Cancer Epidemiology 52 (2018) 63–69

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Nationwide analysis on the impact of socioeconomic land use factors and incidence of urothelial carcinoma

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ARTICLE INFO

Keywords:
Environmental exposure
Socioeconomic factor
Smoking
Incidence rates
Urothelial carcinoma

ABSTRACT

Background: Incidence rates for urothelial carcinoma (UC) have been reported to differ between countries within the European Union (EU). Besides occupational exposure to chemicals, other substances such as tobacco and nitrite in groundwater have been identified as risk factors for UC. We investigated if regional differences in UC incidence rates are associated with agricultural, industrial and residential land use.

Methods: Newly diagnosed cases of UC between 2003 and 2010 were included. Information within 364 administrative districts of Germany from 2004 for land use factors were obtained and calculated as a proportion of the total area of the respective administrative district and as a smoothed proportion. Furthermore, information on smoking habits was included in our analysis. Kulldorff spatial clustering was used to detect different clusters. A negative binomial model was used to test the spatial association between UC incidence as a ratio of observed versus expected incidence rates, land use and smoking habits.

Results: We identified 437,847,834 person years with 171,086 cases of UC. Cluster analysis revealed areas with higher incidence of UC than others ($p = 0.0002$). Multivariate analysis including significant pairwise interactions showed that the environmental factors were independently associated with UC ($p < 0.001$). The RR was 1.066 (95% CI 1.052–1.080), 1.066 (95% CI 1.042–1.089) and 1.067 (95% CI 1.045–1.093) for agricultural, industrial and residential areas, respectively, and 0.996 (95% CI 0.869–0.999) for the proportion of never smokers.

Conclusion: This study displays regional differences in incidence of UC in Germany. Additionally, results suggest that socioeconomic factors based on agricultural, industrial and residential land use may be associated with UC incidence rates.

1. Introduction

Urothelial carcinoma (UC) represents the 8th most common death attributed to cancer in men in the United States of America and shows rising incidence rates in both men and women with increasing age [1]. There are approximately 28,500 newly diagnosed patients with UC per year in Germany which represents the fourth highest incidence rate in the European Union (EU) [2].

Urothelial carcinoma may develop in the entire urinary tract, while approximately 90% of tumors are located in the urinary bladder and only 5–10% of carcinomas are found in the upper urinary tract [2,3]. In Germany, bladder cancer occurs nearly three times more often in men than in women [4]. These differences might be explained by higher tobacco consumption in men and a higher work-related exposure to chemicals [5,6]. While incidence rates for UC are increasing [7,8], mortality rates are declining due to optimized diagnostics and accessibility to modern treatment modalities [9].

Tumor incidence rates differ between countries within the EU [10]. Highest incidence rates for UC are found in Spain, whereas Finland has the lowest tumor incidence [7]. Reasons for these differences are still matter of debate [11]. Occupational exposure to chemicals such as aromatic amines, tobacco and nitrite are only some known risk factors

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https://doi.org/10.1016/j.canep.2017.12.001
Received 29 March 2017; Received in revised form 12 November 2017; Accepted 1 December 2017

that might play a potential role for incidence differences [12–14].

There are only few epidemiological studies that have investigated regional differences in tumor incidence. In this study we investigated UC incidence rates in administrative districts in Germany and furthermore analyzed if these incidence rates are related to different socioeconomic factors. These factors are agricultural, industrial as well as residential land use in each administrative district in Germany. We furthermore included information on smoking habits in Germany, to account for the fact that tobacco is considered a major risk factor for UC.

2. Methods

2.1. Data sources and cancer registries

Information on tumor cases and information on corresponding population density was obtained from the German Centre for Cancer Registry Data (ZfKD), Robert-Koch-Institute (RKI). All cases between 2003 and 2010 were included. At time of analysis tumor documentation was available with over 95% completeness in ten federal states (Hamburg, Lower Saxony, Bremen, North Rhine Westphalia 2007–2010 and in the administrative districts of Munster also for 2003–2006, Rhineland Palatinate, Bavaria, Saarland, Brandenburg, Saxony, Thuringia) and between 70% and 95% completeness in five states (Schleswig-Holstein, Hesse, Berlin, Mecklenburg-Western Pomerania, Saxony-Anhalt). In Baden Wuerttemberg in the south west of Germany, tumor documentation was established in 2009 with completeness about 50% until 2010. Data from Baden Wuerttemberg was only used for graphical display and was therefore estimated from available data from 2009 and 2010 and excluded from final analysis to avoid bias.

Documentation was standardized according to International Statistical Classification for Disease German Modification 10th Edition (ICD-10-GM) for the medical care system and the International Classification of Diseases for Oncology (ICD-O-3, 3rd Edition). For the following analysis, only the ICD-10-GM was used. We included all cases with the primary site of an UC of the upper and lower urinary tract (C65, C66 and C67) and carcinoma in situ (D09.0). Aside from information on the completeness of the data set, the total population was provided in age categories of 5 year intervals of respective administrative districts including only patients above 10 years of age.

Furthermore, information on land use in each administrative district in Germany from 2004, the first available data in the observation period from 2003 to 2010, was acquired from the Regional Database Germany (Regionaldatenbank Deutschland, http://www.regionalstatistik.de). Land use was defined as agricultural (A), industrial (I) and residential (R) and calculated as proportions of the total area of the respective administrative districts. Thereby, we used the general notation of the database which refers to the respective land use categories in a very general manor (all kinds of agriculture apart but not forestry, all kinds of industry or business, all kinds of buildings including those from industry).

In order to account for smoking as one of the most relevant risk factor for urothelial carcinoma, we also included general information on smoking habits in Germany in the analysis. However, this information was only available as information in administrative areas which is the next level of administrative unit over administrative district. The information on smoking habits was provided as proportions of never smokers, previous smokers and actual smokers for each age category by the Federal Office for Statistics, Wiesbaden.

We mapped these data sets with information of administrative districts from the Global Administrative Areas database (GADM database, http://www.gadm.org) of the shape of administrative areas of 3rd level in latitude/longitude as coordinate reference system. Here we accounted for administrative district changes and used the GADM database as reference.

2.2. Statistical analysis

Data analysis was performed with R (R Foundation for Statistical Computing, Vienna, Austria) with packages sp, SpatialEpi, epitools rgdal and maptools. We calculated crude and age-standardized incidence rates in women and men in each area using age distribution of the total German population in 2010 as reference. Furthermore, we analyzed the ratio of observed versus expected incidence rates. The expected incidence rate is defined as the overall observed incidence rate in the respective age category and year. After inspection of the incidence rates in federal states with completeness between 70% and 90%, we found that incidence rates first increased and then stabilized in the later phases of the time period. Finally, we used all data from Schleswig-Holstein, Berlin, Mecklenburg-Western Pomerania and Saxony-Anhalt and data starting from 2008 in Hesse and data starting from 2010 in whole North Rhine Westphalia but also from 2003 to 2010 in the Muenster area of North Rhine Westphalia. All together we evaluated 364 administrative districts for statistical analysis and added information from Baden Württemberg as whole for graphical display. Age-category and sex-specific population data was available from 2004 to 2010 whereas age-category and sex-specific population from 2003 was estimated from 2004 data. Kulldorff spatial cluster test was used to detect clusters with high incidence rates. For further statistical analysis, a negative binomial model was used to test the influence of land use information and age adjusted information on smoking rates on the incidence rates by including the expected incidence rates as offset in the regression model. Factors were included either as reported or smoothed including values from neighbouring administrative districts by a 1:1 weighting scheme between the respective administrative district and all neighbouring administrative districts together. We analyzed all potential factors in a univariate analysis and a multivariate analysis which also includes significant pairwise interactions. Finally we performed a sensitivity analysis by restricting to administrative districts with completeness above 95%.

All tests were two-sided and a significance level of $\alpha = 0.05$ was used.

3. Results

3.1. Patient characteristics and incidence

Between 2003 and 2010 a total of 437,847,834 patient years under observation with 171,086 newly diagnosed cases were evaluated (observed cases). Cases where ICD-10-GM classification did not yield a specific tumor location and were not associated to UC were excluded (n = 4840). Median age was 75 years for women and 72 years for men (Table 1). Cumulative incidence was 39.07 cases per 100,000 persons-years, gender specific incidence was 58.60 for men and 20.50 for women per 100,000 person-years. Tumor incidence increased with increasing age for both genders (Fig. 1).

Table 1
Characteristics of patients with urothelial carcinoma.

	Men	Women
Total (n)	125,089	45,997
Incidence (rate, 95% confidence interval) per 100,000 person years	58.6 (58.3, 58.9)	20.5 (20.3, 20.7)
Age median (range)	72 (11–109)	75 (11–106)
Upper urinary tract[a] (n)	7237	4978
Bladder cancer[a] (n)	114,553	39,478

[a] Cases that were not clearly classified as bladder cancer or upper urinary tract cancer were excluded (n = 4840).