Jpn. J. Cancer Res. **92**, 821–828, August 2001

Decrease in Risk of Lung Cancer Death in Males after Smoking Cessation by Age at Quitting: Findings from the JACC Study

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To evaluate the impact of smoking cessation in individuals and populations, we examined the decrease in risk of lung cancer death in male ex-smokers by age at quitting in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study), which was initiated from 1988 to 1990 in Japan. For simplicity, subjects were limited to male non-smokers, and former/current smokers who started smoking at ages 18–22, and 33 654 men aged 40–79 years were included. We modeled the mortality rates in non-smokers and current smokers, and compared the rates in ex-smokers with those expected from the model if they had continued smoking. During the mean follow-up of 8.0 years, 341 men died from lung cancer. The mortality rate ratio for current smokers, compared to non-smokers, was 5.16, and those for ex-smokers who had quit smoking 0–4, 5–9, 10–14, 15–19 and ≥20 years before were 4.84, 3.19, 2.03, 1.29 and 0.99, respectively. The functions of $3.20\times10^{-7}\times(\text{age})^{4.5}$ and $1.96\times10^{-5}\times(\text{age}-29.6)^{4.5}$ fitted the observed mortality rates (per 100 000 person-years) in non-smokers and continuing smokers, respectively. A greater decrease in lung cancer mortality was estimated among those who quit smoking at younger ages. Stopping smoking earlier in life appears preferable to keep the individual risk low. The absolute rate, however, substantially decreased after smoking cessation even in those who quit at ages 60–69, reflecting the high mortality rate among continuing smokers in the elderly.

Key words: Lung cancer — Smoking cessation — Cohort study — Japan

The decrease in lung cancer risk after smoking cessation has been extensively investigated in both case-control and cohort studies. It has been reported that the risk decreases to 30–50% of that in continuing smokers after 10 years of abstinence.[1)] In most of the studies,[2–5)] the risk according to years since cessation has been estimated for all ex-smokers adjusting for age and other variables.

The risk of lung cancer, however, varies according to the time-related factors, that is, attained age, age at starting smoking, duration of smoking, and years since smoking cessation.[6)] The risk for all ex-smokers, therefore, cannot easily be applied to evaluate the impact of smoking cessation on individuals and populations. Moreover, it is impossible to consider the four variables simultaneously because they are mutually interdependent, and the specification of any three factors determines the fourth.

To simplify the issue, Sobue *et al.*[6)] analyzed their dataset of a case-control study limiting subjects to men who started smoking at ages 18 to 22. This enabled them to estimate the risk of lung cancer by age at cessation and the duration of abstinence for the majority of former smokers. Furthermore, they combined the odds ratios derived from their case-control study with additional data on lung cancer incidence rates by smoking status. The incidence rates in non-smokers and continuing smokers were estimated using the mathematical models based on Japanese vital statistics[7)] and the Six-Prefecture Cohort Study in Japan.[8)] The case-control study by Sobue *et al.*, however, may not be compatible with the two cohorts in terms of the subjects' generations and study areas, as they noted.[6)]

In the present study, we attempted to describe the decrease in the risk of lung cancer mortality in males after cessation of smoking by age at quitting using a single dataset from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho

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(JACC Study). We first modeled the mortality rates in non-smokers and current smokers, and then compared the absolute mortality rates in ex-smokers with those expected from the model in non-smokers and continuing smokers.

SUBJECTS AND METHODS

Study subjects We analyzed the dataset from the JACC Study, which has been fully described elsewhere.[9] In brief, the cohort was established from 1988 to 1990, when 110 792 inhabitants (46 465 men and 64 327 women) aged 40 to 79 years completed a questionnaire on lifestyles and medical history. They were enrolled from 45 study areas throughout Japan, mostly when they underwent municipal health check-ups, and were followed up to the end of 1997. Vital status of the subjects was determined using resident registration records in the municipalities, and causes of death were identified from death certificates. Because cell types of lung cancer were seldom cited on death certificates, we analyzed lung cancer as a whole. This investigation was approved by the Ethical Board of the Nagoya University School of Medicine.

Subjects of the present analysis were restricted to men because of the limited number of female ex-smokers (only 992). We excluded 27 men with a previous history of lung cancer, 1428 of unknown smoking status, 2059 former or current smokers of unknown age at the start of smoking, and 432 ex-smokers of unknown age at cessation. Further, the analysis for ex- or current smokers was limited to those who started smoking at ages 18 to 22, which excluded 2638 ex-smokers (24.6%) and 6227 current smokers (27.5%). The remaining 9167 non-smokers, 8091 ex-smokers, and 16 396 current smokers were eligible for the present study. The mean age±standard deviation of the 33 654 subjects was 56.9±10.2 years at their entry.

Lung cancer risk according to years since smoking cessation The end point in this study was defined as death from lung cancer (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]: C34).[10] We counted the follow-up period for each participant from the time of enrollment to the time of death from lung cancer or any other cause, that of moving out of the study area, or the end of 1997, whichever came first. Those who moved out of the area or died from causes other than lung cancer were treated as censored cases. The mortality rate ratios (RR) for death from lung cancer according to years since smoking cessation were estimated by using proportional hazards models,[11] with adjustment for age. To test for a decreasing trend in risk with increasing years since smoking cessation, we coded current smokers as 0, and ex-smokers who had quit 0–4, 5–9, 10–14, 15–19 and ≥20 years before the baseline survey as 1, 2, 3, 4 and 5, respectively, and then included the code in the model as a single variable.[12, 13]

Models for lung cancer mortality rates in non-smokers and current smokers Person-years and numbers of lung cancer deaths were totaled by the age attained during the follow-up (40–44, 45–49, ... , 80–84) for non-smokers and current smokers. Person-years for age 85 or over were excluded due to the sparse data.

To develop mathematical models for lung cancer mortality in current smokers, we assumed that the mortality rate was proportional to the 4.5th power of "the effective duration for cigarette smoking," based on findings from British,[14] US,[15] Norwegian[16] and Japanese[8] studies. As the power in the models for lifetime non-smokers ranged from the 4.0th to the 5.5th in the previous studies,[7, 15–17] we adopted a median value and modeled the mortality rate of lung cancer using the 4.5th power of age.

The expected number of lung cancer deaths for the *i*th age group was then assumed to be

$$K_n \times PY_i \times (age_i)^{4.5}$$

for non-smokers and

$$K_s \times PY_i \times (age_i - \theta)^{4.5}$$

for current or continuing smokers, where PY_i denotes person-years of observation, age_i is the mean age attained during the corresponding follow-up, and K_n and K_s are the parameters for non-smokers and current smokers, respectively. θ is the parameter to estimate the effective duration of smoking.

These parameters were estimated by the maximum likelihood method, assuming that the numbers of deaths, d_i (i=1, 2, ... , 9), are independent Poisson random variables.[8] The goodness of fit of the models was evaluated by the χ^2 value (deviance),

$$G^2 = 2\{\sum_{i=1}^{9}[d_i \log(d_i/\hat{d}_i) + (\hat{d}_i - d_i)]\}$$

where d_i and $\hat{d}_i$ denote the observed and fitted numbers of lung cancer deaths in the *i*th age group, respectively. The detailed statistical methods have been described elsewhere.[18, 19]

Lung cancer mortality rates after smoking cessation For ex-smokers, person-years and the numbers of lung cancer deaths were stratified by age at smoking cessation (45–54, 50–59, ... , 70–79) and attained age (by 10-year age group starting from age at quitting). The groups for age at stopping smoking were set to overlap due to the limited number of lung cancer deaths among ex-smokers. The mortality rate was computed in each stratum, except for one with less than two deaths. Person-years for age 85 or over were also omitted in former smokers because of insufficient data.

We estimated lung cancer mortality rates expected if the ex-smokers had continued smoking by entering the mean attained age in each stratum into the above-mentioned model for current smokers. These expected rates were then compared with the actual ones in ex-smokers. The rates attained at the time of smoking cessation were also estimated using the model and were combined with the actual rates among ex-smokers in a graph to illustrate changes in the mortality rates after cessation of smoking.

RESULTS

A total of 341 men died from lung cancer during the follow-up of 270 801 person-years. The mean follow-up period±standard deviation was 8.0±1.9 years. Table I shows RR for death from lung cancer according to years since quitting smoking at the baseline. A decreasing trend in risk with increasing years after smoking cessation was clearly observed (trend $P=5\times10^{-11}$ for ex- and current smokers). It took more than 20 years for the risk in ex-smokers to approach the level in non-smokers; the RR was 0.99 among those with abstinence of 20 years or more (95% confidence interval [CI], 0.47–2.08). Almost the same RR values were obtained when men with a previous history of any malignant tumor were excluded. When former or current smokers were not limited to those who started smoking at ages 18 to 22, the RR values were somewhat different, but the decreasing pattern of risk was not essentially altered. The RR (95% CI) values for men who had quit 0–4, 5–9, 10–14, 15–19 and ≥20 years before, relative to non-smokers, were 4.46 (2.86–6.96), 2.53 (1.50–4.27), 2.13 (1.20–3.80), 1.22 (0.51–2.91) and 0.97 (0.51–1.85), respectively, and that for current smokers was 4.49 (3.12–6.46). Excluding the first two years of follow-up from the risk period did not materially alter the results.

In Table II, the observed mortality rates of lung cancer among non-smokers and current smokers are compared with the expected figures based on the developed models. The parameters K_n and K_s were estimated as 3.20×10^{-7} and 1.96×10^{-5} per 100 000 person-years, respectively, and θ was set at 29.6 years. The fitted mortality rates well approximated the observed values; the goodness of fit χ^2 (deviance) was 2.85 (degree of freedom=8, P=0.94) for non-smokers and 6.32 (degree of freedom=7, P=0.50) for continuing smokers.

Table III summarizes the lung cancer mortality rates among ex-smokers by age at smoking cessation and attained age, and compares the rates with those expected if they had continued smoking. Ratios of the actual rates to the expected ones considerably decreased with increasing years since cessation in ex-smokers whose ages at quitting were 55–64 or younger; the rates decreased to 30–50% of those expected among continuing smokers in some 20 years. Reduction of the RR after 20 years' cessation was relatively small among those who had stopped smoking at ages 60–69. However, they still demonstrated a substantial rate difference at ages 80–84 (−292 per 100 000 person-years), reflecting the high mortality rate in this stratum. Smoking cessation at ages 65–74 or older was not associated with a substantial decline in the risk. Fig. 1 illustrates the lung cancer mortality rates among ex-smokers after cessation of smoking with the expected rates for non-smokers and continuing smokers derived from the models. It was clearly demonstrated that the younger the age at cessation, the greater the decrease in mortality.

DISCUSSION

We examined the decrease in the risk of lung cancer in males after smoking cessation by their age at quitting.

Lung cancer risk according to years since smoking cessation The decrease in lung cancer risk in males after quitting smoking has previously been investigated in

Table I. Mortality Rate Ratios (RR) for Death from Lung Cancer According to Years since Cessation of Smoking among Male Ex-smokers Who Started Smoking at Ages 18–22

	Person-years	No. of lung cancer deaths	RR[a)]	95% CI[b)]
Non-smokers	74 566.1	32	1.00	
Current smokers	131 874.7	228	5.16	3.56–7.49***[c)]
Ex-smokers				
Years since cessation of smoking				
0–4	16 720.1	36	4.84	3.00–7.79***
5–9	15 319.7	21	3.19	1.84–5.53***
10–14	12 217.6	11	2.03	1.02–4.03*
15–19	6 531.3	4	1.29	0.46–3.63
≥20	13 572.1	9	0.99	0.47–2.08
				Trend $P=5\times10^{-11}$ [d)]

a) Adjusted for age.
b) CI: confidence interval.
c) * $P<0.05$, *** $P<0.001$.
d) Trend for ex- and current smokers.

Japan. Fig. 2A depicts the findings from the previous case-control[3, 4] and cohort studies,[5] together with ours. For comparison, the odds ratios/RR in ex-smokers relative to current smokers were computed from the published data according to years since cessation. Hirayama[5] reported a far more rapid decrease in risk than ours in his Six-Prefec-

Table II. Observed and Expected Lung Cancer Mortality Rates (per 100 000 Person-years) among Male Non-smokers and Current Smokers Who Started Smoking at Ages 18–22

Attained age	Non-smokers					Current smokers				
	Time-weighted mean age	Person-years	No. of lung cancer deaths	Lung cancer mortality rate		Time-weighted mean age	Person-years	No. of lung cancer deaths	Lung cancer mortality rate	
				Observed	Expected[a)]				Observed	Expected[a)]
40–44	43.2	3 082.4	0	0.0	7.4	43.2	7 780.6	0	0.0	2.5
45–49	47.7	8 250.0	1	12.1	11.5	47.6	19 125.7	3	15.7	8.8
50–54	52.6	11 098.8	1	9.0	17.7	52.5	19 405.7	2	10.3	25.5
55–59	57.5	13 098.2	4	30.5	26.5	57.5	19 319.8	15	77.6	62.8
60–64	62.4	12 635.8	3	23.7	38.4	62.6	22 830.2	27	118.3	132.2
65–69	67.4	9 967.2	6	60.2	54.0	67.4	21 403.6	56	261.6	244.2
70–74	72.4	7 113.3	5	70.3	74.6	72.2	12 861.0	56	435.4	420.7
75–79	77.4	5 643.6	8	141.8	101.0	77.2	6 457.4	38	588.5	694.1
80–84	81.8	3 198.4	4	125.1	129.5	81.9	2 426.3	29	1 195.3	1 057.7
Total		74 087.6	32	43.2	43.2		131 610.1	226	171.7	171.7

a) Expected rates (per 100 000 person-years) were computed using the functions of $3.20\times10^{-7}\times(\text{age})^{4.5}$ and $1.96\times10^{-5}\times(\text{age}-29.6)^{4.5}$ for non-smokers and current smokers, respectively. Deviances of the models were 2.85 for non-smokers (degree of freedom=8) and 6.32 for continuing smokers (degree of freedom=7).

Table III. Lung Cancer Mortality Rates among Male Ex-smokers Who Started Smoking at Ages 18–22 by Age at Cessation and Attained Age

Age at cessation of smoking (mean)	Attained age		Person-years	No. of lung cancer deaths	Lung cancer mortality rate (per 100 000 person-years)			
	Range	Time-weighted mean			Observed (A)	Expected for continuing smokers (B)[a)]	Rate ratio (A/B)	Rate difference (A−B)
45–54	55–64	60.5	8 240.8	3	36.4	99.4	0.37	−62.9
(49.3)	65–74	69.0	5 916.8	8	135.2	293.9	0.46	−158.7
	75–84	78.4	1 340.8	3	223.8	777.7	0.29	−554.0
50–59	50–59	57.8	1 865.2	2	107.2	65.2	1.64	42.0
(54.2)	60–69	65.2	10 590.5	17	160.5	186.8	0.86	−26.2
	70–79	73.7	4 293.6	8	186.3	492.6	0.38	−306.2
55–64	55–64	62.7	3 035.9	4	131.8	133.9	0.98	−2.1
(58.9)	65–74	69.5	9 411.3	19	201.9	314.3	0.64	−112.4
	75–84	78.2	2 458.1	6	244.1	761.0	0.32	−516.9
60–69	60–69	67.1	2 985.0	4	134.0	236.6	0.57	−102.6
(63.2)	70–79	74.4	6 012.4	17	282.7	529.2	0.53	−246.4
	80–84	81.8	791.6	6	758.0	1 049.9	0.72	−292.0
65–74	65–74	72.3	1 671.4	5	299.1	426.2	0.70	−127.1
(68.2)	75–84	78.9	3 010.8	25	830.3	809.7	1.03	20.7
70–79	70–79	77.0	1 055.5	8	757.9	677.8	1.12	80.1
(72.2)	80–84	82.1	715.6	8	1 118.0	1 073.6	1.04	44.4

a) Expected rates (per 100 000 person-years) were computed using the function of $1.96\times10^{-5}\times(\text{age}-29.6)^{4.5}$ for continuing smokers.

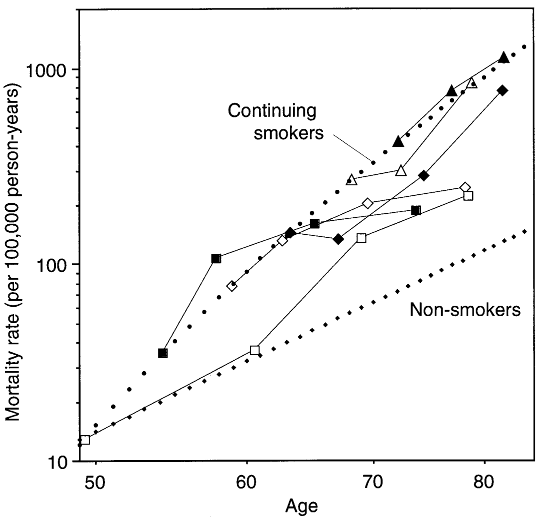

Fig. 1. Log-log plot of lung cancer mortality rate versus age among non-smokers, and ex- or continuing smokers who started smoking at ages 18–22. □, ■, ◇, ◆, △ and ▲ denote ex-smokers who quit at ages 45–54, 50–59, 55–64, 60–69, 65–74 and 70–79, respectively.

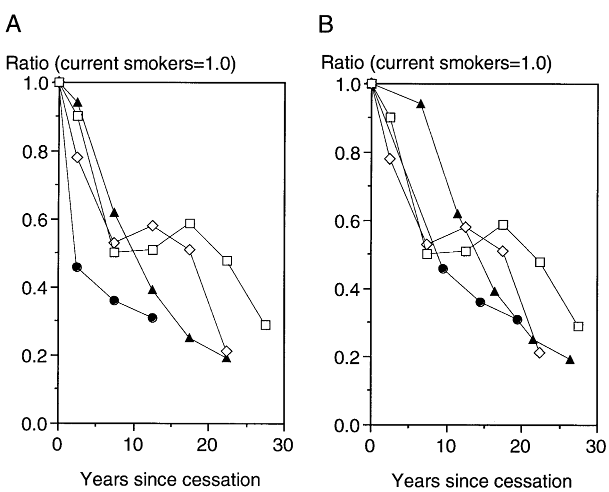

Fig. 2. Decreasing patterns of lung cancer risk in males after quitting smoking in the case-control and cohort studies in Japan (A), and the graph re-drawn adding half of the mean follow-up period to years since cessation in the cohort studies (B). Odds ratios/RR in ex-smokers relative to current smokers were computed from the published data.[3–5] □ Sobue *et al.*,[3] ◇ Gao *et al.*,[4] ● Hirayama *et al.*[5] and ▲ this study.

ture Cohort Study; the rate of lung cancer death was reduced to 46% of the level in current smokers after only 1–4 years of abstinence.

Cohort studies, however, may overestimate the speed of reduction in risk because they usually fix the number of years since smoking cessation in ex-smokers at the baseline survey. The years actually increase during the follow-up, which causes each group of years since quitting to include person-years with a longer period after cessation. The overestimation may be larger in the Six-Prefecture Cohort Study than in this investigation because it followed the subjects much longer (14.0 versus 8.0 years on average).[5] This would partly explain the different pattern of risk reduction between the two cohorts.

If the former smokers at baseline surveys of the cohort studies had not resumed smoking during the follow-up, about a half of the mean follow-up period, on average, should be added to years since cessation. When 7.0 and 4.0 years are added to years since quitting in the Six-Prefecture Cohort Study and the JACC Study, respectively, the risk reduction after cessation of smoking appears fairly consistent among the four studies (Fig. 2B). Stopping smoking seems to halve the risk of lung cancer in male smokers in 10 to 19 years. This considerable decline in risk might be expected if cigarette smoking affects not only the initiation of lung carcinogenesis but also its late stages, that is, its promotion.[20]

The smoking rate in Japanese men has been gradually declining, having decreased from 82% in 1965 to 54% in 1999 (The Japan Tobacco Incorporation [formerly the Japan Monopoly], unpublished data). Male ex-smokers, therefore, have dramatically increased since the 1960s, when Hirayama's study was initiated. They accounted for only 3.3% of the total male person-years in that study,[5] while 24.0% of our subjects reported themselves as former smokers. The proportions of ex-smokers among the controls of the two case-control studies were 31.7%[3] and 38.7%.[4] Furthermore, per capita tobacco consumption has been increasing,[21] and filter-tipped and low-tar cigarettes have become popular in Japan.[9] Thus, the backgrounds of ex-smokers in the Six-Prefecture Cohort Study may substantially differ from those in the other three studies. It is rather surprising, therefore, that the decreasing pattern in lung cancer risk among ex-smokers in Hirayama's cohort was fairly consistent with those in the other studies.

Models for lung cancer mortality rates in non-smokers and current smokers Mizuno *et al.*[8] modeled lung cancer mortality rates in male current smokers using the data from the Six-Prefecture Cohort Study. They reported that "the effective duration of cigarette smoking" in their study was considerably shorter than that in the British Doctors Study,[14] and attributed that to the cigarette shortage in Japan during and immediately after World War II.[21] The subjects in their analysis would have suffered from the shortage because they were aged 25 to 49 in 1950.

On the other hand, our subjects were around 0–39 years old at that time, so the younger generations had not experienced the shortage. Given the similar mean ages at starting smoking in the two cohorts (20.3 years in the Six-

Prefecture Cohort[8] versus 19.9 years in our study), a smaller parameter θ (and a longer effective duration of smoking) might have been expected in the present analysis. Nevertheless, the parameter (29.6 years) was almost identical to that in the Six-Prefecture Cohort (29.4 years).[8] In the present study, most (89.7%) of the men who died from lung cancer were born before 1933 and were 18 years old or more in 1950. Thus, the tobacco shortage during the 1940s might still be affecting the lung cancer scene in Japan.

The expected mortality rate in male non-smokers aged less than 50 was apparently higher than that in continuing smokers (Table II). Smaller precision in the parameter estimate for non-smokers may explain this, despite the minimal deviance of the model; the K_n was estimated based on only 32 lung cancer deaths. More person-years of experience is certainly required to establish a more stable function to predict the mortality rate.

We also tried the 4.0th power model for non-smokers because it was applied to the Japanese vital statistics data by Mizuno *et al*.[7] The model, however, did not fit the observed data as well as the model with the 4.5th power; the deviance was 3.67 and 2.85 for the 4.0th and the 4.5th power, respectively. We therefore decided to use the 4.5th power model.

Lung cancer mortality rates after smoking cessation In this study, a greater decrease in lung cancer mortality was estimated among those who quit smoking at younger ages. Stopping smoking earlier in life appears preferable to keep the individual risk low.

Those who stopped smoking at ages 60–69 (mean 63.2) showed only a 28% decrease after about 20 years' abstinence, which is far lower than those who quit at younger ages. The absolute rate, however, substantially decreased even in this group, reflecting the high mortality rate among continuing smokers in the elderly. Discouraging smoking, therefore, may still be useful in this age group for population-level prevention.

Unlike Sobue and co-workers,[6] we failed to find a substantial decrease in the risk of lung cancer death among those who quit smoking at ages 65–74 or older. This may partly be ascribable to the fact that the number of lung cancer deaths was still small when categorized by age at cessation and attained age. The relatively short observation period precluded estimation of the mortality rates after abstinence of 20 years or over in this group, so that we might have underestimated a possible long-term decrease in the risk. In addition, our cohort study might be subject to misclassification of smoking status due to its change after the baseline survey. The benefit of smoking cessation may have been underestimated particularly in older age groups because older current smokers at the baseline would have been more likely to have become ex-smokers than younger ones during the follow-up.[22] Further investigations with a longer observation and multiple assessments of smoking habits[23] are warranted to examine the relevance of smoking cessation to the risk of lung cancer especially in older populations.

Although this study focused on the decrease in lung cancer risk after smoking cessation, stopping smoking benefits smokers not only in reducing the risk of lung cancer, but also in a vast range of disease prevention and health promotion. The US Surgeon General's report[1] concluded that smoking cessation had major and immediate health benefits for men and women of all ages based on an extensive review of epidemiological studies. This conclusion was confirmed by 40 years' observation of male British doctors.[23] In that study, even those who quit smoking at ages 65–74 showed age-specific mortality rates beyond age 75 years appreciably lower than those who continued.

We examined the decrease in lung cancer risk after smoking cessation in detail, involving far more former smokers than the Six-Prefecture Cohort Study.[5] However, some methodological issues, in addition to those mentioned above, should be kept in mind when interpreting the findings.

First, some smokers may have quit due to symptoms of lung cancer itself. Although excluding first years of follow-up from the risk period did not materially alter our conclusions, this "quitting-ill" effect might have resulted in an underestimate of the risk reduction after smoking cessation.[24]

Second, we did not include the amount of cigarettes smoked daily in the model for continuing smokers. We did attempt to construct a model for current smokers including the number of cigarettes smoked per day. The model, however, poorly fitted the observed data, mainly because the sample size was insufficient to group current smokers by both age and the number of cigarettes smoked. Not considering the amount of cigarette consumption may have resulted in a slight underestimation of the risk reduction in those who stopped smoking at younger ages. This is because the smoking dose decreased with increasing age at quitting in the present study; the mean numbers of cigarettes smoked per day were 24.0, 23.2, 22.3, 21.9, 21.5 and 21.3 among those quit at ages 45–54, 50–59, 55–64, 60–69, 65–74 and 70–79, respectively.

Finally, the decreasing pattern in one age group at abstinence was determined using data from several generations or birth cohorts. Differences in backgrounds and lifestyles across generations might confound the findings. It would be better to consider cohort effects to assess the risk of lung cancer death in ex-smokers more precisely. The effects may be included in the mathematical models by stratifying the subjects according to birth cohorts in addition to age, and by introducing parameters for birth cohorts into the models. Unfortunately, however, the relatively short follow-up (mean: 8.0 years) in the present study prevented us from differentiating the effects of age and birth cohorts. We therefore estimated the change in lung cancer risk among ex-smokers using age-specific mortality rates over different birth cohorts, making the most of the available data. A longer follow-up will enable us to examine the trend in mortality among those who quit smoking in a given age range in each birth cohort.

In conclusion, a greater decrease in the risk of lung cancer death was expected among those who quit smoking at younger ages. The absolute mortality rate, however, appreciably declined after smoking cessation even in those who quit at ages 60–69.

ACKNOWLEDGMENTS

The authors express their sincere appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study Group, and also to Dr. Haruo Sugano, the former Director of Cancer Institute of Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study.

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This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (C)(2) (No. 12218216) from the Ministry of Education, Science, Sports and Culture of Japan. The JACC Study has also been supported by Grants-in-Aid for Scientific Research from the same Ministry (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102 and 11181101).

(Received March 2, 2001/Revised May 28, 2001/Accepted June 6, 2001)

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