Lung Cancer and Occupational Risk Factors in Greece

Christos Chatzis, MD, MIH, PhD
Georgia Danaka, MD
Athena Linos, MD, MPH, PhD
Stephen N. Kales, MD, MPH
David C. Christiani, MD, MPH, MS

This study estimated the proportion of lung cancer in Greece that was attributable to occupational exposure. Two hundred eighty-two patients with lung cancer and 494 controls were interviewed about their socioeconomic characteristics, sex, age, and occupational, smoking, and residential histories. Each subject was classified as exposed or unexposed to known occupational lung carcinogens. Because of the small number of females exposed, only males were included in the multivariate analyses. When the occupationally exposed subjects were compared with the unexposed subjects and an adjustment for smoking was made, the relative risk for lung cancer was 2.9 (95% confidence interval, 1.95–4.31). If 5% to 10% of the Greek population were occupationally exposed, the attributable risk would be 9.9% to 16.6%, respectively. Occupational exposures conferred an additional risk that was approximately threefold that of smoking alone. Risks increased in a dose-response fashion with increasing cigarette consumption.

Smoking is the strongest factor causally associated with the development of lung cancer[1–3]; however, other factors with independent, additive, and/or synergistic actions have also been implicated. Occupational exposure to carcinogens and carcinogenic processes is significant among these causative factors.[4] The detection of occupational and other causes of lung cancer makes preventive efforts more effective.

Estimates of the proportion of lung cancer attributed to occupational exposures range between 1% and 40%.[4] Such differences may be attributed to many factors, such as variation among populations in the proportion of persons exposed to occupational carcinogens, different criteria used in the definitions of both carcinogens and "exposure," and in the methodology and interpretation of the epidemiologic data.[5]

In the case-control study presented here, we estimated the relative and attributable risks of lung cancer in Greece that were caused by occupational exposures. This enabled us to estimate the fraction of lung cancer cases that was theoretically preventable by the limitation of exposure to known occupational carcinogenic factors. We also analyzed the interaction between occupational exposure and cigarette smoking.

Materials and Methods

This case-control study included 776 persons sampled from three university hospitals in Athens during 1987–1988. The cases were nonconsecutive patients with newly diagnosed primary lung cancer. One au-

From the Department of Hygiene and Epidemiology, Athens Medical School, Athens, Greece (Dr Chatzis, Dr Danaka, Dr Linos); the Department of Environmental Health (Occupational Health Program), Harvard School of Public Health, Boston, Mass. (Dr Kales, Dr Christiani); The Cambridge Hospital, Cambridge, Mass., and Harvard Medical School, Boston, Mass. (Dr Kales); the Pulmonary/Critical Care Unit, Massachusetts General Hospital/Harvard Medical School, Boston, Mass., and the Center for Occupational and Environmental Medicine, Massachusetts Respiratory Hospital, Braintree, Mass. (Dr Christiani)

Address correspondence to: Christos Chatzis, MD, MIH, PhD, Department of Hygiene and Epidemiology, Athens Medical School, M. Asias 75 (Goudi) 11-527, Athens, Greece.

TABLE 1
Distribution of Cases of Lung Cancer and Controls (Males and Females), by Age and Sex

Age	Cases [n (%)] Males	Cases [n (%)] Females	Controls [n (%)] Males	Controls [n (%)] Females	Total [n (%)]
0–49	33 (12 8)	2 (8.0)	83 (18.1)	3 (17.6)	121 (15.6)
50–59	61 (23.7)	7 (28.0)	112 (24.5)	8 (22.2)	188 (24.2)
60–69	100 (38 9)	7 (28.0)	161 (35.2)	16 (43 1)	284 (36.6)
70 -	63 (24.5)	9 (36 0)	101 (22.1)	10 (25.9)	183 (23 6)
Total	257 (33 1)	25 (3.2)	457 (58.9)	37 (4.8)	776 (100.0)

thor (C.C.) regularly visited the three hospitals, and all new cases that were present at the time of these visits were referred to him. During the study period, 282 patients with histologically verified lung cancers of all stages were recruited. The controls were two groups of persons (n = 494) selected from the same hospitals. The first group consisted of 230 visitors to the hospital. This provided a group of controls from the general population. The second group consisted of 264 patients, half of whom were hospitalized for fractures and the other half for minor eye problems. These groups were selected as hospital-based controls because neither trauma nor ophthalmologic conditions were expected to be related to exposure. The hospitals accept patients (including those requiring emergency treatment) from the greater Athens metropolitan area and are among the referral centers for most of central and southern Greece. Therefore, the pool from which both groups of controls were obtained was presumed to be comparable to that of the lung cancer cases.

The controls were matched to the cases by sex and age. Table 1 lists the distribution of cases and controls by age and sex. Men comprised 90.43% of the cases and 92.5% of the controls. The cases and the controls were briefly informed about the purposes of the investigation. In Greece it is not mandatory for doctors to inform patients that their disease is malignant. All patients are informed about their illnesses in accordance with the degree of information and detail that they seek. Therefore, the study can be considered "blind" with regard to many patients' knowledge of the malignant nature of their diagnoses. This fact should make recall bias less likely.

The cases and the controls were interviewed at the hospital, using an extensive closed-ended interview based on the American Thoracic Society questionnaire.[6] Specific questions included age, socioeconomic status (indicated by educational level), occupational and residential history, marital status, and smoking and dietary habits. Smoking habits were stratified by cigarette-years, where cigarette-years = (cigarettes/day) × (years of smoking).

A detailed report of each patient's occupational history was obtained via three series of questions. First, subjects were asked to report all current and all past occupational activities they had ever engaged in. The next phase of the interview gathered more information on each specific occupational activity they had ever practiced during their lives. This additional information included the duties and description of each job, the duration of each job, and the identification of each company where they had worked (company's name and employer's name and address). The third group of questions focused specifically on occupational activities that have been implicated in the etiology of lung cancer by the International Agency for Research on Cancer (IARC). These occupations are listed in Tables 2 and 3.[7] This phase of the interview determined how many of these activities each subject had ever been involved in.

TABLE 2
Occupations Implicated by the International Agency for Research on Cancer (IARC) in the Etiology of Lung Cancer (1982)—Group 1: Sufficient Evidence of Human Carcinogenesis

Auramine manufacture
Boot and shoe manufacture and repair (certain exposures)
Coal gasification (older processes)
Coke production (certain processes)
Furniture manufacture (wood dusts)
Isopropanol manufacture (strong acid process)
Nickel refining
Rubber industry (certain occupations)
Underground hematite mining (with radon exposure)

Questionnaire data were computerized and analyzed with univariate analytical methods using the chi-square test and also with multivariate logistic regression models to control for possible confounding factors, such as smoking and socioeconomic status, and to estimate the relative risk for lung cancer that was associated with occupational exposure to carcinogens.

The proportion of lung cancers attributable to occupational exposure to lung carcinogens was calculated using the following mathematical expression:

$$\text{Attributable Risk \%} = \frac{\Pr(RR - 1)}{\Pr(RR - 1) + 1} \times 100\%$$

where RR is the relative risk for lung cancer for occupational exposure and

TABLE 3
Other Occupational Exposures

Exposure Category (present study)	Potentially Related Process(es) or Chemical(s) (rated by the IARC, 1982)	Summary Evaluation* (by the IARC, 1982)
Asbestos	Asbestos	1
Construction and building	Asbestos	1
	Wood dusts	1
Textile industry	Benzidine	1
Petroleum and oil products	Shale oils	1
	Mineral oils	1
	Soots (polycyclic aromatic hydrocarbons)	1
Colouring agents and dyes	Benzidine	1
Metal casting furnaces	Coke, coal tars, soots	1
Carpenters	Carpentry and joinery	3
	Wood dusts	1

* IARC rating: 1, sufficient evidence of carcinogenicity to humans; 3, not classifiable.

Pr is the prevalence of the investigated exposure in the population.

Results

Participation rates for the eligible cases and controls both exceeded 98%. For both cases and controls, men accounted for over 96% of those exposed to one or more of the occupations implicated in the etiology of lung cancer by the IARC. The number of women exposed among both cases and controls was very small: three and one, respectively. To determine whether there was a difference in exposure to the implicated occupational activities between control patients and control visitors, their prevalences of exposure were calculated. These rates were quite similar: 12.9% for control patients and 12.6% for control visitors. Therefore, these two groups were combined in subsequent analyses to increase the power of the study.

Tables 4 and 5 list the distribution of cases and controls by exposure to one or more of the occupations implicated by the IARC in the etiology of lung cancer. The overall relative risk of developing lung cancer was significantly increased (3.0; 95% confidence interval [CI], 2.01–4.33) for those exposed. Because of the limited number of women in the sample exposed to occupations implicated in the etiology of lung cancer, only men (n = 714) were included in Table 5. Again, the overall relative risk of lung cancer when smoking was controlled for was statistically significant (2.9; 95% CI, 1.95–4.31). The occupations and exposures identified in our sample included the following: materials containing asbestos, metal casting furnaces, coloring agents and dyes, petroleum and oil products, the textile industry, carpenters, tanning processes, and building and construction. The relative risk of developing lung cancer was increased for each of these individual occupational exposures; however, it was only statistically significantly for exposure to asbestos (2.7; 95% CI, 1.54–4.65) and building and construction (2.8; 95% CI, 1.66–4.66).

Table 6 lists male and female cases and controls by the number of cigarettes smoked daily. As expected, the relative risk increased with the number of cigarettes smoked per day. The relative risk of lung cancer for all cases and controls who smoked was increased (3.3; 95% CI, 2.07–5.29). It must be noted that a large number of both cases and controls were heavy smokers, as are most Greek men. The fact that 40% of the cases smoked over 70 cigarettes per day, however, is exceptional. This extent of smoking was not found in the controls. A large proportion of the controls did not smoke at all or smoked much less.

The interaction between smoking and working in occupations implicated in the etiology of lung cancer is presented in Fig. 1. In this analysis, smoking habits were stratified by cigarette-years, where cigarette-years = cigarettes/day × years of smoking. Because of the limited number of women in the sample exposed to occupations implicated in the etiology of lung cancer, only men were included in this analysis. Except for nonsmokers (only 4%, or 9 of 256, of the male cases were never-smokers), occupational exposure to a carcinogen or carcinogenic process conferred a risk that was approximately threefold that of smoking, and this risk increased in a dose-dependent fashion with smoking habit. The relative risks and 95% CIs for smoking without occupational exposure were as follows: <900 cigarette-years, 3.9 (95% CI, 1.8–8.4); 900 to 1480 cigarette-years, 4.8 (95% CI, 2.2–10.2); and >1480 cigarette-years, 8.0 (95% CI, 3.8–16.9). For smoking with occupational exposure, the relative risks and 95% CIs were as follows: <900 cigarette years, 13.5 (95% CI, 5.4–33.8); 900-

TABLE 4
Distribution of Cases and Controls (Males and Females), by Exposure to One or More Occupations Implicated in the Etiology of Lung Cancer*

Implicated Occupations	Cases [n (%)]	Controls [n (%)]	Total [n]
Exposed	85 (30.1)	63 (12.7)	148
Nonexposed	197 (69.9)	431 (87.2)	628
Total	282 (36.3)	494 (63.7)	776

* Relative risk = 3.0 (95% confidence interval [CI], 2.01–4.33); χ^2 = 35.2, $P < 0.001$.

TABLE 5
Relative Risks of Lung Cancer, by Each Category of Occupational Exposure (yes, no), Controlling for Smoking (males only)

Occupational Exposure Category	Not Exposed: Cases (*n* = 174)	Not Exposed: Controls (*n* = 396)	Exposed: Cases (*n* = 82)	Exposed: Controls (*n* = 62)	RR	95% CI
Occupation implicated in etiology of lung cancer	174	396	82	62	2.9	1.95–4.31
Occupational exposure to asbestos	215	430	41	30	2.7	1.54–4.65
Construction and building	209	426	47	32	2.8	1.67–4.67
Textile industry	243	446	13	12	2.0	0.89–4.41
Petroleum and oil products	243	446	13	12	1.8	0.78–3.99
Coloring agents and dyes	238	454	8	4	3.2	0.93–11.19
Metal casting furnaces	251	456	5	2	4.2	0.98–18.15
Carpenters	252	458	4	0	5.3	0.66–32.21

TABLE 6
Distribution of Cases and Controls (Males and Females), by Smoking Habit (expressed in number of cigarettes per day)*

Cigarettes per Day	Cases (*n* = 282)	Controls (*n* = 494)	RR	Total Number of Subjects (*n* = 776)
0	27	129	1.0	156
1–45	68	127	2.6	195
46–74	73	123	2.9	196
>74	114	115	4.7	229

* $\chi^2 = 39.4$; $P < 0.001$.

1480 cigarette-years, 17.1 (95% CI, 6.5–44.7); and >1480 cigarette-years, 19.2 (95% CI, 7.9–46.1).

The comparison of cases and controls by educational level showed that people who had a higher educational level were over-represented among the controls. Specifically, a low educational level (<7 years) was found in 73.0% of cases and 62.1% of controls, while a high educational level (>12 years) was found in 10.9% of controls and 6.4% of the cases ($\chi^2 = 9.29$, $P < 0.01$). These differences were then controlled for by using a multivariate logistic model for 714 observations (males only). The dependent variable was the presence or absence of lung cancer, and the independent variables were smoking (expressed in cigarette-years), level of education, and exposure to one or more occupations implicated in the etiology of lung cancer. The relative risk for lung cancer, based on occupational exposure, remained almost tripled (2.9; 95% CI, 2.38–3.53). For cases with occupational exposure, the relative risk for developing lung cancer based on smoking was also significantly increased (2.15; 95% CI, 1.69–2.73). No significant effect was found for educational level (1.04; 95% CI, 0.97–1.18).

Finally, the relative risks of each specific occupational exposure were also calculated by using multivariate analyses. As in the univariate analyses, the relative risk of developing lung cancer was increased for each of these individual occupational exposures; however, it was only statistically significantly for exposure to asbestos (2.78; 95% CI, 1.64–4.69).

Using a relative risk of 3, based on the multivariate analysis, and assuming that 5% of the country's population is exposed to occupational lung carcinogens, an attributable risk percentage of 9.9% is obtained. Assuming that 10% of the country's population is exposed to these occupations, the attributable risk percentage is 16.6%.

Discussion

Our study indicates that occupational risk factors contribute significantly to the development of lung cancer in Greece. Specifically, the relative risk for lung cancer was significantly increased (2.9; 95% CI, 2.01–4.33) among persons with exposure to one or more of the occupations implicated in the etiology of lung cancer by the IARC. In addition, occupational exposure to a carcinogen or carcinogenic process conferred an additional risk that was multiplicative with the increased risk due to smoking. Finally, while the majority of lung cancers are attributable to cigarette smoking, we estimated that approximately 10%–17% of lung cancers in Greece are attributable to occupational exposures. Because Greece is a member of the European Economic Community, industrial hygiene and work safety programs have been evolving there rapidly over the last 20 years, as they have elsewhere in Europe. Because lung cancers require a long latency period between the original exposure and the diagnosis of cancer, many of the relevant exposures occurred decades before our study. As in other

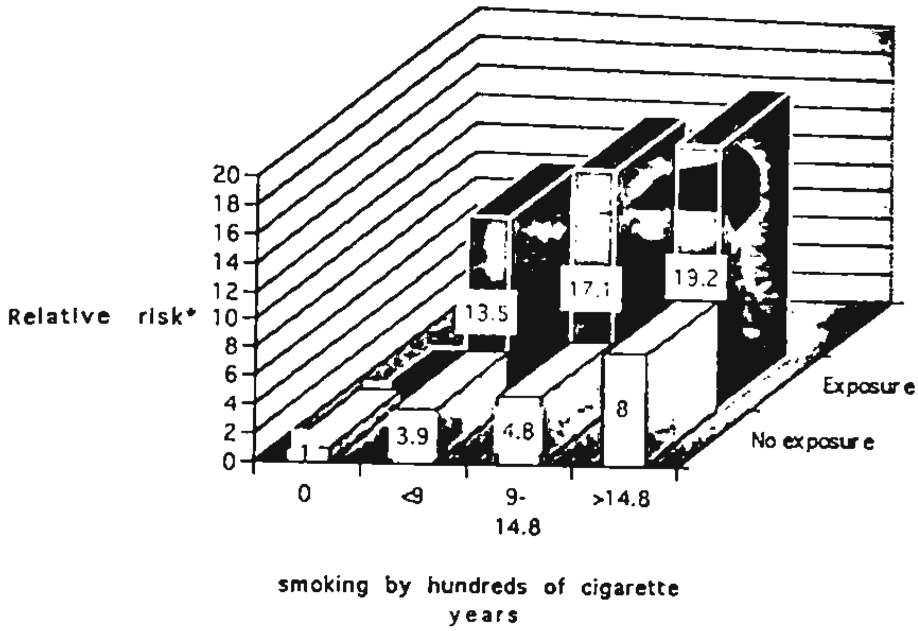

Fig. 1. Risk of lung cancer in Greek men as a function of smoking and exposure to occupations implicated in lung cancer by the International Agency for Research on Cancer.

countries, many of these exposures preceded the recognition of various occupational risk factors for lung cancer and modern hygiene controls and occupational standards.

The potential limitations and biases of this study must be acknowledged. First, two groups of controls were used: visitors to the hospitals where cases were being treated and patients hospitalized for problems other than lung diseases and/or cancers (fractures and eye problems). Preliminary analyses, however, found no substantial differences between the two groups in the prevalence of exposure (13% in both groups). There was also no difference in the crude relative risks, using each control group separately. This allowed us to combine both groups of controls to increase the power of our study and proceed with further statistical analyses.

We chose our control groups to represent the general population as well as hospitalized patients with conditions expected to be unrelated to the exposures being studied. Other epidemiologic studies in Greece have also used hospital visitors as controls.[8,9] It has been a practical and culturally acceptable method of obtaining controls from the general population. The second control group we used comprised patients hospitalized with conditions not expected to be related to the exposures being studied. Because their symptoms are believed to be unrelated to environmental factors, orthopedic[9-12] and ophthalmologic[13] patients have been used in other case-control studies of cancer in Greece.

Recall bias is always a concern in case-control studies, but we feel it is an unlikely explanation for our results. First, in Greece, it is not mandatory for doctors to inform patients that their disease is malignant, and many of the cases were unaware that they suffered from cancer. Second, at the time of the study (1987–1988), most Greeks had very little appreciation of possible etiologic relationships between occupational exposures and cancer.

While the interviewers were not blinded to disease status, the use of a standardized, closed-ended interview process that sought occupational exposures through three separate series of questions was very unlikely to differentially misclassify exposure. Random misclassification of exposure, on the other hand, would have biased results toward the null. Therefore, to the extent that this occurred, our results underestimate the true risks of occupational exposure.

Selection bias is also theoretically possible, but there is no reason to speculate that exposed persons with lung cancers would be hospitalized at a higher rate than would nonexposed individuals. Differential participation rates among exposed and nonexposed persons cannot explain the results since participation rates exceeded 98% in cases and controls.

The potential confounding factors of sex, cigarette smoking, and socioeconomic status (indicated by educational level) were accounted for by multivariate analyses. Because of the limited number of women who participated in this investigation, female respondents were removed from the multivariate analyses. The smoking habits of cases and controls were examined using two methods: number of cigarettes smoked per day and number of cigarette-years, which was considered to be a more exact expression of lifelong exposure. In our study, 90% of the cases and approximately 75% of the controls were smokers. Consequently, smoking was a powerful risk factor and a strong confounder in this study.

Nonetheless, multivariate analysis showed that exposure to one or more of the occupations implicated in the etiology of lung cancer by the IARC increased risk independently of smoking status. Controlling for smoking changed the relative risk only a small amount (2.95 vs 2.9), in agreement with other studies.[4,14] We also found a significantly increased risk of lung cancer for occupations involving exposure to asbestos fibers and building and construction work. On the other hand, the relative risks for other individual exposures were consistently increased but without statistical significance, possibly because of the small sample sizes of these groups.

In the univariate analysis, we found that 30% of the cases and 13% of the controls had been exposed to one or more occupations implicated in the etiology of lung cancer. However, the percentage of the general population occupationally exposed is not known. Nonetheless, on the basis of census and other data, it is reasonable to assume that at least 5% of the Greek population works in an occupation implicated in the etiology of lung cancer. With this assumption, the attributable risk is 9.9%. If we assume that 10% of the Greek population is exposed to such occupations, then the attributable risk reaches 16.6%. These estimates are similar to those found in studies in the United States, which had attributable risks of 9%[15] and between 14% and 24%,[16,17] and that of Damber and Larsson,[18] who found an attributable risk of 9% in Northern Sweden. On the other hand, Wang et al[19] found an attributable risk of 2% in China. It is likely, however, that they underestimated the actual population's attributable risk because of the use of patients with other non-lung cancers as controls.

Our results for occupational exposures are similar to those from other investigations. For example, Kjuus et al[20] calculated the relative risk of lung cancer as 2.3, on the basis of occupational exposures to lung carcinogens. Pastorino et al[21] found a relative risk of 2.1, and Kvale et al[22] found a relative risk of 2.1 (1.7 when adjusted for smoking). Blot et al[23] calculated the relative risk of lung cancer to be approximately 2 for those subjects working in iron foundries.

For those subjects exposed to asbestos, Hinds et al[24] calculated a relative risk of lung cancer of 12.6, while in our study the relative risk was 2.8, which is closer to the ones found in other studies. For example, Morabia et al[15] calculated a relative risk of 1.8; Martischnig et al,[25] 2.4; and Damber and Larsson,[18] 2.6 for 1 year or more of exposure and 3.6 for 20 or more years of exposure, respectively. A meta-analysis of 28 studies by Hughes and Weill[26] found overall relative risks of 1.23 for those subjects with nearly exclusively chrysotile exposure and 2.17 for persons with amphibole or mixed-fiber exposure. These differences in relative risk among studies could be due to differences in intensity and/or duration of exposure to asbestos, as well as to differences in the type of fiber(s) involved. Hinds et al[24] found a higher relative risk among subjects who were classified as having "high asbestos exposure."

For those subjects exposed to construction and building, we found a relative risk of 2.79, which is similar to the relative risk of 2.0 found by Harrington et al[27] for construction workers in Georgia. Similarly, Coggon et al[28] found relative risks of 1.7 for "building laborers" and 1.8 for "construction workers," while Morabia et al[15] found a relative risk of 1.9 for "construction laborers." Wang et al[19] found smaller but still elevated relative risks for Chinese construction workers: 1.21 for males and 1.63 for females (the latter failed to reach statistical significance). Again, the study by Wang et al may have underestimated risks because of the use of patients with cancers other than lung cancers as controls. Yamaguchi et al[29] found nonsignificantly increased relative risks of 1.95 (95% CI, 0.97–3.94) and 1.79 (95% CI, 0.86–3.71) for building construction and road construction workers, respectively.

Occupational exposure to a carcinogen or carcinogenic process conferred a risk that was approximately threefold that of smoking and that increased in a dose-dependent fashion. This is consistent with the magnitude of the overall relative risk (2.9) for lung cancer, based on occupational exposure in our study. The fact that only nine of the male cases were nonsmokers in our study (and all nine were unexposed) limited our ability to examine the risk of exposure in nonsmokers. Pastorino et al[21] also found that occupational exposures multiplicatively increase the risk of lung cancer in a fashion that is dose-dependent with smoking habit. Yamaguchi et al[29] found the interaction of smoking and occupational exposure to be additive for ironworkers but multiplicative for workers from "other plants." Review of the interaction between smoking and a variety other exposures reveals various patterns of interaction.[30] For example, most evidence suggests a multiplicative interaction for asbestos and uranium mining, while interactions ranging from less than additive to greater than multiplicative are found in studies of various non-uranium miners.

In conclusion, we found that occupational risk factors contribute significantly to the development of lung cancer in Greece and that the risk of occupational exposure appears to be multiplicative of that of smoking. The general agreement of our results with those of investigators from other countries makes chance an unlikely explanation for the increased risks seen with occupational exposure. Given that occupational exposures and smoking appear to interact multiplicatively, reducing exposure to either may have a greater effect than that expected from the separate, individual attributable risks of each.[1,30] Therefore, preventive efforts should focus on both limiting occupational exposures to carcinogens and carcinogenic processes and reducing smoking among the workforce.

Acknowledgments

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Another Atheist

A Minnesota man announced to his pastor that he was leaving the church because he had finally gotten around to reading "that book" the pastor was always quoting from, and he was deeply disappointed. It had a lot of nice things to say about St. Paul, the man moaned, but not a single word about his hometown, Minneapolis.

—From Landers A. *Philadelphia Inquirer*, September 4, 1998, p E2.