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Comparison of Lung Cancer Incidence Rates by Histological Type in High and Low Incidence Countries, with Reference to the Limited Role of Smoking

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To find a clue to lung cancer etiology in Japan, differences in the pattern of lung cancer histology and related time trends between Osaka, Japan, and the North West Region of England were investigated. Material comprised all incident lung cancer cases registered in both regional registries (14,521 in the Osaka Cancer Registry and 29,859 in the North West Regional Cancer Registry). (1) The age-standardized incidence rate of lung cancer was higher in the North West Region than in Osaka (80.4 among males and 20.9 among females per 100,000 population in 1979–82 versus 32.1 and 9.2 respectively). (2) A higher proportion of adenocarcinoma was observed in Osaka (36.3% in males and 62.0% in females) than in the North West Region (12.3% and 18.9% respectively). (3) Using the relative frequencies of each histological type according to sex and age-group, age-standardized incidence rates were calculated for the main lung cancer histological types. It was shown that the incidence rates of adenocarcinoma were similar in the two areas (10.6 in males and 5.3 in females in Osaka versus 10.0 and 3.5 in the North West Region, respectively) while those of squamous cell and small cell carcinomas were much higher in the North West Region than in Osaka. (4) Time trends of incidence rates showed an increase only for adeno- and small cell carcinomas in Osaka. Slight increases were observed for adenocarcinoma in both sexes and for squamous cell carcinoma in females in the North West Region. (5) Considering cigarette consumption and the relative risks of smoking in the two areas, the possible existence of other risk factors for adenocarcinoma in both sexes in Japan, besides active smoking, was suggested.

Key words: Epidemiology — Lung cancer — Histological incidence — Histological distribution — Trends

Histological manifestations of lung cancer are important not only for clinical management but also for etiologic investigations.[1, 2] Thus, studies have been conducted on the histological distribution of lung cancer and time trends using hospital cases[3–5] as well as community-based incident cases.[6–10] Following these studies, it was suggested that the relative frequency of squamous cell carcinoma was high in areas with a high incidence rate of lung cancer and that the frequency of adenocarcinoma was high in Asia or ethnic groups of Asian origin.[4, 6, 7] However, there has been no direct, comparative study on lung cancer histology between a high-risk lung cancer country and a low-risk country such as Japan.

Using population-based registries' data, the authors aimed to estimate the age-standardized incidence rates of the major histological types of lung cancer and to observe the time-trends in two areas: Osaka, Japan and the North West Region, England. The characteristics of these areas regarding lung cancer occurrence are as follows.

Osaka is a large commercial as well as industrial area (1980 census population: 8.5 million) in Japan and it is one of the areas in the world where low lung cancer incidence and mortality are observed in males.[11, 12] The mortality rates, however, have been rapidly increasing in recent years.

The North West Region (NWR)[*4] (1977 population: 4.1 million) is a hospital board

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[*4] Abbreviations: NWR, North West Region (of England); SQ, squamous cell carcinoma; SM, small cell carcinoma; AD, adenocarcinoma; LA, large cell carcinoma.

area in north-western England, covering all of Greater Manchester, Lancashire and a small part of Derbyshire. Like Osaka, much of the region is heavily industrialized. It is one of the areas in the world which has had high rates of mortality and incidence of lung cancer, and where rates have been declining among males,[11-13] in contrast to Japan.

Materials and Methods

Cancer cases are registered in both Osaka and NWR Cancer Registry using cancer reports sent from all medical institutes in each registry area. Routinely these have been supplemented by cancer death certificates.

Table I shows the number of lung cancer cases observed. Subjects in this study were primary lung cancer cases registered in both registries during the period 1974–1982, and represented 14,521 cases in Osaka and 29,859 in NWR. Of all subjects, 7,032 (48.4%) in Osaka and 10,806 (36.2%) in the NWR had histological diagnoses on the cancer notifications received from hospitals (Table I). The observation period is divided into two periods; 1974–78 and 1979–82. The proportion of cases with histological diagnosis was higher in the later period in both areas, as shown in Table I.

In the Osaka Cancer Registry, the International Classification of Diseases for Oncology (ICD-O)[14] was used for coding histological diagnosis. The NWR used the Manual of Tumor Nomenclature and Coding (MOTNAC)[15] up to 1978 and then ICD-O from 1979. Therefore, for the earlier half of the observation period, large cell carcinoma could not be identified in NWR, as there was no specific code for this entity in MOTNAC.

On the basis of the WHO's histological classification of lung tumors,[16] the cases were grouped into four major types and two other related groups: squamous cell carcinoma (SQ), small cell carcinoma (SM), adenocarcinoma (AD), large cell carcinoma (LA), undifferentiated carcinoma unspecified, and other histological types.

The histological distribution was calculated by sex and by 10-year age-group for each and for a combined time period in the two areas. Under the assumption that in the same age-group the cases with unnotified histological diagnoses would have the same histological distribution as the cases with notified histologies, age-standardized incidence rates were estimated for each histological type in each area by the following methods; (1) the lung cancer age-specific incidence rate was multiplied by the appropriate age-specific histologic proportion for each sex, period, and area, (2) the histological type specific incidence rates according to sex and age-group obtained were adjusted to Doll's world population, and age-standardized rates were calculated by sex, histological type and period.

Results

Histological Distribution The histological distribution of lung cancer according to sex and period is shown for each area in Table II. Examining the data in the later period (when the proportion for LA was available in NWR), SQ was the most frequent type in Osaka among males followed by AD, SM, and LA. Among Osaka females, AD was the leading type followed by SQ, SM, and LA.

Among males in NWR, SQ was also the most frequent type but was followed by SM, AD, and LA in that order. Females showed the same ranking of histology as males, but SQ had lower and SM and AD had higher percentages than for males.

Comparing the two areas, a higher frequency of AD in Osaka and that of SQ and SM in NWR were characteristically observed in both sexes.

Table I. Numbers of Lung Cancer Cases Registered and Proportions of Cases with Histological Diagnosis in Two Areas

Area	Sex	No. of all lung cancer cases registered		No. of cases with histological diagnosis		% of cases with histological diagnosis	
		1974–78	1979–82	1974–78	1979–82	1974–78	1979–82
Osaka	Male	5,122	5,422	2,287	3,058	44.7%	56.4%
	Female	1,896	2,081	696	991	36.7	47.6
	Total	7,018	7,503	2,983	4,049	42.5	54.0
NWR	Male	12,796	10,441	4,321	4,024	33.8	38.5
	Female	3,336	3,286	1,196	1,265	35.9	38.5
	Total	16,132	13,727	5,517	5,289	34.2	38.5

Table II. Histological Distribution of Lung Cancer in Osaka and NWR According to Sex and Period

Sex	Histology	Osaka		NWR	
		1974–78	1979–82	1974–78	1979–82
Male	Total	100.0%	100.0%	100.0%	100.0%
	SQ	43.9	40.4	58.3	58.8
	SM	13.0	13.7	18.1	19.0
	AD	34.2	37.8	10.9	13.9
	LA	4.1	5.9	—	2.0
	Undif. ca. unspec.	3.6	1.2	11.9[a]	5.6
	Others	1.2	1.0	0.8	0.7
Female	Total	100.0	100.0	100.0	100.0
	SQ	22.7	18.0	37.0	38.7
	SM	8.6	11.8	30.5	29.9
	AD	59.8	63.6	17.6	20.1
	LA	3.3	4.0	—	2.2
	Undif. ca. unspec.	3.6	0.9	13.6[a]	7.5
	Others	2.0	1.7	1.3	1.6

a) LA in NWR for 1974–78 could not be classified. See text. It was included in the category of "undifferentiated carcinoma unspecified."
Key: SQ = squamous cell carcinoma, SM = small cell carcinoma, AD = adenocarcinoma, LA = large cell carcinoma, Undif. ca. unspec. = undifferentiated carcinoma unspecified, Others = other histological types.

Table III. Histological Distribution of Lung Cancer by Age-group in Osaka and in NWR for 1974–1982

Sex	Histology	Osaka				NWR			
		Age-group				Age-group			
		40–	50–	60–	70–	40–	50–	60–	70–
Male	SQ	30.4%	39.9%	43.1%	47.1%	47.1%	55.7%	60.3%	62.8%
	SM	13.4	15.0	12.9	13.7	23.6	20.3	17.9	16.1
	AD	44.0	36.6	35.2	32.4	15.3	12.8	11.8	11.7
	LA	7.7	5.8	5.0	4.5	—	—	—	—
Female	SQ	11.0	12.1	25.0	23.0	30.8	32.9	42.0	42.3
	SM	4.6	9.2	14.1	9.9	39.7	30.4	29.1	26.3
	AD	74.0	71.4	53.5	59.6	16.4	22.9	16.3	19.0
	LA	4.6	3.2	4.1	3.8	—	—	—	—

—: LA could not be classified for 1974–78 in NWR. See text. Key as in Table II.

The histological distribution by 10-year age-group for the total period is shown in Table III for each area. In males and females, the percentage of SQ increased with age in both areas. Proportions for SM in NWR and AD in Osaka showed a decrease with age.

Before the incidence by histological type was estimated, the representativity of the material from Osaka was examined. Only cases with histological diagnosis were analyzed in the present study which comprised 48% of the total incident cases in Osaka. The proportion of histologically diagnosed cases is usually high in hospital-based series, although inevitably, it contains some bias compared to the population-based data. In Table IV, the present population-based study series (Series 1) was compared with three other study series carried out on a hospital basis in Japan. Series 2 represents the data from the Nation-Wide Lung Cancer Registry[17]; Series 3, the data from the National Cancer Center[18]; and Series 4, the data from the Center for Adult Diseases, Osaka.[19] Series 2 includes data from

Table IV. Comparison of Relative Frequencies of Histological Type among Four Series from Registries in Japan

Histological type	Male				Female			
	Series				Series			
	1	2	3	4	1	2	3	4
No. of cases	3,058	5,810	1,257	537	991	1,677	380	109
SQ	40.4%	46.2%	38.6%	40.8%	18.0%	18.6%	10.8%	13.8%
SM	13.7	12.8	9.6	14.0	11.8	9.1	6.3	11.0
AD	37.8	31.5	32.1	31.7	63.6	63.8	63.2	63.3
LA	5.9	7.4	9.0	10.1	4.0	5.8	9.7	6.1
Undif. ca. unspec.	1.2	1.2	—	0.6	0.9	1.1	—	2.8
Others	1.1	0.9	10.7	5.2	1.7	1.6	10.0	1.8
Period observed	(1979–82)	(1978–80)	(1976–85)	(1977–84)	(1978–80)	(1978–80)	(1976–85)	(1977–84)

Series 1: Data from the Osaka Cancer Registry. Series 2: Data from the Nation-Wide Lung Cancer Registry.[17] Series 3: Data from Hospital Registry of the National Cancer Center.[18] Series 4: Data from Hospital Registry of the Center for Adult Diseases. Osaka.[19] Key as in Table II.

Table V. Estimated Age-standardized Incidence Rates[a] of Lung Cancer by Histological Type in Osaka and in NWR

Sex	Histology	Osaka		NWR	
		1974–78	1979–82	1974–78	1979–82
Male	Total	28.5	32.1	82.5	80.4
	SQ	13.0	13.2	48.3	47.5
	SM	3.6	4.5	14.7	15.3
	AD	9.4	11.8	9.0	11.0
	LA	1.1	1.8	—	1.7
	Undif. ca. unspec.	1.0	0.4	9.7[b]	4.3
	Others	0.3	0.3	0.7	0.5
Female	Total	8.2	9.2	17.1	20.9
	SQ	1.9	1.7	6.4	8.0
	SM	0.7	1.1	5.2	6.4
	AD	4.8	5.8	2.9	4.1
	LA	0.3	0.4	—	0.5
	Undif. ca. unspec.	0.3	0.1	2.3[b]	1.6
	Others	0.1	0.2	0.2	0.3

a) Age-standardized rates (per 100,000 population), adjusted by Doll's world population.
b) LA could not be classified for 1974–78 in NWR (see text). It was included in the category of "undifferentiated carcinoma unspecified."
Key as in Table II.

60 departments of different university medical schools, 10 cancer centers and 49 large- or middle-sized general hospitals in Japan. The proportion of cases with known histologies was 48.4%, 66.0%, 72.9%, and 60.0%, respectively. Although the proportion of "others" was high in Series 3 and the data could not directly be compared with the other series, the ranking order of the main four histological types was the same in each series except for SM and LA among females in Series 3. The proportions for each histological type showed some differences among the four series. However, the proportion of any specific histological type did not increase or decrease with the proportion of cases whose histologies were known.

Age-standardized Incidence Rates by Histological Type Histological type specific age-standardized incidence rates are shown in

Table V. Comparing the rates for the later period between the two areas among males, the rates for SQ and SM were respectively 3.6 and 3.4 times higher in NWR than in Osaka. However, the rates for AD and for LA were quite similar in both areas. The same pattern was observed for females; the rates for SQ and SM were respectively 4.7 and 5.7 times higher in NWR while the rates for AD and LA showed little or no difference between the two areas.

Observing the time trends, the rate for total lung cancer increased in the later period in Osaka in both sexes while a decrease in males and an increase in females was noticed in NWR. The age-standardized rate for SQ showed no change and that for AD showed an increase in Osaka in both sexes. In NWR, rates for SM and AD in both sexes and that for SQ in females increased while SQ in males showed a decline.

Discussion

Possible Bias of Population-based Data in the Present Study Only the cases of lung cancer with histological diagnosis in each area (48% of all registered cases in Osaka and 36% in NWR) were analyzed in the present study. Cases without histological notification are more likely to include; (1) rapidly-growing cancer such as SM or undifferentiated carcinoma, (2) those difficult to examine such as peripheral lung cancer, (3) cancers among aged persons, (4) cancer cases whose doctors failed to send a cancer report to the registry, etc. The extent of possible biases due to such cases remained unknown. However, Table IV[17–19] showed little variation in the proportional distribution of the four major histological types among the four different registry data series in Japan, even though the proportion of histologically known cases was higher in the hospital-based series (Series 2–4).

Comparability of Histological Diagnoses The histological diagnoses of the subjects were those originally given at hospitals or laboratories in the two areas. As there were many difficulties involved in examining the comparability of histological diagnosis on all subjects between the two areas, the authors conducted an exchange "blind review" study of 112 lung cancer specimens randomly collected from a cancer center in Osaka and a university hospital in NWR.[20] All materials were also examined by the WHO Collaborating Center for International Classification (WHO-CC). An 88% concordance was observed for the major histological types between Osaka and NWR, 89% between NWR and WHO-CC and 93% between Osaka and WHO-CC.

Difference in Total Lung Cancer Incidence Rate between Osaka and NWR In Fig. 1, time trends of daily consumption of cigarettes per person over 15 years of age in UK[21] are compared with those in Japan.[22, 23] The increase in daily cigarette consumption in UK occurred 20 years earlier than that in Japan. The low lung cancer incidence in Japan at present may be attributable to a lower consumption of cigarettes in the past, including the steep decrease of consumption around World War II. However, in recent years lung cancer incidence has been increasing rapidly in Japan in keeping with the UK's past experience.

In NWR, total lung cancer incidence has been decreasing among males through all age-groups except those older than 70 years and, inversely, increasing among females. The decrease among males in UK would have mainly resulted from cohort effects influenced by both the decrease in tar content and the decrease in the smoking rate among males in recent years.[24] These factors would not have been effective for the age-groups over 70.

Difference of Rates for Squamous Cell and Small Cell Carcinomas The relative risks of smoking estimated for major histological types of lung cancer are listed in Table VI from four case-control studies recently conducted in Europe[25, 26] and in Osaka.[27, 28] Comparing the results in the four studies, the relative risk of SQ for smokers was found to be 3.5 times higher in Europe than in Japan.

Possible causal factors for the higher incidence of SQ in NWR would be higher tar intake in UK in the past and a higher relative risk (or greater sensitivity) for SQ in NWR where a lower proportion of the population smoke. The age when smoking started might also have been younger in the NWR than in Osaka because the legal smoking age is 20 in Japan but 16 in the UK. However, regrettably, data concerning the true age when smoking started were not available in either area.

Trends of tar intake per adult estimated by Doll and Peto[21] are indicated in Fig. 1. Although total cigarette consumption has been increasing, the trends of average tar intake have been decreasing since 1950. Doll suggested that this decrease was the cause for the recent decrease of lung cancer incidence in the UK. There are no equivalent data on tar intake in Japan, although Hirayama reported that tar content per cigarette decreased to 60% during 1967–1985.[29] It was also observed that filter cigarettes increased from 3% to 90% of the total consumption in the 1960's.[23] On the other hand, total cigarette consumption increased in Japan up until 1975 (Fig. 1). From these figures, tar intake in Japan was estimated to have started to decrease from around 1965–70. The effects of this on the incidence rate in Japan should be observed in the future.

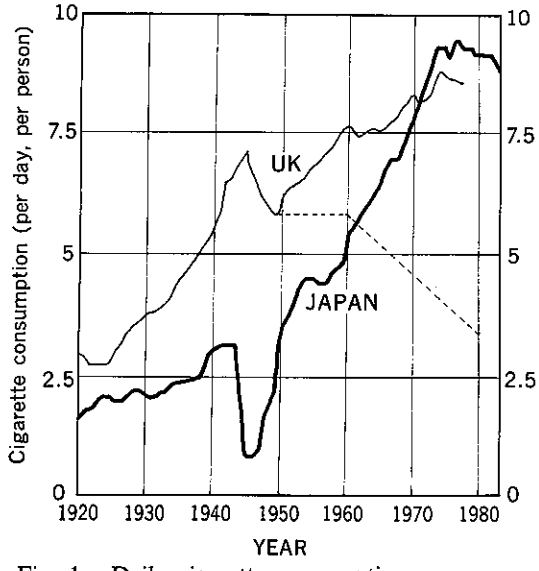

Fig. 1. Daily cigarette consumption per person over 15 years of age in the UK and in Japan. Increasing trends had been observed in both countries except for a limited period during and after World War II then have recently leveled off and started to decrease. Japan is indicated by a thick line (—) and the UK by a thin line (—). The broken line provides an approximate estimate of tar intake per adult in the UK. Sources: Doll and Peto (1981),[21] Shimizu (1979)[22] and Japan Tobacco and Salt Public Corporation (1979–84).[23]

The difference in incidence rates of SM between Osaka and NWR could be explained by the time difference in the spread of smoking in the two areas.

Similarity in the Adenocarcinoma Incidence Rates The relative risks of AD from smoking were similar in the four studies (Table VI). This suggests that the incidence rate of AD should be lower in Osaka than in NWR, because of the later spread of smoking in Japan. However, the incidence rate of AD was similar in both areas. Furthermore, an increase in the relative frequency of AD was observed in many studies. These two considerations may indicate the existence of causal factor(s) other than usual smoking for AD in Japan. Possible risk factors for AD, such as passive smoking,[30–33] a history of disease in childhood,[31] chronic bronchial episodes,[32] simple or complex exposure to indoor or outdoor air pollution, etc. should also be investigated in Japan in association with AD.

Studies Necessary on Histological Types of Lung Cancer in the Two Areas Considering

Table VI. Comparison of Relative Risks of Smoking for Major Histologic Types of Lung Cancer in Four Studies

Area	Year reported	Relative risk				Sample size		Authors
		SQ	SM	AD	LA	Cases	Controls	
Europe	1984	20.9	10.5	3.5	8.0	6,920	13,460	Lubin and Blot[25]
	1985	17.2[a]		3.6[b]		1,217	1,915	Benhamou *et al.*[26]
Japan	1986	6.0	10.3	2.8	4.4	498	498	Nakamura *et al.*[27]
	1986	7.9	10.2	3.6	4.6	1,660	—	Sobue *et al.*[28]

a) Kreyberg I (squamous cell, small spindle oat cell, and "Kreyberg I type cell not distinguished").
b) Kreyberg II (adenocarcinoma type).
Key as in Table II.

the time-difference in the spread of smoking between the UK and Japan and the difference in the relative risks for SQ between Europe and Japan, the answers to the following problems should be sought in the future: (1) why the incidence rate of SQ and the relative risk of SQ from smoking are so conspicuously low in males in Japan compared with England or European countries, and (2) why the incidence rate of AD in both sexes in Japan is at the same level as in England.

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