

Evaluation of Cancer Prevention Strategies by Computerized Simulation Model: Methodological Issues

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A computerized simulation model developed to evaluate the potential impact of primary and secondary prevention is discussed from methodologic perspectives. In the simulation model, named CANSAGE (Cancer Strategy Analysis and Validation of Effect), the natural history of cancer was modeled as a Markovian stochastic process from cancer-free state to death. The lung cancer death rate among Japanese males was projected for 50 years to the year 2041. The simulation showed that the age-adjusted death rate would increase and reach a peak of 166 per 100,000 in 1989 and then decrease to 148 in 2003. It then shows a tendency to increase again, up to 255 in 2028. This change may be attributed to a lower smoking initiation rate among those born in the 1930s. Promotion of mass screening programs exhibits a more prompt effect than antismoking efforts, but the reduction in annual deaths is expected to be only 11%, even if a 100% participation is realized by the year 2000. The reduction in smoking initiation rate, on the other hand, begins to show a visible effect very slowly. It was predicted that a 1% annual reduction in smoking initiation rate would result in a 20% decrease in the number of deaths in 2041. The smoking cessation program is in the middle 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%. The combined application of all three preventive measures seems essential to realize the most effective reduction in lung cancer deaths. — *Environ Health Perspect* 102(Suppl 8):67–71 (1994)

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Introduction

The incidence and mortality rates of cancer have been changing dynamically, reflecting changes in the prevalence of risk factors, promotion of effective screening programs, or improvement of survival rate by new treatment technologies. Therefore, to make the medical and public health services more effective, the forecasting of future trends in cancer incidence and mortality is of particular importance in planning and policy making for health resource allocation. In this article, we discuss a simulation model, CANSAGE (Cancer Strategy Analysis and Validation of Effect) (1,2), which we developed for lung cancer among Japanese males. This model was developed to simulate

potential impacts of both primary and secondary preventive measures on the future incidence and mortality rates. An increase in the lung cancer death rate has been noted among Japanese males in recent decades (3,4). It has been argued that cigarette smoking plays a substantial role in this epidemic and emphasis has been placed on the importance of antismoking efforts (5). On the other hand, the Japanese government recommends a community-based mass screening program as a preventive measure of primary choice. Therefore, evaluation of the potential impacts of smoking cessation programs and mass screening for lung cancer is of crucial importance to plan a comprehensive prevention strategy on a nationwide basis.

Model Description

The simulation model CANSAGE is based on a set of formulas that describe the natural history of cancer as a Markovian stochastic process from cancer-free to preclinical, clinical, and finally to terminal state (Figure 1). We adopted the Markovian stochastic process as the basic structure for several reasons. First, we decided to incor-

porate the preclinical asymptomatic stage into our model, so that the effect of screening can be evaluated in terms of the increase in the number of cases detected and treated successfully during the preclinical stage. Second, we noticed that only limited information is available to evaluate the parameters in the simulation model and that most information for cancer incidence, mortality, and survival is given as yearly

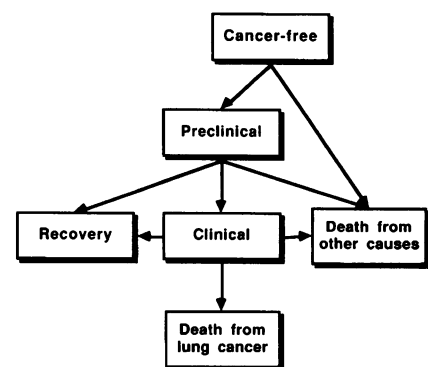


Figure 1. Markovian stochastic model of the natural history of lung cancer.

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aggregate data. Therefore, we decided to make our model as simple as possible, including parameters that are estimable from epidemiologic and clinical data.

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 4th power of age among nonsmokers and by a power of 4.5 of the effective year of smoking among current smokers as follows (6,7):

Rate = r_n (age)⁴ for nonsmokers,

Rate = r_s (effective year of smoking)^{4.5} for current smokers.

The effective year of smoking is the duration of smoking minus the period of cancer growth that 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 (7). 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. (7). The reduction in the relative risk among exsmokers was assumed to be 3% per year, which was estimated recently by a case-control study in Japan (8). The annual smoking cessation rate among smokers was estimated to be 0.46% by regression analysis of the increase in exsmokers among ever-smokers by age (1). The age-specific smoking rates for this analysis were obtained from the National Health Survey of Japan conducted in 1980 (9).

The transition probabilities from preclinical to clinical, clinical to recovery, and clinical to death were estimated simultaneously by the least squares method (1), minimizing the departure of survival functions in the model from the observed survival curves in cases detected by screening and through symptoms (10). The estimated transition probabilities were 0.64 per year, 0.13 per year and 0.69 per year for preclinical to clinical, clinical to recovery, and clinical to death, respectively. The transition probability from preclinical to recovery was estimated to be 0.16/year for participants of 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 (11). The screening participation rate among Japanese males aged 55 to 79 was assumed to be 10% during the period 1973 to 1989 (12).

The probability of death from other causes was estimated separately for smokers, exsmokers, and nonsmokers, based on the age-specific death rates among Japanese

males during 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 (13).

Simulation Procedure

Simulation was conducted separately for smokers, exsmokers and nonsmokers, then results were 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 determined so that the simulated lung cancer death rates during 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 1981 to 1987. For those aged 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 was from 1981 to 2041; 1981 to 1987 was included for the iterative fitting procedure described above. The smoking initiation rates thus estimated in the process of simulation were then compared with observed rates in Nagano Prefecture (40,324 male partici-

pants of a mass screening program in 1988) and in Fukuoka Prefecture (9609 male participants of a mass-screening program in 1986) to check the validity of this procedure.

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. Death rates adjusted to the 1985 model population (14) were used as the index of impact. Two scenarios were provided for the smoking initiation rate among the younger cohorts: the same smoking initiation rate as the cohort born in 1951, and a decrease in the smoking initiation rate at a rate of 1%/year. The smoking cessation rate that originally was set at 0.46%/year was modified to 1, 3, and 5%/year to evaluate the effects of smoking cessation programs on the future deaths. To see the impact of increased participation in screening program, the annual screening rate, originally set at 10%, was modified to 100% in the year 2000 by increasing 10%/year from 1992 to 2000.

Results

Observed and simulated death rates are illustrated in Figure 2 in 5-year age groups from 55 to 59 through 75 to 79. The simulation results displayed in Figure 2 were for those born before 1952, whose smoking initiation rates were available. The observed death rates showed increasing

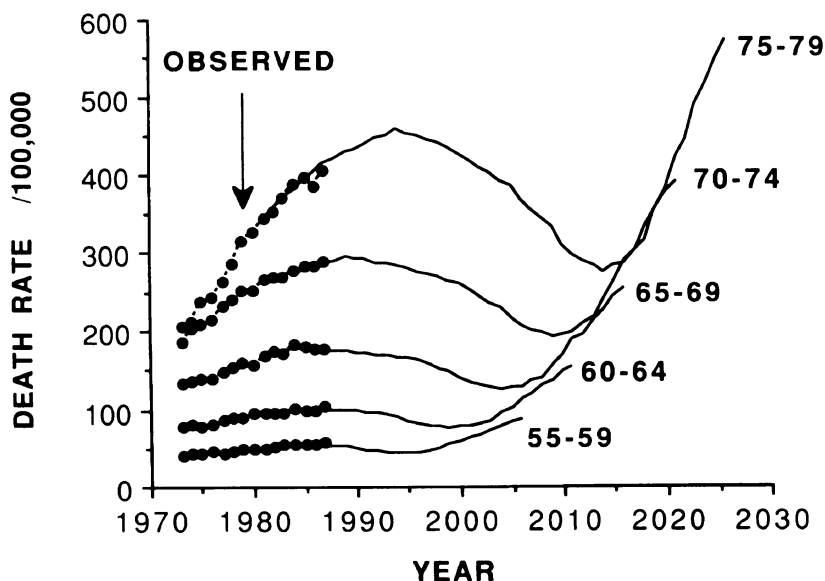


Figure 2. Observed (circles) and projected (lines) lung cancer death rates among Japanese males by 5-year age groups.

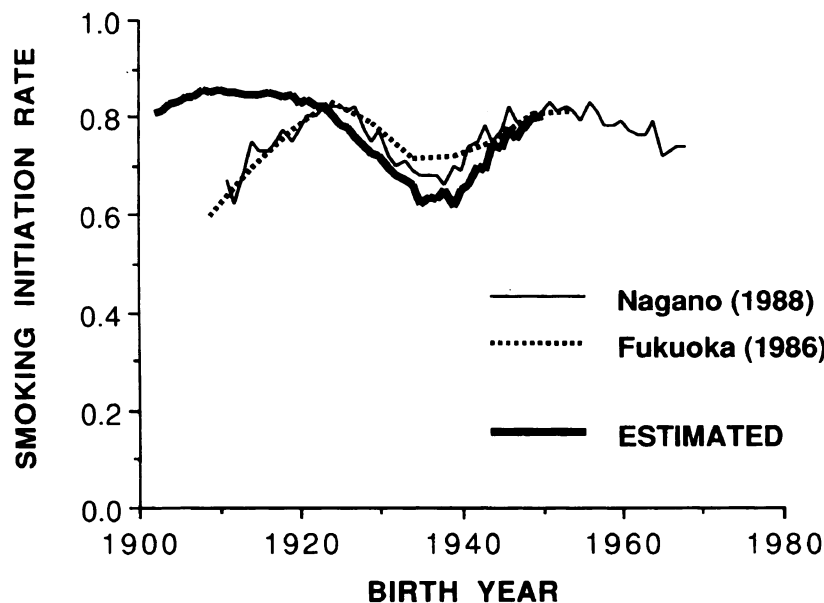


Figure 3. Smoking initiation rates among Japanese males estimated by the simulation as compared to those observed in Nagano and Fukuoka prefectures.

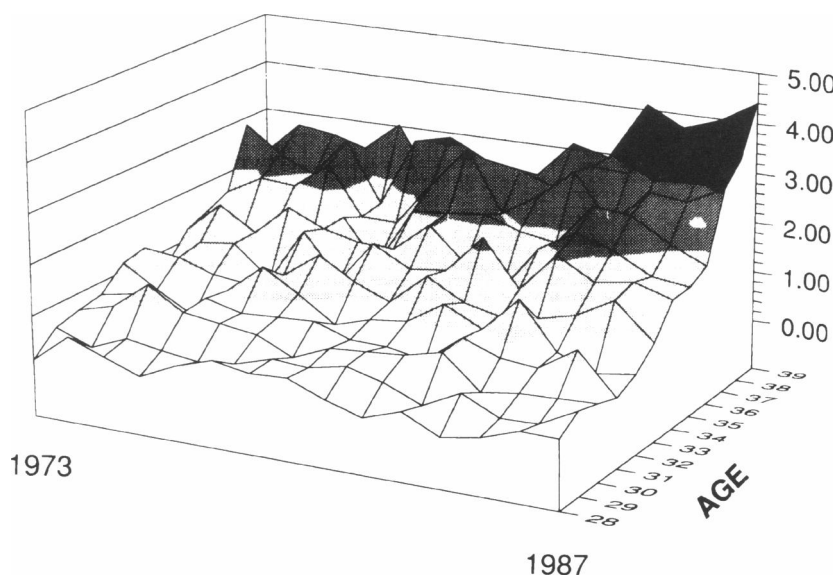


Figure 4. Lung cancer death rates observed among Japanese males aged 28 to 39 during 1973 to 1987.

tendencies in all age groups, with steeper increases in older age groups. The simulated death rate in the 75 to 79 age group showed the largest changes with three phases. It reaches a peak of 457 per 100,000 in 1994, then decreases to the lowest level of 276 per 100,000 in 2014. It shows a tendency to increase again and reaches 616 per 100,000 in 2035. The peak and bottom of the 70 to 74 age group are 296 per 100,000 in 1989 and 190 per 100,000 in 2009, respectively. The shift of

the peak and bottom toward the earlier years indicates that they reflect higher and lower death rates in specific birth cohorts. The peaks correspond to the 1915 to 1919 birth cohort and the bottom to the 1935 to 1939 cohort. The projected death rates for the other age groups showed similar but smaller changes.

The smoking initiation rates estimated by simulation are illustrated in Figure 3. The estimated smoking initiation rate decreased from around 85% among the

Table 1. Poisson regression equations fitted to the increase in lung cancer death rates per million by year 1973 to 1987.

Age	Slope	S.E.	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 ^b
35	0.24	0.25	0.95	0.339
36	0.94	0.25	3.77	0.0002 ^c
37	0.84	0.29	2.93	0.003 ^b
38	0.80	0.31	2.54	0.011 ^a
39	1.27	0.32	3.99	0.00006 ^c

^a $p < 0.05$. ^b $p < 0.01$. ^c $p < 0.001$.

cohorts born prior to 1920 to around 65% among the cohorts born in the 1930s. The rate then showed another rising trend, returning to the level of 80% in the cohort born around 1950. The lower smoking initiation rates among the cohorts born in the 1930s were confirmed by observed rates in Nagano and Fukuoka prefectures (Figure 3). In fact, the observed death rates among those aged 36 to 39 showed an increase during the period from 1983 to 1987 (Figure 4). This age group corresponds to the cohort born between 1944 and 1951, who showed an increase in smoking initiation rate (Figure 3). This was also confirmed by Poisson regression equations fitted to observed death rates as statistically significant increases among those aged 34 and 36 to 39 (Table 1).

The simulation results for six scenarios on the smoking initiation rate, smoking cessation rate, and screening rate are illustrated with the age-adjusted death rate as the index in Figure 5. In the present-status simulation noted in the first scenario, in which the smoking initiation rate of 80%, smoking cessation rate of 0.46% per year, and annual screening rate of 10% persist in the future, the age-adjusted lung cancer death rate is predicted to change with four phases. It reaches the first peak of 166 per 100,000 in 1989. It then decreases to 148 per 100,000 in 2003, shows an increase to 255 per 100,000 in 2028, and stays at that level 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 increase and reached a plateau of 61% in 2029.

Among the five prevention strategies labeled 2 through 6 in Figure 5, the increase in screening rate exhibits the most prompt effect on lung cancer deaths. The number of lung cancer deaths decreases to 89% of that of present-status simulation in 2003 and stays at that level thereafter. On

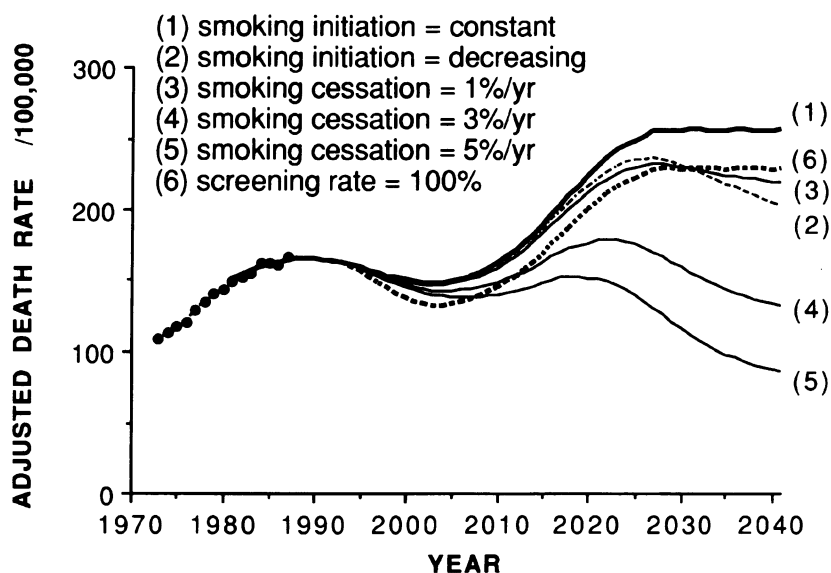


Figure 5. Lung cancer death rates projected according to the six scenarios for the future smoking status and screening (solid and broken lines), as compared to the observed death rates (circles). The death rates are adjusted to the 1985 model population of Japan.

the other hand, of the five prevention strategies, the modification of smoking initiation rate is the slowest to begin to show a visible effect. The number of lung cancer deaths stays as high as 98% of the present-status simulation until 2019. It then shows a tendency to decrease to 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 becomes visible earlier than the reduction in smoking initiation rate but later than the 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. These 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

The projection of future cancer trends can be done by various methods. The most widely used is fitting of linear or nonlinear models to incidence or mortality data and projection using the estimated regression equations. This method gives us a relatively reliable estimate for short-term trend but it does not work well for a long-term trend of more than a few decades, which depends on risk transitions and changes in medical and public health practices. An alternative method used by many epidemiologists is to calculate the incidence or mortality rate expected for a hypothetical population with a certain prevalence rate of risk factor, based on the relative risk and the prevalence rate of the risk factor measured in the real population. This method is useful to make an insight into a limiting state that might be achieved in the long run, but it cannot be used to predict a dynamic change in cancer occurrence because it does not take time into account.

The present method based on the Markovian stochastic process is a hybrid of the two methods mentioned above, in the sense that the effects of smoking and screening were incorporated as time-dependent factors and that fitting procedure was adopted by leaving the birth cohort specific smoking initiation rate as a variable to be fitted. Several features should be mentioned for the present method. First, the

Markovian stochastic model is flexible in model building. Modeling can be started from the simplest model with only a causal factor and an outcome such as death, and then can be improved by incorporating additional compartments. Second, it is easy to evaluate the parameters in the model, based on existing epidemiologic and clinical data, since the transition rates connecting two compartments in the model are the same as annual rates reported in epidemiology literature and in government statistics.

The present method might have sacrificed reliability of results by pursuing simplicity in model building and parameter setting. To assess the sensitivity of simulation results for a subtle change in parameter values, the value of each parameter was modified to 90 and 110%, and the change in the number of lung cancer deaths in 2001 was compared (1). Of six parameters examined, the transition rate from clinical to recovery caused the largest change (1.4%), followed by the transition rate from clinical to lung cancer death (Table 2). The influences were less marked for other parameters.

One interesting finding in the present analysis of observed lung cancer death rates is an increasing trend of age-specific death rates in the 36 to 39 age group (Table 1, Figure 4). This age group corresponds to the 1934 to 1937 birth cohort in 1973 and the 1948 to 1951 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-smokers' rates (=current + exsmokers) observed in Nagano Prefecture (1988) were 69% for the 1934 cohort and 82% for the 1953 cohort (Figure 3). A similar trend in ever-smoker's rate was observed in Fukuoka Prefecture (1986); 72% in the 1932 to 1936 cohort versus 81% in the 1952 to 1956 cohort. The 1935 to 1939 birth cohort became 20

Table 2. Relative changes in the number of lung cancer deaths in 2001 when the parameter values are modified to 90% and 110%.

Parameter	Modified parameter value, %	
	90%	110%
Pr (clinical to recovery) ^a	+1.40	-1.40
Pr (clinical to lung cancer death)	-1.13	+0.99
Annual risk reduction in ex-smokers	+0.86	-0.70
Screening sensitivity	+0.13	-0.13
Pr (preclinical to recovery)	+0.13	-0.13
Pr (preclinical to clinical)	+0.07	-0.05

^aPr (A to B) indicates the transition probability from state A to state B.

years old from 1955 to 1959, coinciding with the rapid increase in the sale of filtered cigarettes beginning in the late 1950s. In fact, the annual sale of cigarettes increased from 100 billion in the 1950s to 300 billion in 1975, more than 95% of which were filtered cigarettes. The smoking initiation rate was higher than 80% before 1945, possibly due to wartime rationing of cigarettes to soldiers. It then decreased, 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 restoration.

The present study predicted that the lung cancer death rates, those in 70 to 79 age group in particular, would 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 increase again, reflecting

the increase in smoking initiation rate among those born after 1940. Therefore, it is crucially important 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 both 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 the present persistent 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 (Figure 5). 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, raising the smoking cessation rate is difficult because of nicotine addiction (15). The promotion of screening participation seems the most promising in realizing 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 that the disadvantages of one measure can be offset by the others.

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