LUNG CANCER 1982

Editors:
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Lung Cancer 1982

General Lectures and Special Topics presented at
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Introduction

On the occasion of the III Conference on Lung Cancer, in Tokyo in 1982, being held under the auspices of the International Association for the Study of Lung Cancer (IASLC), three General Lectures and three Special Topics have been arranged. These Lectures and Topics are not only of current interest but are also of practical importance in the field of lung cancer research. Those who are giving these talks are distinguished scientists at the forefront of their respective fields. Their generous contribution to this Conference is greatly appreciated.

Although through steady efforts the results of lung cancer treatment are improving gradually, the average cure rate in Japan still remains at only 14%, according to the data reported in 1980. It will therefore be necessary to expend even more strenuous efforts to achieve early detection by improving diagnostic methods, and by the use of X-rays and endoscopy as well as laser and tumor markers. It goes without saying that mass-screening must be carried out effectively. On the other hand, in daily practice we are faced with a large number of patients with advanced lung cancer. For these patients, it is very important that new chemotherapeutic agents be developed, that the best combinations of these agents be determined, and that various methods such as immune therapy, irradiation, thermotherapy and laser therapy be used.

At the same time, it is a matter of urgence that the actual causes of lung cancer be identified and that ways to prevent its occurrence be established. For this purpose, basic research as well as a detailed epidemiological survey for each patient (bedside epidemiology) will become increasingly important in the future.

The purpose of this booklet is to provide comprehensive and up-to-date information for those actually engaged in the research, diagnosis and treatment of lung cancer and for all who are otherwise interested in these areas.

Finally, I sincerely hope that this Conference, which is being attended by experts from all over the world, will prove to be a milestone in the conquest of lung cancer.

Shichiro Ishikawa
Tokyo, March 1982

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Epidemiological aspects of lung cancer in the Orient

Takeshi Hirayama

The available information on the epidemiology of lung cancer in the Orient will be summarized under the following headings: (1) patterns of occurrence, (2) host factors, (3) environmental factors and (4) strategies for control.

Patterns of occurrence

Time trends

The mortality due to lung cancer has been increasing rapidly. Until a few years ago, the number of deaths in Japan from pulmonary tuberculosis was far higher than that from lung cancer. As registered in 1947, the death toll due to pulmonary tuberculosis was 121,912, which was 152 times that registered for lung cancer (768 cases). This balance has decreased each year. In 1972, the number of pulmonary tuberculosis deaths (11,983) was lower than the number of lung cancer deaths (12,290). The figures were 6144 and 21,294, respectively, in 1980. If the current pace continues, the death rate for lung cancer is expected to catch up, within a decade at the latest, with that of stomach cancer in Japan. The death rates are on the increase in each age group in both males and females. It is noteworthy that the rate has been increasing even in cohorts born in 1940–1944, which suggests that a limited effect of low-tar cigarettes has appeared since 1965, the cumulative mortality rate for lung cancer by age 39 being 3.2, 3.6 and 4.5 per 100,000 in cohorts born in 1930–1934, 1935–1939 and 1940–1944, respectively (1). This increasing incidence and mortality are seen in nearly all countries, including those of the Orient.

In Shanghai, the standardized mortality rates for lung cancer in males were 28.5, 44.2 and 52.0 per 100,000 in 1963–1965, 1972–1975 and 1976–1979, respectively. In females, the rates were 11.1, 16.8 and 18.3, respectively (Gao Yu-Tong).

In Singapore Chinese, the standardized lung-cancer incidence rates were 12.9, 56.9 and 68.0 per 100,000 in 1950–1961, 1968–1972 and 1973–1977, respectively. In females, the rates were 3.2, 17.3 and 20.0, respectively (Cancer Registry, Singapore).

In Korea, the relative frequencies of lung cancer to cancer of all sites were 4.1%, 11.2% and 12.5% in 1958–1967 (Ref. 11), in 1975 (Ref. 12) and in 1979 (Ref. 13), respectively, in 10,408, 2382 and 1279 males. In females, the percentages were 0.7, 2.7 and 3.6, respectively, in 16,513, 2584 and 1263 cases.

In the Philippines, the relative frequencies of lung cancer were 6.9%, 13.5% and 19.9% in 1958–1967, 1968–1973 and 1977, respectively, in 771, 6771 and 1258 males. In females, the percentages were 1.2, 3.0 and 6.1 in 1309, 9721 and 1409 cases, respectively (Philippine Cancer Society).

In the Radiotherapy Department, Postgraduate Institute, Chandigarh, India, the relative frequencies of lung cancer were 6.1%, 7.7%, 8.0% and 10.0% in 1971, 1974, 1977 and 1980, respectively, in males out of 525, 752, 789 and 813 male cancer cases. The percentages for females were 1.4, 0.3, 0.1 and 0.8, respectively, in 592, 556, 808 and 987 cancer cases.

In most developed countries, mortality among females is increasing rapidly, while in males it is less steep or almost saturating, thus reflecting different trends in smoking habits. In the Orient, however, the disease is generally on the increase, in both males and females, thus reflecting similar trends in smoking habits.

International variations

The highest rates of lung cancer are found in the United Kingdom and Finland, the lowest in Asia and Africa (2, 3). The variation is generally less in females. Roughly speaking, these rates parallel both the diagnostic level and prevalence of cigarette-smoking in each country.

Clustering within countries

Clustering is almost universally noted in urban areas, again probably reflecting the higher prevalence of smoking plus the combined effect of high-risk occupations and possibly also of indoor and outdoor air pollution. The lung cancer map recently made in China is also in line with the tendency in other countries.

Migration

Rates for immigrants from low-risk areas tend gradually to converge to the risk of the host country. This tendency is particularly marked when people from low-risk areas migrate to cities or countries with a high prevalence of cigarette-smoking (4).

Host factors

Sex

Relatively speaking, a lower sex ratio in lung cancer is a feature in Asia. However, in Europe and North America, the ratio is falling, with a more rapid increase in incidence in females.

Age

A steep rise is seen with increasing age. A linear increase is observed on a log-log graph.

Genetic predisposition

Although environmental influences predominate, there is an interaction between familial susceptibility and cigarette-smoking. Investigation of genetic differences in the inducibility of aryl hydrocarbon hydroxylase will hopefully explain some of the mechanisms of this interaction.

Precancerous lesions

Epithelial metaplasia, dysplasia and scars in lung parenchyma are regarded as precancerous lesions which would affect the cell type of carcinoma. Environmental influences, such as cigarette-smoking, must be the main factor.

Predisposing morbid conditions

A higher incidence in former tuberculosis patients is reported (15). An increased incidence of adenocarcinoma is reported (16) in patients with scleroderma, the main features being a female preponderance and a positive correlation with the intensity of sclerodermic interstitial pulmonary fibrosis.

Multiple primary neoplasms

Lung cancer appears occasionally in combination with other smoking-associated cancers (e.g. laryngeal or bladder cancer). This information is important for the prevention of secondary cancer.

Environmental factors

Socioeconomic status

A characteristic socioeconomic variation in lung cancer incidence which differs greatly in each country is probably related to the patterns of cigarette-smoking in each community. In India and Sri Lanka, people of lower socioeconomic status smoke Bidis rather than cigarettes.

Tobbaco

The association with cigarette-smoking is quite strong in males and is also significant in females. The attributable risk in males from cigarette-smoking often exceeds 70%. In females, more cases were observed to be under the influence of passive smoking. The lung cancer risk in non-smoking wives was observed to be 1.61 and 2.08 when husbands smoke 1–19 and 20 or more cigarettes daily compared to women with non-smoking husbands (prospective study, Japan) (Fig. 1) (10). Similar results were reported from Greece in a case-control study. Since side-stream smoke of cigarettes contains a higher concentration of carcinogens than main-stream smoke, these data, when further confirmed, will be of great importance for public health.

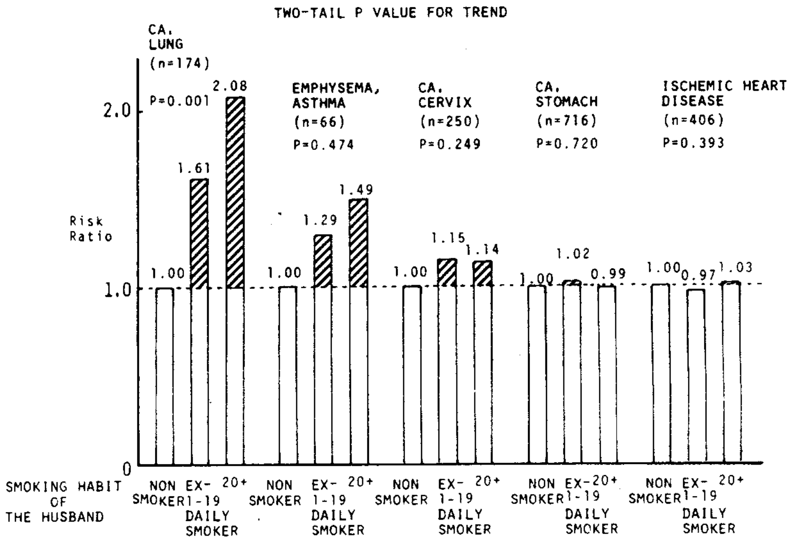


FIG. 1. *Age-occupation standardized mortality ratio for selected causes of death in non-smoking women according to smoking habits of husbands. Prospective study, Japan, 1966–1979.*

Tumors associated with cigarette-smoking and other air-borne carcinogens are mainly squamous-cell carcinoma and small-cell (oat-cell) carcinoma. The proportion of adenocarcinomas is higher in females. This is of interest since most passive smokers inhale side-stream smoke through the nose instead of through the mouth.

Daily cigarette-smoking proved to be the most important cause of lung cancer in Japan in the ongoing prospective study conducted by the present writer, the relative risk and attributable risk being 4.13 and 69.42%, respectively, in males. The study includes 265,118 adults aged

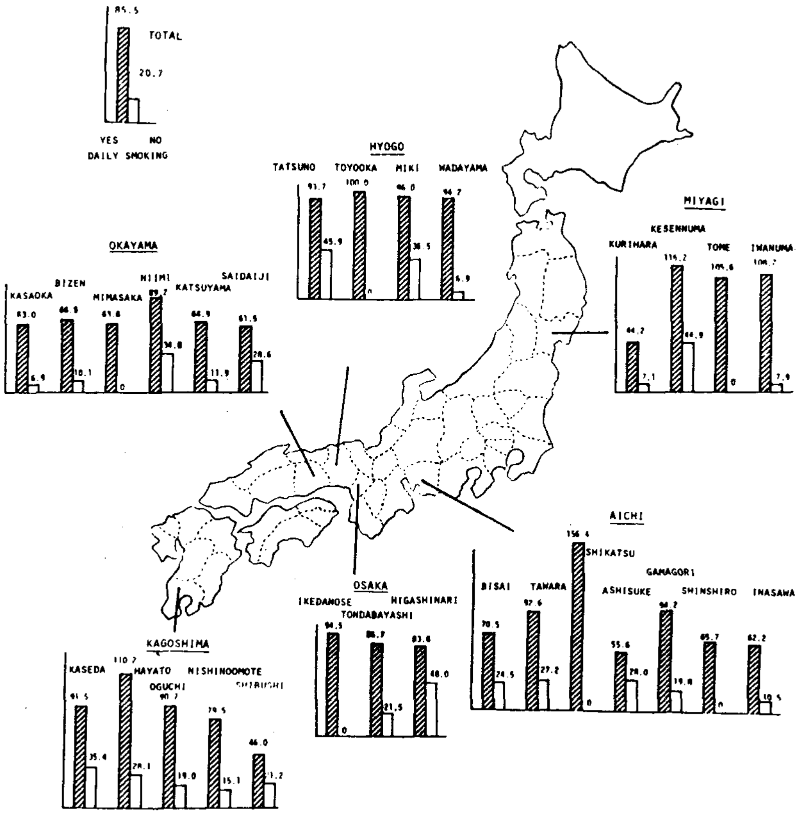


FIG. 2. *Standardized mortality rate for lung cancer according to habits of smoking and health center districts. Prospective study (males), Japan, 1966–1978.*

40 years and above comprising 91–99% of the census population in 29 health center districts. These people were interviewed from October to December, 1965 (5–7). These interviews were held at the time of the Japanese census in 1965. A record-linkage system was established between the risk-factor records (collected in 1965 and checked in 1971 and 1976), a current residence list obtained by specially planned annual census, and death certificates. During 13 years' follow-up, there have been 3,060,499 (1,369,937 males and 1,690,562 females) observed person-years. A total of 39,127 deaths occurred during this period (22,946 males and 16,181 females). The number of lung cancer deaths was 1244 (940 males and 304 females). The subjects were generally healthy at the time of interview and they were grouped according to their smoking habits into non-smokers, occasional smokers, ex-smokers and daily smokers. Standardized mortality rates of lung cancer were calculated over the 13-year period. In any of 29 health center districts where the study was performed, daily cigarette-smokers showed a far higher standardized mortality rate for lung cancer than non-smokers (Fig. 2). There was a clear-cut dose-response relationship, the standardized mortality rates for lung cancer being 20.7, 42.2, 77.0, 104.4, 141.5 and 177.6 in non-smokers, daily smokers of less than 9, 10–14, 15–24, 25–49 and

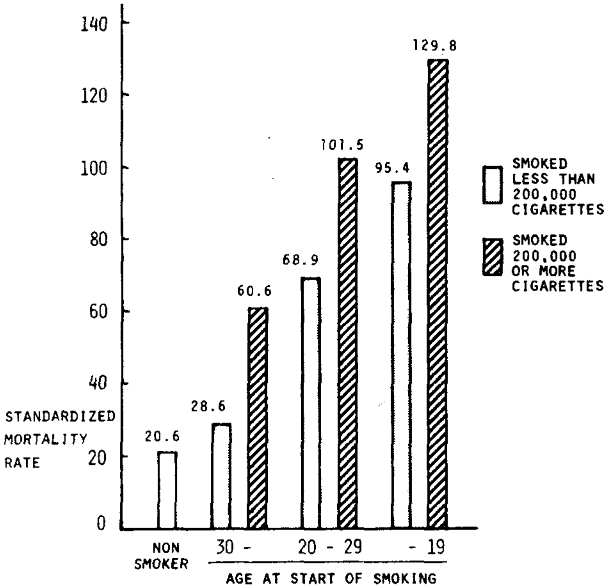


FIG. 3. *Standardized mortality rate for cancer of the lung according to age at start of smoking and total number of cigarettes smoked.*

50 cigarettes, respectively. For each category of cigarette-smoking, the risk was higher for those who began smoking in their teens (Fig. 3). Such early-age starters showed about 5 times higher risk of lung cancer compared to non-smokers. The fact that both the age at start of smoking and the total amount of smoking independently influence the risk of lung cancer indicates that carcinogens included in cigarette smoke must be operating both as initiators and promoters.

A similar dose-response relationship was observed in China, the Philippines and India by case-control studies.

In Buhan, China, a study conducted in 1977 on 148 males with lung cancer (diagnosed in 1974–1977) and age-matched (with 5-year range) controls (non-cancer, non-respiratory cases) revealed that the risk of cigarette-smoking was 1.00, 1.26, 1.48, 2.19 and 3.58 in non-smokers, daily smokers of less than 5, 6–10, 11–19 and 20 or more cigarettes, respectively (Buhan Medical School, 1977).

In the Philippines, case-control studies conducted by the author on 150 male lung cancer cases and 203 controls (stomach cancer) registered at the Philippine Cancer Society revealed that the relative risk was 1.00, 1.08, 1.79, 2.40, 3.43, 4.90 and 17.15 in non-smokers, daily smokers of 1–9, 10–19, 20–29, 30–39, 40–49 and 50 or more cigarettes, respectively.

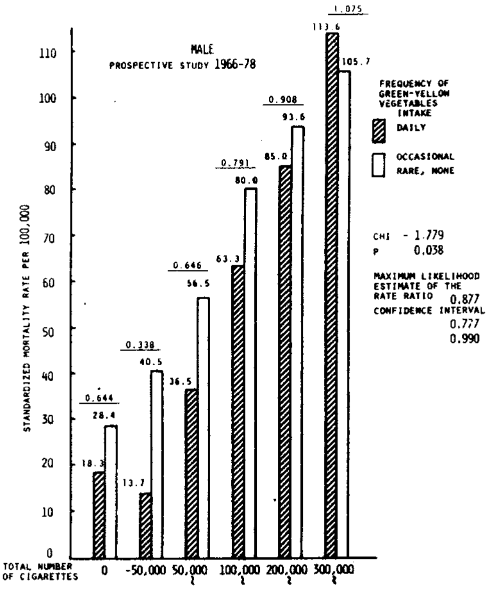
In Bombay, India, case-control studies conducted on 792 pairs of lung cancer cases and matched controls showed that the relative risk was 1.0, 3.1 and 9.5, respectively, in non-smokers, daily smokers of less than 20, 20 and more cigarettes, respectively. Bidi-smoking was also reported to enhance the risk of lung cancer, the relative risk being 19.3 (Ref. 14).

Alcohol

Although there is an association with alcohol consumption, this has not been demonstrated independently of cigarette-smoking.

Diet

Vitamin A deficiency may increase the risk of lung cancer in man. Persons observed in a prospective study in Japan were divided into those who took green-yellow vegetables daily and those who did not and also by socioeconomic status. Green-yellow vegetables are defined as those containing over 1000 International Units of beta-carotine per 100 g: e.g. carrots, spinach, green pimento, pumpkin, green lettuce, chives, leek (green), turnip leaves, asparagus (green), chicory and parsley. For daily consumers of green-yellow vegetables, the age-adjusted death rates for



OBSERVED PERSON-YEARS			185433	16123	69253	276835	217364	148883
			61380	4965	25946	107886	87944	68999
LUNG CANCER DEATHS	GREEN-YELLOW VEGETABLES INTAKE	DAILY OBS.	34	3	25	175	185	169
		DAILY EXP.	39.2	3.0	28.0	174.5	190.2	155.1
		OTHERS OBS.	17	2	15	86	82	73
		OTHERS EXP.	14.8	1.0	12.0	77.5	87.8	81.9

THE HETEROGENECITY CHI-SQUARE 5.925 N = 5
TWO-SIDED P = 0.314

FIG. 4. *Standardized mortality rate for lung cancer according to total number of cigarettes smoked and frequency of consumption of green-yellow vegetables.*

lung cancer were 44.8 per 100,000, whereas non-daily-consumers had rates of 58.8 in higher social classes. The ratio is 0.76. This ratio increases slightly with a decrease in social status, but the risk-lowering effect remains throughout. Green-yellow vegetable consumption was then cross-tabulated with smoking: consumers of green-yellow vegetables showed a lower risk of lung cancer for both smokers and non-smokers. This was found to be significant for both males and females. There is a dose-response relationship between the total number of cigarettes ever smoked and the lung cancer risk and in each category of smoking; daily consumers of green-yellow vegetables showed a lower standardized mortality rate for lung cancer compared to non-daily consumers, except for those who had smoked over 300,000 cigarettes in the past (Fig. 4). The beneficial effect of daily consumption of green-yellow vegetables is absent in those who started smoking in their teens. From green-yellow vegetables, there is an estimated intake of 640 IU of vitamin A and 75.2 mg of vitamin C in 1970 in Japan. This amount of vitamin A is 44% of the total daily intake in Japan. The vitamin C represents 23% of the total daily intake. Thus, if green-yellow vegetables play a protective role, the main candidate must be vitamin A, followed by vitamin C, plus perhaps other unknown factors. Similar studies are expected to be conducted in other countries in the Orient.

Radiation

The lung cancer risk is reported to be high in those who work in mines with high atmospheric radon (e.g. uranium, fluorspar and hematite mines). An increased risk was also observed in patients irradiated for spondylitis. The increased risk in atomic bomb survivors in Hiroshima and Nagasaki does not seem to be explained on the basis of smoking or occupational exposure alone.

Occupation

Hazardous industries for lung cancer include uranium, hematite, fluorspar and asbestos mining, milling and manufacture of coal-gas in gas and steel works, as well as exposure to nickel and chrome ore dust.

Specific carcinogens include arsenic, asbestos, mustard gas, polycyclic aromatic hydrocarbons, radon products, and bis(chloromethyl) ether. The multiplicative effect of cigarette-smoking and asbestos exposure has been noted. Similar situations may exist with other occupational carcinogens. Each of these occupations was also found to be an important risk factor for lung cancer in Japan. For instance, metal workers were found to have a significantly higher risk of lung cancer.

Material used is derived from the Vital Statistics, 1960–1967, Japan, and the Census Report, 1965, Japan. According to the 1965 census in Japan, there were 377,100 males classified as metal workers. During the period 1960–1967, there were 39,255 lung cancer deaths. Of these, 232 lung cancer deaths occurred in metal workers. This is excessive when compared to the expected number of deaths (176.54), which was obtained by applying the age-specific mortality rates from lung cancer from each year to the age-specific census population of these workers (9). The excess deaths from lung cancer in metal workers were noted in 1960–1963 and in 1964–1967. Excess deaths from lung cancer were observed also in workers in the mining and quarrying industries (population 2,152,000). The observed number of lung cancer deaths totaled 151; expected, 127.93 ($\chi^2 = 4.16$, $P < 0.05$). No other occupations showed excess deaths from lung cancer in this study.

The higher risk of lung cancer in metal workers was also observed in the on-going prospective study in Japan. For all groups, the