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Lung Cancer Risk Comparison among Male Smokers between the "Six-prefecture Cohort" in Japan and the British Physicians' Cohort

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We estimated the effective duration of cigarette smoking using the data of lung cancer mortality among male smokers of a large-scale cohort study in Japan and evaluated its role in the lung cancer risk difference between male smokers of the Japanese cohort and the British physicians' cohort. By selecting male cohort members who answered that they had started smoking at ages 18–22 (average = 20.3), the subjects of our analysis, which numbered 49,013, were made relatively homogeneous in terms of age at which smoking was started. Assuming lung cancer mortality to be proportional to the 4.5th power of the effective duration of cigarette smoking, i.e., $(\text{age}-\theta)^{4.5}$, as was proposed on the basis of the British cohort study by Doll and Peto, the parameter θ was estimated to be 29.4 for male smokers aged 40–64 in 1966; therefore, the estimated duration of cigarette smoking was, on average, 9.1 years (95% confidence interval = 5.8–11.6) shorter than that calculated from the reported age at which smoking was started. Our findings suggested that the low lung cancer mortality relative to daily cigarette consumption in Japan resulted from the shorter duration of cigarette smoking in the Japanese cohort, possibly due to the severe shortage of cigarettes during and shortly after World War II. Once the effective duration of cigarette smoking was adjusted, lung cancer mortality in the range of 5–34 cigarettes per day was fairly comparable to that observed among the cohort of male British physicians.

Key words: Duration of cigarette smoking — Lung cancer — British physicians — Japanese men — Six-prefecture cohort study

Cigarette smoking is a strong determinant of lung cancer risk but the magnitude of the relative risk in relation to the amount of daily cigarette consumption is apparently several times lower in Japan than that found in studies conducted in the US and European countries.[1-4] In order to shed some light on the mechanisms which caused such lower risks of lung cancer associated with smoking in Japan, we analyzed, as will be reported in this paper, lung cancer mortality among male Japanese smokers with statistical models which assumed lung cancer mortality to be proportional to the 4.5th power of the effective duration of cigarette smoking, following Doll and Peto.[5] They reported that the annual lung cancer incidence among male regular smokers among British physicians who started smoking at ages 16–25 and consumed 40 or less cigarettes per day can be expressed by the function

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

This statistical model indicates that duration of smoking is a strong determinant of the risk and that the risk increases with dose rate, i.e., daily cigarette consumption, in a linear-quadratic, rather than linear, fashion. Herein we report the results obtained from an analysis of the data available from the "six-prefecture cohort study," which followed 265,000 residents aged 40 or over from 29 public health districts in six prefectures throughout Japan during the period 1966–81,[6,7] and compare the results with those obtained in the British physicians' cohort study.

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MATERIALS AND METHODS

Study population From October to December 1965, a questionnaire survey was conducted for all residents aged 40 or older in 29 public health districts in six selected Japanese prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama and Kagoshima). Questionnaires, which had been distributed among all the residents, were retrieved, in most cases, right after the 1965 National Census by a home visit of public health nurses and midwives who were trained for a standardized method of interview. At the time of home visits the interviewers reviewed the questionnaires filled in by the respondents and made inquiries regarding unclear answers and unanswered questions in order to make the information on the questionnaires accurate and complete. The interviewers numbered, on average, 50 in each public health district and about 1,500 in total.

The six prefectures were selected because they geographically represent the entire country and all but

Kagoshima had prefectural cancer registration systems (in this paper we dealt with lung cancer mortality rather than incidence as tumor registry data were not readily available from all six prefectures under study). Respondents to the survey numbered 122,261 men and 142,857 women and the proportions of the respondents obtained from a calculation based on the 1965 National Census population were 94.8% in total and 99.8%, 91.4%, 91.3%, 93.8%, 95.2% and 99.2% in the prefectures of Miyagi, Aichi, Osaka, Okayama, Hyogo and Kagoshima, respectively. The age and sex distribution of the respondents has been reported elsewhere.[6, 7]

A one-page questionnaire used in the survey included questions about smoking, drinking and dietary habits, occupation, marital status and so on. Inquiry regarding smoking history consisted of questions about number of cigarettes smoked per day, types of tobacco, age when smoking was started, regular smoker or not, and, for ex-smokers, years since cessation of smoking. The amount of daily cigarette consumption was unknown for only 6% of current daily cigarette smokers.

At the beginning of each follow-up year, a migration survey was conducted through reference to the local residence registration and those who were found to have migrated from the residential public health districts during the previous year were excluded from the mortality follow-up thereafter. During the 16-year follow-up period, 8% of the respondents migrated from the original districts. The deaths were annually ascertained through checking against vital statistics death schedules kept at each public health center, with the permission of the Ministry of Health and Welfare. The causes of death were coded by one of the authors (T.H.), using the 7th Revision of the International Classification of Diseases.

From among the entire cohort, we selected the male regular smokers who answered that they had started smoking between 18 and 22 years of age for simplification of our analysis (there were negligibly few smokers who smoked only tobaccos other than cigarettes). In addition, we excluded those aged 65 or over in 1966 and restricted the range of attained ages to 40–79, since Doll and Peto had excluded those who attained age 80 or over. Thus, the number of subjects used in our analysis was 49,013, i.e., 40.1% of the whole male cohort members, and from among them 615 lung cancer deaths were identified during 1966–81.

Statistical methods Person-years and the numbers of lung cancer deaths were aggregated and stratified by the age (40–44, 45–49, ..., 75–79) attained during the observation period, daily cigarette consumption (1–4, 5–14, 15–24, 25–34, 35+) and four-year intervals of follow-up (1966–69, 1970–73, 1974–1977, 1978–81).

In our analysis we used statistical models assuming the expected number of lung cancer deaths, $E[D_{ijk}]$, to be

$$PY_{ijk} \times K_j \times (\text{age}_{ijk} - \theta)^{4.5}$$

for cell ijk, which corresponds to the observation in the follow-up interval k for smokers belonging to the daily cigarette consumption category j who were at age i. Here, PY_{ijk} is the number of person-years, age_{ijk}, the mean age attained during the corresponding follow-up interval and K_j the proportional parameter for the daily cigarette consumption category j. θ is the parameter to estimate the effective duration of smoking by subtracting it from the attained age. Note here that the parameter θ was held at a common value for all the cigarette-amount categories analyzed in this paper unless otherwise specified, and that the relative risk (RR) for cigarette smoking group j, RR_j, relative to, for example, smoking group 1 can be calculated as the ratio between K_j and K_1.

Parameters were estimated by the method of maximum likelihood,[8] assuming that the numbers of deaths D_{ijk} are independent Poisson random variables. A more detailed description of the statistical methods is available elsewhere.[9]

RESULTS

In Table I, the person-years of observation and the number of lung cancer deaths are presented according to categories of cigarettes smoked per day and attained age. On average, the subjects started smoking at the age of 20.3, which did not vary substantially either by cigarettes consumed per day or by the age at the beginning of the follow-up within the ranges analyzed here (data not shown). The smokers who smoked 1–4 cigarettes per day were excluded in the following analyses, because of the paucity of the data, as can be seen in Table I.

Using a statistical model, $K_1 \times RR_j \times (\text{age} - \theta)^{4.5}$, which assumed lung cancer mortality to be proportional to the 4.5th power of the effective duration of cigarette smoking, the duration defining parameter θ was estimated to be 29.4 on average. Hence, the effective duration of cigarette smoking was, on average, 9.1 years (95% confidence interval=5.8–11.6) shorter than the calculated duration based on the averaged reported age at which smoking had started (=20.3), which was obtained from the survey conducted in 1965. The results were not substantially modified by age or daily cigarette consumption within the range analyzed here. However, a slightly smaller estimate of θ was obtained in the period of 1966–73 than in the period of 1974–81 (the difference was not statistically significant). The lung cancer mortality rate ratio (relative risk) was estimated to be 1.7, 2.5 and 2.7 for those who smoked 15–24, 25–34, and 35 or more cigarettes a day, respectively, when compared to those who consumed 5–14 cigarettes per day.

In Tables II and III, the observed lung cancer deaths and mortality are compared with the expected values

Table I. Person Years and Lung Cancer Deaths Observed during the 16-Year Follow-up from the Year 1966 to 1981 Categorized by the Attained Age and the Number of Cigarettes Smoked per Day

Attained age	Number of cigarettes smoked per day[a)]				
	1–4	5–14	15–24	25–34	35+
40–44	241.6 (0)[b)]	11767.6 (0)	19349.8 (0)	1996.7 (0)	660.0 (0)
45–49	711.3 (0)	29658.5 (1)	48652.9 (8)	5052.2 (1)	1678.9 (0)
50–54	1148.2 (0)	44670.4 (6)	72296.4 (19)	7452.6 (1)	2640.4 (2)
55–59	1400.3 (0)	52308.1 (16)	81144.9 (46)	8146.9 (5)	3289.1 (3)
60–64	1520.9 (0)	48858.0 (33)	67491.3 (70)	6653.5 (12)	2827.5 (4)
65–69	1282.6 (0)	37822.9 (53)	46319.0 (105)	4295.8 (15)	1906.7 (8)
70–74	753.7 (2)	19942.3 (43)	21898.1 (85)	2025.3 (14)	830.7 (6)
75–79	290.1 (1)	6178.7 (21)	5997.9 (32)	515.2 (3)	221.7 (0)
Total	7348.8 (3)	251206.4 (173)	363150.3 (365)	36138.1 (51)	14055.0 (23)

a) For the categories of 1–4, 5–14, 15–24, 25–34 and 35+ cigarettes per day numbers of subjects in the year (1966) of entry were 567, 18,395, 26,344, 2,658 and 1,049, respectively, and average numbers of cigarettes smoked per day were 3.1, 9.5, 18.4, 28.7 and 41.7, respectively.
b) Person years and number of lung cancer deaths in parentheses.

Table II. Observed and Expected Numbers of Lung Cancer Deaths (Goodness of Fit Table)

Attained age	Number of cigarettes smoked per day			
	5–14	15–24	25–34	35+
40–44	0 (0.2)[a)]	0 (0.5)	0 (0.1)	0 (0.0)
45–49	1 (1.5)	8 (4.1)	1 (0.6)	0 (0.2)
50–54	6 (6.4)	19 (17.6)	1 (2.7)	2 (1.0)
55–59	16 (17.4)	46 (45.8)	5 (6.8)	3 (3.0)
60–64	33 (33.9)	70 (79.3)	12 (11.5)	4 (5.2)
65–69	53 (48.2)	105 (100.5)	15 (13.7)	8 (6.5)
70–74	43 (43.8)	85 (81.6)	14 (11.1)	6 (4.9)
75–79	21 (21.5)	32 (35.5)	3 (4.5)	0 (2.1)
Total	173 (172.9)	365 (364.9)	51 (51.0)	23 (22.9)

Deviance=16.8, degree of freedom=27.
a) Observed and expected (in parentheses) numbers of lung cancer deaths. Expected numbers were calculated by the following function, (person years/100,000)$\times K_1 \times RR_j \times ((\text{age}-\theta)/100)^{4.5}$, where parameters were estimated by the maximum likelihood method: $\theta=29.4$, $K_1=10002.84$, $RR_1=1$ for the group having smoked 5–14 cigarettes per day, $RR_2=1.7$ for the group having smoked 15–24 cigarettes per day, $RR_3=2.5$ for the group having smoked 25–34 cigarettes per day and, $RR_4=2.7$ for the group having smoked 35 or more cigarettes per day.

obtained from the model described above. The observed and the expected values approximated to each other and the goodness of fit chi-square value (deviance) was 16.8 (DF=27), indicating an excellent fit of the model to the observed data.

As can be judged from Tables II and III, lung cancer mortality increased linearly for the range of daily cigarette consumption of 5–34 (note here that the dose range of 40 cigarettes or over was excluded in the analysis of Doll and Peto). The observed lung cancer mortality per 100,000 for this dose range was basically well described by the following estimated equation,

$$\alpha \times (\text{cig}+\beta) \times ((\text{age}-\theta)/100)^{4.5},$$

where cig is number of cigarettes smoked per day and the dose response is assumed to be linear. The deviance was 58.0 (DF=75) and the values of α, β and θ were estimated to be 810.2, 3.2 and 29.5, respectively. For the model described in the footnote of Table II, which assumed no particular dose-response shape, an almost identical value of θ, 29.4, was obtained in this dose-range, and the deviance was 55.2 (DF=74).

In order to compare our results with those obtained in the British physicians' cohort study, maximum likelihood estimates of average number of cigarettes smoked per

Table III. Observed and Expected Lung Cancer Mortality Rate per 100,000 Person Years (Goodness of Fit Table)

Attained age	Number of cigarettes smoked per day			
	5–14	15–24	25–F34	35+
40–44	0.0 (1.4)[a]	0.0 (2.4)	0.0 (3.5)	0.0 (3.8)
45–49	3.4 (4.9)	16.4 (8.4)	19.8 (12.4)	0.0 (13.3)
50–54	13.4 (14.3)	26.3 (24.3)	13.4 (35.8)	75.7 (38.7)
55–59	30.6 (33.3)	56.7 (56.5)	61.4 (83.4)	91.2 (90.1)
60–64	67.5 (69.4)	103.7 (117.5)	180.4 (172.7)	141.5 (185.5)
65–69	140.1 (127.6)	226.7 (217.0)	349.2 (319.4)	419.6 (341.9)
70–74	215.6 (219.7)	388.2 (372.7)	691.3 (550.3)	722.3 (589.3)
75–79	339.9 (347.7)	533.5 (591.6)	582.3 (865.8)	0.0 (942.6)
Total	68.9 (68.8)	100.5 (100.5)	141.1 (141.1)	163.6 (162.9)

a) Observed and expected (in parentheses) lung cancer mortality rates per 100,000 person-years. Expected rates were calculated from the function described in Table II.

Table IV. Observed and Estimated Average Numbers of Cigarettes Smoked per Day Derived from the Doll and Peto Dose-Response Model

	Number of cigarettes smoked per day		
	5–14	15–24	25–34
Observed	9.5	18.4	28.7
Estimated[a]	13.2	19.2	24.5
95% confidence interval[b]	11.7–14.6	17.7–20.3	20.3–28.6

a) Estimated average daily cigarette consumption, cig, was obtained from the following model separately for three ranges of amount of daily cigarette consumption by the maximum likelihood method: lung cancer mortality per 100,000 person years $=27.3\times(\text{cig}+6)^2\times((\text{age}-29.4)/100)^{4.5}$.
b) 95% confidence interval was calculated with θ fixed at 29.4.

day, cig, were obtained separately for the three ranges of daily cigarette consumption in Table IV, using the following model with θ of 29.4.

$$\text{Lung cancer mortality per 100,000} =27.3\times(\text{cig}+6)^2\times((\text{age}-\theta)/100)^{4.5},$$

which is the Doll-Peto model described in the introduction if θ takes a value of 22.5. The estimated cig was similar to the observed one for medium smokers, who consumed 15–24 cigarettes per day, once duration of cigarette smoking was adjusted. On the other hand, for light smokers (5–14 cigarettes per day) the estimate of average number of cigarettes smoked daily was larger than the observed one by 3.7 while for heavy smokers (25–34 cigarettes per day) the estimate was smaller by 4.2.

DISCUSSION

Cigarette shortage in Japan There was a marked cigarette shortage[10] in Japan during and shortly after the second world war: Tominaga[11] reported that the average annual cigarette consumption per adult aged 15 or over was 1130 in 1940, 1140 in 1943, 950 in 1944, 310 in 1945, 310 in 1946, 360 in 1947, 660 in 1948, 1000 in 1949 and 1220 in 1950. The subjects used in our analysis must have been affected by the cigarette shortage[10–13] in the 1940s in Japan because they were of ages 20–44 in 1945. In Britain there was also a cigarette shortage, but it was of a shorter duration and on a smaller scale,[14] so that the effect of the shortage on smoking habits in that country seemed to have been too small to affect the lung cancer risk.

Effect of cigarette shortage In Doll and Peto's model, 22.5 years were subtracted from attained age to calculate the "physiological" smoking duration for their subjects, whose mean age when smoking began was 19.2 years, because " once it starts growing a lung cancer probably usually takes a few years to become clinically evident."[5] If it was assumed that it took the same number of years (3.3 years $=22.5-19.2$) for the tumors to become clinically evident in both of the cohorts, our results suggest that the effective duration of cigarette smoking in the Japanese cohort was about 5.8 ($=9.1-3.3$) years shorter than that calculated from the reported ages at which smoking was started (if the mean survival period of lung cancer is to be taken into account as well, the difference will become smaller by roughly 10–20%). The value of 5.8 years corresponds well to the above-mentioned duration of marked cigarette shortage. Furthermore, once 9.1 ($=29.4-20.3$) years were subtracted from the durations of cigarette smoking that can be

Table V. Observed and Expected Lung Cancer Death Rates by the Number of Cigarettes Smoked per Day Derived from the Doll and Peto Model with θ of 29.4.

Range of daily cigarette consumption	Average number of cigarettes smoked per day	Lung cancer death rate	
		Observed	Expected
5–14	9.5	68.9	45.0
15–24	18.4	100.5	95.3
25–34	28.7	141.1	183.7

Expected rate was calculated based on the expected number of cases derived from the Doll-Peto model with $\theta=29.4$: lung cancer mortality per 100,000 person years $=27.3\times(\mathrm{cig}_j+6)^2\times((\mathrm{age}-29.4)/100)^{4.5}$, where cig_j is observed average number of cigarettes smoked per day for each of three cigarette dose categories.

expected from the age when smoking began, the lung cancer mortality in the range of 15–24 cigarettes per day was found to be fairly close to what was expected from the equation reported by Doll and Peto[5] (Table V), suggesting that the difference of the lung cancer risk between the Japanese and the British cohorts might be explained by the severe cigarette shortage which lasted 4–6 years in the former cohort, during World War II and shortly thereafter.

One might argue that even in the period when there was a shortage of cigarettes, smokers were at least able to smoke a few cigarettes and, therefore, the shortage could be accounted for by reduced daily cigarette consumption instead of shorter duration of cigarette smoking. Nevertheless, we considered the shorter duration of smoking mainly, because, as can be judged from the Doll-Peto model, the effect of daily cigarette consumption seems to be far weaker than that of duration of smoking, as the risk is proportional to the 4.5th power of the latter.

Observed and estimated dose In our analysis, the duration-defining parameter θ was assumed to be common to all the smokers regardless of amount of cigarette consumption. If, however, θ was allowed to be different among the three cigarette smoking categories, 5–14, 15–24 and 25–34, and observed amounts of cigarettes per day were used in the Doll-Peto model, the duration-defining parameter θ was estimated to be smaller, by only 2–3 in value, for light smokers and larger for heavy smokers, respectively (data not shown), to make the estimates of lung cancer mortality shown in Table V equal to the observed mortality. Therefore, the true dose-response shape might be closer to the Doll-Peto model, which assumed a linear-quadratic form, while the observed dose response was linear in the Japanese cohort in the range of 5–34 cigarettes smoked per day. For the smokers who smoked 35 or more cigarettes per day (mean=41.7), the Doll and Peto dose-response model was not necessarily expected to hold because the dose-rate range of their analysis was limited to 1–40 and therefore did not include the mean dose-rate of 41.7.

Effect of cessation of smoking In our analysis, we used the information on smoking habits obtained in a survey conducted in 1965. A sample survey conducted in 1971 for 7,507 individuals randomly selected from among the 265,118 subjects revealed a fairly good concordance of smoking information between the 1965 and 1971 surveys: 84.3% of subjects gave exactly the same answers to the question regarding whether they smoked daily, occasionally, rarely or did not smoke (unpublished data); therefore baseline smoking status in 1965 was used in the current analysis. The effects of the cessation of smoking occurring during the observation period should not, however, be ignored although a random sample survey revealed that in the 1965–71 period less than 1% of smokers (4.1% in six years) had stopped smoking (unpublished results). No extensive monitoring of smoking habits was carried out on this cohort during the subsequent follow-up years.

In order to estimate the magnitude of the possible biases which might have affected the results presented in this paper, we conducted a simple simulation analysis. The results suggested that if a fixed proportion of smokers of about 1% quit smoking every year and, therefore, 16% had done so during the 16-year observation period, the corrected durations of smoking for regular smokers became even shorter, by at most one year in magnitude, i.e., θ = 30–31, because the curve of age-specific mortality rates was fitted by a function which represents a curve with a larger curvature (with the exponent of 4.5). On the other hand, the cessation of smoking has the effect of making estimates of the number of cigarettes smoked per day derived from the Doll and Peto dose-response model low — another possible explanation for our result that the obseved dose-response was linear for the Japanese cohort.

In conclusion, the estimated duration of cigarette smoking was, on average, 9.1 years (95% confidence interval = 5.7–11.6) shorter than that calculated from the reported ages at which smoking had started, when lung cancer mortality was assumed to be proportional to the 4.5th power of duration of smoking. Once the effective duration of cigarette smoking was adjusted, lung cancer mortality in the range of 5–34 cigarettes per day was fairly comparable to that observed among the cohort of male British physicians.

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