Jpn. J. Cancer Res. 82, 273–279, March 1991

Lung Cancer Risk among Exsmokers

Tomotaka Sobue,[1] Takaichiro Suzuki,[1] Isaburo Fujimoto,[1] Minoru Matsuda,[1] Osamu Doi,[1] Takashi Mori,[2] Kiyoyuki Furuse,[2] Masahiro Fukuoka,[3] Tsutomu Yasumitsu,[3] Osamu Kuwahara,[4] Michio Ichitani,[5] Toshihiko Taki,[6] Masayoshi Kuwabara,[7] Kazuya Nakahara,[8] Shozo Endo,[9] Kenji Sawamura,[9] Masahiko Kurata[9] and Shoji Hattori[9]

[1]The Center for Adult Diseases, Osaka, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537, [2]National Kinki Central Hospital for Chest Diseases, 1180 Nakasone-cho, Sakai 591, [3]Osaka Prefectural Habikino Hospital, 3-7-1 Habikino, Habikino 583, [4]National Toneyama Hospital, 5-1-1 Toneyama, Toyonaka 560, [5]Osaka Red Cross Hospital, 5-53 Fudegasaki, Tennoji-ku, Osaka 543, [6]Tazuka Kofukai Medical Research Institute, Kitano Hospital, 3 Nishioogimachi, Kita-ku, Osaka 530, [7]Kansai Denryoku Hospital, 2-1-7 Fukushima, Fukushima-ku, Osaka 553, [8]First Department of Surgery, Osaka University Hospital, 1-1-50 Fukushima, Fukushima-ku, Osaka 553, and [9]Osaka Anti-Lung Cancer Association, 4-6-5 Doshomachi, Chuo-ku, Osaka 541

Lung cancer risk among exsmokers according to years since cessation of smoking was assessed by means of a case-control study. The case series consisted of 1,052 lung cancer patients who were newly diagnosed and admitted to eight hospitals in Osaka in 1986–88. Smoking histories were compared with those of 1,111 controls admitted to the same hospitals during the same period without any diagnosis of smoking-related disease. The odds ratio of lung cancer for exsmokers compared to current smokers was estimated to be 0.90, 0.50, 0.51, 0.59, 0.48 and 0.29, for 1–4, 5–9, 10–14, 15–19, 20–24 and ≥ 25 years after cessation of smoking, respectively. Risk reduction appeared to be greater for those who smoked less than the 1200 cigarette index, compared to those who smoked more. In classification according to histologic type, small cell and large cell carcinoma showed a rapid decrease compared to adenocarcinoma, while squamous cell carcinoma showed an intermediate pattern. Quantitative estimates for reduction of lung cancer risk among exsmokers can be used for projecting lung cancer incidence in the future, by assuming future trends of smoking prevalence, as well as for health education among individual smokers.

Key words: Lung cancer — Exsmoker — Odds ratio

It has been established through various epidemiologic studies that cigarette smoking is causally related to lung cancer.[1,2] It is estimated in Japan that 67% of lung cancer incidence among males is attributable to smoking.[3] However, this does not mean that if all smokers quit smoking, lung cancer incidence could be immediately reduced to this extent. This is because the risk of lung cancer among smokers will not decrease to the nonsmoker's level immediately after cessation of smoking. In the US, the smoking rate among males has decreased from 50% to 30% during the past two decades.[4] As a result, mortality rates of lung cancer at ages below 45 began to decline after 1980, but at ages above 50, when most lung cancer occurs, mortality rates of lung cancer continued to rise at least until 1986.[5] In Japan, lung cancer incidence in males has been increasing rapidly, while the smoking rate for males has been decreasing gradually.[3] This discrepancy cannot be explained if lung cancer risk among smokers decreases to the nonsmoker's level within a short period after cessation of smoking.

Based on the analysis of age-sex-period specific mortality rates in the US, it is projected that lung cancer mortality will maintain its current high level up to the year 2000, even if the smoking rate continues to decrease to 15% in 2000, and the effect of smoking control activities on lung cancer mortality will not become apparent until 2020.[6] In this analysis, it is assumed that the decrease of cigarette consumption leads to a decrease in lung cancer mortality with a lag time of 24 years, which was determined by goodness-of-fit during the period when lung cancer incidence and the smoking rate were both increasing. In order to conduct this type of projection more precisely, however, it is necessary to know how the risk of lung cancer decreases after cessation of smoking among individual exsmokers.

In the US and Europe, reduction of risk for lung cancer among exsmokers has been observed by cohort studies,[7–12] and case-control studies.[13–16] A large-scale case-control study conducted in Western Europe showed that lung cancer risk among exsmokers who had given up smoking 10 years before was approximately half of that for people who continued to smoke.[13] For those who had smoked for 19 years or less, lung cancer risk after not smoking for 10 years was roughly the same as that for lifelong nonsmokers. For those who had smoked for 20

years or more, however, risks remained substantially raised even after 10 years of not smoking.[13] In contrast, some cohort studies have shown that the risk of lung cancer reached the level of nonsmokers after 10 years of not smoking,[9, 11] while other cohort studies have indicated a much slower decrease.[7, 8, 10, 12]

However, in Japan, the incidence of lung cancer is still low,[17] the frequency of adenocarcinoma, which is less related to smoking, is higher,[18] and the history of a high prevalence of cigarette smoking among the general population is rather short[19, 20] compared to the US and Europe, so that the results obtained in these countries cannot be directly applied to Japan.

In Japan, there has been one large-scale cohort study for estimating the risk reduction of lung cancer among exsmokers, in which smoking habits were investigated only once at the time of initial survey and followed up for over 16 years.[21, 22] This study showed that the mortality rate of lung cancer in daily smokers tended to approach the level of nonsmokers within five to ten years after cessation of smoking. To estimate these risks, however, additional surveys should be conducted after the initial survey to observe changing smoking habits among the study population, particularly when the follow-up period is long, such as 16 years. Therefore, the results from this study may not be accurate, especially those within a short period, such as 5 years, after cessation of smoking. A case-control study, in which changes in smoking habits can be observed up to the diagnoses of cases and controls, can avoid this type of problem, although it will suffer from other sources of bias.

This study aims to investigate the risk of lung cancer among exsmokers according to years since cessation of smoking in Japan, by means of a case-control study.

MATERIALS AND METHODS

According to the Osaka Cancer Registry, 2,481 primary lung cancer patients (1,809 males and 672 females) were diagnosed in Osaka Prefecture in 1985.[23] Of these, about one-quarter were registered from the top eight hospitals, which have special departments for lung cancer. These eight hospitals participated in a multicenter, hospital-based case-control study with the support of the Osaka Anti-Lung Cancer Association.

Both cases and controls were collected from patients newly admitted to the eight hospitals from January 1, 1986 to December 31, 1988, and their ages ranged from 40 to 79 years at the time of admission. In the above eight hospitals, all wards for lung cancer and one or two wards for other diseases were involved in this study. All newly admitted patients in these wards were investigated by means of a self-administered questionnaire at the time of admission to the hospital.

A uniform questionnaire was used in all hospitals, designed specially for this study, which included questions on smoking status, i.e. whether they were smoking or not at present, and if so, the age at which the smoker had started, and the average amount smoked per day. If the smoker had quit smoking, the age at which the smoker had quit was also asked.

Smoking habits were classified into 3 categories, current smoker, exsmoker, and nonsmoker. Exsmoker was defined as those who had smoked regularly in the past and quit smoking 1 year or more before the date of admission. For current smoker and exsmoker, smoking intensity was classified according to the cigarette index, which was calculated by multiplying the average number of cigarettes smoked per day by the number of years of smoking.

Among patients with other diseases, those with smoking-related diseases (cancer of oral cavity, nasal sinus, pharynx, larynx, esophagus, pancreas, kidney, bladder, cervix uteri; chronic obstructive pulmonary diseases; coronary heart diseases, atherosclerosis of the aorta, arteriosclerotic peripheral vascular diseases; peptic ulcer; and chronic sinusitis) were excluded from the analysis.

A total of 1,079 lung cancer patients and 1,369 patients with other diseases were investigated for males, and 295 lung cancer patients and 1,073 patients with other diseases for females. However, females were not included in this analysis because of the limited number of exsmokers. Among male lung cancer patients, there were 737 current smokers, 286 exsmokers, 29 nonsmokers, and 27 patients with unknown smoking status, and the corresponding numbers were 633, 352, 126 and 35 for male patients with other diseases, respectively. Patients with unknown smoking status were excluded from the analysis. Also, 69 lung cancer patients and 65 patients with other diseases were excluded because detailed smoking information, such as the age at which they had started smoking or the average number of cigarettes smoked per day, was missing for exsmokers or current smokers. Therefore, analysis was conducted on 1,052 male lung cancer patients as cases, and 1,111 male patients with other diseases as controls. No matching procedure was performed between cases and controls.

Adjusted odds ratios of current smoker versus exsmoker were calculated by the Mantel-Haenszel method[24] using 3 levels of cigarette index ($\leq$599, 600–1199, 1200$\leq$) and eight age categories (5-year intervals) at admission. The trend for linearity was evaluated by the extended Mantel-Haenszel test.[24] Analysis was conducted with the PROC FREQ subroutine in the computer program SAS.[25]

RESULTS

All cases were microscopically confirmed, and had the following distribution of histologic type[26]; squamous cell carcinoma 408 (39%), adenocarcinoma 410 (39%), small cell carcinoma 128 (12%), large cell carcinoma 80 (8%), and other histologic types 26 (2%). For cases who were current smokers, the above distribution was 292 (40%), 270 (37%), 101 (14%), 58 (8%), and 16 (2%), respectively, while for cases who were exsmokers, the distribution was 114 (40%), 115 (40%), 27 (9%), 20 (7%), and 10 (3%), respectively. The proportion of adenocarcinoma was slightly lower among current smokers than exsmokers, while those of small cell carcinoma and large cell carcinoma were slightly higher in current smokers than exsmokers. For nonsmokers, most of the cases (25 out of 29) were adenocarcinoma.

Controls were diagnosed as having the following diseases; stomach cancer 302 (27.1%), other cancer 277 (27.9%), benign tumor 87 (7.8%), circulatory disease 76 (6.8%), respiratory disease 153 (13.8%), infectious disease 89 (8.0%), digestive disease 31 (2.8%), neuro-

Table I. Distribution of Age and Smoking Status at Admission in Cases and Controls

Characteristics	Case		Control	
	No.	%	No.	%
Age				
40–49	86	8.2	194	17.5
50–59	266	25.3	385	34.7
60–69	398	37.8	330	29.7
70–79	302	28.7	202	18.2
Smoking status				
Current smoker	737	70.1	633	57.0
Exsmoker	286	27.2	352	31.7
Nonsmoker	29	2.8	126	11.3

Table II. Odds Ratios[a] of Lung Cancer according to Years since Cessation of Smoking

Years since cessation of smoking	Case		Control		Odds ratio
	No.	%	No.	%	
0[b]	737	72.0	633	64.3	1.00[c]
1–4	128	12.5	116	11.8	0.90
5–9	67	6.5	92	9.3	0.50
10–14	35	3.4	50	5.1	0.51
15–19	24	2.3	31	3.2	0.59
20–24	15	1.5	23	2.3	0.48
≥25	17	1.7	40	4.1	0.29

a) Adjusted by age and cigarette index.
b) Baseline category. Risk for current smoker relative to nonsmoker was 4.5.
c) Test for linear trend, $P<0.05$.

Table III. Odds Ratios[a] of Lung Cancer according to Years since Cessation of Smoking by Cigarette Index

Years since cessation of smoking	Cigarette index		
	1–599	600–1199	1200–
0	1.00[b]	1.16	1.50
1–4	0.84	0.85	1.63
5–9	0.59	0.42	0.97
≥10	0.49	0.44	0.82

a) Adjusted by age.
b) Baseline category. Risk for current smoker who had smoked for 1–599 cigarette index relative to nonsmoker was 4.0.

Table IV. Odds Ratios[a] of Lung Cancer according to Years since Cessation of Smoking by Histologic Type

Years since cessation of smoking	Histologic type[b]							
	Sq		Ad		Sm		La	
	No.[c]	OR[d]	No.	OR	No.	OR	No.	OR
0[e]	292	1.0	270	1.0	101	1.0[f]	58	1.0[f]
1–4	52	0.9	44	0.9	17	0.8	12	1.1
5–9	32	0.6	22	0.5	7	0.4	4	0.4
≥10	30	0.4	49	0.7	3	0.1	4	0.3

a) Adjusted by age and cigarette index.
b) Sq, squamous cell carcinoma; Ad, adenocarcinoma; Sm, small cell carcinoma; La, large cell carcinoma.
c) Number of cases.
d) Odds ratio.
e) Baseline category. Risks for current smoker relative to nonsmoker: 28.0 (Sq), 2.1 (Ad), unable to estimate because no nonsmoker existed among cases (Sm), 5.6 (La).
f) Test for linear trend $P<0.05$.

logical or psychological disease 26 (2.3%), congenital disorder 18 (1.6%), endocrinal disease 15 (1.4%), and others 37 (3.3%).

Table I shows the distribution of age and smoking at admission for cases and controls. Age distribution tended to be higher in cases than in controls. The proportion of current smokers was higher in cases, while that of exsmokers and nonsmokers was higher in controls.

Table II shows the odds ratios of developing lung cancer according to years since cessation of smoking. A comparison was made between current smokers and exsmokers. The odds ratio gradually decreased from unity to 0.29 as years passed after cessation of smoking. The test for linear trends showed statistical significance. The risk of lung cancer among current smokers was estimated to be 4.5 times higher compared to that among nonsmokers. Therefore, those who have quit smoking for 25 years or more still have a 1.3 times higher risk of lung cancer than nonsmokers.

Table III shows the odds ratios of developing lung cancer according to years since cessation of smoking and the cigarette index. The decreasing patterns of odds ratios were almost the same for cigarette index groups 1–599 and 600–1199, but they tended to be slower for cigarette index group 1200 or over.

Table IV shows the odds ratios of developing lung cancer according to years since cessation of smoking and histologic type. Decreasing patterns of odds ratios were steeper in small and large cell carcinoma than in adenocarcinoma. Squamous cell carcinoma showed an intermediate pattern.

DISCUSSION

To our knowledge, this is the first study in Japan which has attempted to evaluate the risk of developing lung cancer among exsmokers according to years since cessation of smoking, by means of a case-control approach. The risk of exsmokers compared to current smokers decreased rapidly over the first 10 years after cessation of smoking. After that, the decrease became slower, and the risk was still elevated 20 years or mors after cessation of smoking. These results suggest that the role of cigarette smoking in lung carcinogenesis can be divided into two parts. One is related to promoting activity which may be diminished immediately after the cessation of smoking. The other is related to initiating activity which remains for an extended period after the cessation of smoking.

Table V summarizes the results from the previous case-control studies[13, 15, 16] and the cohort studies[7–10] on

Table V. Reduction of Lung Cancer Risk among Male Exsmokers according to Years since Cessation of Smoking in Previous Studies

Authors (Year)	Subgroup	Current vs. non[a]	Years since cessation of smoking						
			0	1–4	5–9	10–14	15–19	20–24	25+
Case-control study									
Lubin *et al.* (1984)[13]		9.0[b]	1.0	1.07	0.71	0.56	0.43	0.43	0.29
Benhamou *et al.* (1989)[15]		15.9[c]	1.0	1.5	0.7	0.5	0.4[d]		
Wynder and Stellman (1977)[16]	KB I[e]	32.3	1.0	1.67[f]	0.77[g]	0.53[h]	0.42[i]	0.15[j]	
	KB II	10.7	1.0	1.33	0.55	0.62	0.50	0.11	
Cohort study									
Doll and Peto (1976)[7]		15.8	1.0	1.10	0.37	0.34	0.13[k]		
Hammond and Horn (1958)[8]	<1 pack[l]	16.9	1.0		0.62[m]	0.14[n]			
	1 pack+	46.2	1.0		0.49	0.39			
Hammond (1966)[9]	<1 pack	6.5	1.0	0.71	0.15	0.06[o]			
	1 pack+	13.7	1.0	0.88	0.53	0.08			
Rogot and Murray (1980)[10]		11.3	1.0	1.7	0.7	0.4	0.4	0.2[p]	
Hirayama (1987)[22]		4.4	1.0	0.46	0.36[q]				

a) Odds ratio of lung cancer for current smoker versus nonsmoker.
b) From reference 27.
c) Calculated by the authors from the data in reference 28.
d) 15 years or more. *e*) Kreyberg type I.
f) 1–3 years. *g*) 4–6 years. *h*) 7–10 years. *i*) 11–15 years.
j) 16 years or more. *k*) 15 years or more.
l) Average number of cigarettes smoked per day.
m) 1–10 years. *n*) 11 years or more. *o*) 10 years or more. *p*) 20 years or more. *q*) 5 years or more.

lung cancer risk among exsmokers. For comparison, risk reduction for exsmoker relative to current smoker was recalculated for studies in which excess risks for exsmoker relative to nonsmoker were presented. The odds ratios observed in this study for various cessation periods were very similar to those observed in large-scals case-control studies conducted in Western Europe[13, 15] and the US,[16] despite some differences in smoking habits, lung cancer incidence, and distribution of histologic types between these countries.

On the other hand, the results obtained from most of the cohort studies showed more rapid reductions than those from case-control studies. This difference can probably be attributed to two factors. First, in most cohort studies, smoking habits were surveyed only once at the beginning of follow-up, and the years since cessation of smoking were fixed at that time. This caused each category of years since cessation to contain person-years over a longer period since cessation, because the actual period since cessation increases as the follow-up period increases. As a result, the reduction of lung cancer risk within shorter periods after cessation will be overestimated, if the risk decreases as the period since cessation increases. In the US Veterans' study,[10] the number of years since cessation was increased by one year with each year of follow-up, which resulted in slower reductions within a short period after cessation, compared to other cohort studies. Only in the British physicians' study[7] were three additional surveys conducted during 20 years of follow-up. However, even in this study, years since cessation were still at 5–7 year intervals.

Second, most of the cohort studies were initiated in the 1950s–60s, while most of the case-control studies have been conducted more recently. In the US, it was reported that earlier cohorts were less exposed to cigarette smoking than recent cohorts, in terms of the age at which smoking begins and the daily number of cigarettes smoked.[29] It has also been shown that risk reduction among heavy smokers was less than among light smokers in this study and other previous studies.[13, 21] Therefore, the different periods in which the investigations were conducted could partly explain the different results.

This study showed more rapid risk reduction for small and large cell carcinoma, compared to adenocarcinoma, which is consistent with other studies.[14] This may suggest that smoking contributes mainly to the later stage of carcinogenesis for small and large cell carcinoma, while it contributes mainly to the earlier stage for adenocarcinoma.

Lung cancer is not the only disease related to cigarette smoking. It has been reported that risk reduction after cessation of smoking is most rapid for influenza and pneumonia, followed by cardiovascular diseases, such as coronary heart diseases, while the risk of lung cancer continues for an extended period.[10] This was supported by results from an autopsy study, which showed that abnormalities in bronchial epithelium, such as atypical nuclei, remained among exsmokers for as long as 10 years after cessation of smoking.[30]

This study contains some methodological problems to be discussed. First, smoking status observed in hospital controls may not represent that in the general population from which the cases were derived. Based on the results from the population survey conducted in Osaka in 1983–85, rates of current smokers, exsmokers and nonsmokers were estimated to be 62.9%, 22.2% and 14.9%, respectively, adjusting to the age distribution of the controls in this study. On the other hand, rates of current smokers, exsmokers and nonsmokers in the controls after excluding smoking-related diseases were 57.0%, 31.7% and 11.3%, respectively. Therefore, the rate of exsmokers was relatively high in this control group, probably because hospital patients tend to quit smoking even when their diseases are not related to smoking. Difference in time between the population survey and the present study could partly explain the different rates for exsmokers, because the cessation rate has recently been increasing. However, caution is necessary in concluding that risk reduction among exsmokers would be overestimated if the rate of exsmokers in the control group is overestimated. This problem may also exist with other previous case-controls studies,[13–16] in which hospital controls were used.

Second, a substantial proportion of controls consisted of cancer patients, especially stomach cancer. Although use of cancer controls has various merits and drawbacks, it is obviously not appropriate to choose controls from a single disease entity. When stomach cancer was excluded from the controls, however, the results did not show substantial change.

Third, the reasons why individuals quit smoking were not investigated in this study. However, some of the patients quit smoking due to symptoms which appeared as a result of lung cancer. Therefore, the risk reduction of lung cancer within a short period after cessation of smoking may be underestimated. Actually, an elevated risk of lung cancer relative to current smokers was observed for exsmokers within a short period after cessation of smoking in the previous cohort studies[8, 9] as well as case-control studies.[15, 16]

Fourth, exsmokers may not be the same as current smokers in terms of various life style factors other than smoking, which might cause different lung cancer incidence between the two groups. It is reported that exsmokers consume more vegetables and fruits than current smokers,[31] and this is expected to decrease the risk of lung cancer.[32] Actually, among controls in this study, more exsmokers ate green-yellow vegetables daily (42%)

than current smokers (30%). However, the effects of smoking cessation showed very little change after making adjustments for daily green-yellow vegetable intake. The same question may be raised when comparing exsmokers for longer duration after cessation and those for shorter duration. Comparison between these two groups in terms of green-yellow vegetable intake, however, showed no substantial difference, which suggests that the effect of this type of bias would also be small.

Quantitative estimates for reduction of lung cancer risk among exsmokers can be used for projecting lung cancer incidence in the future, by assuming future trends of smoking prevalence. They can also be used for health education programs for individual smokers. These programs should be promoted, especially for smokers among the younger generation, for whom a rapid decrease of lung cancer risk can be expected.

ACKNOWLEDGMENTS

This study was partly supported by Grants-in-Aid for Cancer Research from the Japanese Ministry of Health and Welfare (2-3). The authors wish to thank the late Dr. Shizuo Okada for his contribution to this study. Thanks are also due to the staff at the collaborating hospitals, whose contributions to the collection and processing of data made this study possible, and to Ms. Yumi Murai for her excellent technical assistance.

(Received October 31, 1990/Accepted December 26, 1990)

REFERENCES

1) A Report of the Surgeon General. "The Health Consequence of Smoking: Cancer," DHHS(PHS) 82-50179 (1982). Office on Smoking and Health, U.S. Department of Health and Human Services, Rockville, Maryland.
2) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 38. "Tobacco Smoking" (1986). International Agency for Research on Cancer, Lyon.
3) Tominaga, S. Smoking and cancer. *In* "Cancer Prevention, Progress in Cancer Clinics Series No. 22," ed. by S. Takayama, pp. 10–17 (1988). Medical View, Tokyo (in Japanese).
4) A Report of the Surgeon General. "The Health Consequence of Smoking: Nicotine Addiction," DHHS Publ. No. (CDC) 88-846 (1988). Office on Smoking and Health, US Department of Health and Human Services, Rockville, Maryland.
5) Devesa, S. S., Blot, W. J. and Fraumeni, J. F., Jr. Declining lung cancer rates among young men and women in the United States: a cohort analysis. *J. Natl. Cancer Inst.*, **81**, 1568–1571 (1989).
6) Brown, C. C. and Kessler, L. G. Projections of lung cancer mortality in the United States: 1985–2025. *J. Natl. Cancer Inst.*, **80**, 43–51 (1988).
7) Doll, R. and Peto, R. Mortality in relation to smoking: 20 years' observation on male British doctors. *Br. Med. J.*, **2**, 1525–1536 (1976).
8) Hammond, E. C. and Horn, D. Smoking and death rates-report on forty-four months of follow-up of 187,783 men. *J. Am. Med. Assoc.*, **166**, 1294–1308 (1958).
9) Hammond, E. C. Smoking in relation to the death rates of one million men and women. *Natl. Cancer Inst. Monogr.*, **19**, 127–204 (1966).
10) Rogot, E. and Murray, J. L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.*, **95**, 213–222 (1980).
11) Cederlof, R., Friberg, L., Hrubec, Z. and Lorich, U. The relationship of smoking and some social covariates to mortality and cancer morbidity. A ten year follow-up in a probability sample of 55,000 Swedish subjects, age 18–69, Part 1 and Part 2, (1975). Department of Environmental Hygiene, The Karolinska Institute, Stockholm.
12) Ockene, J. K., Kuller, L. H., Svendsen, K. H. and Meilahn, E. The relationship of smoking cessation to coronary heart disease and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). *Am. J. Public Health*, **80**, 954–958 (1990).
13) Lubin, J. H., Blot, W. J., Berrino, F., Flamant, R., Gillis, C. R., Kunze, M., Schmael, D. and Visco, G. Modifying risk of developing lung cancer by changing habits of cigarette smoking. *Br. Med. J.*, **288**, 1953–1956 (1984).
14) Lubin, J. H. and Blot, W. J. Assessment of lung cancer risk factors by histologic category. *J. Natl. Cancer Inst.*, **73**, 383–389 (1984).
15) Benhamou, E., Benhamou, S., Auquier, A. and Flamant, R. Changes in patterns of cigarette smoking and lung cancer risk: results of a case-control study. *Br. J. Cancer*, **60**, 601–604 (1989).
16) Wynder, E. L. and Stellman, S. D. Comparative epidemiology of tobacco-related cancers. *Cancer Res.*, **37**, 4608–4622 (1977).
17) Waterhouse, J., Muir, C. S., Shanmugaratnam, K. and Powel, J. (ed.) "Cancer Incidence in Five Continents, Vol. IV," IARC Scientific Publications No. 42 (1982). IARC, Lyon.
18) Hanai, A., Benn, T., Fujimoto, I. and Muir, C. S. Comparison of lung cancer incidence rates by histologic type in high and low incidence countries, with reference to the limited role of smoking. *Jpn. J. Cancer Res.*, **79**, 445–452 (1988).
19) Fujimoto, I. Trend of lung cancer incidence in Japan. *In* "Lung Cancer, Progress in Cancer Clinics Series No. 6," ed. by S. Takayama, pp. 168–175 (1986). Medical View, Tokyo (in Japanese).

20) Hirayama, T. The problem of smoking and lung cancer in Japan with special reference to the rising trend in age-specific mortality rate by number of cigarettes smoked daily. *Jpn. J. Cancer Res.*, **78**, 203–210 (1987).
21) Hirayama, T. Epidemiology of lung cancer. *In* "Lung Cancer, Progress in Cancer Clinics Series No. 6," ed. by S. Takayama, pp. 176-181 (1986). Medical View, Tokyo (in Japanese).
22) Hirayama, T. "Preventive Oncology," pp. 237–243 (1987). Mediscience, Tokyo (in Japanese).
23) Osaka Prefectural Health Department, Osaka Medical Association, and Center for Adult Diseases, Osaka. "Annual Report of the Osaka Cancer Registry, No. 45; Cancer in Osaka, 1985" (1989). Osaka Prefectural Health Department, Osaka (in Japanese).
24) Breslow, N. E. and Day, N. E. "Statistical Methods in Cancer Research, Vol. I The Analysis of Case-Control Studies," IARC Scientific Publications No. 32, pp. 122–159 (1980). IARC, Lyon.
25) The FREQ Procedure. *In* "SAS User's Guide: Statistics, Version 5 Edition," pp. 403–432 (1985). SAS Institute, Cary, NC.
26) The World Health Organization. Histological typing of lung tumors, second edition. *Am. J. Clin. Pathol.*, **77**, 123–136 (1981).
27) Lubin, J. H., Blot, W. J., Berrino, F., Flamant, R., Gillis, C. R., Kunze, M., Schmahl, D. and Visco, G. Patterns of lung cancer risk according to type of cigarette smoked. *Int. J. Cancer*, **33**, 569–576 (1984).
28) Benhamou, S., Benhamou, E., Tirmarche, M. and Flamant, R. Lung cancer and use of cigarettes: a French case-control study. *J. Natl. Cancer Inst.*, **74**, 1169–1175 (1985).
29) Harris, J. E. Cigarette smoking among successive birth cohorts of men and women in the United States during 1900–80. *J. Natl. Cancer Inst.*, **71**, 473–479 (1983).
30) Auerbach, O., Stout, A. P., Hammond, E. C. and Garfinkel, L. Bronchial epithelium in former smokers. *N. Engl. J. Med.*, **267**, 119–125 (1962).
31) Kato, I., Tominaga, S. and Suzuki, T. Characteristics of past smokers. *Int. J. Epidemiol.*, **18**, 345–354 (1989).
32) Hirayama, T. "Preventive Oncology," pp. 244–248 (1987). Mediscience, Tokyo (in Japanese).