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Using established occupational respiratory cancer risk factors for assessing the internal validity in an unmatched case-control study in the Campania Region of Italy, 1988-1990

L'uso dei fattori noti di rischio per i tumori respiratori professionali per accertare la validità interna in uno studio caso-controllo non appaiato nella Regione Campania 1988-1990

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Summary

***Background*. It is important to ensure the validity of softer epidemiological data such as occupational histories. Validation of the larger case-control study, on the well-established confounders of tobacco and alcohol consumption and from which the present dataset derives, has strongly supported the utility of our dataset. As a further step in validating our dataset, we examined the specificity of several workplace risk factors in relation to respiratory tract cancers. *Aim*. The purpose of the paper is to determine whether classical risk factors, as well as those of acid mists, for various respiratory tract cancers could be corroborated in our dataset. *Patients and methods*. Using unconditional logistic regression, and controlling the effects of age, tobacco and alcohol consumption, we examined the association between numerous occupational exposures and respiratory tract cancers as part of an extensive occupational cancer case-control study of 513 male hospitalized patients in the Campania Region of Italy. Our dataset for this sub-study included exposure in-**

Riassunto

***Premessa*. È importante garantire la validità di dati epidemiologici non quantitativi, quali le storie lavorative. L'elaborazione di un più ampio studio caso-controllo, basata sui noti fattori di confondimento, quali consumo di tabacco e di alcool, e da cui derivano i dati qui riferiti, ha nettamente sostenuto la validità dei presenti risultati. Un ulteriore elemento di validazione è stato costituito dall'esame di una serie di fattori di rischio professionali specifici rispetto al rischio di neoplasie dell'apparato respiratorio. *Finalità*. Scopo di questo lavoro è di verificare se le associazioni dei classici fattori di rischio e, inoltre, l'esposizione ad aerosol acidi, rispetto a diverse neoplasie del sistema respiratorio, risultino confermate dai nostri dati. *Pazienti e metodi*. Mediante regressione logistica non condizionale e controllando gli effetti dell'età e del consumo di tabacco ed alcool, abbiamo esaminato l'associazione tra numerose esposizioni professionali e la prevalenza di neoplasie del sistema respiratorio, come parte di un esteso studio caso-controllo su 513 uomini ricoverati nella Regione**

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formation on up to 20 major groups of workplace chemicals, with the target cancers of the lung (n = 111), the larynx (n = 35), and the naso/nasal/pharynx (n = 22), for a total of 168 respiratory tract cancer cases. Each of the specific respiratory tract case groupings was compared with 247 other unmatched patients without any of these cancers or oral cavity cancers, including patients having any other reason for hospitalization. *Results*. The results demonstrate statistically significant associations between established occupational exposures (asbestos/lime/cement, dyes, acids and welding fumes) and respiratory tract cancers. *Discussion*. Our findings are consistent with the literature. The finding of a statistically significant association between acid exposure and lung cancer (OR = 3.84) warrants replication through other studies; a non-significant, but elevated association between acid exposure and laryngeal cancer (OR = 2.18), consistent with the recent literature, might be because of low statistical power. *Conclusion*. Corroborative trends in established findings add credibility to the dataset for exploring more deeply the hypothesis of an acid association with bladder cancer. Eur. J. Oncol., 12 (1), 23-29, 2007

Key words: **acids, lung cancer, laryngeal cancer, nasopharyngeal cancer, respiratory tract cancers, occupational epidemiology, internal validity**

Campania. I dati di questa sezione dello studio comprendevano la storia della esposizione a fino a 20 principali gruppi di agenti chimici professionali e i dati delle neoplasie polmonari (n = 111), laringee (n = 35), nasali e naso-faringee (n = 22), per un totale di 168 neoplasie del sistema respiratorio. Ognuno degli specifici raggruppamenti di neoplasie respiratorie è stato confrontato con 247 altri pazienti non appaiati privi delle suddette neoplasie o di neoplasie del cavo orale, ma affetti da altre patologie che ne avevano richiesto il ricovero. *Risultati*. I risultati dimostrano associazioni statisticamente significative tra agenti professionali riconosciuti (asbesto/calce/cemento, pigmenti, acidi e fumi di saldatura) e neoplasie dell'apparato respiratorio. *Discussione*. Le nostre osservazioni sono in accordo con la letteratura. L'osservazione di un'associazione statisticamente significativa tra esposizione ad acidi e cancro polmonare (OR = 3,84) richiede ulteriori indagini in futuri studi. Un'associazione non significativa, ma elevata, tra esposizione ad acidi e cancro laringeo (OR = 2,18), in accordo con la recente letteratura, potrebbe essere attribuita a ridotta potenza statistica. *Conclusioni*. Le tendenze confermative di osservazioni consolidate offrono credibilità ai dati al fine di verificare più approfonditamente l'ipotesi di un'associazione tra esposizione ad acidi e cancro vescicale. Eur. J. Oncol., 12 (1), 23-29, 2007

Parole chiave: **acidi, cancro polmonare, cancro laringeo, cancro nasofaringeo, neoplasie del sistema respiratorio, epidemiologia occupazionale, validità interna**

Introduction

Occupational epidemiology studies have long demonstrated the association between workplace exposure to asbestos, lime, cement, welding fumes, dyes, and acids in the development of various cancers of the respiratory tract[1]. Of course, cigarette smoking is the single most important aetiological factor in respiratory tract cancers[1].

Because valid data are foundational to scientific discovery, we made extensive efforts to explore the internal validity of our dataset. Internal validity was examined because of the internal comparisons that were to be made.

In our first examination of the dataset for internal validity, both tobacco and alcohol consumption were included and were shown to be reliably recorded[2]. If, in addition, classical relationships between established carcinogens and the various respiratory cancer sites could be demonstrated, controlling the effects of tobacco and alcohol consumption, then the utility of our dataset for more pioneering examinations of the connection between acid exposure and other cancer development could be undertaken with greater confidence. Greater confidence would stem from corroborative findings both through the testing of established occupational risk factors, as well as in the assessment of the classical confounders of tobacco and alcohol consumption.

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[3] and a strong association has been demonstrated between occupational acid exposure and upper respiratory tract (laryngeal) cancers[4,5]. We

postulated a mechanism of a reduced pH in the pathogenesis of bladder cancer after, in our initial exploration of the dataset[2], we uncovered an increased risk of bladder cancer in relation to a history of workplace exposure to acids.

Because of the pioneering nature of our obligation to further examine the relationship between occupational acid exposure and the development of bladder cancer[6], we subjected our dataset to more rigorous examination based on established occupational exposures in relation to respiratory tract cancers.

This sub-study is a methodological assessment of internal validity. It was designed to establish corroborative evidence for the primary hypothesis of an association between acid exposure and respiratory tract cancers and, in turn, with bladder cancer[6]. The literature has thus been only selectively reviewed.

Patients and methods

Briefly, the dataset used in this study is a subset of a larger dataset described in detail by Jhangri *et al*[2]. The data were collected in the Campania Region (around the city of Naples), southern Italy, from 1988 through 1990, with a view to testing various associations between selected cancers and occupational exposures to selected chemical agents and dusts. The internal validity of the dataset was initially established, based on the testing of relationships between the classical confounders of tobacco and alcohol consumption in relation to cancer development, and is published as the first in this series of three papers[2]. The methods have been described there, in full. This paper describes an extension of this exercise by examining established occupational risk factors in relation to respiratory tract cancers.

Questionnaire-administered information was solicited on major demographic factors, smoking and alcohol histories, 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, naso/nasal/pharyngeal, and oral cavity cancers. 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 one of the target respiratory tract cancers. The controls were all the people having various other ailments, but not bladder or any of the oral cavity cancers.

Occupational histories were analyzed as described in Jhangri *et al*[2]. 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.

Because of established risk factors for respiratory tract cancers, 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 20 chemical and/or particulate categories examined specifically through the exposure assessment component of this study. In addition, lifestyle attributes (including tobacco and alcohol consumption) were examined and controlled in our modelling.

The tobacco variable was handled as described in Jhangri *et al*[2] by categorizing it into four different levels, namely "no/very low", "low", "moderate", and "high". A cigarette-pack-year-equivalent (CPYE) for the purposes of this study is considered a pack a day for the duration of a year.

We forced alcohol into our model to see what, if any, effect it would have on the risk in the specific respiratory tract cancer modelled. The variables of wine, beer and liquor were combined to create an index of total alcohol consumption measured as alcohol gram-year-equivalents (AGYE)[2]. Total lifetime alcohol consumption, akin to the smoking variable, was then categorized into four levels: "no/very low", "low", "moderate", and "high".

The effect of age on respiratory tract cancers is well established: the older a person, the higher the risk. To control for this, age has been included as a confounder in all modelling.

No matching was done in the design of this study, so unconditional logistic regression was used to fit all models with the various combinations of confounders mentioned above to calculate the respective odds ratios (ORs). All model fitting was done employing the statistical package SPSS for Windows[7]. All testing has been done at the 5% level of significance; borderline statistical significance is reported if $0.05 < p < 0.10$.

Results

Table 1 shows the characteristics of the study population in this sub-study on age, education, marital status, place of birth, place of residence, recruitment source, case-control status, and on tobacco and alcohol consumption. The respective distributions do not differ from the dataset described in our full dataset[2]. Like the full dataset, this sub-study population has a relatively low level of education; the vast majority are married; most were born and live in the target area; and slightly less than half of

Table 1 - Characteristics of the study population, Campania Region, Italy, 1988-1990

Variables	Population	
	N.	%
Age (in years)		
35-44	43	10.4
45-54	91	21.9
55-64	151	36.4
65-74	130	31.3
Education[a]		
Unable to read and write	30	7.3
Elementary, any level	277	67.7
Junior high school	62	15.2
Senior high school	31	7.6
University degree	9	2.2
Marital status[b]		
Married	365	88.6
Separated/divorced/widower	24	5.8
Bachelor	23	5.6
Place of birth		
Urban, greater Naples	268	64.6
Urban, non-greater Naples	7	1.7
Rural	120	28.9
Non-Campania Region	20	4.8
Place of residence		
Urban, greater Naples	292	70.4
Urban, non-greater Naples	6	1.4
Rural	117	28.2
Recruitment source of patients		
Pascale Institute	214	51.6
Cardarelli Hospital	201	48.4
Case-control status		
Respiratory tract cancers	168	40.5
Lung cancer	(111)	(26.8)
Laryngeal cancer	(35)	(8.4)
Naso/nasal/pharyngeal cancers	(22)	(5.3)
Controls	247	59.5
Tobacco consumption[c]		
No/very low (<5 CPYEs)[d]	76	18.4
Low (5-29 CYPEs)	63	15.2
Moderate (30-59 CYPEs)	149	36.0
High (≥ 60 CYPEs)	126	30.4
Alcohol consumption[e]		
No/very low (<600 AGYEs)[f]	71	17.3
Low (600-2,499 AGYEs)	191	46.6
Moderate (2,500-4,999 AGYEs)	87	21.2
High (≥ 5,000 AGYEs)	61	14.9
Total	415	100.0

[a] 6 missing values
[b] 3 missing values
[c] 1 missing value
[d] Cigarette-pack-year-equivalents
[e] 5 missing values
[f] Alcohol-gram-year-equivalents

the study population (both cases and controls) was recruited at the Cardarelli Hospital (a general hospital).

In Table 2, alcohol consumption, controlling both for age and tobacco consumption, is a significant predictor for laryngeal cancer, and for all respiratory tract cancers, but in the latter overall category, it is clearly driven by its strong influence on laryngeal cancer; it is of borderline significance with elevated and exposure-response risk for "naso/nasal/pharyngeal" cancer, and is not implicated in the development of lung cancer. Tobacco, on the other hand, is uniformly implicated in each of the respiratory cancer sites considered. There is no significant interaction between alcohol and smoking in relation to any of the respiratory tract cancers.

In Tables 3 and 4, ORs in the lung cancer comparisons are adjusted for age and tobacco consumption; and for age, tobacco and alcohol consumption for all the other cancers (i.e., laryngeal, naso/nasal/pharyngeal and respiratory tract cancers).

In Table 3, we examine the relationship between four of the major industrial economic groupings and the development of the various respiratory tract cancers. Three associations were found to be significant: two protective and one deleterious. Protective effects were for naso/nasal/pharyngeal cancers and for respiratory tract cancers among the "professional/clerical/commerce/services" sector. The deleterious effect was for laryngeal cancer among the "mining/manufacturing/building" sector. Patients in the "police/military/transportation" sector tended to be protected from naso/nasal/pharyngeal cancers, whereas those in the "mining/manufacturing/building" sector tend to be at increased risk for naso/nasal/pharyngeal cancers and for respiratory tract cancers, and the "farming" sectors tend to be at increased risk for naso/nasal/pharyngeal cancers, with borderline significance. The "professional/clerical/commerce/services" sector is protected from laryngeal cancer and from respiratory tract cancers, with borderline significance. While few of the point estimates attained statistical significance, their general direction tends to be consistent with the literature.

Because of the rôle of both age and tobacco consumption in the development of numerous cancers, we examined the association among all 20 exposures assessed in this study in relation to the various respiratory tract cancers. Table 4 shows that, among those exposures for which sufficient numbers of people were exposed, acid exposure achieved significance as a risk factor for lung cancer. The more classical effects of asbestos, lime and cement were significantly implicated in all respiratory tract sites. Dyes and welding fumes were significantly associated with only lung cancer development.

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 lung, laryngeal, naso/nasal/pharyngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Variables	Type of cancer							
	Lung		Laryngeal		Naso/nasal/pharyngeal		Respiratory tract	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Tobacco consumption[a]								
No/very low (<5 CPYEs)	1.00		1.00				1.00	
Low (5-29 CPYEs)	2.11	0.73-6.14	1.16	0.21-6.22	1.91	0.34-10.92	1.89	0.80-4.43
Moderate (30-59 CPYEs)	4.37**	1.84-10.41	4.22*	1.16-15.07	3.18	0.63-15.97	4.05**	2.02-8.14
High (≥ 60 CPYEs)	9.25**	3.88-21.04	5.19*	1.38-19.57	6.39*	1.18-34.54	7.51**	3.68-15.32
Alcohol consumption[b]								
No/very low (<600 AGYEs)	1.00		1.00				1.00	
Low (600-2,499 AGYEs)	1.37	0.65-2.92	3.80§	0.82-17.61	3.24	0.64-16.32	1.86§	0.96-3.59
Moderate (2,500-4,999 AGYEs)	2.11§	0.92-4.86	5.32*	1.03-27.43	4.04	0.62-26.39	2.64*	1.26-5.53
High (≥ 5,000 AGYEs)	1.90	0.77-4.69	5.80*	1.05-32.01	5.15§	0.83-32.04	2.59*	1.16-5.77

[a] ORs adjusted for age
[b] ORs adjusted for age and tobacco consumption
* $p < 0.05$, ** $p < 0.01$, § $p < 0.1$

Table 3 - Odds ratios (ORs) and 95% confidence intervals (CIs) for industries for lung, laryngeal, naso/nasal/pharyngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Industrial categories[a]	Patients		Type of cancer							
	N. = 415	%	Lung[b]		Laryngeal[c]		Naso/nasal/pharyngeal[c]		Respiratory tract[c]	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Professional/clerical/ commerce/services	161	38.8	0.70	0.42-1.15	0.46§	0.20-1.05	0.19**	0.06-0.63	0.56*	0.36-0.88
Police/military/ transportation	93	22.4	0.99	0.56-1.74	0.63	0.24-1.69	0.17§	0.02-1.34	0.81	0.48-1.36
Mining/manufacturing/ building	224	54.0	1.15	0.72-1.86	3.21**	1.35-7.62	2.43§	0.90-6.56	1.46§	0.95-2.25
Farming	118	28.4	1.08	0.64-1.84	0.90	0.38-2.17	2.24§	0.80-6.26	1.17	0.73-1.88

[a] These categories are not mutually exclusive
[b] ORs adjusted for age and tobacco consumption
[c] ORs adjusted for age, tobacco and alcohol consumption
* $p < 0.05$, ** $p < 0.01$, § $p < 0.1$

Discussion

The rôle of each variable – age, tobacco, and alcohol consumption – is replicated here, consistent with the state of knowledge about the influence of each of these in relation to the various cancer sites studied. Tobacco smoking has been established as the single most significant risk factor for respiratory tract cancers and the exposure-effect relationship is strong.

To further determine the consistency of our dataset with the published literature, we examined the rôles of asbestos, lime and cement, dyes and, finally, welding fumes as independent predictors of lung cancer. In each instance in our dataset, we found that asbestos, lime and cement (OR = 1.73, p = 0.045) as well as welding fumes (OR = 3.92, p = 0.049) are independent risk factors for lung cancer after controlling for age and tobacco consumption.

In Table 4, the significance of dyes in the development of lung cancer (OR = 3.83, p = 0.014) is also classically related. This is likely to be related, in our relatively more crude industrial hygiene assessments, to such dyes as chromate pigment and black dyes containing carbon.

We minimized bias in exposure assessment by insuring that both the industrial medicine specialist and the hygienists were unaware (i.e., "blind") of the patients' case or control status when assessing exposures[2]. The classifi-

Table 4 - Odds ratios (ORs) and 95% confidence intervals (CIs) for industrial hygienist-assigned agents for lung, laryngeal, naso/nasal/pharyngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Exposure categories[a]	Patients		Type of cancer							
	N. = 415	%	Lung[b]		Laryngeal[c]		Naso/nasal/pharyngeal[c]		Respiratory tract[c]	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Acids	24	5.8	3.84**	1.42-10.37	2.18	0.39-12.15	1.58	0.15-16.39	3.30*	1.25-8.72
Adhesive/glue	32	7.7	1.14	0.49-2.65	0.91	0.25-3.37	0.52	0.06-4.25	0.99	0.46-2.14
Aromatic amines	2	0.5								
Asbestos	27	6.5	1.57	0.61-4.01	1.56	0.39-6.12	2.52	0.58-10.88	1.72	0.74-3.98
Asbestos/lime/cement	120	28.9	1.73*	1.02-2.95	3.34**	1.54-7.23	4.54**	1.69-12.17	2.08**	1.30-3.31
Benzene	2	0.5								
Chromium	4	1.0								
Coal tar and asphalt	16	3.9	0.64	0.15-2.65	2.11	0.46-9.72	3.31	0.66-16.60	1.38	0.48-4.00
Dyes	17	4.1	3.83*	1.31-11.23	1.06	0.12-9.45			2.48§	0.87-7.02
Iron dusts	50	12.0	1.99§	0.96-4.10	1.69	0.60-4.73	1.35	0.33-5.54	1.74§	0.91-3.33
Lead	11	2.7	3.24§	0.80-13.13	2.11	0.20-22.07			2.46	0.65-9.30
Leather (include tanning)	22	5.3	0.74	0.22-2.44	1.53	0.39-6.09	0.96	0.11-8.43	0.96	0.37-2.48
Lime/cement	101	24.3	1.56	0.89-2.74	3.29**	1.49-7.26	3.66*	1.36-9.88	1.91**	1.17-3.12
Mineral oil	53	12.8	1.02	0.50-2.08	1.65	0.64-4.28	0.64	0.14-3.07	1.01	0.54-1.89
Oil and gas	50	12.0	1.06	0.52-2.17	1.22	0.42-3.52	0.40	0.05-3.28	0.90	0.47-1.73
Pesticides	86	20.7	1.23	0.69-2.20	0.93	0.35-2.49	1.45	0.47-4.46	1.20	0.72-2.03
Rubber/plastics	12	2.9	0.78	0.19-3.18	0.79	0.09-6.96			0.66	0.18-2.39
Solvents	41	9.9	1.69	0.77-3.72	2.12	0.70-6.42	0.94	0.19-4.58	1.67	0.83-3.39
Varnishes	41	9.9	0.84	0.36-1.94	1.42	0.48-4.16	1.02	0.26-3.91	1.04	0.52-2.10
Welding fumes	13	3.1	3.91*	1.03-14.95	1.63	0.16-16.48	2.03	0.19-22.10	3.33§	0.97-11.47
Wood dusts	33	8.0	1.54	0.69-3.42	0.34	0.04-2.67	0.69	0.08-5.78	1.07	0.49-2.32

[a] These categories are not mutually exclusive
[b] ORs adjusted for age and tobacco consumption
[c] ORs adjusted for age, tobacco and alcohol consumption
* $p < 0.05$, ** $p < 0.01$, § $p < 0.1$
Note: blank entries signify insufficient cases for OR computation

cation of occupational exposure by our industrial hygienist was never standardized with the work of others and this could account for the apparent slight discrepancies between what we have identified as being consistent or inconsistent with the published literature. Indeed, in a recent paper by Shangina *et al*[8] they were, by their methods of exposure assessment, unable to replicate the established link between both asbestos exposure and laryngeal cancer, and between acid exposure and laryngeal cancer. It is clear that consistency across all study populations is not always achievable.

We attempted to determine in our dataset whether any pattern of bias on the part of the industrial hygienist towards acid assignment was evident. After scrutinizing each variable, no pattern of bias in favour of acid exposure could be detected.

Conclusions and recommendations

This study presents findings corroborative of other published work associating the very same workplace exposures with the development of the respiratory tract cancer sites studied here.

Our findings in this paper support the validity demonstrated in our first paper in this series[2]. In the present paper, we have demonstrated not only effects consistent with what we know about the confounders of age, tobacco and alcohol consumption, but also with the established carcinogens of asbestos, lime and cement, dyes and welding fumes. In addition, with regard to acid exposure and laryngeal cancer, the point estimates are elevated even though they do not achieve statistical significance.

This paper strongly implicates lung cancer with workplace exposure to acids. We also note that acids are implicated, even if not statistically significantly, in each of the cancer sites examined. This is suggestive of a possible information bias that could be operating in the dataset. The question of whether any such bias may have been operating at the time of abstracting the occupational histories and/or in their coding was not able to be assessed at the time the data were gleaned. As noted above, however, every effort was made to ensure that the data abstraction and coding were done blind of any knowledge of cancer

type. Our examination of this question supports the objectivity with which the data had been coded. Indeed, this fact contributes to a greater level of confidence in our findings. Of course, any new findings that have come to the surface or that are suggested through our analyses would need to be replicated through further research in other studies.

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References

1. Boffetta P, Weiderpass E. Respiratory cancer. In Stellman JM (Ed.) Encyclopaedia of Occupational Health and Safety. Fourth Edition. Geneva: International Labour Office (ILO): 1998, 10.78-10.81.
2. Jhangri GS, Soskolne CL, Pagano G, *et al*. Alcohol and tobacco variables in the assessment of internal validity in an unmatched case-control study of occupational cancer in the Campania Region of Italy, 1988-1990. Eur J Oncol 2007; 12 (1): 15-22.
3. International Agency for Research on Cancer. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 54. Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. Lyon: IARC, 1992.
4. Soskolne CL, Zeighami EA, Hanis NM, *et al*. Laryngeal cancer and occupational exposure to sulfuric acid. Am J Epidemiol 1984; 120: 358-69.
5. Soskolne CL, Jhangri GS, Siemiatycki J, *et al*. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. Scand J Work Environ Health 1992; 18: 225-32.
6. Soskolne CL, Jhangri GS, Pagano G, *et al*. 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. Eur J Oncol 2007; 12 (1): 31-9.
7. SPSS for Windows. Release 15.0. Chicago, Il, SPSS Inc, 2006.
8. Shangina O, Brennan P, Szeszenia-Dabrowska N, *et al*. Occupational exposure and laryngeal and hypopharyngeal cancer risk in central and eastern Europe. Am J Epidemiol 2006; 164: 367-75.