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A 50-Year Projection of Lung Cancer Deaths among Japanese Males and Potential Impact Evaluation of Anti-smoking Measures and Screening Using a Computerized Simulation Model

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The lung cancer death rate among Japanese males was projected for 50 years to the year 2041 by a computerized simulation model. Long-term effects of anti-smoking measures and mass screening on lung cancer deaths were also evaluated. The simulation showed that the age-adjusted lung cancer death rate would increase and reach a peak of 166 per 100,000 in 1989 and then decrease to 148 per 100,000 in 2003. It then shows an increasing tendency again, up to 255 per 100,000 in 2028. The smoking initiation rates estimated from the observed lung cancer death rates showed that the changes in death rates may be attributed to a lower smoking initiation rate among those born in the 1930's. Promotion of mass screening programs is effective more quickly than anti-smoking measures but the reduction in annual cancer deaths is expected to be only 11%, even if 100% participation is achieved by the year 2000. A reduction in smoking initiation rate, on the other hand, affects lung cancer deaths very slowly. It was predicted that a 1% annual reduction in smoking initiation rate would result in a 20% decrease in the number of lung cancer deaths in 2041. A smoking cessation program is intermediate with regard to promptness. The predicted reductions in lung cancer deaths in 2041 were 13%, 47%, and 66%, respectively, when the annual smoking cessation rate was increased from 0.46% (present status) to 1%, 3%, and 5%. In conclusion, the combined application of all three preventive measures seems essential to realize the most effective reduction in lung cancer deaths.

Key words: Lung cancer — Epidemiology — Simulation — Smoking — Screening

An increase in lung cancer death rate has been noted among Japanese males in recent decades.[1,2] In particular, the increase among those over 70 years of age is more marked than in younger age groups. It has been argued that cigarette smoking plays a substantial role in this epidemic and emphasis has been placed on the importance of anti-smoking measures.[3] A community-based mass screening program is also recommended by the Japanese government as a preventive measure for lung cancer deaths. The effectiveness of mass screening was evaluated recently by a case-control study, and the reduction in risk of dying from lung cancer was estimated to be approximately 28%.[4]

In our previous study,[5] the lung cancer death rates among Japanese males were projected to 2001, using a computerized simulation model named CANSAVE (Cancer Strategy Analysis and Validation of Effect). This simulation study showed that the increase among aged males would continue until the late 1990's and that this increase would slow down and turn to a decreasing phase by the year 2001. The potential impact of smoking cessation programs and mass screening for lung cancer were also evaluated for the 10-year period 1991 to 2000 but the simulation period was not sufficient to assess the long-term effects of these preventive measures.

The objective of the present study was to project lung cancer deaths to 2041, i.e., for 50 years from the present, and to evaluate the long-term effects of anti-smoking measures and mass screening on the lung cancer deaths in this period.

MATERIALS AND METHODS

The simulation model CANSAVE is based on a set of formulae which describe the natural history of cancer as a Markovian stochastic process from cancer-free to a preclinical, clinical, and finally a terminal state (Fig. 1). The details of the simulation model have been described elsewhere.[5] The transition probabilities from preclinical to clinical, clinical to recovery, and clinical to death were estimated simultaneously by the least-squares method,[5] minimizing the departure of survival functions in the model from the observed survival curves in cases detected by screening and through symptoms.[6] The estimated transition probabilities were 0.64/year, 0.13/year and 0.69/year for preclinical to clinical, clinical to

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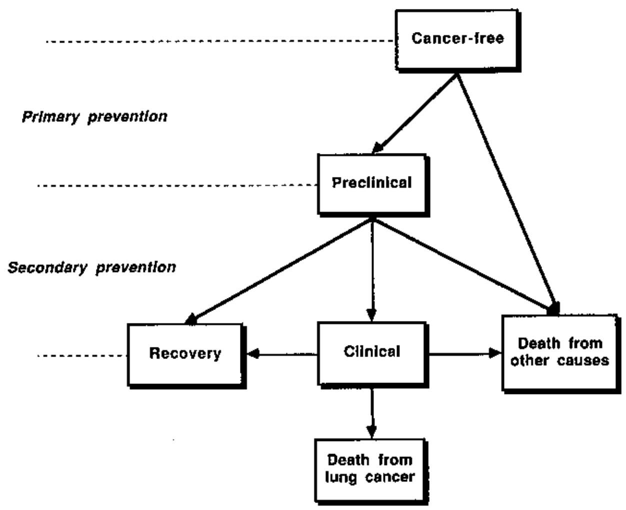

Fig. 1. Markovian stochastic model of the natural history of lung cancer.

recovery, and clinical to death, respectively. The transition probability from preclinical to recovery was estimated to be 0.16/year for participants in annual screening and was assumed to be zero for nonparticipants. The sensitivity of the screening test for lung cancer was assumed to be 0.62.[7] The screening participation rate among Japanese males aged 55 to 79 was assumed to be 10% during the period 1973 to 1989.[8] The annual smoking cessation rate among smokers was estimated to be 0.46% by regression analysis of the increase in ex-smokers among ever-smokers by age.[5] The age-specific smoking rates for this analysis were obtained from the National Health Survey conducted in 1980.[9] The probability of death from other causes was estimated for smokers, ex-smokers, and nonsmokers, separately, based on the age-specific death rates among Japanese males during the period 1973 to 1989. The death rates thereafter were assumed to be constant and the rates in 1989 were applied. In estimating the death rates for different smoking status, the relative risk of death from all causes was assumed to be proportional to the exponential of the duration of smoking as follows[10]:

$$RR = 1.02 \exp(\text{smoking duration}).$$

One of the key issues in modeling the natural history of lung cancer is how to formulate the effect of smoking on the pathogenesis of cancer. We assumed that the lung cancer death rate increases in proportion to the 4'th power of age among non-smokers and to the 4.5'th power of the effective years of smoking among current smokers as follows[11, 12]:

$$\text{Rate} = r_n(\text{age})^4 \qquad (1)$$

for non-smokers,

$$\text{Rate} = r_s(\text{effective years of smoking})^{4.5} \qquad (2)$$

for current smokers.

The effective years of smoking denotes the duration of smoking minus the period of cancer growth, which was assumed to be independent of cigarette smoking, and was given on a birth cohort basis; 22.4 years for the cohorts born after 1933, up to 31.0 years for the cohort born in 1902.[12] The parameters r_n and r_s were set at 0.15×10^{-5} and 1.7×10^{-5} per 100,000, respectively, based on estimates reported by Mizuno *et al.*[12] The reduction in the relative risk among ex-smokers was assumed to be 3% per year, which was estimated recently by a case-control study in Japan.[13] Simulation results were generated for smokers, ex-smokers and nonsmokers separately, then added to obtain the numbers of deaths from lung cancer for each age and calendar year. In projecting the lung cancer death rate of each birth cohort, the proportion of individuals who started smoking in that birth cohort was set so that the projected lung cancer death rates during the period 1981 to 1987 became the closest to the observed death rates in the same period. An iterative method was used for this procedure. The mortality data used as the reference were the death rates observed among Japanese males over 36 years of age during the period from 1981 to 1987. For age 36 to 39, Poisson regression equations were fitted to the increases in age-specific death rates to smooth the random fluctuations due to small numbers of deaths. The simulation period for the present study was from 1981 to 2041, of which the period from 1981 to 1987 was included for the iterative fitting procedure described above. The estimated smoking initiation rates were compared with observed rates in Nagano Prefecture (40,324 male participants in a mass screening program in 1988) and in Fukuoka Prefecture (9,609 male participants in a mass-screening program in 1986). These screening data come from a hospital in Nagano Prefecture and a screening provider organization in Fukuoka Prefecture, which offer annual screening programs to residents on a community basis as well as to farmers and other workers on a work-site basis.

The potential impact of prevention programs on future lung cancer deaths was evaluated with regard to changes in the smoking initiation rate, the smoking cessation rate, and the annual screening rate. The lung cancer death rate adjusted to the 1985 model population[14] and the total number of lung cancer deaths among those aged 55 to 79 were used as the indices of impact. Two different scenarios were considered for the smoking initiation rate among the younger cohorts: (1) the same smoking initiation rate as the cohort born in 1951 and (2) linear decrease in the smoking initiation rate at a rate of 1% per year. The smoking cessation rate which was originally set at 0.46% per year was modified to 1%, 3% and 5% per year to evaluate the effects of smoking cessation programs on future lung cancer deaths. To see the impact of increased participation in screening for lung cancer, the annual screening rate, which was originally set at 10%, was modified to 100% in the year 2000 by increasing it at 10% per year from 1992 to 2000.

RESULTS

The smoking initiation rates estimated by fitting simulation results to the observed lung cancer death rates are illustrated in Fig. 2. It was noted that the smoking initiation rate decreased from around 85% among the cohorts born prior to 1920 to around 65% among the cohorts born in the 1930's. The rate then showed an increasing trend again, returning to the level of 80% in the cohort born around 1950. The lower smoking initiation rates among the cohorts born in the 1930's showed a good agreement with the observed rates in Nagano and Fukuoka prefectures, as shown in Fig. 2. The observed and projected lung cancer death rates displayed for selected cohorts born in 1930, 1935 and 1945 (Fig. 3) showed that the 1935 birth cohort actually had lower risk of lung cancer death than the 1930 and 1945 birth cohorts, as reflected in the estimated smoking initiation rate. Poisson regression equations fitted to observed lung cancer death rates are shown in Table I. Statistically significant increases were found during the period 1973 to 1987 among those aged 34, and 36 to 39. The observed death rates among those aged 36 to 39, which were referred to in the iterative fitting procedure, are displayed in Fig. 4. No sign of deceleration of the increase was observed in this age group. These increases among younger birth cohorts also indicated that the increasing trend in estimated smoking initiation rates in the cohorts born in the 1940's reflects the actual increase in lung cancer death rates. It was also noted that the observed rates in the two regions were lower than the estimated rates in the cohorts born prior to 1920. The smoking initiation rate among the cohorts born in the 1950's and 1960's showed a decreasing tendency in Nagano Prefecture.

The observed and projected lung cancer death rates are illustrated for 5-year age groups from 55–59 to 75–79 in Fig. 5. A constant smoking initiation rate of 80% in the 1952–1986 birth cohorts was assumed in this simulation. The observed death rates showed increasing tendencies in all age groups, with the steepest increase in the 75–79 age group followed by the 70–74 age group. The projected death rate in the 75–79 age group showed the largest changes, with four phases. It reaches a peak of 457 per

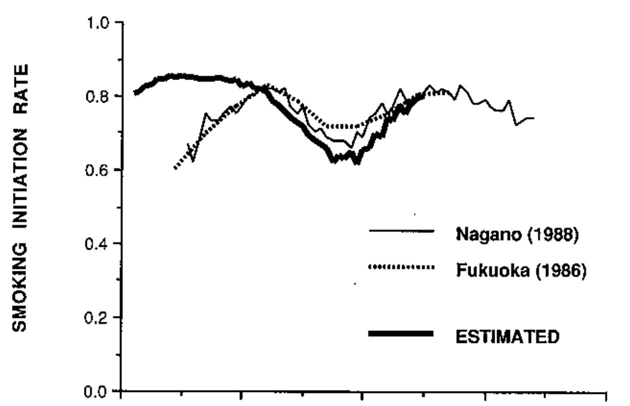

Fig. 2. Observed and estimated smoking initiation rates by birth cohort.

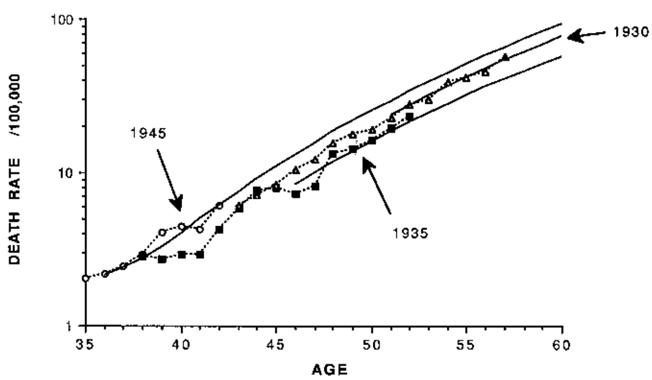

Fig. 3. Observed and projected lung cancer death rates in selected birth cohorts.

Table I. Poisson Regression Equations Fitted to the Increase in Lung Cancer Death Rates (per Million) by Year 1973 to 1987

Age	Slope	SE	t	P-value
30	−0.31	0.17	−1.78	0.076
31	−0.01	0.18	−0.38	0.969
32	0.00	0.20	0.02	0.985
33	0.09	0.21	0.43	0.664
34	0.66	0.24	2.72	0.006**
35	0.24	0.25	0.95	0.339
36	0.94	0.25	3.77	0.0002***
37	0.84	0.29	2.93	0.003**
38	0.80	0.31	2.54	0.011*
39	1.27	0.32	3.99	0.00006***

* $P<0.05$. ** $P<0.01$. *** $P<0.001$.

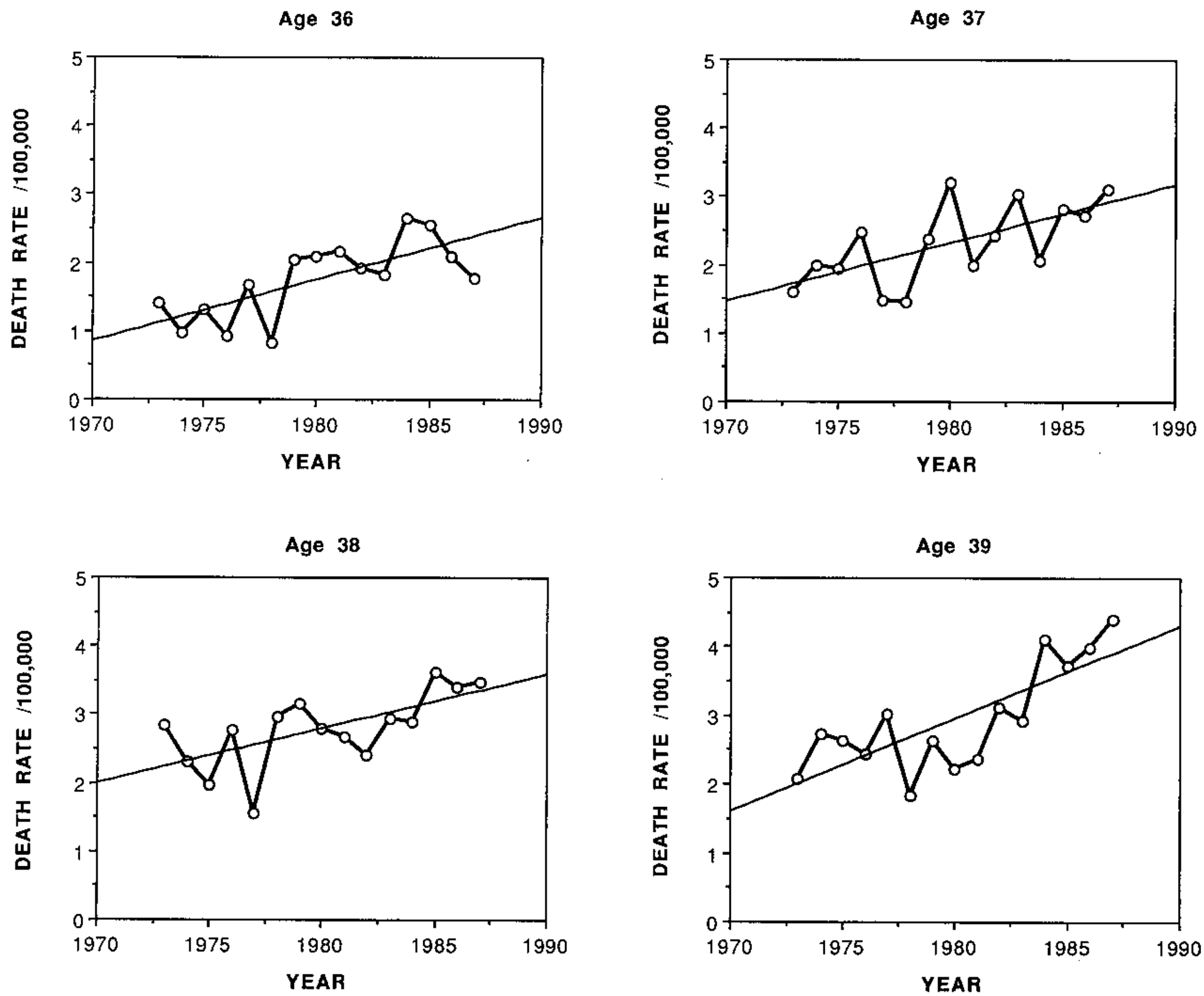

Fig. 4. Increase in lung cancer death rates among Japanese males aged 36 to 39.

100,000 in 1994, then decreases and reaches the lowest level of 276 per 100,000 in 2014. It shows an increasing tendency again and reaches a plateau of 616 per 100,000 in 2035. The constant death rate thereafter resulted from the assumption of constant smoking initiation rate among those born after 1951. The peak and trough for the 70–74 age group are 296 per 100,000 in 1989 and 190 per 100,000 in 2009, respectively. The shift of the peak and trough toward the earlier years indicates that they reflect higher and lower death rates in specific birth cohorts. The peak corresponds to the 1915–19 birth cohort and the trough to the 1935–39 cohort. The projected death rates for the other age groups showed similar but smaller changes. The constant death rates seen in later years resulted from the assumption of constant smoking initiation rates among those born after 1951.

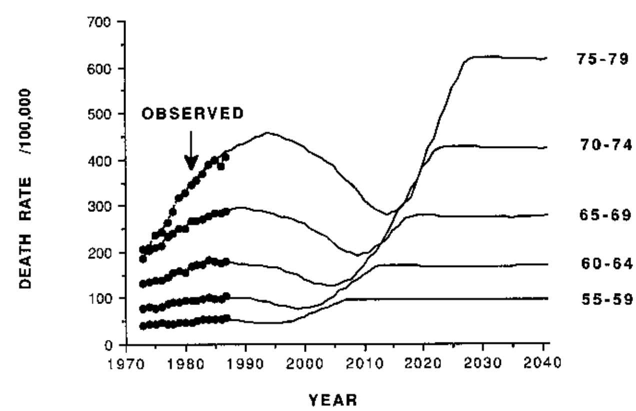

Fig. 5. Observed (circle) and projected (line) lung cancer death rates by 5-year age groups.

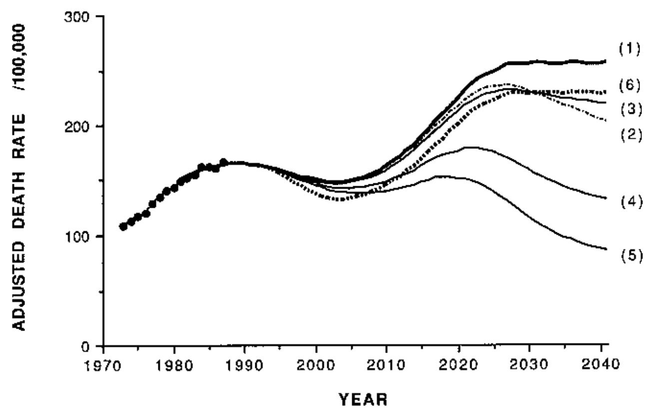

Fig. 6. Observed (circles) and projected (lines) lung cancer death rates adjusted to the 1985 model population of Japan. Scenario (1) is a present-status simulation, in which the smoking initiation rate is constant (80%) among those born after 1951, the annual smoking cessation rate is 0.46%, and the screening rate is 10%. In scenarios (2) to (6), one of the above mentioned settings is modified; the smoking initiation rate decreases at a rate of 1% per year in scenario (2), the smoking cessation rate is set at 1% (3), 3% (4), or 5% (5), and in scenario (6), the screening rate increases from 10% in 1991 to 100% in 2000 and thereafter.

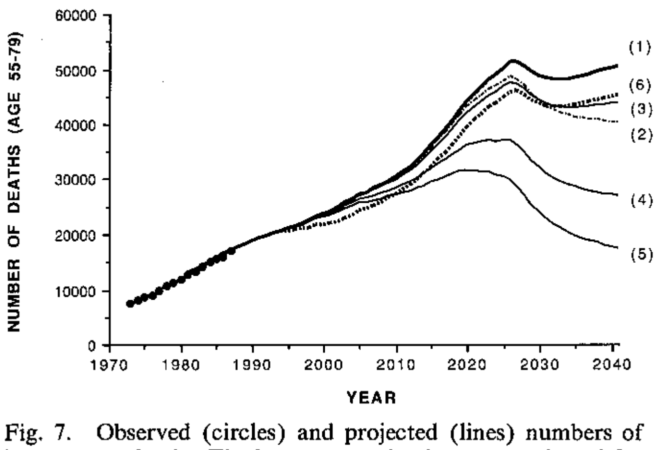

Fig. 7. Observed (circles) and projected (lines) numbers of lung cancer deaths. The lung cancer deaths were projected for six different scenarios of varying smoking and screening status. The parameter settings are the same as in Fig. 6.

The simulation results for six different scenarios as regards smoking initiation rate, smoking cessation rate and screening rate are illustrated with the age-adjusted death rate as the index in Fig. 6 and with the number of deaths among those aged 55 to 79 in Fig. 7. In the present-status simulation, in which the smoking initiation rate of 80%, smoking cessation rate of 0.46% per year and the annual screening rate of 10% persist in the future, the age-adjusted lung cancer death rate is predicted to change with four phases [scenario (1) in Figs. 6 and 7]. It reaches the first peak of 166 per 100,000 in 1989. It then decreases to 148 per 100,000 in 2003, shows an increasing tendency up to 255 per 100,000 in 2028, and stays at this level thereafter. The number of lung cancer deaths, on the other hand, shows a monotonic increase up to 51,225 in 2026, decreases slightly to 47,973 in 2033, and increases again thereafter. In this scenario, the overall smoking rate among those aged 55 to 79 was predicted to decrease from 64% in 1981 to 51% in 2001. It then showed an increasing tendency and reached a plateau of 61% in 2029.

Among the five prevention strategies [scenarios (2)–(6) in Figs. 6 and 7], the increase in screening rate exhibits the most rapid effect on lung cancer deaths. The number of lung cancer deaths decreases to 89% of that of the present-status simulation in 2003 and stays at this level thereafter. Of the five prevention strategies, the modification of smoking initiation rate, on the other hand, is the slowest to show an effect. The number of lung cancer deaths stays as high as 98% of the present-status simulation until 2019. It then shows a decreasing tendency and reaches 80% in 2041. It was predicted that the overall smoking rate among those aged 55 to 79 would decrease to 41% in 2041 in this scenario. The predicted smoking initiation rate was 30% among the cohort born in 2000. The effect of increase in smoking cessation rate appears earlier than that of reduction in smoking initiation rate but later than that of increase in screening rate. When the three levels of increase in annual smoking cessation rate (1%, 3% and 5%) were compared with regard to the relative decreases in the number of lung cancer deaths, the differences between the three scenarios were within 5% until 2005. The differences become more marked thereafter and the numbers of lung cancer deaths in the 3% and 5% annual cessation scenarios become 61% and 40%, respectively, of the 1% annual cessation scenario in 2041. The overall smoking rate among those aged 55 to 79 was predicted to decrease to 46%, 17% and 6% resulting from 1%, 3% and 5% annual cessation, respectively.

DISCUSSION

One interesting finding in the present analysis of observed lung cancer death rates is an increasing trend of age-specific death rates in the 34 to 39 age group (excluding 35), as shown in Table I and Fig. 4. This age group corresponds to the 1934–39 birth cohort in 1973 and the 1948–1953 birth cohort in 1987. The smoking initiation rate estimated from these mortality data was 66% for the 1934 birth cohort versus 80% for the 1950 birth cohort.

The ever-smoker's rates (=current+ex-smokers) observed in Nagano Prefecture (1988) were 69% for the 1934 cohort and 82% for the 1953 cohort, as shown in Fig. 2. A similar trend in ever-smoker's rate was observed in Fukuoka Prefecture (1986); 72% in the 1932–36 cohort versus 81% in the 1952–56 cohort. Therefore, it can be inferred that the observed increase in lung cancer death rate was due to the increase in the smoking initiation rate in the corresponding birth cohort.

The fact that no increasing trend was observed in the 30–33 age group can be interpreted in various ways. First, it might be explained by the existence of the 14-year latency period of smoking-caused lung cancer. Secondly, the factor raising the lung cancer death rates at earlier times may have subsided because the smoking initiation rate stopped increasing in the cohort born after 1953. Finally, it may also be explained by inadequate statistical power in detecting a positive trend due to the small number of deaths in younger age groups. According to the analysis of lung cancer mortality by Mizuno *et al.*,[12] the death rate among smokers expressed by Equation (2) does not exceed that among non-smokers expressed by Equation (1) until the age of 34. This also suggests the existence of a 14-year latency period, independently of the present analysis. The second hypothesis is supported by the observed ever-smoker's rate in Nagano Prefecture as displayed in Fig. 2. The ever-smoker's rate reached a peak of 83% in the 1956 birth cohort then decreased to 74% in the 1968 birth cohort. A similar decreasing tendency was observed in the National Health Survey conducted in 1980; 81% in the 1946–1955 cohort versus 72% in the 1956–1960 cohort.[9] In summary, it can be inferred that the three factors are all to some extent related to the stable death rates for those under 34 years of age.

The estimated smoking initiation rates in the 1923–1950 birth cohorts showed satisfactory agreement with the observed ever-smokers' rates in Nagano and Fukuoka prefectures, as shown in Fig. 2. On the other hand, the difference between estimated smoking initiation rate and observed ever-smokers' rate becomes more marked in the cohort born prior to 1923. This might be explained by a difference in life expectancy between smokers and non-smokers, resulting in a larger proportion of non-smoking survivors in the older age group. Ohtaki[10] proposed that the proportion of smokers may decrease from 70% to as low as 30% solely as a result of better survival among non-smokers. Given that the smoking initiation rate in the cohort born prior to 1923 was closer to the estimated rates, factors related to the lower smoking initiation rates among those born in the 1930's must be sought. The 1935–39 birth cohort became 20 years old from 1955 to 1959, coinciding with the rapid increase in the sale of filtered cigarettes beginning in the late 1950's. In fact, the annual sale of cigarettes increased from 100 billion in the 1950's to 300 billion in 1975, and more than 95% of the latter was filtered cigarettes. The smoking initiation rate was higher than 80% possibly due to wartime rationing of cigarettes to soldiers. It then decreased after World War II, probably due in some part to economic difficulties. The increase in smoking initiation rate afterward might well be explained by the sale of filtered cigarettes as mentioned, together with nationwide economic recovery.

Though the prediction of lung cancer death rates in the near future is not a primary objective of the present study, a comparison of predicted death rates with observed ones recently reported for 1989 and 1990[15, 16] may provide information on the reliability of the present simulation. It was predicted in the present study that the age-adjusted death rate among males aged 55 to 79 would reach a peak of 166 per 100,000 in 1989 and then would begin to decline. The observed age-adjusted death rates for 1989 and 1990 were 174.15 and 173.99, respectively. The observed rate apparently showed a peak in 1989 but it is also true that an increasing trend can be recognized for the observed age-adjusted death rates from 1973 to 1990. The age-specific death rates observed in 1990 were 53.5, 113.7, 190.8, 301.9, and 422.6 for the 55–59, 60–64, 65–69, 70–74 and 75–79 age groups, respectively. The corresponding predicted death rates were 48.6, 98.9, 171.3, 293.5, and 431.4, respectively. The predicted death rates in the 70's showed good agreements, within 3% of the observed rates. The death rates for age 55 to 69, on the other hand, showed poorer agreements, around 10% lower than the observed rates. One possible explanation for this underestimation is that the actual smoking initiation rate for this cohort was higher than that estimated. In fact, the smoking initiation rates estimated for those born in the 1920's and 1930's were lower than the rates observed in Nagano and Fukuoka, as shown in Fig. 2. The difference between observed and estimated smoking initiation rates was up to 12% for Nagano and 14% for Fukuoka. Therefore, the predicted downward trend shown in Fig. 5 might be exaggerated to some extent, because of this underestimation of smoking initiation rate.

The present study predicts that the lung cancer death rates, those in 70–79 age group in particular, will begin to decrease within 10 years. The results of the present study suggest that this future decrease is due to the lower smoking initiation rates in specific birth cohorts and that the death rate will thereafter increase again, reflecting the increase in smoking initiation rate among those born after 1940. Therefore, it is crucial to implement effective preventive measures as soon as possible. Three kinds of preventive measures, i.e., lowering smoking initiation rate, promotion of smoking cessation, and increased screening participation, seem to have characteristic advantages and disadvantages. Lowering the smoking initiation rate at an annual rate of 1% will result in a 20% decrease in the number of lung cancer deaths as well as the adjusted death rate in 2041 when compared with persistence of the present initiation rate of 80% among those born after 1950. Achievement of a 1% annual reduction in smoking initiation rate does not seem to be difficult, as shown in the observed smoking initiation rate in Nagano Prefecture. However, it should also be noted that the effect of reducing the smoking initiation rate will be realized most slowly compared with the other measures. The effect of smoking cessation is realized earlier than the effect of reducing the smoking initiation, as shown in Figs. 6 and 7. Moreover, it is the only measure by which the predicted increase in the number of lung cancer deaths in the coming 50 years can be prevented effectively. The number of lung cancer deaths in 2041 can be reduced to 17,000, the 1987 level, by achieving a 5% annual smoking cessation rate. However, it should also be noted that raising the smoking cessation rate is difficult because of nicotine addiction.[17] The promotion of screening participation seems the promising approach to achieve a rapid decrease in lung cancer deaths. However, the fact that lung cancer deaths can be lowered by only 10% by achieving 100% screening participation indicates that primary prevention is more important in the long run. In conclusion, all three preventive measures should be implemented simultaneously so the disadvantages of any one measure can be offset by the advantages of the others.

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