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Family history of cancer and the risk of bladder cancer: A case–control study from Italy

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ABSTRACT

Background: A family history of bladder cancer has been associated with the risk of bladder cancer, but quantification of the excess risk in different populations is still a relevant issue. Further, the role of a family history of other cancers on the risk of bladder cancer remains unclear.
Methods: We analyzed data from an Italian case–control study, including 690 bladder cancer cases and 665 hospital controls. Odds ratios (ORs) were estimated through unconditional logistic regression models, adjusted for sex, age, study center, year of interview and further for education, smoking and sibling's number.
Results: The OR for family history of bladder cancer was 2.13 (95% confidence intervals (95%CIs) 1.02–4.49) from the model with partial adjustment, and 1.99 (95%CI 0.91–4.32) after additional adjustment for smoking and siblings' number, based on 23 cases (3.3%) and 11 controls (1.7%) with a family history of bladder cancer. The fully adjusted OR was 3.77 when the relative was diagnosed at age below 65 years. Smokers with a family history of bladder cancer had a four-fold increased risk compared to non-smokers without a family history. Bladder cancer risk was significantly increased among subjects with a family history of hemolymphopoietic cancers (OR = 2.97, 95%CI 1.35–6.55). Family history of cancer at other sites showed no significant association with bladder cancer risk.
Conclusion: This study confirms an approximately two-fold increased risk of bladder cancer for family history of bladder cancer, and indicates a possible familial clustering of bladder cancer with cancers of the hemolymphopoietic system.

1. Introduction

In Europe, bladder cancer is the fourth most frequent neoplasm in men, accounting for more than 118,000 new cases and more than 39,500 deaths each year. In most populations, rates for women are substantially lower than those for men [1].

In Europe, about 50% of male bladder cancers and 30% of female ones are attributed to tobacco smoking [2]. Other environmental exposures implicated in bladder cancer etiology include past occupational exposure to aromatic amines, arsenic and possibly chlorination byproducts in drinking water, chronic urinary tract infection, history of diabetes, schistosomiasis, and metabolic syndrome [3–7]. Moreover, several studies have indicated an inverse association with consumption of fresh fruit and vegetables [8].

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Over ten epidemiological studies assessed the association between family history of bladder cancer and bladder cancer risk, indicating an increased risk for one or more first-degree relatives with bladder cancer [9–11]. Most of these studies also estimated higher risks for an early occurrence of the diseases [12–16]. However, an analysis within the Nordic Twin Study of Cancer – including 203,691 twins from nationwide registries in Denmark, Finland, Norway and Sweden – suggested that hereditability is weaker for bladder cancer (30%, 95%CI 0–67%) than for other cancers such as prostate, colorectal and breast cancers [17], and an earlier report based on the nationwide Icelandic cancer registry found a greater risk for more distant relatives than for first-degree ones [18]. Most – though not all [13,19] – studies investigating familial risk according to tobacco smoking indicated higher familial risks among smokers [12,14,20,21]. Information on familial clustering of bladder cancer with other types of cancers is inconsistent. Direct associations were reported mainly for family history of hemolymphopoietic cancers, but also for family history of prostate, cervical, lung, brain, kidney, and stomach cancers [13,15,16,21,22].

In this article we provide original data on the relationship between bladder cancer risk and self-reported history of bladder and other types of cancer among first-degree relatives, using data from an Italian multicentric case–control study [24]. We also specifically investigated the combined effect of family history and tobacco smoking on bladder cancer risk.

2. Material and methods

2.1. 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 centers, including Pordenone and Milan in northern Italy and Naples and Catania in southern Italy [23]. Cases were 690 patients aged 25–80 years (median age 67 years) with incident urothelial carcinoma of the bladder and no history of other neoplasms, admitted to major general hospitals in the study areas. Nearly all bladder cancers (n = 642, 93%) were confirmed by histological testing on tumor tissue specimens from biopsy or surgery, and three additional cases were confirmed by cytology only. Almost all cases (n = 633, 92%) were transitional-cell carcinomas (six cases were squamous-cell carcinomas and three were other specified carcinomas; information was missing for 45 cases). According to the 2016 WHO grading system [24], overall 268 cancers (38.8%) were non-invasive (i.e., TNM pTis/Ta), 192 were T1 (27.8%), and 159 (23.0%) were muscolo-invasive (other T); 307 (44.5%) were well or moderately differentiated (grading, G1–G2) and 312 (45.2%) were poorly differentiated or undifferentiated (G3–G4).

The control group included patients without a history of cancer admitted to the same network of hospitals as the cases for a wide spectrum of acute conditions unrelated to tobacco or alcohol consumption or long-term dietary modifications. Controls were frequency-matched to cases by study center, sex, and 5-year age group; 690 controls were initially recruited. 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). Of these, 28.9% were admitted for traumas, 22.1% for non-traumatic orthopedic disorders, 39.9% 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 participating hospitals.

Trained interviewers administered a structured questionnaire to study participants during their hospital stay. Less than 5% of approached cases and controls refused the interview. Information was collected on sociodemographic factors, anthropometric measures, lifetime alcohol drinking, occupational exposure to selected chemical substances, a problem-oriented medical history, and habitual diet in the 2 years before diagnosis (for cases) or interview (for controls). With reference to smoking, we recorded lifetime smoking status (i.e., never, former, or current), daily number of cigarettes/cigars and grams of pipe tobacco smoked, age at starting, duration of the habit, and age at stopping for former smokers. We also recorded the number of sisters and brothers and, for parents and siblings, sex, year of birth, vital status, current age or age at death, and – if the relative had a history of cancer – cancer site and age at diagnosis.

2.2. Statistical analysis

We estimated the odds ratios (ORs) and the corresponding 95% CIs for bladder cancer according to family history of cancer of the bladder or of other sites using unconditional logistic regression models. A first model included terms for age (in quinquennia, categorically), sex, study center (categorically), year of interview (continuous) and education (<7, 7–11, ≥ 12 years, categorically). In a second model, additional adjustment for smoking (never, former, current: <15, 15–24, ≥ 25 cigarettes/day, categorically) and number of siblings (0–1, 2, 3–4, ≥ 5, categorically) was performed. Potential confounders were selected on the basis of prior knowledge about relationships between these factors and bladder cancer. We also investigated possible interaction between family history of bladder cancer and tobacco smoking, and estimated the ORs for the combinations of the two factors. The interaction test was performed comparing the difference in -2 log likelihood of the model with and without the interaction term to the χ^2 distribution with one degree of freedom.

In a further analysis, we used a family-based population approach to determine whether first-degree relatives (i.e., parents and siblings) of case probands had an excess risk of bladder cancer, or of other selected outcomes, compared to first-degree relatives of control probands. Thus, we built the cohort of all first-degree relatives of cases and controls, considering each relative as a study unit. The following endpoints were analyzed: (1) bladder cancer, (2) all hemolymphopoietic cancers (as family history of hemolymphopoietic cancers was significantly associated with the risk of bladder cancer in the primary analysis), (3) all cancers, and (4) all deaths. Cohort members (i.e., relatives of cases and controls) were followed from their birth until the occurrence of the endpoints of interest or the censoring age (i.e., current age if the relative was alive or age at death, for endpoints other than any deaths). Hazard ratios (HRs) for the endpoint occurrence were estimated using marginal Cox proportional hazard models, with a robust estimation of the covariance matrix to account for the dependency of observations within families, and adjusted for sex of the relative and proband smoking habits. Using the case–control status of the study participant as the predictor variable allowed estimation of the HRs for developing the endpoint for relatives of cases compared to relatives of controls. Bladder cancer cases and controls reported, respectively, 3522 and 3447 first-degree relatives. Three hundred and fifty-three (10%) relatives of cases and 327 (9.5%) relatives of controls were excluded from the cohort because of missing or incomplete data on one of the following variables: vital status, current age/age at death, history of cancer, and cancer site and age at diagnosis for those who reported a cancer. Thus, the final cohort included 3169 and 3120 relatives, respectively, among cases and controls.

All analyses were performed with SAS 9.4 statistical software (SAS Institute, Cary, NY).