RESEARCH ARTICLE

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

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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

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Introduction

Diabetes mellitus (DM) and cancer are two common severe chronic diseases that lead to many deaths (Jemal et al., 2011; Nolan et al., 2011). Prostate cancer, a common cause of cancer mortality in men, is one of the most frequently diagnosed malignancies (Jemal et al.,2011). In developed countries, prostate cancer is the second most frequently diagnosed cancer, and the third most common cause of death from cancer in men (Damber and Aus, 2008). Identifying risk factors for prostate cancer is critically important to develop potential interventions and to expand our understanding of the biology of this disease (Foulkes, 2008; Hoffman, 2011; Mori et al., 2011). Besides, there are more than 250 million people with diabetes worldwide, and this number is expected to reach 380 million in 20 years (Nolan et al., 2011). Type 2 diabetes is an increasing epidemic in Asia, characterized by rapid rates of increase over short periods and onset at a relatively young age and low body mass index (Chan et al., 2009). Several studies have suggested that diabetes significantly increases the risk of different cancers, and the association between diabetes and cancer is of clear importance (Kasper and Giovannucci, 2006; Barone et al., 2008; McGrowder et al., 2012). In contrast with various other malignancies, published data obtained from population-based studies indicate that the risk of prostate cancer may have an inverse relationship with DM (Bonovas et al., 2004; Kasper and Giovannucci, 2006). 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

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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 o be 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).

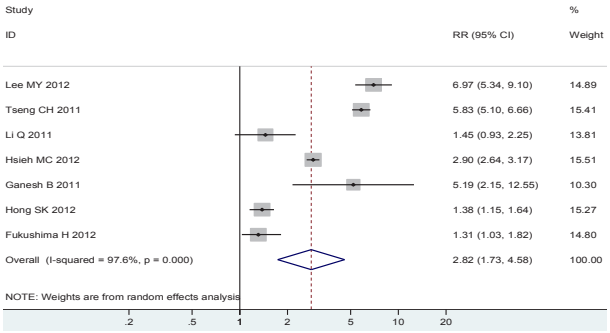

Figure 1. Pooled Unadjusted Relative Risk for the Association Between Diabetes and Risk of Prostate Cancer (Diamonds represent study-specific relative risks or summary relative risks with 95% confidence intervals; horizontal lines represent 95% confidence intervals)

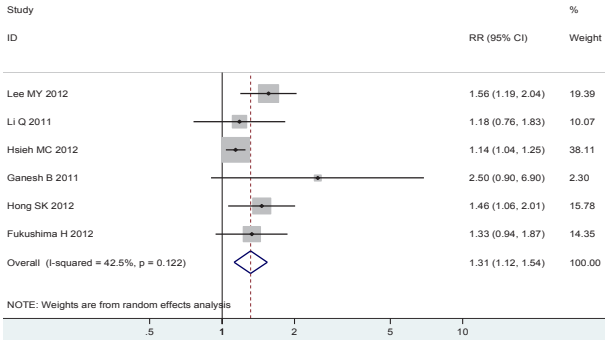

Figure 2. Pooled Adjusted Relative Risk for the Association Between Diabetes and Risk of Prostate Cancer (Diamonds represent study-specific relative risks or summary relative risks with 95% confidence intervals; horizontal lines represent 95% confidence intervals).

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 ($I^2 = 97.6\%$). 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 ($I^2 = 42.5\%$, 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

studies, unadjusted RR (95% CI) = 3.71 (95% CI, 2.19–6.27), adjusted RR (95% CI) = 1.26 (95% CI, 1.01–1.57); For case-control studies, unadjusted RR (95% CI) = 1.65 (95% CI, 1.09–2.48), adjusted RR (95% CI) = 1.44 (95% CI, 1.15–1.81)).

Publication bias

Funnel plot and Egger's test were performed to assess the possible publication bias in this meta-analysis. There was no funnel plot asymmetry for the meta-analysis of the association between DM and pancreatic cancer risk. Besides, the P value for Egger's regression asymmetry test was 0.330, suggesting a low probability of publication bias.

Discussion

The present meta-analysis findings provide strong evidence that DM is associated with an increased risk of prostate cancer in Asians, which was based on the large amount of published data giving greater information to detect significant differences. Totally, 7 studies including four cohort studies and three case-control studies with a total of 1,751,274 subjects were brought into this meta-analysis. Meta-analyses showed that people with diabetes had a significant increase in risk of developing prostate cancer under both unadjusted estimates and adjusted estimates ($RR_{unadjusted}$ =2.82; 95% CI, 1.73–4.58; $RR_{adjusted}$ = 1.31; 95% CI, 1.12–1.54). Sensitivity analyses and subgroup analyses by study design supported the concept of DM as a susceptible factor of prostate cancer.

To the best of our knowledge, DM has been associated with increased risk of numerous cancers including cancers of the pancreas, liver, breast, kidney, colon, and female reproductive organs (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 group, 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. Bedsides, future studies may further assess this association by analyzing Type 1 and Type 2 diabetes separately.

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