Diabetes Mellitus Reduces Prostate Cancer Risk - No Function of Age at Diagnosis or Duration of Disease

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Abstract

Background: Prior studies examining the relation between diabetes mellitus (DM) and prostate cancer risk have reported controversial findings. We examined this association by conducting a detailed meta-analysis of the peer-reviewed literature. Methods: A comprehensive search for articles of MEDLINE and EMBASE databases and bibliographies of retrieved articles published up to November, 2012 was performed. Methodological quality assessment of the trials was based on the Newcastle-Ottawa Scale and the meta-analysis was performed using STATA 12.0. Dose-response regression was conducted with SPSS 19.0. Results: We included 29 studies in the meta-analysis (13 case-control studies, 16 cohort studies), and found an inverse association between DM and prostate cancer (relative risk (RR) 0.84, 95% confidence interval (CI), 0.78-0.91). An inverse association was also observed in non-Asian populations (RR 0.81, 95% CI 0.76-0.87) and population-based studies (RR 0.80, 95% CI 0.77-0.91). No statistical significance was found of the association between prostate cancer risk and the duration of DM (p=0.338), and risk seemed not related with the age of DM diagnosis. Conclusions: This study suggested an inverse relationship between DM and prostate cancer, but without links to duration of disease or age of diagnosis.

Keywords: Diabetes mellitus - meta-analysis - prostate cancer

Introduction

The number of people with diabetes mellitus (DM) is rapidly increasing because of population ageing, urbanization and lifestyle changes (Zimmet et al., 2001). It has become a major public health issue not only in developed countries, but also in developing countries. Numerous human cancers are reported to be associated with DM. Increased risk of carcinomas of liver (Lee et al., 2011), colon (Jin, 2008), pancreas (Ben et al., 2011), kidney (Joh et al., 2011), endometrium (Weiderpass et al., 1997), esophagus (Jiang et al., 2012) and thyroid (Aschebrook-Kilfoy et al., 2011) is seen among patients with DM. Studies investigating the association between DM and prostate cancer (PCa), however, have shown a controversial result, although most of the studies revealed that DM may be associated with a lowering of the risk for PCa.

The first meta-analysis including 14 studies (Wynder et al., 1971; Ragozzino et al., 1982; Checkoway et al., 1987; Thompson et al., 1989; Smith et al., 1992; La Vecchia et al., 1994; Steenland et al., 1995; Coughlin et al., 1996; Wideroff et al., 1997; Giovannucci et al., 1998; Will et al., 1999; Rosenberg et al., 2002; Tavani et al., 2002; Weiderpass et al., 2002) was published in 2004 by Bonovas et al (2004). Later in 2006, another meta-analysis containing 19 studies (Wynder et al., 1971; Ragozzino et al., 1982; Mishina et al., 1985; Thompson et al., 1989; Smith et al., 1992; Steenland et al., 1995; Coughlin et al., 1996; Will et al., 1999; Rosenberg et al., 2002; Tavani et al., 2002; Weiderpass et al., 2002; Coker et al., 2004; Lightfoot et al., 2004; Zhu et al., 2004; Gonzalez-Perez et al., 2005; Rodriguez et al., 2005; Tavani et al., 2005) was published (Kasper et al., 2006). They both showed that diabetic patients have a statistically significant (9% in 2004 and 16% in 2006) decrease in the risk of developing PCa.

A total of 13 relevant studies on the association between DM and PCa have been published since 2006, consisting of 8 prospective studies (Calton et al., 2007; Velicer et al., 2007; Leitzmann et al., 2008; Kasper et al., 2009; Wallstrom et al., 2009; Waters et al., 2009; Li et al., 2010; Lee et al., 2012) and 5 retrospective ones (Gong et al., 2006; Pierce et al., 2008; Baradaran et al., 2009; Pelucchi et al., 2011; Turner et al., 2011). With more than 30,000 additional PCa cases, we aimed to re-analyze this relationship further by conducting an updated detailed meta-analysis with focusing on the effect of time, namely the duration since DM was diagnosed and the age of patient when DM was diagnosed.
Selection of Published Studies

A literature search was conducted using the search terms: “diabetes mellitus” or “DM” or “diabetes” combined with “prostatic neoplasms” or “prostatic cancer” or “prostate neoplasms” or “PCa”. These same search terms were applied for both Medline and Embase search engines to retrieve all potentially relevant English articles (until November, 2012). Cited references of retrieved articles and review articles were chosen for reviewing to identify any additional relevant studies. The titles and abstracts of studies identified in the computerised search were read through carefully to exclude any article that was obviously irrelevant. The full text of the remaining articles was carefully read.

Our search and selection process is illustrated in Figure 1. Titles and abstracts of 876 publications were reviewed and 841 were discarded because they were not examining the relationship between the two diseases, they were not epidemiologic studies, or they were not human studies. Bibliographies were also searched with 4 additional publications. The full text of the 39 articles were read through carefully by Xu. The decisions on inclusion and exclusion were made by Jiang and Xu. Studies were excluded if they did not provide enough data to allow calculation of relative risks (RRs) with 95% confidence intervals (CI). Besides, publications were excluded if the exposure was metabolic syndrome (Laukkanen et al., 2004) or hyperglycemia (Grundmark et al., 2010), or controls were men with benign prostatic hyperplasia (Checkoway et al., 1987; Rosenberg et al., 2002), or the outcome was PCa mortality (Coughlin et al., 1996, Will et al., 1999) or recurrence (Chan et al., 2005). Additionally, publications were excluded if they were designed to clarify the association between DM and severity of PCa among patients having radical prostatectomy (Abdollah et al., 2011), or radiation therapy (Mitin et al., 2011), or having a prostate biopsy (Moreira et al., 2011) due to elevated PSA level. Another three studies (Gallus et al., 2007; Pourmand et al., 2007; Tseng, 2011) were excluded since later studies reported on same study population. Finally, 29 publications were chosen for the meta-analysis.

Data Extraction and Quality Assessment

Data were extracted by Jiang and Xu with independent evaluation of the eligibility of all selected studies by using a unified data form. The items included in the data form were as follows: study name, journal name, country and study design, study population (case and control), range for follow-up, effect estimates with 95% CIs for the association of DM and PCa, raw data where provided, and matched or adjusted variables in analysis. The two lists from the authors were compared, and disagreements were resolved by consensus.

RR were recorded or calculated. Among all the 29 studies that were included in our analysis, effect estimates differed from odds ratio (OR), hazard ratio (HR), incidence density ratio (IDR), to standardized incidence ratio (SIR). Due to the rare occurrence of PCa, we assumed that all of these measures would give a similar effect estimate and they were considered equally in the overall effect estimate. To assess the study quality, a 9-star system on the basis of the Newcastle-Ottawa Scale was used in which a study was judged on 3 broad perspectives as follows: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest for case-control or prospective studies, respectively.

Statistical Analysis

Publication bias was evaluated using both the Begg’s funnel plot and the Egger plot. We examined between-study heterogeneity by using Cochran’s Q and I² statistics (Higgins et al., 2003). Fixed-effects model (by using the inverse variance method (Woolf, 1955)) was presented if the P value for heterogeneity was <0.10 or if I² was >50%. Otherwise we would use the random-effects model (by using the method of DerSimonian and Laird (DerSimonian et al., 1986)). We transformed the RR to a natural log scale and then calculated the SEs.

Sensitivity analyses were done to identify trends among subpopulations within the overall study. Subgroups included: (a) study design (case-control compared with prospective studies), (b) source of control (hospital-based control compared with population-based control), (c) study population (Asians compared with non-Asians) and (d) adjusted for BMI or obesity.

We also conducted a dose-response regression using generalized least square trend estimation (Greenland et al., 1992) of RR and length of time being diabetic by means of SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) to evaluate the association between the two diseases. In consideration of that time since DM diagnosis was stratified differently among the studies, assigned value of duration was used in dose-response regression models. For intervals, the midpoint of the interval was chosen. For the open-ended upper interval, the value arbitrarily assigned was 20% higher than the low end of the interval. Additionally, we used the METAINF command in STATA to evaluate the influence that any one study had on the overall effect estimate. This analysis omitted one study at a time and determined the pooled effect estimate.

Results

Literature Search

As listed in Table 1, our systematic literature search...
| Study | Year of publication | Location | Year(s) of study | Study design | Total no. (case/control) | No. of Pca | Age (case/control) | Effect estimate | Variables Included in adjustment |
|-------|---------------------|----------|------------------|-------------|------------------------|------------|-------------------|----------------|-----------------------------|
| Wynder 1971 | U.S. | 1968-1969 | Case-control | 70(300/400) | 22 | 35-59 | OR | 1.19 (0.61-2.3) |
| Ragozinni 1982 | U.S. | 1945-1969 | Cohort | NR | 9 | NR | SIR | 1.2 (0.5-2.2) |
| Mishina 1985 | Japan | 1976 | Case-control | 100/100 | 100 | NR | RR | 1.17 (0.9-1.39) |
| Thompson 1989 | U.S. | 1972-1987 | Cohort | 1776(100/1676) | 54 | 50-84 | RR | 0.5 (0.2-1.7) |
| Steenland 1995 | U.S. | 1971-1975 | Cohort | NR | 156 | 25-74 | SIR | 1.45 (0.78-2.71) |
| Wideroff 1997 | Denmark | 1977-1989 | Cohort | 109581 | 498 | 64 | OR | 0.9 (0.8-1.0) |
| Giovannucci 1998 | U.S. | 1986-1994 | Cohort | 47781 | 1369 | 40-75 | RR | 0.63 (0.54-0.89) |
| Will 1999 | U.S. | 1959-1960 | Cohort | (6086/298979) | 2523 | NR | SIR | 1.06 (0.81-1.36) |
| Tavani 2002 | Italy and Greece | 1983-1997 | Two-case-control combined | 1616 | 608 | 67/70 | OR | 1, 2, 5, 8, 26 |
| Weiderpass 2002 | Sweden | 1965-1994 | Cohort | (21087/114863) | 2455 | 61.7 | OR | 1, 2, 5, 8, 26 |
| Coker 2004 | U.S. | 1999-2001 | Case-control | 800 | 407 | 65-79 | OR | 0.64 (0.45-0.91) |
| Lightfoot 2004 | Canada | 1995-1999 | Case-control | (760/1632) | 760 | 45-84/45-84 | SIR | 1.07 (0.68-1.66) |
| Zhu 2004 | U.S. | 1992-1995 | Nested case-control | 2200 | 1100 | 40-84/40-84 | RR | 0.64 (0.43-0.95) |
| Tavani 2005 | Italy | 1991-2002 | Case-control | (1294/1451) | 1294 | 75/75 | OR | 1, 7, 10 |
| Gonzalez-Perez 2005 | Spain | 1995-2001 | Nested case-control | (2183/10000) | 2183 | 72/72 | OR | 1, 2, 3, 4, 5, 6 |
| Rodriguez 2005 | U.S. | 1992-2001 | Cohort | (10053/62617) | 5318 | 50-74 | RR | 0.72 (0.59-0.87) |
| Gong 2006 | U.S. | 1994-1997 | Cohort | 10258 | 1936 | 63-75 | OR | 0.66 (0.52-0.83) |
| Velicer 2007 | U.S. | 2000-2002 | Cohort | (2788/3261) | 35329 | 63-63/61.5 | HR | 1, 10 |
| Calton 2007 | U.S. | 1995-2000 | Cohort | (3029/294287) | 11193 | 63-62/1 | RR | 0.83 (0.64-1.07) |
| Pierce 2008 | U.S. | 1993-1996 | Case-control and 2002-2005 | 35065 | 2745 | 1294 | RR | 0.71 (0.59-0.92) |
| Calton 2008 | U.S. | 1993-2001 | Cohort | (2183/10000) | 2183 | 72/72 | OR | 1, 2, 3, 4, 5, 6 |
| Rodriguez 2005 | U.S. | 1992-2001 | Cohort | (10053/62617) | 5318 | 50-74 | RR | 0.72 (0.59-0.87) |
| Gonzalez-Perez 2005 | Spain | 1995-2001 | Nested case-control | (2183/10000) | 2183 | 72/72 | OR | 1, 2, 3, 4, 5, 6 |
| Kasper 2009 | U.S. | 1986-2004 | Cohort | 47781 | 4511 | 60/153.7 | HR | 1.5, 9, 13, 22, 25, |
| Water 2009 | U.S. | 1993-2005 | Cohort | 86303 | 5941 | 47-55 | HR | 1.5, 7, 8, 9, 10, |
| Wallstrom 2009 | Sweden | 1995-2005 | Cohort | (10825/75478) | 817 | 45-73 | OR | 0.81 (0.74-0.89) |
| Turner 2010 | U.K. | 2002-2006 | Nested-case control | 7770 | 1291 | 62-65 | HR | 0.78 (0.53-1.14) |
| Li 2010 | Japan | 1995-2003 | Cohort | (1291/4679) | 1291 | 62-65 | HR | 1.33, 21, 22, 24, |
| Pelucchi 2011 | Italy | 1991-2002 | Case-control | 2745 | 188 | 66-66/75-75 | OR | 1.18 (0.76-1.83) |
| Lee 2012 | Taiwan | 1999-2009 | Cohort | (48878/438919) | 2205 | NR | OR | 0.98 (0.72-1.34) |

Table 1: Descriptive Characteristics of Studies Included in the Meta-analysis

Included a total of 29 articles on DM and PCa risk published between 1971 and 2012 in the final analysis. We excluded 5 articles (Checkoway et al., 1987; Smith et al., 1992; La Vecchia et al., 1994; Coughlin et al., 1996; Rosenberg et al., 2002) articles included in the two previous meta-analyses. The two articles by Checkoway et al (Checkoway et al., 1987) and Rosenberg et al (Rosenberg et al., 2002) were excluded because the controls were men with benign prostatic hyperplasia (BPH). The two articles by Smith et al. (1992) and Coughlin et al. (1996) were excluded because their outcomes were mortality of PCa. And we excluded the article by La Vecchia et al. (1994) because the results from this study were republished in a later article (Tavani et al., 2002). Since the recent meta-analysis, another 13 relevant articles were published and included in our final analysis.

Study Characteristics and Quality Assessment

Descriptive data of the studies included in our analysis were summarized in Table 1. The study-design types were as follows: prospective cohort studies (n=16), population-based case-control studies (n=9), and hospital-based case-control studies (n=4). Studies were conducted in U.S. (n=16), Italy (n=3), Japan (n=2), Sweden (n=2), U.K.
As shown in Figure 2, our overall analysis of 29 studies showed a 16% reduction in risk of PCa and DM (RR 0.84, 95% CI, 0.78-0.91). Statistically significant heterogeneity was observed in the study results (Q = 124.54, P<0.0001, I² = 77.5%). There was no indication of a publication bias either from the result of Egger's test (P = 0.488) or Begg's test (P = 0.856).

Table 2. Summary Risk Estimates of the Association Between Diabetes Mellitus and Prostate Cancer Risk

| No. of studies | Heterogeneity test | RR(95%CI) | Q  | P   | I² (%) |
|----------------|--------------------|----------|----|-----|--------|
| All studies*  |                    | 0.84(0.78-0.91) | 124.54 | <0.0001 | 77.50% |
| Study design  |                    |          |    |     |        |
| Case-control studies* |                | 0.82(0.71-0.94) | 32.15 | 0.001 | 62.70% |
| Cohort studies* |                  | 0.85(0.78-0.94) | 92.08 | <0.0001 | 83.70% |
| Population based* |                | 0.80(0.68-0.93) | 22.67 | 0.04  | 64.70% |
| Hospital based* |                  | 0.92(0.77-1.11) | 7.78  | 0.051 | 61.40% |
| Study population |                |          |    |     |        |
| Asian*        |                    | 0.99(0.59-1.66) | 16.12 | <0.0001 | 87.00% |
| Non-Asian*    |                    | 0.81(0.76-0.87) | 89.26 | <0.0001 | 72.00% |
| Adjustment    |                    |          |    |     |        |
| BMI-adjusted* |                    | 0.81(0.75-0.87) | 33.72 | 0.001 | 61.40% |
| BMI not adjusted* |                | 0.80(0.80-1.02) | 41.86 | 0.0001 | 66.60% |

*Pooled relative risk (RR) was calculated using the random effects model

(n=1), China (n=1), Iran (n=1), Canada (n=1), Greece (n=1), and Denmark (n=1). Most individual studies were matched or adjusted for a wide range of potential confounders as listed in Table 1.

Overall Analyses
As shown in Figure 2, our overall analysis of 29 studies showed a 16% reduction in risk of PCa and DM (RR 0.84, 95% CI, 0.78-0.91). Statistically significant heterogeneity was observed in the study results (Q = 124.54, P<0.0001, I² = 77.5%). There was no indication of a publication bias either from the result of Egger’s test (P = 0.488) or Begg’s test (P = 0.856).

Subgroup Analyses
The effects of DM on PCa risk in subgroup meta-analyses are shown in Table 2. When stratified by study design, the analysis of cohort studies yielded a RR of 0.85 (95% CI 0.78-0.94), whereas the analysis on case-control studies yielded a RR of 0.82 (95% CI 0.71-0.94). Significant protective effects of DM on PCa were also observed in non-Asian populations (RR 0.81, 95% CI 0.76-0.87) and population-based studies (RR 0.80, 95% CI 0.68-0.93). Since obesity is a protective effect confirmed by a meta-analysis published in 2006 by MacInnis et al. (MacInnis et al., 2006), we did a sub-analysis depended on adjustment of BMI or obesity. For the 14 studies that adjusted for BMI or obesity, the RR was 0.81 (95% CI, 0.75-0.87).

Duration of DM: We were also interested in determining if there was an association between length of time being diabetic and PCa risk. As listed in Table 3, 9 articles (Will et al., 1999; Tavani et al., 2002; Zhu et al., 2004; Rodriguez et al., 2005; Tavani et al., 2005; Pierce et al., 2008; Baradaran et al., 2009; Kasper et al., 2009; Turner et al., 2011) were included in our analysis containing of different stratification of duration since DM...
We also tried to determine the association between the age of diabetes mellitus (DM) diagnosis and prostate cancer (PCa) risk. Our findings were in accordance with the results of previous meta-analyses. No clear bias was apparent. As an example, we present the funnel plot and the Egger plot of the trials used in our subgroup analysis of studies which accounted for BMI or obesity, a statistically significant inverse association with DM risk. Our findings were consistent with the inverse association between DM and PCa risk observed in the previous meta-analysis. We analyzed possible publication bias by using both the Begg’s funnel plot and the Egger plot of the trials used for all of the evaluated comparisons of outcomes. No clear bias was apparent. As an example, we present the funnel plot of subgroup analysis of case-control studies showing no obvious asymmetry (Figure 5).

**Publication Bias Analyses**

We analyzed possible publication bias by using both the Begg’s funnel plot and the Egger plot of the trials used for all of the evaluated comparisons of outcomes. No clear asymmetry was apparent. As an example, we present the funnel plot of subgroup analysis of case-control studies showing no obvious asymmetry (Figure 5).

**Discussion**

This is an updated meta-analysis that examined the association between DM and PCa risk. Our findings were in accordance with the results of previous meta-analyses. With more than 30,000 additional PCa cases, our analysis is given greater power to evaluate this relationship. It is noteworthy that our study is the first to examine the association between length of time being diabetic and PCa risk.

In our subgroup analysis of studies which adjusted for BMI or obesity, a statistically significant inverse association with PCa risk was still observed with a 19% reduction in risk of PCa and DM. Obesity was a confounding factor since MacInnis et al. (MacInnis et al., 2006) found a weak positive association between obesity and the risk of PCa through a meta-analysis of 56 studies (31 cohort studies and 25 case-control studies). A number of studies have tried to uncover the potential mechanism of this phenomenon. It was suggested that PCa may be more difficult to detect among obese men because (a) a thorough digital rectal examination is more difficult to perform in obese men, (b) obese men may have lower PSA values (Baillargeon et al., 2005; Pater et al., 2012) which may make obese men less likely to be referred for a prostate needle biopsy, and (c) obese men have larger sized prostates (Freedland et al., 2006) which may make detection of an existing cancer (needle) less likely, given an equally sized tumor and an equal number of biopsy cores obtained. However, due to the significant heterogeneity of the studies, we failed to conduct a subgroup analysis based on BMI classification.

As listed in Figure 4, association between DM and PCa risk was quite irregular across various subgroups of men defined by BMI (normal weight, overweight, and obesity). No significant association was found between risk for total PCa and the length of time since DM diagnosis. This result might be influenced by the significant heterogeneity between the 9 studies included in analysis. Some individual studies though revealed a significant tendency (p trend <0.0001 in the article by Baradaran et al. (2009); p trend was 0.01 in the article by Kasper et al. (2009); and p trend <0.05 in the article by Zhu et al. (2004)). DM is a chronic disease with metabolic syndromes. After DM diagnosis, patients probably will alter his life-style, eating habits, as well as take medications. Among dietary factors, milk, dairy products, calcium, and polyunsaturated fat intake are associated with a higher PCa risk, while protective dietary factors include high vegetable consumption, particularly tomatoes (Gunnell et al., 2003). Metformin as the most common medication used in the management of type 2 DM, has also been suggested a decreased relative risk of PCa (Wright et al., 2009). These changes after DM diagnosis will contribute to the protective effect of DM on PCa, and may explain the PCa risk decreases as the time since DM diagnosis increases to some degree. However, it is not possible to control for all these factors since any such life-style or pharmaceutical factors that could account for the inverse association with DM could have important clinical implications. Besides, diabetic patients have a lower insulin level which may postpone the development of PCa as discussed below. The risk of PCa may decrease with increasing time since DM diagnosis, possibly because worsening of diabetes and declining of insulin levels.

An unordered distribution was observed when we compared the age of DM diagnosis with PCa risk. Most articles included in our analysis did not specify the age of DM diagnosis. We did a dose-response regression by means of SPSS. As shown in Figure 3, we found no evidence of statistically significant departure from linearity (p=0.338).

**Sensitivity Analyses**

In sensitivity analyses, we recalculated the combined results by excluding one study per iteration. The 28 study-specific RRs ranged from a low of 0.79 (95%CI 0.70-0.91) to a high of 0.86 (0.78-0.96).

**Age of DM diagnosis**

We also tried to determine whether the risk for PCa differed with the age when DM was diagnosed. However, we were not able to study this due to lack of power and different stratification among studies. As shown in Figure 4, it seemed that there was no obvious difference of risk for PCa if the patient was diagnosed of DM in younger or in older age.

**Publication Bias Analyses**

We analyzed possible publication bias by using both the Begg’s funnel plot and the Egger plot of the trials used for all of the evaluated comparisons of outcomes. No clear asymmetry was apparent. As an example, we present the funnel plot of subgroup analysis of case-control studies showing no obvious asymmetry (Figure 5).
patients’ DM type (type 1 DM or type 2 DM). Since the average age at onset of type 1 DM is usually younger than type 2 DM, the unclassification of DM type will probably confound the relationship between them. Two articles both revealed that patients diagnosed of DM before 30 might have a relatively lower risk of PCa than those diagnosed of DM after 30 (Kasper et al. (2009) RR 0.55, 95%CI 0.3-1.03; Pierce et al. (2008) RR 0.27, 95%CI 0.07-0.96). But both articles did not offer detailed follow-up time and the average age of this subgroup. If they were younger or the mean follow-up time was shorter than the others, the protective effect might be exaggerated.

In conclusion, our analysis revealed a strong and significant protective effect of DM on PCa risk. And the risk of PCa seemed not related with increasing time since DM diagnosis, as well as age of the patient when DM was diagnosed. The limitations of this meta-analysis should also be considered. First, we included high-quality studies based on the Newcastle-Ottawa Scale, but we still observed some significant between-study heterogeneity across all of the studies. We did subgroup analysis depend on study design and study population, but limited improvement was seen. Second, we hypothesized a statistical model in order to cover the different classification methods of the length of time since DM diagnosis. Better designed prospective trials are needed to test and verify the tendency. Third, we are unable to clarify the association between PCa risk and type 1 or type 2 DM separately, which made the result less persuasive. Since the average age at onset of type 1 DM is usually younger than type 2 DM, contributing to different length of time of exposure to insulin and testosterone.

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