Diabetes Mellitus and Prostate Cancer Risk in Asian Countries: a Meta-analysis

Xiang-Ju Long1*, Shan Lin1, Ya-Nan Sun2, Zhen-Feng Zheng1

Abstract

**Background/Aims:** Diabetes mellitus (DM) is widely considered to be associated with risk of cancer, but studies investigating the association between DM and prostate cancer in Asian countries have reported inconsistent findings. We examined this association by conducting a detailed meta-analysis of studies published on the subject. **Methods:** Cohort or case-control studies were identified by searching Pubmed, Embase and Wanfang databases through May 30, 2012. Pooled relative risk (RR) with its corresponding 95% confidence interval (95% CI) were calculated using the random-effects model. Subgroup analyses were performed by the study type. **Results:** Finally, we identified 7 studies (four cohort studies and three case-control studies) with a total of 1,751,274 subjects from Asians. DM was associated with an increased risk of prostate cancer in Asians (unadjusted RR= 2.82, 95% CI 1.73–4.58, P < 0.001; adjusted RR= 1.31, 95% CI 1.12–1.54, P = 0.001). Subgroup analyses by study design further confirmed an obvious association. **Conclusion:** Findings from this meta-analysis strongly support that diabetes is associated with an increased risk of prostate cancer in Asians.

**Keywords:** Diabetes mellitus - prostate cancer - meta-analysis - Asian populations

However, previous meta-analysis only included studies from Caucasians, and there was no study from Asians (Bonovas et al., 2004; Kasper and Giovannucci, 2006). A few studies published recently investigated the association between DM and prostate cancer in Asian countries. But the findings from these studies were inconsistent (Li et al., 2010; Tseng, 2011; Hsieh et al., 2012; Lee et al., 2012). To provide more precise estimates for DM and prostate cancer risk in Asians, we performed a meta-analysis of observational studies including cohort studies and case-control studies.

**Materials and Methods**

**Literature search and selection criteria**

Cohort or case-control studies were identified by searching Pubmed, Embase and Wanfang databases through May 30, 2012. The search strategy used medical subject heading (MeSH) terms and keywords: diabetes or diabetes mellitus; and prostate cancer or prostate carcinoma. We also reviewed the reference lists to identify additional relevant studies. No language restrictions were imposed. All searched studies were retrieved, and their bibliographies were checked for other relevant publications. Studies were included in the meta-analysis if (1) studies from Asian countries; (2) cohort or case-control design; (3) one of the exposures was DM; (4) one of the outcome of interests was prostate cancer; and (5) relative risk (RR), odds ratio (OR), hazard ratio (HR) or
standardized incidence/mortality rate (SIR/SMR) with their corresponding 95% confidence intervals (95% CI) (or data to calculate them) were available. The major reasons for exclusion of studies were: (1) case-only studies; (2) review papers; (3) containing overlapping data. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Data extraction

We extracted the following data from each study: the first author’s last name, publication year, year of the study conducted, country, sample size, participant characteristics (age and sex), methods of ascertainment of diabetes and outcome, the follow-up period, estimate effects with their 95% CIs, and covariates adjusted for in the analysis. When studies provided more than one RR according to the duration of diabetes before prostate cancer was diagnosed, we extracted and combined the RRs for individuals diagnosed with diabetes more than 1 year prior to the diagnosis of prostate cancer. We did not contact the prime investigators of these studies for further information.

Statistical analysis

We included studies in this meta-analysis reporting different measures of RR, OR, HR and SIR/SMR. To assess heterogeneity among studies, we used the I2 statistic, and a value more than 50% is considered that severe heterogeneity existed (Higgins et al., 2003). Pooled RR with corresponding 95% CI was derived with the method of DerSimonian and Laird using the assumptions of a random-effects model, which accounts for heterogeneity among studies (DerSimonian and Laird, 1986). Data were stratified into subgroups on the basis of study design, which was done to examine consistency across varying study designs with different potential biases. Publication bias was evaluated using the funnel plot and Egger’s test, and a P value of less than 0.05 was considered statistically significant (Egger et al., 1997). All statistical analyses were performed using STATA, version 1.0 (STATA, College Station, TX, USA). For all tests, a probability level of less than 0.05 was considered statistically significant.

Results

Studies characteristics

The primary computerized literature search identified 1227 records. Examination of these records yielded 9 potentially relevant publications for further review (Li et al., 2010; Tsugane and Inoue, 2010; Ganesh et al., 2011; Tseng, 2011; Chiou et al., 2012; Fukushima et al., 2012; Hong et al., 2012; Hsieh et al., 2012; Lee et al., 2012). After evaluation by reading full text carefully, two studies were further excluded including one case-only study (Chiou et al., 2012) and one review (Tseng, 2011). Finally, we identified 7 studies (four cohort studies and three case-control studies) with a total of 1,751,274 subjects (8480 prostate cancer cases) (Li et al., 2010; Ganesh et al., 2011; Tseng, 2011; Fukushima et al., 2012; Hong et al., 2012; Hsieh et al., 2012; Lee et al., 2012). Of these, four were cohort studies (Li et al., 2010; Tseng, 2011; Hsieh et al., 2012; Lee et al., 2012), and three were case-control studies (Ganesh et al., 2011; Fukushima et al., 2012; Hong et al., 2012). There were three from Taiwan (Tseng, 2011; Hsieh et al., 2012; Lee et al., 2012), two from Japan (Li et al., 2010; Fukushima et al., 2012), one from Korea (Hong et al., 2012) and one from India (Ganesh et al., 2011). DM was determined on the basis of a positive history in all 7 studies. Potential confounders (at least for age) were controlled in most of the studies, except in one the confounders adjusted for were not indicated clearly (Tseng, 2011).

DM and prostate cancer risk

As shown in Figure 1, the pooled unadjusted RR with its 95% CI was 2.82 (95% CI, 1.73–4.58) for individuals with diabetes compared with individuals without diabetes or general population (P < 0.001), with significant heterogeneity among these studies (I2 = 97.6%). When we restricted the meta-analysis to those studies controlled for potential confounders, the pooled adjusted RR with its 95% CI was 1.31 (95% CI, 1.12–1.54) for individuals with diabetes compared with individuals without diabetes or general population (P = 0.001), without obvious heterogeneity among studies (I2 = 42.5%, Figure 2).

Subgroup meta-analyses by study design showed DM is associated with an increased risk of prostate cancer in both case-control studies and cohort studies (For cohort
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Bonovas et al., 2004). Therefore, the likelihood of an important protective factor for prostate cancer in diabetic patients cancer (Gann et al., 1996). Lower level of testosterone is associated with an elevated risk of prostate cancer (Salazar-Martinez et al., 2000; Chen et al., 2010; Onitilo et al., 2012). The overwhelming evidence suggests that cancer incidence is increased in patients with DM, while prostate cancer is an exception. Kasper et al. (2006) and Bonovas et al. (2004), two separate research groups, similarly demonstrated that a decreased incidence of prostate cancer is observed in diabetic patients compared to non-diabetic patients in Caucasian populations, implying a protective effect. However, Snyder et al. (2010) found that pre-existing diabetes affected the treatment and outcomes of men with prostate cancer, although the findings needed to be further explored. Besides, studies published to evaluate the association between DM and prostate cancer in Asian countries exhibit inconsistent results (Li et al., 2010; Tseng, 2011; Hsieh et al., 2012; Lee et al., 2012). Apparently, the associations of patients with DM and prostate cancer risk in Asian and Caucasian populations are different. Several factors such as environmental factors, family history, duration of diabetes, type of diabetic medication, duration of medication use, and different genetic backgrounds might contribute to the different result, which should be clarified in further studies. It has been suggested that testosterone is associated with an elevated risk of prostate cancer (Gann et al., 1996). Lower level of testosterone is a protective factor for prostate cancer in diabetic patients (Bonovas et al., 2004). Therefore, the likelihood of an important population selection or publication bias may result in the contradictory results. Thus, there was a need to perform a meta-analysis of published data investigating the association between DM and prostate cancer risk to shed some light on these contradictory findings.

In our meta-analysis, the pooled unadjusted RR (RR unadjusted = 2.82; 95% CI, 1.73–4.58) for individuals with diabetes compared with individuals without diabetes or general population showed that DM was associated with prostate cancer risk in Asian population (Figure 1). Furthermore, the pooled adjusted RR (RR adjusted = 1.31; 95% CI, 1.12–1.54) for individuals with diabetes compared with individuals without diabetes or general population accordingly demonstrated that DM is associated with an increased risk of prostate cancer in Asians (Figure 2). Subgroup analyses by study design further identified the significant association between DM and prostate cancer. Sensitivity analyses by sequential omission of any individual studies also did not materially alter the overall combined RRs (data were not shown). This meta-analysis strongly support that diabetes is associated with an increased risk of prostate cancer in Asians.

Nevertheless, some limitations must be taken into account when interpreting the findings in the meta-analysis. First, the association between DM and prostate cancer risk may be affected by the types of DM (Type 1 or Type 2). However, little data on this aspect was reported in those included studies, and we were unable to make subgroup analyses by the type of DM. Further studies with accurate type of diabetes are needed to identify this association between DM and risk of prostate cancer. Second, we could not exclude the possibility of undetected bias owing to the limitations of case-control design, although four studies followed a prospective cohort design were enrolled in our meta-analysis. More prospective studies are expected to investigate whether differences of genetic backgrounds might interpret the contradictory findings among different DM populations. Third, the influence of bias in the present analysis could not be completely excluded because studies with positive results were easier published than with negative results.

In conclusion, the present meta-analysis shows a significant association between DM and increased risk of prostate cancer in Asians. Besides, future studies may further assess this association by analyzing Type 1 and Type 2 diabetes separately.

Acknowledgements

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References

Barone BB, Yeh HC, Snyder CF, et al (2008). Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA, 300, 2754-64.

Bonovas S, Filioussi K ,Tsantes A (2004). Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia, 47, 1071-8.
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Chan JC, Malik V, Jia W, et al (2009). Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA, 301, 2129-40.
Chen CQ, Fang LK, Cai SR, et al (2010). Effects of diabetes mellitus on prognosis of the patients with colorectal cancer undergoing resection: a cohort study with 945 patients. Chin Med J (Engl), 123, 3084-8.
Chiou WK, Hwang JS, Hsu KH, et al (2012). Diabetes mellitus increased mortality rates more in gender-specific than in nongender-specific cancer patients: a retrospective study of 149,491 patients. Exp Diabetes Res, 2012, 701643.
Damber JE, Aus G (2008). Prostate cancer. Lancet, 371, 1710-21.
DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. Control Clin Trials, 7, 177-88.
Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315, 629-34.
Foulkes WD (2008). Inherited susceptibility to common cancers. N Engl J Med, 359, 2143-53.
Fukushima H, Masuda H, Kawakami S, et al (2012). Effect of diabetes mellitus on high-grade prostate cancer detection among Japanese obese patients with prostate-specific antigen less than 10 ng/mL. Urology, 79, 1329-34.
Ganesh B, Saoba SL, Sarade MN, et al (2011). Risk factors for prostate cancer: An hospital-based case-control study from Mumbai, India. Indian J Urol, 27, 345-50.
Gann PH, Hennekens CH, Ma J, et al (1996). Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst, 88, 1118-26.
Higgins JP, Thompson SG, Deeks JJ, et al (2003). Measuring inconsistency in meta-analyses. BMJ, 327, 557-60.
Hoffman RM (2011). Clinical practice. Screening for prostate cancer. N Engl J Med, 365, 2013-9.
Hong SK, Oh JJ, Byun SS, et al (2012). Impact of diabetes mellitus on the detection of prostate cancer via contemporary multi (≥ 12)-core prostate biopsy. Prostate, 72, 51-7.
Hsieh MC, Lee TC, Cheng SM, et al (2012). The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the taiwanese. Exp Diabetes Res, 2012, 413782.
Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. CA Cancer J Clin, 61, 69-90.
Kasper JS, Giovannucci E (2006). A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev, 15, 2056-62.
Lee MY, Lin KD, Hsiao PJ, et al (2012). The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism, 61, 242-9.
Li Q, Kuriyama S, Kakizaki M, et al (2010). History of diabetes mellitus and the risk of prostate cancer: the Ohsaki Cohort Study. Cancer Causes Control, 21, 1025-32.
McGrrowder DA, Jackson LA, Crawford TV (2012). Prostate cancer and metabolic syndrome: is there a link? Asian Pac J Cancer Prev, 13, 1-13.
Mori M, Masumori N, Fukuta F, et al (2011). Weight gain and family history of prostate or breast cancers as risk factors for prostate cancer: results of a case-control study in Japan. Asian Pac J Cancer Prev, 12, 743-7.
Nolan CJ, Damm P, Prentki M (2011). Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet, 378, 169-81.
Onitilo AA, Engel JM, Glurich I, et al (2012). Diabetes and cancer I: risk, survival, and implications for screening. Cancer Causes Control, 23, 967-81.
Salazar-Martinez E, Lazcano-Ponce EC, Lira-Lira GG, et al (2000). Case-control study of diabetes, obesity, physical activity and risk of endometrial cancer among Mexican women. Cancer Causes Control, 11, 707-11.
Snyder CF, Stein KB, Barone BB, et al (2010). Does pre-existing diabetes affect prostate cancer prognosis? A systematic review. Prostate Cancer Prostatic Dis, 13, 58-64.
Tseng CH (2011). Diabetes and risk of prostate cancer: a study using the National Health Insurance. Diabetes Care, 34, 616-21.
Tsunage S, Inoue M (2010). Insulin resistance and cancer: epidemiological evidence. Cancer Sci, 101, 1073-9.