Lung Cancer Incidence Rates by Histologic Type in High- and Low- Risk Areas; A Population-Based Study in Osaka, Okinawa, and Saku Nagano, Japan

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We investigated lung cancer incidence by histologic type using the data from population-based cancer registries in high- risk (Osaka and Okinawa) and low-risk (Saku Nagano) areas. Since the proportion of cases with histologic types identified was not sufficiently high, sex- and age-specific incidence rates by histologic type were estimated assuming that the distribution of histologic types was the same across the same sex and age groups regardless of reporting status. Compared to Saku in Nagano Prefecture, the cumulative risk of lung cancer incidence rates in Osaka and Okinawa were 1.3 and 1.5 times higher for males and 1.3 and 1.2 times higher for females, respectively. When divided by histologic type, male adenocarcinoma and small cell carcinoma were 1.6-2.1 times higher in Osaka and Okinawa, while squamous cell carcinoma was 1.6 times higher only in Okinawa compared to Saku Nagano. In females, squamous cell carcinoma and small cell carcinoma were 2.5-3.3 times higher in Osaka and Okinawa compared to Saku Nagano, while adenocarcinoma was almost equal in the 3 areas. These results indicate that the pattern of incidence of lung cancer by histologic type may differ between high- and low-risk areas. *J Epidemiol*, 1999 ; 9 : 134-142

lung cancer, incidence, histologic type, cancer registry, geographic difference

Although the lung-cancer incidence in Japan has been relatively low, i.e., approximately half that in the US and UK ¹⁾, there has been a considerable variation in lung cancer risk within Japan. In 1990, the highest age-adjusted mortality rate (per 100,000) was observed in Okinawa Prefecture followed by Osaka Prefecture: 57.8 and 54.4 for males and 15.2 and 14.8 for females, respectively ²⁾. On the other hand, the lowest lung-cancer mortality rate was observed in Nagano Prefecture: 33.1 for males and 8.3 for females. Trends in age-adjusted mortality rates for lung cancer from 1960 to 1995 show that this variation by prefecture has increased (Fig. 1). This indicates that the burden of risk factors, either known or unknown, may differ among prefectures even within this country.

Accumulated data showed that the magnitude of the association among several etiologic factors and lung cancer differs by histologic type. Squamous cell carcinoma and small cell carcinoma are strongly associated with cigarette smoking showing 10- to 20-fold increase among current smokers compared to non-smokers, while adenocarcinoma is associated with a 2- to 5-fold increase ^{3,4)}. Small cell carcinoma and squamous cell carcinoma are predominantly affected by occupational exposures to such substances as chloromethyl ethers, chromium, mustard gas or radon ⁵⁾. On the other hand, prior lung disease, such as tuberculosis infection, is primarily associated with adenocarcinoma ⁶⁾. Therefore, the distribution of histologic type may be different between high- and low- risk areas for lung

Received October 19, 1998 ; accepted January 20, 1999.

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cancer if the underlying risk factors are different between those areas.

In order to find a clue to the geographical difference of lung cancer risk, we compared lung cancer incidence by histologic type in two high-risk areas (Osaka and Okinawa) and one low-risk area (Saku Nagano), using the data from population-based cancer registries.

MATERIALS AND METHODS

The locations of Osaka, Okinawa and Nagano Prefecture are shown in Fig. 2. Osaka Prefecture, which is in the middle of Honshu Island, consists of mostly industrial and surrounding residential areas. Okinawa Prefecture comprises a series of remote southern islands with a subtropical climate. Nagano Prefecture is located in the inland region of Honshu Island and consists mostly of mountainous rural areas. The populations of Osaka, Okinawa and Nagano Prefecture in the 1990 Census

Figure 1. Trends in age-adjusted lung cancer mortality rates by Prefecture in Japan. Japanese model population (1985) was used as standard population.

Figure 2. Map showing locations of Osaka Prefecture, Okinawa Prefecture, and Saku area in Nagano Prefecture.

were (in million) 8.734, 1.222 and 2.157, respectively.

In Osaka and Okinawa Prefecture, prefecture-wide population-based cancer registries have been operating since 1962 and 1988, respectively ⁷. In Nagano Prefecture, although no such registry yet exists, population-based cancer registry has been operating since 1990 in the Saku area of Nagano (Saku shi and Minami-Saku Gun), which covers 110,000 residents.

In all three cancer registries, cancer cases are registered using cancer reports forwarded from all medical institutions in the target areas. These reports are also routinely supplemented by cancer death certificates. The percentage of death certificate only cases (DCO%) was 23.8%, 27.0% and 7.5% in Osaka (1990-93), Okinawa (1989-92) and Saku Nagano (1990-94), respectively.

Cancer sites were classified according to ICD-9 in three cancer registries ⁸. Histologic types of lung cancer have been coded using ICD-O-M in Osaka⁹, while in Okinawa and Saku Nagano, a more simplified classification was used, i.e. squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma and others, using WHO's histological classification of lung tumors ¹⁰. In Osaka, ICD-O-M code has been used and these were divided into four major types according to WHO's histological classification, 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 were accumulated during the periods 1990-93, 1988-92 and 1990-96 in Osaka, Okinawa and Saku Nagano, respectively.

During the above study periods, 13,448, 2,099 and 371 lung cancer cases were ascertained through the cancer registries in

Osaka, Okinawa and Saku Nagano, respectively. The proportion of cases with a diagnosis of histologic type was 60.7%, 50.9% and 68.7% in Osaka, Okinawa and Saku Nagano, respectively. These percentages were not sufficiently high for directly estimating the incidence by histologic type. Therefore, the following procedure was employed for estimating sex- and age-specific incidence rates by histologic type, on the assumption that the distributions of histologic types in the same sex and age groups were the same between those with and without identified histologic type. First, sex- and age-specific (5-year age group) incidence rates were calculated for all histologic types combined, including cases without a diagnosis of histologic type. Second, sex- and age-specific (10-year age group) proportions of each histologic type among the cases with a diagnosis were calculated for four major histologic types. Finally, the sex- and age-specific incidence rate (5-year age group) was multiplied by the corresponding sex- and age-specific proportion to estimate sex- and age-specific incidence rates by histologic type. Based on the estimated sex- and age-specific incidence rates, the cumulative risks from 0 to 74 and

from 0 to 79 years of age were calculated ¹¹.

To evaluate the geographic difference in terms of chance variation, age-adjusted rate ratios were calculated using Poisson regression analysis. Study subjects were limited to those 40-79 years-old. Variables included in the model were age (5-year age group) and area. The population number for the denominator of incidence rate was multiplied by the proportion of cases with a diagnosis of histologic type, so that the actual number of such cases could be used as a 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 the SAS program was used for the actual calculation ¹².

RESULTS

Compared to Saku Nagano, the cumulative risk of lung cancer incidence rates in Osaka and Okinawa were 1.3 and 1.5 times higher for males and 1.2 and 1.2 times higher for females, respectively (Table 1). When compared by age group in males, the lung cancer incidence rate showed no great difference among the three geographical areas in males below age group 55-59, whereas the rates of those above age group 60-79 in Osaka and Okinawa were 1.5-1.8 times higher than those in Saku Nagano. In females, higher rates of lung cancer in Osaka and Okinawa compared to Saku Nagano were observed throughout most age groups.

Table 2 showed the cumulative risk for lung cancer incidence by histologic type in the three geographic areas. In all areas, squamous cell carcinoma was the most frequent histological type in males while adenocarcinoma was predominant in females. In males, the cumulative risk of squamous cell carcinoma was higher in Okinawa than in Osaka and Saku Nagano, while the risk of adenocarcinoma was higher in both Osaka and Okinawa than in Saku Nagano. Small cell carcinoma was higher in both Osaka and Okinawa, while large cell carcinoma was lower in Okinawa than in Osaka and Saku Nagano. In females, the cumulative risk of squamous cell carcinoma was higher in both Osaka and Okinawa than in Saku Nagano, while that of adenocarcinoma was similar in all three areas. Small cell carcinoma seemed to be higher in Osaka than in Saku Nagano, and at an intermediate level in Okinawa. Large cell carcinoma seemed to be lower in Okinawa than in Osaka and Saku Nagano. Almost the same patterns were observed in the cumulative risk of lung cancer from age 0 to 79.

Table 3 showed the age-adjusted rate ratio for lung-cancer incidence, taking the rate in Saku Nagano as a reference. Compared to Saku Nagano, age-adjusted rate ratios for total lung cancer for males were 1.32 and 1.45 times higher in Osaka and Okinawa, respectively, and in females, they were 1.29 and 1.23 times higher. When compared by age group,

Table 1. Age-specific lung cancer incidence rates (per 100,000) in Osaka, Okinawa and Saku Nagano.

Age group	Male			Female		
	Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96	Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96
40-44	11.7	7.3	9.9	5.4	4.9	3.7
45-49	17.7	13.8	15.4	8.5	10.8	12.3
50-54	33.0	29.6	46.2	13.5	13.7	8.7
55-59	75.2	76.8	73.0	26.4	30.7	12.4
60-64	147.5	190.8	137.9	40.4	35.7	33.6
65-69	275.4	336.2	199.4	71.1	75.7	70.7
70-74	421.4	502.8	274.1	112.5	100.9	83.8
75-79	594.5	556.9	396.6	160.7	133.6	107.8
Cumulative risk (0-74 y.o.) *	48.3	56.6	37.5	14.0	13.8	11.4
Cumulative risk (0-79 y.o.) *	76.1	82.5	56.4	21.9	20.4	16.7
Total no. of cases	9,594	1,501	268	3,854	598	103
Proportion of cases with histological type (%)	62.7	52.8	70.5	55.8	46.2	64.1

* per 1,000

Table 2. Cumulative risk for lung cancer (per 1,000) by histologic type in Osaka, Okinawa and Saku Nagano.

Age range	Histologic type	Male			Female		
		Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96	Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96
0-74	Squamous	18.5	27.2	16.2	2.5	2.8	1.0
	Adeno	17.6	20.7	11.5	8.6	9.1	8.6
	Small	9.0	7.3	4.6	2.0	1.3	0.5
	Large	3.2	1.1	4.1	0.6	0.3	0.8
0.79	Squamous	30.6	42.5	26.1	4.4	4.6	1.6
	Adeno	26.9	28.6	16.4	12.6	12.9	12.2
	Small	14.6	10.5	6.5	3.4	2.0	1.2
	Large	4.7	1.5	6.5	1.0	0.4	1.3

higher rate ratios in Osaka and Okinawa were observed only in the older age group in males, while in females no great difference was observed between the two age groups.

When classified by histologic type, a higher rate ratio was observed in Okinawa for male squamous cell carcinoma. This trend was seen only in the older age group, while rather lower rate ratios were observed for the younger age group. For male adenocarcinoma, higher rate ratios were observed both in Osaka and Okinawa, and this trend was similar for both age groups. Rate ratios for male small cell carcinoma were 2.14 and 1.68 times higher in Osaka and Okinawa, respectively, and

this increased risk seemed to be greater in the older age group. For male large cell carcinoma, rate ratios were somewhat lower, especially in Okinawa. In females, higher rate ratios were observed both in Osaka and Okinawa for squamous cell carcinoma. For female adenocarcinoma, no differences in rate ratios were observed among the three areas. Rate ratios for female small cell carcinoma were 3.30 and 2.06 times higher in Osaka and Okinawa, respectively. For female large cell carcinoma, rate ratios were somewhat lower, especially in Okinawa.

Table 3. Age-adjusted rate ratio (95% confidence interval) for lung cancer incidence when Saku Nagano was defined as a reference.

Histologic type	age	Male			Female		
		Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96	Osaka 1990-93	Okinawa 1988-92	Saku Nagano 1990-96
All	All	1.32 (1.14-1.51)	1.45 (1.25-1.68)	1.00	1.29 (1.02-1.62)	1.23 (0.96-1.57)	1.00
	40-59	0.95 (0.69-1.34)	0.88 (0.61-1.26)	1.00	1.45 (0.75-2.80)	1.61 (0.81-3.18)	1.00
	60-79	1.38 (1.19-1.61)	1.59 (1.35-1.87)	1.00	1.27 (0.99-1.62)	1.16 (0.89-1.51)	1.00
Squamous	All	1.14 (0.91-1.44)	1.58 (1.23-2.03)	1.00	2.53 (1.05-6.13)	2.79 (1.11-7.01)	1.00
	40-59	0.51 (0.30-0.87)	0.53 (0.29-0.98)	1.00	— (—)	— (—)	1.00
	60-79	1.29 (0.99-1.66)	1.85 (1.41-2.44)	1.00	2.43 (1.00-5.88)	2.47 (0.97-6.27)	1.00
Adeno	All	1.55 (1.17-2.04)	1.72 (1.27-2.33)	1.00	1.00 (0.73-1.38)	1.05 (0.74-1.49)	1.00
	40-59	1.55 (0.77-3.12)	1.57 (0.75-3.28)	1.00	1.23 (0.51-2.98)	1.40 (0.56-3.51)	1.00
	60-79	1.54 (1.14-2.09)	1.78 (1.28-2.47)	1.00	0.97 (0.69-1.36)	0.97 (0.66-1.43)	1.00
Small	All	2.14 (1.36-3.39)	1.68 (1.03-2.76)	1.00	3.30 (1.06-10.31)	2.06 (0.61-6.91)	1.00
	40-59	1.42 (0.45-4.43)	1.21 (0.36-4.11)	1.00	— (—)	— (—)	1.00
	60-79	2.29 (1.40-3.76)	1.75 (1.02-3.01)	1.00	3.09 (0.99-9.67)	1.85 (0.54-6.31)	1.00
Large	All	0.74 (0.46-1.18)	0.22 (0.11-0.45)	1.00	0.69 (0.25-1.90)	0.33 (0.09-1.26)	1.00
	40-59	1.36 (0.33-5.51)	0.30 (0.05-1.81)	1.00	0.37 (0.05-2.78)	0.00 (0.00-0.00)	1.00
	60-79	0.66 (0.40-1.09)	0.22 (0.10-0.49)	1.00	0.79 (0.25-2.53)	0.53 (0.13-2.22)	1.00

DISCUSSION

This study showed that the distribution of histologic types differed in high- and low-risk areas of lung cancer in Japan. In males, adenocarcinoma and small cell carcinoma were higher in Osaka and Okinawa compared to Saku Nagano, while squamous cell carcinoma was high only in Okinawa. In females, squamous cell carcinoma and small cell carcinoma were higher in Osaka and Okinawa, while adenocarcinoma was almost equal in the three areas. For both sexes, however, large cell carcinoma was low, particularly in Okinawa. This implies that poorly differentiated carcinoma tended to be diagnosed as squamous cell carcinoma or adenocarcinoma in Okinawa, while in Osaka and Saku Nagano they tended to be diagnosed as large cell carcinoma.

The age-adjusted death rate for lung cancer in 1990 showed

a 1.6-1.8 fold difference between the one low-risk area (Nagano) and the two high-risk areas (Okinawa and Osaka)²⁾, while the cumulative risk of lung cancer incidence in the present study showed only a 1.2-1.5 fold difference among those areas. This may be because of chance fluctuations due to the small population covered by the Saku Cancer Registry, or because of a real variation in lung cancer risk within Nagano Prefecture. Since that standardized mortality ratio for lung cancer in 1988-92 showed no great difference in lung cancer risk between the Saku area and the entire Nagano Prefecture (71.1 for males and 74.0 for females in all of Nagano Prefecture, and 77.9 for males and 72.2 for females in Saku only)¹³⁾, the latter possibility is less likely.

The prevalence of smokers has a great impact on lung cancer risk in each area, since cigarette smoking is a major determinant for lung cancer risk. Based on a baseline survey in the

Table 4. Crude proportion (%) of histologic type among lung cancer cases in population-based cancer registries in Japan.

Sex	Source/Area	Histologic type				No. of cases with histologic type *
		Squamous	Adeno	Small	Large	
Male	Cancer incidence in five continents (1988-92)					
	Hiroshima City	39.0	43.4	14.1	2.9	856
	Miyagi Prefecture	41.1	31.2	13.5	14.0	2,295
	Nagasaki Prefecture	36.5	41.1	14.5	7.3	1,775
	Osaka Prefecture	37.8	37.1	17.1	7.5	7,292
	Present study					
	Osaka (1990-93)	37.5	36.6	17.6	6.6	6,020
	Okinawa (1988-92)	46.6	36.5	12.5	1.9	792
	Saku Nagano (1990-96)	42.3	29.6	13.2	11.6	189
Female	Cancer Incidence in five continents (1988-92)					
	Hiroshima City	18.7	67.6	9.7	2.5	330
	Miyagi Prefecture	9.2	72.2	6.9	10.1	748
	Nagasaki Prefecture	14.6	73.8	7.1	3.5	677
	Osaka Prefecture	17.8	62.7	13.3	4.9	2,590
	Present study					
	Osaka (1990-93)	18.0	61.4	13.5	4.2	2,150
	Okinawa (1988-92)	19.2	65.9	9.4	1.8	276
	Saku Nagano (1990-96)	7.6	77.3	6.1	6.1	66

* Unspecified carcinoma/cancer was removed

Japan Public Health Center-based Prospective Study for Cancer and Cardiovascular Diseases¹⁴, the age-adjusted prevalence of current smokers among residents aged 40-59 years was 52.9%, 45.3% and 56.6% for males, and 12.3%, 7.7% and 7.5% for females in Suita (Osaka), Ishikawa (Okinawa) and Saku (Nagano) health center districts, respectively. Correspondingly, the age-adjusted prevalence of former smokers was 24.8%, 25.7% and 24.3% for males, and 2.9%, 2.6% and 2.2% for females. The average number of cigarettes smoked per day among current smokers was 27.0, 22.3 and 22.9 for males, and 15.1, 15.1 and 12.5 for females, and mean age at initiation of smoking was 20.3, 21.1 and 20.5 for males, and 26.6, 29.6 and 28.9 for females, respectively. This indicates that females in Osaka tended to be more heavily exposed to cigarette smoke compared to those in Okinawa and Saku Nagano, while in males there seemed to be no substantial difference in exposure to cigarette smoke among three areas at least for this age group when compared by the above factors.

Male squamous cell carcinoma showed different patterns, i.e., high in Okinawa and low in Osaka and Saku Nagano. This seems to be difficult to explain by environmental factors, because exposures to various industrial emissions are generally low in Okinawa. One possibility is that Okinawa has a special history of tobacco sales because of the US Occupation from after World War II to 1972. During this period, private tobacco companies in Okinawa had been manufacturing local brands of cigarettes. In 1972, the Japan Monopoly succeeded the local tobacco industry in Okinawa, and has been providing

Japanese national brands while continuing to manufacture some brands only for local use in Okinawa. Since these local brands have a higher tar yield, they were reported that to be more strongly associated with lung cancer risk, especially for squamous cell carcinoma, compared to the non-Okinawa brands¹⁵. It is also reported that human papilloma virus may have some role in lung carcinogenesis in Okinawa, especially for squamous cell carcinoma¹⁶.

In males, the risk of adenocarcinoma was higher in Osaka and Okinawa than in Saku Nagano, while in females there was no difference among the three areas. Although the reasons are not clear, this may be explained by the possibility that certain risk factors other than smoking, such as prior tuberculosis infection, affect only smokers, and that the prevalence of such risk factors is high in Osaka and Okinawa but low in Saku Nagano. In females, squamous cell carcinoma and small cell carcinoma, both strongly related to cigarette smoking, showed the same pattern, i.e., high in Osaka and Okinawa, and low in Saku Nagano. Although this implies that cigarette smoking would be the major risk factor, actually the prevalence of smokers is not high in Okinawa. Further investigation is needed to identify specific risk factors in Okinawa.

Any interpretation of detailed findings should be done with caution, however, because several limitations exist in this study. First, the comparison of incidences in different areas may not be valid, since the validity of cancer registries varies among areas. When all histologic types are combined, the comparison may be little biased, since the same tendency was

observed in mortality. However, since the proportion of cases with histologic type differed (high in Saku Nagano and low in Okinawa), comparison of incidence by histologic type may be biased. Although only limited data are available to verify this concern, crude proportions of histologic type have been reported from three other cancer registries in Japan, i.e., Hiroshima, Miyagi and Nagasaki (Table 4). When unspecified carcinoma/cancer is removed, the range of variation in the proportion for each histologic type almost overlapped that observed in the present study. This indicates that the proportion observed here was not extraordinary.

Second, we assumed that in the same sex and age groups the cases without a diagnosis of histologic type would have the same distribution of histologic types as the cases with such a diagnosis. Although this may not prove valid, there is no practical alternative approach. The proportion of cases with histologic types reported to the registries for the age group 70 or more was low (50.8%, 41.7% and 58.9% in Osaka, Okinawa and Saku Nagano, respectively). At the same time, however, the proportion of cases with a histologic diagnosis for the age group 50-59 was still 72.6%, 60.8% and 78.8%, which is also insufficiently high. Since it is rather unrealistic to suppose that physicians would determine the treatment regimen without information on histologic type for this age group, the histologic type would have actually been diagnosed, but perhaps not reported to the registry. If this is the case, the assumption we have made will not be severely biased for younger age groups, since it is unlikely that a particular histologic type was not reported selectively.

Third, we did not conduct systematic reviews of past pathological materials. The criteria for the diagnosis of histologic type may vary with each pathologist, especially in different areas. Previous pathological review studies showed high agreement rates for squamous cell carcinoma, adenocarcinoma and small cell carcinoma among eight pathologists in Japan¹⁷ and between pathologists in Japan and the UK¹⁸. Both studies showed a relatively low agreement rate for large cell carcinoma, which was actually observed for Okinawa in the present study. Although the impact of this misclassification will not be large because of so few cases, caution is needed in any interpretation.

Fourth, we did not take into account detailed clinical information of lung cancer, such as location of tumor or grade of differentiation, in the analysis. Since it is reported that poorly differentiated adenocarcinoma is more strongly associated with cigarette smoking than well differentiated adenocarcinoma¹⁹, different exposure to cigarette smoking will influence not only for the distribution of histologic type but also that of grade of differentiation. Unfortunately, population-based cancer registries do not collect detailed clinical information systematically, because priority is set to seek high registration rate by simplifying the information collected as much as possible. Further

research will be needed in this regard using the data from hospital-based studies, in which detailed clinical information of lung cancer is available for most cases.

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

Accumulated data showed that trends in lung cancer incidence differ by histologic type²⁰⁻²³. Most of the studies in the US and European countries showed a relative increase in adenocarcinoma as compared to squamous cell carcinoma in both males and females, especially in younger age groups. In Japan similar trends have been reported from the Osaka Cancer Registry using the data from 1974-1993²⁴. The most influential factor for this trend is speculated to be a change on the type of cigarette from high-tar nonfiltered cigarette to low-tar filtered cigarette. Since filters tend to remove larger particles in the cigarette smoke and larger particles tend to deposit in larger bronchus, it will reduce the amount of deposition mainly in larger bronchus, where squamous cell carcinoma usually arise. Moreover, since low-tar filter cigarette smokers tend to inhale deeply to compensate for nicotine intake, cigarette smoke will reach to more peripheral regions where adenocarcinoma mainly occur.

It is reported that around 1980, crude (not age-adjusted) proportion of adenocarcinoma was higher in Japan (Osaka) for both males and females (male 37.8%, female 63.6%) than those in the US (male 26.8%, female 40.8%) and in the UK (male 13.9%, female 20.1%)¹⁸. In 1988-92, proportion of adenocarcinoma in males became almost the same level in Japan (37.1%) and the US (34.2%) but still low in the UK (16.1%), while in females that was still high in Japan (62.7%) than in the US (42.5%) and the UK (23.1%)¹. Although increasing trends of adenocarcinoma have been observed in most countries, absolute level of proportion and magnitude of changing trends vary by each country. Therefore, underlying causes may not be the same and further research is needed for clarifying the real causes in each country.

In summary, the pattern of incidence of lung cancer by histologic type was different between high-risk areas (Osaka and Okinawa) and a low-risk area (Saku Nagano). This may be due to a different distribution of either known or unknown risk factors. A hospital-based case-control study covering these three areas is now ongoing in order to elucidate which factors contribute to the differences in lung cancer risk in these areas.

ACKNOWLEDGEMENTS

This study was supported in part by a Grant-in-Aid from the

Ministry of Health and Welfare of Japan for Comprehensive 10-year Strategy for Cancer Control. The authors wish to thank the Osaka Cancer Registry, the Okinawa Cancer Registry and the Saku Cancer Registry for providing information. We are also grateful to the entire staff of the collaborating hospitals in the three cancer registry areas, whose contribution to the collection and processing of data made this publication possible. We also thank Ms. T. Sugiyama for her technical assistance.

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