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A hospital-based case-control study of urinary bladder cancer in relation to occupational exposure to acids in the Campania Region of Italy, 1988-1990

Studio caso-controllo su una casistica ospedaliera sui tumori della vescica urinaria in relazione all'esposizione professionale ad acidi nella Regione Campania, 1988-1990

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Summary

***Background*. The lifetime risk for urinary bladder cancer in the United States ranges from 0.5%-3%, depending on gender and ethnic group, with Caucasian males having the highest rate. Occupational exposures account for one-quarter of this risk in Caucasian males, and chemicals are central to creating this workplace hazard. Past research indicates that the aryl amines, benzidine, 2-naphthalene, and aniline dyes, are the main chemicals associated with bladder carcinogenesis. *Aim*. Because long-term, high-level occupational exposure to strong-inorganic-acid mists containing sulphuric acid is an established carcinogen, the relationship between occupational acid exposure and bladder cancer was tested as part of an extensive occupational cancer case-control study of 513 male hospitalized patients in the Campania Region of Italy. *Patients and methods*. The full dataset included exposure information on up to 20 major groups of occupational chemicals with the target cancers of lung (n = 111), laryngeal (n = 35), naso/nasal/pharyngeal (n = 22), oral cavity (n = 23) and bladder (n = 75). For this study, cases (n = 75) were defined as people with bladder cancer, while**

Riassunto

***Premessa*. Il rischio di carcinoma vescicale nel corso della vita, negli Stati Uniti, varia dallo 0,5 al 3%, in base al genere e al gruppo etnico, col tasso più elevato tra i maschi di razza caucasica. L'esposizione professionale a diversi agenti chimici determina un quarto di questo tasso di rischio tra i maschi di razza caucasica. Studi precedenti indicano un ruolo eziologico nel cancro vescicale per le arilamine, la benzidina, il 2-naftalene e i coloranti all'anilina. *Finalità*. Poichè l'esposizione professionale prolungata ed intensa ad aerosol di acidi inorganici forti, contenenti acido solforico, svolge riconosciuta azione oncogena, è stata esaminata la relazione tra esposizione professionale ad acidi e cancro della vescica, come parte di un esteso studio caso-controllo sui tumori professionali in 513 soggetti maschi ricoverati in strutture ospedaliere della Regione Campania. *Pazienti e metodi*. La raccolta dati dello studio più ampio comprendeva informazioni su esposizioni a fino a 20 principali gruppi di agenti chimici professionali e sulle neoplasie specificamente associate del polmone (n = 111), laringe (n = 35), nasofaringe (n = 22), cavità orale (n = 23) e vescica (n = 75). Per questo studio, i casi (n = 75) erano definiti come**

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controls (n = 270) were other unmatched patients with oral cavity cancers (but none of the other three target cancers) or patients with any other reason for hospitalization. Unconditional logistic regression was used to fit the acid-bladder cancer model controlling the effects of tobacco and age. Other confounders, such as alcohol and coffee consumption (the only dietary variable in our dataset) are discussed and considered, but neither was significant. *Results*. The results demonstrate an adjusted statistically significant association between occupational acid exposure and bladder cancer (OR = 4.09; p = 0.028). *Discussion*. The implications of this new finding in humans are discussed, both in the context of existing evidence, and in light of the 1992-IARC designation based on research to that time demonstrating the rôle of acid mixtures in the causation of upper respiratory tract cancers. *Conclusion*. Further research is warranted to replicate this finding. Eur. J. Oncol., 12 (1), 31-39, 2007

Key words: **acids, bladder cancer, carcinogen, occupational epidemiology, retrospective exposure assessment**

persone affette da carcinoma vescicale, mentre i controlli (n = 270) erano pazienti non appaiati affetti da tumore del cavo orale (ma di nessuna delle altre neoplasie summenzionate), o pazienti ricoverati per altre patologie. È stata usata l'analisi di regressione logistica non condizionale per il modello acidi-cancro vescicale nel controllo degli effetti del tabacco e dell'età. Sono stati presi in esame altri fattori confondenti, quali il consumo di alcool e caffè (le sole variabili dietetiche nella nostra raccolta dati), ma nessuno dei due era significativo. *Risultati*. I risultati dimostrano una relazione aggiustata statisticamente significativa tra esposizione professionale ad acidi e cancro della vescica (OR = 4,09; p < 0,028). *Discussione*. Sono discusse le implicazioni di questa nuova osservazione sull'uomo, sia nel contesto delle informazioni esistenti, che alla luce della designazione della IARC (1992) basata sugli studi dell'epoca che dimostravano un'associazione eziologica tra miscele di acidi ed insorgenza di neoplasie delle vie respiratorie superiori. *Conclusioni*. Si rendono necessari ulteriori studi per confermare le presenti osservazioni. Eur. J. Oncol., 12 (1), 31-39, 2007

Parole chiave: **acidi, cancro vescicale, cancerogeno, epidemiologia professionale, determinazione retrospettiva dell'esposizione**

Introduction

In epidemiology, descriptive and correlational studies characterize the patterns of disease by clarifying both their distribution and determinants. These analyses then can be complemented with case-control studies in communities at high risk for a particular cancer, elucidating the factors that may contribute causatively to the development of cancer. High-risk communities include those who work with certain chemicals and chemical mixtures.

Descriptive studies have shown that the incidence rates of bladder cancer continue to increase in most populations, particularly among men. According to the Encyclopaedia of Occupational Health and Safety[1], bladder cancer continues to be a disease of significant importance, noting that it accounted for about 3.5% of all malignancies in the world in 1980. Further noted is the fact that in 1985, bladder cancer was estimated to be 11th in frequency on a global scale, being the eighth most common cancer among men, with a male to female ratio of three to one. In Denmark, a high incidence country, the rates of bladder cancer are increasing by about 8.5% every five years. On the other hand, among the Chinese in Hong Kong rates continue to decline steadily, but their bladder cancer rates still remain more than twice as high compared with Chinese people in Shanghai and Singapore[1].

Bladder cancer incidence is increasing for Caucasian males in both the United Kingdom and the United States of America (USA)[2]. In the USA, the lifetime risk for a Caucasian male to develop bladder cancer is 3%. The risk for black males and Caucasian females is approximately one-half of that, and the risk for black females is one-sixth that of Caucasian males[3]. The net effect of this risk is that approximately 49,000 Americans contract bladder cancer and 9,700 die from it annually[3].

While cigarette smoking is the single most important aetiological factor in bladder cancer, accounting for some 50% of bladder cancer in western populations, occupational exposures rank second[1]. Descriptive studies provide an important aetiological clue; almost a quarter of the risk of bladder cancer for Caucasian males is attributable to occupational exposures[1,4]. This fact is not surprising when one considers that occupational exposures and bladder cancer have been inextricably linked

since the turn of the 20th Century, when it was noted that there was an association between dyestuff manufacturing and bladder cancer[5]. The notion of occupational chemicals being associated with bladder carcinogenesis also has a biological explanation: these chemicals would be metabolized to some degree by the body, possibly activating and deactivating toxic functional groups. It then is probable that many of these chemicals will be excreted in some form through the urine, and thus will be in contact with the bladder, increasing the risk of bladder cancer under a promotional mechanism. The bladder's normal resistance to such chemicals could easily be compromised by a pre-existing susceptibility, an infection, or by other more direct-acting chemicals, leading to an increased risk of bladder cell carcinogenesis[6].

Occupational risk factors for urinary bladder cancer could be identified as either specific chemicals, or a type of occupation that uses these chemicals. Known carcinogens of the urinary bladder include aromatic and aryl amines such as benzidine and beta-napthylamine[4, 7]. The biotransformation of these cancer-causing chemicals involves the breakdown of these amines by N- and O-acetyl-transferases to active carcinogenic metabolites including, among others, arylnitronium ions[8]. Suspected bladder carcinogens include acrylic fibres, photographic products, chlorine, polyethylene[9], as well as less toxic aromatic amines such as o-toluidine[4]. Meanwhile, people in the chemical[10-14], clothing manufacture[10], textile dye (especially those that use aniline dyes)[3, 9, 12, 14], aluminum smelting[3, 10, 11], rubber[3], and printing press[12] industries are all at increased risk of bladder cancer. Aircraft/ship officers[10, 14], people with high exposure to diesel and traffic fumes (especially truck drivers)[3, 9, 14], machinists[11], tailors and tar and asphalt exposure jobs[14] are other major occupations known to be at increased risk for bladder cancer.

The acid chemical group has not been identified as a risk in any human epidemiological studies of bladder cancer[15], despite the fact that, by the same principle discussed earlier for aryl amines, acid metabolites of some form could, theoretically, manifest in the urine and become carcinogenic to the bladder. Animal studies have shown that the sodium salts of organic acids such as sodium saccharin, sodium ascorbate and even sodium chloride (it has only weak effects) do promote bladder tumours in rats via a precipitate in the urine which is both cytotoxic and abrasive[16]. However, ammonium chloride completely blocks any tumour-producing effects of sodium saccharin[16]. Still, acid derivatives of these salts, such as ascorbic acid, did not promote any tumour growth, and bladder tumour formation by sodium salts has not been seen in higher animals such as mice, monkeys or man. Also, it should be noted that in excess of 85% of bladder tumours are superficial transitional cell carcinomas (TCCs)[1, 4]. These TCCs will rarely turn into bladder cancer, so as with most other tumours, bladder tumours are likely to be benign.

This study provides the first evidence for a link between occupational acid exposure and bladder cancer. In 1992, the International Agency for Research on Cancer (IARC) classified "occupational exposures to strong-inorganic-acid mists containing sulphuric acid" as a definitive human carcinogen[17] and a strong association has been shown between occupational acid exposure and upper respiratory tract (laryngeal) cancers[18, 19]. Thus, the possible association between occupational acid exposure and bladder cancer was deemed to be worth investigating as an off-shoot of a larger cancer dataset collected in the Campania Region of Italy. In our initial exploration of that dataset[20], a clear connection between bladder cancer and occupational acid exposure manifested and is explored in depth in this paper.

Patients and methods

Briefly, the dataset used in this study is a subset of a larger dataset described in detail by Jhangri *et al*[20]. The data were collected in the Campania Region (around Naples), Italy, from 1988 through 1990, with a view to testing various associations between the targeted cancers and occupational exposures to selected chemical agents and dusts, much akin to the method employed by Siemiatycki *et al*[9] in Montreal, Canada. The internal validity of the dataset has been established and is published as the first and second in this series of three papers[20, 21]. The methods have been described in full[20].

The questionnaire solicited information on major demographic factors, smoking and alcohol history, and a full occupational history. The 513 patients were classified into cases and controls as follows: the target cancers in the entire dataset were classified into five sites: bladder, lung, laryngeal, oral cavity, and naso/nasal/pharyngeal. If a person had only one of these particular cancers, he was considered a case for that particular group. If a person had more than one of the target cancers, he was discarded completely from the analysis. For this analysis, cases were people who had only urinary bladder cancer and none of the other four cancers. The controls were all the people having various other ailments or oral cavity cancers, but none the other three target cancers.

Occupational histories were analyzed, blind to case or control status, by a team of industrial hygienists according to whether a person was exposed or not to a series of twenty chemicals or dusts, or to combinations of these,

known to exist in the greater Naples region. Each participant thus had an individual array of twenty occupational agents for which exposure had occurred in any one of up to eight jobs recorded throughout their working lifetime. Duration of employment was the only exposure-related information recorded in connection with each job, not as exact dates from entry to and exit from each job, but only as the year of entry and exit. There was no information pertaining either to concentration or frequency associated with each job-related exposure. As one of the twenty exposure categories, "acids" were considered to be all types of acids to which a worker could possibly have been exposed in any particular workplace. The variable was not split into specific types of acid because of the lack of complete information solicited at interview, and because of any subsequent loss of statistical power that would arise should such a split even have been possible.

Because of established risk factors for bladder cancer, we controlled for as many of these in our analyses as possible, examining both potential for confounding and interaction. In particular, we were able to explore the potential influence of other risk factors by virtue of the other 19 chemical and/or particulate categories examined specifically through the exposure assessment component of this study. In addition, lifestyle attributes (including tobacco, alcohol and coffee consumption) were examined and controlled in our modelling. While lifetime coffee consumption was recorded at interview, we found no significant association between this variable and bladder cancer, and thus we dropped coffee from all further analyses.

The tobacco variable was handled by categorizing it into 4 different levels, namely "no/very low", "low", "moderate", and "high", thus allowing for three dummy variables in the logistic regression to fit a model for bladder cancer based on cigarette-pack-year-equivalents[20]. A cigarette-pack-year-equivalent (CPYE) for the purposes of this study is considered a pack a day for the duration of a year. Because alcohol consumption has been implicated as being a risk factor for bladder cancer in one study[22], in other studies such a connection has not been able to be made[3].

We also introduced alcohol into our model to see what, if any effect it would have on the risk of bladder cancer. The variables of wine, beer and liquor were combined to create an index of total alcohol consumption measured as alcohol-gram-year-equivalents (AGYEs)[20]. Total lifetime alcohol consumption, akin to the smoking variable, was then categorized into four levels: "no/very low", "low", "moderate", and "high".

Age and place of residence are two demographic variables that could possibly confound the bladder cancer relationship. The effect of age on bladder cancer, as with most cancers, is simple - the older a person is, the higher the risk. To control for this, age has been included as a confounder in all modelling. Stratification by place of residence (urban *vs* rural) demonstrates that the excess risk found in this study in driven by those participants having an urban residence; there were no instances of workplace acid exposure among rural bladder cancer cases in this study.

All analyses were done with the group of 75 bladder cases and the 270 eligible controls. None were matched, so unconditional logistic regression was used to fit all models with the various confounders mentioned above and to calculate the respective odds ratios (ORs). All model fitting was done employing the statistical package SPSS for Windows. All testing was done at the 5% level of significance.

Results

The demographic composition of the participants in this study is shown in Table 1. Cases tend to be older than controls; the population has a relatively low level of education; the vast majority are married; most were born and live in the target area; slightly more than half of the study population (both cases and controls) was recruited at the Cardarelli Hospital (a general hospital); most (89%) of the cases have been smokers, while three-quarters of the controls had smoked; cases and controls consumed approximately similar amounts of alcohol. All participants who were considered exposed to occupational acids originated from the greater Naples area.

There is no significant interaction between alcohol and smoking in relation to bladder cancer. From Table 2, when alcohol and tobacco are examined as independent risk factors for bladder cancer, tobacco is significant, but alcohol is not an independent predictor of bladder cancer.

In Table 3, we examine the relationship between four of the major industrial economic groupings and the development of bladder cancer. The only association detected was a protective one, of borderline significance, with the "police/military/transportation" sector. No other major economic sector revealed any association with bladder cancer. Because of the rôle of both age and tobacco consumption in the development of numerous cancers, we examined the association between all 20 exposures assessed in this study in relation to bladder cancer. Table 4 shows that, among those exposures for which sufficient numbers of people were exposed, only acid exposure achieved borderline significance as being associated with the development of bladder cancer.

Table 1 - Demographic and lifestyle data used for the bladder cancer study, Campania Region, Italy, 1988-1990

Variables	Population					
	Cases (with bladder cancer)		Controls (without any target cancer)		All (cases + controls)	
	N. = 75	%	N. = 270	%	N. = 345	%
Age (in years)						
35-44	2	2.7	34	12.6	36	10.4
45-54	9	12.0	48	17.8	57	16.5
55-64	30	40.0	99	36.7	129	37.4
65-74	34	45.3	89	33.0	123	35.7
Education[a]						
Unable to read and write	7	9.3	15	5.7	22	6.5
Elementary, any level	49	65.3	178	67.2	227	66.8
Junior high school	14	18.7	44	16.6	58	17.1
Senior high school	5	6.7	24	9.1	29	8.5
University degree	0	-	4	1.5	4	1.2
Marital status[b]						
Married	68	90.7	242	90.3	310	90.4
Separated/divorced/widower	6	8.0	16	6.0	22	6.4
Bachelor	1	1.3	10	3.7	11	3.2
Place of birth						
Urban, greater Naples	58	77.3	168	62.2	226	65.5
Urban, non-greater Naples	3	4.0	8	3.0	11	3.2
Rural	10	13.3	78	28.9	88	25.5
Non-Campania Region	4	5.3	16	5.9	20	5.8
Place of residence						
Urban, greater Naples	62	82.7	185	68.5	247	71.6
Urban, non-greater Naples	3	4.0	6	2.2	9	2.6
Rural	10	13.3	79	29.3	89	25.8
Recruitment source of patients						
Pascale Institute	47	62.7	114	42.2	161	46.7
Cardarelli Hospital	28	37.3	156	57.8	184	53.3
Tobacco consumption[c]						
No/very low (< 5 CPYEs)[d]	8	10.7	65	24.2	73	21.2
Low (5-29 CPYEs)	13	17.3	49	18.2	62	18.0
Moderate (30-59 CPYEs)	27	36.0	96	35.7	123	35.8
High (≥ 60 CPYEs)	27	36.0	59	21.9	86	25.0
Alcohol consumption[e]						
No/very low (< 600 AGYEs)[f]	17	23.3	57	21.3	74	21.8
Low (600-2,499 AGYEs)	35	47.9	127	47.6	162	47.6
Moderate (2,500-4,999 AGYEs)	12	16.4	48	18.0	60	17.6
High (≥ 5,000 AGYEs)	9	12.3	35	13.1	44	12.9

[a] 5 Missing values (controls)
[b] 2 Missing values (controls)
[c] 1 Missing value (control)
[d] Cigarette-pack-year-equivalents
[e] 5 missing values (2 cases and 3 controls)
[f] Alcohol-gram-year-equivalents

Table 2 - Odds ratios (ORs) and 95% confidence intervals (CIs) for tobacco consumption as measured by cigarette-pack-year-equivalents (CPYEs) and alcohol consumption as measured by alcohol-gram-year-equivalents (AGYEs) for bladder cancer, Campania Region, Italy, 1988-1990

Variables	Unadjusted			Adjusted for age			Adjusted for age and tobacco consumption		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Tobacco consumption									
No/very low (< 5 CPYEs)	1.00			1.00					
Low (5-29 CPYEs)	2.16	0.83-5.60	0.115	2.74	1.03-7.34	0.044			
Moderate (30-59 CPYEs)	2.29	0.98-5.34	0.057	2.32	0.98-5.46	0.055			
High (≥ 60 CPYEs)	3.72	1.57-8.82	0.003	3.22	1.34-7.71	0.009			
Alcohol consumption									
No/very low (< 600 AGYEs)	1.00			1.00			1.00		
Low (600-2,499 AGYEs)	0.92	0.48-1.78	0.814	0.84	0.43-1.64	0.838	0.72	0.36-1.43	0.348
Moderate (2,500-4,999 AGYEs)	0.84	0.36-1.93	0.678	0.66	0.28-1.55	0.658	0.55	0.23-1.32	0.181
High (≥ 5,000 AGYEs)	0.86	0.35-2.14	0.750	0.75	0.30-1.88	0.746	0.55	0.21-1.44	0.224

Table 3 - Odds ratios (ORs) and 95% confidence intervals (CIs) for industries and bladder cancer, Campania Region, Italy, 1988-1990

Industrial categories[a]	Patients		Adjusted for age and tobacco consumption		
	N. = 345	%	OR	95% CI	p-value
Professional/clerical/commerce/services	151	43.8	1.46	0.85-2.50	0.175
Police/military/transportation	75	21.7	0.50	0.25-1.02	0.056
Mining/manufacturing/building	179	51.9	1.24	0.73-2.10	0.424
Farming	95	27.5	0.61	0.33-1.14	0.119

[a] These categories are not mutually exclusive

Because no bladder cancer case outside of the urban Naples area was exposed to acids, we separated out the urban patients in our analysis. Table 5 shows that among the urban Naples' participants, a statistically significant OR of 4.09 (p = 0.028) is achieved, adjusted for both age and tobacco consumption. This demonstrates an association between workplace acid exposure and the incidence of bladder cancer. We further attempted to determine if an exposure-response relationship could be demonstrated in this dataset. When we set the cut-point for duration of exposure to acids at 10 years (i.e., less than 10 years *versus* greater than or equal to 10 years), an elevated but non-significant OR for those exposed for less than 10-years was found (OR = 3.04, p = 0.407), and a statistically significant elevated OR for the longer-term exposure was attained (OR = 4.46, p = 0.039). However, because of small numbers, the instability of this trend manifests as the duration of exposure cut-point is extended beyond 10 years. It is only at the 25-year cut-point that an exposure-response relationship is again evident with a non-significant OR = 3.56 (p = 0.158) for less than 25 years of exposure to acids, and for 25 or more years, the OR of 4.67 is of borderline significance (p = 0.078).

Discussion

Tobacco smoking has been established as the single major risk factor for urinary bladder cancer. If smoking is moderate or excessive, smoking can increase the risk of bladder cancer by a factor of 2 to 5[3]. A marked decrease in this risk is noted in the first 2-4 years after a person ceases to smoke, but the risk level never returns to that before starting to smoke tobacco (baseline)[23]. A major reason for smoking being such a large risk factor for bladder cancer is because tobacco smoke itself contains aryl amines which, as noted above, are known bladder carcinogens. Epidemiologic studies of the timing of bladder cancer indicate that these aryl amines in tobacco smoke exert a late-stage carcinogenic effect that is compatible with a two-stage theory of bladder carcinogenesis[12].

Table 4 - Odds ratios (ORs) and 95% confidence intervals (CIs) for industrial hygienist-assigned agents and bladder cancer, Campania Region, Italy, 1988-1990[a]

Exposure categories[b]	Patients		Unadjusted			Adjusted for age and tobacco consumption		
	N. = 345	%	OR	95% CI	p-value	OR	95% CI	p-value
Acids	15	4.3	2.52	0.87-7.33	0.089	2.97	0.98-9.03	0.055
Adhesive/glue	22	6.4	0.34	0.08-1.50	0.155	0.33	0.07-1.47	0.145
Aromatic amines	1	0.3						
Asbestos	16	4.6	1.20	0.38-3.87	0.746	1.08	0.32-3.58	0.902
Asbestos/lime/cement	78	22.6	0.74	0.39-1.41	0.357	0.69	0.36-1.35	0.280
Benzene	3	0.9						
Chromium	3	0.9						
Coal tar and asphalt	16	4.6	1.68	0.57-5.00	0.350	1.56	0.50-4.83	0.439
Dyes	8	2.3						
Iron dusts	33	9.6	1.17	0.50-2.71	0.714	1.22	0.51-2.92	0.661
Lead	8	2.3	0.51	0.06-4.19	0.529	0.63	0.07-5.36	0.627
Leather (include tanning)	17	4.9	0.47	0.10-2.08	0.466	0.61	0.13-2.82	0.529
Lime/cement	67	19.4	0.66	0.32-1.33	0.242	0.64	0.31-1.31	0.223
Mineral oil	44	12.8	1.42	0.69-2.91	0.343	1.55	0.73-3.29	0.253
Oil and gas	43	12.5	1.68	0.83-3.41	0.152	1.81	0.86-3.80	0.116
Pesticides	65	18.8	0.60	0.29-1.25	0.171	0.56	0.27-1.18	0.130
Rubber/plastics	11	3.2	0.79	0.17-3.76	0.772	0.82	0.17-3.99	0.804
Solvents	28	8.1	1.22	0.50-2.99	0.663	1.41	0.56-3.56	0.467
Varnishes	33	9.6	1.17	0.50-2.71	0.714	1.23	0.52-2.92	0.636
Welding fumes	9	2.6	1.83	0.45-7.51	0.400	2.33	0.51-10.54	0.273
Wood dusts	26	7.5	0.85	0.31-2.33	0.747	0.79	0.28-2.22	0.655

[a] Blank entries signify insufficient cases for OR computations
[b] These categories are not mutually exclusive

Table 5 - Odds ratios (ORs) and 95% confidence intervals (CIs) for acids and bladder cancer, Campania Region, Italy, 1988-1990

Area	Unadjusted			Adjusted for age			Adjusted for age and tobacco consumption		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Urban only	3.14	0.97-10.09	0.055	3.89	1.15-13.14	0.028	4.09	1.16-14.39	0.028
All (urban + rural)[a]	2.52	0.87-7.33	0.089	2.68	0.91-7.95	0.075	2.97	0.98-9.03	0.055

[a] No case among rural residents had any history of acid exposure; only 2 controls had a history of acid exposure. Among urban residents, six cases out of 65, and six controls out of 191 had a history of acid exposure

Women have been studied extensively in the association of occupational exposure and bladder cancer[9, 10, 14], but, in this study, only males were studied. Therefore, the effect of gender on the occupational acid-bladder cancer association could not be explored.

The low level of education may be partially explained in that the choice of public (*vs* private) hospitals could be influenced locally by socio-economic factors, including income and level of education.

As a methodological nicety, we also conducted all analyses excluding the 23 oral cavity cancers from the controls to eliminate any potential for over-matching. Only a single such patient had a record of acid exposure. Without this category of cancers, the ORs were only marginally lower, and the degree of statistical significance was also marginally reduced; any result that was statistically or borderline significant with the full set of controls (n = 270) remained so. In essence, the findings are not materially altered by the exclusion of this group of cancer patients and the conclusions remain unaffected.

As with most other diseases, bladder cancer has a host of dietary factors that either enhance or decrease the risk. Since no dietary information other than coffee consumption was solicited in this study, we were not able to control for the potential effect of any other dietary confounders in our examination of the acid-bladder

cancer relationship. Despite this, a brief overview of diet's effect on bladder cancer is both pertinent and necessary.

It has been shown that an increase in sodium intake[24] and fat intake[3, 24] increase the risk of bladder cancer, while vitamin A-containing foods (especially ones with beta carotene and other carotenoids)[3, 24, 25] and polyunsaturated fats (such as margarine) have a protective effect against bladder cancer[25]. Vitamin C is thought to possibly slow the advancement of bladder carcinogenesis once it has begun[25]. Protein intake has been seen to increase[25] and decrease[24] the risk of bladder cancer, so the association between protein and bladder cancer is inconclusive. Other commonly suspected dietary risk factors in the past were ground coffee[2] and artificial sweeteners. However, current research indicates that artificial sweeteners do increase the risk of bladder cancer, and that coffee's association with bladder cancer is quite weak, non-existent or dependent on an unknown set of factors[3]. The latter has been demonstrated in our dataset.

There are a few other possible confounders that should be taken into account in attempting to understand the association between acid exposure and bladder cancer. This study lacked the depth of data to investigate these causes, but since they are much less common than the ones mentioned above, they are not of great concern and they are mentioned here only for the sake of completeness. Some immunosuppressive drugs such as cyclophosphamide can idiophathically cause bladder cancer[6]. Also, ionizing radiation and phenacetin-containing antibiotics can iatrogenically cause bladder cancer if overused[3]. Bladder infections caused by schistosomiasis and bilharzia have been suspected in the increase of bladder cancer risk as well. While any sort of bladder infection would compromise the bladder's capability to withstand a carcinogenic attack to some degree, the infections caused by the above two diseases are ones that are commonly linked with bladder cancer. Since these two diseases are largely endemic to Africa[3], they were not known in the target populations.

The association between bladder cancer and exposure to diesel exhausts[26], to arsenic[27-29], and to drinking water and the disinfection by-products related to chlorination and other disinfection by-products[30-33] have been more recently studied, but such exposures were not assessed in this study.

Slow metabolism has been linked to bladder cancer[8]. Perhaps a similar mechanism is possible for acids. Vineis, using bladder cancer as a model, has described epidemiological models of carcinogenesis[34]. These approaches may be helpful for extending the connection with acids found in the present study.

Conclusions and recommendations

This study presents a new finding, associating workplace acid exposure with the development of bladder cancer. Biochemically, inhaled or ingested chemical products are broken down by the body into their various metabolites. The majority of these metabolites pass through the bladder in some form as the body processes and then excretes them. Proximity to and direct contact with the bladder provides the opportunity for promotional effects in bladder cells.

Our finding is rather compelling by virtue of the internal validity of the dataset, the ability to control for some of the well-established risk factors for bladder cancer (in particular, being able to control for a heavy amount of tobacco consumption in the form of smoking), relatively high and statistically significant ORs despite the relatively small case group, and the consistency of the finding across our various analyses in this sub-study. Despite this apparently compelling support for a positive association, caution is needed in generalizing this finding until both confirmatory evidence and adequate mechanistic studies can be added to extend the work initiated by our analysis.

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