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Air Pollution and Lung Cancer in Trieste, Italy

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To investigate the relation between air pollution and histologic type of lung cancer, the authors conducted a case-control study among men who had died in Trieste, Italy, from 1979 to 1981 and from 1985 to 1986. Through the local autopsy registry, 755 cases of lung cancer and 755 controls were identified. Information on smoking habits, occupation, and place of residence was obtained from each subject's next of kin. Air pollution at the residence of each subject was estimated from the average value of total particulate at the nearest monitoring station. Logistic regression was used to evaluate the effect of residence and air pollution on lung cancer after adjustment for age, smoking habits, likelihood of exposure to occupational carcinogens, and social group. The risk of lung cancer increased with increasing level of air pollution for all types of lung cancer combined (p = 0.022), for small cell carcinoma (p = 0.016), and for large cell carcinoma (p = 0.049). Compared with inhabitants of the residential area, residents of the rural area had a relative risk (RR) of 0.6 (95% confidence interval (CI) 0.4-1.0). The RR was 1.5 (95% CI 1.0-2.2) for residents of the center of the city and 1.4 (95% CI 1.0-2.1) for residents of the industrial area. In the center of the city, the excess risk was almost completely restricted to small cell carcinoma (RR = 2.0) and to large cell carcinoma (RR = 2.6). In the industrial area, the risk was increased especially for adenocarcinoma (RR = 2.1). These results provide evidence that air pollution is a moderate risk factor for certain histologic types of lung cancer. *Am J Epidemiol* 1995;141:1161–9.

air pollution; case-control studies; environmental exposure; histology; lung neoplasms; urban health

The mortality and incidence rates of lung cancer are higher in urban areas than in rural areas (1–7). Although this gradient has been reduced progressively in the last 20 years, in most countries there is still a 20–50 percent excess risk in urban, compared with rural, areas (8). It has been suggested that air pollution may be a cause of lung cancer in urban populations (7) because lung carcinogens generated by car exhausts and house heating are present in urban air (9–13). However, historical differences in the diffusion of smoking habits between urban and rural populations (14) also may explain the urban/rural gradient. In addition, emissions from certain industries are known to increase the lung cancer risk of surrounding populations (15), and their effect may overshadow the effect of air pollution in certain areas due to vehicular traffic and domestic heating. Because occupational exposures to lung carcinogens have been historically more prevalent in urban than in rural populations (7, 15), the potential confounding effect of occupational factors also must be considered as an alternative explanation of the urban/rural gradient in lung cancer risk.

A number of analytical studies have been conducted to estimate the relative importance of urban air pollution in the etiology of lung cancer after adjustment for smoking and/or occupational exposures. In general, these studies have shown that subjects exposed to "high to medium" levels of air pollution have a relative risk (RR) up to 1.5 higher than subjects exposed to lower levels (15). As a consequence, between five and 10 cases per 100,000 males per year would be attributable to air pollution in urban areas (16). However, some of the excess risk of lung cancer associated with air pollution in analytical studies may be explained by residual confounding and/or interaction with cigarette smoking (17). Finally, little is known about the relation between air pollution and different histologic types of lung cancer.

To further investigate the relation between urban and industrial air pollution and certain histologic types of lung cancer, we conducted a case-control study in Trieste, Italy. Results based on the same study and pertaining to occupation have been published elsewhere (18). The following characteristics of the study setting are of special interest:

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- Trieste has had an early spread of smoking and urbanization, well reflected in high mortality from lung cancer as compared with the rest of Italy (19).
- Until 1990, Trieste was the site of the only cancer registry of the northeastern part of Italy.
- The mobility of the population is very low (i.e., about 2.5 percent of approximately 250,000 inhabitants changed residence between 1970 and 1979) (20).
- Environmental measurements have been conducted in the area since the early 1970s.

MATERIALS AND METHODS

The cases were identified at the Trieste Cancer Registry, which is accredited by the World Health Organization and functionally associated with the Department of Pathology of the local university. The registry obtains information on cancer cases and deaths primarily from biopsies (99 percent of all the biopsies performed in the province of Trieste are seen at the Department of Pathology) and from autopsies (about 73 percent of all the deaths in the province had received an autopsy in 1985). In addition, less than 1 percent of the cases classified by the registry as lung cancer are based on death certificates.

A total of 938 men who died of primary lung cancer (*International Classification of Diseases*, Ninth Revision, code 162) in the province of Trieste from 1979 to 1981 and from 1985 to 1986 and who underwent autopsy were identified through the records of the Trieste Cancer Registry. The study was performed in two different periods because of administrative problems related to the availability of personnel and funds. For 182 cases, we were unable to contact their next of kin, and for one subject the place of last residence was outside the province of Trieste. Therefore, 755 (80.6 percent) histologically confirmed cases were included in the final study group. The cases included squamous cell carcinoma (N = 267; 35 percent), small cell carcinoma (N = 218; 29 percent), large cell carcinoma (N = 90; 12 percent), adenocarcinoma (N = 158; 21 percent), and other histologic types (N = 22; 3 percent). The histopathology of the lung carcinomas was determined after each of the slides was reviewed by three pathologists and an agreement was obtained.

For each case, one male subject of similar age (±2 years) who died within the same 6-month period was randomly selected from the registry of the Department of Pathology where the autopsy records are reported. Subjects were eligible as controls if they had died of causes other than chronic lung diseases or cancer of the upper aerodigestive tract, urinary tract, pancreas, liver, and gastrointestinal system. A total of 160 subjects who were selected as controls were substituted by other eligible subjects because a next of kin could not be traced. Thus, it was necessary to identify 915 subjects so that a total of 755 controls (83 percent) would be enrolled. Controls had died of ischemic heart disease (29.9 percent), cerebrovascular disease (18.9 percent), other cardiovascular disease (16.1 percent), gastrointestinal disease (18.8 percent), respiratory disease (9.1 percent), urological disease (3.2 percent), infectious disease (2.8 percent), other malignant neoplasms (1 percent), metabolic disease (0.1 percent), and trauma (0.1 percent).

For each study subject, either his wife or child was interviewed by telephone between 1 and 3 years after his death by means of a structured questionnaire. Interviewers were not aware of the case-control status and never mentioned the cause of death of the subject. Information was collected about general demographic characteristics, smoking habit, occupational history, and place of the last residence. A complete residential history was not sought because we estimated that less than 10 percent of the study subjects had probably moved during the preceding 40 years. About 10 percent of the interviews were repeated within 6 months to evaluate the reproducibility of the data. Although no formal validation analysis was conducted, information from the original interview was considered to be of good quality.

To classify smoking habit, the average number of cigarettes smoked per day was calculated by dividing the lifetime cigarette consumption by the mean duration of smoking among the present and former smokers. For cigar or pipe smokers (n = 15), 1 g of tobacco was considered to be equivalent to one cigarette. Occupational information included job titles, industries, place of work and/or employer's name, and duration of employment for each job title. Based on a review of the IARC Monographs Programme (21), likelihood of occupational exposure to lung carcinogens was assessed by an occupational physician (M.B.) and a team of industrial hygienists who were not informed of the case-control status of the subjects. In addition, the social status of a subject was assessed based on his last job title.

Geographic analysis

The four major sources of air pollution in Trieste historically have been the traffic and house heating in the center of the city, a shipyard, an iron foundry, and an incinerator. Therefore, for each subject, the distance was calculated between his last residence and the central square of the city, the shipyard, the iron foundry, and the incinerator. Three distances were chosen for analysis: the distance between the subject's

residence and the central square (*urban distance*); the smallest of the distances between his residence and the shipyard, the iron foundry, and the incinerator (*industrial distance*); and the smaller between the urban and the industrial distances (*urban-industrial distance*). The distribution of these distances among controls was used to define the boundaries of five geographic areas (figure 1): *the center of the city* is the area defined by the lowest decile of urban distance; *industrial area* is the area defined by the lowest decile of industrial distance; the *mixed area* is the area defined by the third and fourth decile of urban-industrial distance; the *residential area* is the area defined by the fifth, sixth, seventh, eighth, and ninth decile of urban-industrial distance; the *rural area* is the area defined by the highest decile of urban-industrial distance. The industrial area was divided further in three equal-sized subareas centered on the points of emissions: the *shipyard area*, the *iron foundry area*, and the *incinerator area*.

Quantitative assessment of air pollution

From 1972 to 1977, the Department of Health of the Province of Trieste organized a network of 28 monitoring stations (i.e., deposimeters) to assess the value of the total daily deposition of particulate. This measure was used in Europe at the time as an indirect, although relatively valid, marker of air pollution (22, 23). For each deposimeter, we obtained the exact location and the average particulate deposition level recorded. Levels of particulate deposition have clear geographic patterns. The average level of particulate deposition at the 15 monitoring stations located in the residential areas was 0.210 g/m^2/day. Corresponding average values were 0.249 at the three stations of the mixed area, 0.721 at the seven stations of the industrial area, 0.329 in the only station of the center of the city, and 0.270 in the two stations of the rural area. Although the latter value is probably not representative of the rural environment because it was taken near two highways, it was used in the analysis. To link this environmental measure to our study, for each study subject we identified which of the 28 stations was closest to his residence and attributed to the subject the corresponding level of particulate deposition. For the evaluation of the relation between lung cancer and level of air pollution, subjects were categorized according to the approximate tertile of the distribution of particulate deposition among controls.

We also obtained information on current levels of carbon monoxide, nitrogen oxides, nitrogen dioxide, sulphur dioxide, and ozone, which are monitored by the Trieste Department of Health at four stations located at the central square, at the iron foundry, at the incinerator, and at one coffee roasting plant within the mixed area.

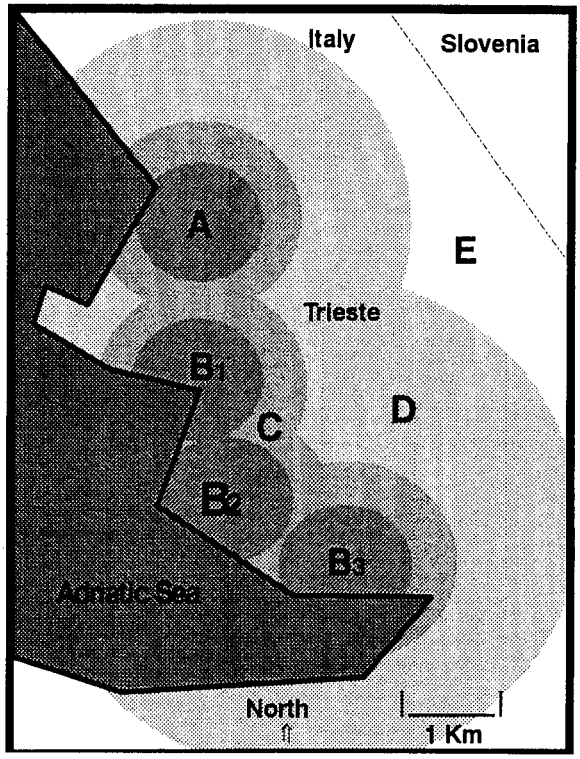

FIGURE 1. Definition of areas of residence according to distance from center of city and industrial area, Trieste, Italy. A, center of city; B_{1-3}, industrial area; B_1, shipyard area; B_2, iron foundry area; B_3, incinerator area; C, mixed area; D, residential area; E, rural area.

Data analysis

The exposure odds ratio for the geographic and environmental parameters of pollution was calculated by logistic regression as an estimator of the relative risk (24). The matching factor (age) and potentially confounding variables such as average number of cigarettes smoked per day (four levels: nonsmokers, 1–19, 20–39, ≥40 cigarettes/day), exposure to occupational carcinogens (none, possible, likely), and social group (white collar, blue collar skilled, blue collar unskilled) were evaluated in multivariate logistic regression models. A statistical trend test was performed by using equally spaced ordinal scores corresponding to increasing values of the exposure variable (i.e., level of particulate deposition) in a conditional logistic model. All p values are two tailed and 95 percent confidence intervals are used throughout the paper.

Interaction between smoking and environmental variables was evaluated in two ways. First, the relative risks for area of residence and level of particulate deposition were compared across levels of cigarette smoking and likelihood of occupational exposure to carcinogens. Second, interaction terms calculated by

multiplying the ordinal value of environmental variables by the level of smoking (or occupational exposure) were added to simpler models, and their significance was tested by the likelihood ratio statistic (24).

RESULTS

General characteristics

The mean age of the cases is 69 (range 37–93) years, which does not vary markedly by histologic type. The mean age of the controls is 70 (range 36–98) years. Table 1 displays the distribution of lung cancer cases and controls by histologic type, average number of cigarettes per day, and category of occupational exposure to carcinogens. Cigarette smoking is strongly associated with all histologic types of lung cancer, although smoking is relatively more frequent among cases of squamous carcinoma, small cell carcinoma, and large cell carcinomas than among cases of adenocarcinoma. Exposure to occupational carcinogens is associated with all types of lung cancer.

Geographic areas and historical markers of air pollution

The relative risks of lung cancer by histologic type and area of last residence are displayed in table 2. When compared with inhabitants of the residential area, residents of the rural area have a decreased risk of lung cancer for all histologic types of cancer. By contrast, the relative risk of lung cancer for residence in the center of the city is increased for all types of lung cancer, although the increases are significant only for small cell carcinoma and large cell carcinoma. The risk of lung cancer is increased among residents of the industrial area; however, results are significant for all types combined and adenocarcinoma only. When subareas within the industrial area were analyzed separately, they had different patterns of risk. Residence in the proximity of the incinerator is significantly associated with all types of lung cancer combined, with squamous carcinoma, with small cell carcinoma, and with adenocarcinoma. Because relatively few people resided in the proximity of the iron foundry, estimates for this subarea, although elevated for all types except adenocarcinoma, are particularly imprecise. The only histologic type significantly associated with residence in the proximity of the shipyard is adenocarcinoma.

The distribution of cases and controls by level of particulate deposition is displayed in table 3. The risk of lung cancer increases significantly with an increasing level of particulate deposition for all types of lung cancer combined ($p = 0.022$), for small cell carcinoma ($p = 0.016$), and for large cell carcinoma ($p = 0.049$).

TABLE 1. Relative risks of lung cancer by histologic type and distribution of potentially confounding variables: Trieste, Italy, 1979–1981 and 1985–1986

	Lung cancer														No. of controls
	Squamous			Small cell			Large cell			Adenocarcinoma			Other	All			
	N	RR*,†	95% CI*	*N*	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI		*N*	RR	95% CI	
Total	267			218			90			158			22	755			755
Average no. of cigarettes/day																	
0‡	6	1.0		6	1.0		1	1.0		7	1.0		2	22	1.0		199
1–19	75	8.5	3.6–20	61	6.4	2.7–15	28	18.9	2.5–140	53	5.0	2.2–11	8	225	6.7	4.2–11	272
20–39	107	16.3	7.0–38	92	14.0	5.9–33	33	31.2	4.2–231	61	8.3	3.7–19	9	302	12.8	7.9–21	198
≥40	79	28.6	12–69	59	23.4	9.7–57	28	65.7	8.7–493	37	12.1	5.1–28	3	206	21.3	13–36	86
Occupational exposure to carcinogens																	
No‡	86	1.0		69	1.0		32	1.0		59	1.0		9	255	1.0		351
Possible	95	1.3	0.9–2.0	92	1.6	1.1–2.5	37	1.7	0.9–3.2	51	1.2	0.7–1.9	7	282	1.4	1.1–1.9	279
Likely	86	2.7	1.7–4.1	57	2.2	1.4–3.7	21	2.3	1.1–4.6	48	2.5	1.5–4.2	6	218	2.5	1.8–3.4	125

* RR, relative risk; CI, confidence interval.
† Relative risk was estimated from a multiple logistic regression model that also included terms for age, cigarette smoking, occupational exposure to carcinogens, and area of residence.
‡ Reference category.

TABLE 2. Relative risks of lung cancer by histologic type and area of last residence: Trieste, Italy, 1979–1981 and 1985–1986

	Lung cancer																No. of controls
	Squamous			Small cell			Large cell			Adenocarcinoma			Other	All			
	N	RR*,†	95% CI*	*N*	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI		*N*	RR	95% CI	
Total	267			218			90			158			22	755			755
Area of last residence																	
Rural	15	0.6	0.3–1.1	16	0.8	0.4–1.5	4	0.7	0.2–2.0	9	0.6	0.3–1.4	0	44	0.6	0.4–1.0	73
Residential‡	100	1.0		78	1.0		27	1.0		59	1.0		12	276	1.0		304
Mixed	95	1.2	0.8–1.7	64	1.1	0.8–1.7	34	1.8	1.0–3.2	46	1.0	0.7–1.6	8	247	1.2	0.9–1.5	226
Industrial	29	1.2	0.7–2.1	26	1.4	0.8–2.5	10	1.6	0.7–3.7	28	2.1	1.2–3.6	1	94	1.4	1.0–2.1	76
Shipyard	12	0.7	0.3–1.4	9	0.7	0.3–1.6	5	1.2	0.4–3.3	18	1.9	1.0–3.6	1	45	1.0	0.6–1.6	47
Iron foundry	7	2.3	0.8–6.9	5	2.4	0.7–7.9	3	3.4	0.8–15	1	0.6	0.1–4.8	0	16	1.7	0.7–4.1	12
Incinerator	10	2.4	1.0–5.9	12	3.3	0.5–11	2	2.3	0.5–11	9	3.7	1.4–9.2	0	33	2.6	1.3–5.1	17
Center of the city	28	1.2	0.7–2.1	34	2.0	1.2–3.4	15	2.6	1.2–5.3	16	1.1	0.6–2.2	1	94	1.5	1.0–2.2	76

* RR, relative risk; CI, confidence interval.

† Relative risk was estimated from a multiple logistic regression model that also included terms for age, four levels of cigarette smoking, three levels of exposure to occupational carcinogens, and three social levels.

‡ Reference category.

TABLE 3. Relative risks of lung cancer by histologic type and level of particulate deposition: Trieste, Italy, 1979–1981 and 1985–1986

Level of particulate deposition (g/m²/day)	Lung cancer															No. of controls
	Squamous			Small cell			Large cell			Adenocarcinoma			All			
	N	RR*,†	95% CI*	*N*	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI	
<0.175‡	67	1.0		48	1.0		22	1.0		43	1.0		188	1.0		219
0.176–0.298	103	1.3	0.9–1.9	74	1.2	0.8–1.9	25	1.0	0.5–1.8	48	0.9	0.6–1.4	256	1.1	0.8–1.5	274
>0.298	97	1.2	0.8–1.7	96	1.7	1.1–2.5	43	1.7	0.9–3.0	67	1.3	0.8–2.0	311	1.4	1.1–1.8	262
χ^2 for trend		0.58			5.80			3.87			1.75			5.29		
p		0.44			0.016			0.049			0.186			0.022		

* RR, relative risk; CI, confidence interval.

† Relative risk was estimated from a multiple logistic regression model that also included terms for age, four levels of cigarette smoking, three levels of exposure to occupational carcinogens, and three social levels.

‡ Reference category.

Interaction

The distribution of cases and controls according to geographic area and level of pollution was stratified by level of cigarette smoking (table 4). Among nonsmokers, the relative risk of lung cancer is increased for all areas of residence when compared with the residential area and for high level of pollution compared with low level. Among smokers the relative risk for residence in the center of the city and the industrial area, as well as for high level of air pollution, is not clearly modified by level of cigarette smoking.

Subjects who were never exposed to occupational carcinogens had a moderate excess risk of lung cancer if they were residents in the center of the city, in the industrial area, or in an area with high particulate deposition (data not shown). Such an excess increased slightly with increasing likelihood of occupational exposure to carcinogens. In any case, logistic regression models that included terms for interaction were not statistically significantly different from simpler models (data not shown).

Current levels of air pollution

The highest concentrations of carbon monoxide, nitrogen oxides, and nitrogen dioxide have been found at the central square in the center of the city, with mean monthly values of 3.6 mg/m^3, 218 μg/m^3, and 65 μg/m^3, respectively. The highest mean levels of ozone have been measured within proximity of the incinerator (39.0 μg/m^3), and the highest levels of sulphur dioxide (SO_2) have been found at the iron foundry (30.9 μg/m^3). The station located in the mixed area has had the lowest levels of carbon monoxide and ozone and intermediate levels of nitrogen oxides, nitrogen dioxide, and sulphur dioxide. No stations are currently located in the residential or rural areas. However, occasional monitoring campaigns display minimal levels of carbon monoxide, nitrogen dioxide, and sulphur dioxide in the rural area.

DISCUSSION

All histologic types combined

The study findings support the hypothesis that air pollution is a risk factor for lung cancer in Trieste. In fact, environmental and geographic analyses consistently estimate a 40–50 percent excess risk for a high level of pollution and for the center of the city and the industrial area. Subareas within the industrial areas show different patterns of lung cancer risk: no excess for the area surrounding the shipyard, moderate nonstatistically significantly elevated risk for the iron foundry area, and significantly elevated risk for the

TABLE 4. Relative risks of lung cancer by selected areas of residence, level of air pollution, and level of cigarette smoking: Trieste, Italy, 1979–1981 and 1985–1986

	Average no. of cigarettes/day															
	0				1–19			20–39				≥40				
	Cases	Controls	RR*,†	95% CI*	Cases	Controls	RR	95% CI	Cases	Controls	RR	95% CI	Cases	Controls	RR	95% CI
Area of residence‡																
Industrial	3	21	1.4	0.3–8.9	27	32	0.9	0.5–1.6	43	15	2.3	1.2–4.5	21	8	1.3	0.5–3.2
Center of the city	5	21	2.4	0.6–9.6	24	27	1.1	0.6–2.1	41	21	1.6	0.9–3.0	24	7	1.8	0.7–4.7
Level of particulate deposition (g/m²/day)§																
0.176–0.298	8	74	3.0	0.7–12	81	97	1.0	0.6–1.6	106	75	1.2	0.7–1.6	61	28	1.0	0.5–1.9
>0.298	11	62	3.7	1.0–15	85	103	1.0	0.7–1.6	127	66	1.7	1.1–2.8	88	31	1.3	0.7–2.4

* RR, relative risk; CI, confidence interval.
† Relative risk was estimated from a multiple logistic regression model that also included terms for age, occupational exposure to carcinogens, and social class.
‡ The residential area is the reference category.
§ A level of particulate deposition <0.175 is the reference category.

area surrounding the incinerator. By contrast, the rural area that surrounds the city of Trieste has a 40 percent significantly decreased risk of lung cancer.

The epidemiologic evidence on air pollution and lung cancer was reviewed in 1990 (15). More recently, two additional studies (32, 44) have been published. In brief, a total of eight cohort studies (25–32) and 12 case-control studies (33–44) have been published based on data from nine different countries. Seven cohort studies compared urban with rural populations (25–31), and one recent cohort study employed semiquantitative levels of air pollution (32). Some case-control studies used geographic data (33–38), and some qualitative or semiquantitative levels of air pollution, as exposure variables (39–44). When results were adjusted for smoking, the relative risk for men ranged from 1.0 to 1.6 in the European and American studies (25–40, 42, 44); the relative risk was 1.8 in the Japanese study (41) and 2.5 in the Chinese study (43). In general, cohort studies did not show interaction between air pollution and smoking, whereas the magnitude of interaction varied in case-control studies.

Histologic types of lung cancer

Urban air pollution appears to play a specific role in the etiology of small cell and large cell carcinoma. In Trieste, urban air pollution had been characterized in the past by high particulate deposition and currently by high levels of carbon monoxide, nitrogen oxides, and ozone, and intermediate levels of sulphur dioxide. Air pollution in the center of the city has been higher than in other areas for many decades. Initially, the pollution was probably due to fossil fuels combustion associated with house heating, whereas during the last 20 years, transportation has been the prevailing source of pollution.

The effects of industrial air pollution may vary according to histologic type of lung cancer and industrial process. The industrial area has had many waves of air pollution associated with different industrial developments: circulation of asbestos fibers from the shipyard from the 1940s to the 1970s; particulate and sulphur oxides pollution from the iron foundry during the 1960s, 1970s and 1980s; general air pollution from the incinerator from the early 1970s to the present. As a consequence, it is plausible that the shipyard and associated asbestos exposure may have entailed an environmental risk of adenocarcinoma, and the incinerator area carried a strong, albeit geographically isolated, risk of all histologic types.

The literature on histologic type of lung cancer and air pollution is very sparse. Wu-Williams et al. (45) found that the positive association between the level of indoor smoke generated by heating and cooking practices and lung cancer in China was similar for squamous/oat cell cancers and adenocarcinoma among women. In another study conducted in China, Xu et al. (43) found that the association with indoor air pollution was stronger with squamous and small cell carcinoma than for adenocarcinoma, whereas excess risks associated with outdoor air pollution were seen for squamous and oat cancer and adenocarcinoma. An assessment of lung cancer risk factors by histologic category by Lubin and Blot (46) shows that in general, both cigarette smoking and occupational exposure have stronger associations with squamous and small cell cancers than with adenocarcinoma. However, occupational exposure to asbestos appears to be more strongly associated with adenocarcinoma than with other types of lung cancer (47). This is supported by the present finding of a significant excess of adenocarcinoma in the proximity of the shipyard.

Additional considerations

A number of methodological issues must be addressed. Selection bias was unlikely in this study. Conditions for the presence of selection bias would have been a differential inclusion of deceased subjects in autopsy lists according to cause of death (i.e., lung cancer vs. other causes) and area of residence. This is unlikely for a number of reasons. First, autopsies are conducted on practically all subjects who die in the local hospitals, independent of the clinical cause of death; and no authorization is required from relatives of the deceased persons. Second, admissions to the local hospitals are centralized and do not depend on the subjects' area of residence. Third, there is no reason to believe that the cases of lung cancer who live in the center of the city or in the industrial area tend to die in the hospital more frequently than subjects from other areas and differentially from the controls.

The use of deceased (prevalent) cases has been discussed as a possible source of bias. In fact, prevalence case-control studies tend to identify factors related to improved survival as risk factors for being sick (48). In this study, both cases and controls are deceased. Bias could occur if the area of residence is a factor that relates to improved survival for lung cancer but not for other causes of death. In Trieste, the level of health care is very homogeneous and does not depend on the area of residence. In addition, analyses were adjusted for social group to eliminate potential confounding related to socioeconomic status.

Results cannot be explained by a subjective definition of geographic areas. In fact, areas were defined based on the distribution of controls. Instead, the relative risk for the center of the city and the industrial area would have been higher if the rural area had been

included in the reference category. In addition, any misclassification of residence due to the use of an incomplete residential history has caused, if anything, an underestimation of the relative risk. Environmental estimates confirm that the center of the city and the industrial area had higher levels of pollution than other areas and that pollution is positively associated with lung cancer. We are aware that the levels of particulate deposition used in the rural area were probably largely overestimated. This is confirmed by current very low levels of air pollution. This misclassification in the rural area probably caused an underestimation of the relative risk in the high and intermediate categories of the distribution of particulate deposition. In general, any possible random misclassification of exposure due to an incomplete environmental assessment diluted the association between air pollution and lung cancer.

Confounding was addressed in the analysis by including terms for age, average number of cigarettes, occupational exposure to carcinogens, and social group. Inclusion of other terms such as age when an individual began to smoke did not modify the estimates. Residual confounding by other factors associated both with the disease and with residence in polluted areas cannot be ruled out. For example, we did not collect information about chronic pulmonary diseases such as tuberculosis, which used to be prevalent in the area. With regard to potential confounding by residential radon exposure, a known moderate risk factor for lung cancer, a recent assessment of radon levels in the province of Trieste showed that the average radon concentration was highest in the rural area (121–142 Bq/m^3), lowest in the center of the city (35 Bq/m^3), and relatively low in the other areas described in our paper (42 Bq/m^3). Therefore, confounding by radon exposure cannot explain our results. Finally, our analyses do not allow firm conclusions on the magnitude of interaction between markers of air pollution, cigarette smoking, and occupational exposure.

In conclusion, our study provides further evidence that air pollution is a moderate risk factor for lung cancer. This risk varies according to histologic type and to category of air pollution. Future studies on air pollution and lung cancer should focus on the relations between specific air pollution components and lung cancer histology.

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