Jpn. J. Cancer Res. 80, 727–731, August 1989

Smoking and Lung Cancer Mortality in Japanese Men: Estimates for Dose and Duration of Cigarette Smoking Based on the Japan Vital Statistics Data

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For the purpose of understanding human carcinogenesis and making a quantitative prediction of lung cancer mortality in a general population of Japanese males, we evaluated a statistical model which assumes lung cancer mortality to be proportional to the 4.5th power of the effective duration of cigarette smoking among smokers and to the 4th power of age among nonsmokers, using Japan Vital Statistics data. For the male birth cohorts aged 30–69 in 1965 in the age range of 40–79, studied by quinquennial calendar time intervals from 1955 to 1985, it was found that, (i) for nonsmokers, the estimated lung cancer mortality rate was comparable to the rates reported in the US or Britain, assigning 20 to 25% proportions of nonsmokers, (ii) for smokers, the estimated duration of smoking was shorter than would be expected from the age when smoking was started according to various epidemiological surveys, and (iii) the estimated average numbers of cigarettes smoked per day by smokers were similar to those obtained by epidemiological studies, when these were estimated by incorporating a part of Doll and Peto's dose-response relationship. Also discussed is the possibility of assessing lung cancer mortality risk for Japanese male smokers by means of the statistical model, $\alpha\times$(cigarettes smoked per day $+\beta$) $\times$ (age $-$ (age started smoking) $-\gamma)^{4.5}$.

Key words: Lung cancer mortality — Dose and duration of cigarette smoking — Vital Statistics — Japanese males — Quantitative risk assessment

Doll and Peto[1)] reported that the annual lung cancer incidence for regular smokers among British male physicians was expressed by the function:

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

One important implication here is that lung cancer incidence is proportional to the 4.5th power of the effective duration of smoking. As for nonsmokers, lung cancer incidence was observed to be proportional to the 4th power of age in the US and Britain.[2-6)] Considering the importance of the quantitative assessment of lung cancer risk using statistical models for understanding human carcinogenesis and predicting lung cancer mortality in a general population, we conducted a series of statistical analyses using Japan Vital Statistics data. The purpose of the analysis was to examine the validity of the statistical model mentioned above and, if necessary, to make modifications to fit the model to Japanese men. Herein we report the results of a Poisson regression analysis. In addition, we discuss the associations of lung cancer mortality with the proportions of smokers, effective duration of smoking and number of cigarettes smoked per day. Also discussed is the possibility of quantitative assessment of the lung cancer risk for Japanese male smokers and nonsmokers.

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MATERIALS AND METHODS

We analyzed lung cancer mortality among quinquennial birth cohorts of Japanese men aged 30–34, 35–39,..., 65–69 in 1965 using the Japan Vital Statistics for every five years from 1955–85, which were published by the Ministry of Health and Welfare of Japan. For every fifth calendar year (1955, 1960,..., 1985), only the data for the age range of 40–79 were selected and used in our analysis because at age 80 or over lung cancer diagnosis might have been less reliable in the past and at ages under 40 the data were sparse.

In our analysis, it was assumed that lung cancer mortality among smokers was proportional to the 4.5th power of the effective duration for smoking, and that that for nonsmokers was proportional to the 4th power of attained age. For birth cohorts specified by age i in 1965, the expected number of lung cancer deaths for those having attained age j in a certain year, $E[N_{ij}]$, was taken as the sum of lung cancer deaths for smokers and non-smokers:

$$E[N_{ij}]=P_{ij}\times S\times Ks_i\times(\text{age}-\theta_i)^{4.5}+P_{ij}\times(1-S)\times Kn\times\text{age}^4,$$

where P_{ij} is the corresponding population number, N_{ij} the number of lung cancer deaths, S the proportion of smokers and θ_i the parameter to define effective duration of cigarette smoking. Ks_i and Kn are parameters reflecting lung cancer mortality among smokers of cohort i and nonsmokers, respectively. Average number of cigarettes consumed per day by smokers among cohort i can be calculated, using the estimated value of Ks_i. Note here that the following assumptions were also made, for the sake of simplicity, in deriving the equation presented above: (i) male population consisting of only nonsmokers and regular smokers, (ii) proportion of smokers to be constant regardless of the time and age range considered here and (iii) Kn to be constant over time.

Detailed information on smoking was not available in the 1940s to 1960s. As for the proportion of smokers, however, it could be assumed in the range of 70–85%, as will be discussed later. The analyses were conducted separately for different values of constant proportion of smokers: 100%, 85%, 80%, 75% and 70%. Maximum likelihood estimates of paremeters, Kn, Ks_i and θ_i, were obtained with errors to follow a Poisson distribution.[7, 8)]

Note here that θ_i can be related to the age when smoking was started and that Ks_i can be transformed into the dose rate, the average numbers of cigarettes smoked per day, for cohort i, as will be discussed later.

Table I. Maximum Likelihood Estimates of Ks for Eight Birth Cohorts Specified by Age in 1965 under Four Different Assumptions of Proportion of Smokers

Birth cohorts specified by age in 1965	Assumed proportions of smokers, S				
	100%	85%	80%	75%	70%
30–34	40.5[a)]	58.6	62.9	66.4	71.1
35–39	59.4	82.9	88.1	94.0	100.7
40–44	89.9	131.7	139.4	149.3	159.9
45–49	108.3	153.0	162.4	173.4	185.7
50–54	109.0	150.2	159.5	170.2	182.3
55–59	116.7	154.5	164.4	175.1	187.6
60–64	95.4	122.8	130.9	139.2	149.1
65–69	86.3	112.8	119.2	127.9	137.0

a) Maximum likelihood estimates of Ks multiplied by 10^{12} were obtained from Poisson regression analysis with the number of expected lung cancer deaths, $E[N_{ij}] = P_{ij} \times S \times Ks_i \times (\text{age} - \theta_i)^{4.5} + P_{ij} \times (1-S) \times Kn \times \text{age}^4$, where P_{ij} is the corresponding population number, N_{ij} the number of lung cancer deaths, S the assumed proportion of smokers, Ks_i and θ_i the parameters for the smokers of cohort i, and Kn the parameter for nonsmokers.

RESULTS

Maximum likelihood estimates for parameters Ks, θ and Kn are shown in Tables I, II and III: for smokers, the estimated values of Ks and θ of quinquennial birth cohorts under assumed values of proportion of smokers in Tables I and II, respectively, and for nonsmokers, the estimates of Kn and calculated age specific rates per 100,000 for the age range of 40–79 in Table III.

The significance of incorporating a parameter for nonsmokers, Kn, was confirmed by the reduction of goodness of fit, Pearson chi-square statistic, from 137.2 (degree of freedom, 27) to 125.2 (degree of freedom, 26) by the addition of the parameter in the model ($P < 0.001$).

As shown in Tables I and II, estimates for both Ks and θ were highly dependent on quinquennial birth cohorts. Ks showed larger values for the birth cohorts aged 45–59

Table II. Maximum Likelihood Estimates of θ

Birth cohorts specified by age in 1965	Assumed proportions of smokers, S	
	100%	70–85%
30–34	20.2	22.4
35–39	22.4	24.2
40–44	26.0	28.1
45–49	27.5	29.3
50–54	28.4	30.1
55–59	30.1	31.5
60–64	29.7	31.0
65–69	31.7	33.2

See the footnote for Table I. Estimates of θ for S=70–85% were the same, due to the simple nature of the proposed model.

Table III. Maximum Likelihood Estimates of Kn and Corresponding Age-specific Lung Cencer Mortality under Assumed Values of Proportions of Smokers

S	Kn ($\times 10^{-13}$)	Attained age							
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
		Estimated lung cancer mortality per 100,000							
85%	211.2	6.9	10.7	16.0	23.1	32.2	43.8	58.3	76.1
80%	158.4	5.2	8.0	12.0	17.3	24.1	32.8	43.7	57.0
75%	126.7	4.1	6.5	9.7	13.9	19.4	26.4	35.1	45.8
70%	105.6	3.5	5.4	8.1	11.6	16.2	22.0	29.3	38.2

See the footnote for Table I.
S: assumed proportion of smokers.

in 1965, while other cohorts showed smaller values. θ, however, showed an almost monotonic decrease from older to younger birth cohorts, from 31.0 for the birth cohort aged 60–64 in 1965 to 28.1 for the cohort aged 40–44 in 1965 under the assumed proportion of smokers, 70–85%.

For the estimates of *Kn*, as will be discussed later, the calculated age-specific lung cancer mortality estimates were comparable with those observed in the series of nonsmokers among the US whites and British doctors, if the proportion of smokers, *S*, can be assumed to have been 75–80%.

DISCUSSION

In our analysis, it was assumed that lung cancer mortality among smokers was proportional to the 4.5th power of the effective duration of smoking, and that that for nonsmokers was proportional to the 4th power of attained age, implying, as pointed out by Breslow and Day,[7] that relative risk increases with duration of cigarette smoking. The validity of these assumptions, particularly for the Japanese population, has not been well established, although similar statistical models based on the above mentioned assumptions fitted well the data obtained from a large-scale Japanese cohort study.[9] As will be discussed below, our results obtained under these assumptions did not conflict with the existing data on the number of cigarettes smoked per day and lung cancer mortality among non-smokers.

In interpreting our results, it is necessary to know how high was the prevalence of smokers and what is the time lag between smoking and lung cancer occurrence. It has been recognized that a country's lung cancer mortality starts to increase a few decades after cigarette usage increases in the country,[6, 10] indicating that lung cancer mortality should be related not to the smoking habits in the current period, 1965–1985, but to those some 10–30 years earlier. The proportion of smokers in the 1950s and 60s was reported by Fujimoto,[11] who gave values of 80% in 1951 and 82% in 1965, while Tominaga[12] reported 75.9% in 1958 and 83.7% in 1966, supporting our assumption that the proportion of smokers was 70–85%. This high prevalence of smoking habits in Japanese men might be due to the rationing system during World War II which distributed cigarettes equally to all Japanese men.[13]

Lung cancer mortality among nonsmokers Estimates for age-specific lung cancer mortality among male nonsmokers obtained from our analysis (Table III) were comparable to those reported by Garfinkel[14] (Table IV) and Doll[2] when the proportion of smokers was assumed to be 75–80%, considered to be the most likely level. Analysis of 265,000 Japanese men and women also showed *Kn* from 135 to 185 with an approximate confidence interval of 80% and no statistically significant time trend of lung cancer mortality among nonsmokers.[9, 15] Based on our results and the other reports mentioned above, the following function,

$$(100\sim180)\times(\text{age}/100)^4,$$

would predict lung cancer mortality among Japanese male nonsmokers per 100,000, if there is no time trend in lung cancer mortality in the latter half of this century.

Estimated average number of cigarettes smokerd per day *Ks* for each birth cohort might be regarded as reflecting average number of cigarettes smoked per day (Table V), which was obtained by solving the following equation,

$$Ks=0.273\times10^{-12}\times(\text{cigarettes/day}+6)^2,$$

where the right-hand side is a part of the equation reported by Doll and Peto.[1] Numbers of cigarettes smoked per day calculated in such a way were 18–19 for the cohorts aged 45–59 in 1965 and 15–16 for the cohorts

Table IV. A Review of Age-specific Lung Cancer Mortality per 10^5 for Male Nonsmokers in the US Whites[14]

Reported by	Attained age						
	45–49	50–54	55–59	60–64	65–69	70–74	75–79
American Cancer Society 25-State study (N=94,000)							
1960–64	(4.0)	(5.3)	10.5	17.0	18.6	32.3	32.7
1964–68	(5.1)	8.8	11.6	17.3	29.4	26.4	41.5
1968–72		(8.8)	8.3	17.5	34.3	19.2	58.6
Dorn's study of US veterans (N=54,000)							
1955–59			12.0	11.2	25.1	39.9	37.8
1960(Jan)–64(Dec)				(10.7)	16.9	40.5	15.0
1965(Jan)–69(Dec)				(48.0)	43.5	38.2	47.2

Numbers in parentheses indicate less that 5 deaths in the age group.
N=numbers of nonsmokers for the study population.

Table V. Calculated Number of Cigarettes Smoked per Day Based on Estimated Values of *Ks*

Birth cohort specified by age in 1965	Proportion of smokers, *S*				
	100%	85%	80%	75%	70%
30–34	6.2	8.6	9.1	9.6	10.1
35–39	8.7	11.4	12.0	12.6	13.2
40–44	12.1	16.0	16.6	17.4	18.2
45–49	13.9	17.7	18.4	19.2	20.1
50–54	14.0	17.5	18.2	19.0	19.8
55–59	14.7	17.8	18.5	19.3	20.2
60–64	12.7	15.2	15.9	16.6	17.4
65–69	11.8	14.3	15.0	15.6	16.4

Number of cigarettes smoked per day was derived from the following equation, $Ks = 0.273 \times 10^{-12} \times (\text{cig/day} + 6)^2$, where the right-hand side is a part of the function reported by Doll and Peto[2] (see the text).

aged 60–69 if the proportions of smokers were 75–80%. These results seem to coincide with the report[11] that the average number of cigarettes smoked per day by adult smokers was 15 in 1955, 16 in 1960, 17 in 1965, and 20 in 1970. These values were also similar to the average numbers of cigarettes smoked per day by smokers in the above-mentioned large-scale cohort data.[9, 15]

Estimates for age when smoking was started Theta should be discussed in terms of age at which smoking was started. Doll and Peto[1] assigned 22.5 for the group of smokers who started smoking between 16 and 25 years of age (mean = 19.2 years), taking into account the fact that it takes a few years for a lung cancer to become clinically evident once it starts growing. Since we dealt with mortality data, another small constant, such as 0.5, which corresponds to mean survival years of lung cancer, should be added to the number to make it about 4. Subtracting this constant, 4, from each θ_i gives 24–27 for cohorts aged 40–64 in 1965. Most of these values still seem slightly larger by about 2–4 (and even more for older cohorts) than the values for average age of starting smoking of male smokers among the above-mentioned 265,000 subjects (unpublished data by T. Hirayama). This may indicate that the effective duration of cigarette smoking was several years shorter, among the cohorts aged around 20 or over in the 1940s, than that calculated from the reported age at which smoking was started, because the smoking habits of the males among those cohorts were affected by the shortage of cigarettes in the past, particularly, during and shortly after World War II. In Japan, annual per capita consumption of cigarettes for persons 15 years of age and over was reported to have started to increase from the turn of the century and reached 1140 in 1943, but sharply decreased to 310 immediately after World War II, then quickly recovered and increased and reached the world's highest level around 1975.[11–13, 16] It cannot be denied that some larger constant can be added to the age of starting smoking for people who started smoking in the later years of life. The estimates of both *Ks* and θ for younger cohorts, especially for those aged 30–39 in 1965, seemed to be unstable, nonetheless.

A statistical model for practical use in quantitative risk assessment For practical purposes, we tentatively propose to express lung cancer mortality (per 100,000) among Japanese average male smokers by the function,

$$K \times (\text{cig} + 6) \times ((\text{age} - (\text{age started smoking}) - w)/100)^{4.5},$$

where K is 650–700 and w, 4–7. This model assumes the lung cancer risk to increase linearly with the dose, cig + 6, as opposed to the model used by Doll and Peto, who found that lung cancer risk is proportional to the second power of the exposure to cigarettes consumed regularly by British physicians, based on information obtained from surveys in 1951, when the study was initiated, and in the subsequent 7th and 15th years of the follow-up. Their results on dose-response between cigarettes smoked per day and lung cancer risk seems to be dependent on the data points corresponding to 30 or more cigarettes per day as far as we can see from the figure presented in their report.[1] We do not, however, mean to rule out a quadratic increase of the risk with the dose in Japanese male smokers because, in this country, there were not many heavy smokers who smoked 30 or more cigarettes per day regularly from youth. Assessment of lung cancer risk in terms of cigarette smoking using the function proposed above will of course be the next step of our study. However, the following points should be taken into account in such a quantitative risk assessment in future[12]: (i) the percentage of smokers among adult males has decreased from the highest, 83.7%, in 1966 to 65.6% in 1984 and (ii) filter-tipped and/or low-tar cigarettes have become increasingly popular in recent years, while (iii) the average number of cigarettes smoked per day has increased and reached 24.9 for males in 1984. In addition, for a reliable future prediction, the changing pattern of histological distribution of lung cancer in recent years should also be taken into consideration in our models, especially for younger cohorts, where our estimates still seem to be unstable.[17, 18]

ACKNOWLEDGMENTS

We are greatly indebted to Dr. T. Hirayama, for having kindly provided information on the large-scale Japanese cohort. This research was supported in part by Grant No. 62-6 from the Ministry of Health and Welfare of Japan.

(Received April 12, 1989/Accepted June 7, 1989)

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