Journal of Epidemiology and Community Health, 1985, **39**, 244–250

A case control study of lung cancer in Florence, Italy. I Occupational risk factors

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SUMMARY A case control study of lung cancer in Florence, Italy was performed to investigate occupational risk factors for both men and women. The case series (n = 376) comprised all incident, histologically confirmed cases of primary lung cancer occurring in a three year period. Controls (n = 892) were patients in the same hospital of similar age, sex, date of admission, and smoking status with discharge diagnoses other than lung cancer or suicide. A detailed occupational history was collected from each subject directly. Logistic regression models were used to calculate odds ratios for specific occupations compared to all others. Among men, the lung cancer risk for bricklayers using firebrick and other refractory materials was elevated (adjusted odds ratio 6·5, 95% limits 2·1 and 20·9). Female hat makers, probably exposed to arsenic while making felt hats, had an elevated risk of lung cancer (6 cases versus 0 controls, p = 0·01). Risks in other occupations are discussed.

The industrial environment contains chemical and physical hazards which increase the workers' risk of developing various kinds of cancer; and lung cancer is perhaps the foremost among these. A study of occupational determinants of lung cancer risk was undertaken in Florence, Italy with two primary objectives: first, to study the occupations of this particular area, some of which are now either uncommon or performed very differently in the countries in which epidemiological studies have been concentrated; and, secondly, to direct cancer prevention activities of the health services with which the authors are affiliated.

The major industries of the region around Florence are the manufacture of consumer goods such as pottery, glass, and textiles. Metropolitan Florence contains about one million inhabitants engaged in diverse industries covering most major categories except the "heavy" industries such as chemicals, iron and steel, motorcars, etc. The province of Florence is a larger region including an additional 500 000 inhabitants in small towns and rural areas

A case control design was chosen for this "hypothesis generating" study. The subjects were all incident cases of lung cancer, or hospital controls, so that detailed interviews for full occupational histories could be performed with the subjects themselves. All cases were of histologically confirmed primary lung cancer which permitted analysis by histological type of tumour. Because it was clear from the outset that smoking was both a major determinant of lung cancer and also of little interest in this particular study, the design specified collecting a control series which matched the case series with respect to the distribution of smoking status ("category matching"). This method was used so that the analysis would be relatively efficient with respect to control for smoking.

Methods

CASES

All histologically confirmed cases of primary lung cancer admitted in the three year period 1981–3 to the Hospital of S Maria Nuova were potential cases. S Maria Nuova is the regional general hospital and referral centre for all lung cancers occurring in the Province of Florence. All diagnoses were confirmed by a single pathologist (MS). All cases not resident in the province of Florence were excluded.

CONTROLS

Controls were drawn from the Medical Service of the same hospital. Excluded were patients with lung cancer and attempted suicides, and persons not resident in the Province. The following procedure was used to select controls. For each case, one or two controls were identified of the same sex, age plus or minus five years, date of admission within three months, and smoking status in seven categories: non-smokers; smokers of less than 15 cigarettes per day; 15–30 cigarettes; more than 30 cigarettes; and ex-smokers in the same three levels of intensity. No cases were lost due to a failure to find a suitable control.

EXPOSURE INFORMATION

All cases and controls were interviewed within a few days of their first admission by one of three nurses employed full time in epidemiological research. Each of the nurses interviewed similar numbers of cases and controls. Although it was not possible to conceal case/control status from the interviewers, hospitalised patients in Italy are generally not told if they have cancer, and the subjects in this study were aware only that the purpose of the interview was for medical research.

A structured questionnaire was used to collect information on demographics including age, place of residence and birth, and all jobs held for more than one year. A standard ILO occupational coding system was used to classify jobs into 21 major classes and 251 subclasses.[1] Each patient was asked about chemical exposures in an open-ended format, and then a list of 16 known or suspected carcinogens was used to elicit additional exposure information.

Towards the end of the data collection period it became clear that while cases were coming from throughout the Province of Florence, controls were coming in greater proportion from the more urban metropolitan area. This arose because a few small hospitals in the more rural areas of the Province admitted noncancer patients from areas nearby, and thus these prospective controls were not available for the study. Because of residence-occupation associations which seemed likely to occur, the case and control series were restricted further to those who were resident in the metropolitan area of Florence, a sub region of the Province, in which residents would almost always go to the S Maria Nuova hospital.

DATA ANALYSIS

Controls were "category matched"[2] to cases as described above. The method of data analysis chosen, therefore, was unconditional logistic regression in which the potential confounding factors, age and smoking status in five categories (all ex-smokers were put into one group due to their small numbers), were always included in the models. Men and women were analysed separately. The anti-logarithms of the beta values for exposure variables were interpreted as measures of effect (odds ratios) conditional on all other terms in the model. Stability of the effect estimates was assessed by 95% confidence intervals for the odds ratios: exp (beta − 1·96(SE), beta + 1·96(SE)).[2] Odds ratios were not calculated for models with less than five exposed cases. Odds ratios for each occupation were calculated comparing the exposed cases and controls to all others.

Results

No cases or controls refused to be interviewed. Five hundred and ninety-two cases (547 men, 45 women) and 1036 controls (955 men, 81 women) were interviewed. After restricting both series to residents of metropolitan Florence, 376 cases (340 men, 36 women) and 892 controls (817 men, 75 women) were available for analysis. Table 1 shows that the category matching was successful in yielding case and control series nearly uniform in age and smoking distribution.

The primary discharge diagnoses of controls were as follows: other cancers, ICD (8th revision, International Classification of Disease) 140–239, exclusive of 162 (6·5%); acute and chronic cardiovascular diseases, ICD 390–458 (53·8%); accidents, ICD 800–999 (0·2%); digestive tract disease, ICD 390–458 (8·9%); respiratory tract diseases, ICD 460–519 (5·8%); ill-defined diseases, ICD 780–796 (8·3%); and other diseases (16·5%).

The histological diagnoses of cases are shown in table 2. The expected sex distribution of histological type is seen, women showing fewer squamous tumours and more adenocarcinomas. Table 3 shows the distribution of histological types by smoking status for men. Non-smokers and smokers of a smaller quantity of cigarettes are less likely to have squamous tumours than are heavy smokers and ex-smokers.

Bivariate analysis showed that there was a strong association between the region of birth and case/control status. Those who had been born in southern Italy showed much lower lung cancer risk than those born in north and central Italy. To adjust for this difference related to area of birth, we considered cases and controls from two large areas: the south, comprising essentially all of Italy south of Rome;* and the centre-north, being the remainder of the country. This is the usual division of the country

Table 1 *Number of cases and controls according to age and smoking category*

	Cases		*Controls*	
Age (yr) at admission	*n*	%	*n*	%
(a) *Men*				
Under 45	21	6·2	44	5·4
45–54	68	20·0	152	18·6
55–64	127	37·3	292	35·7
65–74	104	30·6	256	31·3
Over 74	20	5·9	73	8·9
Consumption of cigarettes/day				
Non smokers	6	1·8	19	2·3
Smokers of:				
<15	32	9·5	77	9·5
15 to 30	137	40·5	332	41·0
>30	66	19·5	135	16·7
Ex smokers	99	28·7	254	30·5
Total	340	100·0	817	100·0

	Cases		*Controls*	
Age (yr) at admission	*n*	%	*n*	%
(b) *Women*				
Under 45	1	2·3	2	2·7
45–54	8	22·2	13	17·3
55–64	14	39·0	30	40·0
65–74	12	33·3	28	37·3
Over 74	1	2·8	2	2·7
Consumption of cigarettes/day				
Non smokers	11	30·6	37	49·3
Smokers of:				
<15	7	19·4	15	20·0
15 to 30	8	22·2	16	21·3
>30	2	5·6	1	1·3
Ex smokers	8	22·2	6	8·1
Total	36	100·0	75	100·0

corresponding to strong cultural and economic differences. While 7% of cases were born in the south, 13% of controls were from this region. This effect, which is investigated in detail in another paper,[3] was accounted for in all analyses for occupational risks by including in all models a dummy variable for place of birth—south *v* centre-north.

OCCUPATIONS OF MEN

The data from work histories were analysed in two ways: the "usual job" (the one of longest tenure for each subject) and "ever-worked" jobs. The average number of jobs per subject was 1·6 for male cases and 1·5 for male controls, and for females 1·2 for both cases and controls. No subject had held more than five jobs in a lifetime. In analyses using "ever-worked" data, each subject could be counted for more than one job.

*Regions of Abruzzi-Molise, Basilicata, Calabria, Campania, Puglia, Sicily, and Sardinia

Table 2 *Distribution of cell types for all male and female lung cancer cases*

	Males		*Females*		*Total*	
Cell type	*n*	%	*n*	%	*n*	%
Squamous	247	72·7	23	63·9	270	71·8
Small cell	41	12·1	4	11·1	45	12·0
Adenocarcinoma	27	7·9	7	19·4	34	9·0
All others*	25	7·3	2	5·6	27	7·2
Total	340	100·0	36	100·0	376	100·0

*Includes large cell and primary lung cancer, not further classified.

Table 4 shows the number of male cases and controls who had ever worked in the major occupational categories, along with the respective crude and adjusted odds ratios. The adjusted odds ratios are conditional on age, smoking, and place of birth as described above. For all occupational classes with 30 or more cases, an examination of the subclasses of occupation was performed.

Four major classes had within them specific occupations with odds ratios greater than 1·0. These classes were transportation, agriculture, construction, and metal work (table 5). The occupation of taxi driving has an odds ratio marginally greater than 1·0, while the other four have 95% confidence limits including the null.

Only one major class of occupation, stone, clay, and glass, had an odds ratio different from 1·0 with 95% probability. Table 6 shows that the risk appeared to be associated with the single specific occupation of bricklaying involving refractory bricks which are used for furnaces and other high temperature operations. While the numbers were too small to test for an increase in risk with increasing years worked, the average number of years in this occupation was 8·8, with an average latency (period from first employment until hospital admission) of 31·4 years. One case had a latency of five years, and the others ranged from nine to 56 years.

An "excess risk" of lung cancer in an occupation could in fact be due to a deficit in controls in that occupation, and this is of particular concern when subjects with cardiovascular disease are used as controls because diet, physical exertion, and stress demands may cause considerable variations in cardiovascular disease rates among occupations. However this bias is unlikely to explain the particular finding among bricklayers because cardiovascular diseases were actually more frequent among stone, clay, and glass workers than in other occupations. When the control series was restricted to all non-cardiovascular diseases, the adjusted odds ratio

Table 3 *Distribution of cell types by smoking category in male lung cancer cases*

	Squamous		Small cell		Adenocarcinoma		All other		Total	
Smoking category	n	%	n	%	n	%	n	%	n	%
Non and light smoker *	24	63	5	13	4	11	5	13	38	100
Smoker	148	72	27	13	16	8	14	7	205	100
Ex-smoker	75	77	9	9	7	7	6	6	97	100
Total	247	73	41	12	27	8	25	7	340	100

*Includes non-smokers (n = 6) and smokers of less than 15 cigs/day.

Table 4 *Frequency of "ever worked" occupations in men, for the major occupational titles, and crude and adjusted odds ratios (adjusted for age, smoking, and place of birth)*

			Odds ratios		
				Adjusted	
Occupation	Cases	Controls	Crude	PE	95% CL
Administrative	44	116	0·9	0·9	0·7–1·3
Retail sales	105	259	1·0	1·0	0·7–1·3
Transportation	45	99	1·1	1·1	0·7–1·6
Agriculture	60	157	1·1	1·1	0·7–1·4
Food processing	12	48	0·6	0·6	0·3–1·1
Paper, printing	11	16	1·7	1·6	0·7–3·5
Stone, clay, glass	30	42	1·8	1·8	1·1–2·9
Chemicals	16	30	1·3	1·2	0·6–2·2
Construction	62	155	0·9	1·0	0·7–1·4
Electrical work	12	37	0·8	0·7	0·4–1·4
Utility work	9	19	1·1	1·1	0·5–2·5
Woodwork	13	47	0·6	0·6	0·3–1·1
Metal work	71	153	1·1	0·9	0·8–1·5
Textiles	18	33	1·3	1·2	0·7–2·3
Leather work	4	18	0·5	0·5	0·7–2·1
All other	22	43			
Total	534	1272			

PE = point estimate; 95% CL = 95% confidence limits.

Table 5 *Frequency of some specific occupations "ever worked" among men for which crude odds ratios are greater than 1·0, with crude and adjusted odds ratios (adjusted for age, smoking, and place of birth)*

			Odds ratios		
				Adjusted	
Occupation	Cases	Controls	Crude	PE	95% CL
Metal finishing	5	2	5·9	2·9	0·8–10·9
Structural metal work	6	6	2·4	1·8	0·6–5·4
Taxi driving	20	25	1·9	1·8	1·0–3·4
Train conductor	7	10	1·7	1·4	0·5–3·9
Welding	7	5	3·3	2·8	0·9–8·5

for this occupational category was 2·3 compared with 1·8 when all controls were used.

Data were available from the medical records of all cases concerning any previous diagnoses of pneumoconiosis. Nine cases had a prevous diagnosis of silicosis, and of these five were in the major

Table 6 *Frequency of some specific occupations "ever worked" among men in the major class, stone, clay, and glass, with crude and adjusted odds ratios (adjusted for age, smoking, and place of birth)*

			Odds ratios		
				Adjusted	
Occupation	*Cases*	*Controls*	*Crude*	*PE*	*95% CL*
Bricklaying firebrick*	11	4	6·9	6·5	2·1–20·9
Pottery	7	11			
Pottery decoration	1	3			
Cement manufacture	1	6	1·2	1·3	0·7–2·3
Stone mason	5	8			
Glass	1	5			
All other	6	6			
Total	32	43			

*In Italian: "fornaciai di mattoni, laterizi".

category of stone, clay, and glass workers. None of these, however, was in the category of bricklayers, firebrick. There were no reported cases of asbestosis.

Among the specific substances about which each subject was asked were silica, asbestos, and hydrocarbons. None of these was found to be associated with an increased risk of lung cancer. These data are unlikely to be reliable, however, because the great majority of both cases and controls reported being unaware of their exposure to any substances at all.

OCCUPATIONS OF WOMEN

A similar analysis was performed on the female cases, although the small numbers restricted the occupations that could be investigated. Also, because of the small numbers, the logistic models for occupational risks did not include the variable for place of birth. This variable appeared to be protective also in women, but the odds ratio was not significantly different from 1·0 at the 95% level. Table 7 summarises the data on the major occupational classes for women. The only occupation with more than five cases, and with an odds ratio significantly different from 1·0, was the major class of garment work (odds ratio 3·5, 95% limits 1·2–10·5). The subclasses of garment workers are shown in table 8, and it is apparent that the risk is again limited to one group—hat makers. Six cases and no controls reported this occupation (ever worked data) so the point estimate cannot be calculated. Nevertheless the difference is quite significant ($p = 0·01$). When the other types of garment workers are examined, the risk is close to 1·0. Average duration of employment as a hat maker was long—22·2 years (range 2–44)—and latency was even longer, averaging 47·8 years (range 32–59).

Histological diagnoses were available for all cases, and these were examined for possible cell type specific occupational risks. Because squamous

Table 7 *Frequency of "ever worked" occupations in women, for the major occupational titles, and crude and adjusted odds ratios (adjusted for age and smoking)*

			Odds ratios		
				Adjusted	
Occupation	*Cases*	*Controls*	*Crude*	*PE*	*95% CL*
Administrative	3	10	—*	—	
Retail sales	7	19	0·7	0·7	0·3–1·9
Agriculture	1	9	—	—	
Paper, printing	2	4	—	—	
Woodwork	1	1	—	—	
Metal work	1	3	—	—	
Garment work	9	9	2·4	3·5	1·2–10·5
Leather work	2	2	—	—	
Housewife	17	31	1·3	1·3	0·5–2·9
Total	43	88			

*Odds ratios not calculated when less than five cases.

Table 8 *Frequency of specific occupations "ever worked", among women in the major class of garment work, with crude and adjusted odds ratios (adjusted for age and smoking)*

Occupation	Cases	Controls	Odds ratios Crude	Adjusted PE	Adjusted 95% CL
Hat making	6	0			*
Seamstress	5	7	1·4	1·1	0·3–4·1
Pressing	0	1			
All others	0	1			
Total	11	9			

*p = 0·01 for Mantel-Haenszel chi-square test of crude table.

tumours formed such a high percentage of all the cancers (71·8%), it was difficult to identify cell type specific risks. The numbers of non-squamous tumours were too small to be modelled, and when the case series was restricted to squamous tumours the results were similar to those of all types combined.

Discussion

Italy is now experiencing one of the highest lung cancer death rates for men of working age in the world.[4] Tuscany, where Florence is located, is among the six regions with the highest rates in Italy.[5] While smoking may well be the major cause of this epidemic,[6] occupational risk factors deserve consideration. Florence is the third most productive metropolitan area in Italy, and many of its industries have not been well studied. This research generated hypotheses about potential occupational lung cancer risks in Florence.

The requirement of histological confirmation of all cases meant that the case series almost certainly comprised only true primary lung cancers. The preponderance of squamous tumours among men and in smokers is consistent with findings in other studies.

The control series consisted of hospitalised patients with a variety of discharge diagnoses. Cardiovascular diseases were the largest group of diagnoses, but the possibility of biases introduced through the use of such controls—for example, a "healthy worker effect"—was checked by comparing results of the full control series with those using only the noncardiovascular controls. No differences in occupational risks were observed.

The restriction of both the case and control series to subjects resident in the metropolitan area did not significantly change the similar distributions of cases and controls with respect to the confounding factors age, sex, and smoking (table 1). However, the ability to test the risks of certain more rural occupations was lost.

An unexpected finding was the strong protective effect of being born in the south of Italy. For the purpose of exploring occupational risks it was necessary to treat this effect as a confounder and to include it in all models. The independent effect of being born in the south is explored in detail in another paper.[3]

Male workers in the major class of stone, clay, and glass workers had a significantly elevated risk of lung cancer compared with workers in all other industries. This risk is due entirely to a high odds ratio for workers in the occupation of bricklaying, firebrick. Their lung cancer risk, after adjusting for age, smoking, and place of birth effects, was 6·5 times greater than for all other occupations. The latencies of these 11 cases were consistent with an environmental carcinogen with the exception of one case with a latency of only five years. Exposures were fairly short (mean 8·8 years) but not so short that they detract from the finding. Because of small numbers it was not possible to look for a dose effect of increasing exposure in this group. Potential carcinogenic exposures in this occupation are asbestos,[7] silica,[8] and fuel combustion products.[9] No industrial hygiene studies are available on the work environments of these particular workers, and subjects rarely reported exposures to any known carcinogens regardless of their occupation. Based on the distributions of latencies for the controls, it appears that this occupation continues to be practised by small but significant numbers in Florence, and an industrial hygiene study is warranted to search for potential carcinogenic exposures.

The elevated odds ratios for the five occupations shown in table 5 might be due to actual carcinogenic exposures, but because the numbers of exposed cases are small, and the odds ratios marginal, no further exploration of these groups is possible.

Nineteen out of 36 female cases, and 40 out of 71 controls had ever worked outside the home. Effect estimates could be calculated for only three main occupational classes (table 7), and one of these, garment work, showed an elevated odds ratio. Of the 11 jobs in garment work that women reported, six were in hat making. No controls reported this occupation, indicating a significant elevation in risk for this occupation. The other types of garment work seemed to confer no excess risk. Numbers of years of hat work were high, averaging 22·2 years. Latencies were even longer, the shortest latency being 32 years.

Hat making was an important industry in Italy in the first half of the century,[10] going into decline about 1960. It employed largely women and produced primarily felt hats. The long latencies are probably explained by the fact that the industry had all but died out, so that the only people with significant exposure are the few old enough to have worked in the industry during the 1940s and 1950s.

Workers in the Italian hat industry in this era were heavily exposed to mercury and other chemicals including arsenic.[11] Arsenic is a known lung carcinogen, and this might be the causal agent behind the observed excess risk. Because this is an old industry, continuing risk from hat making seems unlikely, but this should be confirmed by industrial hygiene surveys of the modern hat industry.

A full and detailed occupational history was collected from all cases and controls in person. As a result we were able to analyse the risks not only from general occupational classes but from specific jobs. In this way slightly elevated odds ratios for two major occupational classes were shown to be due to high risks in a single job within each class, thus identifying the place to search for a specific carcinogenic risk. The industrial base of Florence is diverse, and so only a few occupations have a workforce large enough to permit this detailed analysis to be made.

Nevertheless this study has identified previously unsuspected occupational risks of lung cancer which will be followed up with more detailed investigations.

We gratefully acknowledge B J Stone for assistance in data analysis, and Joseph F Fraumeni Jr and William J Blot for advice and guidance (Environmental Epidemiology Branch, National Cancer Institute, Bethesda, USA); the physicians of the Pneumonology Department of S Maria Nuova Hospital, Florence, Italy for assistance in case finding; and ICRETT (UICC) for a fellowship for EB which permitted the completion of the data analysis.

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