Original Article

Modeling the Mortality Reduction Due to Computed Tomography Screening for Lung Cancer

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BACKGROUND: The efficacy of computed tomography (CT) screening for lung cancer remains controversial because results from the National Lung Screening Trial are not yet available. In this study, the authors used data from a single-arm CT screening trial to estimate the mortality reduction using a modeling-based approach to construct a control comparison arm. **METHODS:** To estimate the potential lung cancer mortality reduction because of CT screening, a previously developed and validated model was applied to the screening trial to predict the number of lung cancer deaths in the absence of screening. By using age, gender, and smoking characteristics matching those of the trial participants, the model was used to simulate 5000 trials in the absence of CT screening to produce the expected number of lung cancer deaths along with 95% confidence intervals (95% CIs), while adjusting for healthy volunteer bias. **RESULTS:** There were 64 observed lung cancer deaths in the screening cohort (n = 7995), whereas the model predicted 117.7 deaths (95% CI, 98 deaths-139 deaths), indicating a mortality reduction of 45.6% ($P < .001$). When a more conservative healthy volunteer adjustment was applied, 111.3 lung cancer deaths were predicted (95% CI, 91 deaths-132 deaths), for a lung cancer-specific mortality reduction of 42.5% ($P < .001$). **CONCLUSIONS:** The results of the current study indicate that CT screening along with early stage treatment can reduce lung cancer-specific mortality. This mortality reduction is greatly influenced by the protocol of nodule follow-up and treatment, and the length of follow-up. ***Cancer*** **2011;117:2703–8.** © *2011 American Cancer Society.*

KEYWORDS: lung cancer, computed tomography screening, mortality reduction, 2-stage clonal expansion (TSCE) model, healthy volunteer effect.

Modeling has been effectively used to identify the effect of screening and early treatment on the mortality from a particular disease. Most recently, it was used to evaluate the effect of screening and adjuvant therapy on mortality from breast cancer.[1] This report was the result of the collaborative efforts of a consortium of investigators, the Cancer Intervention and Surveillance Modeling Network (CISNET), sponsored by the National Cancer Institute.

The CISNET collaborators have also developed models to estimate the number of deaths for different cancers in the United States and have validated them using a common national database. These models are useful in addressing those questions that arise in evaluating screening for any cancer such as who should be screened; the frequency of the screening; and the estimated mortality reduction, if any, as a result of screening.

We used a lung cancer (LC) mortality model developed within the CISNET collaboration to address the potential mortality reduction in a cohort that has undergone computed tomography (CT) screening for LC. We used the model to simulate the expected number of LC deaths that would be found in the absence of screening in a cohort that had actually undergone CT screening. The simulation thus provided a control comparison with which to estimate the LC mortality reduction due to screening.

MATERIALS AND METHODS

We developed and applied a model[2] for determining the number and timing of deaths from LC based on the smoking history and age of the person when they had their first, baseline, low-dose CT scan of the chest. We applied the model to a

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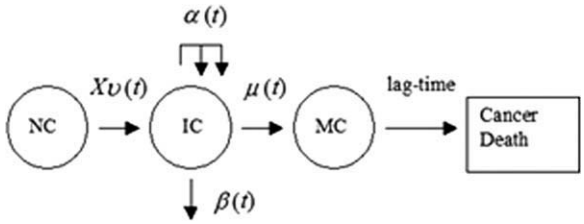

Figure 1. The 2-stage clonal expansion model is shown. NC indicates normal cell; IC, intermediate cell; MC, malignant cell.

cohort of volunteers who underwent CT screening for LC[3-6] in New York State (NYS) and for whom mortality follow-up using the National Death Index was available.

The Model

Predictions and simulations of LC mortality were performed using a 2-stage clonal expansion (TSCE) model,[7] previously used in the context of LC,[8-10] and modified and validated by us as part of the CISNET Lung Group's Smoking Base Case project.[2] The TSCE model is depicted in Figure 1.

The TSCE model assumes that a normal cell (NC) mutates into an initiated cell (IC) in the first transition, according to a Poisson process with intensity $\nu(t)$, in which t denotes the age. There are X NCs in the tissue at birth or maturity, depending on the tissue. The IC can then duplicate or die according to a birth-death process with parameters $\alpha(t)$ and $\beta(t)$, respectively, or further mutate into a malignant cell (MC) for the second transition with rate $\mu(t)$. After a time lag, this malignant cell is assumed to develop into a cancerous tumor with probability 1. The parameters of the TSCE model are piecewise constant over time and the model depends on the entire smoking history through these parameters. Under piecewise constant parameters, the survival function of time to the first MC can be calculated exactly using recursive formulas outlined by Heidenreich et al.[11]

This TSCE model was fit using a resampling-based method allowing for estimation of risk factor-dependent parameters from the combination of case-control data and prospective mortality rate data. The data for fitting smoking-related parameters came from a University of Texas MD Anderson Cancer Center (MDACC) case-control study of LC[12] and the LC incidence/mortality rates came from the Cancer Prevention Study-1[13] and the Nurses' Health Study[8] for males and females, respectively. The following parameters define the TSCE model depending on smoking measured in packs per day (ppd) and age t under a fixed lag time of 6 years.[2]

Table 1. Parameter Estimates of the TSCE Lung Cancer Model Fitted to Mortality Rates from CPS-1 for Men and NHS for Women

Parameter	α_0	γ_0	$\nu_0 X$	α_1	α_2
Males (CPS-I)	2.99	0.069	2.17	2.66	0.35
Females (NHS)	4.6	0.071	1.93	2.3	0.35

TSCE indicates 2-stage clonal expansion; CPS-1, Cancer Prevention Study-1; NHS, Nurses' Health Study.

$$X = 10^7$$
$$\nu(t) = \nu_0 X(1 + a_1 \times \sqrt{ppd})$$
$$\mu(t) = \nu_0(1 + a_1 \times \sqrt{ppd})$$
$$\alpha(t) = \alpha_0(1 + a_2 \times \sqrt{ppd})$$
$$\gamma(t) = \alpha(t) - \beta(t) - \mu(t) = \gamma_0(1 + a_2 \times \sqrt{ppd})$$

Estimates of the relevant parameters are shown in Table 1.

Healthy Volunteer Adjustment

Consideration was given with regard to how to account for "healthy volunteer bias," as demonstrated by Thomson et al[14] and Pinsky et al.[15] This is a term used to describe an effect often observed in volunteer-based studies in which volunteers might be in better health than the general population, usually because of specific eligibility criteria. The effect results in the observed incidence of disease being lower than that in the population. This effect has been demonstrated in smokers[14] and in a screening trial.[15] Because the eligibility requirements for this screening study included that participants be asymptomatic at the time of enrollment, we expected such a bias to exist. Symptoms of LC as defined in the eligibility requirements were hemoptysis (bloody cough), persistent hoarseness with worsening cough, and unexplained weight loss.

The previously described model was thus adjusted using a method we previously developed to exclude people who would have presented with symptoms before their age at entry, or in other words, conditioned the simulation on individuals being asymptomatic at the time of entry into the screening study. An exponential distribution was used to approximate the empirical distribution of the time interval from clinical LC (or onset of symptoms) to death from LC. The mean of this exponential distribution was found using survival time data on 1190 newly diagnosed LC patients at MDACC. An overall Kaplan-Meier (KM) survival curve was created from these data by reweighting

the stage-specific (AJCC stage I-stage IV) KM curves by the observed incidence proportions obtained from Surveillance, Epidemiology, and End Results (SEER) 17. The overall KM survival curve indicated a median survival time of 17 months from the diagnosis of LC until death. This distribution was approximated by an exponential distribution with a mean λ of 2.0 years found through the following formula: $\lambda = (1/\ln(2))x_{med}$. This distribution is used in the LC mortality simulation routine to adjust for any healthy volunteer effect. As part of a sensitivity analysis, λ was varied to determine the effect of this assumption on the prediction of LC deaths.

Simulation of LC Mortality

The probability that an individual will not die of LC by age t is defined as the survival probability, denoted as $S(t)$. In this model, $S(t)$ depends on an individual's smoking history, d, with age at initiation, age at cessation, and number of cigarettes smoked per day, and will be referred to as $S(t;d)$. Expected LC mortality for the study was simulated based on the individual-level data on smoking history as well as the age at enrollment, t_0, and age at the end of follow-up, t_1, provided for the NYS cohort. LC mortality was simulated using the following routine.

For each individual, a uniform (0, $S(t_0; d)$) random variable, u, was drawn.

A. If u was $\leq S(t_1)$, then no LC death occurred during follow-up and the simulation was retired.
B. If u was $> S(t_1)$, then LC death occurred during follow-up at age, t^*, computed by inverting the survival function, $u = S(t^*)$. Then, to adjust for healthy volunteer effect, the length of time between LC diagnosis (or symptom onset) and death was simulated (exponentially distributed with a mean of 2 years) and an age at LC diagnosis was calculated by subtracting from the age at death.
    a. If the age at LC diagnosis was greater than the age at enrollment, the simulation was retired.
    b. If the age at LC diagnosis was less than the age at enrollment, the simulation was rejected and the individual was simulated again.

The cumulative and yearly number of LC deaths per follow-up year were then calculated for each simulated study. The simulation was repeated 5000 times to compare expected LC mortality and to produce 95% confidence intervals (95% CIs). The CIs were estimated using the 2.5% and 97.5% quantiles of the 5000 simulated studies.

This approach was validated against the heavy smokers control arm (non-asbestos–exposed) of the Carotene and Retinol Efficacy Trial (CARET)[16] including 6877 individuals (3797 males and 3080 females). The CARET study was a double-blind, placebo-controlled trial of the effect of beta-carotene and retinol in the prevention of cancer. The TSCE model and healthy volunteer adjustment were able to closely predict 357.9 LC deaths over the course of follow-up versus the observed 364 LC deaths. Because CARET was comprised of heavy-smoker participants who were similar to those found in the NYS cohort, we expected the model and adjustment to provide reasonable estimates of risk in the NYS group.

The NYS Cohort (N = 7995)

The NYS cohort was comprised of 7995 asymptomatic volunteers with no prior history of LC who had no asbestos exposure and were ages 50 to 84 years (average age, 66 years) at the time of enrollment with a history of cigarette smoking (average of 48 pack-years). The average age at the initiation of smoking was 17.7 years in the cohort comprised of 2756 current smokers and 5239 former smokers. All participants provided informed consent under Institutional Review Board-approved protocols at their respective institutions. Baseline screenings were performed between 1993 and 2004 (median, 2001). Of the 7995 participants, 5863 underwent a repeat screening within 7 to 18 months of the baseline screening. Age and smoking history were documented at the time of enrollment; 90% of participants were white and >50% had attended college.

If a participant in the NYS cohort was not confirmed to be alive on December 31, 2005, a National Death Index search was performed to determine whether he/she had died before that date and, if so, the cause of death was ascertained from the death certificate. For each member of the cohort, the duration of follow-up was calculated from the time of enrollment to the latest closing date of follow-up or to death before that date, whichever came earlier.

Standardized Mortality Ratio

The standardized mortality ratio (SMR), defined as the ratio of total observed to total expected deaths in the NYS cohort, was calculated using the expected deaths obtained from the model, together with its lowest attainable significance level (P value) and its 95% CI.[17]

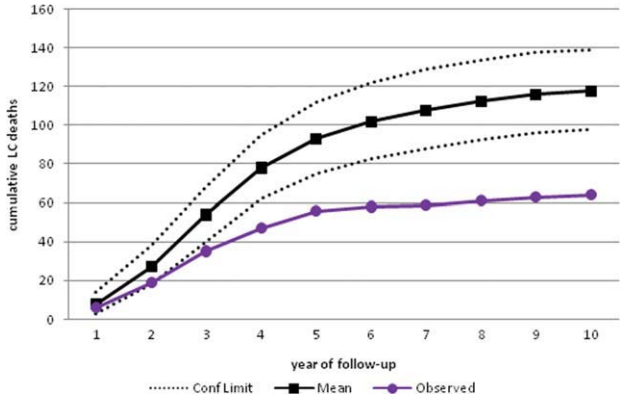

Figure 2. Cumulative expected and observed number of deaths in the New York State cohort are shown starting with baseline enrollment (time 0) with healthy volunteer adjustment with a mean length of 2.0 years. LC indicates lung cancer; Conf Limit, confidence limit.

RESULTS

In the NYS cohort of 7995 volunteers, 64 participants died of LC. Figure 2 depicts the cumulative number of expected and observed deaths from LC in the NYS cohort with the 95% CI. The expected number of LC deaths in the absence of screening was 117.7 (95% CI, 98 deaths-139 deaths) using a healthy volunteer adjustment with a mean of 2 years. The number of cumulative LC deaths leveled off after 5 years because of the decrease in person-years of observation, as seen in Figure 3.

Another approach to determining the mortality reduction is to calculate the SMR. The SMR was significant even when the patients who were noncompliant with the screening schedule were included (64 of 117.7 = 0.544, indicating a mortality reduction of 45.6% [95% CI, 34.7%-54.0%; $P < .001$]). Figure 4 shows a histogram of the total number of lung cancer deaths for the 5000 simulated NYS cohorts.

Because the healthy volunteer interval may be extended because of the eligibility requirement that patients be not just cancer free but also asymptomatic at the time of enrollment, a sensitivity analysis was performed to analyze the effect of assumptions relating to the length of this interval. Data regarding symptom presence and duration in the 1190 LC patients from MDACC were used to further estimate the length of the symptom-extended healthy volunteer interval. As described previously, KM curves were analyzed and an exponential distribution with estimated mean length of 2.3 years was found to describe the time between symptom onset and death from LC. By using this adjustment, simulations were repeated but conclusions did not change, with 111.3 predicted LC deaths (95% CI, 91 deaths-132 deaths). The estimated SMR of 0.575 still demonstrated a highly significant ($P < .001$) LC-specific mortality reduction of 42.5% (95% CI, 29.7%-51.5%). Figure 5 shows a graph of the cumulative number of LC deaths per follow-up year for each of the 2 healthy volunteer interval length adjustments.

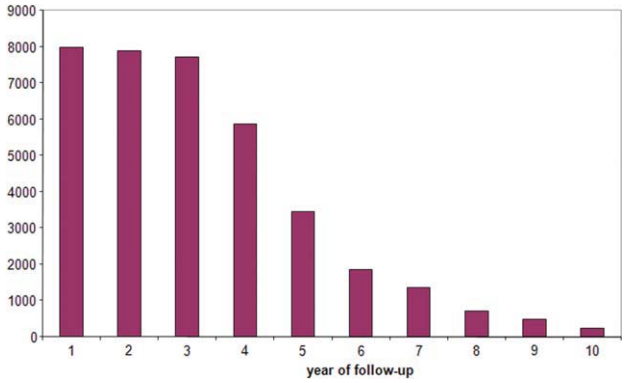

Figure 3. Person-years of observation are shown as per follow-up year.

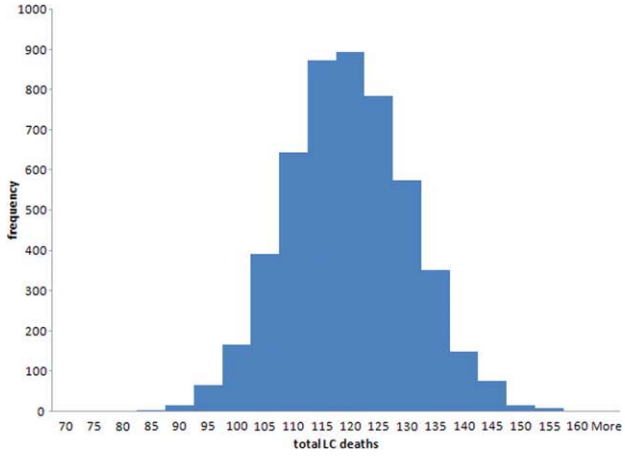

Figure 4. Histogram of the total number of lung cancer (LC) deaths for the 5000 simulated studies is shown.

DISCUSSION

For the NYS cohort, the model predicted 117.7 LC deaths over the 10 years of follow-up after adjusting for the healthy volunteer effect, compared with the 64 observed deaths. This analysis suggests that the CT screening protocol followed by its associated early treatment do provide a mortality benefit. In this analysis, we chose to use an exponential distribution with a mean of 2.0 years to model the time between clinical LC diagnosis and death based on

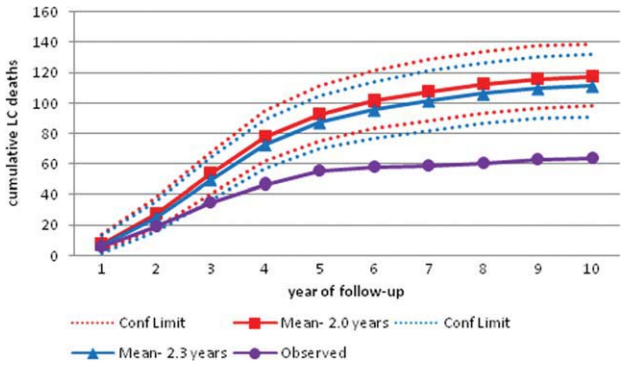

Figure 5. Cumulative lung cancer (LC) deaths are shown. Modeled data were corrected for the healthy volunteer effect using 2 different values for the mean time from diagnosis to LC death (red indicates 2 years; blue, 2.3 years). Dotted lines denote the limits of the corresponding 95% confidence intervals (Conf Limit). The observed cumulative death counts (shown in purple) were plotted for comparison.

survival time data from 1190 newly diagnosed LC patients at MDACC. The underlying TSCE risk model and this exponential distribution were validated against the control arm of CARET, in which it was able to accurately predict the number of LC deaths.

Adjustments for the healthy volunteer effect are important in the context of screening studies. Pinsky et al[15] recently demonstrated substantially lower than expected overall mortality in both arms of the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial, which could only partially be explained by the demographic and risk profile differences between trial participants and the general population. The authors hypothesized that subjects with certain chronic diseases or conditions that strongly predispose to death over the next 5 to 10 years were unlikely to volunteer for the PLCO. Therefore, the PLCO trial population, as well as other screened populations,[18,19] does not represent the general population in terms of mortality. However, Pinsky et al[15] noted that cancer incidence and mortality in the PLCO trial (excluding cancers for which the participants were screened) were closer to those in the general population than overall mortality, although standardized incidence ratios and SMRs for individual cancers varied widely and were lower than in the general population. The study by Pinsky et al[15] does not report the SMR for LC specifically (because LC is one of the cancers for which the population is being screened) or the risk factor-adjusted SMR for all cancers combined. A healthy volunteer effect in the NYS study, resulting in part from the fact that participants with symptoms suggestive of LC are not eligible for the study, justifies the corrections applied in the current analysis. It is important to note that our analysis takes into account the gender and smoking histories of study participants, which obviates the necessity of further risk factor adjustments. Because the exact magnitude of the healthy volunteer effect in the context of LC is not possible to estimate, this constitutes one of the limitations of the current analysis. Although assuming a healthy volunteer interval of 2 years may not be a fair generalization nationally, the choice of this longer interval resulted in the exclusion of more simulated patients with LC, which in turn reduced the contrast between the expected and observed mortality and made the comparison more conservative. Nevertheless, the SMR remained significant even when a longer time interval from symptoms to LC death estimated for the MDACC population was assumed. This time interval is likely to be longer than that for an average LC patient in the United States.

Other modeling approaches have been used to evaluate the effectiveness of CT screening.[20,21] McMahon et al[20] used the Lung Cancer Policy Model, a comprehensive microsimulation model of LC development, progression, treatment, and survival. It compared model results in the absence of screening with the Mayo Clinic CT screening study[22] and found a mortality reduction of 28% in cumulative LC mortality from 5 annual rounds of screening. It is interesting to note that when the model and methods presented in this article were used to simulate LC deaths using gender and smoking history data from the Mayo Clinic CT screening study cohort,[22] it also predicted a 28% reduction in LC mortality although the reduction was not statistically significant (95% CI, −11% to 48%). Another study comparing the mean sojourn times of 6 published CT screening studies estimated a potential 23% reduction in LC mortality under annual CT screening after 10 years of follow-up.[21] A third study[23] used a model to estimate the mortality reduction of CT screening of 3210 participants in 3 studies (Istituto Tumori, Mayo Clinic, and Moffitt Cancer Center) and reported no reduction in mortality. It is possible that the model of Bach et al[23] is not well applicable to the Italian Istituto Tumori study[24] because of differences in the chemical composition of US and European cigarettes. In addition, the study by Bach et al did indicate a mortality reduction in the Mayo Clinic CT screening study,[22] which although not statistically significant, appears to be consistent throughout the duration of the study (as shown in panel K of Figure 1 in the study by Bach et al)[23]; however, this effect was lost when the 3 studies were combined. Finally, the higher risk of LC noted in the H. Lee Moffitt Cancer Center study,[25] because of the high prevalence of patients

with chronic obstructive pulmonary disease, might not have been adequately taken into account. Further, the predicted confidence interval in the Bach et al. study was consistent, with as much as a 30% reduction due to lung cancer.

The efficacy of CT scanning as a screening tool for LC is an important and contested topic. As more data become available, it should become apparent whether it can be reliably used to lower LC mortality. If it is proven effective, then more analyses will be needed to determine which individuals should be screened, how often they should be screened, and how the nodules detected should be managed. The results from the randomized National Lung Screening Trial are anticipated but may not fully answer questions regarding efficacy because, to our knowledge, instead of being offered the standard of care, with no screening recommended, the control group is being screened with x-rays, which will bias results toward underestimating any observed mortality benefit.

CONFLICT OF INTEREST DISCLOSURES

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