic men was calculated, and the 95% CI was estimated by Taylor series approximation (18). To minimize the possibility that diabetes might be caused by prostate cancer during a different period, several lag time sensitivity analyses were performed by excluding patients with diabetes duration of <1, <3, and <5 years.

In Taiwan, the National Health Research Institute recommends yearly screening of prostate cancer by digital rectal examination and prostate-specific antigen (PSA) determination for men aged ≥50 years or ≥45 years for those with a family history. The PSA cutoff is set at 4.0 ng/mL. If either examination is abnormal, prostate biopsy guided by transrectal ultrasonography is recommended. The cancer detection rate under this guideline was much lower in Taiwan (0.96–1.3%) than in the Western countries (3–5%); and population-based PSA

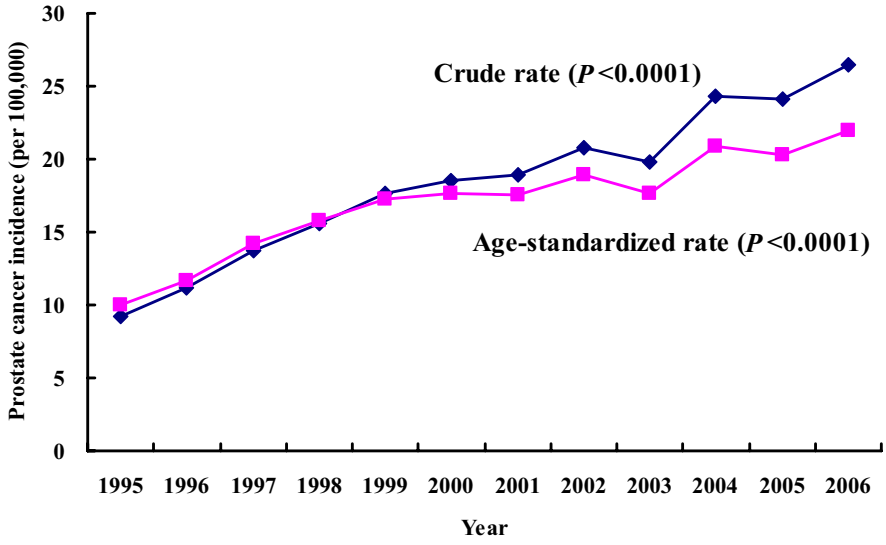

Figure 2—*Trends of prostate cancer incidence in the general population of Taiwan from 1995 to 2006 (◆, crude rate; ■, age-standardized rate using the 2000 WHO population as referent). (A high-quality color representation of this figure is available in the online issue.)*

screening program is not considered as cost effective (19). Therefore PSA test is not paid by the NHI when used for screening purpose in clinical practice. To evaluate whether the use of PSA test differed between those with and without diabetes, χ^2 test compared the frequency of PSA test in 2003–2005 by diabetes status among men for all ages and for age ≥40 years.

Logistic regression calculated the adjusted odds ratios (ORs). Prostate cancer was the dependent variable, and the independent variables included age (<40, 40–64, 65–74, and ≥75 years), diabetes duration (nondiabetes, <1, 1–3, 3–5, and ≥5 years), comorbidities, medications, living region, and occupation. The comorbidities (ICD-9-CM codes) included hypertension (401–405), chronic obstructive pulmonary disease (490–496, a surrogate for smoking), stroke (430–438), nephropathy (580–589), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, 440–448), eye disease (250.5, 362.0, 369, 366.41, 365.44), obesity (278), and dyslipidemia (272.0–272.4). Medications included statin, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, sulfonylurea, metformin, insulin, acarbose, pioglitazone, and rosiglitazone. Comorbidities and medications were counted only as they appeared before 2003 to assure temporal correctness of cause and effect (prostate cancer). The NHI insurants were classified according to occupation, and this served as a

Table 1—*Rates (per 100,000) and risk ratios of 3-year cumulative incidence of prostate cancer from 2003 to 2005 in diabetic and nondiabetic men by age*

	Three-year cumulative incidence by age (years)			
	All ages	40–64	65–74	≥75
Diabetes of any duration				
Diabetic men				
n of prostate cancer	362	75	120	166
n of diabetic men	52,133	26,476	9,959	8,715
Rate in diabetic men	694.38	283.28	1,204.94	1,904.76
Nondiabetic men				
n of prostate cancer	527	174	159	181
n of nondiabetic men	442,509	128,587	17,841	13,168
Rate in nondiabetic men	119.09	135.32	891.21	1,374.54
Risk ratio	5.83 (5.10–6.66)	2.09 (1.60–2.74)	1.35 (1.07–1.71)	1.39 (1.12–1.71)
Excluding diabetes diagnosed <1 year				
Diabetic men				
n of prostate cancer	342	67	112	162
n of diabetic men	47,789	24,000	9,342	8,242
Rate in diabetic men	715.65	279.17	1,198.89	1,965.54
Nondiabetic men				
n of prostate cancer	527	174	159	181
n of nondiabetic men	442,509	128,587	17,841	13,168
Rate in nondiabetic men	119.09	135.32	891.21	1,374.54
Risk ratio	6.01 (5.25–6.88)	2.06 (1.56–2.73)	1.35 (1.06–1.71)	1.43 (1.16–1.76)
Excluding diabetes diagnosed <3 years				
Diabetic men				
n of prostate cancer	292	52	96	144
n of diabetic men	39,014	19,064	8,005	7,238
Rate in diabetic men	748.45	272.77	1,199.25	1,989.50
Nondiabetic men				
n of prostate cancer	527	174	159	181
n of nondiabetic men	442,509	128,587	17,841	13,168
Rate in nondiabetic men	119.09	135.32	891.21	1,374.54
Risk ratio	6.28 (5.45–7.25)	2.02 (1.48–2.75)	1.35 (1.05–1.73)	1.45 (1.17–1.80)
Excluding diabetes diagnosed <5 years				
Diabetic men				
n of prostate cancer	233	40	75	118
n of diabetic men	29,868	14,100	6,493	6,052
Rate in diabetic men	780.10	283.69	1,155.09	1,949.77
Nondiabetic men				
n of prostate cancer	527	174	159	181
n of nondiabetic men	442,509	128,587	17,841	13,168
Rate in nondiabetic men	119.09	135.32	891.21	1,374.54
Risk ratio	6.55 (5.62–7.64)	2.10 (1.49–2.95)	1.30 (0.99–1.70)	1.42 (1.13–1.79)

surrogate for socioeconomic status. The living region served as a surrogate for geographical distribution of some environmental exposure. Occupation was categorized as follows: I: civil servants, teachers, employees of governmental or private business, professionals, and technicians; II: people without particular employers, self-employed, or seamen; III: farmers or fishermen; and IV: low-income families supported by social welfare or veterans. Living region was categorized as Taipei, Northern, Central, Southern, and Kao-Ping and Eastern. The regressions were performed for all ages and for age ≥40 years, separately. Because earlier analyses showed a significantly higher frequency of PSA test in the diabetic patients, additional logistic models were created by including PSA test as an additional independent variable to control for its potential confounding effect.

Analyses were conducted using SAS statistical software, version 9.1 (SAS Institute, Cary, NC). Data were expressed as mean (SD) for continuous variables or number (%) for categorical variables. $P < 0.05$ was considered as statistically significant.

RESULTS—Figure 2 shows the crude and age-standardized incidence trends in the general population. Both are increasing significantly ($P < 0.0001$).

Table 1 shows the 3-year cumulative incidences and the risk ratios between the diabetic and nondiabetic men in different ages. The cumulative incidence markedly increased with age in either the diabetic or nondiabetic men. Risk ratio analysis showed that diabetic patients had a higher risk than nondiabetic men in all age groups. However, divergent associations with regard to age were noted: those in the youngest age of 40–64 years had the highest risk ratio, followed by those in the oldest of ≥75 years, and those aged 65–74 years had the lowest risk ratio.

Diabetic patients did show a higher frequency in the use of PSA test in either the analysis for all ages or for age ≥40 years (Table 2).

Table 3 shows the results of the logistic regressions. The results were similar in models without (model I) or with (model II) PSA as an additional independent variable. In model II only the ORs for the different subgroups of diabetes duration and PSA test are shown. Age was a remarkable risk factor, and diabetes duration showed a nonlinear increase in the risk. Nephropathy, ischemic heart disease, dyslipidemia, living region, and occupation were significant, whereas chronic obstructive pulmonary disease was borderline significant. None of the medications was significant.

CONCLUSIONS—The trends of prostate cancer were increasing significantly in 1995–2006 (Fig. 2), and diabetes was associated with an increased risk at any duration (Tables 1 and 3), with the highest risk ratio observed in the youngest age of 40–64 years (Table 1).

Although some recent studies still favored a protective effect of diabetes in Caucasians (6,7), a recent population-based case-control study in the US concluded that diabetes was not associated with prostate cancer (OR = 0.98, 95% CI: 0.76–1.27) and that the protective effect of diabetes might be because of a confounding of a mixture with type 1 diabetes (20). In the current study, patients with type 1 diabetes were excluded and its confounding is minimal.

Diabetes was unlikely caused by prostate cancer, because the association was consistent in different analyses (Table 1). Diabetes diagnosed 5 years before prostate cancer can hardly be a consequence of the carcinogenic process. Another possibility for an increased incidence in the diabetic patients is because of screening bias (Table 2). However, our analysis did not support such a possibility because the conclusions remained the same when PSA test was also included in the logistic analyses (model II of Table 3).

Heterogeneity may exist in the association between diabetes and prostate cancer. Some suggested that recent-onset diabetes may increase, but long-standing diabetes might reduce the risk (21). In the current study, although prostate cancer risk increased with increasing diabetes duration in unadjusted models (data not shown), the adjusted models showed that the highest risk was observed at diabetes duration of 1–3 years and then declined gradually (Table 3). Recently serum creatinine is shown to be significantly predictive for prostate cancer risk (22). Our finding of a significantly higher risk of 27% in patients with nephropathy (Table 3) confirmed such an observation. Some suggested that patients with more severe diabetes might have lower level of PSA and lower risk of prostate cancer (23). However, the current study showing a higher risk of prostate cancer associated with nephropathy, ischemic heart disease, and dyslipidemia (Table 3) argued against a simple scenario. With increasing duration and severity of diabetes, chronic complications may set in and interfere with the association between diabetes and prostate cancer. Some suggested that diabetes might only convey a higher risk of more advanced prostate cancer (11,24). However, we did not have sufficient information for analysis.

It is interesting to observe an effect modification by age with the highest risk ratio observed at the youngest age of 40–64 years (Table 1). One explanation is that a higher mortality from other causes in the older diabetic patients before the development of prostate cancer may obscure the relationship, as opposed to the youngest age group who might have been exposed to inflammatory and carcinogenic effects of diabetes for a longer period of time. Such a relationship simply might not have been captured by case-control designs.

Some commonly used medications did not affect the risk (Table 3). However, geographical distribution and socioeconomic status, as indicated by living region and occupation, respectively, did significantly impact the risk (Table 3). People living in metropolitan Taipei

Table 2—*Examination of PSA in 2003–2005 by status of diabetes for all ages and age ≥40 years in Taiwanese men*

	Diabetes				
	No		Yes		
Examination of PSA	*n*	%	*n*	%	*P* value
All ages					
No	441,829	99.85	51,662	99.10	<0.0001
Yes	680	0.15	471	0.90	
Age ≥40 years					
No	158,928	99.58	44,681	98.96	<0.0001
Yes	668	0.42	469	1.04	

Table 3—*Mutually adjusted ORs for prostate cancer derived from cumulative incident cases from 2003 to 2005*

Variables	All ages		Age ≥40 years	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model I				
Age, years				
<40	Referent			
40–64	30.25 (17.62–51.91)	<0.0001	Referent	
65–74	164.57 (95.10–284.81)	<0.0001	5.44 (4.50–6.58)	<0.0001
≥75	239.01 (137.40–415.76)	<0.0001	7.89 (6.45–9.67)	<0.0001
Diabetes duration, years vs. nondiabetics				
<1	1.25 (0.79–1.96)	0.3386	1.25 (0.80–1.96)	0.3352
1–3	1.45 (1.08–1.95)	0.0130	1.43 (1.06–1.92)	0.0198
3–5	1.40 (1.05–1.86)	0.0224	1.40 (1.05–1.87)	0.0218
≥5	1.30 (1.06–1.60)	0.0129	1.30 (1.06–1.60)	0.0130
Hypertension, yes vs. no	1.12 (0.94–1.33)	0.2037	1.12 (0.94–1.34)	0.1922
Chronic obstructive pulmonary disease, yes vs. no	1.15 (0.99–1.33)	0.0657	1.16 (1.00–1.34)	0.0535
Stroke, yes vs. no	0.98 (0.81–1.17)	0.8004	0.98 (0.82–1.17)	0.8057
Nephropathy, yes vs. no	1.27 (1.04–1.53)	0.0172	1.27 (1.05–1.54)	0.0161
Ischemic heart disease, yes vs. no	1.29 (1.09–1.52)	0.0026	1.28 (1.08–1.51)	0.0035
Peripheral arterial disease, yes vs. no	0.95 (0.74–1.21)	0.6606	0.95 (0.74–1.21)	0.6595
Eye disease, yes vs. no	1.21 (0.84–1.75)	0.3161	1.21 (0.84–1.75)	0.3123
Obesity, yes vs. no	0.80 (0.26–2.51)	0.7037	0.81 (0.26–2.55)	0.7228
Dyslipidemia, yes vs. no	1.42 (1.19–1.70)	0.0001	1.41 (1.18–1.69)	0.0002
Statin, yes vs. no	1.14 (0.90–1.46)	0.2760	1.15 (0.90–1.47)	0.2567
Fibrate, yes vs. no	0.93 (0.73–1.19)	0.5782	0.94 (0.74–1.19)	0.5897
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, yes vs. no	1.07 (0.86–1.34)	0.5422	1.07 (0.86–1.34)	0.5427
Calcium channel blocker, yes vs. no	0.91 (0.72–1.15)	0.4299	0.91 (0.72–1.15)	0.4274
Sulfonylurea, yes vs. no	1.07 (0.78–1.46)	0.6873	1.07 (0.78–1.46)	0.6903
Metformin, yes vs. no	0.79 (0.56–1.11)	0.1796	0.79 (0.56–1.11)	0.1781
Insulin, yes vs. no	0.52 (0.21–1.27)	0.1501	0.51 (0.21–1.27)	0.1481
Acarbose, yes vs. no	1.00 (0.49–2.02)	0.9901	1.00 (0.49–2.02)	0.9905
Pioglitazone, yes vs. no	0.77 (0.10–5.75)	0.7955	0.77 (0.10–5.77)	0.7979
Rosiglitazone, yes vs. no	0.88 (0.43–1.80)	0.7180	0.88 (0.43–1.80)	0.7206
Living region				
Northern vs. Taipei	0.83 (0.68–1.01)	0.0604	0.84 (0.69–1.02)	0.0756
Central vs. Taipei	0.66 (0.54–0.81)	<0.0001	0.68 (0.56–0.83)	0.0002
Southern vs. Taipei	0.44 (0.35–0.57)	<0.0001	0.46 (0.36–0.58)	<0.0001
Kao-Ping and Eastern vs. Taipei	0.48 (0.39–0.60)	<0.0001	0.49 (0.40–0.61)	<0.0001
Occupation				
II vs. I	0.67 (0.52–0.86)	0.0015	0.68 (0.53–0.88)	0.0028
III vs. I	0.78 (0.64–0.95)	0.0126	0.77 (0.63–0.94)	0.0116
IV vs. I	0.83 (0.70–0.99)	0.0370	0.84 (0.71–0.99)	0.0475
Model II*				
Diabetes duration, years vs. nondiabetics				
<1	1.207 (0.766–1.904)	0.4175	1.209 (0.767–1.907)	0.4139
1–3	1.410 (1.046–1.900)	0.0242	1.381 (1.022–1.866)	0.0357
3–5	1.387 (1.036–1.857)	0.0278	1.389 (1.038–1.859)	0.0270
≥5	1.266 (1.028–1.559)	0.0267	1.266 (1.027–1.559)	0.0269
PSA test, yes vs. no	13.490 (10.899–16.697)	<0.0001	13.374 (10.799–16.563)	<0.0001

Refer to RESEARCH DESIGN AND METHODS for the categories of occupation. *Model II: additionally adjusted for PSA test; only the ORs for diabetes duration and PSA test are shown.

region had the highest risk, and the risk seemed to decline gradually with lesser urbanization as shown from the ORs, much deviating from unity from Northern to Central, Southern, and Kao-Ping and Eastern region (Table 3). People with a higher socioeconomic status as indicated by occupation I also suffered from a higher risk (Table 3). The reasons for such discrepancy with regard to geographical distribution and socioeconomic status await further exploration.

This study has several strengths. It is population based with a large nationally representative sample. The database included outpatients and inpatients, and we caught the diagnoses from both sources. Cancer is considered as a severe morbidity

by the NHI, and most medical copayments can be waived. Therefore the detection rate would not tend to differ among different social classes. The use of medical record also reduced the potential bias related to self-reporting.

Limitations included a lack of actual measurement of confounders such as obesity, smoking, alcohol drinking, family history, lifestyle, diet, hormones, and genetic parameters. In addition, we did not have biochemical data for evaluating their impact. Finally, the follow-up interval is probably too short to plausibly account for the likely induction time needed between the onset of diabetes and the biological changes leading to prostate cancer.

In summary, this study shows an increasing trend of prostate cancer in Taiwan and a link between diabetes and prostate cancer, which is more remarkable in the age of 40–64 years. Therefore, the observation that diabetes confers a lower risk of prostate cancer might not be universal. Insulin or other oral antidiabetic agents are not, but nephropathy, ischemic heart disease, and dyslipidemia are significantly associated with prostate cancer. The association between prostate cancer and these comorbidities suggests a more complicated scenario in the link between prostate cancer and diabetes at different disease stages. Given that the population is aging, the incidence of prostate cancer is increasing, and the incidence of type 2 diabetes is also increasing (25). The impact of prostate cancer on the population should warrant public health attention.

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C.-H.T. researched data and wrote the article.

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