

## Review

# A Meta-analysis of Diabetes Mellitus and the Risk of Prostate Cancer

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## Abstract

**Background:** Studies investigating the association between diabetes mellitus and prostate cancer have reported inconsistent findings. We examined this association by conducting a detailed meta-analysis of the studies published on the subject. **Methods:** MEDLINE and EMBASE databases and bibliographies of retrieved articles were searched. Studies investigating the relationship between diabetes mellitus and prostate cancer were included in the meta-analysis. Potential sources of heterogeneity between studies were explored and publication bias was evaluated. Pooled relative risk (RR) was calculated using the random-effects model. Numerous relevant subgroup analyses were also done. **Results:** We included 19 studies, published between 1971 and 2005, in the meta-analysis and found an inverse association between diabetes mellitus and prostate cancer [RR, 0.84, 95% confidence interval (CI), 0.76-0.93, *P* for heterogeneity  $\leq$  0.01]. For cohort studies alone, the RR was 0.81 (95% CI, 0.71-0.92, *P* for heterogeneity  $\leq$  0.01) and for

case-control studies alone, the RR was 0.89 (95% CI, 0.72-1.11, *P* for heterogeneity = 0.02). The significant heterogeneity was mitigated in some of the subgroup analyses. For studies conducted before prostate-specific antigen screening was introduced as a common procedure, the RR was 0.94 (95% CI, 0.85-1.03, *P* for heterogeneity = 0.15), and for studies conducted after this time, the RR was 0.73 (95% CI, 0.64-0.83, *P* for heterogeneity = 0.10). For studies that adjusted for three or more potential confounders, the RR was 0.74 (95% CI, 0.65-0.85, *P* for heterogeneity = 0.06) and for studies that adjusted for less than three potential confounders, the RR was 0.93 (95% CI, 0.86-1.02, *P* for heterogeneity = 0.18).

**Conclusion:** This study suggests an inverse relationship between diabetes and prostate cancer. Potential biological mechanisms underlying this association, as well as possible biases, are discussed. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2056-62)

## Introduction

Diabetes mellitus (DM) has been associated with increased risk of numerous cancers including cancers of the pancreas, liver, biliary tract, endometrium, kidney, colon, and esophagus (1-4). Studies investigating the association between diabetes and prostate cancer, however, have shown that diabetes may be associated with lower risk for this cancer.

A meta-analysis including 14 studies published through 2002 was done by Bonovas et al. and was published in 2004 (5). The analysis showed that diabetic patients have a statistically significant (9%) decrease in the risk of developing carcinoma of the prostate (5). It was reported that there was essentially no difference seen between cohort and case-control studies, nor did excluding any one study significantly change the pooled relative risk.

Since the time Bonovas et al. conducted their meta-analysis, six relevant studies on the association between DM and prostate cancer have been published. These reports are from both prospective and retrospective studies and include ~11,000 additional prostate cancer cases (6-11). With the added statistical power of having >20,000 prostate cancer cases as opposed to ~9,000 cases, in order to provide insight into the pathophysiology of prostate cancer, we aim to analyze this relationship

further by conducting an updated detailed meta-analysis. This updated analysis will allow us to expand the discussion of possible implications and interpretations of the findings.

Five of the six recent studies were conducted after the use of prostate-specific antigen (PSA) screening had become a widespread method for prostate cancer screening. The implementation of PSA testing may have changed the scope of disease that was diagnosed as prostate cancer. Prior to screening, disease was detected mostly at the clinical level. Clinically diagnosed prostate cancer is often an advanced cancer that had a high potential for metastasis. Prostate cancer screening is able to detect disease at a much earlier and/or localized stage and it is not yet clear whether all of these PSA-detected cancers have the potential to evolve into clinically detectable disease.

With the additional studies done in the PSA-testing era, we are now able to do a subgroup analysis of men diagnosed before and after this time. This subgroup analysis will allow us to investigate the role that screening may play in the reported association between DM and prostate cancer. Due to limitations of the source material, we were not able to specifically analyze the differences between advanced versus localized tumors, examining associations in the pre-PSA and PSA screening era may provide insight into the many different types of prostate cancer. In addition to the PSA-testing subgroups and subgroups similar to those reported by Bonovas et al. (ref. 5; by study design), in this meta-analysis, we were able to investigate those that did or did not control for body mass index (BMI), included or excluded prostate cancer cases that were diagnosed within the first year after DM diagnosis, and studies that adjusted for less than three or for three or more covariates. The details and results of our analyses are presented here.

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## Materials and Methods

**Selection of Published Studies.** MEDLINE and EMBASE were used to identify literature published through February 2006 that related to both the exposure (diabetes mellitus) and outcome (prostate cancer) of interest. The search terms used were all combinations of prostatic neoplasm, prostatic cancer, or prostate cancer, and diabetes or diabetes mellitus. All languages were included in the literature search. Figure 1 illustrates our search and selection process. The titles of the primary 325 publications identified were reviewed and 280 were discarded although they were identified by our search terms. They were discarded because the studies did not investigate the relationship between the two diseases, they were not epidemiologic studies, or they were not human studies. Of the 325 publications, 45 abstracts were read. Bibliographies were also searched for publications not identified in our database searches and 10 additional publications were found. A total of 55 abstracts were read. Of the 55 abstracts, 34 publications were retrieved for further investigation. If the exposure was not DM (i.e., it was a metabolic syndrome or hyperglycemia; refs. 12, 13), or the controls were not simply non-DM (i.e., controls were benign prostatic hyperplasia cases; ref. 14), or the outcome was not prostate cancer incidence or mortality (i.e., it was prostate cancer recurrence; ref. 15), then the publications were excluded. Additionally, if there were no effects estimates reported or not enough raw data for a relative risk to be calculated, the publication was also excluded (16-19). We identified and excluded a total of 15 publications because of one of the above reasons. Finally, 19 publications were chosen for the meta-analysis.

**Data Extraction.** Data from these studies was extracted by J.S. Kasper. Publications were read by E. Giovannucci in order to check original data extraction. A data extraction form was used to collect the following information: (a) authors, study location, dates of study, date of publication, journal, title; (b) number and age of participants; (c) study design; (d) exposure definition; (e) outcome definition; (f) information on cohort where applicable; (g) information on control group where applicable; (h) effect estimates and 95% confidence intervals (CI); (i) raw data where provided; (j) control for covariates; and (k) other notes. Similar to Bonovas et al. (5), for studies in which effects estimates were reported for more than one set of adjustments, we chose the most adjusted estimate.

Relative risks (RR) were recorded or calculated, when needed. Some studies reported an odds ratio (OR), incidence density ratio (IDR), or standardized incidence ratio (SIR). Due to the rare occurrence of prostate cancer, we assumed that all of these measures would give a similar effect estimate and they were considered equally in the overall effect estimate.

Most publications in our analysis did not specify the patient's DM type. Based on the age of participants at DM diagnosis and the distribution of type 1 diabetics versus type 2 diabetics in the general population, it was assumed that most diabetic study participants were type 2 diabetics.

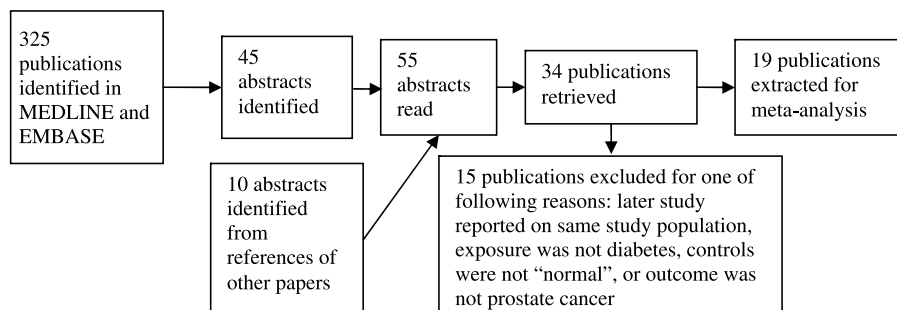
**Statistical Analysis.** Publication bias was evaluated using both the Begg's funnel plot and the Egger plot. The Begg's test is based on adjusted rank correlation and determines whether there is significant correlation between effect estimates and their variances (20). The fewer correlations there are, the more likely it is that the studies were selected in the absence of publication bias. The Egger test is based on a regression model in which the standard normal deviate is regressed against precision (21). It is typically more sensitive than the Begg's funnel plot.

Overall effects estimates were calculated using the DerSimonian-Laird method for a random-effects model. This method was chosen over a fixed-effect model because of a high degree of between-study heterogeneity. The Mantel-Haenszel (22) fixed-effect model was also used in the event that we found little between study heterogeneity. We transformed the RR to a natural log scale and then calculated the SEs.

Between-study heterogeneity was assessed using Cochran's  $Q$ , a  $\chi^2$  statistic. This was used to test whether the differences between studies was due to chance. A  $P$  value close to 1 suggests a high probability that the observed heterogeneity was due to sampling error.

Sensitivity analyses were done to identify trends among subpopulations within the overall study. Subgroups included: (a) study design, (b) included in the time frame of previous meta-analysis (5) versus other studies, (c) pre-PSA versus PSA era screening, (d) adjusted for <3 or for  $\geq 3$  covariates, (e) adjusted for BMI or obesity, (f) type of reported effect-estimate. For the subgroups analysis, if a report did not discuss whether they included or excluded prostate cancer cases diagnosed within the first year of DM diagnosis, we assumed they were included (6, 7, 9-11, 23-26). Additionally, if a publication reported effect estimates for both, we used the data for when the first year post-DM diagnosis was excluded. For subgroup *c*, we considered earlier than 1990 as the time when PSA screening was not commonly used ("pre-PSA"), and 1990 or later as the era when this test was widespread ("PSA era"). For studies that spanned numerous years, we considered the middle year as the determining date. For subgroups *d* and *e*, if a publication did not report what was adjusted for, we counted it as no adjustments. Subgroup *e* was done because of the correlation between high BMI and DM. The use of measured versus self-reported body measures was not considered as it has been reported that the two are highly correlated (27). The subgroup analysis that compared studies which adjusted for three or more covariates was analyzed in order to access the extent to which covariates influenced the results. We used three covariates as the demarcation because it enabled us to create similar size subgroups.

A cumulative meta-analysis was done. This evaluates the cumulative effect estimate over time. 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.



**Figure 1.** Flowchart representing the publication selection process.

**Table 1. Descriptive characteristics of studies used in the meta-analysis**

Study, year of publication	Location and year(s) of study	Study design (cohort name, if applicable)	Total no. of men in study	No. of prostate cancer cases (no. of exposed cases)	Effect estimate (95% CI)	Variables included in adjustment
Wynder et al., 1971 (37)	U.S., 1968-1969	Case-control	700	300 (22)	OR, 1.19 (0.61-2.30)	NR
Ragozzioni et al., 1982 (31)	U.S., 1945-1969	Cohort (with DM)	NR	9 (9)	SIR, 1.2 (0.5-2.2)	1
Mishina et al., 1985 (24)	Japan, 1976	Case-control	200	100 (7)	RR, 1.17 (0.90-1.39)	NR
Thompson et al., 1989 (35)	U.S., 1972-1987	Cohort	1,776	54 (NR)	RR, 0.5 (0.2-1.7)	NR
Smith et al., 1992 (25)	Britain, 1967-1969	Cohort (Whitehall)	18,274	97 (1)	RR, 0.78 (0.11-5.83)	1
Steenland et al., 1995 (32)	U.S., 1971-1975	Cohort (NHANES1)	NR	156 (NR)	RR, 1.45 (0.78-2.71)	1, 5, 21, 22, 24, 25
Coughlin et al., 1996 (23)	U.S., 1973-1990	Cohort (MRFIT)	348,874	826 (14)	RR, 0.77 (0.43-1.36)	7, 21, 22, 23
Wideroff et al., 1997 (34)	Denmark, 1977-1989	Cohort (with DM)	109,581	498 (498)	SIR, 0.9 (0.8-1.0)	1, 20
Giovannucci et al., 1998 (30)	U.S., 1986-1994	Cohort (HPFUS)	47,781	1,369 (76)	RR, 0.63 (0.54-0.89)	1, 5, 7, 11, 12, 13, 17, 18, 19
Will et al., 1999 (36)	U.S., 1959-1960	Cohort (cancer prevention study)	305,065	2,523 (65)	IDR, 1.06 (0.81-1.36)	1
Weiderpass et al., 2002 (33)	Sweden, 1965-1994	Cohort (with DM; in-patient registry)	135,950	2,455 (2,455)	SIR, 0.91 (0.87-0.94)	1
Tavani et al., 2002 (29)	Italy and Greece, 1983-1997	Two case-controls combined	1,616	608 (43)	OR, 1.07 (0.68-1.66)	1, 2, 5, 8, 26
Rosenberg et al., 2002 (26)	U.S., 1984-1986	Case-control	509	320 (34)	OR, 0.60 (0.34-1.06)	1, 7, 16
Zhu et al., 2004 (11)	U.S., 1982-1995	Nested case-control (US-PHS)	2,200	1,110 (50)	OR, 0.64 (0.43-0.95)	7, 14, 15
Coker et al., 2004 (6)	U.S., 1999-2001	Case-control	800	393 (72)	OR, 0.64 (0.45-0.91)	1, 7, 10
Lightfoot et al., 2004 (8)	Canada, 1995-1999	Case-control	2,392	760 (62)	OR, 0.71 (0.53-0.96)	1
Rodriguez et al., 2005 (9)	U.S., 1992-2001	Cohort (cancer prevention study II)	72,670	5,318 (343)	RR, 0.67 (0.60-0.75)	1, 5, 7, 8, 9, 10, 11, 12, 13
Tavani et al., 2005 (10)	Italy, 1991-2002	Case-control	2,745	1,294 (90)	OR, 1.02 (0.75-1.40)	1, 5, 8, 9, 22, 26, 27
Gonzalez-Perez et al., 2005 (7)	Spain, 1995-2001	Nested case-control (GPRD)	12,183	2,183 (153)	OR, 0.72 (0.59-0.87)	1, 2, 3, 4, 5, 6

Abbreviations: 1, age; 2, calendar year; 3, nonsteroidal anti-inflammatory drug; 4, history of prostatism; 5, BMI; 6, use of health care; 7, race; 8, education; 9, family history of prostate cancer; 10, PSA testing; 11, fat intake; 12, lycopene intake; 13, calcium intake; 14, aspirin; 15,  $\beta$ -carotene; 16, coronary heart disease; 17, vasectomy; 18, energy intake; 19, fructose intake; 20, obesity; 21, income; 22, smoking; 23, cholesterol; 24, alcohol intake; 25, recreational physical activity; 26, center; 27, calories, NR, none reported.

## Results

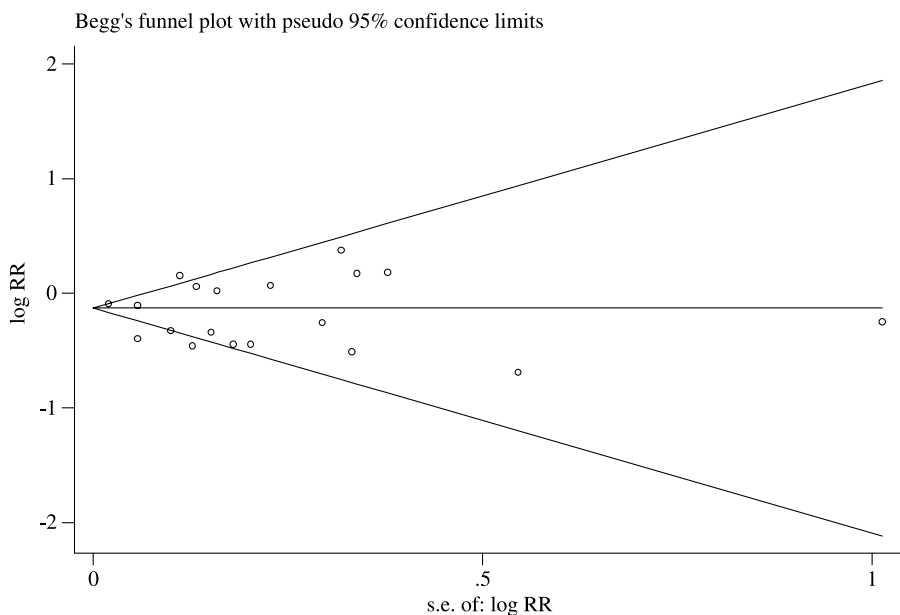
As listed in Table 1, we identified 19 publications. A previous meta-analysis that was reported on the same topic included 14 reports published in 2002 or earlier (5). We included 12 of the 14 studies published in Bonovas et al. The report by Checkoway et al. (14) was excluded because the controls were men with benign prostatic hyperplasia, and we excluded La Vecchia et al. (28) because the results from this study were republished in a later report (29). This later report was included in both Bonovas et al. (5) and our analysis. We also identified and included a report by Mishina et al. that was published in 1985 that was not included in Bonovas et al.'s meta-analysis (24). Finally, we identified six relevant studies that were published after 2002 and included these in our analysis (6-11). The 19 studies that were included in the meta-analysis were published between 1971 and 2005. Sixteen (6-10, 23-26, 29-34) of the 19 studies assessed only cancers that were histologically confirmed. The remaining three (11, 35, 36) were based on self-reports. The analysis by Bonovas et al. included ~9,000 prostate cancer patients and our analysis included 20,373 prostate cancer cases. Some studies excluded (8, 30, 31, 33-37) and some included (6, 7, 9-11, 23-26, 29, 32) prostate cancer cases diagnosed within the first year of DM diagnosis. The number of diabetics with prostate cancer was >3,994. This number could not be determined precisely because two publications did not report the number of exposed cases in their studies, although they were still included in the meta-analysis (32, 35).

Begg's funnel plot had the expected funnel shape (Fig. 2). Begg's test ( $P = 0.75$ ) and the Egger test for publication bias ( $P = 0.42$ ) indicated that there was little or no publication bias in our analysis.

To determine the amount of heterogeneity that existed between the 19 studies, we did a Cochran's  $Q$  test. Because we found a high degree of heterogeneity ( $Q = 61.3$  on 18  $df$ ;  $P \leq 0.01$ ), we chose a random-effects model over a fixed-effect model. In a random-effects model including all studies, we found DM to be associated with a lower risk for prostate cancer. The pooled effect estimate was RR, 0.84 (95% CI, 0.76-0.93; Fig. 3).

Subgroup analyses were done in order to identify sources of heterogeneity (Table 2). When cohort studies were analyzed alone, we determined that the pooled RR was 0.81 (95% CI, 0.71-0.92). Using case-control studies alone, we found that the pooled RR was 0.89 (95% CI, 0.72-1.11). Either cohort or case-control studies alone had a high degree of heterogeneity (for cohort studies,  $P < 0.01$ ; for case-control studies,  $P = 0.02$ ).

We determined that the pooled RR for the studies published in the same time frame as was included in Bonovas et al. was 0.92 (95% CI, 0.83-1.02; Table 2). The heterogeneity for this subgroup was  $P = 0.04$ . We also did an analysis of only the studies published after their analysis. The pooled effect estimate for this subgroup was 0.71 (95% CI, 0.64-0.80). The  $P$  value for this group was 0.24, indicating that there was less heterogeneity between studies that were published either in and before 2002, or after this time, than there was in the overall analysis.



**Figure 2.** Funnel plot of log RR of developing prostate cancer, according to the SEs of all studies in analysis. Y-axis, RRs on the logarithmic scale; X-axis, SE. The horizontal line is drawn at the pooled log RR. Begg-Mazumdar test ( $P = 0.75$ ) and Egger test ( $P = 0.42$ ).

To determine if the effect estimate between DM and prostate cancer changed after PSA screening was introduced as a common procedure, we did another subgroup analysis (Table 2). The RR for pre-PSA was 0.94 (95% CI, 0.85-1.03;  $P$  for heterogeneity = 0.15), and the RR for PSA era was 0.73 (95% CI, 0.64-0.83;  $P$  for heterogeneity = 0.10).

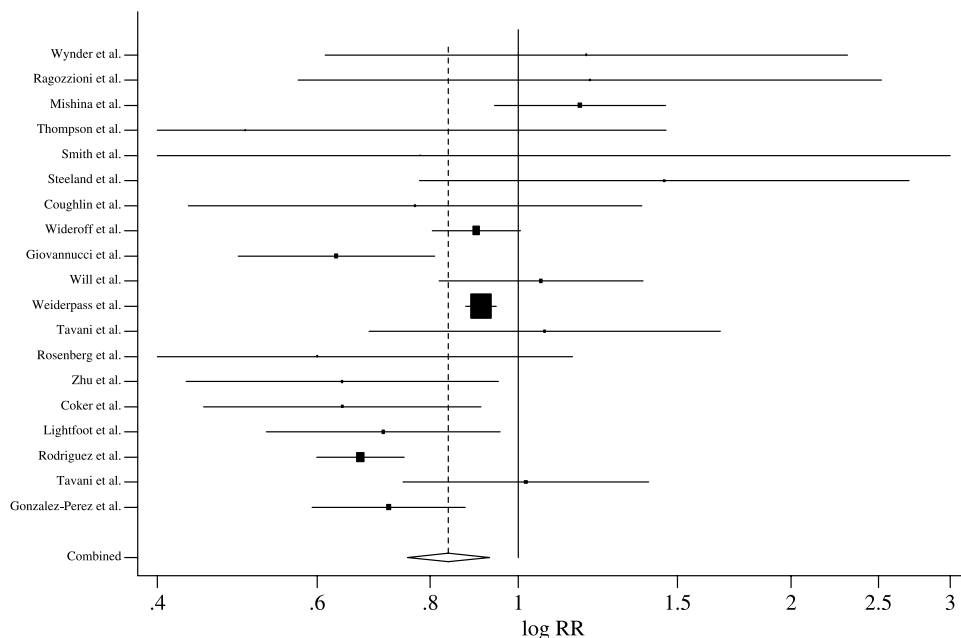
Many of the studies in our analysis only adjusted for one covariate (typically age). Therefore, we examined if more thoroughly adjusting for potential confounders affected the pooled RR and degree of heterogeneity (Table 2). The effect estimate for studies that adjusted for three or more confounders was RR, 0.74 (95% CI, 0.65-0.85). The  $P$  value for heterogeneity for these 10 studies was 0.06, suggesting less heterogeneity in this subgroup than in the overall analysis. Similar results were found if the subgroups were less than or equal to one covariate adjusted for versus more than one. We also evaluated the effect that adjusting for BMI and obesity had on the overall effect estimate. For the seven studies that adjusted for BMI or obesity, the RR was 0.82 (95% CI,

0.69-0.97), and for the 12 studies that did not adjust for BMI and obesity, the RR was 0.87 (95% CI, 0.76-0.99).

We determined the pooled RR for studies that either did or did not exclude prostate cancer cases that were diagnosed within a year of being diagnosed with DM (Table 2). The RR for studies that excluded prostate cancer cases that were diagnosed within the first year post-DM diagnosis was 0.87 (95% CI, 0.78-0.98;  $n = 8$ ;  $P$  for heterogeneity = 0.04). For studies that included prostate cancer cases that were diagnosed within the first year post-DM diagnosis, the RR was 0.83 (95% CI, 0.69-0.99;  $n = 11$ ;  $P$  for heterogeneity < 0.01).

When subgroup analyses were done for publications that reported only RR, only OR, SIR or IDR, or RR and OR together (i.e., not SIR or IDR), similar effect estimates were found [RR only, 0.88 (95% CI, 0.69-1.1); OR only, 0.76 (95% CI, 0.67-0.90); SIR or IDR, 0.91 (95% CI, 0.88-0.94); or RR and OR, 0.83 (95% CI, 0.72-0.95)].

There were three subgroup analyses we were interested in doing but were not able to due to insufficient data. We wanted



**Figure 3.** Analysis of studies that examined the association between diabetes mellitus and prostate cancer. RRs and 95% CI for all studies and the overall effect estimate are reported in the log scale. Among diabetics, the overall RR for prostate cancer is statistically significant at 0.84 (95% CI, 0.76-0.93).

**Table 2. Overall effect estimates for DM and prostate cancer according to study characteristics**

Study	No. of studies	Random-effects model; overall RR (95% CI)	Heterogeneity between studies, <i>P</i> value
All	19	0.84 (0.76-0.93)	<0.01
Cohort	12	0.81 (0.71-0.92)	<0.01
Case-control	7	0.89 (0.72-1.11)	0.02
Published in time frame covered in Bonovas et al. (5)*	13	0.92 (0.83-1.02)	0.04
Published after Bonovas et al.(5)	6	0.71 (0.64-0.80)	0.24
Pre-PSA (middle year ≤1989)	12	0.94 (0.85-1.03)	0.15
PSA era (middle year ≥1990)	7	0.73 (0.64-0.83)	0.10
Adjusted for three or more potential confounders	10	0.74 (0.65-0.85)	0.06
Adjusted for less than three confounders	9	0.93 (0.86-1.02)	0.18
Adjusted for BMI or obesity	7	0.82 (0.69-0.97)	<0.01
Did not adjust for BMI or obesity	12	0.87 (0.76-0.99)	0.04
Exclude first year post-DM diagnosis <sup>†</sup>	8	0.87 (0.78-0.98)	0.04
Include first year post-DM diagnosis <sup>†</sup>	11	0.83 (0.69-0.99)	<0.01

\*Same studies as in Bonovas et al. except that we excluded two studies and included one additional study. The first was excluded (14) because the controls were not non-prostate cancer; they were benign prostatic hyperplasia. The second (28) was excluded because the results were re-reported in another publication (29). The publication by Mishina et al. (24) was also included.

<sup>†</sup> Either they reported that they included first year postdiagnosis or it was not reported, in which case, we assumed that all years were included.

to examine the relationship between DM and more aggressive prostate cancer, but because only two publications (9, 30) reported an analysis by prostate cancer stage, we were not able to study this. We were also interested in determining if there was an association between length of time being diabetic and prostate cancer risk, but we were not able to study this due to lack of power; only three studies (9, 29, 30) reported this information. Finally, we wanted to compare studies that reported incidence with those that reported mortality as outcomes. Because only two studies reported only mortality (23, 25), we were unable to do this analysis.

A cumulative meta-analysis was done to evaluate the cumulative effect estimate over time. In 1971, Wynder et al. reported a nonsignificant effect estimate of 1.18 (37). Between 1971 and 1998, there were seven publications. In 1998, the cumulative RR reached 0.92. Between 1998 and 2005, 10 more publications, added cumulatively, resulted in the overall effect estimate of 0.84.

The METAINF command in STATA was used to evaluate the effect that any one study had on the overall effect estimate. Excluding any one study did not significantly change the pooled RR. The range for pooled RR when any one study was left out was 0.81 to 0.86.

## Discussion

This is the second published meta-analysis that examined the association between diabetes mellitus and prostate cancer. In this analysis, there are more than twice as many prostate cancer cases than the previous analysis, giving greater power to evaluate this relationship. We were also more capable of evaluating any differences between the pre- and post-PSA testing eras. In addition to the PSA-testing subgroups, in this meta-analysis, we were able to investigate those that did or did not control for BMI, included or excluded prostate cancer cases that were diagnosed within the first year after DM diagnosis, studies that adjusted for less than three or three or more covariates, and compared results from cohort analyses and case-control studies. This study showed that diabetic men have a statistically significant 16% decreased risk of developing prostate cancer.

There was significant heterogeneity between studies in the overall analysis. This heterogeneity was decreased when subgroup analyses were done. When studies were grouped by publication date (before or after the previous meta-analysis was done; ref. 5), both subgroups showed an inverse association between DM and prostate cancer and there was less heterogeneity between studies. Also, when a pooled RR was determined for the subgroup of studies that adjusted for

three or more covariates, we found fewer variations between studies. These findings suggest that the high degree of heterogeneity between studies in the overall analysis may be due to residual confounding factors.

Some reports have proposed that diabetic men are more likely to be screened for PSA levels (30). If men with DM were tested for PSA levels more often than the general population, the prostate cancer incidence among diabetics would be artificially inflated over the general population. This would push the association from inverse towards null. Because there is a smaller risk of prostate cancer in diabetics, detection bias probably did not artificially create or enhance the inverse association. Another way we showed that detection bias probably did not significantly affect the overall effects estimate was by determining the RR before and after the advent of PSA testing. As reported in Results, the RR for the pre-PSA era was 0.94 and the RR for the PSA era was 0.73. If diabetic men were screened more for PSA after 1990, we would expect to see increased prostate cancer incidence, and therefore, a less inverse association. What we found, however, was that after 1990, the association was even more inverse, arguing against detection bias.

To further investigate the role of detection bias, we determined effect estimates for studies that either did or did not exclude prostate cancer cases that were diagnosed within a year of the patient being diagnosed with DM. The pooled RR for these two subgroups did not vary significantly.

There are two other ways in which detection bias may play a role in the observed overall inverse correlation. It has been shown that DM is associated with increased risk of benign prostatic hyperplasia, which is characterized by enlargement of the prostate (38). The chance of a biopsy detecting cancerous cells in a prostate may simply be diluted as a prostate grows in size. Another scenario is that diabetics with increased PSA levels may opt not to have a biopsy more often than a non-diabetic patient, perhaps due to more concomitant serious medical conditions. Both of these possibilities can be explored in future studies.

One alternate explanation for a causal inverse association between DM and prostate cancer is that an additional factor affects the risk of both diseases independently. In possible contradiction to this scenario, however, some studies show a temporal association between DM and a decreased risk of prostate cancer (9, 29, 30). It is also possible that the association is not causal in that upon DM diagnosis, a patient may alter his life-style in order to control his DM. He may inadvertently also alter his potential for prostate cancer. Diabetics may take a variety of medications, including statins. Although these drugs may directly affect the patient's potential of developing prostate cancer, it was not possible to control for these, as it

is not discussed in the source material. The identification of any such life-style or pharmaceutical factors that could account for the inverse association with DM could have important clinical implications.

The stronger inverse association between DM and "PSA era" cancers (includes cancers that are detected at the clinical level and those identified after PSA testing) as opposed to DM and "pre-PSA" cancers (includes primarily clinically detected cancers) may highlight the biological differences between these two groups of cancers. Because PSA testing is able to identify cancers that are well differentiated, more benign, and have not metastasized, the cancers in this group may possibly be more influenced by environmental factors including pathophysiological changes experienced by patients with DM.

The metabolic and hormonal environment of some diabetic men is consistent with protection from prostate cancer. Two hormonal changes that may mediate this response are decreased insulin or testosterone levels. Initially, many type 2 diabetics are hyperinsulinemic, but with lack of good blood glucose control and worsening DM, the levels of both insulin and testosterone may decline for some.

Insulin is positively associated with the growth of both normal and cancerous prostate cells, and therefore, decreased insulin may have a growth-inhibitory effect on these cells. Insulin has been shown to be a growth factor for prostatic epithelium *in vitro* (39), to stimulate growth of a rat prostate cancer cell line *in vitro* (40), and is associated with higher incident (41) and recurrent (42) prostate cancer. Therefore, long-term diabetic patients that experience reduced levels of circulating insulin may be at a reduced risk of developing prostate cancer.

Three of the studies in our analysis examined the effect estimate of DM and prostate cancer over time, and found that with increasing time since DM diagnosis, there was a decreased risk of prostate cancer (9, 29, 30). These patients may suffer from long-term exposure to low insulin levels and this may contribute to decreased prostate cancer risk directly or indirectly. One potential hormone that could mediate this response is leptin; an adipocyte hormone that modulates energy utilization. Leptin levels may be decreased with a prolonged state of hypoinsulinemia (43), and leptin is positively associated with risk of advanced prostate cancer (44).

Another way in which hypoinsulinemia may also decrease prostate carcinogenesis is by limiting the bioavailability of insulin-like growth factor I (IGF-I). In an insulin-deficient environment, IGF-binding protein I is up-regulated, resulting in less circulating IGF-I (45-47). Furthermore, several prospective studies show that IGF-I is an important risk factor for prostate cancer (48-51). IGF-I is a growth regulator that has been shown to be associated with carcinogenesis (52), and activation of IGF-I receptors stimulates the proliferation of prostate cancer cells in an IGF-I-dependent manner (50, 53).

In both animal and human studies, there is evidence suggesting that diabetics experience decreased testosterone levels. Jackson and Hutson showed that diabetic rats have reduced testosterone levels (54). Similarly, studies in men show that as blood glucose levels increase, there is also a simultaneous decrease in testosterone levels (55, 56).

High testosterone levels may increase the risk of prostate cancer and it is therefore low testosterone levels which may be protective. In prostate cells, testosterone is converted to the more active androgen, dihydrotestosterone. Both hormones bind to the androgen receptor, forming a complex that binds to DNA, increasing transcription and possibly proliferation of both normal and cancerous prostate cells (53, 57). Further evidence of an association between testosterone and prostate cancer includes evidence that eunuchs do not develop prostate cancer (58). In addition to these studies suggesting that testosterone is a central factor in the development of prostate cancer, some prospective studies suggest that

increased testosterone may be a risk factor for prostate cancer (59, 60). Mantzoros and colleagues conducted a meta-analysis and reported that men whose total testosterone is in the highest quartile are 2.34 times more likely to develop prostate cancer (60).

Because obesity has also been reported to cause low testosterone levels in men (61), the relationship between obesity and prostate cancer must also be discussed. It has been shown that adult adiposity does not correlate with prostate cancer risk (62) but that preadult obesity may protect against advanced prostate cancer (RR, 0.72; 95% CI, 0.47-1.10) as well as metastatic prostate cancer (RR, 0.38; 95% CI, 0.19-0.77; ref. 62). This may suggest a preadult hormonal environment that has more influence on prostate cancer development than any changes later in life. In this analysis, the inverse association between DM and prostate cancer risk was evident even in studies that controlled for BMI.

The overall evidence for an inverse association between DM and prostate cancer is strong and seems to be getting stronger as more studies are conducted. Studying these biological clues has provided insight into the genetic, metabolic, and hormonal changes of prostate cancer. The overall health effect of DM is not beneficial but these data will provide us unique insight into furthering our understanding of the process of prostate cells becoming malignant.

Future research should focus on some of the limitations in the current literature. Men who develop DM early in life, as opposed to later in life, likely have a different lifetime exposure to insulin and testosterone. Therefore, studies that examine type 1 and type 2 DM separately, and studies that investigate the association between a man's lifetime exposure to these hormones and rates of prostate cancer will provide valuable insight into the biological mechanisms behind this disease. Studying the effect of DM on hormones potentially related to prostate cancer will provide insight into prostate cancer carcinogenesis. It will also be interesting for researchers to look specifically at the association between DM and either advanced or localized prostate cancer. Additionally, most of the studies that have examined the relationship between DM and prostate cancer have enrolled predominantly White men in their studies. Considering that race is reported to be one of the strongest risk factors for DM, conducting more racially diverse studies will contribute new insights into prostate carcinogenesis, and allow for greater generalizability.

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