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A Case-Control Study on Occupational Lung Cancer Risks in an Industrialized City of Japan

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A hospital-based case-control study was conducted to evaluate occupational risks of lung cancer in an industrialized city of Japan. The lung cancer cases were obtained from 3 major hospitals in the city. The control group consisted of patients with a variety of diseases hospitalized in the same wards of the same hospitals as the cases. After matching on sex, 5-year age category and hospital, 144 cases and 676 controls comprised the study group. A self-administered questionnaire was used to obtain lifetime job histories and smoking status. The conditional logistic regression model was used to estimate relative risks after controlling for smoking and employment in other jobs. The workers in shipbuilding, ironworks and other plants (mostly chemical plants) showed statistically significant increases in lung cancer risk with relative risks of 6.18, 2.02, and 2.66, respectively. An increase in risk with the duration of employment was also observed in the "other plants" category. Building and road construction workers also showed increased relative risks, 1.95 and 1.79, but they were not significant. When the risk was evaluated on the exposure chemicals, the workers exposed to inorganic acids and bases had significantly increased risk. The workers exposed to asbestos, dust or organic chemicals also showed increased risk but the effects were not significant. The combined effect of smoking and employment in ironworks showed a good fit to an additive model, while that in the "other plants" category was closer to a multiplicative model.

Key words: Lung cancer — Epidemiology — Occupation — Chemical exposure

It is well recognized that a certain proportion of lung cancer occurrence is attributable to occupational exposures to carcinogens in the workplace. Doll and Peto[1] estimated that approximately 15% of lung cancer among American men resulted from occupational exposures. The proportions of lung cancer attributable to occupational exposures were also estimated from case-control studies conducted in various regions throughout the world by Vineis and Simonato.[2] It was pointed out that the attributable fraction varied widely, from less than 5% to 40%, according to the proportion of exposed individuals in that population.

In Japan, rather few epidemiologic studies have been reported on occupational risks of lung cancer, though the country has been industrialized since the turn of this century. This does not mean at all that the occurrence of occupational lung cancer is rare in this country. In fact, case-control studies reported recently from various regions of Japan showed higher risk of lung cancer among workers of certain occupations. Tsugane *et al.*[3] reported that workers exposed to respiratory irritants such as dust, metals and exhaust fumes were at a higher risk of developing lung cancer, the relative risk for squamous cell carcinoma being as high as 17.0. Increased risk was also reported among women occupationally exposed to iron ore metals by Shimizu *et al.*[4]

In the light of these findings, we conducted a hospital-based case-control study in Kitakyushu City, an industrialized city of Japan, to identify occupational risk factors for the development of lung cancer. Relative risks were estimated for selected occupations suspected *a priori* to be at higher risks. Interaction of occupational risks with smoking was also analyzed.

MATERIALS AND METHODS

One hundred and fifty-one histologically confirmed lung cancer cases hospitalized in three major hospitals located in the study area were identified from the period July 1, 1989 to September 1, 1990. All patients hospitalized during the same study period and in the same wards with diseases other than lung cancer constituted the control group. A total of 934 patients were identified for the control group. Cases and controls were matched on the admitted hospital, sex and 5-year age category at admission. Of the 151 lung cancer cases and 934 controls,

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6 cases and 253 controls were excluded from the analysis due to lack of matching in the same categories. Five cases were also excluded from the control group because lung cancer was suspected but not histologically confirmed. In the end, 144 cases (117 males and 27 females) and 676 controls (479 males and 197 females) constituted the study group.

A self-administered questionnaire was used to obtain information on past occupation and smoking status. The same questionnaire was administered to both case and control groups in a blind manner to avoid information bias. Lifetime occupational histories were obtained for the seven job categories selected *a priori* as high risk jobs; (1) mining, (2) steel manufacturing (3) ironworks, (4) building construction, (5) road construction, (6) shipbuilding and (7) working in any plants other than those listed above. The age at start of work and years engaged were also obtained for each category. History of exposures to chemicals and other hazards in the workplace was also questioned. The following chemical exposures were listed in the questionnaire for yes/no responses; organic solvents, lead, cadmium, nickel, chromium, asbestos, acrylonitrile, arsenic and beryllium. A free format question was also included in the questionnaire for obtaining information on other exposures. The smoking status was categorized into never-smoker, ex-smoker, current smoker with 20 cigarettes or less per day, and current smoker with more than 20 cigarettes per day. An individual was classified as a current smoker if the time of smoking cessation was within two years from admission to the hospital.

The conditional logistic regression analysis was used to estimate relative risks of developing lung cancer after controlling for other job categories and smoking.[5] The SAS program package was used to perform the conditional logistic analysis.[6] Relative risks were calculated for the selected job categories and exposures to the selected exposure chemicals. The independent variables included in the model were binary indicator variables as listed in Table I.

The duration of employment was dichotomized and two binary indicator variables for shorter and longer employment were included into the logistic regression model to evaluate the change in lung cancer risk with duration of employment in occupations with significantly high risks. Improvement in model fit was checked by the likelihood ratio statistic at the 5% significance level.

The interaction of occupational risk and smoking was evaluated by incorporating three binary interaction terms for joint effects of employment in high risk work categories and smoking, including ex-smokers, in the logistic regression models. Relative risks expected under the assumptions of additive and multiplicative models were calculated from the relative risks for the smoking status and for the occupations estimated by the conditional logistic analysis with interaction terms as follows[7]:

$$RR_{(\text{smoking})\times(\text{occupation})} = RR_{(\text{smoking})\times(\text{no occupation})} + RR_{(\text{no smoking})\times(\text{occupation})} - 1$$

for additive model and

$$RR_{(\text{smoking})\times(\text{occupation})} = RR_{(\text{smoking})\times(\text{no occupation})} \times RR_{(\text{no smoking})\times(\text{occupation})}$$

for multiplicative model.

RESULTS

The relative risks of developing lung cancer among individuals engaged in the selected work categories are shown in Table I. The relative risk was significantly increased at the 5% level among workers engaged in shipbuilding (RR=6.18), "other" plants (RR=2.66), and ironworks (RR=2.02). Smokers including ex-smokers were at high risk; current smokers with more than 20 cigarettes a day showed the highest risk (RR=12.14), followed by current smokers with 20 cigarettes or less a day (RR=3.75), and ex-smokers (RR=2.90).

The workers in "other plants" and ironworks categories were further analyzed by dividing each job category into two subgroups according to the duration of employment, with the cutoff point of 15 years (Table II). This cutoff point was determined so that the controls were apportioned approximately equally to the two subgroups. Shipbuilding was not analyzed with regard to the duration of employment, since the number of lung cancer cases was too small. Though none of the at-risk work categories showed significant improvement in fit when the duration of employment was taken into account, an increasing tendency in relative risk was observed in the "other plants" category.

The past history of occupational exposures, which was obtained by yes/no questions for selected substances as well as by a free format question, was classified into 6 categories; (1) inorganic acid/base, (2) asbestos, (3) dust excluding asbestos, (4) organic chemicals, (5) metals, and (6) others, and relative risks were estimated by the conditional logistic model, controlling for the smoking and concomitant exposures (Table III). The workers exposed to inorganic acid or base showed a significant increase in risk at the 5% level (RR=4.03). The chemicals classified into this category were sulfuric acid, hydrochloric acid, phosphoric acid, ammonia, ammonium sulfate, and lime. The workers exposed to asbestos, dust, organic chemicals, and "others" also showed increased risks but the effects were not statistically significant.

The combined effects of employment in at-risk work categories and smoking were evaluated by including in-

Table I. Relative Risks and 95% Confidence Intervals for Selected Work Categories and Smoking Status, Simultaneously Estimated by the Conditional Logistic Regression Model

	Relative risk	95% confidence interval	Number of exposed	
			case	control
Shipbuilding	6.18	1.54–24.88	6	5
Ironworks	2.02	1.06–3.88	20	47
Building construction	1.95	0.97–3.94	18	39
Road construction	1.79	0.86–3.71	21	40
Steel manufacturing	0.92	0.54–1.56	26	110
Coal mining	0.78	0.38–1.64	17	55
Other plants	2.66	1.43–4.94	24	49
Current smoker 21+/day	12.14	5.10–28.90	28	56
Current smoker −20/day	3.75	1.89–7.47	48	191
Ex-smoker	2.90	1.43–5.90	44	162

Table II. Improvement in Model Fitting by Incorporating Parameters for Duration of Engagement in Other Plants and Ironworks

	Relative risk	95% confidence interval	Improvement in model	
			Chi square	d.f.
Other plants overall	2.66	1.43–4.94		
15 years or less	2.25	1.01–5.03	0.42	1
more than 15 years	3.37	1.32–8.61		
Ironworks overall	2.02	1.06–3.88		
15 years or less	2.37	1.08–5.20	0.48	1
more than 15 years	1.49	0.49–4.52		

Table III. Relative Risks and 95% Confidence Intervals for Selected Exposure Categories

	Relative risk	95% confidence interval	Number of exposed	
			case	control
Inorganic acid/base	4.03	1.05–15.51	5	5
Asbestos	1.94	0.49–7.78	4	13
Dust	1.52	0.40–5.83	5	10
Organic chemicals	1.28	0.44–3.71	9	24
Metals	0.39	0.08–1.93	3	15
Others	1.69	0.33–8.59	3	6

The concomitant exposures and smoking status were controlled for by the conditional logistic regression model.

teraction terms in the logistic regression equations. The relative risks thus obtained were then compared with the risk estimates calculated under the assumptions of additive and multiplicative effects (Fig. 1). The increase in the relative risk among workers in the "other plants" category was closer to the multiplicative model, while that among workers in ironworks looked closer to the additive model.

The analysis of risk by histologic types was not possible in the present study because of the inadequate number of

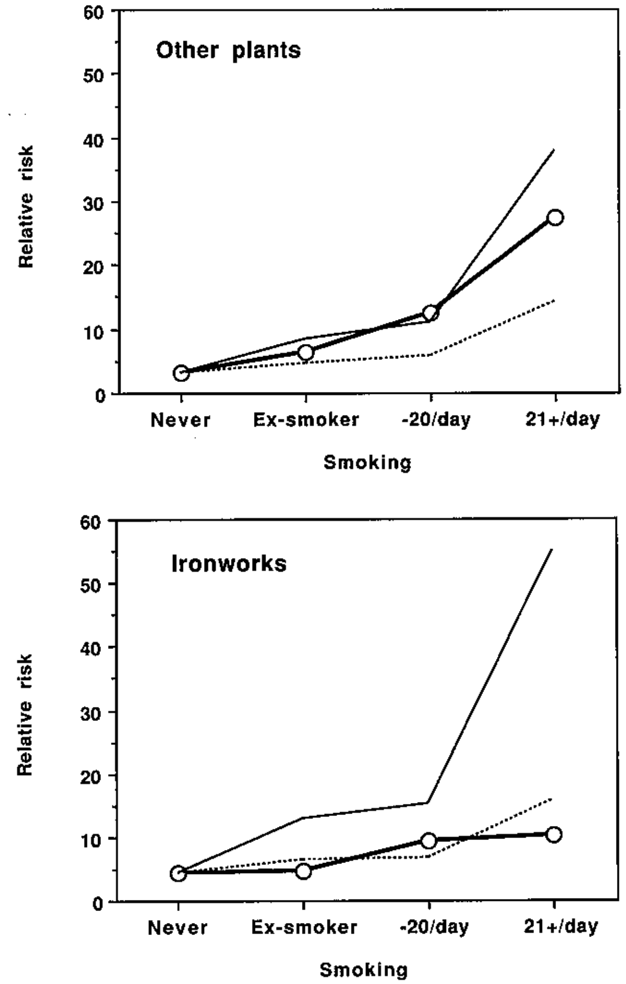

Fig. 1. Evaluation of combined effects of smoking and employment in ironworks and "other plants" by comparing interaction models (solid line with circles) with additive models (dotted line) and multiplicative models (solid line). Interation terms were included in the logistic regression equations in the interaction models.

lung cancer cases. Among 144 cases of lung cancer analyzed, 48 cases (33.3%) were squamous cell carcinoma and 52 cases (36.1%) were adenocarcinoma. Of the lung cancer cases engaged in ironworks (20 cases), 8 (40.0%) were squamous cell carcinoma and 6 (30.0%) were adenocarcinoma, showing no marked difference. The distribution in the cases engaged in the "other plants" did not show any difference either; 5 of 24 cases (20.8%) were squamous cell carcinoma and 8 cases (33.3%) were adenocarcinoma. In contrast, 4 of 6 cases (66.7%) engaged in the shipbuilding occupation were adenocarcinoma, while only one was squamous cell carcinoma.

DISCUSSION

Kitakyushu City, where the cases and controls were collected in the present study, has been a center for large-scale steel and chemicals manufacturing since the beginning of this century. Of the 496,000 workers living in the city as of 1985, 106,000 (21%) were employed in production industries, and 55,000 (11%) in the construction industry.[8] According to the Vital Statistics of 1985,[9] the standardized mortality ratio (SMR) of lung cancer in Kitakyushu City was as high as 125.3 for males and 139.8 for females when compared to the whole country. Thus, it is important to identify and evaluate occupational risks of lung cancer in the city from a public health viewpoint.

With regard to the design of the present study, the selection of controls and the data collection by the questionnaire should be considered as potential sources of bias in relative risk estimation. Hospital controls were selected instead of population controls for two reasons. First, we noticed that the plants are aggregated in limited districts of the city and that workers tend to visit hospitals close to the worksite. Secondly, the hospitals selected for the present study do not cover all the lung cancer cases in the city, nor do they represent all the hospitals in the city. Therefore, population controls such as neighborhood controls are not likely to represent the population at risk, from which the cases were sampled.

Since the information on occupational history and smoking was obtained by a self-administered questionnaire, certain proportions of cases and controls might have been misclassified for occupational history and smoking status. However, the direction and magnitude of misclassification are not likely to be different between cases and controls, because the same questionnaire was administered to both groups in a blind manner. Therefore, the relative risks could be underestimated because of the misclassification but they are unlikely to be overestimated, since a nondifferential misclassification always biases a relative risk toward the null.[10]

The workers in the shipbuilding industry showed the highest relative risk among the seven job categories selected for the present study. A number of epidemiologic studies have been published on the risks of lung cancer among shipyard workers, most of which reported significant results.[11, 12] According to a meta-analysis conducted by Vineis and Simonato,[2] age- and smoking-adjusted relative risks ranged from 1.3 to 1.9 for shipyard and dockyard workers. Exposures to welding fumes and asbestos were considered to be the most likely causes for the elevated risk. A significant increase in risk (RR=1.8) was found among shipyard welders with a latency of more than 10 years in a case-control study conducted in

Los Angeles County.[13] Significantly elevated relative risks were also reported among shipyard workers in Hawaii who were exposed to asbestos over 15 years (RR=1.4) or 30 years (RR=1.7).[14] The relative risk of 6.18 found in the present study is higher than those reported thus far. However, further epidemiological investigations are necessary to assess the magnitude of risk more precisely, since the number of lung cancer cases was small. One feature to be noted is the predominance of adenocarcinoma in the lung cancer among shipyard workers. There has been an argument that adenocarcinoma could be regarded as the predominant pulmonary "asbestos" cancer."[15] On the other hand, Kijuus *et al.*[16] reported similar relative risks for squamous cell carcinoma (RR=2.7) and adenocarcinoma (RR=2.2) among workers exposed to asbestos.

An increase in lung cancer risk was also observed among workers employed in ironworks. Those workers were likely to have been exposed to welding fumes and other exhaust fumes while operating machines such as lathes and drilling machines. A significantly elevated risk (RR=3.2) was reported for welders in New Mexico.[17] A non-significant increase in relative risk (RR=2.93) was also reported for welders in Italy.[18] A positive relationship between lung cancer risk among young males and exposure to exhaust fumes was found in a case-control study in Japan.[3] The absence of a time-response relationship (Table II) raises the possibility that the exposure level was higher among workers employed more recently.

Workers in plants other than coal mining, steel manufacturing, ironworks, building and road construction, and shipbuilding industries exhibited a significantly increased risk of lung cancer in the present study. Most of the plants included in this category were expected to be chemical plants, as indicated by the reported exposures in the workplace (Table III). Increased risks of lung cancer among workers in the chemical industry were also reported by several studies. In a case-control study in Norway,[16] a significant increase (RR=2.6) was found among workers employed in chemical and related process works. In a case-control study in northern Italy,[18] a non-significant increase of risk (RR=1.57) was also found among workers in the chemical industry. A prospective cohort study conducted in Norway found a non-significant increase of lung cancer incidence (SIR=2.86) among chemical process workers.[19]

When the exposures to chemicals were analyzed in relation to lung cancer risk, a significantly elevated risk was found among workers exposed to inorganic acids and bases. The case-control study by Kjuus *et al.*[16] also found a significant positive association between exposures to gases such as ammonia, nitrogen oxides, chlorine and sulfur dioxide and lung cancer risk (RR=1.6). An elevated risk among workers exposed to sulfur dioxide was also found in a nested case-control study of workers employed in a chemical company.[20] Workers exposed to asbestos, dust and organic chemicals also showed increased relative risks in the present study but none of them was statistically significant.

Elevated relative risks were found for building and road construction workers in the present study, though they were both non-significant. Non-significant increases of risk were found in two case-control studies conducted in Norway (RR=3.0)[16] and in northern Italy (RR=1.23).[18] In a case-control study in New Mexico,[17] no excess risk was found among construction workers (RR=0.9) but a non-significant increase was found among painters (RR=2.7). A prospective cohort study in Norway also found a moderate increase in lung cancer incidence (SIR=2.02) among those whose longest work history was construction, but again the increase was not statistically significant.[19] In summary, there is no evidence that building or road construction workers are at high risk of lung cancer.

In the present study, workers in the steel manufacturing industry did not show any increase in lung cancer risk (RR=0.7). Recently, a cohort study in France reported a significantly elevated SMR (=2.04) among workers employed in ferrochromium or stainless steel production.[21] A nested case-control study in a cohort of Ontario steel production workers also reported positive association of lung cancer mortality with the duration of employment.[22] In a meta-analysis of 5 US case-control studies by Vineis *et al.*,[12] a statistically significant relative risk of 1.2 among workers in the steel production industry was found. Historically, increased risk of lung cancer was found among coke-oven workers in steel plants in Pittsburgh.[23] However, the meta-analysis by Vineis *et al.*[12] did not find any significant increase in lung cancer risk among workers in coke plants, RR being 0.7 with a 95% confidence interval of 0.02 to 21.2. The exposure levels might have been different between studies, resulting from occupational hygienic countermeasures and use of protective devices. Inclusion of workers with various levels of worksite exposures in the present study might have lowered the overall relative risk to some extent.

Coal mining was selected as a suspected high risk job because a positive geographical correlation between the standardized mortality ratio of lung cancer and coal industries was found in an epidemiologic study in Japan.[24] The present study area was well-known for coal mining though most of the coal mines were closed a few decades ago. The number of workers employed in the coal mining industry totalled approximately 6,000 in 1965. The present study did not show any increase in lung cancer risk among Japanese coal miners (RR=0.78). Two case-control studies conducted in the United

States and the Netherlands also did not find any significant increase in lung cancer risk among coal miners.[25, 26] It may be concluded that there is no evidence that Japanese coal miners are at higher risk of developing lung cancer.

The combined effect of smoking and employment in ironworks was found to be closer to the additive model as shown in Fig. 1. On the other hand, when the combined effect of smoking and working in "other plants" were examined, the relative risk increases in accordance with the multiplicative model. Therefore, it may be inferred that the risk associated with ironworks is likely to be operating independently of smoking. On the other hand, the risk associated with working in "other plants" is likely to be interdependent with smoking, suggesting that these two risk factors play different roles in the pathogenic pathway.

Very few reports have been published in Japan on the lung cancer risk among workers in the shipbuilding, ironworks or chemical plants. Further investigations are needed to confirm these findings and to identify specific chemicals or other risk factors causing the increased risk observed.

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