Smoking Habits, Local Brand Cigarettes and Lung Cancer Risk in Okinawa, Japan.

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To disclose the association between smoking habits and lung cancer in Okinawa, Japan, we analyzed the data from a case-control study conducted from 1988 to 1991. The analysis, based on 333 cases and 666 age-, sex- and residence-matched population controls, provided the following major findings. (a) The odds ratios (ORs) for current smokers relative to nonsmokers were much greater for squamous cell carcinoma than for adenocarcinoma. The OR was 9.82 for squamous cell carcinoma and 2.18 for adenocarcinoma in males, 28.2 and 1.14, correspondingly, in females. (b) Males who quitted smoking for 20 years or more demonstrated no elevated lung cancer risk. (c) Among male current smokers, the more the number of cigarettes smoked per day, the higher the lung cancer risk for both cell types, but particularly for squamous cell carcinoma. In contrast, deep smoke inhalation significantly increased the risk for adenocarcinoma in particular. (d) Okinawan brand cigarettes were more strongly associated with the risk, compared with other brand ones. This finding might partly explain the higher frequency of lung cancer in males with the relatively lower smoking rate in Okinawa.

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Cigarette smoking is the most established risk factor for lung cancer⁶. An association of lung cancer, with such detailed smoking habits as years since cessation of smoking among ex-smokers, number of cigarettes smoked per day, age at starting smoking, fraction smoked per cigarette, cigarette type (with or without a filter) and smoke inhalation, has been investigated in many countries⁷-⁹. In Japan, however, only a few epidemiological studies have focused such detailed smoking habits. Sobue et al. ⁷,⁸ have intensively examined this issue by a case-control study in Osaka, which recruited more than 1,000 patients with lung cancer. More than half of the controls, however, were patients with other cancers, particularly stomach or breast cancer. Although the patients with cancers strongly related to smoking were excluded from the controls, those weakly linked with smoking, such as stomach cancer³², might have biased their estimated risk. Their findings on smoking habits, therefore, have to be confirmed by other case-control studies in Japan.

In Okinawa, southwest islands in Japan, the highest male lung cancer mortality rates were observed among the 47 prefectures in Japan in 1985 and 1990 ¹¹, ¹². The mortality rate among males in 1990 (per 100,000 population, age-adjusted by World Population ¹³) was 38.2 in Okinawa prefecture ¹⁴, whereas 30.3 for all Japan ¹⁵. The incidence rate of male lung cancer is also higher in Okinawa as compared to that in all Japan. In 1988, it was 44.0 (per 100,000 population, age-adjusted by World Population) in Okinawa prefecture ¹⁶, whereas 35.7 for all Japan ¹⁵. Nevertheless, the smoking rate among males in

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We conducted this study from January 1988 to November 1991 in Okinawa, Japan. The details of the study design and the characteristics of the subjects have been described elsewhere. In brief, to be eligible as cases in the present study, patients had to have initially and histopathologically been diagnosed as having primary lung cancer at the National Okinawa Hospital, at 40-89 years of age, and to be residents of the Okinawan main islands (Okinawa, Miyako and Ishigaki islands) at diagnosis. Patients aged 90 years or over were not eligible for a direct interview, and those with other malignancies were excluded. A total of 477 eligible cases were identified in the study period. Of these patients, 130 (27%) had died or were too ill to be interviewed when we tried to contact them. Fourteen (3%) patients refused an interview. Finally, we interviewed 333 patients (70%).

Controls were randomly selected from the general population of the Okinawan main islands (40-89 years old), using the electoral registers for the study period from 1988 to 1991. The random sampling was designed to select 5 eligible controls who were matched to each case for sex, age (±2 years) and residence (within the area covered by one health center), and two controls per case were taken from them. Those with a previous history of lung cancer or other malignancies were excluded from the controls.

Epidemiological information was collected by a direct interview of the study subject him/herself, using a standardized questionnaire, by well-trained public health nurses. Subjects were asked whether they have ever smoked or not, and if smoked, they were asked about the average number of cigarettes smoked per day five years before interview, age at starting smoking, fraction smoked per cigarette, cigarette type (with or without a filter) and smoke inhalation (no, moderately, deeply). When a smoker had quit smoking, the age at cessation was also recorded. Cases and controls were divided into three categories according to their smoking habits: nonsmokers, ex-smokers and current smokers. Ex-smokers were defined as those who had smoked regularly and stopped smoking 5 years or more before the interview. For cigarette brands, we examined those most frequently consumed after 1972, because the cigarette brands available in Okinawa dramatically changed in that year when the Okinawan islands were returned from US to Japan. Other epidemiological information collected by an interview included routine demographic data such as date of birth, marital status, and educational attainment; residential history; previous episodes of illness; family history of cancer; occupational history; drinking habits; dietary practices and intake frequency of selected foodstuffs; consumption of various beverages such as coffee, tea, milk, juice, and soft drinks; reproductive history for women; and personality traits.

The strength of the association between lung cancer and smoking habits was measured as an odds ratio (OR). The ORs were obtained by using conditional multiple logistic regression analysis. Unconditional logistic models including age (continuous variable) and the potentially confounding covariates, however, were used when analyzing data by cell type or smoking status. In the analysis by cell type, the ORs were calculated for squamous cell carcinoma and adenocarcinoma by sex, since all the male patients with small cell carcinoma were previous or current smokers; i.e., the ORs for ex- and current smokers could not be computed. Small cell carcinomas in women and carcinomas of other cell types were too few for the separate analysis by cell type. The ORs according to years since cessation of smoking among ex-smokers, and number of cigarettes smoked per day among current smokers were computed only for males, since female ex- and current smokers were too few for this stratification.

To examine the effects of detailed smoking habits, unconditional logistic analysis that focused on male current smokers was conducted. The variables included in the model were attained age (continuous variable), age at starting smoking (19 or less, 20-29, 30 or more), number of cigarettes smoked per day (1-19, 20-29, 30 or more), fraction smoked per cigarette (1/2 or less, 1/2-3/4, almost all), cigarette type (with or without a filter) and smoke inhalation (no, moderately, deeply). The test for trend in this logistic regression analysis was performed by categorizing the exposure variable and treating the scored variable as a continuous one. Subjects with missing information for the variables in the model were excluded from the corresponding analysis.

The ORs for male ex- and current smokers who most frequently consumed Okinawan brand cigarettes were also obtained by unconditional logistic models, adjusting for age, age at starting smoking, fraction smoked per cigarette, cigarette type, smoke inhalation, number of cigarettes smoked per day (for current smokers), and years since quitting smoking (for ex-smokers). Missing values in the covariates were replaced by mode values in this analysis.
RESULTS

Table 1 shows the distribution of our study subjects by sex and age. The age distribution among cases was almost identical with that among controls in both sexes. In male patients (n=245), squamous cell carcinoma, adenocarcinoma and small cell carcinoma accounted for 46.9% (n=115), 43.3% (n=106) and 8.2% (n=20), respectively. In females, adenocarcinoma was the most frequent cell type (67.0%, n=59), followed by squamous cell carcinoma (21.6%, n=19) and small cell carcinoma (9.1%, n=8).

The ORs for lung cancer among ex- and current smokers by sex and cell type are shown in Table 2. The ORs for squamous cell carcinoma were much greater than those for adenocarcinoma in both sexes. In males, the OR for current smokers relative to non-smoker was 9.82 (95% confidence interval (CI): 2.36-41.0) for squamous cell carcinoma, and 2.18 (1.00-4.76) for adenocarcinoma. In females, the corresponding ORs were 28.2 (7.55-105) and 1.14 (0.49-2.61), respectively. The ORs tended to be smaller for ex-smokers than for current smokers, except for all cell types and adenocarcinoma in females.

Table 3 presents the ORs for lung cancer according to years since smoking cessation among ex-smokers, and number of cigarettes smoked per day among current smokers in males. The risk among those who quit smoking for 20 years or more approached that among non-smokers; the OR relative to non-smokers being 1.00 (95% CI: 0.35-2.83). The ORs for squamous cell carcinoma were much larger than those for adenocarcinoma in all categories among ex- and current smokers.

Table 4 summarizes the ORs for lung cancer according to

| Table 1. Distribution of the study subjects by sex and age. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Males           |                 | Females         |                 |
|                 | Cases/Controls  |                 | Cases/Controls  |                 |
|                 | N   %           | N   %           | N   %           | N   %           |
| Age             |                 |                 |                 |                 |
| 40-49           | 13 5.3          | 22 4.5          | 13 14.8         | 26 14.8         |
| 50-59           | 29 11.8         | 60 12.2         | 17 19.3         | 33 18.8         |
| 60-69           | 104 42.4        | 214 43.7        | 27 30.7         | 57 32.4         |
| 70-79           | 83 33.9         | 162 33.1        | 25 28.4         | 46 26.1         |
| 80-89           | 16 6.5          | 32 6.5          | 6 6.8           | 14 8.0          |
| Total           | 245 100.0       | 490 100.0       | 88 100.0        | 176 100.0       |
| Mean age        | 66.9            | 67.1            | 63.7            | 63.7            |
| SD              | 9.2             | 9.1             | 11.7            | 11.9            |

| Table 2. Odds ratios (ORs) for lung cancer among ex- and current smokers by sex and cell type. |
| Cell type        | Smoking habits | Males          | Females         |
|                 |                | Cases/Controls | OR   95% CI     | Cases/Controls | OR   95% CI     |
| Squamous cell carcinoma |                |                |                 |                |                 |
| Nonsmokers      | 10 65          | 1.00           |                 | 50 145         | 1.00           |
| Ex-smokers      | 54 140         | 2.43           | 1.16-5.06 ⋆     | 5 5            | 5.33           | 1.21-23.5 ⋆     |
| Current smokers | 181 284        | 4.40           | 2.19-8.85 ⋆⋆⋆⋆   | 33 26          | 4.37           | 2.21-8.62 ⋆⋆⋆⋆   |
| Adenocarcinoma  |                |                |                 |                |                 |
| Nonsmokers      | 2 65           | 1.00           |                 | 3 145          | 1.00           |
| Ex-smokers      | 27 140         | 6.16           | 1.42-26.7 ⋆     | 1 5            | 9.76           | 0.85-112 ⋆      |
| Current smokers | 86 284         | 9.82           | 2.26-41.0 ⋆⋆    | 15 26          | 28.2           | 7.55-105 ⋆⋆     |

Squamous cell carcinoma and adenocarcinoma: adjusted for age. ⋆: p<0.10, ⋆*: p<0.05, ⋆⋆: p<0.01, ⋆⋆⋆: p<0.001
Table 3. Odds ratios (ORs) for lung cancer according to years since quitted smoking among ex-smokers, and number of cigarettes smoked per day among current smokers in males by cell type.

|                          | All cell types | Squamous cell carcinoma | Adenocarcinoma |
|--------------------------|----------------|-------------------------|----------------|
|                          | Case/Controls | OR 95%CI                 | Case/Controls  | OR 95%CI               |
| Nonsmokers               | 10 65 1.00    |                         | 2 65 1.00     |                         |
| Ex-smokers               |                |                         | 8 65 1.00     |                         |
| Years since quitted      |                |                         |                |                         |
| 5-9                      | 19 48 2.48 1.04-5.92 * | 11 48 7.47 1.58-35.3 * | 7 48 1.23 0.42-3.64 |
| 10-19                    | 27 44 3.63 1.58-8.44 **| 12 44 8.95 1.91-42.0 ** | 13 44 2.49 0.95-5.53 # |
| 20-                      | 7 47 1.00 0.35-2.83 | 3 47 2.05 0.33-12.8   | 3 47 0.54 0.14-2.16   |
| Current smokers          |                |                         |                |                         |
| Number of cigarettes/day |                |                         |                |                         |
| 1-19                     | 30 105 1.80 0.81-4.02 | 13 105 3.95 0.86-18.1 # | 16 105 1.30 0.52-3.21 |
| 20-29                    | 79 129 4.01 1.91-8.41 *** | 40 129 10.4 2.43-44.3 ** | 30 129 1.93 0.84-4.44 |
| 30-                      | 69 48 9.19 4.20-20.1 *** | 33 46 24.0 5.46-105 *** | 27 48 4.53 1.89-10.9 *** |

Squamous cell carcinoma and adenocarcinoma : adjusted for age.
#: p<0.10, *: p<0.05, **: p<0.01, ***: p<0.001

Table 4. Odds ratios (ORs) for lung cancer according to smoking characteristics among male current smokers by cell type.

|                          | All cell types | Squamous cell carcinoma | Adenocarcinoma |
|--------------------------|----------------|-------------------------|----------------|
|                          | Case/Controls | OR 95%CI                 | Case/Controls  | OR 95%CI               |
| Age at starting smoking  |                |                         |                |                         |
| -19                      | 42 74 1.00    |                         | 21 74 1.00    |                         |
| 20-29                    | 130 183 1.69 1.03-2.75 * | 61 183 1.53 0.83-2.83 | 52 183 1.66 0.84-3.27 |
| 30-                      | 8 25 1.00 0.41-2.71 | 4 25 0.84 0.25-2.88   | 4 25 1.38 0.39-4.84   |
| Test for trend           |               | p=0.22                  | p=0.56-        | p=0.27                  |
| Number of cigarettes/day |                |                         |                |                         |
| 1-19                     | 30 105 1.00    |                         | 13 105 1.00  |                         |
| 20-29                    | 79 129 2.07 1.24-3.46 ** | 40 129 2.63 1.31-5.29 ** | 30 129 1.38 0.69-2.77 |
| 30-                      | 69 48 4.80 2.68-8.59 *** | 33 48 5.64 2.64-12.1 *** | 27 48 3.22 1.50-6.93 *** |
| Test for trend           |               | p=1 X 10^{-4}           | p=6 X 10^{-4} | p=0.003                 |
| Fraction smoked per cigarette |            |                         |                |                         |
| <1/2                     | 13 26 1.00    |                         | 4 26 1.00    |                         |
| 1/2-3/4                  | 104 165 1.01 0.45-2.26 | 45 165 1.07 0.32-3.53 | 48 165 1.10 0.39-3.09 |
| Almost all               | 63 91 0.83 0.36-1.95 | 37 91 1.32 0.38-4.54 | 20 91 0.70 0.23-2.18 |
| Test for trend           |               | p=0.45                  | p=0.45        | p=0.27                  |
| Cigarette type           |                |                         |                |                         |
| With a filter            | 174 271 1.00 |                         | 81 271 1.00  |                         |
| Without a filter         | 5 9 0.98 0.30-3.18 | 5 9 2.21 0.66-7.40 | 0 9 0.00     |
| Smoke inhalation         |                |                         |                |                         |
| No (puff only)           | 33 72 1.00    |                         | 16 72 1.00    |                         |
| Moderately               | 75 145 1.13 0.65-1.96 | 38 145 1.18 0.57-2.44 | 29 145 1.26 0.57-2.77 |
| Deeply                   | 73 67 2.08 1.13-3.65 * | 32 67 1.92 0.87-4.26   | 33 67 3.05 1.52-7.01 ** |
| Test for trend           |               | p=0.011                 | p=0.084       | p=0.004                 |

Adjusted for age and other variables listed on this table.
*: p<0.05, **: p<0.01, ***: p<0.001

The detailed smoking habits among male current smokers by cell type. The more the number of cigarettes smoked per day, the higher the risk of lung cancer (test for trend: p=1 X 10^{-7} for all cell type, 6 X 10^{-6} for squamous cell carcinoma, and 0.003 for adenocarcinoma). Number of cigarettes per day appeared to have a greater effect on squamous cell carcinoma than on adenocarcinoma. The OR for those smoked 30 cigarettes or more per day relative to those with less than 20 cigarettes was 5.64 (95% CI: 2.64-12.1) for squamous cell carcinoma and 3.22 (1.50-6.93) for adenocarcinoma. Deep smoke inhalation
increased the risk particularly for adenocarcinoma; the OR (95% CI) for deep inhalers versus non-inhalers being 3.05 (1.32-7.01). Inhalation was seemingly linked also with the risk for squamous cell carcinoma (trend p=0.084). Age at starting smoking, fraction smoked per cigarette and cigarette type were not significantly associated with the risk, though non-filter cigarettes showed a greater risk for squamous cell carcinoma (OR: 2.21).

Table 5 shows the ORs for male ex- and current smokers who most frequently consumed Okinawan brand cigarettes. Predominant use of Okinawan brand cigarettes was significantly associated with an increased risk particularly for squamous cell carcinoma; the OR being 1.45 (95% CI: 1.02-2.07) for all cell types and 1.75 (1.10-2.78) for squamous cell carcinoma. Brand A Okinawan cigarettes were linked with an elevated risk (OR: 1.81 (95% CI: 1.07-3.06) for all cell types and 2.45 (1.29-4.64) for squamous cell carcinoma). Those who most frequently smoked local brand B seemingly experienced a greater risk for all cell types (OR: 1.40, 95% CI: 0.94-2.10, p=0.099).

### DISCUSSION

The cases included in the present study were not collected in a population-based setting. Nevertheless, the geographical distribution of the patients who visited the National Okinawa Hospital during the study period was almost identical to that of patients who died of lung cancer in Okinawa prefecture, as described in the preceding report. This implies that the cases identified in the hospital well represent the lung cancer patients in Okinawa.

Another issue in our study might be a non-respondent bias. Thirty percent of the patients could not be interviewed, usually because they were dead or too ill. The distribution of sex, age and histologic type of our cases, however, was quite comparable with that of all the patients with lung cancer newly diagnosed in the hospital during the same period. Furthermore, the prevalence of ever smokers among all the patients was almost identical to that among the cases in our study; 94.9% in males and 43.4% in females. The corresponding figures in our cases were 95.9% and 43.2%, respectively. It is unlikely, therefore, that a non-respondent bias in the cases could distort the risk estimates for smoking habits substantially. The exact response rate of the controls could not be obtained. However, we can assume the response rate to be well beyond 50%, since we successfully set up two controls from the first and second potential controls on most occasions, and only rarely required candidates from the remaining eligible controls or additional ones.

The present study confirmed that the smoking is significantly linked with lung cancer risk, also in Okinawa. It took more than 20 years after smoking cessation to reduce the risk among ex-smokers to the level of nonsmokers; being very comparable figures in the previous reports in Japan and Western countries.

Smoke inhalation was more predominantly associated with adenocarcinoma than with squamous cell carcinoma. This endorses the finding by Sobue and his colleagues that the difference in the risk between non-inhalers and inhalers appeared to be smaller for squamous cell carcinoma than for other histologic types. In countries other than Japan, several, but not all, studies have demonstrated similar findings. These findings would be biologically plausible, since most adenocarcinomas originate from the peripheral regions of the lung, and thus, carcinogen in cigarette smoke must be delivered to the
The smoke inhalation level, which was examined in our study, would not objectively be measured. The patients were, however, rarely informed about their histologic type of lung cancer, and the interviewers did not know the cell type at all. The effect modification by cell type, therefore, could not be explained by a recall bias.

Fraction smoked per cigarette was not independently related to the risk in our study, in contrast with a case-control study in Osaka. Smokers in Okinawa seemed to consume a much longer fraction per cigarette than those in Osaka, because more than 90% of male current smokers among our controls smoked half or more fraction per cigarette (Table 4). This different proportion would have made it difficult to detect the effect of the fraction smoked per cigarette.

Unlike other investigations, younger age at starting smoking did not increase the risk among current smokers in our study. Age at starting smoking might possibly have a smaller influence on lung cancer in Okinawa than that in other areas of Japan, whereas number of cigarettes smoked per day demonstrated a greater effect. The OR for current smokers who smoked 30 cigarettes or more per day, relative to those who smoked less than 20 cigarettes, was 4.8, 1.7, and 1.1 in Okinawa (present study), Osaka, and Tokai area, respectively.

Another time-related factor for smoking habits might be duration of smoking. It is, however, essentially determined by the other two factors; i.e., attained age and age at starting smoking. We could not, therefore, include attained age, age at starting smoking and duration of smoking simultaneously in one model of multivariate analysis.

Okinawan brand cigarettes seemed to be more strongly associated with lung cancer risk in males than other brands. Before the return of the Okinawan islands from US to Japan in 1972, private tobacco companies in Okinawa had been manufacturing local brand cigarettes. In 1972, the Japan Monopoly succeeded to the tobacco industry in Okinawa, and since then, the monopoly has been providing the Japanese national brands of cigarettes in Okinawa, but has also continued manufacturing some local brand cigarettes only for local use in this area. This gave us an unique opportunity to evaluate the risk of Okinawan brand cigarettes on lung cancer. Local brand cigarettes might possibly explain, in part, the higher frequency of lung cancer in males in Okinawa, despite their relatively lower smoking rate. When considering the possible relationship between the use of Okinawan brand cigarettes and higher incidence of lung cancer in Okinawa, popularity and cheapness of the brands (They cost only about half or two thirds compared with other brands) would probably be an important public health issue in this area.

In short, our study disclosed the following major findings.
(a) The ORs for current smokers relative to nonsmokers were much greater for squamous cell carcinoma than for adenocarcinoma. (b) The risk among males who quitted smoking for 20 years or more approached that among nonsmokers. (c) Among male current smokers, the more the number of cigarettes smoked per day, the higher the lung cancer risk for both cell types, but particularly for squamous cell carcinoma. In contrast, deep smoke inhalation increased the risk for adenocarcinoma in particular. (d) Okinawan brand cigarettes were more strongly associated with lung cancer risk in males compared with other brand ones, which might partly explain the higher frequency of lung cancer in males with the relatively lower smoking rate in Okinawa.

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