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Blood cadmium may be associated with bladder carcinogenesis: The Belgian case–control study on bladder cancer

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Abstract

Background: The aim of this study was to assess the relationship between exposure to cadmium and bladder cancer risk. *Methods:* We conducted a case–control study in Belgium and measured the blood levels of cadmium in 172 bladder cases and 359 population controls. The data were analyzed as tertiles after logarithmic transformation. Cut-off points were based on the levels among the controls. Logistic regression was performed to calculate odds ratios (ORs) for bladder cancer occurrence with corresponding 95% confidence intervals (95% CI). *Results:* After adjustment for sex, age, and occupational exposure to PAHs or aromatic amines, the OR for cadmium was 8.3 (95% CI 5.0–13.8) comparing the highest to the lowest tertile (p for trend <0.001). Additional adjustment for smoking (current cigarette smoking status, years of cigarette smoking and number of cigarettes smoked per day) decreased the OR, however it remained strongly significant (OR: 5.7; 95% CI 3.3–9.9). *Conclusion:* Our study suggests that individuals with increased exposure to cadmium have an increased risk of bladder cancer. Future studies should expand on this investigation by studying a larger number of bladder cancer patients and by collecting extensive information on the lifetime occupational, residential, and environmental exposures to clarify the role of cadmium in bladder cancer.

Keywords: Bladder cancer; Cadmium; Risk factor; Case-control study; Confounding variables; Gender; Age; Smoker; Cigarettes; Zinc smelters; Occupational exposure; Residential exposure; Environmental exposure

1. Introduction

An estimated 357,000 bladder cancer cases occurred worldwide in 2002, making this the ninth most common cause of cancer for both sexes combined. There were 145,000 deaths, with population-based 5-year survival rates ranging from 40 to 80% depending on whether non-invasive lesions are included in the computation. Bladder cancer is relatively common in developed countries, where 63% of all incident cases are diagnosed [1]. Tobacco is the main risk factor. Approximately, half of male urinary tract cancer and one-third of female urinary tract cancer might be attributable to cigarette smoking [2]. Occupational exposure, particularly to aromatic amines and polycyclic aromatic hydrocarbons (PAH), may play an important role in perhaps 10% of bladder cancers [3]. Less well studied is the relationship between exposure to cadmium and the risk of bladder cancer. Cadmium and its compounds have been classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC). Occupational exposure to cadmium and its compounds occurs mainly in the form of airborne dust and fume. Occupations in which the highest potential exposures occur include cadmium production and refining, nickel–cadmium battery manufacture and zinc smelting [4]. Smoking is another important

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source of cadmium exposure. One cigarette contains approximately 0–6.67 μg of cadmium [5]. Food (meat, fish, and leafy vegetables) is also an important source of cadmium. Increases in soil cadmium, by human activities, results in an augmentation in the uptake of cadmium by plants. Meat, fish and fruit generally contain similarly cadmium levels and values of 5–10 μg/kg fresh weight are representative for these food classes. Certain shellfish contain higher concentrations; values in excess of 50–100 μg/kg fresh weight are considered normal. The daily dietary intake (adults in USA) is estimated at 30–40 μg [6]. However, only 1–3 μg/day of that cadmium from food is absorbed and enters the body. Smokers may take in an additional 1–3 μg of cadmium into their body per day from each pack of cigarettes smoked [7].

The body has limited capacity to respond to cadmium exposure, as the metal cannot be metabolized to less toxic species and is poorly excreted [8]. Its biological half-time is estimated at 15–20 years [9]. In the human body, the main portion of the cadmium body burden is found in the liver, kidney and other tissues (particularly muscle, skin and bone). Once absorbed cadmium has distributed throughout the body, the amounts of faecal and urinary excretion are approximately equal [7]. Concentrations of cadmium in blood in normal populations range from 0.4 to 1.0 μg/L for non-smokers and 1.4–4 μg/L for smokers. Previous population based studies in Belgium indicated blood cadmium levels among the controls varied between 0.40 μg/L (95% CI: 0.36–0.45) [10], 0.70 μg/L (95% CI: 0.40–1.30) [11] and 1.25 μg/L [12].

Belgium is one of the most important cadmium-producing countries worldwide. Starting from 1974, the atmospheric emissions from the zinc smelters have been reduced dramatically. Nevertheless, as a consequence, people living in several areas of the country, such as parts of the province Limburg, remain exposed to heavy metals, cadmium in particular [13].

The aim of this study was to assess the association between blood cadmium levels and the risk on bladder cancer. Blood cadmium is considered to reflect current exposure rather than whole body burdens, while urinary cadmium reflects total burden of cadmium [7].

2. Material and methods

2.1. Study population and data collection

We conducted a population based case–control study among 172 cases and 359 controls, in the Belgian province of Limburg. All cases were diagnosed with histological confirmed transitional cell carcinoma of the bladder between 1999 and 2004. Cases were selected from the Limburg Cancer Registry and approached through urologists and general practitioners. Due to the strict privacy law in Belgium, the population register is not directly accessible to researchers. A request was made to the ''Kruispuntbank'' of the social security for simple random sampling, stratified by municipality and socio-economic status, among all citizens above 50 years of age of the province. An invitation letter was sent to the selected subjects through the ''Kruispuntbank''. All participants were Caucasians. Informed consent was obtained from all study subjects. The study was approved by the ethical review board of the Medical School of the Catholic University of Leuven. Three trained interviewers visited cases and controls at home. Information by structured interview was collected on medical history, lifetime smoking history, family history of bladder cancer, 20-year residential history, lifetime occupational history and a standardized food frequency questionnaire, derived from the IMMIDIET study [14]. Occupational exposure to PAHs, aromatic amines and diesel were blindly coded by two experienced experts in occupational hygiene.

A blood sample was drawn by venipuncture, after each interview. Blood samples for cases and controls were analyzed in random order, with the case status unknown to the laboratory staff (Algemeen Medisch Laboratorium, Antwerp, accreditation certificate of the Belgian government). Cadmium concentrations were determined by ICP-mass spectrometry.

2.2. Statistical analysis

The data were analyzed as tertiles after logarithmic transformation. Cut-off points were based on the levels among the controls. The effect of the cadmium levels on the risk of bladder cancer was estimated by odds ratios (ORs) and corresponding 95% confidence intervals (95% CI), which were derived from unconditional logistic regression analyses. We adjusted for sex, age, current cigarette smoking status, years of cigarette smoking and number of cigarettes smoked per day and occupational exposure to PAHs or aromatic amines. We stratified the results by cigarette status (never/ever), high versus low vegetable, fruit, potatoes, meat and fish daily intake (g/day) in order to assess effect modification. Low and high food intake were defined as intake below or above the mean intake in the controls. All analyses were performed using STATA version 8 [15].

3. Results

Table 1 shows demographic and descriptive characteristics of cases and controls. As expected, relatively more women were included in the control group (39.5%) compared with the case group (13.4%) and the smoking prevalence in the controls was lower than in the cases (never smokers: 16.9 and 40.4%, respectively). Cases were slightly older (mean age: 67.2 years, S.D. 9.9) than controls (mean age: 63.7 years, S.D. 9.2). 83.6% of the controls and 75.6% of the cases lived at the same area for the past 20 years.