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 smokers (OR 1.31) and current smokers (OR 1.42), 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).
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 −2log-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; 95% CI: 1.14–3.42).

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

| Centre | Cases | % | Controls | % | P-value |
|--------|-------|---|----------|---|---------|
| Aviano | 242   | 35.1 | 250 | 37.6 | 0.28 |
| Milan  | 241   | 34.9 | 238 | 35.8 | 0.78 |
| Naples | 129   | 18.7 | 100 | 15.0 | 0.34 |
| Catania | 78    | 11.3 | 77  | 11.6 | 0.34 |

**Sex**

|       | Cases | %       | Controls | %       | P-value |
|-------|-------|---------|----------|---------|---------|
| Men   | 595   | 86.2    | 561      | 84.4    | 0.33    |
| Women | 95    | 13.8    | 104      | 15.6    |         |

**Age (years)**

| Age   | Cases | %       | Controls | %       | P-value |
|-------|-------|---------|----------|---------|---------|
| <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)**

| Education | Cases | %       | Controls | %       | P-value |
|-----------|-------|---------|----------|---------|---------|
| <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**

| Tobacco smoking | Cases | %       | Controls | %       | P-value |
|-----------------|-------|---------|----------|---------|---------|
| Never smokers   | 96    | 14.1    | 237      | 35.6    |         |
| Ex-smokers      | 310   | 45.5    | 284      | 42.7    |         |

**Current smokers (cigarettes per day)**

| Current smokers | Cases | %       | Controls | %       | P-value |
|-----------------|-------|---------|----------|---------|---------|
| <15             | 79    | 11.6    | 53       | 8.0     |         |
| 15–24           | 127   | 18.7    | 68       | 10.2    |         |
| ≥25             | 69    | 10.1    | 23       | 3.5     | <0.001  |

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

| Diabetes | Cases (%) | Controls (%) | OR* (95% CI) |
|----------|-----------|--------------|--------------|
| No       | 578 (83.8)| 608 (91.4)   | 2.09 (1.46–3.01) |
| Yes      | 112 (16.2)| 57 (8.6)     |              |

**Sex**

| Sex   | Cases (%) | Controls (%) | OR* (95% CI) |
|-------|-----------|--------------|--------------|
| Men   | 37 (5.4)  | 19 (2.9)     | 1.92 (1.06–3.48) |
| Women | 301 (44.5)| 317 (48.5)   |              |

**Age at diabetes (years)**

| Age at diabetes | Cases (%) | Controls (%) | OR* (95% CI) |
|-----------------|-----------|--------------|--------------|
| <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)**

| Duration of diabetes | Cases (%) | Controls (%) | OR* (95% CI) |
|----------------------|-----------|--------------|--------------|
| 1–<3                 | 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) |

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**Abbreviations:** CI—confidence interval; OR—odds ratios.

**Adjusted for study centre, sex, age, year of interview, education, and tobacco smoking.

**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 ≥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, in which both BMI and diabetes mellitus are risk factors. In conclusion, our data support a role of diabetes in bladder cancer etiology, 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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