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Geographic Pattern of Lung Cancer in Japan and Its Environmental Correlations

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Standardized lung cancer mortality ratios, 1969–1978, for basic administrative units of Japan were related to various environmental characteristics by multiple regression analysis. Elevated lung cancer mortality was demonstrated in the areas along the sea coast, particularly those with fishing ports, low socioeconomic status, and high level of air pollution. High mortality was also observed in coal mining areas and areas with shipyards. Data on tobacco expenditures provided partial adjustment for the effects of cigarette smoking on these correlations.

Key words: Geography of lung cancer — Fishing port — Air pollution — Coal mining — Shipyard

Geographic patterns of morbidity and mortality of diseases can often provide leads to causality. For this purpose, cancer mortality maps have been published in several countries, including Japan.[1] One of the most interesting Japanese cancer maps was that for lung cancer (Fig. 1). Clustering of elevated mortality was found in industrialized districts such as Tokyo, Osaka and North Kyushu. Higher lung cancer mortality was also observed in areas along the sea coast in various parts of Japan. Reasons for the clustering are not clear, but an earlier analysis of environmental characteristics suggested associations of lung cancer with urbanization status, smelters, coal mines, sea coast and fishing port.[2] In this paper we extend this hypothesis-generating work, correlating the distribution of lung cancer mortality in Japan with various geographic, environmental and industrial characteristics at a smaller area level (administrative units), within which there is less heterogeneity of exposure than in the larger geographic levels (prefectures) studied previously. Although cigarette smoking is the dominant cause of lung cancer in Japan, at least among males, such correlations may signal the presence of environmental determinants of this cancer amenable to evaluation through subsequent analytical study at the individual level.

MATERIALS AND METHODS

Average standardized mortality ratios (SMR) for lung cancer (ICD 8th Revision Code 162) were calculated for the 10-year period 1969–1978 by the Research Committee on Geographical Distribution of Diseases[1] for each of the 3,341 basic administrative units (ward, city, town and village), which will be referred to as areas, hereafter. The SMRs for each area were calculated by dividing the number of lung cancer deaths observed in the area by an expected value. Expected values were based on the age-specific mortality rates during the study period in Japan and age-specific population of each area in 1973, estimated from 1970 and 1975 census populations by linear interpolation. Areas in Okinawa Prefecture, which returned to Japanese jurisdiction in 1976, were not included in this study because of poor availability of areal characteristics.

For 662 areas, data on several environmental characteristics were available for correlation with the lung cancer SMR. These areas included nearly all areas with populations exceeding 50,000, while excluding nearly all those with populations less than 5,000 (Table I). Environmental characteristics included urbanization categorization, population density, socioeconomic status, air pollution designation, and expenditure for tobacco. In addition, measures of industrial activity were obtained for each area.

The population density of each area in 1973 was obtained from the 1970 and 1975 census populations by linear interpolation. For socioeconomic

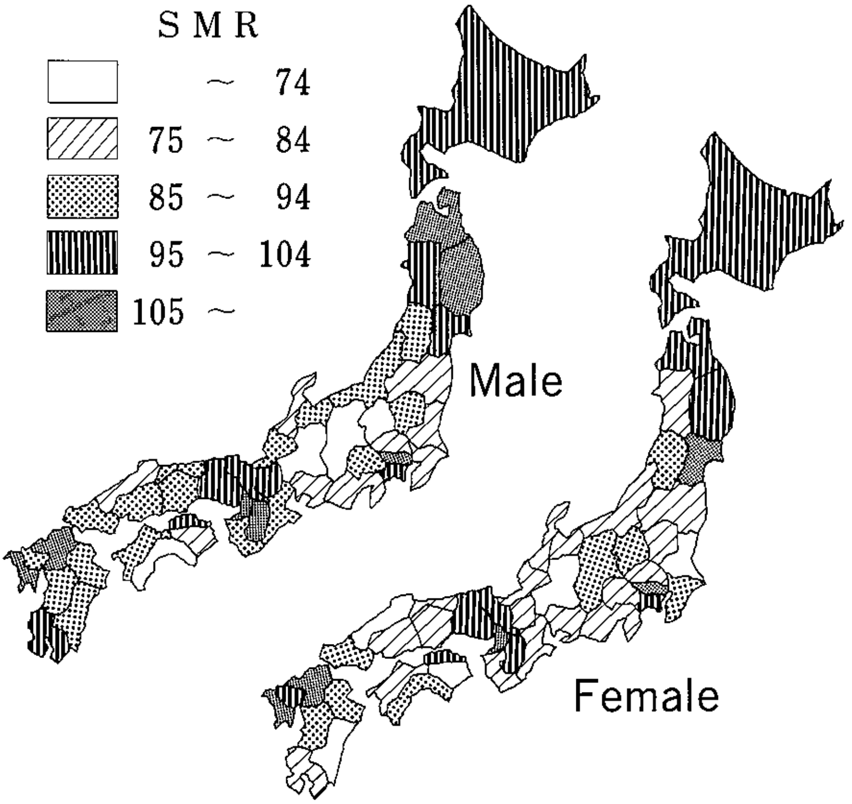

Fig. 1. Average standardized mortality ratios (SMR's) according to sex and prefecture, 1969–1978. (SMR of 100 corresponds to the national mortality rate of 20.4 per 100,000 population for males and 7.5 for females.)

Table I. Population Size of All Areas in Japan and of Areas Included in the Regression Analysis

Population	All Japan		Areas included	
	Male	Female	Male	Female
– 499	19	17		
500 – 999	65	61		
1,000 – 1,999	245	212		
2,000 – 4,999	1,234	1,150	9	5
5,000 – 9,999	797	869	18	20
10,000 – 19,999	398	425	170	144
20,000 – 49,999	308	325	246	267
50,000 – 99,999	110	113	108	111
100,000 – 199,999	85	88	84	87
200,000+	27	28	27	28
Total	3,288	3,288	662	662

status, Engel's coefficient, an index of family expenditure for food divided by total expenditure, was used. Expenditure for tobacco was also obtained for each of the 662 areas from the National Survey of Family Income and Expenditure conducted in 1959, 1964 and 1969. Two indices of air pollution were used. One was the average atmospheric concentration of sulfur dioxide for each year of 1973–1977. The other was the administrative designation for air pollution control. An area with "high" air pollution was defined as an area where an areawide pollutant load control program for atmospheric sulfur dioxide is required, and an area with "mild" air pollution was defined as an area where a stricter standard for the concentration of emitted sulfur dioxide than in the other areas is applied by the Anti-Air Pollution Law. Each area that contained an operating or closed mine (for mining gold, silver, platinum, copper, iron sulfate, zinc, lead, mercury, molybdenum, iron, manganese, tungsten, uranium, tin, chromium, antimony, thorium, silica, nickel, coal or lignite) or a smelter or ironworks was identified according to the information from the Mine Control Bureau, Ministry of International Trade and Industry of Japan. Areas that contained petroleum and coal industries, or asbestos industries (cement, slate, brake, textile, duct, spray, packing, sheet, paper and washer manufacture) were obtained from the Factory Directory in Japan.[3] A list of fishing ports was obtained from the Ministry of Agriculture, Forestry and Fisheries, and location of shipyards from the Maritime Promotion Association. Each small area was also classified for activity in the following manufacturing industries: food, textile, clothing, wood and its products, furniture, pulp and paper, printing and publication, chemicals, iron, nonferrous metal, metal products, machinery, electric machines, and measuring. An area was said to have activity in an industry if the manufacturing output in that industry was more than 10% of the area's total manufacturing output in 1963.[4]

Weighted multiple regressions were employed to link the SMR for each area to the various indices. For each area the weight was directly proportional to the square root of the area's person years at risk during 1969–1978, and hence inversely proportional to the standard error of the estimated value of the standardized mortality ratio. Weighting inversely proportional to the variance of the SMR was not done in order to avoid assigning much greater importance to the very heavily populated areas. However, results varied little between the two weighting schemes. Regressions using logarithms of the SMR were also run, since there was some skewness in the distribution of SMRs. Results were qualitatively similar, and the only results presented are those from the log-transformed runs, in which the variables combine in a multiplicative scale in affecting lung cancer risk. Separate regression analyses were conducted for males and females.

Among the independent environmental variables, six major variables were chosen on *a priori* grounds for all regression models: urbanization status, population density, air pollution categorization, Engel's coefficient, tobacco expenditure, and designation as a sea-coast fishing port. Additional variables were examined for contribution to lung cancer mortality after adjustment for these six factors.

RESULTS

Geographical Pattern of Lung Cancer Mortality in Japan Table II presents average standardized mortality ratios for the 662 areas included in the regression analysis and for all administrative units according to urbanization status. The more urbanized the areas, the higher the mortality from lung cancer for each sex.

Table III lists the estimated percentage increases in the SMR for lung cancer associated with the major variables included in the baseline regression analysis. (The estimated increase for a variable is an estimated regression coefficient, which provides a measure of the increment to the SMR associated with the variable.) Urbanization status was

Table II. Average Standardized Mortality Ratios (SMRs) for Lung Cancer, 1969–1978, in Japan and Areas Included in the Regression Analysis according to Sex and Urbanization Status

Urbanization status	All Japan			Areas included		
	Number of areas	Male	Female	Number of areas	Male	Female
Ward	91	118.7[a]	124.2	90	118.5	124.0
City	630	98.7	97.5	535	98.3	96.9
Town	1,978	91.5	85.6	37	94.1	93.2
Village	589	81.4	77.6			

a) SMR of 100 corresponds to the national mortality rate of 20.4 per 100,000 population for males and of 7.5 for females.

Table III. Predicted Percent Increases in SMRs for Lung Cancer Associated with Areal Environmental Variables

Variable		% increase ± standard error	
		Male	Female
Urbanization status	Ward vs. county	6.9 ± 5.9	21.4 ± 8.2
	City vs. county	3.1 ± 5.0	13.4* ± 7.0
Population density	per 1,000/km^2 increase	0.8** ± 0.2	1.0** ± 0.3
Sea coast-fishing port	Fishing port vs. inland	14.4* ± 1.7	8.6** ± 2.4
	Sea coast vs. inland	6.2** ± 2.3	4.4 ± 3.2
Engel's coefficient	per 1% increase	0.9** ± 0.2	1.0** ± 0.3
Air pollution	High vs. low	13.3** ± 2.5	11.8** ± 3.5
	Mild vs. low	6.3** ± 1.9	5.3* ± 2.6
Tobacco expenditure	per 100 Yen increase	1.2** ± 0.5	−0.2 ± 0.7

* $0.01 < P < 0.05$, ** $P < 0.01$.

significantly associated with mortality only for females after adjusting for the other variables. However, rates in both sexes rose with population density, becoming 0.8% higher for males and 1.0% higher for females for each 1,000/km^2 increase of population density. Since the lowest population density among the areas included in the regression analysis was 10/km^2 and the highest was 25,693/km^2, the maximum differences in the population density will correspond to a 22.6% elevation of lung cancer for males and a 30.2% elevation for females. Areas along the sea coast without fishing ports had an estimated 6.2% higher mortality from lung cancer for males than inland areas. Similar trends, although not statistically significant, were seen among females. The excess was greater (14.4% and 8.6% higher, respectively for males and females) in coastal areas with fishing ports. Mortality was also directly related to Engel's coefficient: areas with the highest values (coefficient of 51%) and those of low socioeconomic status, tended to have the highest lung cancer rates in both sexes. Even after controlling for urbanization, population density, coastal location, and socioeconomic status, areas with high and mild air pollution had 13.4% and 6.3%, respectively, higher lung cancer mortality for males and 11.9% and 5.3%, respectively, for females than in the areas with low air pollution. Finally, lung cancer mortality for males increased 1.2% for every 100 Yen increase of tobacco expenditure in 1959. Tobacco expenditure for the areas included in the regression analysis ranged from 71 Yen to 1,047 Yen, corresponding to an estimated 12% increase in lung cancer mortality for males.

No significant associations between atmospheric sulfur dioxide concentrations during 1973–1977 and lung cancer mortality were detected.

Industrial Factors After adjusting for the influences of the six major variables mentioned above, the industrial variables (presence of industrial facilities) were tested for the relationship to lung cancer mortality among males. Lung cancer mortality among males was significantly elevated in areas with four kinds of industrial facilities; closed mine, petroleum and coal industries, coal mine and shipyard. Table IV shows the predicted increases in the standardized mortality ratio associated with these industries.

Areas with closed mines averaged 6.1% higher mortality from lung cancer among males. Areas with operating mines also had elevated mortality but without statistical significance. None of the individual categories of operating and closed mines, except coal, showed a significant association with lung cancer mortality. Petroleum and coal industries were associated with slightly increased lung cancer mortality after controlling for the six major variables, but the association

Table IV. Predicted Increase in Standardized Mortality Ratio for Lung Cancer among Males Associated with Selected Industrial Variables

Industry	% increase ± standard error
Closed mine	6.1±2.9
Petroleun and coal industries	3.9±1.7
Coal mine	14.3±4.6
Shipyard	7.1±3.2

became weaker after further adjusting for the presence of closed mines, coal mines, and shipyards. In the areas with shipyards, lung cancer mortality was elevated by 6.9%, even after adjusting for the higher SMRs in coastal areas where the shipyards tend to be located.

No other industrial factor showed a significant positive or negative association with lung cancer mortality in the regression analysis based on areal data.

Discussion

In an ecological study like this, it should be noted that an association between lung cancer mortality and an environmental factor may not necessarily represent an association at the individual level or a causal relationship. Rather, the association may serve as a lead to further investigation. As noted below, some of these leads appear plausible.

In this study, coastal areas showed an elevated mortality from lung cancer for both sexes, and the SMRs were higher still in coastal areas with fishing ports. Many heavy industries tend to be aggregated along the sea coast in Japan, but our analyses adjusted for the presence of certain suspect industries as well as activity in a variety of manufacturing industries. Indeed, shipbuilding activity accounted for some but not all of the coastal excess. Part of the remainder may be related to the fishing industry, since fishermen's lung cancer was reported to be higher in England and Wales, and in Japan,[5] but not in Canada.[6] In addition, two case-control studies in the United States have associated work in the fishing industry with two- to threefold increased risk of lung cancer.[7,8] Exposure to diesel exhausts and lubricating oil in small engine rooms or cabins may occur, though working conditions for Japanese fishermen may differ from those in western countries. Further studies at the individual level are required before conclusions can be reached regarding lung cancer among fishermen and the extent to which this influences the geographic pattern of lung cancer in Japan.

The positive association between shipyards and lung cancer mortality shown in this study is consistent with an increased mortality rate from lung cancer observed in shipbuilding counties of the United States.[9] Cohort and case-control studies also showed an elevated relative risk of lung cancer among shipyard workers.[10,11] An elevated relative risk associated with asbestos exposure has also been demonstrated in a case-control study carried out in Yokosuka, Japan, the site of Japanese and U.S. naval bases as well as many shipyards.[12] Asbestos inhaled directly by asbestos workers and indirectly by the other workers in shipbuilding or repair may be responsible for this relationship.

Although recent epidemiological studies in Great Britain and the United States showed no significant excess deaths from lung cancer among coalminers,[13-15] a case-control study showed an increased risk of lung cancer among coal miners in Japan.[16] Our correlation study also shows an elevated lung cancer mortality in the areas with coal mines. Coal miners are often heavily exposed to coal dust, and also to other dusts containing silica, depending upon the quality of the coal vein. Silica is well known as a substance which causes severe pneumoconiosis, but may also cause lung cancer.[17,18] Data on the levels of radon, a known lung carcinogen,[19] in coal mines in Japan are not available. The excess risk of lung cancer detected in both case-control[16] and ecologic studies in Japan, adds to the incentive to evaluate mine exposures to radioactivity, silica, and other inhaled substances.

One of the more interesting findings of this investigation is the elevated SMR for lung cancer in areas designated as requiring air pollution control. This result is in line with an epidemiological study indicating a moderately increased risk in Japan in the 1960s.[20] General air pollution, however, has been difficult to assess as a risk factor for lung cancer. In their review of the causes of cancer, Doll and

Peto[21] indicate that air pollution probably acounts for about 10% or less of all lung cancer in the United States. We observed 12–13% higher SMRs in high compared to low pollution areas in Japan after controlling for tobacco expenditures and other variables. There may be some interaction between air pollution and smoking and/or ccupational exposures, as suggested in a recent case-control study in the United States.[22] Case-control studies in the United States and Sweden have linked elevated lung cancer rates to specific contaminants in the air, including arsenic and other metal pollutants.[23, 24] In our study, atmospheric sulfur dioxide was not correlated with lung cancer mortality, but administrative designation by the Anti-Air Pollution Law was. There could be several inferences to account for this apparent discrepancy: 1) sulfur dioxide may not be an appropriate index of air pollution related to lung cancer; 2) atmospheric sulfur dioxide in 1973 and later may not represent the geographical differences in air pollution in the 1960's, when the air pollution was far more severe; 3) administrative designation may be a more comprehensive index of the air pollution of the area, particularly in the past; 4) air pollution may be associated with occupational exposures to carcinogenic substances. Further studies may be necessary on this point.

None of the major manufacturing industries was significantly correlated with lung cancer. The categorization of major manufacturing industry in this study may not be an adequate index for geographical epidemiology, however, because it is determined by output (monetary value of goods produced) and may not adequately represent the population exposed. The distribution of numbers of persons working in various occupations within the areas would have been more desirable as an index of industry, but was not available.

Population density and poorer socioeconomic status were also positively associated with lung cancer mortality for each sex. It is unlikely that lung cancer is transmitted among crowded people like an infectious disease or that poverty itself is a cause of lung cancer. Rather these indices are likely surrogates for factors that may increase risk of lung cancer, including perhaps cigarette smoking and/or air pollution — although partial adjustment was obtained through adjustment for tobacco expenditure and air pollution control designation.

The data on the environmental variables used in this study were rather new and the intervals between these variables and end-results (lung cancer mortality) were shorter than the estimated latent period of the cancer. The industrial activities and air pollution categories used in this study should be regarded as representatives of geographical differences in those in the past, because it is not likely that an industry having been declining in one area would have been developing in another area, or *vice versa,* in Japan at the same time.

In summary, this geographic analysis has found significant correlates of lung cancer mortality, including air pollution status and certain industrial activities of the individual areas. Some accounting of the role of smoking, the major cause of lung cancer in Japan, was possible, and the results were often consistent with prior observations, so that the leads produced may help to stimulate analytic epidemiologic investigations to clarify the environmental determinants of lung cancer.

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