

TOBACCO, OCCUPATION AND NON-TRANSITIONAL-CELL CARCINOMA OF THE BLADDER: AN INTERNATIONAL CASE-CONTROL STUDY

Joan FORTUNY¹, Manolis KOGEVINAS^{1*}, Jenny CHANG-CLAUDE², Carlos-Alberto GONZÁLEZ³, Martine HOURS⁴, Karl-Heinz JÖCKEL⁵, Ulrich BOLM-AUDORFF⁶, Elsebeth LYNGE⁷, Andrea 'T MANNETJE¹, Stefano PORRU⁸, Ulrich RANFT⁹, Consol SERRA¹⁰, Anastasia TZONOU¹¹, Jürgen WAHRENDORF² and Paolo BOFFETTA¹²

¹Respiratory and Environmental Health Research Unit, IMIM, Barcelona, Spain

²German Cancer Research Center, Epidemiology Department, Heidelberg, Germany

³Research Institute for Clinical Epidemiology, Mataró, Spain

⁴Epidemiology Institute, Claude Bernard University, Lyon, France

⁵Institute for Medical Information Technology, Biometry and Epidemiology, Essen, Germany

⁶Hesse Ministry for Women, Employment and Social Affairs, Wiesbaden, Germany

⁷Danish Cancer Society, Copenhagen, Denmark

⁸Institute of Occupational Health, University of Brescia, Brescia, Italy

⁹Medical Institute of Environmental Hygiene, Heinrich-Heine University, Düsseldorf, Germany

¹⁰Center for Studies, Medical Programs and Services, Parc Tauli Foundation, Sabadell, Spain

¹¹Department of Hygiene and Epidemiology, Medical School of Athens, Athens, Greece

¹²Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France

Transitional-cell carcinoma is the dominant histological type of malignant tumors of the urinary bladder. There is limited information on risk factors for non-transitional-cell carcinoma (NTCC) of the bladder. We used data from 9 case-control studies on bladder cancer from 6 European countries to examine the association between NTCC, tobacco smoking and occupation. Information on 146 cases diagnosed with NTCC were matched by age, gender and study center to 727 non-cancer population or hospital controls and also with 722 transitional-cell-bladder-cancer controls. Lifetime smoking and occupational history were evaluated. A statistically significant excess risk for NTCC was observed for current smoking [odds ratio (OR) = 3.61, 95% confidence interval (CI) 2.08–6.28]. The risk increased with higher tobacco consumption (OR for highest tertile of pack-years = 7.01, 95% CI 3.60–13.66). The risks were higher for squamous-cell carcinomas than for other types of NTCC. Among major occupational groups, a significant excess risk was seen for field-crop and vegetable-farm workers (OR = 2.06, 95% CI 1.03–4.10). These results indicate that NTCC of the bladder is associated with smoking and specific occupations. The risk pattern seems to differ, in part, from that observed for transitional-cell carcinoma of the bladder. *Int. J. Cancer* 80:44–46, 1999.

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In industrialized countries, transitional-cell carcinoma is the dominant histological type of malignant tumors of the urinary bladder. Non-transitional-cell carcinoma of the bladder represents only 5 to 7% of all bladder tumors, comprising about 3% of squamous-cell carcinomas, 2% of adenocarcinomas, 1% of undifferentiated carcinomas and a smaller percentage of minor histologies such as small-cell carcinomas and lymphomas (DeVita *et al.*, 1993). Most studies assessing risk factors for bladder cancer in industrialized countries have not studied non-transitional-cell carcinoma separately, mainly because of small numbers. A single existing study from the USA (Kantor *et al.*, 1988) is based on less than 100 cases, and identified smoking as a risk factor for squamous-cell carcinoma. Two studies in Africa have given contradictory results regarding the risk associated with smoking and non-transitional-cell carcinomas (Vizcaino *et al.*, 1994; Bedwani *et al.*, 1997). Clinical studies and limited epidemiological evidence indicate that severe long-standing cystitis may be associated with squamous-cell carcinoma of the bladder (Polsky *et al.*, 1976; Dolin *et al.*, 1994). Studies in Africa have associated chronic urinary-tract infection by *S. haematobium* with squamous-cell carcinoma, a relationship that appears to be less strong for transitional-cell carcinomas (IARC, 1994). We used data from 9

European case-control studies on bladder cancer to examine the association between non-transitional-cell carcinomas, tobacco smoking and occupation.

MATERIAL AND METHODS

The pooled data set forms part of a wider project examining occupational cancer in the European Union (Kogevinas *et al.*, 1998). The 9 case-control studies (González *et al.*, 1989; Rebelakos *et al.*, 1985; Moller Jensen *et al.*, 1987; Claude *et al.*, 1988; Hours *et al.*, 1994; Porru *et al.*, 1996; Bolm-Audorff *et al.*, 1993; Greiser and Molzahn, 1997; C. Serra personal communication) were selected from all studies conducted in the European Union that included detailed lifetime information on occupation and tobacco smoking and information on histological type of bladder cancer (Table I). Information on medical conditions leading to chronic inflammatory processes was not available in most studies and, therefore, could not be examined in the pooled analysis. The 146 subjects diagnosed with non-transitional-cell carcinoma constitute the case series in this analysis. They include 49 squamous-cell carcinomas, 16 adenocarcinomas, 28 undifferentiated carcinomas, and 53 other or non-specified non-transitional-cell carcinomas types. The mean age for non-transitional-cell carcinoma cases was 66 years, 83% of them were men and 73% were ever-smokers.

For each case we randomly selected 2 sets of controls (matching ratio 1:5) from all potentially eligible controls of the same age (± 5 years), gender and study center. The first control series constituted of 727 non-cancer controls selected from the original control series. Of the 9 studies selected, 5 had originally selected hospital controls (Rebelakos *et al.*, 1985; Claude *et al.*, 1988; Hours *et al.*, 1994; Porru *et al.*, 1996; Bolm-Audorff *et al.*, 1993), 3 studies population controls (Moller Jensen *et al.*, 1987; Greiser and Molzahn, 1997; C.

Grant sponsor: European Commission, Europe Against Cancer; Grant number: SOC 96-200742 05F02; Grant sponsor: Generalitat (Government) of Catalunya; Grant number: CIRIT/1995 SGR 00434; Grant sponsor: Fondo de Investigación Sanitaria, Ministry of Education, Spain; Grant number: 97/1105E.

*Correspondence to: Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), 80 Doctor Aiguader Rd., Barcelona 08003, Spain. Fax: (34)93-2213237. E-mail: kogevinas@imim.es

Received 26 May 1998; Revised 3 August 1998

TABLE I – DESCRIPTION OF THE 9 EUROPEAN BLADDER-CANCER CASE-CONTROL STUDIES INCLUDED IN THE POOLED ANALYSIS

Study area (reference)	Number of transitional-cell-carcinoma cases	Number of non-transitional-cell-carcinoma cases		
		All	Squamous-cell carcinoma	Period of enrollment
Spain (González <i>et al.</i> , 1989)	471	26	7	1983–1986
Greece (Rebelakos <i>et al.</i> , 1985)	278	22	11	1980–1982
Denmark (Moller Jensen <i>et al.</i> , 1987)	356	33	6	1975–1981
Germany (Claude <i>et al.</i> , 1988)	397	24	15	1977–1985
France (Hours <i>et al.</i> , 1994)	111	5	0	1984–1986
Italy (Porru <i>et al.</i> , 1996)	349	6	0	1992–1993
Germany (Bolm-Audorff <i>et al.</i> , 1993)	294	6	1	1989–1992
Germany (Greiser and Molzahn, 1997)	904	10	7	1990–1994
Spain (C. Serra, personal communication)	206	14	2	1993–1995
Total	3,366	146	49	

TABLE II – CIGARETTE SMOKING AND RISK FOR NON-TRANSITIONAL BLADDER CANCER

Smoking status and pack-years (py)	Cases ¹	Non-cancer controls ¹	Cancer controls (TCC) ¹	All non-transitional-cell cancer cases (n = 146)		Squamous-cell carcinoma cases (n = 49)	
				Non-cancer controls OR (95% confidence interval) ²	Cancer controls (TCC) OR (95% confidence interval) ²	Non-cancer controls OR (95% confidence interval) ²	Cancer controls (TCC) OR (95% confidence interval) ²
Non-smokers	27	220	109	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Ex-smokers (all)	41	267	247	1.41 (0.79–2.51)	0.58 (0.31–1.28)	2.19 (0.77–6.27)	0.91 (0.30–2.76)
0.06–21.51 py	23	145	97	1.56 (0.82–3.00)	0.86 (0.43–1.71)	2.21 (0.67–7.28)	1.09 (0.31–3.82)
21.52–40.51 py	9	65	76	1.41 (0.59–3.34)	0.42 (0.17–1.00)	2.75 (0.67–11.34)	1.02 (0.24–4.30)
40.52+ py	9	57	74	1.61 (0.66–3.92)	0.42 (0.17–1.01)	3.70 (0.75–18.15)	0.79 (0.17–3.77)
Current smokers (all)	65	185	306	3.61 (2.08–6.28)	0.79 (0.44–1.40)	5.31 (1.95–14.48)	1.19 (0.42–3.35)
0.06–21.51 py	11	47	49	2.16 (0.97–4.84)	0.85 (0.37–1.94)	2.52 (0.57–11.18)	0.91 (0.20–4.01)
21.52–40.51 py	17	73	122	2.68 (1.29–5.56)	0.50 (0.24–1.05)	4.14 (1.13–15.16)	0.78 (0.22–2.85)
40.52+ py	37	65	135	7.01 (3.60–13.66)	1.01 (0.53–1.91)	11.30 (3.36–37.97)	1.53 (0.49–4.77)

¹Excluded 13 cases (5 squamous-cell carcinomas), 55 non-cancer and 60 cancer controls, smoking other types of tobacco (pipes, cigars).²OR adjusted for age, gender and study center.

Serra personal communication) and one study used both (González *et al.*, 1989). Among the studies including hospital non-cancer controls, 2 selected them from patients in urological boards, one from accident/trauma patients, 2 from patients in various departments with diagnoses not associated with smoking or occupation and one from a combination of urological patients and general wards. The mean age of the non-cancer controls included in this analysis was 67 years, 83% were men and 64% were ever-smokers. The second, constituted of 722 subjects with transitional-cell carcinoma of the bladder who were originally included in the studies as part of the case series. This group's mean age was 67 years, 83% were men and 77% were ever-smokers. Squamous-cell-carcinoma cases were analyzed as a separate sub-group, which had a mean age of 68.4 years, 85.7% of men and 74.9% of ever-smokers.

Subjects were classified by smoking status (never, ex, current smoker of cigarettes) and by cumulated pack-years of cigarettes categorized in tertiles and stratified by smoking status. Lifetime occupational history for jobs held for more than 6 months was available in 8 out of 9 studies. In the Greek study, only the longest held occupation was coded. Occupations were reclassified using the International Standard Classification of Occupations (International Labor Office, 1969). Conditional logistic regression was used, and (OR) were adjusted for age, gender and center, and the 95% (CI) were calculated using the SAS statistical package.

RESULTS

A 3-fold statistically significant increased risk for non-transitional-cell carcinoma was observed for current tobacco smoking (Table II). Among current smokers, the risk increased with pack-years of cigarette smoking (p value for linear trend = 0.001), with a 7-fold risk for the highest tertile of pack-years (40.52 + pack-years). The

OR for smoking were consistently lower for the combined non-transitional-cell-carcinoma group than for the transitional-cell-carcinoma cases, indicating that tobacco smoking is less strongly associated with the conjunct of these histologies than with transitional-cell carcinoma. Specifically for squamous-cell carcinoma, however, the risk associated with smoking was higher than for other types of non-transitional-cell carcinomas and was similar to the risk observed for transitional-cell carcinoma (Table II).

A 2-fold statistically significant excess risk was observed for all NTCC and for squamous-cell carcinoma, in subjects employed as field-crop and vegetable-farm workers, as compared with non-cancer controls (Table III). Among other occupational groups, a statistically significant excess risk of non-transitional-cell carcinoma was observed for working proprietors, catering and lodging (4 cases OR = 5.40, 95% CI = 1.04–27.98). No excess risk was observed for workers in occupations such as rubber processing, textiles and dye manufacturing, which have been consistently associated with excess risk for transitional-cell carcinoma of the bladder.

DISCUSSION

In this pooled analysis of case-control studies, we examined the association between smoking, occupation and risk for non-transitional-cell carcinoma of the bladder. We relied on the histological diagnosis of the original studies. The proportion of non-transitional cell carcinomas among all bladder cancers differed by study and was higher in the earlier studies (González *et al.*, 1989; Rebelakos *et al.*, 1985; Moller Jensen *et al.*, 1987; Claude *et al.*, 1988) than in those conducted in the 1990s (Hours *et al.*, 1994; Porru *et al.*, 1996; Bolm-Audorff *et al.*, 1993; Greiser and Molzahn, 1997; C. Serra, personal communication). The diagnosis of squamous-cell carcinoma was probably highly specific, but other

TABLE III – OCCUPATION AND RISK FOR NON-TRANSITIONAL-CELL CARCINOMAS OF THE BLADDER OR AND 95% CI ARE ADJUSTED FOR AGE, GENDER, SMOKING AND STUDY

Occupation (ISCO Codes)	Non-cancer controls			Transitional-cell-cancer controls		
	Cases/ controls	OR	CI 95%	Cases/ controls	OR	CI 95%
Professional, technical and related workers (1)	13/72	0.99	0.50–1.95	13/59	1.13	0.58–2.21
Administrative and managerial workers (2)	3/23	0.72	0.20–2.56	3/21	0.73	0.21–2.52
Clerical and related workers (3)	25/117	1.02	0.60–1.73	25/137	0.87	0.52–1.46
Sales workers (4)	18/127	0.54	0.30–1.44	18/112	0.67	0.37–1.21
Service workers (5)	26/131	0.89	0.53–1.52	26/121	1.04	0.62–1.76
Working proprietors, catering and lodging (51)	4/4	3.65	0.74–18.06	4/3	5.40	1.04–27.98
Agricultural, animal husbandry and forestry workers, fishermen and hunters (6)	47/204	1.25	0.82–1.91	47/145	1.36	0.88–2.07
Field crop & agricultural workers (622)	17/59	2.06	1.03–4.10	17/56	1.98	0.98–4.01
Production workers, transport equipment operators and laborers (7 + 8 + 9)	85/424	0.93	0.61–1.44	85/446	0.81	0.53–1.25

non-transitional-cell carcinomas had been identified in some centers by exclusion, *i.e.*, as any bladder tumor not classified as transitional-cell carcinoma. Histological misclassification and inter-center variability in histopathological practices may have affected the risk estimates for the group of non-transitional-cell carcinomas as a whole, but it is unlikely that this bias has seriously affected the risk estimates for squamous-cell carcinoma.

In these European populations, tobacco smoking appears as a major risk factor for non-transitional-cell carcinoma in men and in women, a finding consistent with the results of the studies in the US (Kantor *et al.*, 1988) and Egypt (Bedwani *et al.*, 1997). The risk for tobacco smoking appears higher for squamous-cell carcinoma other non-transitional cell carcinomas histologies (adenocarcinomas, undifferentiated and other).

The main occupational group having an excess risk in this European study were farmers. The higher frequency of squamous-cell carcinoma in Egypt and other African countries has been attributed to infestation with *S. haematobium* (Vizcaino *et al.*, 1994; Bedwani *et al.*, 1997; IARC, 1994), mainly through exposure

in agricultural activities. The prevalence of this infection in Europe has been very low and it is, therefore, unlikely that the increased risk can be attributed to *S. haematobium*. Other occupations which have been associated with high risk for transitional-cell carcinomas of the bladder (Silverman *et al.*, 1996; Kogevinas *et al.*, 1998), were not at high risk for NTCC. Even though this pooled data set includes more non-transitional-cell carcinomas cases than earlier studies, its size is small to detect risks for specific occupations.

In conclusion, NTCC of the bladder is associated with smoking and with specific occupations. The risk pattern seems to differ, in part, from that observed for transitional-cell carcinoma of the bladder.

ACKNOWLEDGEMENTS

J.F. had an IMAS fellowship for medical students, Barcelona, Catalonia, Spain. We thank Mr. A. Tobías, Dr. X. Castellsagué and Mr. D. McFarlane for helping in data management and statistical analysis.

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