Quantitative relationship between cumulative cigarette consumption and lung cancer mortality in Japan

Naohito Yamaguchi,a Yumiko Mochizuki-Kobayashib and Osamu Utsunomiya²

Background Sufficient evidence has been accumulated to demonstrate the causal relationship between cigarette smoking and lung cancer risk. Therefore, the lung cancer risk of a country is supposedly determined by the amount of cigarettes consumed in the country, but this quantitative relationship has yet to be clarified at a national level.

Objective To find the quantitative relationship between cigarette smoking and subsequent lung cancer risk at a national level.

Methods The quantitative relationship between cigarette smoking and lung cancer mortality is formulated as a function of cumulative cigarette consumption. The formulae for ages 25–29 to 70–74 are estimated by examining the increment of the lung cancer death rate in relation to the unit increase in cumulative cigarette consumption in different birth cohorts. The validity of the quantitative relationships is then examined by comparing lung cancer deaths expected from the formulae with observed deaths in past studies.

Results Cumulative cigarette consumption was found to have increased in later birth cohorts for all ages of males and females. The age-specific lung cancer death rates from 35–39 to 70–74 were found to increase in proportion to cumulative cigarette consumption. Comparison of the results with past studies showed good agreement.

Conclusion The change over time in the lung cancer death rate of males and females in Japan can be explained fairly well by the increase in cumulative cigarette consumption at the national level.

Keywords Lung cancer, mortality trend, cumulative cigarette consumption, birth cohort, Japan

Accepted 10 May 2000

Sufficient evidence has been accumulated to demonstrate the causal relationship between cigarette smoking and lung cancer risk. Epidemiological studies conducted in many countries have repeatedly reported increased risk of lung cancer among cigarette smokers compared to non-smokers.¹ ² The increasing gradient of cancer risk associated with increased exposure level, often called the dose-response relationship, provides a sound basis for assessing the causality. Lung cancer risk has been shown by many studies to increase with the increasing amount of cigarettes smoked daily as well as with increased duration of smoking.³ ⁶

¹ Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Japan.
² National Institute of Public Health, Japan.
³ School of Medicine Keio University, Japan.
Reprint requests: Naohito Yamaguchi, Chief, Cancer Information and Epidemiology Division, National Cancer Center Research Institute, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

In the light of the strong association between cigarette smoking and lung cancer risk, the dose-response relationship observed in several international studies should also be observed at a national level. However, the relationship between cigarette consumption and lung cancer risk is not apparently straightforward in Japan, when examined at the national level. According to the data provided by Japan Tobacco Industry Inc., the former Japan Tobacco Monopoly Bureau,² the smoking prevalence in Japan still remains at a higher level than in many European and northern American countries, 57.5% among males and 14.2% among females in 1996, as compared to 27.7% among males and 22.5% among females in the US in 1993, and 28% among males and 26% among females in the UK in 1994.⁵ On the other hand, the lung cancer incidence and mortality rate in Japan is reportedly lower than that in Western Europe and the US.⁹ ¹⁰ The prevalence of smoking in Japan is decreasing, especially among men⁷ but the lung cancer death rate has been increasing in both males and females. The death rates per 100 000 among males and females, when adjusted to the 1985 population model of Japan, increased from 13.6 and
4.8 in 1960 to 47.5 and 12.5 in 1995, respectively.\(^\text{10}\) This apparent contradiction between falling smoking prevalence and increasing lung cancer death often causes the public, and even some health professionals, to question the effectiveness of tobacco control for the prevention of lung cancer.

When attempting to find a dose-response relationship at the national level, smoking prevalence is not a good indicator for the cumulative dose of cigarette smoking. Obviously, one's risk of lung cancer is related to the amount of cigarettes smoked in one's lifetime. Therefore, the lung cancer risk of a country is supposedly determined by the amount of cigarettes consumed in the country in the past. We have previously reported that, in addition to smoking prevalence, the amount of cigarettes smoked daily should be taken into consideration.\(^\text{11}\) In the present study, the definition of cumulative cigarette consumption up to a certain age is estimated by adjusting the cumulative dose of cigarette smoking. Obviously, one's risk of lung cancer is related to the amount of cigarettes smoked in one's lifetime, in an attempt to find the quantitative relationship between cigarette smoking and subsequent lung cancer risk. To our knowledge this is the first report which has successfully identified the quantitative relationship at the national level. This relationship can be used for the quantitative evaluation of potential impact of smoking control at the national level.

**Materials and Methods**

**Quantitative model for the relationship between cigarette consumption and lung cancer mortality**

In this study, we attempt to formulate the quantitative relationship between cigarette smoking and lung cancer mortality in terms of the cumulative cigarette consumption, which is defined as the total number of cigarettes consumed in one’s life up to a certain age. For a current smoker, it is postulated that the cumulative cigarette consumption up to a certain age determines the lung cancer death rate on that age. For an ex-smoker, the reduction of risk after cessation is incorporated in the model by adjusting the cumulative cigarette consumption by the following formula:

\[
CCC^* = \frac{CCC}{[1 + (YY_{0.5})]}
\]

where CCC denotes the actual amount of cigarettes smoked in the past, CCC\(^*\) denotes the adjusted cumulative cigarette consumption, \(Y\) denotes the years after smoking cessation, and \(Y_{0.5}\) denotes the years after cessation, by which the risk of lung cancer death is reduced to half of continuous smokers. In the present study, \(Y_{0.5}\) is set at 15 years, based on published reports.\(^\text{12,13}\)

**Analysis of lung cancer death rate in relation to cumulative cigarette consumption**

In the present study, the definition of cumulative cigarette consumption is extended to a birth cohort, i.e. people born in the same year, only some of whom are smokers. The cumulative cigarette consumption up to a certain age is estimated by summing, over age, the age-specific per capita cigarette consumption of the cohort. The per capita cigarette consumption at a certain age of a birth cohort can be estimated by dividing the annual cigarette sales by the number of smokers of that age. Since there are no other data available, this study has to rely on the data reported by Japan Tobacco Industry, Inc. For the present study, the cumulative cigarette consumption up to age 25, 30, 35, 40, 45, 50, 55, 60, 65 and 70 was estimated for males and females, separately, based on the smoking prevalence from 1965 to 1996 and the annual cigarette sales from 1920 to 1996. Smoking prevalence data for age groups 20–29, 30–39, 40–49, 50–59, and \(\geq60\) are available for those born in 1940–1971, 1930–1961, 1920–1951, 1910–1941, and 1900–1931, respectively. The smoking prevalence in earlier years, for which no actual data for younger age groups are available, is assumed to be the same as the earliest available value. For example, the smoking prevalence for age 20–29 among those born in 1900–1939 is assumed to be the same as that of 1940. The age-specific smoking prevalence from age 20 to 70 is then estimated by interpolation and extrapolation, assuming that the data of smoking prevalence for age 20–29, 30–39, 40–49, 50–59 and \(\geq60\) represent the prevalence at the age 25, 35, 45, 55, and 65, respectively.

For a certain 5-year age group, the lung cancer death rate varies by gender and also by birth cohort. This difference gives an opportunity to estimate quantitatively the increment of lung cancer death rate for that 5-year age group in relation to the unit increase in cumulative cigarette consumption. This analysis is done for both genders combined as follows:

\[
\text{LDR}_{ij} = A_i + B_i \times \text{CCC}^*_{ij}
\]

where LDR\(_{ij}\) and CCC\(^*\)\(_{ij}\) denote the lung cancer death rate and cumulative cigarette consumption of age group \(i\) (20–24, 25–29, ..., 70–74) and birth cohort \(j\) (for each calendar year from 1900 to 1951), and \(A_i\) and \(B_i\) denote parameters to be estimated. The cumulative cigarette consumption CCC\(^*\)\(_{ij}\) is the lifetime consumption prior to the observation of lung cancer death. In summing the cumulative cigarette consumption for a certain birth cohort, the reduction in lung cancer risk in ex-smokers is taken into account by Equation (1). The parameters \(A_i\) and \(B_i\) are estimated for each age group \(i\).

**Validation of estimated functions by comparison with published data**

As the next step, the validity of the quantitative relationship based on Equation (2) is examined by comparing lung cancer deaths expected from the equation with observed deaths in past studies. The prerequisite for such studies is that the cumulative cigarette consumption of the study subjects can be estimated from reported data. The lung cancer incidence or mortality in the study subjects should also be available. Since there is no epidemiological study satisfying this prerequisite in Japan, the following two studies were selected.

The first data set is from a prospective cohort study of the American Cancer Society in the US.\(^\text{14}\) The expected number of lung cancer deaths is calculated and compared with observed deaths for men aged 55–74 who started smoking between ages 15 and 24. For women, the expected number of lung cancer deaths is calculated for all smokers combined because the total observed person-years were not sufficient to enable subset analysis. The number of cigarettes consumed daily was reported for five categories: 0, 1–9, 10–19, 20–39, and \(\geq40\). To calculate the cumulative cigarette consumption, 0, 5, 15, 30, and 50 cigarettes are assigned for these categories, respectively. The person-years of observation were provided for 5-year age groups from 55 to 74, which can be used to calculate the
expected number of lung cancer deaths by applying the lung cancer death rates expected from Equation (2).

The second data set is from the prospective cohort study of British male physicians. The number of incident cases of lung cancer was reported with observed person-years for different categories of cigarette consumption: 0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, and 35–39 per day. The smokers started smoking between 15 and 24 years of age (average age 19.2 years). The strength of this data set is that the smokers were restricted to those whose daily cigarette consumption varied by less than 5 cigarettes during the follow-up. This enables precise estimation of the cumulative cigarette consumption of the cohort. The average number of cigarettes consumed per day were reported as 0, 2.7, 6.6, 11.3, 16.0, 20.4, 25.4, 30.2, and 38.0 for the categories of 0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, and 35–39 per day, respectively, and these values are used to calculate the cumulative cigarette consumption. The results of the present study are used to estimate the expected number of lung cancer deaths, while the observed number are incident cases of lung cancer. Taking into account the low survival rate among lung cancer patients, it was decided that the observed number of lung cancer cases can be compared with the expected number of lung cancer deaths.

Results

Estimation of cumulative cigarette consumption

The cumulative cigarette consumption was estimated for those born 1900–1951 (Figure 1). Except for a temporary decrease corresponding to the deficit of sales shortly after World War II, the cumulative cigarette consumption was found to have increased in later birth cohorts for all ages of males and females. As can be seen, the increases seem to have occurred uniformly across different age groups. The increment of cumulative consumption by one-year shift in year of birth ranged from 600 to 3800 for males and from 80 to 510 for females. The ratio of cumulative cigarette consumption among males to females was approximately 5:1.

Analysis of lung cancer death rate in relation to cumulative cigarettes consumption

For the 5-year age groups 35–39 to 70–74, the lung cancer death rates of different birth cohorts of males and females were plotted against the cumulative cigarette consumption (Figure 2). Note that the vertical axes were adjusted in different age groups, so that the increasing trends could be observed. A statistically significant positive correlation was observed for the lung cancer death rates of those aged 35–39 to 70–74 in relation to corresponding cumulative cigarette consumption. When the correlation was examined in Figure 2, the difference in lung cancer death rate between males and females seems to be explained solely by the difference in cumulative cigarette consumption.

Validation of estimated functions by comparison with published data

In the cohort study of the American Cancer Society, the observed lung cancer deaths for male and female smokers were 33 and 248, whereas the numbers expected from Equation (2) were 32.4 and 248.0, respectively, showing excellent agreement. The observed numbers for male and female never-smokers were 77 and 27, whereas the numbers expected from Equation (2) were 59.8 and 13.9, respectively. The agreement for never-smokers was not so good as for current smokers.

In the cohort study of British physicians, the observed incident cases of lung cancer were reported by nine different smoking categories (Table 1). The expected numbers of lung cancer deaths estimated from the observed person-years and cumulative cigarette consumption are also shown in Table 1. The observed total number of lung cancer incident cases showed good agreement with the number of cases expected from the present study; 175 versus 170.78 with O/E = 1.02. When the observed numbers in different smoking categories were compared with expected values, the agreement varied by smoking categories. For never-smokers, the observed versus expected (O/E) ratio was 0.86 ($\chi^2 = 0.09$, $P = 0.76$). For smokers, the O/E ratio ranged from 0.54 to 1.97. The $\chi^2$ value for the nine smoking categories from never to 35–39 cigarettes a day was 15.9 (9 d.f., $P = 0.07$). According to the quantitative analysis of the cohort data by Doll and Peto, the lung cancer incidence rate was shown to increase in proportion to the smoking duration raised to the power of 4.5. In comparison, the slope of linear equations shown in Figure 2 was found to increase in proportion to the 4.4th power of age–20 (Figure 3). Thus, it was suggested that the increasing slope of linear equations by age reflected implicitly the effect of increasing smoking duration.
Discussion

The present study introduced the idea of cumulative cigarette consumption and showed successfully that the lung cancer death rate of Japanese males and females in the age groups 35–39 to 70–74 increased in proportion to the cumulative cigarette consumption at a national level. The aim of this study is not to prove the causal relationship between cigarette smoking and lung cancer death, but to provide quantitative formulae by which lung cancer mortality at a national level can be analysed and predicted from the cigarette smoking of the Japanese population. In this regard, the results of the present

Figure 2 Linear relationships between cumulative cigarette consumption and lung cancer death rate. The 5-year death rates from 35–39 to 70–74 were plotted against the cumulative cigarette consumption up to ages 35 to 70, respectively. As indicated by the square of correlation coefficient, the linear relationships are highly significant, especially for older age groups.
study seem to be promising, because the fit of the linear equations to the observed data is highly significant (Figure 2). The results of the present study were further validated by applying the equations to two cohort studies in the US and UK. The comparisons of observed and expected lung cancer deaths in the American cohort study and incident cases in the British cohort study both showed good agreement. Furthermore, the slope of linear equations increases in proportion to the 4.4th power of smoking duration. This is in good agreement with the British cohort study, in which the lung cancer incidence rate increased in proportion to the 4.5th power of smoking duration.

This study also provides an answer to the question often raised by the public and even some health professionals: ‘Why are the lung cancer death rates in Japan increasing in both males and females when the smoking prevalence keeps decreasing in males and does not change over decades in females?’ The results of the present study provide a good tool with simple mathematical formulae to show visually why and how the lung cancer death rate is increasing in Japan. The increase in cumulative cigarette consumption, as shown in Figure 1, can explain the increase in lung cancer mortality of males and females by simply applying the linear equations shown in Figure 2. There are arguments that the increase in lung cancer incidence and mortality among women could be due to factors other than cigarette smoking, and efforts are being made to identify such factors. The present study showed successfully that no other factors than smoking are necessary to explain the increase in lung cancer mortality of both males and females in Japan.

The quantitative formulae are also useful for predicting the future of lung cancer mortality in Japan. An increasing trend was seen in the cumulative cigarette consumption in most ages of males and females (Figure 1). If this trend continues in the future, the lung cancer death rate in Japan can be predicted to continue increasing according to the regression lines shown in Figure 2. The impact of tobacco control at the national level on lung cancer mortality in the future can also be assessed using these formulae.

Several issues relate to the validity of the present study. First, the data on smoking prevalence are obtained by the Japan Tobacco Industry Inc. for marketing purposes. The details of the sampling scheme and data collection procedures are not open to public. Nevertheless, we had to rely on this data because there is no other information on past smoking prevalence. Recently, the Ministry of Health and Welfare conducted the first survey of tobacco use in Japan, and the smoking prevalence in Japan was estimated at 52.8% for males and 13.4% for females. This shows a good agreement with Japan Tobacco Industry Inc. data. Furthermore, it is noteworthy that the increase in cumulative cigarette consumption reflects mainly the increase in national cigarette sales (Figure 4), as we have previously reported.

The increase in cigarette sales in Japan seems to parallel economic growth after World War II but there might be other factors which have increased alongside cigarette sales. For example, the dietary habits of the Japanese are known to have changed rapidly in the 1960s and 1970s. Therefore, it is theoretically possible that factors other than cigarette smoking are causing the increase in lung cancer mortality in Japan. This possibility has to be considered, but it seems unlikely, however, because the results of present study showed good agreement with the cohort studies in the US and UK, where dietary habits did not change.

Environmental factors, such as air pollution and occupational exposures, are known to relate to lung cancer incidence and

### Table 1

<table>
<thead>
<tr>
<th>No. of cigarettes smoked per day</th>
<th>0</th>
<th>1–4</th>
<th>5–9</th>
<th>10–14</th>
<th>15–19</th>
<th>20–24</th>
<th>25–29</th>
<th>30–34</th>
<th>35–39</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>O&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>13</td>
<td>51</td>
<td>26</td>
<td>34</td>
<td>28</td>
<td>175</td>
</tr>
<tr>
<td>E&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.65</td>
<td>1.53</td>
<td>7.41</td>
<td>17.08</td>
<td>22.71</td>
<td>45.16</td>
<td>27.11</td>
<td>25.21</td>
<td>19.93</td>
<td>170.78</td>
</tr>
<tr>
<td>O/E ratio</td>
<td>0.86</td>
<td>1.97</td>
<td>0.54</td>
<td>0.70</td>
<td>0.57</td>
<td>1.13</td>
<td>0.96</td>
<td>1.35</td>
<td>1.41</td>
<td>1.02</td>
</tr>
</tbody>
</table>

<sup>a</sup> Observed numbers of incidence cases.

<sup>b</sup> Expected numbers of incidence cases, based on regression equations in the present study.

**Figure 3** The logarithm of slope for the linear equations of lung cancer death rate against cumulative cigarette consumption (Figure 2) increasing in proportion to the logarithm of age–20. This indicates that, given the same amount of cumulative cigarette consumption, the lung cancer death rate increases in proportion to the 4.4th power of smoking duration.

**Figure 4** The increasing trend of national cigarette sales in Japan. After a temporary deficit during the post war period, the cigarette sales showed a continuous increasing tendency until 1970.
these have increased during the period of rapid industrialization. However, they are unlikely to be the major causes of the rise in lung cancer mortality in Japan, because the reported relative risk of lung cancer in relation to air pollution is too small to explain the observed increase in Japan. The population at risk of occupational exposures to lung carcinogens is also too small to explain the nationwide increase in lung cancer deaths.

Finally, the validity of the analytical methods in the present study have to be discussed. Simple regression analysis was applied to the data of both males and females combined (Figure 2). Methodologically, separate analyses for males and females might yield different slopes and intercepts by sex. In fact, the figures for some age groups suggest this difference in Figure 2. Nevertheless, separate analysis was not conducted in the present study, because linear increasing patterns were obvious visually in Figure 2. In addition, the simple regression lines are much easier to handle in assessing and predicting the change in lung cancer mortality according to changes in cigarette consumption. However, it should be noted that the correlation coefficients in Figure 2 have to be interpreted carefully because the combined analysis of males and females would increase the coefficients spuriously.

In conclusion, we propose cumulative cigarette consumption as a new measure of the burden of cigarette use in a country. It was shown that the change over time in the lung cancer death rate of males and females can be explained fairly well by the change in cumulative cigarette consumption. The use of cumulative cigarette consumption is further shown to be valid by the consistency between observed and expected lung cancer death rate among lifetime non-smokers, ex-smokers and smokers of different numbers of cigarettes. To examine the validity of the present study, the results should be applied to the national cigarette consumption in other countries to estimate the lung cancer mortality rate.

Acknowledgement

This study was supported in part by the Grant-in-Aid for Cancer Research (8-1) by Ministry of Health and Welfare, Japan. This study was done as an activity of the WHO Collaborating Centre for Reference on Smoking and Health in the National Cancer Center, Japan.

References