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Lung Cancer Incidence Rate for Male Ex-smokers According to Age at Cessation of Smoking

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Lung cancer incidence rate after the cessation of smoking was assessed for male ex-smokers according to the age at cessation, using the results from a case-control study for ex-smoker versus continuing smoker, and the lung cancer incidence rate function for continuing smoker estimated from Japan Vital Statistics and the "Six-prefectural Cohort Study" in Japan. This hospital-based case-control study consisted of 776 lung cancer cases (553 current smokers and 223 ex-smokers) and 772 controls (490 current smokers and 282 ex-smokers) who started smoking at ages 18–22. The odds ratio of developing lung cancer for ex-smokers compared to continuing smokers according to years since the cessation of smoking was estimated for four age groups (55–64, 60–69, 65–74 and 70–79). Given that the number of years since cessation of smoking is the same, reduction of the odds ratio appeared to be greater for the younger age group than for the older age group, reflecting the shorter period of exposure for the younger age group. Lung cancer incidence rate (per 100,000) was assumed to be expressed by the following function; $1.7\times10^{-5}\times(\text{age}-24.3)^{4.5}$ for continuing smokers and $0.15\times10^{-5}\times(\text{age})^{4}$ for nonsmokers. Lung cancer incidence rate among ex-smokers according to years since cessation was then estimated to be the above function multiplied by the odds ratio from the case-control study for each age group. In contrast to the greater reduction of the odds ratio among younger ex-smokers, reduction of the incidence rate, in terms of rate difference, was considerably greater for older ex-smokers due to a high incidence rate of lung cancer for older continuing smokers. This indicates that the absolute magnitude of reduction of the lung cancer incidence rate after cessation of smoking is greater for older ex-smokers, although the relative magnitude of reduction is greater for younger ex-smokers.

Key words: Lung cancer — Ex-smoker — Incidence

Accumulated data have revealed that the risk of lung cancer decreases after the cessation of smoking compared to that for continuing smokers. It is reported that the risk of lung cancer among ex-smokers after 10 years of abstinence decreases to 30 to 50 percent of that of continuing smokers.[1]

At the same time, however, several analytic issues were raised in the study of lung cancer risk among ex-smokers, especially concerning the methods of adjustment for time-related factors of smoking history.[1] In previous case-control studies, the odds ratio among ex-smokers according to years since cessation of smoking was adjusted by both age at observation and duration of smoking.[2-5] However, since four time-related factors on smoking history, namely, age at starting smoking, age at observation, duration of smoking and duration of abstinence, are interdependent, specification of any three factors fixes the fourth. Assuming that current smokers and ex-smokers of a given attained age smoked for the same duration, the age at starting smoking among ex-smokers must be younger than for current smokers. Therefore, methods that attempted to allow each of these four time-related factors to vary freely are inappropriate and provide a biased description of the variation in risk following cessation.[6]

One of the solutions to this problem is to restrict study subjects to those who started smoking at the same age and to calculate odds ratios without adjustment for duration of smoking. Then, the odds ratio for ex-smokers according to years since cessation of smoking can be assessed for different ages at observation. In Japan, because those aged under 20 years have been prohibited to smoke by law since 1900, most smokers start smoking regularly at around 20 years of age. This allows us to restrict study subjects to those who started smoking at around 20 years of age without substantial loss of numbers.

It has been reported that the relative risk of lung cancer after cessation of smoking decreases more rapidly for ex-smokers with a shorter past duration of smoking.[1] In order to evaluate the impact of smoking cessation on the public, however, it is also important to assess the reduction of lung cancer risk among ex-smokers in terms of absolute risk. This can be assessed by large-scale cohort studies or case-control studies with additional information on lung cancer incidence rate by smoking status. Doll and Peto[7] reported that the annual lung cancer incidence rate for smokers among British male physicians was expressed by the function:

$$0.273\times10^{-12}\times(\text{cigarettes/day}+6)^2\times(\text{age}-22.5)^{4.5}$$

which indicates that the lung cancer incidence rate for smokers increases in proportion to the 4.5th power of effective duration of smoking. For nonsmokers, it has been observed that the lung cancer incidence rate is proportional to the 4th power of age in the US and UK.[8-12] Mizuno *et al.* applied this function to the data from Japan Vital Statistics[13] and the "Six-prefectural Cohort Study,"[14] and obtained parameters which fit the Japanese male population. These can be used to estimate the lung cancer incidence rate among ex-smokers after cessation of smoking in combination with the results from the above case-control study.

The purpose of this study was to investigate the risk of lung cancer among ex-smokers according to years since cessation of smoking by attained age group and the lung cancer incidence rate among ex-smokers after the cessation of smoking according to age at cessation.

SUBJECTS AND METHODS

Study subjects were collected in a multicenter hospital-based case-control study, which was previously reported.[5] Briefly, both cases and controls were collected from newly admitted patients to eight hospitals in Osaka Prefecture from January 1, 1986 to December 31, 1988. These patients were investigated by a self-administered questionnaire at the time of admission to the hospital. The questionnaire included questions about smoking status, i.e. whether the patients smoke or not at present, and if so, the age at which the smoker started and the average amount smoked per day. If the smoker had quit smoking, the age at which the smoker quit smoking was also asked. Smoking habits were classified into 3 categories, current smoker, ex-smoker, and nonsmoker. Ex-smoker was defined as a person who had smoked regularly in the past and had quit smoking 1 year or more before the date of admission.

Among controls with other diseases, 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 sinuitis) were excluded from the analysis.

A total of 1,079 lung cancer patients and 1,146 patients with other diseases were investigated for males, and 295 lung cancer patients and 1,073 patients with other diseases for females. Females were not included in this analysis because of the limited number of ex-smokers. For males, there were 737 current smokers, 286 ex-smokers, 29 nonsmokers, and 27 patients with unknown smoking status among lung cancer patients, and the corresponding numbers were 633, 352, 126 and 35 for patients with other diseases. Nonsmokers and patients with unknown smoking status were excluded from the analysis. Therefore, analysis was conducted on 1,023 male lung cancer patients as cases, and 985 male patients with other diseases as controls. Of these cases and controls, the odds ratio of getting lung cancer was calculated only for 776 cases and 772 controls who had started smoking at ages 18–22.

All cases were microscopically confirmed, and had the following distribution of histologic type; squamous cell carcinoma 288 (37%), adenocarcinoma 301 (39%), small cell carcinoma 101 (13%), large cell carcinoma 64 (8%), and other histologic type 22 (3%). Controls were diagnosed as having the following diseases; stomach cancer 225 (29%), other cancer 198 (26%), benign tumor 46 (6%), circulatory disease 42 (5%), respiratory disease 106 (14%), infectious disease 63 (8%), digestive disease 25 (3%), neurological or psychological disease 16 (2%), congenital disorder 12 (2%), endocrinal disease 11 (1%), and others 28 (4%).

Odds ratio was calculated by the Mantel-Haenszel method, adjusted by the average number of cigarettes smoked using 3 levels (<14, 15–24, $25<$). This was conducted separately for four groups of attained age (55–64, 60–69, 65–74, 70–79). Because of the limited number of study subjects, these age groups were set to overlap. For each age group, mean age at admission was calculated using the data for both cases and controls. Also, mean age at cessation was calculated to be mean age at admission minus mean years since cessation for each category of years since cessation. Analysis was conducted with the PROC FREQ in the SAS computer program.[15]

Based on the findings by Doll and Peto,[7] it is assumed that the annual lung cancer incidence rate increases in proportion to the 4.5th power of the effective years of smoking among continuing smokers and to the 4th power of age among nonsmokers as follows.

Equation (1) Rate $= r_s$ (effective years of smoking)$^{4.5}$ for continuing smokers

Equation (2) Rate $= r_n$ (age)^4 for nonsmokers

The effective years of smoking denotes the duration of smoking minus the period of cancer growth, which is assumed to be independent of smoking. Applying this function to the data from Japan Vital Statistics and the "Six-prefectural Cohort Study," Mizuno *et al.* reported estimates of the parameters which fit the Japanese male population. The "Six-prefectural Cohort Study" was initiated in six selected Japanese prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama and Kagoshima) in 1965, and 122,261 males and 142,857 females aged 40 or older at that time were followed for 16 years.[16] Since only lung cancer mortality was available in both data, the parameters were originally estimated for lung cancer mortality in the Japanese population. In the above function, however, the difference between incidence and mortality is only the length of time for clinical manifestation in the period of independent cancer growth. Therefore, the estimates for mortality can be converted to the estimates for incidence by subtracting the mean length of time for clinical manifestation. This was done in a recent paper by Yamaguchi *et al.*[17] Again, since these parameters were originally estimated for each birth cohort of Japanese men, they were averaged for simplicity. As a result, effective years of smoking was set to be age minus 24.3 years for continuing smokers in this study. The parameters r_s and r_n were set at 1.7×10^{-5} and 0.15×10^{-5} per 100,000, respectively, based on the estimates reported by Mizuno *et al.*[8]

The annual lung cancer incidence rate for ex-smokers was calculated to be the annual lung cancer incidence rate for continuing smokers for the age at admission multiplied by the odds ratio from the case-control study for both years since cessation of smoking and age group. Based on equation (1), the annual lung cancer incidence rate for the age at cessation was calculated using the mean age at cessation for each category of years since cessation. These incidence rates for the age at cessation and for the age at admission are linked in Fig. 1 to illustrate the change in the lung cancer incidence rate for ex-smokers after the cessation of smoking.

RESULTS

Table I shows the distribution of the age at admission to the hospital, years of smoking and years since the cessation of smoking for ex-smokers according to smoking status at admission and age at starting smoking. For cases, years of smoking tended to be longer for those who started smoking at an earlier age, while this was not clear for controls mainly because of younger ages at admission among controls. Further analysis was focused on 776 cases and 772 controls who started smoking at ages 18–22.

Table II shows the odds ratios of developing lung cancer according to years since cessation of smoking by age group. Comparison was made between current smokers and ex-smokers, defining current smokers as the reference group. The odds ratio gradually decreased from unity as years passed since cessation for all age groups. Reduction of the odds ratio appeared to be greater for the younger age group.

Table III shows annual lung cancer incidence rates for ex-smokers according to age at the cessation of smoking by attained age group using the lung cancer incidence function and the results from the above case-control

Table I. Distribution of Age at Starting Smoking, Mean Age at Admission, Mean Years of Smoking and Mean Years since Cessation of Smoking in Cases and Controls

Smoking status at admission	Age at starting smoking	Case				Control			
		No.	Mean age at admission	Mean years of smoking	Mean years since cessation	No.	Mean age at admission	Mean years of smoking	Mean years since cessation
Current smoker	10–17	109	60.7	44.9	–	68	55.4	39.5	–
	18–22	553	62.8	43.1	–	490	58.2	38.6	–
	23+	75	65.0	36.9	–	75	61.3	33.7	–
	Total	737	62.7	42.7	–	633	58.3	38.1	–
Ex-smoker	10–17	28	67.8	43.4	8.7	24	56.5	29.6	10.8
	18–22	223	64.2	36.9	7.7	282	61.1	31.2	10.1
	23+	35	69.2	28.9	12.6	46	64.5	24.7	12.3
	Total	286	65.2	36.5	8.4	352	61.2	30.2	10.4

Table II. Odds Ratios of Lung Cancer Risk According to Age at Admission and Years since Cessation of Smoking for Those Who Started Smoking at Ages 18–22

Age at admission (mean)	Years since cessation of smoking	Mean age at cessation	Case/Control	Odds ratio (95% CI[a])
55–64	0[b]	–	169/167	1.00[c]
(59.1)	1–4	57.2	30/33	0.85 (0.49–1.47)
	5–9	52.6	14/29	0.47 (0.25–0.92)
	10+	41.2	14/40	0.34 (0.18–0.64)
60–69	0[b]	–	197/135	1.00[c]
(63.9)	1–4	62.0	35/27	0.87 (0.50–1.49)
	5–9	57.5	24/26	0.61 (0.34–1.10)
	10+	44.3	22/42	0.35 (0.20–0.59)
65–74	0[b]	–	183/109	1.00[c]
(68.6)	1–4	66.6	32/19	0.96 (0.51–1.80)
	5–9	62.0	26/20	0.69 (0.36–1.32)
	10+	48.9	27/35	0.41 (0.23–0.72)
70–79	0[b]	–	140/58	1.00[c]
(73.3)	1–4	71.2	31/15	0.85 (0.43–1.70)
	5–9	66.9	15/13	0.49 (0.23–1.06)
	10+	53.9	25/21	0.50 (0.27–0.94)

a) Confidence interval.
b) Current smoker at the time of admission to the hospital.
c) Reference group.

Table III. Annual Lung Cancer Incidence Rate among Ex-smokers According to Age at Cessation of Smoking for Those Who Started Smoking at Ages 18–22

Age at admission (mean)	Years since cessation of smoking	Mean age at cessation	Annual lung cancer incidence rate for smoker/ex-smoker (per 100,000)		
			For age at cessation	For age at admission	Rate difference
55–64	0[a]	–	–	147.1	0.0[b]
(59.1)	1–4	57.2	114.2	125.0	−22.1
	5–9	52.6	58.0	69.1	−78.0
	10+	41.2	5.7	50.0	−97.1
60–69	0[a]	–	–	263.1	0.0[b]
(63.9)	1–4	62.0	210.9	228.9	−34.2
	5–9	57.5	119.0	160.5	−102.6
	10+	44.3	12.2	92.1	−171.0
65–74	0[a]	–	–	435.8	0.0[b]
(68.6)	1–4	66.6	354.0	418.3	−17.5
	5–9	62.0	210.9	300.7	−135.1
	10+	48.9	30.9	178.7	−257.1
70–79	0[a]	–	–	686.0	0.0[b]
(73.3)	1–4	71.2	563.3	583.1	−102.9
	5–9	66.9	365.4	336.1	−349.9
	10+	53.9	71.0	343.0	−343.0

a) Current smoker at the time of admission to the hospital.
b) Reference group.

comparison. In terms of a rate difference in the lung cancer incidence rate, risk reduction among ex-smokers was considerably greater for the older age group than for the younger age group, mainly because the incidence rate itself is high for this age group.

Figure 1 illustrates lung cancer incidence rates for ex-smokers after the cessation of smoking, based on the data in Table III. Incidence curves for continuing smoker and nonsmoker groups were drawn using the values calculated by equations (1) and (2), respectively. Reduc-

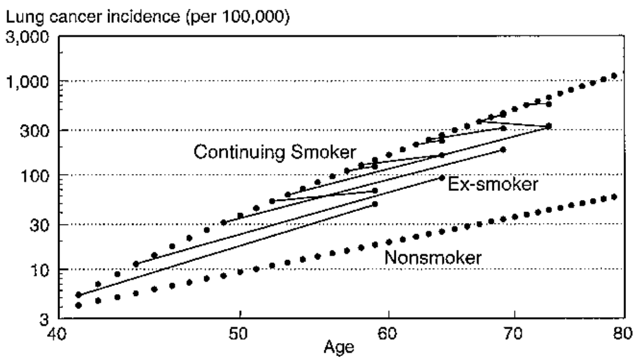

Fig. 1. Log-log plot of lung cancer incidence versus age for continuing smokers and ex-smokers who started smoking at ages 18–22 and nonsmokers.

tion of lung cancer incidence rate among ex-smokers was substantial for those who stopped smoking at a younger age. Also, reduction within 1–9 years after the cessation of smoking appeared to be greater than that after 10 years or more. As far as this figure is concerned, the lung cancer incidence rate for ex-smokers remained elevated for 10 yeas or more after cessation compared to that for nonsmokers.

DISCUSSION

This study showed that the risk of lung cancer among ex-smokers steadily declines after the cessation of smoking compared to continuing smokers. In terms of the odds ratio, substantial risk reduction can be expected for those who stopped smoking at a younger age, such as before 50 years, while only limited risk reduction is evident for those who stopped smoking at an older age, such as after 60 years. This is because the effect of accumulated exposure to smoking for longer durations would likely remain for longer periods. Similar findings were reported in the US,[18, 19] i.e., that lung cancer risk declined less steeply with increasing abstinence for older ex-smokers.

In terms of a difference in the lung cancer incidence rate, however, there would be a substantial decrease of lung cancer risk even for the older age group within a short period after the cessation of smoking, because the lung cancer incidence rate itself is high for this age group.

Risk reduction appeared to be greater for the period of 1–9 years after the cessation of smoking than for the period of 10 years or over. This indicates that smoking contributes, to some extent, to the later stages of carcinogenesis of lung cancer, and that removing the exposure leads to risk reduction within a short period. However, findings that the lung cancer incidence rate for ex-smokers would not reach the level of nonsmokers for a long period after cessation indicates that smoking also contributes to the early stages of carcinogenesis. Several mathematical models have been used to assess the relative magnitude of the effect of cigarette smoking on the early and late stages of lung carcinogenesis. Although the number of ex-smokers may be insufficient to allow precise quantification, several models suggest the relative importance of smoking in the late stage of carcinogenesis.[6, 20]

As stated above, the incidence of lung cancer for ex-smokers never reaches the level for nonsmokers in Fig. 1. It seems to parallel the incidence curve of nonsmokers, which indicates that the relative risk at the age of smoking cessation freezes after cessation. In the study, however, direct comparison between ex-smoker and nonsmoker groups was not conducted because of the limited number of nonsmokers among cases. The odds ratios (95% confidence interval) for continuing smokers versus nonsmokers were 3.76 (1.67–8.48), 16.05 (5.23–49.25), 6.44 (2.80–14.82), and 11.59 (4.91–27.37) for the age groups 55–64, 60–69, 65–74, and 70–79, respectively, which was not stable enough for further calculation of incidence rates. On the other hand, the relative risk values for continuing smokers versus nonsmokers calculated from equations (1) and (2) were 8.5, 11.1, 13.9 and 16.9 for ages 60, 65, 70, and 75, respectively. Since these values of relative risk seem slightly higher than those calculated from the actual case-control comparison, risk reduction among ex-smokers shown in Fig. 1 may be slightly underestimated.

In a study of British physicians, it was reported that the absolute incidence rate of lung cancer freezes at the level reached when smoking stopped,[21] which is not consistent with the findings here. As stated in a report of the Surgeon General, however, the effect of cessation on lung cancer risk can be modified by various factors, such as duration of smoking, daily cigarette consumption, inhalation practices, different tobacco products, and age at cessation.[1] Further research should be conducted to clarify the magnitude and rapidity of the risk reduction with smoking cessation.

In a previous paper,[5] the odds ratio for ex-smokers according to years since the cessation of smoking was adjusted by both age at admission and Cigarette Index (the average number of cigarettes smoked per day multiplied by the number of years of smoking). As a result, the odds ratio for ex-smokers was estimated to be 0.90 and 0.50 for 1–4 and 5–9 years after cessation of smoking, respectively. These estimates were similar to those in this paper. Theoretically speaking, however, the age at starting smoking is earlier for ex-smokers than continuing smokers, when attained age and duration of smoking are equalized between ex-smokers and continuing smokers.

Therefore, overmatching in the previous paper would lead to an underestimated risk reduction, especially for a long period after cessation. Further research with a sufficient number of study subjects will be required to clarify this problem.

This study contains some methodological problems. As stated in the previous report,[5] the proportion of ex-smokers among hospital controls tends to be higher than that in the general population. This may lead to the overestimation of the reduction of lung cancer risk among ex-smokers. Moreover, including a substantial proportion of stomach cancer patients among controls may cause a bias within the estimate. Reasons for quitting and life-style factors associated with smoking cessation may also be influential factors.

In addition, there are some problems specific to this study. First, because of the lack of reliable data on lung cancer incidence rates by smoking status, data from three different sources were combined to estimate the lung cancer incidence rate among ex-smokers. Therefore, comparability between these data should be considered. Data from Japan Vital Statistics used in the study consisted of lung cancer mortality for those aged 30–69 years in 1955–85.[13] Data from the "Six-prefectural Cohort Study" involved only those born before 1925, and mortality was observed in 1966–81.[14] On the other hand, the case-control study consisted of those aged 40–79 years at admission to the hospital in 1986–88. Therefore, the case-control study contained study subjects born later than those documented in the other studies, although it is unknown whether the change in lung cancer risk among ex-smokers versus continuing smokers differs by generation. Incidence for continuing smokers shown in Table III was slightly higher than the incidence rate in 1986 estimated from nine population-based cancer registries in Japan, in which the age-specific male lung cancer incidence rates were 147.5, 229.1, 348.1 and 446.9 for the age groups of 60–64, 65–69, 70–74 and 75–79, respectively.[22] This is because the incidence rates from cancer registries cover not only smokers but also nonsmokers. Another difference is that study subjects in the case-control study were derived mainly from Osaka Prefecture, while the other two studies employed nationwide data. It has been reported that the standardized mortality ratio for lung cancer in Osaka is the highest in Japan.[23] Again, it is unknown whether the change in lung cancer risk among ex-smokers versus continuing smokers differs by area. In the case-control study, subjects were limited to those who started smoking at ages 18–22. Subjects were also limited to those who started smoking at ages 18–22 in the "Six-prefectural Cohort Study," while no data on smoking was available from Japan Vital Statistics.

Second, rather broad ranges of age were used dividing the subjects into four different age groups, mainly because of the limited number of study subjects in each age group. Although a broad range of age may result in a bias due to unbalanced distribution of subjects in terms of age between cases and controls, only slight change was actually observed after adjustment using 5-year stratification. Again, a large-scale case-control study will be necessary to estimate precisely the risk function for ex-smokers in the future.

In conclusion, anti-smoking activities are potentially effective for younger people, although they will require a long latent period. Current statistics show, however, that the smoking rate among the young is increasing. This indicates the urgency of promoting anti-smoking activities for young people in Japan. On the other hand, a substantial reduction of lung cancer risk, in terms of rate difference, was observed for the older age group even for a short period after cessation. This indicates that it is never too late to quit smoking and that benefits do cover all age groups.

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