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ARTICLE

Diabetes mellitus and risk of bladder cancer: a meta-analysis

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Abstract
Aims/hypothesis Epidemiological evidence indicates that individuals with diabetes mellitus have an increased risk of several cancers. We performed a systematic review with meta-analysis to evaluate the association between diabetes and risk of bladder cancer.
Methods Pertinent studies were identified by searching MEDLINE (from January 1966 to July 2006) and by reviewing the reference lists of retrieved articles. We included case–control and cohort studies reporting relative risk (RR) estimates with 95% CIs (or data to calculate them) of bladder cancer associated with diabetes. Studies of type 1 diabetes were not included. Summary RRs were calculated using a random-effects model.
Results A total of 16 studies (seven case–control studies, three cohort studies and six cohort studies of diabetic patients) fulfilled the inclusion criteria. Analysis of all studies showed that diabetes was associated with an increased risk of bladder cancer, compared with no diabetes (RR=1.24, 95% CI 1.08–1.42). There was strong evidence of heterogeneity among these studies ($p<0.0001$). Stratification by study design found that diabetes was associated with an increased risk of bladder cancer in case–control studies (RR=1.37, 95% CI 1.04–1.80, $p_{\text{heterogeneity}}=0.005$) and cohort studies (RR=1.43, 95% CI 1.18–1.74, $p_{\text{heterogeneity}}=0.17$), but not in cohort studies of diabetic patients (RR=1.01, 95% CI 0.91–1.12, $p_{\text{heterogeneity}}=0.35$).
Conclusions/interpretation Findings from this meta-analysis suggest that individuals with diabetes may have a modestly increased risk of bladder cancer.

Keywords Bladder cancer · Bladder neoplasms · Diabetes mellitus · Case–control studies · Cohort studies · Epidemiology · Meta-analysis · Review

Abbreviations
RR relative risk

Introduction

Bladder cancer represents the fourth and ninth most common malignancy in US men and women, respectively [1]. In the USA in 2005, it has been estimated that there will be more than 63,000 new cases of bladder cancer and that 13,000 people will die from the disease [1]. The most important risk factor for bladder cancer is cigarette smoking, which is implicated in approximately 50% of the bladder cancer deaths in men and 30% in women [2].

Diabetes mellitus is a serious and growing health problem in the USA, where it affects about 17 million people [3]. Epidemiological evidence indicates that individuals with diabetes have increased risk of several types of cancer, notably cancers of the pancreas [4], breast [5], endometrium [6], liver [7], colon [8] and rectum [8]. Diabetes may also be a risk factor for bladder cancer, but findings from epidemiological studies are inconsistent. We

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used meta-analysis as a systematic approach to review published studies evaluating the association between diabetes and the risk of bladder cancer.

Materials and methods

Retrieval of studies

We conducted a computerised search of Medline for literature published in any language between January 1966 and July 2006, using the search term 'diabetes' combined with 'bladder cancer' or 'bladder neoplasm'. We also manually reviewed the reference lists of relevant publications to search for additional studies.

Inclusion and exclusion criteria

In this meta-analysis, we included studies that fulfilled the following criteria: (1) presented original data from case–control or cohort studies; (2) had diabetes mellitus as the exposure of interest; (3) had bladder cancer incidence or mortality as the outcome of interest; and (4) provided relative risk (RR) estimates with confidence intervals or enough data to calculate them. We did not consider studies in which the exposure of interest was type 1 diabetes, defined as early age (≤30 years) of diagnosis.

Data extraction

We extracted the following information from each publication: the first author's last name; publication year; study design; type of control (in case–control studies); study location; age and sex of subjects; sample size (cases and controls or cohort size); diabetes assessment (type of diabetes); variables controlled for in the analysis; and RR estimates with CIs for bladder cancer associated with diabetes. From each study, we extracted the risk estimate that was adjusted for the greatest number of potential confounders. Results for bladder cancer incidence were chosen when provided; otherwise, mortality results were included.

Statistical analysis

We included in this meta-analysis studies reporting different measures of RR: case–control studies (odds ratio), cohort studies (rate ratio), and cohort studies of diabetic patients using external population comparisons (standardised incidence/mortality ratio). In practice, these three measures of effect yield similar estimates of RR because the absolute risk of bladder cancer is low.

For each study, the RR and its corresponding standard error were transformed to their natural logarithms to stabilise the variance and to normalise the distributions. The standard error was calculated from the CI provided in each study. Summary RRs and their 95% CIs were calculated with the method of DerSimonian and Laird by the use of the assumptions of a random effects model that considers both within- and between-study variation [9]. We examined possible heterogeneity in results across studies using the Q and I^2 statistics [10]. For the Q statistic, a p value of less than 0.10 was considered representative of statistically significant heterogeneity. I^2 is the proportion of total variation contributed by between-study variation [10]. To assess for publication bias, we constructed a funnel plot (i.e. a plot of study results against precision) and applied regression methods to determine funnel plot asymmetry, as suggested by Egger et al. [11]. For Egger's test, a p value of less than 0.10 was considered representative of statistically significant publication bias. We did subgroup analyses to examine potential sources of heterogeneity according to study design, type of control in case–control studies, geographical region and publication year. We also evaluated the impact of adjustment for smoking and BMI on the association between diabetes and the risk of bladder cancer. All statistical analyses were performed with STATA, version 9.0 (STATA, College Station, TX, USA).

Results

Search results

We identified eight case–control studies [12–19], three cohort studies [20–22] and seven cohort studies of hospitalised diabetic patients using external population comparisons [23–29]. One case–control study [12] was excluded because no measure of the RR was reported and the RR could not be calculated. We also excluded one cohort study that comprised patients with type 1 diabetes, defined as early age (≤30 years) of diagnosis [29]. Thus, a total of 16 studies met our inclusion criteria (Electronic supplementary material, Table 1). Most studies were conducted either in North America (n=8) or Europe (n=6); the remaining two studies were from Israel and Korea. The study population in 13 studies consisted of men and women [13–18, 21, 23–28], two studies consisted entirely of men [19, 22] and one study included women only [20].

Meta-analysis

Analysis of all 16 studies showed that diabetes was associated with a statistically significant increased risk of bladder cancer, compared with no diabetes (RR=1.24, 95% CI 1.08–1.42). There was strong evidence of between-study heterogeneity (Q=49.49, p<0.0001, I^2=69.7%). Stratifica-

tion by study design showed that diabetes was associated with a statistically significant increase of approximately 40% in the risk of bladder cancer in case–control and cohort studies, but was not associated with risk in cohort studies of diabetic patients (Fig. 1). There was statistically significant heterogeneity among the case–control studies (Q=18.44, p=0.005, I^2=67.5%) but not among the cohort studies (Q=3.55, p=0.17, I^2=43.7%) or among the studies of diabetic patients (Q=5.59, p=0.35, I^2=10.5%). There was no statistically significant difference (p=0.54) in the summary estimate between population-based case–control studies (RR=1.26, 95% CI 1.02–1.54) and hospital-based case–control studies (RR=1.52, 95% CI 0.86–2.68).

We conducted stratified analyses according to geographical region, publication year, and adjustment for smoking and BMI (Table 1). The summary estimates were significantly higher for studies conducted in North America than in Europe (p=0.07), for studies published in 2000 or later than for studies published before 2000 (p=0.01), and for studies that reported smoking-adjusted RRs than for those that did not control for smoking (p<0.0001). The summary estimate was similar for studies that adjusted for BMI and for studies that did not. There was statistically significant heterogeneity within most subgroups.

The funnel plot showed some asymmetry (data not shown), reflecting the relative absence of studies with small sample sizes and inverse associations. However, Egger's test for publication bias was not statistically significant (p=0.12).

Discussion

The overall results of this meta-analysis of 16 studies indicate that diabetes is associated with a modest increase in the risk of bladder cancer. However, there were differences in the summary results between study designs. Whereas the summary estimates for case–control and cohort studies indicated that individuals with diabetes may have an approximately 40% increased risk of bladder cancer, the summary estimate of studies of hospitalised diabetic patients did not indicate an excess risk of bladder cancer in diabetic patients compared with the general population.

There are several potential limitations that should be considered when interpreting the results of this meta-analysis. First, because our analyses are based on observational studies, confounding cannot be excluded as a potential explanation for the observed association. Cigarette smoking has consistently been associated with an increased risk of bladder cancer [2], and increasing evidence also suggests that smoking may be a risk factor for diabetes [30]. Eight studies in this meta-analysis controlled for smoking, and seven of these studies showed a statistically significant positive association of diabetes with the risk of bladder cancer. Another possible confounder is obesity, which is a strong risk factor for type 2 diabetes [31]. However, findings on the relation between obesity and bladder cancer risk are limited and inconsistent [20, 32–35]. Only three studies in the present meta-analysis, including the Cancer Prevention Study II [21], the Iowa Women's Health Study [20] and a case–control study [19], controlled for BMI. In the Cancer Prevention Study II [34], obesity (BMI ≥30 kg/m^2) was associated with a statistically non-significant increase of 34% in the risk of bladder cancer in women but was not related to risk in men. In contrast, the Iowa Women's Health Study reported a statistically significantly lower risk of bladder cancer among obese women compared with women with a low BMI [20]. Both

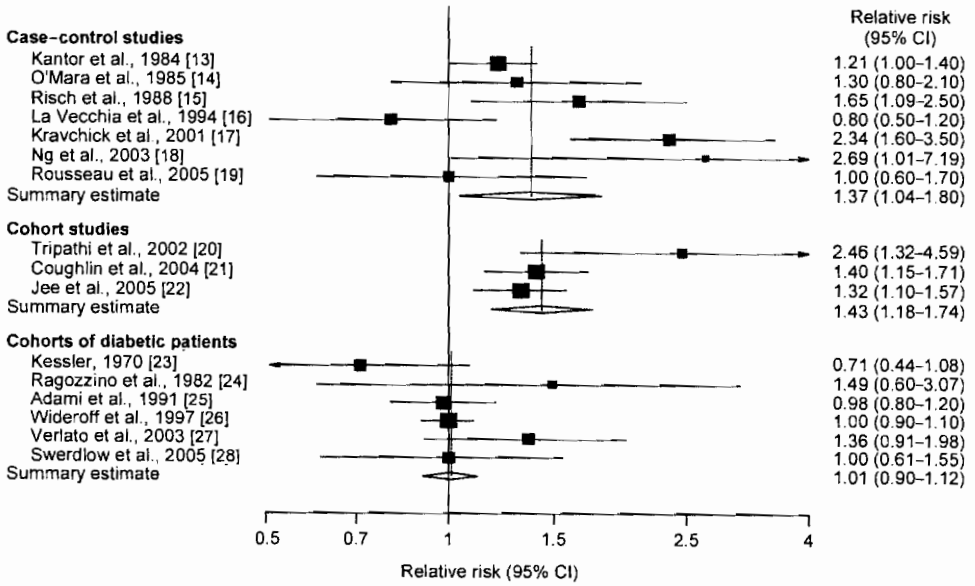

Fig. 1 Relative risks for the association between diabetes mellitus and bladder cancer in case–control studies, cohort studies, and cohort studies of diabetic patients. Studies are ordered according to study design and year of publication. The *squares* represent study-specific relative risks, and the size of the squares is proportional to the weight of each study in the summary estimate. The *horizontal lines* represent 95% CIs. The *diamonds* represent the summary relative risk estimates with 95% CIs

Table 1 Summary relative risks for the association between diabetes and bladder cancer by geographical region, publication year, and by adjustment for smoking and BMI

Subgroup	No. of studies	References	Relative risk (95% CI)	Tests for heterogeneity		
				Q	p	I^2 (%)
Geographical region						
North America	8	[13–15, 19–21, 23, 24]	1.29 (1.06–1.56)	14.49	0.04	51.7
Europe	6	[16, 18, 25–28]	1.03 (0.89–1.18)	7.29	0.20	31.4
Other[a]	2	[17, 22]	1.71 (0.98–2.99)	6.81	0.01	85.3
Publication year						
1970–1999	8	[13–16, 23–26]	1.07 (0.93–1.23)	14.48	0.04	51.7
2000–2005	8	[17–22, 27, 28]	1.47 (1.21–1.78)	15.49	0.03	54.8
Adjustment for smoking						
Yes	8	[13, 15, 17–22]	1.48 (1.25–1.77)	16.86	0.02	58.5
No	8	[14, 16, 23–28]	1.01 (0.91–1.11)	7.72	0.36	9.4
Adjustment for BMI						
Yes	3	[19–21]	1.45 (0.99–2.13)	4.74	0.09	57.8
No	13	[13–18, 22–28]	1.20 (1.03–1.39)	38.92	<0.0001	69.2

[a]One study each in Israel and Korea

the Cancer Prevention Study II [21] and the Iowa Women's Health Study [20] showed a statistically significant positive association between diabetes and risk of bladder cancer after controlling for BMI and other potential confounders [20, 21]. The remaining studies in this meta-analysis did not indicate whether BMI was associated with risk of bladder cancer in their study population, and it is therefore unclear whether BMI was a confounder in these studies.

A second limitation concerns methodological issues related to study design. Case–control studies are susceptible to recall and selection biases, which could inflate the RRs. Cohort studies are not subject to such bias, but might be affected by detection bias because patients with diabetes are under increased medical surveillance and thus might be more likely to be diagnosed with bladder cancer at an early stage of the disease. Thirdly, because diabetes is an underdiagnosed disease, some misclassification of exposure is likely; this would tend to attenuate any true relation between diabetes and bladder cancer risk. The overall lack of association of diabetes with the risk of bladder cancer in cohort studies of hospitalised diabetic patients might be due, at least partly, to the fact that the comparison group (i.e. the general population) includes individuals with diabetes, leading to some degree of underestimation of the true RR.

Finally, inherent in any meta-analysis of published studies is the possibility of publication bias. The funnel plot showed some asymmetry, as studies with small sample sizes and low RR were missing. This could indicate publication bias because small studies showing weak or null associations are less likely to be published. The presence of possible publication bias may have resulted in an overestimate of the relationship between diabetes and bladder cancer risk.

The possible mechanisms underlying the association of diabetes with bladder cancer risk are uncertain. In type 2 diabetes, insulin resistance leads to a state of hyperinsulinaemia [36, 37]. Insulin has mitogenic properties and could stimulate tumour growth by increasing bioactive IGF-I, which in turn stimulates cell proliferation and inhibits apoptosis [38]. In the circulation, IGF-I binds mainly to the main IGF binding protein, IGFBP-3 [39]. Several epidemiological studies have implicated IGF-I and IGFBP-3 in the development of prostate, breast and colorectal cancers [40]. IGF-I and IGFBP-3 may also play a role in the development of bladder cancer. In a US case–control study, statistically significantly higher plasma IGF-I concentrations and a higher molar ratio of IGF-I to IGFBP-3 were observed in patients with bladder cancer compared with controls [41]. Studies in animals support a potential role of IGF-I in bladder tumorigenesis [42]. Diabetes is also associated with an increased risk of urinary tract infection [43], which has been related to bladder cancer risk [17].

In summary, the present epidemiological evidence indicates that individuals with diabetes mellitus may have a modestly increased risk of bladder cancer. However, the possibility that the association may be due to bias or confounding cannot be ruled out. More research, both epidemiological and mechanistic, is needed to further clarify the association between diabetes and risk of bladder cancer.

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