

Trends of Lung Cancer Incidence by Histologic Type: A Population-based Study in Osaka, Japan

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We investigated trends of lung cancer incidence from 1974 to 1993 by histologic type, using data from the population-based cancer registry in Osaka, Japan. Since the proportion of cases with histologic types identified was not sufficiently high, sex- and age-specific incidence rates by histologic types were estimated assuming that the distribution of histologic types was the same across the same sex and age group regardless of reporting status. Cumulative risk from 0 to 74 years old for total lung cancer increased 1.3-fold from the period 1974–77 to 1986–89 and then plateaued in the period 1990–93 for both males and females. When divided into histologic types, cumulative risk for incidence of squamous cell carcinoma was almost constant during the study period for both males and females. During the same period, adenocarcinoma increased up to 1.4-fold for both males and females. This increase seemed to have reached a plateau recently for males, but not for females. Small cell carcinoma increased monotonously up to 1.6- to 1.7-fold for both males and females. Large cell carcinoma showed over 2-fold increase for both males and females; however, the estimates fluctuated due to the small number of cases. This study provides further evidence of a relative increase of adenocarcinoma compared to squamous cell carcinoma. Recent trends of tapering increase of lung cancer incidence should be confirmed by further observation.

Key words: Lung cancer — Histologic type — Incidence — Trend — Smoking

Recent trends of lung cancer incidence are showing different patterns by country.¹⁾ In the US and UK, where lung cancer incidences were relatively high and smoking control has been successfully implemented, incidence of lung cancer in males has reached a peak and now is in the decreasing phase, starting from younger age groups. In contrast, in Eastern Europe, where smoking control has been less successful, the incidence is still increasing. These trends have been greatly influenced by the trends of smoking prevalence. It is well known that the magnitude of association between lung cancer and cigarette smoking differs by histologic types. Squamous cell carcinoma and small cell carcinoma show a 10- to 20-fold increase among current smokers compared to non-smokers, while adenocarcinoma shows a 2- to 5-fold increase.²⁾ Therefore, smoking prevalence influences the trends of incidences differently among histologic types.

In the US and Europe, several hospital-based studies,^{3–6)} autopsy series⁷⁾ and population-based studies^{8–16)} have examined the trends of lung cancer incidence by histologic type. In Asian countries there have been hospital-based studies,^{17–20)} and a population-based study.²¹⁾ Most

of the studies showed a relative increase of adenocarcinoma as compared to squamous cell carcinoma in both males and females, especially in younger age groups.

Lung cancer incidence in Japan has been relatively low compared to other countries. It is reported that cumulative risk (0–74 years old) of lung cancer in Japan is 46.6 to 52.3 per thousand in males and 12.5 to 14.2 per thousand in females, i.e., approximately half of the incidences in the US and UK.²²⁾ The distribution of histologic types in Japan shows a higher proportion of adenocarcinoma compared to that in European countries.²²⁾ There are also several reports on the trends of histologic types in Japan from hospital-based studies,^{23, 24)} autopsy series^{25–27)} and a population-based registry.²⁸⁾ Most studies in Japan also showed a relative increase of adenocarcinoma and small cell carcinoma when compared to squamous cell carcinoma in both sexes. Since lung cancer cases from a single hospital or autopsy series may not be representative of all lung cancer cases in the population, it is desirable to investigate the trends using population-based cancer registries, although this method is limited by the small proportion of cases with identified histologic type. We report here the lung cancer incidence trends by histologic type based on data from the population-based cancer registry in Osaka, Japan, extending over 20 years.

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SUBJECTS AND METHODS

Osaka Cancer Registry has been operating since 1962, covering approximately 8,000,000 residents in Osaka Prefecture, Japan.²⁹⁾ Cancer cases are registered using cancer reports forwarded from all medical institutions in Osaka Prefecture. Routinely, these reports are also supplemented with cancer death certificates. During the period of 1962–78, the Registry used the ICD-8³⁰⁾ to classify topography and the SNOF³¹⁾ for histology. In 1979, the classification process was changed and the Registry started using ICD-9³²⁾ and ICD-O-M.³³⁾ According to the WHO's histological classification of lung tumors,³⁴⁾ lung cancer cases were classified into four major types, i.e., squamous cell carcinoma (M: 8051, 8052, 8070–8075), adenocarcinoma (M: 8050, 8140, 8141, 8211, 8250, 8251, 8260–8262, 8480, 8481, 8490, 8550), small cell carcinoma (M: 8033–8035, 8041–8043) and large cell carcinoma (M: 8012, 8030–8032, 8230, 8310). Incidence data in 1962–73 were excluded from this study because the proportion of cases with diagnosis of histologic type was low.

From 1974 to 1993, 33,900 male and 13,211 female lung cancer cases were entered in the Osaka Cancer Registry. To investigate secular trends of incidence rates, the study period was divided into five 4-year time periods; 1974–77, 1978–81, 1982–85, 1986–89 and 1990–93. The proportion of cases with diagnosis of histologic type throughout the study period was 60.2% for males and 52.3% for females; these values are not sufficiently high to allow direct estimation of the incidence by histologic type. Therefore, the following procedure was employed for estimating sex- and age-specific incidence rates by histologic type, using the assumption that the distributions of different histologic types in the same sex and age groups were the same between those with and without identified histologic type. First, sex-, age- (5-year age group) and period-specific incidence rates were calculated for all histologic types combined including the cases without diagnosis of histologic type. Second, sex-, age- (10-year age group) and period-specific proportions of each histologic type among the cases with the diagnosis were calculated for four major histologic types. Finally, the sex-, age- and period-specific incidence rate (5-year age group) was multiplied by the corresponding sex-, age- and period-specific proportion to estimate sex-, age- and period-specific incidence rates by histologic type. Based on the estimated sex-, age-specific incidence rates, cumulative risk from 0 to 74 and from 0 to 79 years of age was calculated for five 4-year time periods.³⁵⁾

To evaluate the trends of incidence in terms of chance variation, age-adjusted rate ratios were calculated using the Poisson regression analysis. Study subjects were limited to those who were aged 40 to 79 years old. Variables included in the model were age (5-year age group) and

period (4-year interval). The population number for the denominator of incidence rate was multiplied by the proportion of cases with histological diagnosis, so that the actual number of cases with histological diagnosis could be used as the numerator. The analysis was conducted separately by sex and also by 2 age groups (40 to 59 and 60 to 79 years of age). The PROC GENMOD in SAS program was used for actual calculation.³⁶⁾

RESULTS

Table I shows sex- and age-specific lung cancer incidence rates for five 4-year time periods. For both males and females, the incidence increased among the age groups above 55 years of age, while it was rather constant for the age groups less than 54 years of age. Among the age groups above 55 years of age, the magnitude of increase was greater in the older age groups. In the most recent period 1990–93, however, the increase seemed to plateau for most age groups except males of age 80 and above. For both males and females, cumulative risk from 0 to 74 and from 0 to 79 years of age increased 1.3–1.4 times from the period 1974–77 to 1986–89, and then leveled off in the period 1990–93. Out of 33,900 male and 13,211 female lung cancer cases throughout the study period, histologic type was reported for 20,401 (60.2%) cases and 6,908 (52.3%) cases, respectively. Among the cases with histologic type, the proportions of squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma were 38.8%, 36.1%, 15.9% and 7.0% in males, and 19.1%, 60.9%, 12.8%, and 4.6% in females, respectively. The proportion of cases with histologic type increased gradually from the period 1974–77 to 1986–89.

Fig. 1 shows trends of estimated age-specific incidence rates for male lung cancer by histologic type. For squamous cell carcinoma, increasing trends were limited to the age groups above 75 years old. Younger age groups less than 69 years old showed rather decreasing trends. For adenocarcinoma, increasing trends were observed for all age groups. Also, for small cell carcinoma, increasing trends were observed for all age groups, although the slope has leveled off recently for younger age groups. For large cell carcinoma, most age groups showed increasing trends up to the period 1986–89 and then decreased. In females, although relative frequencies of histologic types were different from those in males, chronological changes of each histologic type were similar to those in males (Fig. 2).

Table II showed the trends of cumulative risk for lung cancer incidence by histologic type. Throughout the study period, squamous cell carcinoma was the most frequent histological type in males while adenocarcinoma seemed to dominate in females. Squamous cell carcinoma increased slightly and then decreased for both males and

Table I. Trends of Age-specific Lung Cancer Incidence Rates (per 100,000) in Osaka Cancer Registry, Japan

Age group	Male					Female				
	1974-77	1978-81	1982-85	1986-89	1990-93	1974-77	1978-81	1982-85	1986-89	1990-93
40-44	7.2	6.2	7.0	9.7	11.7	3.7	3.7	4.3	4.2	5.4
45-49	20.2	14.7	17.0	17.9	17.7	7.2	7.7	8.3	6.6	8.6
50-54	34.2	38.3	37.7	36.8	33.0	12.1	11.4	12.9	16.9	13.5
55-59	65.3	70.7	82.3	83.9	75.2	24.2	23.2	25.3	23.5	26.4
60-64	130.1	131.5	136.8	157.0	147.5	31.5	38.2	39.3	37.4	40.4
65-69	209.7	261.9	271.2	269.3	275.4	56.6	64.3	71.3	76.6	71.1
70-74	303.7	358.5	428.7	430.9	421.4	82.4	95.9	107.1	117.1	112.5
75-79	381.3	469.3	523.8	598.3	594.5	90.7	112.5	149.7	157.1	160.7
80-84	321.5	459.0	624.8	668.8	761.6	89.2	134.5	149.0	192.1	193.9
85+	272.1	364.3	563.3	741.8	794.7	71.9	105.9	145.4	195.2	203.1
Cumulative risk (0-74 y.o.) ^{a)}	38.0	43.4	48.1	49.4	48.3	11.0	12.3	13.5	14.2	14.0
Cumulative risk (0-79 y.o.) ^{a)}	56.1	65.6	72.7	77.4	76.1	15.5	17.8	20.8	22.0	21.9
Total no. of cases	3,959	5,224	6,782	8,341	9,594	1,459	1,966	2,615	3,320	3,851
Proportion of cases with diagnosis of histologic type (%)	34.6	56.6	64.6	68.0	62.7	28.6	47.4	56.4	58.3	55.8

a) Per 1,000.

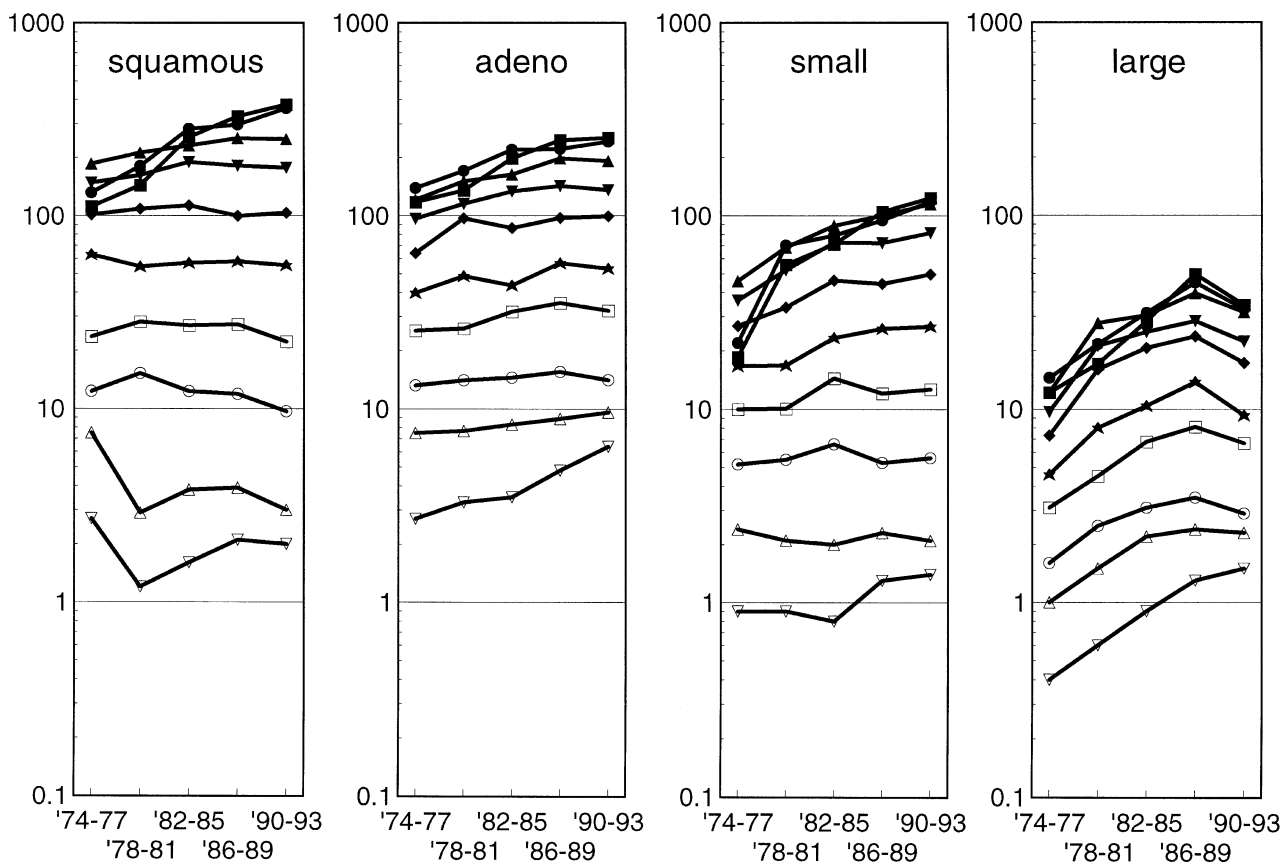


Fig. 1. Trends of age-specific lung cancer incidence rates for males by histologic type in Osaka Cancer Registry, Japan. Squamous, squamous cell carcinoma; adeno, adenocarcinoma; small, small cell carcinoma; large, large cell carcinoma. ■ 85+, ● 80-84, ▲ 75-79, ▼ 70-74, ◆ 65-69, ★ 60-64, □ 55-59, ○ 50-54, △ 45-49, ▽ 40-44.

females. Adenocarcinoma increased to some extent and has plateaued recently for males, while for females this plateau has not yet been observed. Small cell carcinoma increased rapidly for both males and females although the magnitude of cumulative risk itself was small. Large cell

carcinoma also increased and then decreased in the most recent period, 1990–93, for both males and females.

Table III shows age-adjusted rate ratios for the trends of lung cancer incidence taking the rate in 1974–77 as a reference. The age-adjusted rate ratio for total lung cancer

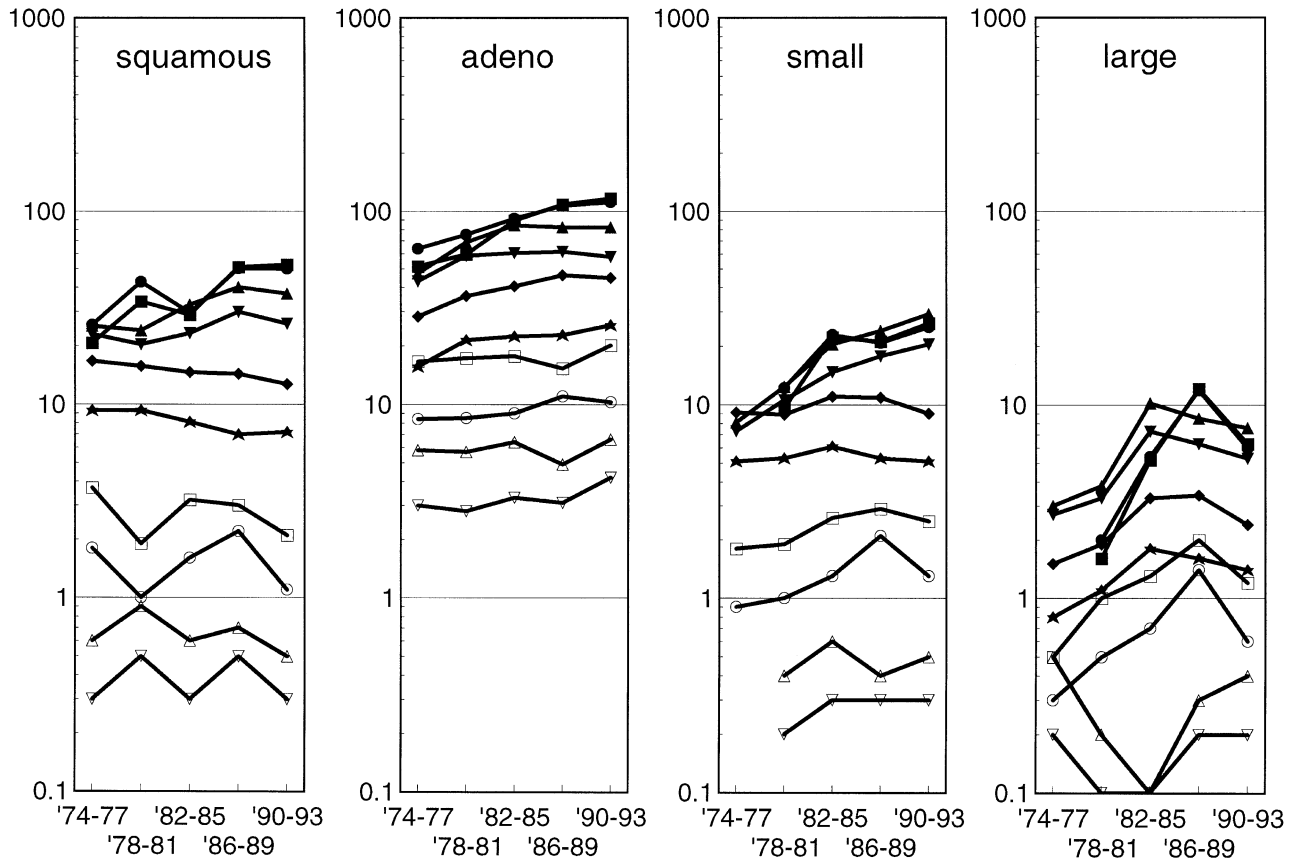


Fig. 2. Trends of age-specific lung cancer incidence rates for females by histologic type in Osaka Cancer Registry, Japan. Squamous, squamous cell carcinoma; adeno, adenocarcinoma; small, small cell carcinoma; large, large cell carcinoma. ■ 85+, ● 80–84, ▲ 75–79, ▼ 70–74, ◆ 65–69, ★ 60–64, □ 55–59, ○ 50–54, △ 45–49, ▽ 40–44.

Table II. Trends of Cumulative Risk for Lung Cancer (per 1,000) by Histologic Type in Osaka Cancer Registry, Japan

Age range	Histologic type	Male					Female				
		1974–77	1978–81	1982–85	1986–89	1990–93	1974–77	1978–81	1982–85	1986–89	1990–93
0–74	Squamous	17.8	18.4	20.0	19.0	18.5	2.8	2.5	2.6	2.9	2.5
	Adeno	12.5	15.6	16.1	18.1	17.6	6.1	7.6	8.0	8.4	8.6
	Small	4.9	6.1	8.3	8.2	9.0	1.2	1.4	1.8	2.0	2.0
	Large	1.4	2.7	3.5	4.1	3.2	0.3	0.4	0.7	0.8	0.6
0–79	Squamous	26.9	28.8	31.2	31.3	30.6	4.0	3.7	4.2	4.9	4.4
	Adeno	18.4	23.0	24.1	27.8	26.9	8.5	11.0	12.2	12.5	12.6
	Small	7.2	9.5	12.6	13.1	14.6	1.6	2.0	2.9	3.2	3.4
	Large	2.0	4.1	5.0	6.1	4.7	0.5	0.6	1.2	1.2	1.0

Table III. Age-adjusted Rate Ratio (95% Confidence Interval) for Trends of Lung Cancer Incidence When the Period 1974–77 Was Defined as a Reference in Osaka Cancer Registry, Japan

Histologic type	Age	Male					Female				
		1974–77	1978–81	1982–85	1986–89	1990–93	1974–77	1978–81	1982–85	1986–89	1990–93
Total	All	1.00	1.13 (1.08–1.17)	1.24 (1.19–1.30)	1.32 (1.26–1.37)	1.28 (1.23–1.33)	1.00	1.12 (1.04–1.21)	1.28 (1.19–1.37)	1.33 (1.25–1.42)	1.34 (1.25–1.43)
	40–59	1.00	1.00 (0.91–1.09)	1.10 (1.01–1.20)	1.14 (1.05–1.24)	1.07 (0.98–1.16)	1.00	0.98 (0.85–1.13)	1.09 (0.95–1.24)	1.10 (0.96–1.25)	1.16 (1.02–1.31)
	60–79	1.00	1.17 (1.11–1.23)	1.29 (1.23–1.35)	1.37 (1.31–1.43)	1.35 (1.29–1.41)	1.00	1.18 (1.08–1.28)	1.35 (1.25–1.47)	1.42 (1.32–1.54)	1.41 (1.31–1.52)
Squamous	All	1.00	1.00 (0.91–1.11)	1.06 (0.96–1.16)	1.04 (0.95–1.15)	1.00 (0.91–1.09)	1.00	0.88 (0.68–1.15)	0.94 (0.74–1.21)	1.05 (0.83–1.33)	0.91 (0.72–1.16)
	40–59	1.00	0.94 (0.77–1.15)	0.89 (0.74–1.08)	0.91 (0.76–1.10)	0.75 (0.62–0.90)	1.00	0.75 (0.41–1.37)	0.93 (0.53–1.62)	1.04 (0.61–1.76)	0.65 (0.37–1.14)
	60–79	1.00	1.02 (0.91–1.15)	1.11 (1.00–1.24)	1.09 (0.98–1.22)	1.08 (0.97–1.20)	1.00	0.91 (0.68–1.22)	0.95 (0.73–1.25)	1.06 (0.82–1.38)	0.97 (0.75–1.26)
Adeno	All	1.00	1.22 (1.09–1.36)	1.26 (1.13–1.40)	1.45 (1.30–1.61)	1.41 (1.27–1.56)	1.00	1.19 (1.02–1.39)	1.31 (1.13–1.52)	1.32 (1.14–1.52)	1.40 (1.21–1.61)
	40–59	1.00	1.06 (0.87–1.29)	1.19 (0.99–1.43)	1.33 (1.12–1.59)	1.30 (1.09–1.55)	1.00	1.00 (0.79–1.27)	1.08 (0.86–1.36)	1.02 (0.82–1.27)	1.22 (0.98–1.52)
	60–79	1.00	1.30 (1.13–1.50)	1.30 (1.13–1.49)	1.52 (1.33–1.73)	1.47 (1.29–1.68)	1.00	1.35 (1.10–1.66)	1.50 (1.23–1.83)	1.56 (1.29–1.89)	1.56 (1.29–1.89)
Small	All	1.00	1.16 (0.97–1.40)	1.54 (1.30–1.83)	1.55 (1.32–1.83)	1.69 (1.44–2.00)	1.00	1.15 (0.79–1.67)	1.53 (1.08–2.16)	1.66 (1.18–2.34)	1.66 (1.19–2.33)
	40–59	1.00	1.00 (0.73–1.38)	1.23 (0.92–1.66)	1.12 (0.83–1.50)	1.15 (0.86–1.54)	1.00	1.46 (0.61–3.47)	2.01 (0.89–4.53)	2.35 (1.07–5.17)	1.87 (0.84–4.16)
	60–79	1.00	1.26 (1.01–1.57)	1.71 (1.39–2.10)	1.78 (1.45–2.18)	1.97 (1.61–2.41)	1.00	1.08 (0.71–1.64)	1.42 (0.97–2.09)	1.52 (1.05–2.22)	1.60 (1.11–2.33)
Large	All	1.00	1.86 (1.36–2.55)	2.38 (1.77–3.22)	2.88 (2.15–3.87)	2.28 (1.69–3.06)	1.00	1.11 (0.56–2.20)	2.03 (1.10–3.75)	2.22 (1.22–4.05)	1.70 (0.93–3.13)
	40–59	1.00	1.53 (0.91–2.56)	2.18 (1.35–3.53)	2.57 (1.61–4.11)	2.30 (1.43–3.69)	1.00	0.97 (0.32–2.89)	1.21 (0.44–3.34)	2.21 (0.86–5.64)	1.48 (0.56–3.89)
	60–79	1.00	2.07 (1.38–3.08)	2.51 (1.71–3.70)	3.08 (2.12–4.49)	2.29 (1.56–3.35)	1.00	1.22 (0.51–2.91)	2.53 (1.15–5.56)	2.28 (1.04–4.98)	1.87 (0.85–4.10)

increased 1.3-fold from the period 1974–77 to the period 1986–89 for both males and females, then in 1990–93 decreased slightly for males and seemed to plateau for females. The magnitude of increase was greater for the age group 60–79 than the age group 40–59 for both males and females. When divided into histologic type, the age-adjusted rate ratio for male squamous cell carcinoma was constant with a slight increase in the intermediate period. For the age group 40–59 in males, a declining trend was observed while for the age group 60–79 the rate ratio slightly increased, then plateaued. Although the trends of squamous cell carcinoma in females was not completely stable, it appeared to be essentially constant throughout the periods. Adenocarcinoma showed a clear increasing trend up to 1.4-fold. The magnitude of increase was greater in older age groups for both males and females. For males, this increase peaked in the period 1986–89 and slightly decreased afterwards for both age groups, while for females a tapering increasing trend was

observed only for the older age group. Small cell carcinoma also showed a monotonous increasing trend up to 1.6- to 1.7-fold for both males and females. This increase was greater in older age groups for males, while for females it appeared to be greater in younger age groups. For large cell carcinoma, an over two-fold increase was observed for both males and females. The ratio then decreased in 1990–93 for both males and females. However, the estimates fluctuated due to the small number of cases.

DISCUSSION

This study has shown that the trends of lung cancer incidence in Osaka, Japan differ by histologic type and the recent trends are not simply monotonous. Cumulative risk of total lung cancer increased 1.4-fold from the period 1974–77 to 1986–89, then plateaued in the period 1990–93 for both males and females. Recent trends of

tapering increase were also observed in mortality statistics. The cumulative risk of mortality (0–74 years of age) for total lung cancer in Osaka Prefecture was 32.1, 36.5, 38.2, 40.2 and 39.8 for males and 8.9, 10.3, 10.7, 11.6 and 11.5 for females in 1974–77, 1978–81, 1982–85, 1986–89 and 1990–93, respectively.³⁷⁾ Decreasing trends of male lung cancer have already been observed in many countries, such as in the UK, Nordic countries and the US, where smoking control activities started earlier and the prevalence of current smokers has been successfully reduced.¹⁾ In Japan, although the prevalence of male current smokers is relatively high, i.e., 57.5% in 1996, it has gradually decreased from 81.8% reported in 1965.³⁸⁾ For females, there has been no report which indicates a substantial decrease of lung cancer incidence so far. However, this study suggests that total lung cancer incidence for females has been leveling off recently. This may be explained by the changing trends in different age groups of female smokers in Japan. Although the crude prevalence of female current smokers in Japan has stayed fairly constant during the last three decades (15.0% in 1965 and 14.2% in 1996), the age-specific prevalence has been declining from 23.0% in 1965 to 14.2% in 1996 for the age group above 60 years old, and increasing steadily for the younger age groups below 29 years old (6.6% in 1965 and 20.3% in 1996).³⁸⁾ Therefore, the tapering effect of lung cancer incidence in females would be mostly influenced by the decreasing smoking prevalence among the older age group.

When examined by histologic type, the increase of incidence in males seemed to have leveled off first for squamous cell carcinoma, followed by adenocarcinoma and large cell carcinoma. However, the trend for large cell carcinoma may not be reliable because of the small numbers of cases. Although small cell carcinoma showed a monotonous increasing trend to the most recent period in males, this increase may not continue much longer, since it plateaued recently in the group younger than 54 years old. In females, the trends by histologic type are not as clear-cut as in males, mainly due to the small number of cases. However, squamous cell carcinoma showed no increasing trend and large cell carcinoma showed a slight decreasing trend recently. As in males, small cell carcinoma showed a rather monotonous increase, but this increase has leveled off in the younger age groups. Adenocarcinoma has been increasing steadily, although this increase appears to have reached a plateau for the groups above 60 years of age. These trends have resulted in a relative increase of adenocarcinoma and small cell carcinoma compared to squamous cell carcinoma for both males and females in Japan.

In the US, all histologic types of lung cancer in males are in a decreasing phase, although the peak of each histologic type differed in time.¹⁵⁾ It is reported that in white

males, the incidence of squamous cell carcinoma reached the peak in 1981, followed by small cell carcinoma and large cell carcinoma in 1986, and finally adenocarcinoma in 1991. Trends of lung cancer incidence by histologic type among males in Japan generally seemed to follow the trends observed in the US. Small cell carcinoma, however, showed somewhat different trends between the two countries. In the US, small cell carcinoma started to decrease before adenocarcinoma, while in this study, it was still increasing up to the latest period. The increasing trend of small cell carcinoma was also observed in other studies in Japan.^{23, 25)} This difference can be partially explained by the change of diagnostic practice in Japan. It has been reported that in the 1960s and 70s, small cell and large cell carcinoma tended to be diagnosed merely as undifferentiated carcinoma, with no distinction between small cell carcinoma or large cell carcinoma, and that the increase in small cell carcinoma was coupled with a decrease of undifferentiated carcinoma.^{23, 25)} In this study, the proportion of undifferentiated carcinoma was 3.3%, 1.6%, 0.7%, 0.3% and 0.3% for males and 3.0%, 1.6%, 0.9%, 0.5% and 0.5% for females, in 1974–77, 1978–81, 1982–85, 1986–89 and 1990–93, respectively. Therefore, a part of the increase in the early period may be explained by the decrease of the cases diagnosed as undifferentiated carcinoma, but this is not so in the later period.

For females, the trend observed in this study differed from that observed in the US, showing no declining trend of lung cancer incidence so far. Since the prevalence of smokers in Japanese females has been increasing among younger age groups, it can be predicted that the current tapering trends will not continue, but will be followed by an increasing phase again. Further observation is needed to address this point.

This study involves some methodological limitations. The first is the assumption that in the same sex and age group, the cases without diagnosis of histologic type would have the same distribution of histologic types as the cases with diagnosis of histologic type. The proportion of cases with histologic types reported to the registry in the most recent period, 1990–93, was still only 62.7% for males and 55.8% for females. These figures are relatively low compared with other studies.^{13, 15)} There are two main reasons why histologic type could not be identified in the cancer registry. One is that lung cancer was diagnosed clinically or histologically, but histologic type could not be determined because no appropriate material for histologic diagnosis was available. The other is that histologic type was actually determined based on histologic diagnosis, but was not reported to the cancer registry. The former is typically the case for elderly patients with advanced stage lung cancer, for whom aggressive diagnostic procedures seemed unwarranted. However, in stage IV cases of the age group 70 years or more, the propor-

Table IV. Distribution of Histologic Types from Various Sources in Japan^{a)}

Sex	Source (period)	Histologic type (%)					Total	(n)
		Squamous	Adeno	Small	Large	Others		
Male	Nation-wide Autopsy (1978–87) ^{b)}	32.0	35.0	19.0	10.0	4.0	100.0	(24,635)
	National Cancer Center (1981–85) ^{c)}	39.8	32.6	10.1	9.2	8.3	100.0	(688)
	Osaka Cancer Registry (1982–85) ^{d)}	39.7	34.4	16.3	7.2	2.5	100.0	(4,382)
Female	Nation-wide Autopsy (1978–87) ^{b)}	16.0	57.0	15.0	7.0	5.0	100.0	(7,805)
	National Cancer Center (1981–85) ^{c)}	11.4	69.1	6.8	6.4	6.3	100.0	(221)
	Osaka Cancer Registry (1982–85) ^{d)}	18.2	61.2	13.2	5.1	2.2	100.0	(1,476)

- a) All figures are simple proportions not adjusted by age.
- b) Morita and Sugano (1990).
- c) Watanabe *et al.* (1987).
- d) Present study.

tion of cases with histologic type was almost the same as in stage I cases of the same age group. On the other hand, although the proportion of cases with histologic type tended to be higher among younger age groups, it was only 72.5% even among the age group 50–59 in 1990–93. Since it is rather unrealistic that physicians would have determined the treatment regimen without information on histologic type for this age group, it is likely that histologic type would in fact have been diagnosed for these cases. Therefore, of the two reasons for the low proportion of cases with histologic type, the latter is likely to be most important. If this is the case, the assumption we have made will not cause severe bias, since it is unlikely that a particular histologic type is selectively not reported to the cancer registry.

It is difficult to check whether or not the assumption mentioned above is valid based on actual data. It can be roughly checked, however, by comparing the distribution of histologic type from various sources (Table IV). Although accurate comparison cannot be made without age adjustment, the distributions from three different sources (autopsy series, hospital series and population-based cancer registry) indicate rather similar patterns, which imply that the assumption is not violated to any great extent.

Second, we did not conduct a systematic review using past pathological materials. The criteria for the diagnosis of histologic type have been changed from WHO 1967 to WHO 1981, as mentioned earlier. It is not certain, however, when the individual pathologists changed their criteria in their routine practice. Moreover, the Japan Lung Cancer Society has its own criteria for diagnosis of histologic type, which are slightly different from the WHO version.³⁹⁾ The most significant difference is that in the WHO classification, solid carcinoma with mucus formation will be classified as adenocarcinoma, while if it does

not contain a glandular pattern, it will be classified as large cell carcinoma under the criteria of the Japan Lung Cancer Society. It is reported that agreement of the histological diagnosis on four major histologic types was 88% between the UK and Japan, when the same pathological slides were reviewed independently by the pathologists of the two countries according to the WHO criteria.⁴⁰⁾ Also, in the same study histological diagnosis of squamous cell carcinoma, adenocarcinoma and small cell carcinoma showed high agreement between the UK and Japan, in the range from 77 to 100%, while large cell carcinoma showed a poor agreement rate (40 to 58%). This implies that histological diagnosis is reasonably consistent for squamous cell carcinoma, adenocarcinoma or small cell carcinoma, but less so for large cell carcinoma.

Third, in the Poisson regression analysis for estimating age-adjusted rate ratios, the actual number of cases with histologic type was used as a numerator. Although this calculation is the simplest method for evaluating chance variation using actual numbers, it puts less weight on the trends in older age groups, since the proportion of cases with histologic type was lower in the older age groups.

The reasons why adenocarcinoma reached the peak later than squamous cell carcinoma, resulting in a relative increase of adenocarcinoma compared to squamous cell carcinoma recently have been discussed, and several factors have been proposed to account for this phenomenon. First, the pathological criteria for classifying histologic types were changed in 1981.³⁴⁾ A pathological review study in Italy found that this change in criteria resulted in a 15% increase of adenocarcinoma and an 11% decrease of squamous cell carcinoma in proportion.⁴¹⁾ We are now conducting a similar pathological review study in two major hospitals in Osaka, which cover approximately 20% of all lung cancer cases in Osaka. Preliminary results showed that the impact of this change was not as signifi-

cant as expected, and may not exceed 4% difference in the proportion of each histologic type in Japan.⁴²⁾ Second, there has been increased utilization of Periodic Acid Schiff (PAS) and alcian blue stain in pathological staining, in addition to the hematoxylin and eosin method. PAS stain has been used to determine the presence of mucin, which is an important characteristic when differentiating adenocarcinoma from large cell carcinoma, although the mere presence of mucin-positive cells does not constitute a diagnosis of adenocarcinoma. Since it was reported that the proportion of adenocarcinoma diagnosed will increase after the introduction of PAS stains,⁴⁾ this may be one of the factors leading to the relative increase of adenocarcinoma. Also, some tumor markers, such as carcinoembryonic antigen (CEA) or neuron adhesion molecule (NCAM), have been used as targets for immunostaining, although these techniques are less frequently used in routine practice. Third, there has also been progress in techniques for diagnosing peripheral small lesions, such as radiologically guided transbronchial biopsy or transcutaneous needle aspiration cytology, which mainly targets adenocarcinoma. These techniques will be effective in diagnosing early-stage lung cancer; however, once cancer progresses, diagnosis can be made rather easily without these techniques. Therefore, this type of progress should not have a major impact on the distribution of histologic type. In the US, diagnostic advances that mainly occurred in the 1980s had little impact on the trends of change in lung cancer incidence by histologic type.¹⁶⁾

Besides these factors, which might have led to an artificial increase of adenocarcinoma, several factors are speculated to have caused a real increase in adenocarcinoma. First, there has been a drastic change in the preferred type of cigarette from high-tar nonfiltered to low-tar filtered in the 1960s. In Japan, 90% of cigarettes on the market was nonfiltered in 1960, while a decade later, 90% was filtered. Since filters tend to remove larger particles in the cigarette smoke and larger particles tend to deposit in the larger bronchi, this change would have reduced the amount of deposition mainly in the larger bronchi, where squamous cell carcinoma usually arises. Moreover, since low-tar filter cigarette smokers tend to inhale deeply to compensate for reduced nicotine intake, cigarette smoke will reach the more peripheral regions where adenocarcinoma mainly occurs.⁴³⁾ It is reported that low-tar cigarettes contain a higher level of nitrate and generate a higher level of tobacco-specific nitrosamines, which specifically induce adenocarcinoma in an animal model.^{44, 45)} Also, it was shown in humans that switching from nonfilter to filter cigarettes will reduce the risk of squamous cell carcinoma, but not the risk of adenocarcinoma.⁴⁶⁾ If these proposals are correct, the association of cigarette smoking with adenocarcinoma must be much greater than has been reported previously. Indeed, it was reported

recently from the US that the relative risk of current smokers versus nonsmokers for adenocarcinoma was greater in a recent cohort study (19.0 for males and 8.1 for females) than in a study conducted two decades ago (4.6 for males and 1.5 for females).¹⁶⁾

Second, it was reported from several case-control studies that smoking cessation can rapidly reduce the risk of lung cancer of small and squamous cell carcinoma types, but only slowly reduces that for adenocarcinoma.^{2, 47, 48)} Since the number of exsmokers has been increasing, this change will result in a relative increase of adenocarcinoma, especially in males.

Third, changing levels of exposure to risk factors other than smoking may influence the trends of histologic distribution. Exposures from occupational environments, such as coal mining or metal refining, which are more closely related to squamous and small cell carcinoma, have been decreased in most developed countries, including Japan. Ambient air pollution with reduced sulfur oxides levels but steady fine particle levels may be another factor to be considered.⁴⁹⁾ Dietary factors, such as intake of vegetables and fruits, also have changed. These factors may also modify the effect of cigarette smoking. In order to disentangle these points, however, further studies are needed to evaluate the effects of various risk factors specifically on histologic type.

The reason why small cell carcinoma has continued to increase, as observed in this study, remains unclear. This increase should be carefully considered, however, because a decreasing trend of small cell carcinoma has been noted in the US, starting soon after the decrease of squamous cell carcinoma in males. It is reported that the proportion of small cell carcinoma in Japan (Osaka), the UK (Scotland) and the US (white) was 16%, 18% and 20% in males, and 13%, 23% and 29% in females, respectively, based on data from population-based registries around 1990.²²⁾ This implies that some unknown factors associated with a westernized life style may be related to the increasing trend of small cell carcinoma.

In summary, trends of lung cancer incidence are now changing from the phase of monotonous increase to a variety of trends which differ by histologic type. It is essential to observe lung cancer incidence by histologic type in order to confirm the real trends. Also, further studies for elucidating risk factors associated with particular histologic types of lung cancer are warranted.

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