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Epidemiologic Survey on Lung Cancer with Respect to Cigarette Smoking and Plant Diet[1]

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This case-control study of lung cancer was based on a cross-sectional questionnaire survey of inpatients at 5 general hospitals in Okinawa, Japan, from 1982 to 1987. The purpose of the study was to clarify the relations of lung cancer to cigarette smoking and plant diet. Ingestion frequencies of 17 major dietary plants and/or herbs were obtained by means of a questionnaire interview. As eligible subjects for a case-control analysis, there were 673 respondents aged over 30 years with clear smoking history, age, sex and diagnosis. Psychiatric patients were excluded. Odds ratios of newly diagnosed lung cancer were calculated by the Mantel-Haenszel procedure. A pair consisted of a case and two controls which were selected randomly by using multivariate caliper matching. Sixty-four pairs matched for age (±5) and sex showed a significantly high odds ratio of 2.9 ($P<0.0005$). However, three male groups who were categorized by the number of cigarettes smoked did not exhibit dose-dependency of lung cancer on smoking. Lung cancer was more prevalent in ex-smokers than in current smokers. Case-control analyses by male generations revealed that lung cancer incidence was age-dependent, and there was a clear dose-response relationship between smoking and lung cancer in males in their sixties. A case-control analysis of each of 17 edible plants based on 44 pairs who were matched for age (±5), sex and smoking history demonstrated that the odds ratio of aloe (*Aloe arborescens* MILL *var. natalensis* BERGER) was 0.5 ($P<0.1$), suggesting that the aloe may prevent human carcinogenesis at various sites.

Key words: Lung cancer — Smoking — Diagnosis plausibility — Diet — Cancer epidemiology

Cancer seldom occurs in plants. One possible explanation of the rarity of plant cancer is the differences in the structures and functions of cell membranes of plants from those of animals. Another possible factor is the presence of natural anti-tumor chemicals such as vitamins. On the other hand, naturally occurring carcinogens, such as cycasin (methylazoxymethanol-β-D-glucoside), bracken and tannin have been found. Little epidemiologic work on the anti-tumor or preventive properties of plants and herbs has been done, though such activities should be clearly identifiable in terms of a smaller risk ratio than 1. Therefore, it might be useful to examine dietary plants for possible associations (negative or positive) with tumors.

One of the dietary customs among the people in Okinawa Prefecture (the Ryukyu islands; the southern area of Japan) is to daily ingest various species of plants, and these plants are also often used in the diet as folk therapy; for instance, aloe as a stomachic or astringent, snake gourd as a diuretic, and wormwood as an antiemetic or hemostatic.[1,2] There are also many wholesale agencies for processing herbs. Some plants are already known to have carcinogenic or anti-tumor activities in animals. Several authors pointed out that balsam pear and aloe have anti-tumor activities.[3–6] Comfrey was found to induce rat hepatomas.[7,8] Therefore, a cross-sectional survey of inpatients has been conducted at the major hospitals in Okinawa since 1982.

In addition, there has been no epidemiologic study of the effect of smoking on human pulmonary carcinogenesis in this area, partly because the prefecture was only returned to Japanese jurisdiction by the US government in 1972. This paper deals firstly with the effects of cigarette smoking on lung cancer occurrence, and discusses the epidemiologic meanings of the relationships between the data, which were collected in a survey at several different facilities, for assessment of data quality. Finally the epidemiologic associations of dietary plants with pulmonary carcinogenesis are examined through a case-control analysis based on the same cross-sectional data.

MATERIALS AND METHODS

Hospital surveys A cross-sectional survey using a questionnaire was conducted on inpatients with the cooperation of the five general hospitals in Naha City in Okinawa Prefecture from December, 1982 to August, 1986. They were Naha City Hospital, National Okinawa Hospital, Okinawa Red Cross Hospital, Ohama Hospital and the

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Surgery Department at Ryukyus University Hospital. All the hospitals except Ohama Hospital are public.

1) Dietary habits: Trained interviewers asked each inpatient to complete a diet questionnaire sheet at the bedside, face to face. The questionnaire was designed to obtain information regarding name, age, sex, residency and dietary habits. Items concerning dietary habits in the questionnaire were concentrated on the daily ingestion of plants when the patients had been in good health before admission to hospital. The plants included 21 species of dietary plants and/or herbs. The questionnaire also had several spaces where a respondent could give information regarding the ingestion of any other plants. Those 21 species of plants were selected on the basis of preliminary data from a food ecological survey in this area (unpublished data). All plant names were printed in both their common Japanese and their Okinawan dialect names.

Interviewers at first explained the purpose of the survey and each plant name to every patient by the use of picture books if necessary, and thereafter asked about the frequencies of plant and/or herb ingestion. Answers were placed in one of the following four categories: "low," "intermediate," "high" and "unclear."

The cooperation of the subjects was very good. Among the above 21 species of dietary plants, data on 17 major species were analyzed. Table I lists their names and methods of ingestion.

2) Medical records: After the questionnaire interview, a doctor or a nurse wrote the diagnosis of each inpatient on the questionnaire sheet. From May of 1987 to June, a medical record survey was performed for the same inpatients in order to confirm the diagnoses. At the same time, we confirmed the cancer history in the pathological examination records, if available.

3) Smoking habits: In a cross-sectional survey from 1982 through 1986, smoking history was obtained for each inpatient and it was recorded on the diet questionnaire sheet. These smoking data were also confirmed in the medical record survey in 1987. Questions on smoking history in the medical records were asked by a doctor or a nurse. The record formats of the smoking history, however, varied from hospital to hospital. Most hospitals did not record starting age, duration of smoking of a smoker, or duration of non-smoking of an ex-smoker. Since most of the smoking histories were recorded as the average numbers of cigarettes which each inpatient smoked daily before he or she was diagnosed with the current disease, or recorded as ex-smokers, the average number of cigarettes smoked and cession of smoking were available in this study.

Coding and quality checks on data All questionnaires were reviewed for completeness in terms of age, sex and residence, and then transcribed onto a computer coding sheet. When the "unclear" column was marked regarding the frequency of ingestion of a plant, or when the patient

Table I. Major Dietary Plants and/or Herbs Included in the Questionnaire

Popular name of plant	Ingestion methodology, effect
Balsam pear (bitter melon)	frying, vinegar, pickles, juice, miso soup, stomachic, anti-diabetic, hemopotatic, astringent
Wormwood	Japanese frying, gruel, spice, anti-emetic, hemopotatic
Aloe	juice, miso soup, stomachic, astringent, laxative, anti-emetic, anti-diabetic, anti-hypertensive agent
Snake gourd	frying, miso soup, stomachic, diuretic
Wandan[a)]	analgesic-antipyretic
Sweet potato leaf	gruel, miso soup
Turmeric	stomachic, drug for common cold
Purslane	antidote
Welsh onion	Sukiyaki, hard-boiled, spice, drug for common cold, diuretic
Comfrey	stomachic
Beefsteak plant	stomachic, drug for common cold, antidote
Kumisu-kuchin[a)]	drug for affecting renal function, anti-diabetic
Guava	fruit, juice, tea, anti-diabetic
Fennel	soup, stomachic
Boxthorn	tonic, analgesic-antipyretic
Hirami-lemon[a)]	fruit, juice, vinegar, stomachic
Papaya	fruit, juice, frying, pickles

a) Names in Japanese.

did not respond, such a response was processed as a missing value.

All of the computerized data were double-checked by the principal investigator for coding accuracy.

Selection of eligible subjects

1) Potential subjects: A total of 836 inpatients in the cross-sectional survey at 5 hospitals were interviewed. Psychiatric inpatients were excluded in this survey. There were no respondents whose age and sex were unknown.

For case-control analysis, the following respondents were excluded: 24 cases who were born outside Okinawa Prefecture; 43 multiple respondents in the questionnaire survey; 7 cases aged less than 20 years; 3 cases without any clear diagnostic data; 110 cases without any clear smoking history. After the above selection, only 2 subjects were less than 30 years old, so the analysis was performed on respondents aged over 30 years. Thus, a total of 673 respondents were selected and stored as "a source group of eligible respondents." Table II shows the age-distribution of these respondents by sex.

2) Matching cases and controls: For a case-control analysis, cases and controls were selected among the above 673 eligible respondents by multivariate caliper matching.[9] Each pair consisted of a case and 2 controls who were matched randomly for age (± 5), sex or smoking history (current/never smoked).

Eligible cancer cases were defined as newly diagnosed lung cancer cases. A total of 7 cancer cases were excluded from the eligible cancer cases. They had had primary lung cancer in the past and had metastasis or an unclear cancer site in the present history.

Eligible controls were also re-sampled from the 673 eligible respondents. Respondents were excluded from the eligible controls if any of the following diseases appeared in their history: malignant neoplasms, immunodeficiency disease and tumor-associated diseases, such as pulmonary emphysema, COPD (chronic obstructive pulmonary disease), B type hepatitis, liver cirrhosis, esophageal varices, and mastopathy.

3) Smoking analysis: For a case-control analysis of smoking and lung cancer, 64 pairs were matched for age and sex among the 673 eligible respondents except ex-smokers. Table III shows the age distributions of these lung cancer cases.

Since women smokers are traditionally rare in Japan, and there is a large sex difference of lung cancer incidence in Japan, we omitted women's data in confirming dose-response relationships between smoking and lung cancer. Age was matched in case-control analyses of these males, and the ex-smokers were analyzed separately. Ex-smokers were defined as people who had stopped smoking more than 6 months before the first detection of disease.

4) Diet analysis: A case-control analysis was separately carried out for each of the 17 species of edible plants in Table I, for the purpose of examining their tumor association. Ex-smokers were excluded.

In this study, two numerical indices were introduced in order to decrease the response bias of data in the questionnaire sheet, which might be due to the respondent's inattention. One type of these responses is clearly a non-response. Thus, the response rate of each inpatient to all 17 questions regarding the ingestion frequencies of plants was examined; this rate is related to the non-response bias on a general questionnaire. The frequency distribution of these rates for the total responders was a Poisson curve. The respondents with non-responses for over 10 species of plants were 8 inpatients among 836 respondents. Since these 8 respondents were less than 1% of the total respondents, they were excluded from the case-control analysis.

Another type of respondent's inattention to a questionnaire is that all answers on the ingestion frequencies of dietary plants are in the same category, such as "intermediate" in our diet questionnaire. Our diet questionnaire had four kinds of answer categories on the ingestion frequency of every dietary plant, as mentioned above. Three categories, except "unclear", were numbered "0", "1" and "2", and the mean of the answered ingestion

Table II. Age-Sex Distribution of Source Group of Eligible Respondents

Age	20–29	30–39	40–49	50–59	60–69	≧70	Total
Men	13	24	34	75	80	78	304
Women	38	51	33	58	75	114	369
Total	51	75	67	133	155	192	673

Ex-smokers were included.

Table III. Age-Sex Distribution of Lung Cancer Cases Matched

Age	30–39	40–49	50–59	60–69	70–79	≧80	Total
Matched by age and sex							
Men	0	2	10	20	6	3	41
Women	0	1	4	6	10	2	23
Total	0	3	14	26	16	5	64
Matched by age, sex and smoking history							
Men	0	1	8	12	4	1	26
Women	0	0	3	6	8	2	19
Total	0	1	11	18	12	3	45

Ex-smokers were excluded.

frequencies of the 17 species of dietary plants was calculated for every respondent. This mean score represents the "mean category answered." Finally, the number of answered categories different from the "mean answered category" was calculated for every respondent. Seventeen respondents had only 2 items that were different from "the mean categories." These poor variations in responses may well be related to inattention during answering. Since 17 respondents amounted to 2.04% of the 836 initial respondents, they were also excluded from the case-control analysis.

Forty-five pairs were matched for age, sex and smoking history (current smoker/never smoked), as shown in Table III.

Estimating relative risk Odds ratios were calculated according to the Mantel-Haenszel procedure for the matched data, and the 95% confidence limits were calculated by use of the Mantel-Haenszel chi-square test statistic.[10]

RESULTS

Sixty-four inpatients with lung cancer in Table III confirm that cigarette smoking had a significantly high odds ratio of 2.9 ($P<0.0005$) and the 95% confidence limits were 1.628 and 5.325.

To verify the existence of a dose-response relationship between smoking and lung cancer, current smokers were divided into three major groups of similar sample size, as shown in Table IV. Each subject in each group was matched for age. The odds ratios in the three groups of current smokers were significant ($P<0.05$) as was that of ex-smokers ($P<0.01$). Namely, we can not confirm dose-dependency of lung cancer on smoking from this table.

Since one reason for this might be age bias in each group, we analyzed the relationship of age with lung cancers in Table V, which summarizes the odds ratios and the mean numbers of cigarettes smoked per day by male generations. Ex-smokers were excluded in this table, and the odds ratios of cases in their thirties and forties were not calculated because there were few eligible subjects. The odds ratio of the subjects in their fifties was not significant, but that of the subjects in their sixties was significant at $P<0.01$ and that of the subjects aged over 70 was significant at $P<0.05$. Therefore, this table suggests the age dependency of lung cancer. It was also clear that the younger groups smoked more heavily. The odds ratio increased in those who were over 50 years and who may have a smoking history of at least 30 years. This means that the smoking period might contribute to the dose-response relationship between lung cancer and smoking.

Table IV. Cigarette-smoking and Lung Cancer among Inpatients Aged Over 30 (Men)

Smoking history	Cancer case (smoked) (No. of pairs)			Cancer case (not smoked) (No. of pairs)			Odds ratio (95% CL)
	0	1	2	0	1	2	
Ex-smoker	8	3	0	7	3	0	6.3 (1.9–21.0)
Current smoker	11	13	6	1	6	4	2.5 (1.2–5.1)
<20 CPD	6	5	0	7	2	1	4.3 (1.3–13.5)
20 CPD	7	6	2	4	6	0	3.3 (0.9–4.6)
>20 CPD	8	2	1	7	2	1	4.5 (1.5–13.2)

CL, confidence limit; CPD, number of cigarettes smoked per day.

Table V. Cigarette-smoking and Lung Cancer among Inpatients by Generation (Men)

Age class	Cancer case (smoked) (No. of pairs)			Cancer case (not smoked) (No. of pairs)			Odds ratio (95% CL)	Mean and SD of CPD
	0	1	2	0	1	2		
50–59	2	4	2	0	1	1	2.7 (0.6–12.4)	11.84±12.81
60–69	8	7	4	0	2	1	5.8 (2.0–17.0)	8.91±15.49
70≦	4	5	1	1	2	0	6.5 (1.4–31.1)	5.29±12.49

CL, confidence limit; CPD, number of cigarettes smoked per day; SD, standard deviation.
Ex-smokers were excluded.

Table VI. Relationships of Cigarette Smoking to Lung Cancer among Inpatients in Their Sixties by Number of Cigarettes Smoked (Men)

Smoking history	Cancer case (smoked) (No. of pairs)			Cancer case (not smoked) (No. of pairs)			Odds ratio (95% CL)
	0	1	2	0	1	2	
Ex-smoker	4	2	0	3	0	0	—
Current smoker							
<20 CPD	4	4	1	1	2	0	3 (0.7–12.6)
20 CPD	4	4	1	1	2	0	6 (1.3–28.9)
>20 CPD	4	1	0	2	1	0	9 (1.4–58.1)

CL, confidence limit; CPD, number of cigarettes smoked per day.

Table VII. Odds Ratios of Dietary Plants to Lung Cancer According to the Mantel-Haenszel Procedure

Plant	Cancer case (ingested) (No. of pairs)			Cancer case (not-ingested) (No. of pairs)			Odds ratio (95% CL)
	0	1	2	0	1	2	
Balsam pear	0	2	40	0	0	3	0.3 (0.1–1.8)
Wormwood	2	10	32	0	1	2	2.8 (0.8–9.6)
Aloe	6	5	2	5	21	6	0.5 (0.3–1.1)
Snake gourd	0	3	41	0	0	1	1.5 (0.2–14.2)
Wandan	0	14	19	0	3	9	0.7 (0.3–1.5)
Sweet potato	4	13	23	0	3	2	3 (1.1–8.3)
Turmeric	3	4	0	16	21	1	0.4 (0.2–1.1)
Purslane	2	5	0	20	17	1	0.5 (0.2–1.3)
Welsh onion	5	12	21	0	3	4	2 (0.9–4.7)
Comfrey	5	0	0	31	8	1	1 —
Beefsteak plant	3	15	5	5	6	11	0.8 (0.4–1.5)
Kumisu-kuchin	6	6	1	18	12	2	1.1 (0.5–2.6)
Guava	8	11	5	5	9	7	1.2 (0.6–2.3)
Fennel	6	3	9	10	12	5	0.7 (0.3–1.5)
Boxthorn	2	0	0	40	3	0	1.3 (0.2–7.9)
Hirami-lemon	1	12	26	1	1	4	1.6 (0.6–4.4)
Papaya	2	10	24	0	0	3	2.3 (0.8–7.3)

CL, confidence limit.
Ex-smokers were excluded.

As the group of males in their sixties had a comparatively larger sample size, they were examined in more detail as shown in Table VI. The results support a dose-response relationship between smoking and lung cancer, because the odds ratios of 20 cigarettes and over were significant ($P<0.1$) and the odds ratio of less than 20 cigarettes per day was not significant. The odds ratio of ex-smokers was not obtained because there were too few cases.

Table VII lists the odds ratio of each of 17 species of edible plants. Aloe had an odds ratio of 0.5, which is significantly less than 1 ($P<0.1$).

DISCUSSION

As mentioned above, we confirmed the reliability of disease diagnosis by medical records several years after the diet questionnaire survey. Approximately 10% of diseases seemed to be different from the previous ones, partly because of the latent time of cancer development. It is obviously necessary for a chronic disease epidemiologist to confirm the medical data periodically after his initial survey, or to compare the medical data of the same cases after a long interval. In a follow-up study,

the diagnosis can be misclassified due to a long latent period of the chronic disease. It is theoretically difficult to avoid an information bias arising from this misclassification when we conduct a cross-sectional survey.

The traditionally recommended approach to solve this kind of bias is pre-formulation of the diagnostic criteria.[11, 12] In this paper, we have employed a reconfirmation approach of well-established epidemiologic phenomena or associations, which have been established world-wide, such as the relationships between cigarette smoking and lung cancer or between the age at first pregnancy and breast cancer.[13, 14] The current results suggest a fair dose-response relationship between cigarette smoking and lung cancer in males in their sixties. Therefore, the diagnosis and smoking data seem to be reliable and valid.

The odds ratio of the male ex-smokers was higher than that of the male smoker group. This was probably because most of the ex-smokers had stopped smoking when they were suffering from respiratory disability, before they were diagnosed as having lung cancer. But in the present study, few respondents clearly indicated the duration of the non-smoking period, so further study is necessary to test the above speculation regarding ex-smokers. In addition, further information on starting ages of smokers and the durations of smoking periods would be useful to establish clear dose-dependency, though such data were not available in this study.

As demonstrated above, the reconfirmation approach of well-established epidemiologic facts is useful to evaluate the quality of the medical data even in a cross-sectional survey. The reconfirmation approach seems to be a variation of the validity scale approach.[15]

We did not compare our results on the odds ratios with those of other surveys. This was because the magnitude of the odds ratio itself is theoretically considered to depend on the existence of other carcinogens and/or anti-carcinogens acting on the same site. Other risk factors than those of interest should coincide in two different populations for comparing the relative risks, because the human population is usually exposed to multiple kinds of risk factors for cancer.[16] However, the dose-dependency of a disease on one risk factor is not lost in the coexistence of other risk factors, so such a relationship is considered to be valid for diagnosis quality assessment.

Quality assessment of the diagnosis after finishing a survey is most difficult. Epidemiologically well-established relationships are rather few, but the reconfirmation of such relationships is an easy, economical and convenient method for this assessment if available. But if we do not succeed in reconfirming such a relationship between risk factor and disease, we can not evaluate which is in error. For quality assessment of the data in an epidemiologic survey, we should employ the reconfirmation approach as well as a pre-formulation of the diagnostic criteria before the survey.

The results of plant epidemiology suggest that aloe prevents human pulmonary carcinogenesis. The pharmacological activities of aloe have been known from ancient times.[17] Several pharmacological substances have been found in aloe. Aloe-emodin was reported to reduce the proliferation of normal or malignant cells such as lymphatic leukemia or sarcoma cells in mice.[4, 5] Aloe-mannan, which is a main polysaccharide component of aloe with M_r 15000, was found to inhibit the growth of implanted sarcoma in mice.[6] Lectin of the aloe was considered to induce systemic anti-tumor immunity in mice.[18] Recently, animal experiments demonstrated anti-metastatic properties of aloe juice.[19]

From our previous study, 17 species of plants in this paper were divided into two major categories; dietary plants and herbs. Aloe was found to be mainly ingested as a herb.[20] The people in Okinawa ingest it as juice. That study also suggested that aloe was preventive against stomach and colon cancer. Therefore, as Indian folklore suggests, aloe "stops cancer formation" if it is ingested,[21] so aloe is suggested to be widely preventive or suppressive against various human cancers. The effective doses of the aloe for prevention and suppression of malignant neoplasms could not be estimated in the present study.

Several biochemical components were also identified in the balsam pear: lectin[22] or guanylate cyclase inhibitor.[23] The lectin was reported to inhibit protein synthesis and to restrict DNA synthesis in target cells.[22] It is considered to reduce the proliferation of normal or malignant cells such as hepatic or leukemic cells in rats.[3] Our present results were suggestive of such preventive activities of the balsam pear, though no statistically significant effect was found.

Hirami-lemon is cultivated uniquely in Okinawa. There have been few studies on its pharmacological activities, but ordinary lemons or oranges were reported to prevent esophageal or colon cancer in rats and humans, due to the high concentrations of vitamin C, vitamin A, beta-carotene, or dietary fiber.[24–26] Fennel was reported to contain an estrogen-like substance, so its association with breast cancer occurrence should be studied.[27] Comfrey is well-known to be carcinogenic in rat livers, possibly due to a pyrrolizine alkaloid.[7, 8, 28, 29] This plant also gave a positive response in the Ames mutagenicity test.[30] Turmeric was suggested to be mutagenic by an FAO/WHO Expert Group, but today it is considered to be neither mutagenic nor carcinogenic.[31, 32]

The results presented here indicate that lung cancer occurrence depends on age as well as smoking. There is also a sex difference of lung cancer incidence as

mentioned above. It is possible, however, that the unclear dose-dependency of male lung cancer on smoking in the present study was due to the influence of dietary plants, especially aloe. However, further epidemiologic study of a larger sample will be necessary to assess the accelerative or suppressive effects of the above species of plants on human carcinogenesis, taking account of other dietary factors such as beta carotene, cholesterol/fats or salt, which are possibly related to lung cancer.

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