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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

Le variabili alcool e tabacco nell'accertamento della validità interna in uno studio caso-controllo non appaiato sui tumori professionali nella Regione Campania, 1988-1990

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Summary

***Aim*. In order to explore whether cancer incidence in organs other than the larynx is associated with occupational exposure to strong inorganic acid mists, a study of 513 in-patients in the Campania Region of Italy was undertaken in the period 1988-1990. *Patients and methods*. All male in-patients, resident in Campania and aged 35-74 years at the time of diagnosis were eligible. Cases comprised confirmed incident diagnoses of cancers of the respiratory tract, and bladder cancer. Controls included patients with a diagnosis of other cancers, as well as non-neoplastic conditions, traumas and burns. Interviewer-administered questionnaires were used to solicit demographic information, lifestyle characteristics, and occupational histories. Retrospective exposure assessments resulted in 20 exposure-specific industrial hygienist classifications. Cigarette smoking was calculated as "cigarette-pack-year-equivalents", and alcohol consumption was calculated as "alcohol-gram-year-equivalents". Cut points were set corresponding to "high", "moderate", "low", and "very low/no" exposure on their respective frequency distributions. *Results*. Case-control comparisons rendered dose-response trends for tobacco and alcohol consumption. In addition, positive associations**

Riassunto

***Finalità*. Per valutare se l'incidenza dei tumori in organi diversi dalla laringe sia correlata all'esposizione lavorativa a miscele di acidi inorganici forti è stato avviato uno studio su 513 pazienti ricoverati in Campania nel periodo 1988-1990. *Pazienti e metodi*. Erano elegibili tutti i pazienti maschi ricoverati, residenti in Campania e di età fra 35 e 74 anni al momento della diagnosi. I casi comprendono diagnosi incidenti confermate di tumori dell'apparato respiratorio e della vescica. I controlli includevano pazienti con diagnosi di altri tumori e di condizioni non neoplastiche, traumi ed ustioni. Per favorire la raccolta di informazioni demografiche, sulle caratteristiche degli stili di vita e sulle storie lavorative sono stati usati questionari sottoposti da un intervistatore. La determinazione retrospettiva delle esposizioni ha portato, in base al parere di igienisti industriali, all'identificazione di 20 categorie espositive. Il fumo di sigarette è stato calcolato come "equivalente di pacchetti di sigarette/anno", ed il consumo di alcool come "equivalente di grammi di alcool/anno". Sono state stabilite categorie corrispondenti ad esposizioni "alte", "moderate", "basse" e "molto basse/nessuna" in base alle rispettive distribuzioni di frequenza. *Risultati*. I confronti caso-controllo**

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regarding occupational risk factors, controlled for age and tobacco consumption, also are consistent with the literature. *Conclusions*. This paper reports the underlying methods of the study and demonstrates the internal validity of our dataset. Well-established lifestyle and occupational cancer risk factors have been able to be replicated here. The specific results linking workplace acid exposure to both respiratory tract cancer and to bladder cancer, controlling for most established risk factors, are published as companion papers in the same issue of the Journal. Eur. J. Oncol., 12 (1), 15-22, 2007

Key words: **urban:rural gradient, occupational history, smoking history, alcohol consumption, dose-response trends**

hanno fornito gli andamenti dose-risposta per i consumi di tabacco ed alcool. Inoltre, anche le associazioni positive riguardanti i fattori di rischio lavorativo, correlati all'età ed al consumo di tabacco, sono concordi con la letteratura. *Conclusioni*. Questo articolo riferisce i metodi alla base dello studio e dimostra la validità interna della nostra serie di dati. Si sono potuti qui riprodurre fattori di rischio tumorali ben riconosciuti correlati allo stile di vita e all'occupazione. I risultati specifici che associano l'esposizione lavorativa ad acidi ai tumori dell'apparato respiratorio e della vescica, controllati in base ai più noti fattori di rischio, vengono pubblicati come lavori correlati in questo stesso numero della Rivista. Eur. J. Oncol., 12 (1), 15-22, 2007

Parole chiave: **gradiente urbano:rurale, storia lavorativa, abitudine al fumo, consumo di alcool, andamenti dose-risposta**

Introduction

In 1992, the International Agency for Research on Cancer (IARC) designated "occupational exposures to strong-inorganic-acid mists containing sulphuric acid" as a Group 1 (definite) human carcinogen[1]. This decision was reached in the presence of available published reports in which laryngeal cancer incidence served as the identified outcome[2, 3]. Within the framework of ongoing studies of occupational acid exposures, the hypothesis was raised that additional cancer sites could be involved, prompting us to undertake the present study, started in 1987.

Access to two in-patient facilities in Naples enabled us to conduct a hospital-based case-control study, including patients having a selection of pre-specified newly-diagnosed cancers, as well as patients with pre-specified non-neoplastic disorders, traumas and burns. The method utilized by Siemiatycki *et al*[4] was adapted to the present study; this method permits cases of cancer to be compared with other cancer cases not having underlying occupational risk factors in common according to the literature.

Patients and methods

Case and control selection criteria

Male in-patients, newly admitted in the period 1988 through 1990, to one of two facilities located in the Regional Capital of Campania, Naples - the National Cancer "Pascale" Institute and the Cardardelli Hospital - were eligible for study provided that they were 35-74 years of age, were first-time admissions to the hospital or re-admissions whose interviews took place within 12 months of the confirmatory diagnosis, and were resident in Campania. Only males were included because of the male worker predominance in the industrial workforce. A minimum of 35 years was selected as the age at which occupationally-induced cancers might begin to be evident in large enough numbers; the upper limit of 74 years was selected as the age by which occupationally-induced cancers would have first arisen. The Pascale Institute is a cancer centre to which patients from most of Southern Italy are referred; the Cardarelli Hospital is the largest general hospital in Southern Italy. Campania is one of several regions of Southern Italy; it has a population of approximately 5 million people.

Respiratory tract cancers, comprising sub-groups of lung, laryngeal, naso-pharyngeal, and nasal cavities, constituted one overall group of cases (n = 168), and bladder cancer constituted a second group of cases (n = 75). Controls included all non-cases for comparison purposes (n = 247), and for bladder cancer included oral cavity (Table 1). Benign lesions of the respiratory tract, *a priori*, were excluded from both case and control groups because of their uncertain aetiologies. Lip cancer (n = 18) was excluded both because of its peculiar aetio-pathogenetic and its anatomic features, preventing these lesions from being classifiable as either cases or controls. Three cases of mesothelioma were also dropped from the dataset owing to their small numbers for statistical purposes. Four patients having an unspecified diagnosis were excluded from both case and control groups.

Table 1 - Case and control definitions and groupings for all comparisons, Campania Region, Italy, 1988-1990

Case definition (ICD-9)	Sample size (N.)	Control definition	Sample size (N.)
Bladder cancer (188)	75	All non-cancer diagnoses, together with all other cancers (excluding all respiratory tract cancers)	270
Respiratory tract cancers (146-149, 160-162)	168	All non-cancer diagnoses, together with all other cancers (excluding bladder cancer and oral cavity cancers)	247
- Lung cancer (162)	111	All non-cancer diagnoses, together with all other cancers (excluding bladder cancer, laryngeal cancer, naso/nasal/ pharyngeal cancers and oral cavity cancers)	247
- Laryngeal cancer (161)	35	All non-cancer diagnoses, together with all other cancers (excluding bladder cancer, lung cancer, naso/nasal/ pharyngeal cancers and oral cavity cancers)	247
- Naso/nasal/pharyngeal cancers (146-149, 160)	22	All non-cancer diagnoses, together with all other cancers (excluding bladder cancer, lung cancer, laryngeal cancer and oral cavity cancers)	247
Oral cavity cancers (141, 144, 145)	23	All non-cancer diagnoses, together with all other cancers (excluding bladder cancer and respiratory tract cancers)	247

Sometimes, interviews were conducted erroneously: the age range (n = 39), the place of residence (n = 37), the time frame for the interview (n = 44), and/or the eligibility of the diagnostic category (n = 25) criteria were not met. Instead of discarding such records, those with age, residence and interview discrepancies were kept and included as cases and/or controls, as appropriate, in separate analyses. Table 1 shows both the case and control definitions and groupings for each sub-group within which comparisons were made, while Table 2 shows the distribution of cases across each of the five major categories of diagnosis and all other cancers as one group.

Each cancer diagnosis included in the study was confirmed by a single histopathologist, unaware (i.e., "blind") of the patient's occupational history. His review resulted in the exclusion of at least 19 patients from the study, owing to the fact that the revised diagnoses were not eligible for inclusion.

Each patient was asked to volunteer to a personal interview within one month of his admission to one of the two in-patient facilities. All interviews were conducted in the period January 1988 through December 1990, by one of five trained interviewers who covered all recorded aspects, including demographic, lifestyle and occupational history information.

Table 2 - Distribution of diagnostic categories, Campania Region, Italy, 1988-1990

Diagnostic categories	Cases	
	N.	%
Bladder cancer	75	14.6
Respiratory tract cancers	168	32.7
- Lung cancer	111	21.6
- Laryngeal cancer	35	6.8
- Naso/nasal/pharyngeal cancer	22	4.3
Oral cavity cancers	23	4.5
All other diagnoses	247	48.2
Total	513	100.0

Demographic information

Date and place of birth, current residence, marital status, and highest level of education obtained were recorded at interview. Age was controlled in all of the analyses reported in this paper. An urban:rural cancer risk gradient was examined in order to verify any influences associated with urban *vs* rural residence. Table 3 presents the characteristics of the study population not only according to age categories, but also according to educational level, marital status, place of birth, place of residence and the recruitment source of the patients.

Lifestyle habits

Tobacco use

Tobacco histories were recorded as a function of cigarette, pipe or cigar smoking. The daily average number of

Table 3 - Characteristics of the study population, Campania Region, Italy, 1988-1990

Demographic variables	Population	
	N.	%
Age (in years)		
35-44	48	9.4
45-54	104	20.3
55-64	190	37.0
65-74	171	33.3
Education[a]		
Unable to read and write	38	7.5
Elementary, any level	343	67.6
Junior high school	81	16.0
Senior high school	36	7.1
University degree	9	1.8
Marital status[b]		
Married	455	89.2
Separated/divorced/widower	31	6.1
Bachelor	24	4.7
Place of birth		
Urban, greater Naples	332	64.7
Urban, non-greater Naples	13	2.5
Rural	144	28.1
Non-Campania Region	24	4.7
Place of residence		
Urban, greater Naples	361	70.4
Urban, non-greater Naples	11	2.1
Rural	141	27.5
Recruitment source of patients		
Pascale Institute	274	53.4
Cardarelli Hospital	239	46.6
Total	513	100.0

[a] 6 missing values
[b] 3 missing values

Table 4 - Frequency distribution of smoking and alcohol histories, Campania Region, Italy, 1988-1990

Variables	Patients with smoking and alcohol histories	
	N.	%
Smoking histories[a]		
Never smoked	49	9.6
Current smoker	351	68.5
Ex-smoker	112	21.9
Alcohol histories[b]		
Wine		
Never drank	67	13.1
Current drinker	413	80.6
Ex-drinker	26	5.1
Only occasionally	6	1.2
Liquor		
Never drank	400	78.3
Current drinker	64	12.5
Ex-drinker	13	2.5
Only occasionally	34	6.7
Beer		
Never drank	414	81.8
Current drinker	47	9.3
Ex-drinker	8	1.6
Only occasionally	37	7.3
Total	513	100.0

[a] One person's smoking status was missing
[b] From 513, there were missing values as follows: 1 from "wine", 2 from "liquor", and 7 from "beer"

each type consumed was recorded, together with the age at which each respective type of tobacco usage was begun. In the case of ex-smokers, the number of years since quitting was recorded.

It was evident that smoking was confined almost exclusively to cigarettes. Hence, smoking histories were calculated based only on cigarette consumption, and expressed as cigarette-pack-year-equivalents (CPYEs). The age at which the person started smoking was taken into account in the analysis. The percent frequency distribution of smoking histories is shown in Table 4.

The CPYEs were categorized into four levels for each of the cancer outcomes studied. The following categories were established: "never smoked/very low-level of smoking" (< 5 CPYEs); "low-level smoking" (5 to less than 30 CPYEs); "moderate-level smoking" (30 to less than 60 CPYEs); and "high-level smoking" (60+ CPYEs). However, if a man started smoking at an age of less than 15 years (n = 169) <u>and</u> his CPYEs are greater than the median of the "low-level" or the "moderate-level" of smoking (n = 65), that person's smoking category is <u>increased</u> from "low-level" to "moderate-level" (n = 17), and from "moderate-level" to "high-level" (n = 48), respectively. For example, a man is a "moderate" level smoker if he has a history of 50 CPYEs. However, if this man started smoking at an age of less than 15 years, then his smoking level would be increased from "moderate" to "high" because his CPYEs are greater than the median in the "moderate" range of 30-60 CPYEs. Similarly, if a man quit smoking 10 or more years ago <u>and</u> he was a "low-level" smoker (n = 25), his smoking level is <u>decreased</u> to the "no/very low" category of smoking. The distribution of CPYEs is shown in Table 5.

The underlying rationale for these minor adjustments in assigning patients to the respective tobacco-consumption categories includes the biological impact probably being greater the earlier in adolescence/puberty that one begins to smoke. Conversely, the longer ago (prior to the cancer diagnosis) that one has quit, the less impact that smoking is likely to have had as a promoter on the development of cancer, and hence the long absence from

Table 5 - 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, lung, laryngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Variables	Patients		Type of cancer							
			Bladder		Lung		Larynx		Respiratory tract	
	N. = 513	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Tobacco consumption[a]										
No/very low (<5 CPYEs)	85	16.6	1.00		1.00		1.00		1.00	
Low (5-29 CPYEs)	80	15.6	2.74*	1.03-7.34	2.11	0.73-6.14	1.16	0.21-6.22	1.89	0.80-4.43
Moderate (30-59 CPYEs)	188	36.7	2.32§	0.98-5.46	4.37**	1.84-10.41	4.22*	1.16-15.07	4.05***	2.02-8.14
High (≥ 60 CPYEs)	159	31.1	3.22**	1.34-7.71	9.25***	3.88-21.04	5.19*	1.38-19.57	7.51***	3.68-15.32
Alcohol consumption[b]										
No/very low (<600 AGYEs)	90	17.8	1.00		1.00		1.00		1.00	
Low (600-2,499 AGYEs)	236	46.6	0.72	0.36-1.43	1.37	0.65-2.92	3.80§	0.82-17.61	1.86§	0.96-3.59
Moderate (2,500-4,999 AGYEs)	103	20.4	0.55	0.23-1.32	2.11§	0.92-4.86	5.32*	1.03-27.43	2.64*	1.26-5.53
High (≥ 5,000 AGYEs)	77	15.2	0.55	0.21-1.44	1.90	0.77-4.69	5.80*	1.05-32.01	2.59*	1.16-5.77

[a] ORs adjusted for age

[b] ORs adjusted for age and tobacco consumption

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, § $p < 0.1$

smoking has resulted in the slight discounting of the overall lifetime level of smoking.

Alcohol consumption

Alcohol consumption was recorded in relation to wine, beer and liquor consumption, and expressed as alcohol-gram-year-equivalents (AGYEs). The AGYEs were determined based on converting 100 grams in 1 litre of wine as containing 10% alcohol; 20 grams in a 50-ml jigger or tot of liquor as containing 40% alcohol; and 33.3 grams in 1 litre of beer as containing 3% alcohol. If patients had stopped consuming alcohol, the number of years ago that they had quit was recorded. The percent frequency distributions for each of wine, liquor, and beer drinker status are shown in Table 4. Kriebel *et al*[5] used similar alcohol equivalents in their study of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies in the United States of America where different patterns of alcohol consumption exist.

The AGYEs were categorized into four levels for each of the cancer outcomes studied. The following categories were established: "never drank/very low-level drinking" (< 600 AGYEs); "low-level drinking" (600-2,499 AGYEs); "moderate-level drinking" (2,500-4,999 AGYEs); and "high-level drinking" (≥ 5,000 AGYEs), and the distribution is shown in Table 5.

<u>Occupational history</u>

Besides recording details of each job change chronologically over a working lifetime, the major occupational sector was recorded at interview. In addition, each patient was asked to identify any of a defined list of occupational agents to which he recalled having been exposed. The latter was used by a single, trained industrial medicine specialist (Di Cintio) to ensure concordance with and completion of a full analysis of the detailed occupational history provided by each patient in arriving at a range of exposures specific to each patient.

Each patient's occupational history was then examined by a team of industrial hygienists. The hygienists classified people's exposures to 20 different occupational agents, taking into account the type of job and its duration. The exposures were assessed retrospectively on two levels:

a) the person was either "exposed" or "not exposed" to the agent in question, and
b) if the person was exposed, the assessment in subsequent analyses was made based on the duration of exposure.

Bias was minimized 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. Table 6 shows the distribution of the 513 patients across 21 occupational exposure categories.

The additional category simply is a grouping of "asbestos" with "lime/cement" owing to the fact that asbestos exposure would also likely be found in the lime/cement category.

The 21 agent-specific categories were consolidated into four broad-based industrial categories and the distribution of patients across these four categories is shown in Table 7.

Table 6 - Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for industrial hygienist-assigned agents for bladder, lung, laryngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Exposure categories[b]	Patients		Type of cancer							
	N. = 513	%	Bladder		Lung		Larynx		Respiratory tract	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Acids	31	6.0	2.97§	0.98-9.03	3.84**	1.42-10.37	1.70	0.32-9.03	2.98*	1.17-7.58
Adhesive/glue	36	7.0	0.33	0.07-1.47	1.14	0.49-2.65	1.02	0.28-3.72	1.02	0.48-2.16
Aromatic amines	2	0.4								
Asbestos	31	6.0	1.08	0.32-3.58	1.57	0.61-4.01	1.46	0.38-5.63	1.71	0.76-3.87
Asbestos/lime/cement	142	27.7	0.69	0.36-1.35	1.73*	1.02-2.95	3.47**	1.63-7.39	2.20**	1.39-3.48
Benzene	3	0.6								
Chromium	5	1.0								
Coal tar and asphalt	25	4.9	1.56	0.50-4.83	0.64	0.15-2.65	2.24	0.52-9.54	1.37	0.48-3.89
Dyes	18	3.5			3.83*	1.31-11.23	0.91	0.10-8.03	2.33	0.83-6.56
Iron dusts	59	11.5	1.22	0.51-2.92	1.99§	0.96-4.10	1.68	0.61-4.63	1.81§	0.96-3.42
Lead	14	2.7	0.63	0.07-5.36	3.24§	0.80-13.13	2.01	0.21-19.62	2.20	0.60-8.12
Leather (includes tanning)	25	4.9	0.61	0.13-2.82	0.74	0.22-2.44	1.57	0.41-6.07	0.93	0.37-2.38
Lime/cement	120	23.4	0.64	0.31-1.31	1.56	0.89-2.74	3.59**	1.65-7.81	2.08**	1.28-3.36
Mineral oil	67	13.1	1.55	0.73-3.29	1.02	0.50-2.08	1.56	0.61-3.97	1.02	0.56-1.89
Oil and gas	63	12.3	1.81	0.86-3.80	1.06	0.52-2.17	1.15	0.40-3.26	0.93	0.49-1.74
Pesticides	103	20.1	0.56	0.27-1.18	1.23	0.69-2.20	0.95	0.36-2.51	1.25	0.75-2.10
Rubber/plastics	15	2.9	0.82	0.17-3.99	0.78	0.19-3.18	0.81	0.09-6.59	0.64	0.18-2.28
Solvents	48	9.4	1.41	0.56-3.56	1.69	0.77-3.72	1.76	0.60-5.20	1.55	0.78-3.09
Varnishes	50	9.7	1.23	0.52-2.92	0.84	0.36-1.94	1.57	0.54-4.59	1.07	0.54-2.14
Welding fumes	17	3.3	2.33	0.51-10.54	3.91*	1.03-14.95	1.55	0.16-14.68	3.06§	0.91-10.30
Wood dusts	41	8.0	0.79	0.28-2.22	1.54	0.69-3.42	0.34	0.04-2.69	1.17	0.55-2.48

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

Table 7 - Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for industries hygienist for bladder, lung, laryngeal and respiratory tract cancers, Campania Region, Italy, 1988-1990

Industrial categories[b]	Patients		Type of cancer							
	N. = 513	%	Bladder		Lung		Larynx		Respiratory tract	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Professional/clerical/commerce/ services	206	40.2	1.46	0.85-2.50	0.70	0.42-1.15	0.49§	0.22-1.11	0.57*	0.37-0.89
Police/military/transportation	109	21.2	0.50§	0.25-1.02	0.99	0.56-1.74	0.64	0.25-1.66	0.80	0.48-1.32
Mining/manufacturing/building	280	54.6	1.24	0.73-2.10	1.15	0.72-1.86	3.22**	1.38-7.49	1.52#	0.998-2.33
Farming	147	28.7	0.61	0.33-1.14	1.08	0.64-1.84	0.99	0.42-2.36	1.23	0.77-1.97

[a] ORs adjusted for age and tobacco consumption
[b] These categories are not mutually exclusive
* $p < 0.05$, ** $p < 0.01$, § $p < 0.1$, # $p = 0.051$

Data quality

The entire dataset was independently verified by a person specially trained in the data coding procedures used throughout this study.

Statistical methods

SPSS 14.0 for Windows[6] was used to perform statistical analyses. A $p < 0.05$ was considered for statistical significance. Odds ratios were calculated based on unmatched contingency table analyses and/or unconditional logistic regression[6,7]. Smoking and alcohol consumption were entered into unconditional logistic regression models as three dummy variables each, adjusted for age[6,7]. Each of the occupational exposure variables was treated as a dichotomy (ever *vs* never) in the models, and results were adjusted by age and tobacco consumption.

Results

The demographic characteristics of the study population according to age, education, marital status, and place of birth categories are shown in Table 3. Of note, 70% of the patients were over 55 years of age; only 7.1% reached senior high school; and approximately 89% were currently married at the time of diagnosis. General income levels are inferred to be low from the list of job titles associated with the work histories of the patients included in this dataset.

Table 3 also shows the place of residence at the time of diagnosis (with 70% being from the greater Naples' urban region, and 28% being from rural Campania); place of birth shows 65% born in greater Naples and 28% born in rural Campania. The populations are relatively stable with approximately 89% having their current area of residence coincident with their area of birth; approximately 53% of the in-patients derived from the Pascale Institute, and 47% from the Cardarelli Hospital. In Table 2, the distribution of diagnostic categories shows that 14.6% (n = 75) are bladder cancer; 21.6% (n = 111) are lung cancer; 6.8% (n = 35) are laryngeal cancer; the balance of approximately 57% (n = 292) comprises all other diagnoses (including neoplastic and non-neoplastic disorders, traumas and burns).

Table 5 shows a consistently steep dose-response trend for smoking within each diagnostic category. With "non-smokers/very low-level smokers" having a baseline risk of 1.0, the highest risk is obtained in the "high" category of smoking, with an odds ratio of 9.25 for lung cancer. Other sites, while high, do not attain this level of risk.

In Table 5, a less discernible pattern is demonstrated for alcohol consumption (controlled for tobacco consumption), with odds ratios among the various respiratory tract cancer sub-groups attaining 3-to-5-fold elevated risks among the "high" category of drinkers as measured in AGYEs.

Table 6 presents the adjusted odds ratios (controlling both for age and tobacco consumption) for each of the major cancer sub-groups that have been compared across all of the 21 exposure categories investigated. All significant risk estimates shown in Table 6 are consistent with the literature. For example, in the incident lung cancer sub-group, exposure to dyes[8], acids[1,8], asbestos/lime/cement[8], and welding fumes[8] all show statistically significant positive associations. In our dataset, five or fewer patients were exposed to any of benzene, aromatic amines and/or chromium. Hence, effects from these exposures could not be examined.

Table 7 shows that patients in the "police/military/transportation" category tend to be protected from bladder cancer, with borderline significance (OR = 0.50, p = 0.056), "professional/clerical/commerce/services" category are protected from respiratory tract cancer (OR = 0.57, p = 0.012), while those in the "mining/manufacturing/building" category are at increased risk for laryngeal cancer (OR = 3.40, $p < 0.01$) and respiratory tract cancer (OR = 1.52, p = 0.051). While few of the point estimates attained statistical significance, their general direction tends to be consistent with the literature.

The crude odds ratios for the different cancer sites according to urban and rural residence at the time of diagnosis were examined. Urban residence was found to be a risk factor for bladder cancer with a crude odds ratio of 2.69 and 95% confidence interval (1.31 – 5.50). For all other cancers studied, the confidence intervals included unity, and hence no urban or rural risk was seen to be associated with any other cancer site.

Selected analyses were undertaken to examine whether more or less stringent definitions pertaining to the eligibility and/or the exclusion criteria would have made any impact on the results as presented. In no instance did the odds ratios differ in either magnitude or direction; indeed, the dose-response relationships shown were at all times maintained when even the full dataset (n = 614) that included cases and controls that were outside of the eligible age range, and/or were not within the time frame for the interview, and/or were not resident in the target areas, was utilized. We did not, however, combine the groups in the interests of increasing power, owing to the trade-off in a loss of specificity in the definition of the respective case and/or control groups.

Discussion

The major aim of this study was to test the hypothesis of acid exposures in relation to the development of cancers other than the larynx. The internal validity of the dataset assembled for this study appears to be confirmed. Many of the well-established lifestyle risk factors (i.e., tobacco and alcohol consumption) and the occupational cancer risk factor associations have been replicated here. Thus, this study serves to corroborate already-established risks, and also to further clarify and more precisely specify the nature of the related dose-response trends.

The tobacco and alcohol effects can be more easily interpreted in the context that consumption was as follows (see Table 5):

- 68% smoked an amount equivalent to a pack per day for at least 30 years;

– 31% smoked an amount equivalent to a pack per day for at least 60 years;
– 82% drank an amount of alcohol equivalent to one litre of wine, or to ten beers (3,000 ml), or to five jiggers or tots (50 ml) of liquor per day for at least 6 years; and
– 36% drank an amount of alcohol equivalent to that noted immediately above per day for at least 25 years.

Anecdotally, it should be noted that, during the period of observation, environmental tobacco smoke was commonplace in Campania. Furthermore, most alcohol consumption was through wine, with minimal liquor and/or beer consumption.

The findings, both from the perspective of specific agents/groupings of agents as well as the overall industrial groupings tend, in general terms, to be consistent with the literature. The consistency extends not only to the direction of the odds ratios, but also to their magnitude.

The urban:rural gradient is demonstrated in this dataset by a significant result showing that urban dwellers are at more than double the risk of bladder cancer.

Because 48 out of 513 (9.4%) diagnoses were based on less firm evidence available to the pathologist, the dataset was re-analysed excluding all 48 such people. The results were unaffected by this re-analysis.

Because 115 of 513 patients (22.4%) were recorded as having been "re-admissions", the dataset was re-analysed excluding all 115 of these patients. Re-admitted patients were recruited into the study provided that their interviews took place within 12 months of the confirmatory diagnosis. Based on a dataset containing 398 patients, the results were examined for those cancers for which cell sizes were not vanishingly small. Once again, the results were unaffected by this re-analysis.

Finally, an analysis was conducted on a further reduced dataset (n = 355) applying the most stringent of the diagnostic eligibility criteria. This, once again, resulted in findings consistent with those reported above with the fuller dataset.

Conclusions

The analyses reported here are confined to an examination of tobacco and alcohol as risk factors, as well as to exposures to 20 occupational agents. The data assembled suggest the validity of the dataset, justifying a more in-depth examination of the associations for which *a priori* testing was intended. The full analyses, testing, among others, the hypothesis of acid exposure in relation to both respiratory tract cancers as well as to bladder cancer, has been undertaken and the findings are published in this issue of the Journal[9, 10].

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