Original Article

Modeling Excess Lung Cancer Risk Among Screened Arm Participants in the Mayo Lung Project

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BACKGROUND: The Mayo Lung Project (MLP) was a randomized clinical trial designed to test whether periodic screening by chest x-ray reduced lung cancer (LC) mortality in men who were high-risk smokers. Among MLP participants, there were more deaths from LC in the screening arm both at the trial's end and after long-term follow-up. Overdiagnosis was cited widely as an explanation for the MLP results, whereas a role for excess LC risk attributable to undergoing numerous chest x-ray screenings largely was unexamined. The authors of this report examined the consistency of the MLP data with a modified 2-stage clonal expansion (TSCE) model of excess LC risk. **METHODS:** By using a simulation model calibrated to the initial MLP data, the authors examined the expected statistical variance of LC incidence and mortality between the screening and control arms. A Bayesian estimation framework using a modified version of the TSCE model to evaluate the role of excess LC risk attributable to chest x-ray screening was derived and applied to the MLP data. **RESULTS:** Simulation experiments indicated that the overall difference in LC deaths and incidence between the study arm and the control arm was unlikely ($P = .0424$ and $P = .0104$, respectively) assuming no excess risk of LC. The authors estimated that the 10-year excess LC risk for a man aged 60 years who smoked and who received 10 chest x-ray screenings was 0.574% ($P = .0021$). **CONCLUSIONS:** The excess LC risk observed among screening arm participants was found to be statistically significant with respect to the TSCE model framework in part because of the incorporation of key risk correlates of age and screen frequency into the estimation framework. ***Cancer* 2010;116:122–31.** *Published 2010 American Cancer Society**

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The Mayo Lung Project (MLP) was a randomized clinical trial designed to test whether a mortality benefit attributable to screening for lung cancer (LC) by chest radiography exists. The MLP is considered a watershed trial, in that it altered views regarding the role of early detection by chest radiography in screening for LC; the interpretations of its findings are still debated. When the MLP began recruiting participants in 1971, the Mayo Clinic endorsed annual chest radiograph screening for smokers. However, in the MLP, despite the detection of greater numbers of early stage cancers in the screening arm, there were more LC deaths in the screening arm than in the control arm.[1,2] After a follow-up study with a median of 20.5 years, an even greater excess of LC deaths was discovered in the screening arm.[3] After a second follow-up study with a median duration of 23.5 years, the difference in the total number of incident cases also increased.[4] The interpretation of these MLP findings by the medical community, was, at best, that they were inconclusive and, at worst, that they contradicted any benefit of screening. Because of the risks associated with early intervention based on a positive and potentially false-positive screening result, no national cancer advisory source currently endorses LC screening in the broader population.[5,6]

It has been proposed that the MLP results are consistent with high rates of overdiagnosis.[3,4,7,8] Overdiagnosis occurs in the event that, through early detection, a disease state is identified that does not shorten the patient's life expectancy.

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However, a pathologic review of the patients who had LC detected in the MLP confirmed the histologic diagnosis of cancer in all patients who were studied, although a higher rate of carcinoma in situ detected in the screening arm was noted.[9] Other studies indicate that the power of the MLP may have been lower than initially planned and that the MLP findings were not inconsistent with a model of moderately aggressive tumor progression and a modest mortality benefit.[10,11] The inconclusive findings of the MLP have also led to debate regarding whether randomized clinical trials are an efficient way to study the benefits of screening.[12,13]

A flaw in the argument that the observed MLP results are consistent with overdiagnosis is that overdiagnosis does not explain the greater number of LC deaths in the screening arm, nor does it explain the greater cumulative LC incidence in the screening arm after extended follow-up. These findings hint at the presence of a systematic source of excess risk that predisposed the screening arm participants to higher rates of LC. Radiation is a known epidemiologic risk factor for many cancers, including LC. The MLP regimen prescribed chest radiographic screening 3 times a year for a period of 6 years, for a total of 18 screens. In practice, some screening arm participants received more than the prescribed number; if a screen was inconclusive, then the participant often would return for a follow-up screen before the next scheduled screen. The objective of the current report is to confront the findings of the MLP study, as well as the hypothesis of overdiagnosis, with independently obtained estimates of the effect of chest x-ray exposure that are calculated using mathematical modeling.

Mathematical Models of Carcinogenesis

It has been established that the process of carcinogenesis is comprised of multiple stages. Mathematical models of this multistage process have been formulated and fit to epidemiologic data, offering a mechanistic explanation of age-related and exposure-related patterns of cancer incidence. According to the 2-stage clonal expansion (TSCE) model, the process of carcinogenesis is governed by 2 rate-limiting stages.[14] A normal cell (NC) first must transform to become an intermediate cell (IC), an irreversible step (initiation). Next, an IC must give rise to a malignant cell (MC), which gives rise to cancer with certainty (transformation). The TSCE model parameterization also accounts for the clonal expansion of ICs (promotion), a key model feature that is used to account for exposure effects, such as smoking in carcinogenesis models of lung cancer.[15] Extensions of the TSCE model include a wide range of multistage stochastic models of carcinogenesis that account for initiation, promotion, and progression.[16,17] An earlier, distinct mathematical model of carcinogenesis by Armitage and Doll allowed for several rate-limiting stages but not for the clonal expansion of ICs.[18]

Atomic Bomb Survivor Data

Estimates of excess LC risk attributable to radiation from medical imaging are based largely on models derived from data on Japanese atomic bomb survivors from Hiroshima and Nagasaki that were collected as part of the extended Life Span Study (LSS). These estimates are approximately 2 orders of magnitude lower than what would be needed to explain the LC incidence trends in the MLP.[19,20] Current estimates of chest x-ray lung organ dose range from 0.06 millisievert (mSv) to 0.25 mSv,[21,22] whereas dose estimates reported at the time of the MLP were higher (approximately 0.7 mSv[23]). Estimates of excess LC risk attributable to chest x-ray rely on linear scaling of estimated excess relative risk per sievert[24]; if the true model is somewhat less than linear, then estimates of excess LC risk based on these models will be higher. Moreover, the excess LC risks derived from the LSS may be underestimated substantially with respect to the MLP cohort, primarily because the MLP participants were older and therefore had longer smoking histories at the time of enrollment.

According to the TSCE model, if the pool of NCs remains constant in adults and radiation acts only to transform NCs to ICs, then the absolute excess LC risk attributable to radiation exposure at a fixed time since exposure should not increase with age at exposure. Several analyses of the LSS data have indicated that it is consistent with a TSCE model parameterization that assumes radiation acts only to induce NCs to become ICs[25,26] (initiation effect). An age-at-exposure effect on radiation-induced initiation rates is rejected despite evidence that birth cohort effects are significant in estimating the parameters of the TSCE model.[25] A study using the Armitage-Doll model also supports the absence of an age-at-exposure effect on stage transition rates for most solid cancers.[27] An analysis that merges data on smoking history and radiation exposure suggests that the observed higher excess relative risk among older LSS individuals is a spurious finding that reflects differences in smoking histories by birth cohort and indicates that the joint effect of radiation exposure and smoking is consistent with an additive

but not with a multiplicative effect.[28] This latter result supports a model in which both radiation exposure and smoking act synchronously to increase the pool of ICs (through initiation), but radiation does not act on the ICs directly (through promotion or transformation).

The original publication of the LSS data reported that the excess LC relative risk was nearly 3 times higher in individuals aged >40 years at exposure compared with individuals between ages 25 years and 39 years at exposure and persisted over time.[29,30] This finding, as discussed, has been attributed to birth cohort differences in smoking histories among LSS participants.[28,30] However, a close inspection of the LSS data in which smoking histories are incorporated indicates that this data subset is approximately 50% the original size with an age-at-exposure distribution shifted to the left because of the requirement that cohort members had to be alive at the time smoking histories were collected. The excess LC mortality risk observed in the MLP is restricted to the group of individuals who were aged ≥60 years at the conclusion of the MLP, a group that had virtually no representation in the combined smoking and LSS dataset.[3,28]

Other modeling studies have suggested that the LSS data are more consistent with a radiation effect on both promotion and initiation[31,32] than with an initiation effect alone. Furthermore, because of a delay in data collection after the bombings, "second-hit" LCs that arose during the earliest time window necessarily were absent from the dataset. In addition, several case-control studies examining the risk of second cancers after radiation treatment for a primary cancer do suggest a significant super-additive effect of smoking and radiation.[33-35]

Theoretical considerations of the TSCE model may help reconcile the conflicting studies on excess LC risk. If radiation acts on both rate-limiting stages, then its observable effect on the second stage will be negligible in younger individuals because of the small number of ICs.[14] Thus, as individuals age, the effect of radiation on the second stage will increase because of the growing population of ICs. Smoking will tend to enhance this effect of age because of its role in promotion and initiation. Consequently, the absence of an age-at-exposure effect and an observed additive relation between smoking and radiation are expected as long as the accumulated number of ICs is small. Current models derived from the LSS data assume that either excess LC risk or excess LC relative risk depend on sex and smoking history but not on age at exposure,[19,20] which is most consistent with a relatively young exposure group, such as the LSS data subset from which they are derived.[28]

The original TSCE model parameterization assumes that, if an acute exposure acts on the second transition rate, then the excess risk will be evident after a short lag time after the exposure. A literal interpretation of the TSCE model is that ICs comprise a homogeneous group of cells, all of which have accumulated a single mutation. The "second hit" occurs when the complementary gene is mutated, resulting in a loss of function phenotype. We allow for the population of ICs to be heterogeneous while sharing a common growth advantage as well as an increased probability of acquiring a subsequent mutation. However, the number of mutations in any particular IC is random, as are the number of total mutations needed to result in a cancer phenotype. It follows that an acute radiation exposure may act on an existing population of ICs either to directly induce a second hit or to irreversibly increase the probability of a second transition.

MATERIALS AND METHODS

Data, Methods, and Models

MLP: Description and essential data

The MLP was initiated in 1971 and completed on July 1, 1983.[1,2] A summary of the MLP findings is presented in Table 1. The original data collected during the MLP trial were made available to Cancer Intervention and Surveillance Modeling Network (CISNET) participants. These data contain individual patient medical and smoking histories at the time of enrollment, annual follow-up questionnaire results, chest x-ray visit dates and findings, cytology results, and death records. Data from the 2 follow-up studies were provided by Pamela Marcus, PhD, of the National Cancer Institute.[3,4] We merged the original MLP data with the follow-up data to form a unified MLP dataset.

Mathematical model of natural course of disease

A mathematical model of the natural course of LC in a screened population was described previously and was calibrated to the initial 7 years of MLP data.[10] We modify the model of the natural course of LC in 2 ways. We use a table of smoking history and age-dependent annual hazard rates to simulate the age at death by causes other than LC. This hazard table was developed by Marjorie Rosenberg, PhD, and was provided as a CISNET resource. Furthermore, we sample age at enrollment from the empirical

Table 1. Lung Cancer Incidence and Mortality in the Mayo Lung Project

Time Frame	Screened Arm	Control Arm	Difference (S−C)
First 7 y			
LC incidence	151	120	31
LC deaths	82*	70	12
Other-cause deaths	608	601	7
After follow-up†			
LC incidence	585	500	85
LC deaths	337	303	34
Other-cause deaths	2151	2139	12

S indicates screening arm; C, control arm; LC, lung cancer.
* Included 5 study-related deaths.
† The median was 20.5 years for mortality data and 23.5 years for incidence data.

distribution of MLP participants. We calibrate to the observed early stage incidence, late-stage incidence, LC deaths, and other-cause deaths in the first 7 years of the MLP (N = 2500).

We project LC mortality and incidence in the follow-up period, extending the time frame of the simulation from 7 years to 24 years. We separately use 2 different models of screening frequency in the follow-up period. The first model assumes that, on completion of the MLP, the screen frequency of adherent screening arm participants reverts to baseline levels of random periodic screening. The second model assumes that, on completion of the MLP, screening arm participants receive annual screening for a period of random duration, averaging 10 years, after which they revert to baseline levels of random periodic screening.

Framework for estimating excess LC risk

We describe a biological framework for estimating excess LC risk resulting from repeated chest x-ray screens. As in the TSCE model, we assume 2 rate-limiting steps in the carcinogenesis process, namely the transition from NCs to ICs and the transition from an IC to the first MC. Because of their smoking histories, we assume that, by age 40 years, MLP participants have accumulated x_0 ICs, which is an exponential random variable with parameter λ: $x_0 \sim \exp(\lambda)$. We assume that a minimum number of z ICs has accumulated in an individual by age 40 years, so that x_0 has a lower bound of z. Whereas the total number x_0 of ICs at age 40 years is stochastic, we assume that, subsequently, the number of ICs increases deterministically each year by a common factor $\{c_i\}$, in which i represents indexing by attained age. The probability that a single IC becomes an MC in a given year is μ_s. Given an a priori set of discrete-time annual probabilities $\{k_i\}$ of developing LC at age i, we can express each k_i in terms of the parameters λ, μ_s, c_i, and z. As in the original natural course of LC model, we assume that the age of LC onset follows a right-skewed triangular distribution, such that $k_i = c(i - 39)$, where c is a constant.

In our model, radiation acts directly on the ICs to increase their genetic instability. For the periods during and before the MLP, we assume that the distribution of age at LC onset is not influenced by radiation exposure because of screening. However, after the MLP has concluded, the probability that an IC becomes an MC increases to $\mu_s + k\mu_r$ for an individual who has received k screens. Consistent with the assumption of the deterministic growth of ICs, it is assumed that the number of ICs is sufficiently large such that radiation exposure does not influence the total number of ICs nor their annual growth rate.

To summarize our estimation methodology, first, we optimize the fit of the triangular LC age-of-onset distribution to the control arm data. This step entails adjusting the probability that a single IC transforms into an MC in a given year to $\mu'_s = \mu_s + \mu_{adj}$ and estimating the ratio $r_{adj} = (\mu_s + \mu_{adj})/\mu_s$ directly from the control group data, where adj is adjusted. Next, we estimate the ratio $r_r = (\mu'_s + \mu_r)/(\mu'_s)$ from the screening arm data and evaluate whether r_r is significantly greater than 1.

Mathematical Formulation of the Model

The annual probability of LC onset at age i in the absence of radiation exposure, k_i, can be expressed as a function of the model parameters as follows:

$$k_i = \int_z^\infty (1-\mu_s)^{\sum_{t=40}^{i-1} x_0 c_t}\left[1-(1-\mu_s)^{x_0 c_i}\right] \lambda e^{-\lambda(x_0 - z)} dx_0,\ i = 40, \ldots, 85. \quad (1)$$

Solving the integral in Equation 1, we obtain:

$$k_i = \frac{-\lambda(1-\mu_s)^{z\sum_{t=40}^{i-1} c_t}}{\left(\sum_{t=40}^{i-1} c_t\right)\ln(1-\mu_s) - \lambda} + \frac{\lambda(1-\mu_s)^{z\sum_{t=40}^{i} c_t}}{\left(\sum_{t=40}^{i} c_t\right)\ln(1-\mu_s) - \lambda}, i = 40, \ldots, 85. \quad (2)$$

We note that

$$c_{40} = 1, \{c_i : i < 40\} = \{0\},\ k_{40} = 1 + \frac{\lambda(1-\mu_s)^z}{\ln(1-\mu_s) - \lambda}.$$

Therefore,

$$\lambda \approx \frac{\mu_s(1-k_{40})}{e^{-\mu_s z} - (1-k_{40})} \quad (3)$$

$$\sum_{t=40}^{i} k_t \approx 1 + \frac{\lambda(1-\mu_s)^{z\sum_{t=40}^{i} c_t}}{(\sum_{t=40}^{i} c_t)\ln(1-\mu_s) - \lambda}.$$

Setting

$$x_i = (1-\mu_s)^{z\sum_{t=40}^{i} c_t}$$

and assigning a value to $\mu_s z$, we can apply the Newton method to solve for each x_i in the following equation:

$$\sum_{t=40}^{i} k_t - 1 \approx \frac{\lambda z x_i}{\ln x_i - \lambda z},$$

and thereby obtain solutions for $\{c_i\}$. Provided that $e^{-\mu_s z}$ is sufficiently greater than $(1 - k_{40})$, the quantity $\mu_s z$ has little influence on the solutions for $\{c_i\}$. In this scenario, the probability that LC onset will occur at age 40 years in an individual with z ICs is negligible, consistent with maximal variance in the number of ICs at age 40 years. If the lifetime probability of IC transition increases from μ_s to $\mu_s + \mu_{adj}$, then we let $r_{adj} = (\mu_s + \mu_{adj})/\mu_s$, and we rearrange Equation 2, resulting in

$$k'_i \approx \frac{-\lambda z (x_{i-1})^{r_{adj}}}{r_{adj}\ln(x_{i-1}) - \lambda z} + \frac{\lambda z (x_i)^{r_{adj}}}{r_{adj}\ln(x_i) - \lambda z}. \quad (4)$$

However, our model assumes that excess LC cases attributable to screening exposure are expected only after the MLP has concluded, resulting in a further modification of Equation 4. We define $r_r = (\mu'_s + \mu_r)/\mu'_s$ and $r = (\mu'_s + k\mu_r)/\mu_s$, in which k is the number of screens received during the MLP, such that the relation between r_{adj}, r_r, and r is defined by

$$r = r_{adj}(1 + (r_r - 1)k)$$

For a screening arm participant who received k screens and completed the MLP at age a, we define

$$r_{a,i} = \sum_{t=a+1}^{i} c_t / \sum_{t=40}^{i} c_t$$

and express the annual probability of lung cancer after age a as follows:

$$k'_i \approx \frac{-\lambda z (x_a^{r_{adj}})(x_{i-1})^{rr_{(a,i-1)}}}{r_{adj}\ln(x_a) + rr_{(a,i-1)}\ln(x_{i-1}) - \lambda z} + \frac{\lambda z (x_a^{r_{adj}})(x_i)^{rr_{(a,i)}}}{r_{adj}\ln(x_a) + rr_{(a,i)}\ln(x_i) - \lambda z}, \forall i > a. \quad (5)$$

Likelihood-Based Estimation of the Model Parameters

We isolate data from the individuals who were alive at the end of the first 7 years of the MLP trial and were eligible for inclusion in the long-term follow-up analysis of LC mortality. Outcomes are coded to reflect 3 possibilities: the participant was alive at the end of the follow-up period, he died of LC, or he died of other causes. If a participant died of other causes or was alive at the end of the follow-up period, then this record is censored with respect to LC onset. Given a censoring event at age t, age at enrollment a_0, we apply the Bayesian data-augmentation algorithm[36] to generate an age of LC onset x from the distribution:

$$\Pr[x = i | a_0, (s+x) \geq (a_0+7)] = \frac{k_i \Pr[s > (t-i)]\mathrm{I}_{\{a_0 \leq i < t\}} + k_i \mathrm{I}_{\{i \geq t\}}}{1 - \sum_{j=40}^{a_0-1} k_j - \sum_{j=a_0}^{a_0+6} k_j \Pr[s \leq (a_0+7-j)]} \quad (6)$$

The time of LC progression from LC onset to death, s, has a distribution that is a convolution of 2 exponential distributions.[10] By using the augmented data, a likelihood function can be defined according to the following 3 scenarios:

Censored data—LC onset at age i after data-augmentation:

$$\Pr[x = i | a_0, (s+x) \geq (a_0+7)] = \frac{k_i \Pr[s > (a_0+7-i)]\mathrm{I}_{\{a_0 \leq i \leq a_0+6\}} + k_i \mathrm{I}_{\{i \geq a_0+7\}}}{1 - \sum_{j=40}^{a_0-1} k_j - \sum_{j=a_0}^{a_0+6} k_j \Pr[s \leq (a_0+7-j)]}$$

Censored data—No LC onset after data augmentation:

Table 2. Simulated Lung Cancer Incidence and Deaths Compared With Mayo Lung Program Data in the 7-Year Period After Prevalence Screening

	Simulated	MLP
Screening arm		
Stage I incidence	70.7	79*
Late-stage incidence	71.4	72†
LC deaths	71.2	82
Other-cause deaths	675.3	608
Control arm		
Stage I incidence	38.1	34
Late-stage incidence	85.9	86
LC deaths	74.4	70
Other-cause deaths	675.7	601

MLP indicates Mayo Lung Project; LC, lung cancer.
* Includes 16 sputum-detected cancers that were not visible by chest radiography at the time of detection.
† Includes 2 sputum-detected cancers that were not visible by chest radiography at the time of detection.

$$\Pr[x=\infty|a_0,(s+x)\geq(a_0+7)] = \frac{1-\sum_{j=a_0}^{85}(k_j\Pr[s>(a_0+7-j)]\mathrm{I}_{\{a_0\leq j\leq a_0+6\}}+k_j\mathrm{I}_{\{j\geq a_0+7\}})}{1-\sum_{i=40}^{a_0-1}k_j-\sum_{i=a_0}^{a_0+6}k_j\Pr[s\leq(a_0+7-j)]}$$

LC death in original follow-up dataset at age t:

$$\Pr[d=t|a_0,(s+x)\geq(a_0+7)] = \frac{\sum_{j=a_0}^{t}k_j\Pr[(t-j)<s<(t-j+1)]}{1-\sum_{j=40}^{a_0-1}k_j-\sum_{j=a_0}^{a_0+6}k_j\Pr[s\leq(a_0+7-j)]}.$$

We estimate r_{adj} using Bayesian data augmentation as follows: 1) augment control arm data n times according to Equations 4 and 6 with the initial condition: $r_{adj}=1$; 2) obtain the maximum likelihood estimate (MLE)of r_{adj} ($\hat{r}_{adj}$) for each of n iterations; 3) compute the mean value of r_{adj} over the n iterations; and 4) repeat Step 1 with the mean of $\hat{r}_{adj}$ from Step 3 until the mean value of $\hat{r}_{adj}$ converges to the starting value.

To estimate r_r, we augment the study arm data n times according to Equations 5 and 6 with the initial conditions $r_{adj}=\hat{r}_{adj}$, $r_r=1$, allowing only r_r to vary in the estimation procedure. To test the significance of $\hat{r}_r$, at each iteration of Step 4, we compute the likelihood ratio, composed of the ratio of the likelihood with $r_{adj}=\hat{r}_{adj}$, $r_r=\hat{r}_r$ to the likelihood with $r_{adj}=\hat{r}_{adj}$, $r_r=1$. According to statistical theory, twice the negative logarithm of the likelihood ratio has a chi-square distribution with 1 degree of freedom. We validate the null distribution by bootstrapping the control arm data n times, applying data augmentation, and computing the P value of the log-likelihood ratio under the chi-square assumption. Under the null distribution, a uniform distribution of P values is expected and observed. If the median P value in the augmented study arm sample (after convergence) is $<.05$, then we conclude that $\hat{r}_r$ is significant.

Simulations Using the Estimated Distribution of {k$_j$} and Calculation of LC Excess Risk

We incorporate the parameter r_r into the original $\{k_i\}$, according to Equation 5, assuming $r_{adj}=1$ to rescale the mortality-derived estimates to fit an incidence distribution. We compute the 10-year excess LC probability for an individual who has received 5, 10, or 20 screens at the conclusion of the MLP for attained ages of 50 years, 60 years, or 70 years. We also incorporate $\{k'_i\}$ into our original simulation model and compare the simulation results with the observed follow-up data on incidence and mortality.

RESULTS

Model Calibration and Stochastic Variability

Table 2 compares the simulated LC incidence and deaths in the first 7 years with the deaths and incidence observed in the MLP. Figure 1 illustrates the simulated mean annual incidence cases for both the stop-screen and ongoing-screen models and the simulated annual LC deaths for the stop-screen model over the duration of the median follow-up period of mortality and incidence. The difference in the simulated mean annual LC deaths between the stop-screen model and the ongoing-screen model is negligible, and only the stop-screen model is shown. Table 3 summarizes these simulation results.

We evaluated the stochastic variability of our simulation results with respect to the observed differences in cumulative LC incidence and mortality (screening − control). Among the 2500 individual trajectories in our simulations, we report the frequency of observing a difference in the cumulative LC incidence $\geq$85 cases after 23.5 years of follow-up. In the stop-screen model, there were 10 such trajectories ($P=.004$); whereas, in the ongoing-screen model, there were 26 such trajectories ($P=.0104$). We also report the frequency of observing a difference in the cumulative LC deaths (screening − control) $\geq$34 cases after 20.5 years of follow-up. In the stop-screen model, there were 132 such trajectories ($P=.0528$) and, in the ongoing screen model, there were 106 such trajectories ($P=.0424$) (Table 4).

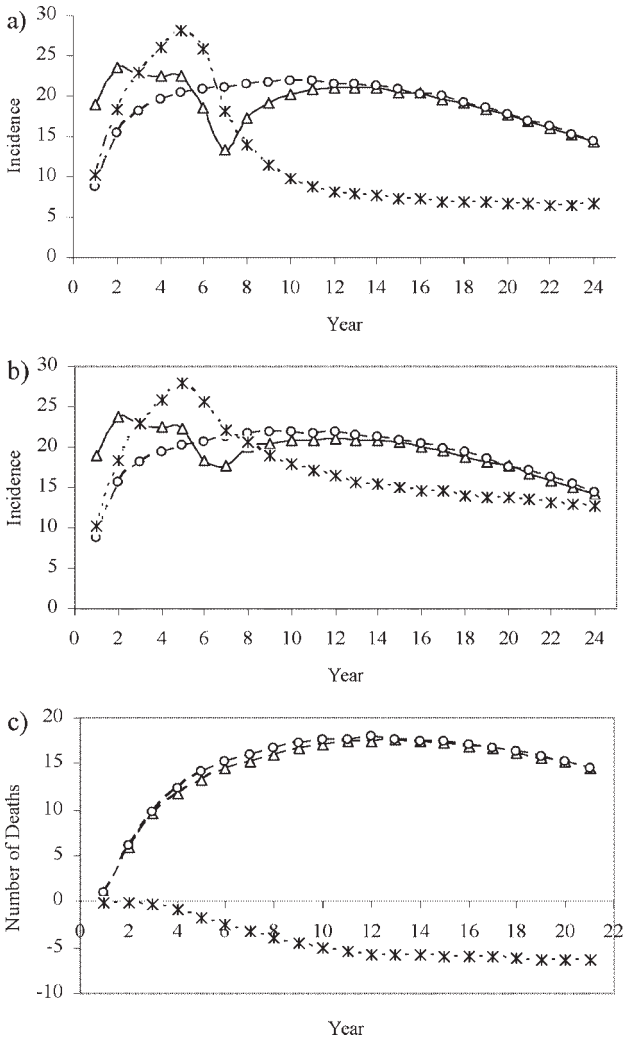

Figure 1. Simulated annual lung cancer (LC) incidence, annual LC deaths, and cumulative differences in LC incidence and LC deaths (screening – control) are shown. (a) Mean counts of LC cases per year are shown, assuming a stop-screen model. (b) Mean counts of LC cases per year are shown, assuming an ongoing screening model. (c) Mean counts of LC deaths per year are shown, assuming a stop-screen model. Open triangles indicate the screening arm; open circles, the control arm; asterisk, cumulative difference.

Maximum Likelihood Estimation of Excess Risk

Beginning with the initial value of $r_{adj} = 0.925$ in the augmentation procedure, we obtain a median MLE of $r_{adj} = 0.925573$ and a mean MLE of 0.9261446 after 120 iterations, illustrating convergence of the estimate of r_{adj}. Next, we verify the assumed null chi-square distribution. The distribution of P values resulting from the likelihood ratio test after 30 iterations is approximately uniform with a median P value of .437. Beginning with the initial values $r_{adj} = 0.925$ and $r_r = 1.008$, we obtain a median MLE of $r_r = 1.00823$ and a mean MLE of $r_r = 1.0080$ after 125 iterations. The median P value resulting from these 125 iterations is $P = .0021$.

Incorporating the parameter $r_r = 1.008$ ($P = .0021$) into the original age-at-onset distribution, we estimate that the 10-year excess LC probability for a man who is a smoker aged 60 years having received 10 chest x-ray screens is 0.574%. The relation between 10-year excess LC probability, attained age, and screen frequency is depicted in Figure 2.

Simulation of the Natural Course of LC Assuming Excess Risk and Stochastic Variability

We repeat the MLP simulations after updating the annual probabilities of LC onset $\{k'_i\}$ with our obtained estimate of r_r. Within the spectrum of 1000 individual trajectories in our simulations, we examined the frequency of observing a difference in the cumulative LC incidence (screening − control) $\geq$85 cases after 23.5 years of follow-up. In the stop-screen model, there were 42 such trajectories ($P = .042$); and, in the ongoing-screen model, there were 53 such trajectories ($P = .053$). We also examined the frequency of observing a difference in the cumulative LC deaths (screening−control) $\geq$34 cases after 20.5 years of follow-up. In the stop-screen model, there were 147 such trajectories ($P = .147$) and, in the ongoing-screen model, there were 115 such trajectories ($P = .115$).

DISCUSSION

The usual interpretation of the MLP findings is that there is strong evidence that screening for LC is plagued by overdiagnosis. In particular, there was no reduction in LC mortality after the trial or after long-term follow-up,[3] and the cumulative incidence of total LC cases in the control arm did not "catch up" to the cumulative incidence of total LC cases in the screening arm.[4] However, overdiagnosis does not explain the excess LC deaths in the screening arm or the steady increase in LC cases after the end of the MLP. At the end of 20.5 years of median follow-up, there were 34 more LC-attributed deaths in the screening arm compared with the control arm. There were 31 more reported LC cases in the screening arm versus the control arm at the end of the initial 7 years of the MLP. At the end of 23.5 years of median follow-up, there were 85 more LC cases detected in the screening arm compared with the control arm.

Table 3. Simulated Lung Cancer Incidence and Deaths Compared With Mayo Lung Project (MLP) Follow-Up Data

	Stop-Screen Model	Ongoing-Screen Model	MLP
Screening arm			
LC incidence	453.6	460.5	585
LC deaths	296.1	293.9	337
Other-cause deaths	2425.6	2425.9	2151
Control arm			
LC incidence	447.1	447.7	500
LC deaths	302.4	302.8	303
Other-cause deaths	2421.1	2420.5	2139

LC indicates lung cancer.

Table 4. Measures of Variation in Cumulative Lung Cancer Incidence and Deaths Within 2500 Simulated Trajectories Over the Median Follow-Up Period*

Measure of Variation	Stop-Screen Model	Ongoing-Screen Model
Minimum incidence difference (S−C)	−100	−95
Maximum incidence difference (S−C)	105	128
No. of trajectories with an incidence difference ≥85	10†	26‡
Minimum difference in LC deaths (S−C)	−96	−99
Maximum difference in LC deaths (S−C)	78	73

S indicates screening arm; C, control arm; LC, lung cancer.
*The median was 20.5 years for mortality data and 23.5 years for incidence data.
†$P = .004$.
‡$P = .0104$.

We examined the stochastic variability within our simulation model that encompassed the time frame of the long-term incidence and mortality follow-up and discovered that the observed long-term incidence and mortality results deviated significantly from the expected mean behavior. A difference in the cumulative incidence of ≥85 cases after 23.5 years of follow-up occurred in only 0.40% and 1.04% of our simulation trajectories in the stop-screen and ongoing screen models, respectively. A difference in the cumulative number of LC deaths of ≥34 cases after 20.5 years of follow-up occurred in only 4% to 5% of trajectories. Although the observed data do lie within the range of variation that our model forecasts, their occurrence would be unlikely.

Although our simulation model forecasts the total number of LC deaths nearly exactly in the control arm, our model underestimates the number of LC incidence cases by 53 cases in the control arm, excluding any projected cases among participants having unknown LC status (Table 3). A key source of information used to assign a participant's LC status was based on next-of-kin questionnaire information.[4] The ability of next of kin to provide accurate information was determined by a sensitivity study based on the ability of next of kin to report LC correctly in patients with already known LC, and the sensitivity was >90%. However, a specificity study demonstrating the ability to correctly report the absence of LC was not performed. Low specificity may have resulted in an inflation of reported LC cases, thereby explaining the lack of consistency between reported LC incidence and mortality in the follow-up period.

We sought a mechanistic explanation for the observed excess LC mortality risk among the screening arm participants. It has been suggested that the initial randomization procedures were flawed, but that hypothesis generally has been discounted.[4,37] The TSCE model predicts an age-at-exposure effect when the population of ICs is large, as would be expected in a population of high-risk smokers. The excess LC mortality in the study arm participants was restricted to trial participants aged >55 years at the time of enrollment and was greatest in individuals aged >65 years at the time of enrollment. Furthermore, among screening arm participants, a greater number of screens received during the MLP trial corresponded to a greater frequency of LC incidence and deaths reported in the follow-up period.

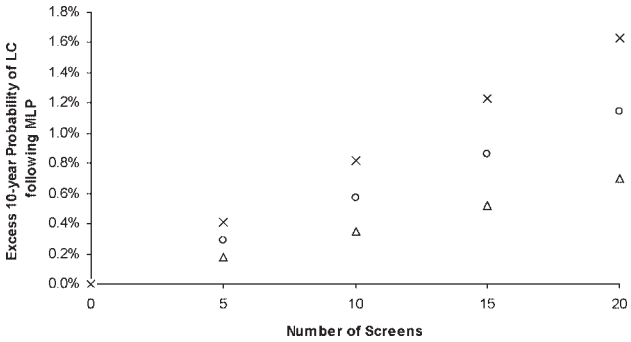

Figure 2. Model-predicted excess 10-year probability of lung cancer (LC) at the conclusion of the Mayo Lung Project (MLP) is shown by attained age and the number of chest x-rays received. Open triangles indicate patients aged 50 years; open circles, patients aged 60 years; crosses, patients aged 70 years.

A Bayesian framework allows us to incorporate a single parameter of excess LC risk, namely, r_r, into an existing distribution of age at onset based on the triangular distribution. An advantage of our model-based estimation methodology is the improved power compared with traditional statistical methods for estimating excess risk. The parameter r_r was identified as highly significant ($P = .0021$), in part because of the ability of our model framework to incorporate key correlates of excess LC risk, namely age, and screen frequency. The model-based predictions of 10-year excess LC probability recapitulate the observed relation between excess LC risk, attained age, and screen frequency at the conclusion of the MLP.

Incorporating excess LC risk into the simulation model of the natural course of LC increases the likelihood of observing the differences in cumulative incidence and mortality (screening − control) as high as those observed in the reported long-term follow-up. We note 2 discontinuities between our estimation procedure and the simulation model. First, because we consider the number of screens as a pre-existing factor in our estimation dataset, we eliminate any LC deaths that occurred within the first 7 years of the MLP, including the excess 12 LC-related and study-related deaths in the study arm. Second, our simulation model of the MLP incorporates an estimate of early stage disease curability of 35% and forecasts a net mortality benefit of 6 to 7 deaths by Year 12. In our estimation procedure, the null hypothesis assumes equivalent LC expected incidence and mortality in the screening and control arms after the conclusion of screening. This latter feature reflects the potentially conservative nature of our estimates of LC excess risk.

In our view, the MLP results reiterate the value of the randomized trial in providing a measure of net mortality benefit given uncertainty of the nature and quantification of the risks and benefits associated with early detection. In contrast to previous reports, the results of the current study suggest that excess LC risk attributable to being a member of the screening arm of the MLP may provide a more satisfactory explanation of the MLP outcome than overdiagnosis. A reliance on an aggregate measure of trial efficacy to reflect 1 potential contributor of efficacy can be misleading. Our analysis further suggests the need for novel quantitative methods to directly estimate the stochasticity of tumor progression and, likewise, overdiagnosis.

With regard to the nature of the excess risk attributable to screening, a natural hypothesis invokes the mutagenic effects of radiation. Our mathematical model has been formulated in such terms. However, other hypotheses might be invoked, such as a weakening of immunity by the stress of unknown nature caused by frequent screening. Because the mutation rate results from a balance between DNA damage and repair as well as the removal of transformed cells, the net effects cannot be attributed easily to a single cause. Ideally, in the future, the risks associated with screening for LC can be understood fully and managed successfully to maximize the number of lives saved by early detection.

CONFLICT OF INTEREST DISCLOSURES

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