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Diabetes mellitus and the risk of bladder cancer: an Italian case–control study

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Background: Diabetes mellitus has been associated with an increased risk of bladder cancer, although the evidence is still open to discussion.

Methods: We examined this association using data from a multicentre Italian case–control study, conducted between 2003 and 2014 on 690 bladder cancer cases and 665 frequency-matched hospital controls. Odds ratios (ORs) for diabetes were estimated by unconditional multiple logistic regression models, after allowance for major known risk factors for bladder cancer.

Results: One hundred and twelve (16.2%) cases and 57 (8.6%) controls reported a diagnosis of diabetes mellitus, corresponding to a multivariate OR of 2.09 (95% confidence interval (CI): 1.46–3.01). Bladder cancer risk increased with duration of diabetes (OR 1.92 for 1–<5 years, 1.63 for 5–<10 years, 2.39 for 10–<15 years, and 2.58 for ⩾15 years). The increased risk of bladder cancer was consistent in strata of age and education, whereas it was somewhat lower (although not significantly) in women (OR 1.18), in never (OR 1.31) and current (OR 1.42) smokers, and in subjects with a body mass index $<25\,kg\,m^{-2}$ (OR 1.48).

Conclusion: The present study provides further support of a role of diabetes in bladder cancer aetiology, although some residual confounding by tobacco, body mass index, or other unmeasured covariates may partly explain the association observed.

In the European Union, bladder cancer is the fifth most common cancer type and the ninth leading cause of cancer mortality, with about 40 000 deaths every year (Ferlay *et al*, 2013; Bosetti *et al*, 2013a). Its major recognised risk factor is tobacco smoking, with smokers having a three- to four-fold excess risk as compared with never smokers (Zeegers *et al*, 2000; IARC, 2004). Other known risk factors for bladder cancer include exposures to a few industrial chemicals (mainly aromatic amines in the past), drinking water contaminants, phenacetin-containing analgesics, and possibly selected aspects of diet (Villanueva *et al*, 2004; Silverman *et al*, 2006; World Cancer Research Fund and American Institute for Cancer Research, 2007; Letasiova *et al*, 2012).

Diabetes mellitus – an important determinant of various common neoplasms (Renehan *et al*, 2010) – has also been associated with an increased risk of bladder cancer, although the evidence is still open to discussion (Larsson *et al*, 2006; Newton *et al*, 2013; Prizment *et al*, 2013; Zhu *et al*, 2013a, b; Cantiello *et al*, 2015). A meta-analysis conducted in 2006 on seven case–control studies, three cohort studies, and six cohort studies in diabetic patients reported an overall relative risk (RR) of 1.24 (95% confidence interval (CI): 1.08–1.42), with a consistent RR in case–control studies (RR 1.37) and in cohort studies (RR 1.43), but no association in the cohorts of diabetic patients (RR 1.01) (Larsson *et al*, 2006). Consistent results were reported in two subsequent meta-analyses based on at least 9 case–control studies and 29 cohort studies, with pooled RRs ranging between 1.35 and 1.45 (Zhu *et al*, 2013a, b). A few studies examining the duration-risk relationship reported conflicting results (Atchison *et al*, 2011; MacKenzie *et al*, 2011; Tseng, 2011; Newton *et al*, 2013; Prizment *et al*, 2013).

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We further examined the association between diabetes and bladder cancer risk using data from a multicentre Italian case–control study (Polesel *et al*, 2014), where information was also available on age at diabetes diagnosis.

MATERIALS AND METHODS

Study participants and data collection. Between 2003 and 2014, we conducted a case–control study on bladder cancer within an established Italian network of collaborating centres, including Aviano and Milan in northern Italy, and Naples and Catania in southern Italy (Polesel *et al*, 2014). Cases were 690 subjects (median age 67 years; range 25–84 years) with incident transitional cell carcinoma of the bladder admitted to major general hospitals in the study areas. Nearly all bladder cancers ($n = 642$, 93.0%) were confirmed by histological testing on tumour tissue specimen from biopsy or surgery and three additional cases were confirmed by cytology only. Overall, 268 cancers (38.8%) were noninvasive (i.e., TNM pTis/Ta) and 351 (50.9%) locally invasive (other T); 307 (44.5%) were well or moderately differentiated (grading, G1–G2) and 312 (45.2%) poorly differentiated or undifferentiated (G3–G4). Controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to tobacco, and alcohol consumption or long-term diet modification. The control group included 690 patients frequency-matched to cases by study centre, sex, and 5-year age group. Twenty-five controls were excluded after enrolment because of inappropriate admission diagnosis, thus leaving 665 eligible controls (median age 66 years; range 27–84 years). Overall, 28.9% of controls were admitted for traumas, 22.1% for non-traumatic orthopaedic disorders, 39.3% for acute surgical conditions, and 9.8% for miscellaneous other illnesses. All study subjects signed an informed consent, according to the recommendations of the Board of Ethics of the study hospitals.

Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay. Refusal was below 5% for both cases and controls. The questionnaire collected information on sociodemographic factors, lifetime smoking and alcohol drinking habits, habitual diet before diagnosis/interview, a problem-oriented medical history, family history of cancer, lifetime occupational history, and exposure to selected chemical substances. Diagnosis of diabetes mellitus and selected other medical conditions (confirmed by a physician) was self-reported and included age at first diagnosis.

Statistical analysis. Odds ratios (OR) according to diabetes, and the corresponding 95% CI, were estimated by unconditional multiple logistic regression models (Breslow and Day, 1980), including terms for study centre, sex, quinquennia of age, year of interview, education (<7, 7–11, ⩾12 years), and tobacco smoking (never, ex-smokers, current smokers of <15, current smokers of 15–24, current smokers of ⩾25 cigarettes per day). Additional models were used to assess the potential modifying effect of selected covariates and heterogeneity was tested computing the difference in −2 log-likelihood of the models with and without the interaction terms. Percent attributable risks were computed using the distribution of risk factors among bladder cases (Bruzzi *et al*, 1985). All statistical analyses were performed with SAS 9.2 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 gives the distribution of bladder cancer cases and controls according to selected variables. Cases and controls had a similar distribution by study centre, sex, and education; cases were slightly older and more frequently smokers than controls.

One hundred and twelve (16.2%) cases and 57 (8.6%) controls reported a diagnosis of diabetes mellitus, corresponding to a multivariate OR of 2.09 (95% CI: 1.46–3.01; Table 2). Further adjustments for body mass index (BMI), alcohol drinking, history of cystitis, and family history of bladder cancer did not meaningfully modify our results. The ORs for diabetes were similar for well/moderately differentiated (OR 2.11; 95% CI: 1.34–3.33) and poorly differentiated/not differentiated (OR 1.98;

Table 1. Distribution of 690 cases of bladder cancer and 665 controls according to centre, sex, age, and other selected variables (Italy, 2003–2014)

	Cases		Controls		
	No.	%	No.	%	*P*-value[a]
Centre					
Aviano	242	35.1	250	37.6	
Milan	241	34.9	238	35.8	
Naples	129	18.7	100	15.0	
Catania	78	11.3	77	11.6	0.34
Sex					
Men	595	86.2	561	84.4	
Women	95	13.8	104	15.6	0.33
Age (years)					
<60	148	21.5	178	26.8	
60–64	107	15.5	119	17.9	
65–69	164	23.8	147	22.1	
70–74	155	22.5	124	18.7	
⩾75	116	16.8	97	14.6	0.061
Education (years)[b]					
<7	292	42.4	273	41.1	
7–11	224	32.5	215	32.3	
⩾12	173	25.1	177	26.6	0.80
Tobacco smoking[b]					
Never smokers	96	14.1	237	35.6	
Ex-smokers	310	45.5	284	42.7	
Current smokers (cigarettes per day)					
<15	79	11.6	53	8.0	
15–24	127	18.7	68	10.2	
⩾25	69	10.1	23	3.5	<0.001

[a]*P*-value for association from χ^2 statistic.
[b]The sum does not add up to the total because of some missing values.

Table 2. ORs of bladder cancer and corresponding 95% CIs according to history of diabetes mellitus (Italy, 2003–2014)

	Cases (%)	Controls (%)	OR[a] (95% CI)
Diabetes			
No	578 (83.8)	608 (91.4)	1[b]
Yes	112 (16.2)	57 (8.6)	2.09 (1.46–3.01)
Age at diabetes (years)			
<40	6 (0.9)	2 (0.3)	2.81 (0.52–15.1)
⩾40	106 (15.4)	55 (8.3)	2.06 (1.43–2.99)
Duration of diabetes (years)			
1–<5	37 (5.4)	19 (2.9)	1.92 (1.06–3.48)
5–<10	18 (2.6)	14 (2.1)	1.63 (0.77–3.44)
10–<15	21 (3.0)	10 (1.5)	2.39 (1.07–5.33)
⩾15	36 (5.2)	14 (3.6)	2.58 (1.32–5.03)
χ^2_{trend} (*P*-value)			14.67 (<0.001)

Abbreviations: CI = confidence interval; OR = odds ratios.
[a]Adjusted for study centre, sex, age, year of interview, education, and tobacco smoking.
[b]Reference category.

95% CI: 1.28–3.06) bladder cancers and for noninvasive (OR 2.39; 95% CI: 1.52–3.75) or locally invasive (OR 1.75; 95% CI: 1.13–2.71) ones. Similar ORs were observed for those with a diagnosis before age 40 years (OR 2.81; 95% CI: 0.52–15.1) or at age 40 years or more (OR 2.06; 95% CI: 1.43–2.99), although the former OR was based on very few diabetic subjects (six cases and two controls). Bladder cancer risk increased with duration of diabetes (OR 1.92, 95% CI: 1.06–3.48 for 1–<5 years; 1.63, 95% CI: 0.77–3.44 for 5–<10 years; 2.39, 95% CI: 1.07–5.33 for 10–<15 years; and 2.58, 95% CI: 1.32–5.03 for ⩾15 years).

The risk of bladder cancer was consistent in the strata of age and education, whereas it was somewhat lower (although not significantly) in women (OR 1.18; 95% CI: 0.39–3.63) compared with that in men (OR 2.29; 95% CI: 1.55–3.39), in never (OR 1.31; 95% CI: 0.56–3.06) and current (OR 1.42; 95% CI: 0.68–2.97) smokers compared with that in ex-smokers (OR 2.89; 95% CI: 1.75–4.76), and in subjects with a BMI $<25\,kg\,m^{-2}$ (OR 1.48; 95% CI: 0.79–2.80) compared with that in subjects with a BMI $\geqslant 25\,kg\,m^{-2}$ (OR 2.55; 95% CI: 1.62–4.01; data not shown in tables). In this population, 8.4% of all bladder cancers were attributable to diabetes.

DISCUSSION

The present study provides further evidence of the importance of diabetes in bladder cancer risk, diabetics having about two-fold excess risk as compared with non-diabetics. A duration-risk relationship was also observed, which supports a causal role of diabetes on this neoplasm.

The RR of bladder cancer found in our study is somewhat higher than the overall risk estimates reported in some meta-analyses (Larsson *et al*, 2006; Zhu *et al*, 2013a, b), which ranged between 1.2 and 1.5. Tobacco smoking – which is the major recognised risk factor for bladder cancer (IARC, 2004) and has been directly associated with diabetes (Willi *et al*, 2007) – was allowed for in the models and did not appear to confound appreciably the association between diabetes and bladder cancer risk in this dataset. However, a stronger excess risk of bladder cancer for diabetes was found in former smokers – likely subjects quitting because of cancer or other health conditions (Gallus *et al*, 2013) – pointing to a possible residual confounding of tobacco smoking. Overweight is a strong determinant of type 2 diabetes, although it has not been strongly associated with bladder cancer risk (Holick *et al*, 2007; World Cancer Research Fund and American Institute for Cancer Research, 2007), and thus cannot explain the association found with diabetes. In our study, the association with diabetes was apparently, although not significantly, stronger in overweight subjects compared to those with regular weight. In any case, adjustment for BMI did not meaningfully modify our risk estimates. As reported previously (Zhu *et al*, 2013a, b), the association between diabetes and bladder cancer was apparently stronger in men compared with that in women, but this may be because of chance, giving the low number of diabetic women in our study.

In our study, we were able to analyse the relation with duration of diabetes, which has been examined in a limited number of studies. Consistently with previous studies (MacKenzie *et al*, 2011; Newton *et al*, 2013; Prizment *et al*, 2013), we found that the excess risk of bladder cancer increases with duration of diabetes, although a few other investigations reported no consistent trend in risk (Atchison *et al*, 2011; Tseng, 2011).

The possible mechanisms explaining the association between diabetes and bladder cancer are unclear. Insulin resistance and hyperinsulinaemia, which characterise diabetes, have been shown to stimulate tumour growth by increasing insulin-like growth factor-1 levels, which in turn may stimulate cell proliferation and inhibit apoptosis (Zhao *et al*, 2003; Vigneri *et al*, 2009). Alternatively, diabetes increases the risk of urinary tract infections (Chen *et al*, 2009), which are directly associated with bladder cancer risk (La Vecchia *et al*, 1991; Michaud, 2007).

Cases and controls in the present study came from comparable catchment areas, were interviewed by uniformly trained interviewers in their hospital settings, had an almost complete participation rate, and were unaware of any particular hypothesis relating diabetes to bladder cancer, thereby reducing the likelihood of potential selection and recall bias. Diagnosis of diabetes and other medical conditions was self-reported and we had no measure of HbA1c levels for diabetic patients, thus some misclassification is possible. However, reliability of information on diabetes provided by hospital controls has been shown to be satisfactory in this network of studies (Bosetti *et al*, 2001). Although hospital controls may not be representative of the general population, the prevalence of diabetes among our controls was consistent with estimates from national population-based surveys (Asciutto *et al*, 2014; National Institute of Health). We were also able to allow for major confounding factors for bladder cancer, including, in particular, careful allowance for tobacco. A further limitation of this study is the lack of information on drugs used for diabetes control, which have been shown to have variable effects on bladder cancer risk (Soranna *et al*, 2012; Bosetti *et al*, 2013b). Moreover, we could not distinguish between type 1 and type 2 diabetes, although most (95%) of our subjects had a diagnosis after age 40 years, thus being likely affected by type 2 diabetes mellitus.

In conclusion, our data support a role of diabetes in bladder cancer aetiology, although some residual confounding by tobacco smoking, BMI, or other unmeasured covariates may partly explain the association observed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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