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A Case-Control Study of Lung Cancer in Nonsmoking Women

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SHIMIZU, H., MORISHITA, M., MIZUNO, K., MASUDA, T., OGURA, Y., SANTO, M., NISHIMURA, M., KUNISHIMA, K., KARASAWA, K., NISHIWAKI, K., YAMAMOTO, M., HISAMICHI, S. and TOMINAGA, S. *A Case-Control Study of Lung Cancer in Nonsmoking Women.* Tohoku J. exp. Med., 1988, **154** (4), 389-397 —— A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR = 4.0 ; $p < 0.05$) and from husband's father (RR = 3.2 ; $p < 0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR = 4.8 ; $p < 0.05$). No appreciable differences in food intakes were observed between cases and controls. ———— lung cancer ; women ; nonsmoker ; passive smoking ; metal exposure

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The causes of lung cancer in Japanese women have not been clearly identified. It is widely accepted that cigarette smoking is causally associated with lung cancer, but the increasing trend in the incidence of lung cancer in Japanese women cannot be explained by smoking alone. The proportion of smokers among Japanese women remained around 15% during the last thirty years (Tominaga 1982) and the most predominant histologic type of lung cancer among them was adenocarcinoma, which was considered to be more weakly associated with smoking as compared to lung cancer of other cell types (Shimizu 1983; Nakamura et al. 1986; Shimizu et al. 1986).

Several studies have been conducted with emphasis laid on passive smoking and lung cancer since the first positive results were presented by Hirayama (1981) and Trichopoulos et al. (1981). Some of these studies showed a clear association of passive smoking with lung cancer (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986; Inoue et al. 1986). However, the results of other studies were equivocal or negative (Garfinkel 1981; Kabat and Wynder 1984; Koo et al. 1984; Wu et al. 1985; Lee et al. 1986).

This paper reports a case-control study of lung cancer in Japanese nonsmoking women, in which passive smoking and other factors such as occupational history, domestic heating system and dietary habits were investigated.

Materials and Methods

Our cases consisted of female patients with primary lung cancer who were treated in 4 hospitals in Nagoya from August 1982 to July 1985. One of the hospitals (Aichi Cancer Center Hospital) was a cancer hospital and the remaining three were general hospitals. Nagoya is the fourth largest city in Japan with a population of 2.1 million and located in the middle of the main island, Honshu.

During the above period 118 female lung cancer patients were pathologically identified. The physicians or nurses asked all of them to fill in a questionnaire for this study on the first or second day of admission to the hospitals. Out of 118 lung cancer patients 4 refused to fill in the questionnaire and 24 reported that they were current or exsmokers. The remaining 90 nonsmoking patients were selected as the cases for the following analyses. The questionnaire mainly consisted of the questions about smoking, occupational history, dietary habits, personal disease history and about the kinds of fuel for cooking. As regards passive smoking, we asked them about the smoking habits or the number of cigarettes smoked per day by parents, siblings, children or husband's parents in the home. We also asked them about the length of time which the woman spent with her husband in the same room, the period of married life and the number of cigarettes smoked by her husband. The passive smoke exposure at working places was assessed only in terms of the presence or absence of smokers. As regards dietary history, we asked the frequency in recent five years of intake of food items and divided into four categories (no intake, 1 or 2 days/week, 3 or 4 days/week, and almost every day). We asked directly the number of glasses of milk and the number of oranges taken per week.

The 90 lung cancers included 69 adenocarcinomas (77%), 13 spuamous cell carcinomas (14%), 4 large cell carcinomas (4%), 3 small cell carcinoma (3%) and 1 adenoid cystic carcinoma (1%). The number of cases in the age group of 30-39, 40-49, 50-59, 60-69, 70-79 and 80+years were 3 (3%), 16 (17%), 28 (31%), 27 (30%), 14 (16%) and 2 (2%) respectively. The minimum and maximum ages of the cases were 35 and 81 years and those

of controls were also 35 and 81 years, respectively. The mean age at admission was 59 years for cases and 58 years for controls.

As a control, we asked female in-patients other than those with lung cancer in the same or adjacent wards of the hospital to fill in the questionnaire as we did for lung cancer patients (i.e., potential controls). We selected two controls matched in terms of hospital (the same hospital), age (± 1 year), and date of admission for each case from these potential controls. For 17 cases we could find only one control which satisfied the criteria. The controls finally used for this analysis comprised 163 patients with the following diseases: breast cancer 67, (41%); diabetes mellitus, 11 (7%); stomach cancer, 11 (7%); hepatitis and other liver diseases, 8 (5%); malignant lymphoma, 7 (4%); heart diseases 5, (3%); hypertension 5, (3%); gall stone, 4 (2%); colorectal cancer 3, (2%); cancer of the uterine cervix 3, (2%); and others 39, (24%).

The logistic regression method was applied to this individually matched case-control study and odds ratio was computed as estimated relative risk for each variable (Breslow et al. 1978; Breslow and Day 1980). The statistical significance was determined by using two-sided p values.

Results

Table 1 shows the risk of female lung cancer for several types of passive smoking. When the mother of a case was a smoker, the relative risk of lung cancer was 4.0 ($p<0.05$). However, the risk was not elevated when her father was a smoker (RR=1.1). High relative risk was observed when the husband's father living with the case smoked in the home (RR=3.2; $p<0.05$). When mother or husband's father was a smoker, the relative risk was 3.3 ($p<0.01$). There was no association between the risk of lung cancer and smoking by husband, siblings or children in the home.

Passive smoke exposure at work was not clearly associated with female lung cancer, although the relative risk was slightly elevated (RR=1.2).

Table 2 shows the combined effect of household smoking by mother and

Table 1. *Relative risks (RR) of lung cancer in nonsmoking women for serveral types of tobacco smoke exposure*

Smoker	Frequency in controls (%)	RR
In the home:		
Husband	56	1.1
Father	41	1.1
Mother	3	4.0*
Husband's father	8	3.2*
Husband's mother	4	0.8
Son(s) or daughter(s)	40	0.8
Brother(s) or sister(s)	32	0.8
Someone at working place	35	1.2

*$p<0.05$.

TABLE 2. *Relative risks of lung cancer in nonsmoking women for smoking by mother and husband's father in the home*

		Smoking by husband's father	
		(−)	(+)
Smoking by mother	(−)	1.0	3.9*
	(+)	6.3	2.8

*$p<0.05$

husband's father. Both of these two variables showed a relatively high risk independently. Particularly, the risk for smoking by husband's father in the absence of smoking by mother was significantly elevated (RR=3.9, $p<0.05$). However, no synergistic effect of the above two variables was observed.

About 60% of the respondents had occupations. No difference was found in the distribution of the occupational categories between cases and controls. However, histories of occupational exposure to specific substances showed high risks of lung cancer. The relative risk for exposure to iron or other metals was 4.8 ($p<0.05$), although the frequency of such exposure was very low in controls. The relative risk for exposure to coal, stone, cement, asbestos or ceramics was 3.3, but it was not statistically significant.

For the analysis of dietary habits, cut points dividing into lower two and higher two categories are arbitrarily chosen in general. We selected the 8/week or more as cutpoint for mandarine oranges in winter and odds ratio of milk was computed for the daily intake. Table 3 shows that there is neither positive nor negative association with food items investigated here. Only chicken showed the low risk of 0.7. We observed no dose-response relationship for these variables.

The personal medical history of silicosis showed the relataive risk of 2.0, but

TABLE 3. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the frequency of food intake*

Food item	Frequency of intake	Frequency of intake in controls (%)	RR
Green-yellow vegetables	≥3 d/w	86	0.9
Fruit	≥3 d/w	86	1.2
Oranges (mandarine)	≥8/w	77	1.0
Milk	≥1 glass/d	76	1.0
Fish	≥3 d/w	55	1.0
Pork	≥3 d/w	22	1.0
Beef	≥3 d/w	20	1.0
Chicken	≥3 d/w	40	0.7

d, days; w, weeks.

TABLE 4. *Relative risks (RR) of lung cancer in nonsmoking women for type of household heating system used in recent years*

Type of household heating system	Frequency in controls (%)	RR
Gas	32	1.0
Kerosene	86	1.6
Coal or charcoal	8	1.7

TABLE 5. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the selected factors (n = 65)*

Factor	RR	
	Crude	Adjusted†
Smoking by mother in the home	3.0	2.1
Smoking by husband's father in the home	3.5*	3.2*
Occupational exposure to iron or other metals	2.8	2.4

†RR of each factor adjusted for other two factors after excluding the pairs in which one of the factors had unknown values.

*$p < 0.05$.

it was not statistically significant. The risk for histories of both chronic bronchitis and asthma was 0.8, and the risk for history of tuberculosis was 1.1.

No appreciable difference was observed between cases and controls in the type of household heating in childhood and in the kinds of fuel for cooking in adulthood. However, a recent use of a kerosene or coal (charcoal) stove for household heating showed a somewhat higher risk (RR = 1.6 and 1.7, respectively). However, neither of them was statistically significant (Table 4).

The frequency of using cooking oil was almost the same in cases and controls.

To confirm the risk associated with each variable described above, we computed the relative risk by using the multiple logistic regression analysis for the main 3 variables. Table 5 shows that the results are almost the same as those in univariate analysis.

DISCUSSION

The presence of a smoking family member does not necessarily indicate that exposure to a sidestream of cigarettes has actually occurred. To know the level of passive smoking, measurement of concentration of cotinine in the urine is useful (Matsukura et al. 1984 ; Wald et al. 1984). However, it is very hard to assess the passive smoking level over a period of several decades because the half-life of serum cotinine is 72 hr. In this analysis we used only the information on smoking history of the respondents, their family members and their colleagues at working

places.

In this study we found a positive association between lung cancer in nonsmoking women and the smoking history of family members, especially that of mother and husband's father. As Japanese children usually spend much longer time with their mother than other family members do, mother's smoking may be a representative index of passive smoking before leaving home at around 20 years of age. Recently we found that the saliva cotinine level of nonsmoking schoolchildren is not high when their fathers were smokers but high when their mothers were smokers in Miyagi, a district of northeastern Japan (unpublished data). After marriage, 35% of women in controls lived with their husband's parents. The final proportion of control women whose husband's father smoked cigarettes in the home was as small as 8%, but that (18%) of cases was somewhat larger. The husband's father may have retired already and may have stayed home much longer than the husbands. There is a possibility that Japanese women may be more frequently exposed to the smoke of cigarettes by their husband's father than that by their husband.

We assessed the total length of period which a woman spent with her husband from the length of the period of marriage and the hours during which she lived in the same room, but no difference was found between cases and controls.

No dose-response relationship was observed between the risk of lung cancer and the history of smoking of mother or husband's father. Usually the respondents remember whether their mother or their husband's father were smokers, but they may be unable to recall the exact number of cigarettes smoked by their mother (especially in childhood) or husband's father in the home.

It has been suggested that beta-carotene and preformed vitamin A decrease the risk of lung cancer (Smith 1982 ; Hinds et al. 1984). We asked a very simple question concerning the frequency of green-yellow vegetable intake, which has been referred to as a protective factor against lung cancer in a large cohort study of Japan (Hirayama 1982). No association was observed between this variable and female lung cancer risk in our study. Most of the respondents had green-yellow vegetables very frequently and we found no difference between cases and controls. There was no dose-response relationship between the frequency of intake of green-yellow vegetables and lung cancer risk.

We also assessed the efficacy of vitamin supplements over a period of more than one year in this analysis, and found the risk of 0.5. However it was not statistically significant.

Other dietay factor such as vitamin C and cholesterol may be related to the development of lung cancer (Hinds et al. 1983, 1984 ; Byers and Graham 1984), but no appreciable association was observed between the risk of lung cancer and the intake of food items listed in this study. To evaluate the effect of dietary habits, more precise measurement of food intake is needed.

A slightly elevated risk for disease history of silicosis is consistent with the

data in recent reports (Finkelstein et al. 1982 ; Lynge et al. 1986), despite the fact that our results were based on the information reported by the respondents and that the number of cases with silicosis was very small. An excess risk of adenocarcinoma of the lung was observed previously for those with occupational exposure to iron or other metals in Nagoya area (Shimizu 1983). Even if the risk for these occupational exposure is confirmed, contribution of these factors is small because the frequency of such exposure is very low in Japan.

Possibly there is some bias in our study. Lung cancer cases were not derived from general population but from the patients of a limited number of hospitals. The proportion of adenocarcinoma patients in our series was ten percent larger as compared with that in total lung cancer patients of this area. The proportion of squamous cell carcinoma showed an opposite tendency (Karasawa 1985). We selected the controls from the same hospitals considering that both cases and controls in the same hospital may have similar backgrounds. However, one of the hospital was a cancer hospital and we had to include many breast cancer patients in the controls. For this reason we compared the status of passive smoking among the breast cancer patients with that among other controls, but we found no difference. Furthermore, the risk of lung cancer for the survivors of cancer of the breast was not high when assessed by the data of a population-based cancer registry (Takano and Okuno ; personal communication).

Our study showed that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

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