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Longitudinal multistage model for lung cancer incidence, mortality, and CT detected indolent and aggressive cancers

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Abstract

It is currently not known whether most lung cancers detected by computerized tomography (CT) screening are aggressive and likely to be fatal if left untreated, or if a sizable fraction are indolent and unlikely to cause death during the natural lifetime of the individual. We developed a longitudinal biologically-based model of the relationship between individual smoking histories and the probability for lung cancer incidence, CT screen detection, lung cancer mortality, and other-cause mortality. The longitudinal model relates these different outcomes to an underlying lung cancer disease pathway and an effective other-cause mortality pathway, which are both influenced by the individual smoking history. The longitudinal analysis provides additional information over that available if these outcomes were analyzed separately, including testing if the number of CT detected and histologically-confirmed lung cancers is consistent with the expected number of lung cancers “in the pipeline”. We assume indolent nodules undergo Gompertz growth and are detectable by CT, but do not grow large enough to contribute significantly to symptom-based lung cancer incidence or mortality. Likelihood-based model calibration was done jointly to data from 6,878 heavy smokers without asbestos exposure in the control (placebo) arm of the Carotene and Retinol Efficacy Trial (CARET); and to 3,642 heavy smokers with comparable smoking histories in the Pittsburgh Lung Screening Study (PLuSS), a single-arm prospective trial of low-dose spiral CT screening for diagnosis of lung cancer. Model calibration was checked using data from two other single-arm prospective CT screening trials, the New York University Lung Cancer Biomarker Center (NYU) (n=1,021), and Moffitt Cancer Center (Moffitt) cohorts (n=677). In the PLuSS cohort, we estimate that at the end of year 2, after the baseline and first annual CT exam, that 33.0 (26.9, 36.9)% of diagnosed lung cancers among females and 7.0 (4.9, 11.7)% among males were overdiagnosed due to being indolent cancers. At the end of the PLuSS study, with maximum follow-up of 5.8 years, we estimate that due to early detection by CT and limited follow-up, an additional 2.2 (2.0, 2.4) % of all diagnosed cancers among females and 7.1 (6.7, 8.0) % among males would not have been diagnosed in the absence of CT screening. We also

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find a higher apparent cure rate for lung cancer among CARET females than males, consistent with the larger indolent fraction of CT detected and histologically confirmed lung cancers among PLaSS females. This suggests that there are significant gender differences in the aggressiveness of lung cancer. Females may have an inherently higher proportion of indolent lung cancers than males, or aggressive lung cancers may be brought into check by the immune system more frequently among females than males.

Keywords

CT screening; multistage; longitudinal model; lung cancer

1.0 Introduction

Cancer of the lung and bronchus is the leading cause of cancer death among men and women in the United States [1]. Lung cancer detection due to symptoms often occurs at late stage when prognosis is poor [2, 3]. This has motivated efforts directed toward determining if early detection and treatment improves lung cancer outcomes [4].

The National Lung Screening Trial (NLST), a randomized controlled trial comparing low-dose spiral computerized tomography (CT) with x-ray detection, was launched in 2002 to test if early detection through CT reduced lung cancer mortality [5]. Initial results were announced on November 10, 2010 by NLST, finding a highly significant 20% reduction in lung cancer deaths among trial participants screened with low-dose spiral CT relative to chest X-ray [6]. These results from NLST trial contrast with previous findings of no benefit from CT screening for lung cancer [7], and with clinical practice guidelines issued by the American College of Chest Physicians in 2007 that do not recommend use of low-dose helical CT for screening for lung cancer except in the context of a well-designed clinical trial [8].

Although the NLST trial found a significant lung cancer mortality benefit from CT screening, it is still not known if this may be confounded by overdiagnosis [9]. Overdiagnosis is defined as cancers that are detected through screening but which would not be detected during the lifetime of the individual if there were no screening [9]. Earlier CT screening studies found higher numbers than expected of early lung cancers, adenocarcinomas, and resectable stage I tumors [7, 10, 11, 12, 13, 14], suggesting that overdiagnosis may occur during CT screening for lung cancer. Overdiagnosis has several components, the most important of which is due to indolent nodules which stop growing or grow so slowly that they would not cause symptoms before death from another cause. However, a small fraction of aggressive cancers may be overdiagnosed due to chance occurrence of other cause death, especially at older ages. Estimation of overdiagnosis is also complicated in cohort studies due to earlier detection of screen detected cancers that would not show up in the absence of screening due to limited cohort follow-up.

Evidence supporting the presence of CT detected indolent cancers comes from a study that included serial evaluation of eighteen lung cancers in at least four successive CT scans, showing variable growth rates including some with nearly horizontal growth curves [14], suggesting that those cancers were indolent. Indolent or slowly progressing cancers likely cause little harm if left untreated [10], but harm increases with treatment due to risks associated with lung cancer resection or other interventions.

Estimation of overdiagnosis, including contributions from indolent nodules, requires information about the expected number of lung cancers that are “in the pipeline” and detectable by CT, and that would contribute to lung cancer incidence or mortality in the

absence of screening. This requires analysis of longitudinal data, e.g. individual events or outcomes of different type that occur at multiple time points [15]. Thus we developed a longitudinal model of lung cancer incidence, CT diagnosis, lung cancer mortality, and other cause mortality that we calibrate to cohort data for unscreened and screened heavy smokers with comparable smoking histories. The longitudinal model represents rate-limiting transitions, or mutations, between normal, pre-malignant, and malignant stages, with stochastic pre-malignant clonal expansion and tumor growth. The goal is to include sufficient biological detail in order to provide reasonable estimates of how many cancers should be “in the pipeline” and detectable by CT, given the smoking histories of the subjects.

The longitudinal model uses multistage methods to represent biological processes including cell mutations, divisions, and death or apoptosis [16, 17, 18]. In the past, multistage models have been generally used for evaluation of a single outcome (incidence or mortality) with survival until occurrence of the first malignant cell. In this paper, we introduce a stochastic observation process to overcome these limitations. This allows us to calculate joint probabilities for lung cancer incidence, CT diagnosis, and mortality as a function of tumor size, rather than survival until first occurrence of a malignant cell.

Other investigators have extended multistage methods for analysis of cancer progression and screening, including Monte-Carlo methods that implement a three-phase progression process following a two-stage model [19], and a simulation algorithm based on the conditional number and size distribution of pre-malignant lesions to evaluate screening and intervention strategies for colorectal cancer [20].

Lung cancer progression has been analyzed previously using a stochastic state-transition simulation model to estimate long term effectiveness of CT in the Mayo CT screening study [21], and a parametric stochastic model for symptomatic detection of lung cancer based on primary tumor volume and disease stage [22]. Other longitudinal analysis methods include latent class models for joint analysis of multiple outcomes [23], a Markov chain model in reverse time for analysis of serial observations as a trigger for intervention [24], and methods for threshold regression with Markov decomposition [25].

The model we present here utilizes maximum likelihood methods for joint analysis of CT screening, lung cancer incidence and mortality, and other-cause mortality. Self-consistency of the model across multiple longitudinal outcomes allows estimation of an indolent fraction that contributes to diagnosis during CT screening. However, the non-constant growth patterns of lung tumors [14] suggests that cancers that appear indolent at a given time may not remain so permanently. It is possible that tumors in an indolent phase may progress or metastasize later [26].

2.0 Material and Methods

2.1 Study Subjects

Calibration to lung cancer incidence and mortality utilized data for heavy smokers in the control arm of the Carotene and Retinol Efficacy Trial (CARET) [27]. Calibration to CT screening utilized data from the Pittsburgh Lung Screening Study (PLuSS) [28]. The calibrated model was applied to CT screening data from the New York University Biomarker Center (NYU) and the H. Lee Moffitt Cancer Center (Moffitt) trials. All subjects included in this analysis were current or former heavy smokers with no or less than 5 years record of asbestos exposure. (See Table 1).

CARET was a multi-center prospective randomized controlled cancer prevention trial (ClinicalTrials.gov Identifier: NCT00712647). This analysis includes 6,878 non-asbestos-exposed subjects among 8,894 randomized to the control group. Median mortality follow-up beginning at randomization was 10.1 years, and maximum was 17.4 years. PLuSS included 3,642 subjects with median mortality follow-up of 4.3 years beginning at baseline CT, with maximum follow-up of 5.8 years. NYU included 1,168 subjects, with this analysis including 1,021 subjects with complete information and fewer than 5 years asbestos exposure. Median mortality follow-up was 2.1 years, and maximum was 8.4 years. Moffitt included 1,140 subjects, with an early entry cohort of 504 subjects having chronic obstructive pulmonary disease (COPD) diagnosis, and a late entry cohort of 636 subjects without requirement of COPD diagnosis. This analysis utilized the 290 subjects in the early cohort and 387 in the late cohort without asbestos exposure. Median mortality follow-up in Moffitt was 4 years, and maximum was 6.9 years.

2.2 Longitudinal multistage observation model

As shown in Figure 1, the longitudinal model combines a multistage lung cancer pathway (upper part of figure) with an effective other-cause mortality pathway (below). The model includes a new stochastic observation process that is used in conjunction with cell mutation, division, and death processes which are the basic elements of current multistage models [16, 17, 18, 29, 30, 31, 32, 33]. There are five types of observations, shown as square boxes in Figure 1, with index k indicating the type of observation. The outcome for an observation is said to be negative if the event has not occurred previously, and positive if it has. Observations of different type utilize different observation parameters to specify the probability for observing a positive outcome as a function of the expected number of malignant cells, which is related to tumor diameter as discussed below. The lung cancer pathway includes four observation types (healthy entry, CT screening, lung cancer incidence, and lung cancer mortality ($k = 0, \dots, 3$, respectively)), while other-cause mortality is represented as observation type ($k = 4$).

The model is calibrated jointly to CARET and PLuSS cohort data using maximum likelihood methods to estimate 19 parameters, p_i for $i = 1, \dots, 19$. The first 13 parameters are associated with the lung cancer pathway, and the remaining six parameters with other-cause mortality. In the lung cancer pathway, parameters p_1 to p_{10} are primarily influenced by data from CARET for incidence and mortality in the absence of screening, while parameters p_{11} – p_{12} relate to CT screening histories and cohort effects in the PLuSS data. Parameters p_{11} models the CT diagnostic sensitivity, p_{12} models the contribution of indolent cancers detectable through CT screening, and p_{13} representing a cohort effect, set equal to one for CARET, and allowed to vary separately for males and females in the CT screening cohorts. We ran extensive Markov Chain Monte Carlo runs to estimate credibility intervals (CI)s for all lung cancer pathway parameters. Other-cause mortality parameters p_{14} to p_{19} were estimated separately for each cohort.

The lung cancer pathway represents three cell populations – normal stem cells, pre-malignant stem cells, and malignant stem cells – labeled by index j . (See Figure 1). The normal stem cell population ($j = 0$) is modeled deterministically as a fixed number N_0 , while pre-malignant ($j = 1$) and malignant ($j = 2$) cell populations (called stages) are modeled stochastically. Indolent malignant populations are specified by ($j = 2'$). Mutation is modeled as an asymmetric cell division process occurring stochastically at rate $\mu_{j,j+1}$ for a parent cell of type j to create an identical daughter cell that replaces the parent cell and a mutated daughter cell labeled by index $j + 1$.

Analysis of the model identifiability indicates that the product of the number of normal stem cells N_0 and the first mutation rate μ_{01} is identifiable, but these numbers are not separately

identifiable. Thus, without loss of generality, we assume there are a constant number $N_0 = 10^8$ of normal stem cells in both lungs combined, based on data from other studies discussed in Section 3.5 and the Supplementary Materials (SM) section, and we estimate the first mutation rate μ_{01} as the first estimated model parameter p_1 .

Pre-malignant and malignant cells undergo division at rates α_j , and death (apoptosis) or differentiation at rates β_j , with clonal expansion rates γ_j defined as the division rate minus the death rate $\gamma_j = \alpha_j - \beta_j$. The pre-malignant cell death rate β_1 is the second estimated parameter p_2 , and the pre-malignant clonal expansion rate γ_1 during time periods when an individual is not-smoking (the background clonal expansion rate) is estimated as the third parameter p_3 .

The effect of smoking is modeled as a non-linear exposure-response relationship that affects the pre-malignant clonal expansion rate γ_1 (making it time-dependent), using parameters p_4 and p_5 .

$$\gamma_1(t) = (p_3 * (1 + p_4 * z_s(t)^{p_5})) \quad (\text{Smoking exposure-response for LC}). \quad (1)$$

with $z_s(t)$ being an individual's smoking rate measured in units of cigarettes per day at age t . (As discussed in Section 4.1, we began with a more general model in which smoking influences both pre-malignant and malignant clonal expansion rates and both mutation rates in the lung cancer pathway through separate exposure-response relationships. Preliminary testing indicated that the only significant exposure-response relationship was on pre-malignant cell clonal expansion. (See Equation 1 and Figure 1.)

The mutation rate from pre-malignant to malignant cell, μ_{12} , is estimated as parameter p_6 , the malignant cell death rate β_2 is estimated as p_7 , and the malignant cell clonal expansion rate is estimated as p_8 .

Other data sources were utilized as inputs to the model to provide rough estimates of the number ($N_0 = 10^8$) of normal stem cells in both lungs and the density of malignant stem cells per unit volume ($\rho = 1.25 * 10^5$ cells/cm³), as discussed in the SI. The estimate of the density ρ is used to translate the expected number of malignant stem cells in the model to tumor volume (expressed as the equivalent diameter of a solid sphere with that volume). We used data on pulmonary tumor size at incidence and death from Geddes [34] to calibrate the median diameter d_k at incidental diagnosis (also referred to as incidence) and at death from lung cancer. Based on these data, we assume lung cancer incidence (observation type $k = 2$) occurs at a median tumor diameter of $d_2 = 3$ cm and lung cancer death ($k = 3$) at median tumor diameter $d_3 = 10$ cm. (The observation parameters ξ_2 and ξ_3 representing lung cancer incidence and death, respectively, are calculated using Equation 25 in Section 3.6).

In calibrating to longitudinal data, some fraction (δ_3) of the incidental lung cancers may not show up as lung cancer deaths when expected, including cancers that are cured or that have survival significantly extended through treatment, or if there is enhanced other-cause mortality due to cancer morbidity and/or misclassification on the death certificate. This is estimated as parameter p_9 . The excess other-cause death fraction (δ_4) is defined as the difference between observed other-cause deaths following lung cancer incidence and the expected number of other-cause deaths according to the other-cause mortality model for individuals not previously diagnosed with lung cancer. The δ_4 fraction is not estimated as a separate model parameter; it is calculated based on the data and other-cause model parameters.

Subjects entering a cohort study frequently have reduced occurrence of cancer incidence or death in the first few years of the study. This is a type of selection bias, called a healthy entry effect. Preliminary analysis indicated that a healthy entry effect was important in these cohorts, with the annual lung cancer diagnosis rate in CARET in year one about half of the rate for years three and beyond, and with similar increasing trends for lung cancer death rates in the first few years for all cohorts. We model the healthy entry effect as if each individual had a negative outcome for a fictitious screen that occurred prior to study entry. This conditions the individuals on being unlikely to have undetected cancers larger than some diameter d_0 , which we estimate as parameter p_{10} . Likelihood ratio test show the healthy entry effect is highly significant. The relative rate for generating indolent cancers [10] compared with malignant cancers is called the indolent fraction, and is estimated using parameter p_{11} . (See Section 2.3).

The diagnostic sensitivity of CT screening for lung cancer depends on tumor size. The sensitivity curve may be identified in terms of the median effective diameter d_1 , estimated as parameter p_{12} , at which cancers are diagnosed with 50% probability through CT screens. The effective diameter is the diameter of a sphere that has volume equal to that of the tumor. Finally, we utilized a parameter p_{13} to represent a cohort effect, which we set equal to one for CARET, and estimated separately for each gender in PLS and other CT screening cohorts. The cohort effect parameter scales rates for the entire lung cancer pathway, acting as a multiplicative factor on the number of normal stem cells N_0 at risk.

Other-cause mortality is also modeled using multistage methods (as a two-stage model) with smoking exposure-response and a single observation process representing other-cause mortality. The TSCE model easily incorporates delayed effects of smoking behavior and appears to provide good fits to the data. However, this is an effective model – the rates can not be interpreted in terms of cell kinetics. We continue to utilize terminology and symbols like those used in the lung cancer pathway to indicate the similarity of mathematical methods. The first transition, μ_{34} is estimated as p_{14} , the effective “death” rate β_4 for the intermediate stage as parameter p_{15} , the background “clonal expansion” rate γ_4 as parameter p_{16} , the smoking exposure response as $\gamma_4(t) = (p_{16} * (1 + p_{17} * z_s(t)^{p_{18}}))$ using parameters p_{17} and p_{18} , and ξ_4 for other-cause mortality observation as parameter p_{19} .

Observations are classified into two categories: hazards (events that may occur at any time) and scheduled observations which occur at definite times. Scheduled observations may be thought of as time-dependent hazards which are concentrated at the time of observation.

The model includes three ordinary hazards: lung cancer incidence, lung cancer mortality, and other-cause mortality. Hazards are modeled with parameters $\xi_k(t)$ that determine the sensitivity curve that relates the probability for a positive outcome for an observation k to the expected number of malignant cells at age t , and to tumor volume as discussed above. We assume these rates remain constant from birth until the earlier of event occurrence (or censoring) at T_k , with $\xi_k(t) = \{\xi_k \text{ for } t \leq T_k; 0 \text{ for } t > T_k\}$.

The model includes two types of scheduled observations: the healthy entry effect and CT screening. Scheduled observations utilize a Dirac delta function to represent the finite probability of a positive outcome from an observation k with sensitivity ξ_{kn} at time T_n , with $\xi_k(t) = \xi_{kn} \delta(t - T_n)$.

A probability generating functions (PGF) represents the joint probability distribution for pre-malignant and malignant cells. We use backward Kolmogorov equations [29, 30] to model the evolution of the PGF for each individual, including changes in cell kinetics that depend on exposure history and progressive conditioning of the process on longitudinal observations. The backward Kolmogorov equations are written as a set of coupled ordinary

differential equations (ODE)s [31, 32, 33]. The ODEs include indicator variables to switch each observation type on or off to calculate separate and joint probabilities for different combinations of events. See Section 3 for further details.

Model parameters are estimated by maximum likelihood methods. (See Table 2). The model transforms individual exposure and observation histories into time-dependent rates for cell division, mutation, death, and observation.

2.3 Modeling indolent and aggressive malignant cancers

We assume indolent cancers initially grow like other cancers, but slow down according to a Gompertz growth process, reaching a maximum diameter of about 1.5 cm, rather than continuing exponential growth. The 1.5 cm Gompertz size parameter was not estimated — it was chosen to make these cancers detectable by CT, while making essentially no contribution to non-screen based lung cancer incidence or death. Likelihood ratio tests indicate that estimation of the fraction of indolent cancers detected by CT does not depend significantly on the choice of asymptotic size for Gompertz growth. We model stochastic Gompertz growth of indolent cancers that begin at time τ as having a growth rate and expected size at time t of

$$\begin{aligned} g(t-\tau) &= b \exp[-a(t-\tau)]. \text{ (Stochastic Gompertz growth),} \\ E[N(t-\tau)] &= [g(t-\tau)]^{-1} = \exp\left[\frac{b}{a}(1 - \exp(-a(t-\tau)))\right], \end{aligned} \quad (2)$$

respectively, where a is the shape parameter and b is the initial growth rate [35, 36, 37]. Assuming that indolent cancers initially grow with rates similar to that of aggressive cancers, we set $b = \alpha_2 - \beta_2$. Further assuming that indolent cancers asymptotically reach a maximum diameter of 1.5 cm with the same density of stem cells ($\rho = 1.25 * 10^5$ cells/cm³) as other cancers, we set $N_{max} = \lim_{t \rightarrow \infty} E[N(t-\tau)] = \exp[\frac{b}{a}] = \rho^{\frac{4}{3}} \pi (1.5/2)^3 \approx \exp(12.305)$. Solving for a , we find $a = (\alpha_2 - \beta_2) / \log(N_{max}) \approx (\alpha_2 - \beta_2) / 12.305$. This expression for a is used in Equations (6', 7') to model stochastic growth of indolent cancers.

2.4 Statistical analysis

We used the longitudinal likelihood for the multistage process, defined in Equations 18–20, to jointly optimize all model parameters. To validate the likelihood methods, we compared annual observed versus expected cases for each outcome, calculating expected cases using the cumulative hazard in Equation 7. Initial comparisons were good, but not perfect — there was a hint of an identifiability problem in estimating CT versus incidental diagnoses when the likelihood was evaluated only at the end of the study. The problem seems to be associated with a degree of collinearity in the likelihood when the model contains alternative high-and low-sensitivity modes of detection. The hazard for earlier CT diagnosis (which has a high sensitivity for detection) is similar to the hazard for later symptomatic diagnosis (which has a lower sensitivity that is compensated by detecting the tumor when it has grown larger due to not being detected by CT). We solved this potential identifiability problem by evaluating the likelihood at two time points: at the end of year two after essentially all CT screening was over, and at the end of study follow-up, and re-optimized the model using a modified likelihood score as the product of these two terms.

With this modification, the likelihood-based methods appear robust in estimating all of the model parameters simultaneously, and the calibrated model provides excellent fits to the data for each outcome, which we validated using χ^2 statistics, $\chi^2 = \sum (\text{obs} - \text{exp})^2 / \text{exp}$ to compare fits between annual counts for each outcome in the data and the expected annual counts using the parameters calibrated by maximizing the likelihood.

We used Markov chain Monte Carlo (MCMC) methods with the modified likelihood to calculate two-sided 95% credibility intervals (CI)s for all model parameters in the lung cancer pathway, using 13 independent chains with each chain consisting of approximately 30,000 iterations after burn-in.

We also evaluated the Bach model annual risk for lung cancer diagnosis, and other-cause mortality [38]. We compared χ^2 values for the longitudinal model with the Bach model, where possible.

2.5 Numerical methods

All programming was done using High Performance FORTRAN software, with computations run in parallel on a computer cluster. Numerical solving of ODEs was done using the LSODE solver [39]. We used “Bhat” software for optimization that includes Simplex, Newton, and modified Davidon-Fletcher-Powell methods [40].

3.0 Theory/Calculation

3.1 Mathematical methods for the longitudinal multistage observation model

We define a continuous time Markov branching process with random variables $N(t) = \{N_j(t)\}$ and $O(t) = \{O_k(t)\}$ for $t > 0$ that represent the number of cells $N_j(t)$ of type j (for $j = 1$), and positive outcomes $O_k(t)$ for observation of type k at time t . We assume the random variable $N_j(t)$ has a state space consisting of non-negative integers labeled by n_j , and $O_k(t)$ has a binary (0, 1) state space labeled by o_k . The state $o_k = 0$ represents a negative outcome for observation k (e.g. not having lung cancer incidence, or no lung cancer diagnosed from a CT screen), while $o_k = 1$ represents a positive outcome (e.g. lung cancer incidence, or lung cancer diagnosed based on a CT screen). We assume cancer may originate from any normal stem cell, with a deterministic number $N_0(t) = 10^8$ of normal stem cells in both lungs combined, as discussed in SI.

We define rates for cell division $\alpha_j(t)$, death $\beta_j(t)$, and mutation $\mu_{j,j+1}(t)$ at time t for stage j , and observations in which cells in stage j contribute independently to positive outcomes for observation type k with rate $\xi_{jk}(t)$. For example, the lung cancer pathway model described here includes two stages, $j = 1, 2$, and four observation processes, $k = 0, \dots, 3$, with all observations related to the expected number of malignant cells ($j = 2$). However, more generally, it is possible to have several cell types contribute to an observation, or have different observations depend on different cell types. (See Figure 1).

Observation processes are represented in the survival and hazard using time dependent observation parameters $\xi_{jk}(t)$. Observation processes may be classified into (ordinary) hazards and scheduled observations. The scheduled observation may also be considered as a hazard that is compressed in time to an instant to represent a lump of probability for having a positive or negative outcome from the observation at that moment in time.

Hazards (rates for events that may occur at any time, conditional on no prior occurrence) include incidence ($k = 2$) and lung cancer mortality ($k = 3$), utilizing observation parameters

$$\xi_{jk}(t) = \begin{cases} \xi_{jk}, & t \leq T_k \quad (\text{Rate cells } j \text{ contribute to hazard } k) \\ 0, & t > T_k. \quad (\text{Not at risk after outcome } k \text{ occurs.}) \end{cases} \quad (3)$$

Scheduled observations include a healthy entry effect ($k = 0$) and CT screening ($k = 1$). Scheduled observations of type k at time T_n with sensitivity ξ_{jkn} are represented using a Dirac delta function as

$$\xi_{jk}(t) = \xi_{jkn} \delta(t - T_n). \quad (\text{Scheduled observation}) \quad (4)$$

For Δt sufficiently small, we define transition probabilities for the lung cancer pathway,

$$P_{n', o' | n, o}(\Delta t) = \text{Prob}[N'(t + \Delta t) = n', O'(t + \Delta t) = o' | N(t) = n, O(t) = o]$$

$$= \begin{cases} \beta_1 n_1 \Delta t & (n'_1 = n_1 - 1, n'_2 = n_2, \{o'_k = o_k\}), & (\text{pre-malig. cell death}). \\ + \beta_2 n_2 \Delta t & (n'_1 = n_1, n'_2 = n_2 - 1, \{o'_k = o_k\}), & (\text{malignant cell death}). \\ + (\alpha_1 n_1 + \mu_{01} N_0) \Delta t & (n'_1 = n_1 + 1, n'_2 = n_2, \{o'_k = o_k\}), & (\text{pre-malig. division, 1st mutation}). \\ + (\alpha_2 n_2 + \mu_{12} n_1) \Delta t & (n'_1 = n_1, n'_2 = n_2 + 1, \{o'_k = o_k\}), & (\text{malignant division, 2nd mutation}). \\ + \xi_{20} \delta(t - T_0) n_2 \Delta t & (n'_1 = n_1, n'_2 = n_2, o'_0 = o_0 + 1), & (\text{healthy entry (scheduled) at } T_0). \\ + \xi_{21} \delta(t - T_1) n_2 \Delta t & (n'_1 = n_1, n'_2 = n_2, o'_1 = o_1 + 1), & (\text{CT screens (scheduled) at } T_1). \\ + \xi_{22} n_2 \Delta t \text{ (for } t < T_2) & (n'_1 = n_1, n'_2 = n_2, o'_2 = o_2 + 1), & (\text{lung cancer incidence hazard}). \\ + \xi_{23} n_2 \Delta t \text{ (for } t < T_3), & (n'_1 = n_1, n'_2 = n_2, o'_3 = o_3 + 1), & (\text{lung cancer death hazard}). \\ + 1 - [(\beta_1 + \alpha_1 + \mu_{12}) n_1 & (n'_1 = n_1, n'_2 = n_2, \{o'_k = o_k\}), & (\text{no change}). \\ + (\beta_2 + \alpha_2 + \sum_k \xi_{2k}(t)) n_2] \Delta t & & \\ + o(\Delta t). & & \end{cases}$$

where $\delta(t - T_k)$ is the Dirac delta function with observation time T_k , and $o(\Delta t)$ represents terms of higher order in Δt that we ignore.

For $t \geq \tau$, we define generating functions [29, 30, 31, 32, 33] for the joint distribution of cells and observations at t . Let $\psi(y, z; \tau, t)$ represent the entire process, with only normal cells and no observations at τ , and $\varphi_j(y, z; \tau, t)$ represent sub-processes beginning with a single type j cell at τ ,

$$\begin{aligned} \psi(y, z; \tau, t) &= E[y^{N(t)} z^{O(t)} | \{N(\tau) = 0\}, \{O(\tau) = 0\}], \\ \varphi_j(y, z; \tau, t) &= E[y^{N(t)} z^{O(t)} | \{N_i(\tau) = \delta_{ij}\}, \{O(\tau) = 0\}], \end{aligned} \quad (5)$$

with $y^{N(t)} = y_1^{N_1(t)} y_2^{N_2(t)}$, $z^{O(t)} = z_0^{O_0(t)} z_1^{O_1(t)} z_2^{O_2(t)} z_3^{O_3(t)}$, $|y_j| \leq 1$, $|z_k| \leq 1$ and δ_{ij} being the Kronecker delta which equals 1 if $i = j$, and 0 otherwise. We limit all model observations to $j = 2$, and simplify the notation in the following by eliminating the j subscript and defining $\xi_k(t) \equiv \xi_{2k}(t)$.

The backward Kolmogorov equations for the (aggressive) lung cancer pathway are [29, 32, 33],

$$\begin{aligned} \frac{d\psi(y, z; \tau, t)}{d\tau} &= -\mu_{01}(\tau) N_0(\tau) (\varphi_1(y, z; \tau, t) - 1) \psi(y, z; \tau, t), \\ \frac{d\varphi_1(y, z; \tau, t)}{d\tau} &= -\alpha_1(\tau) (\varphi_1^2(y, z; \tau, t) - \varphi_1(y, z; \tau, t)) - \beta_1(\tau) (1 - \varphi_1(y, z; \tau, t)) - \mu_{12}(\tau) (\varphi_1(y, z; \tau, t) \varphi_2(y, z; \tau, t) - \varphi_1(y, z; \tau, t)) \\ \frac{d\varphi_2(y, z; \tau, t)}{d\tau} &= -\alpha_2(\tau) (\varphi_2^2(y, z; \tau, t) - \varphi_2(y, z; \tau, t)) - \beta_2(\tau) (1 - \varphi_2(y, z; \tau, t)) - \sum_{k=0}^3 \xi_k(\tau) (\varphi_2(y, z; \tau, t) z_k - \varphi_2(y, z; \tau, t)), \end{aligned}$$

where index $j = 1$ represents pre-malignant clones and $j = 2$ malignant clones, with $\mu_{j,j+1}(\tau) \equiv 0$ for $j = 2$.

We assume Gompertz growth of malignant cells in the indolent lung cancer pathway, solving similar equations as above except for replacing the equation for $\varphi_2(y, z; \tau, t)$ representing exponential growth of malignant clones with $\varphi_2'(y, z; \tau, t)$ representing a Gompertz growth process [35, 36, 37],

$$\begin{aligned}
& \frac{d\varphi_{2'}(y, z; \tau, t)}{d\tau} \\
& = [-\alpha_2(\tau) (\varphi_{2'}^2(y, z; \tau, t) - \varphi_{2'}(y, z; \tau, t)) - \beta_2(\tau) (1 - \varphi_{2'}(y, z; \tau, t))] \exp(\\
& -a(t - \tau)) \\
& - \sum_{k=0}^3 \xi_k(\tau) (\varphi_{2'}(y, z; \tau, t) z_k \\
& - \varphi_{2'}(y, z; \tau, t))
\end{aligned} \tag{6'}$$

where $a = (\alpha_2 - \beta_2)/\log(N_{max}) \approx (\alpha_2 - \beta_2)/12.305$ is the shape parameter for Gompertz growth with N_{max} representing the expected number of stem cells in an indolent tumor that reaches a maximum size of 1.5 cm diameter, as discussed in Section 2.3. We make a change of variable to $s = t - \tau$, with

$$\begin{aligned}
A(s, t) &= \varphi_1(1, z; \tau, t), & B(s, t) &= \varphi_1'(1, z; \tau, t), & C(s, t) &= \varphi_2(1, z; \tau, t), \\
D(s, t) &= \varphi_2'(1, z; \tau, t), & E(s, t) &= -\log(\psi(1, z; \tau, t)), & F(s, t) &= \psi(1, z; \tau, t), \\
G(s, t) &= \psi'(1, z; \tau, t), & H(s, t) &= -\psi'(1, z; \tau, t)/\psi(1, z; \tau, t).
\end{aligned}$$

These definitions lead to the following coupled ODEs for aggressive lung cancer,

$$\begin{aligned}
\frac{dA(s, t)}{ds} &= \alpha_1(t-s) (A^2(s, t) - A(s, t)) + \beta_1(t-s) (1 - A(s, t)) + \mu_{12}(t-s) (A(s, t) (C(s, t) - 1)), \\
\frac{dB(s, t)}{ds} &= \alpha_1(t-s) (2B(s, t)A(s, t) - B(s, t)) - \beta_1(t-s) B(s, t) + \mu_{12}(t-s) (B(s, t) (C(s, t) - 1) + A(s, t) D(s, t)), \\
\frac{dC(s, t)}{ds} &= \alpha_2(t-s) (C^2(s, t) - C(s, t)) + \beta_2(t-s) (1 - C(s, t)) + \sum_{k=0}^3 \xi_k(t-s) C(s, t) (z_k - 1), \\
\frac{dD(s, t)}{ds} &= \alpha_2(t-s) (2D(s, t)C(s, t) - D(s, t)) - \beta_2(t-s) D(s, t) + \sum_{k=0}^3 \xi_k(t-s) D(s, t) (z_k - 1), \quad (7) \\
\frac{dE(s, t)}{ds} &= \mu_{01}(t-s) N_0(t-s) (1 - A(s, t)). \quad (\text{LC cumulative hazard}). \\
\frac{dF(s, t)}{ds} &= \mu_{01}(t-s) N_0(t-s) F(s, t) (A(s, t) - 1). \quad (\text{LC survival}). \\
\frac{dG(s, t)}{ds} &= \mu_{01}(t-s) N_0(t-s) (F(s, t) B(s, t) + G(s, t) (A(s, t) - 1)). \quad (\text{LC density}) \\
\frac{dH(s, t)}{ds} &= -\mu_{01}(t-s) N_0(t-s) B(s, t). \quad (\text{LC hazard}).
\end{aligned}$$

where the cumulative hazard for (aggressive) lung cancer is evaluated as $\int_0^t \lambda(s) ds = E(t, t)$, the probability density as $\dot{F}(t) = G(t, t)$, and the hazard as $\lambda(t) = -S(t)/S(t) = H(t, t)$.

Similar definitions are used to represent Gompertz growth of indolent nodules with shape parameter $a = (\alpha_2 - \beta_2)/\log(N_{max}) \approx (\alpha_2 - \beta_2)/12.305$, with the same definitions as above except for replacing

$$C'(s, t) = \varphi_{2'}(1, z; \tau, t), \quad D'(s, t) = \varphi_{2'}'(1, z; \tau, t)$$

with

$$\begin{aligned}\frac{dC'(s,t)}{ds} &= [\alpha_2(t-s)(C'^2(s,t) - C'(s,t)) + \beta_2(t-s)(1 - C'(s,t))] \exp(-as) + \sum_{k=0}^3 \xi_k(t-s) C'(s,t) (z_k - 1), \\ \frac{dD'(s,t)}{ds} &= [\alpha_2(t-s)(2D'(s,t)C'(s,t) - D'(s,t)) - \beta_2(t-s)D'(s,t)] \exp(-as) + \sum_{k=0}^3 \xi_k(t-s) D'(s,t) (z_k - 1)\end{aligned}\quad (7')$$

For both aggressive and indolent cancers, the initial conditions at $s = 0$ are $A(0, t) = 1$, $B(0, t) = 0$, $C(0, t) = 1$, $D(0, t) = \sum_{k=0}^3 \xi_k(t-s)(z_k - 1)$, $E(0, t) = 0$, $F(0, t) = 1$, $G(0, t) = 0$, and $H(0, t) = 0$.

An effective model for other-cause mortality uses similar equations as above, but with a single “clonal expansion” stage,

$$\begin{aligned}\frac{dI(s,t)}{ds} &= \alpha_4(t-s)(I^2(s,t) - I(s,t)) + \beta_4(t-s)(1 - I(s,t)) + \xi_4(t-s)I(s,t)(z_4 - 1), \\ \frac{dJ(s,t)}{ds} &= \alpha_4(t-s)(2J(s,t)I(s,t) - J(s,t)) - \beta_4(t-s)J(s,t) + \xi_4(t-s)J(s,t)(z_4 - 1), \\ \frac{dK(s,t)}{ds} &= \mu_{34}(t-s)N_0(t-s)(1 - I(s,t)). \quad (\text{OC cumulative hazard}). \\ \frac{dL(s,t)}{ds} &= \mu_{34}(t-s)N_0(t-s)L(s,t)(I(s,t) - 1). \quad (\text{OC survival}). \\ \frac{dM(s,t)}{ds} &= -\mu_{01}(t-s)N_0(t-s)J(s,t). \quad (\text{OC hazard}).\end{aligned}\quad (8)$$

Initial conditions at $s = 0$ are $I(0, t) = 1$, $J(0, t) = \xi_4$, $K(0, t) = 0$, $L(0, t) = 1$, and $M(0, t) = 0$.

3.2 Conditioning on prior observations and exposures

Individuals histories begin at birth, with the individual being at risk for lung cancer incidence, lung cancer mortality, and other-cause mortality (observation types $k_0 = 2, 3, 4$ respectively). Hazards for symptomatic and CT diagnosis are removed from the risk set when a positive outcome (actual diagnosis) occurs, with screening observations included only during the short duration of a screen. Smoking exposures are also generally defined by times when smoking starts, the smoking rate changes, or smoking cessation occurs.

Thus in solving the systems of ODEs in Equations 7–8 for the survival and hazard, it is useful to break the evaluation into intervals $(t_{n-1}, t_n]$ representing periods of constant exposure with no screens or positive observations except possibly at the end of each interval, at times t_n .

Assume an individual is at risk for observations $\{k_n\}$ during the n th time interval, with (T_n, K_n, δ_n) designating the time, observation type, and positive-or-negative outcome, respectively, for the n th event. The individual's covariates on the n th time interval are represented by $Z_n(t) = \{Z(t) : (t_m, k_m, \delta_m), m = 1, \dots, n-1; Z_s(t)\}$, which include prior observation times, events, and outcomes and the individual's prior smoking history $Z_s(t) = \{z_s(u); 0 \leq u \leq t\}$. At times t_m , negative outcomes from observations or censoring events are represented by $\delta_m = 0$, and positive outcomes of observations by $\delta_m = 1$. Following the general approach of Kalbfleish and Prentice for multivariate failure time data with competing risks [41], we define the cause-specific hazard for observation $k \in \{k_n\}$ as

$$\lambda_k^n(t; Z_n(t)) = \lim_{\Delta t \rightarrow 0} \frac{P[t \leq T_n < t + \Delta t, K_n = k, \delta_n = 1 | T_n \geq t; (t_m, j_m, \delta_m), m = 1, \dots, n-1; Z(t)]}{\Delta t} \quad (9)$$

The all-cause failure rate on the n th time interval is

$$\lambda^n(t; Z_n(t)) = \sum_{k \in \{k_n\}} \lambda_k^n(t; Z_n(t)) \quad (10)$$

and the survival on the n th time interval with risks $\{k\}$ is

$$S_{\{k\}}(t_{n-1}, t_n; Z_n(t)) = \prod_{k \in \{k_n\}} \exp \left[- \int_{t_{n-1}}^{t_n} \lambda_k^n(t; Z_n(t)) dt \right]. \quad (11)$$

To evaluate Equations 7–8 backward in time as a function of $s = t - \tau$, we transform the event history into intervals $[s_n, s_{n-1})$ with $s_n \equiv t - t_n$, evaluating from $s = 0$ to $s = t$. Within a time interval, each observation type k can be turned on or off by setting z_k equal to 0 or 1, respectively. For example, setting $z_0 = 1$, $z_1 = 1$, $z_2 = 0$, and $z_3 = 0$ is used to evaluate the survival for the occurrence of lung cancer incidence ($k = 2$) and mortality ($k = 3$), in the absence of CT screening ($k = 1$) and selection for healthy entry ($k = 0$).

Continuous hazards gradually change the survival function. A negative outcome from a scheduled observation also affects the survival, having an immediate impact on the equations for the cell type that “survives” the observation. From Equation 7, a scheduled observation of type k at time t_n is represented by a Dirac delta function $\xi_k(\tau) = \xi_{kn} \delta(t - t_n) = \xi_{kn} \delta(s_n)$. Evaluation of the ODEs from $s = s_n - \Delta s$ to $s = s_n + \Delta s$ generates offsets in the variables C and D in Equations 7, or C' and D' in Equations 7'. The offsets (for $\Delta s \rightarrow 0$) are

$$\begin{aligned} C(s_n + \Delta s, t; Z_n(t)) &= C(s_n - \Delta s, t; Z_n(t)) \exp(\xi_{kn}(z_k - 1)) \\ D(s_n + \Delta s, t; Z_n(t)) &= D(s_n - \Delta s, t; Z_n(t)) \exp(\xi_{kn}(z_k - 1)). \end{aligned} \quad (12)$$

and similarly for C' and D' .

The survival with continuous observations $\{k_n\}$ on intervals n is evaluated by solving the system of ODEs on each time interval beginning at $s = 0$ and ending at $s = t$ including offsets for negative outcomes of scheduled observations that may occur at prior time points t_n' . Survival within one time interval while at risk for observations $\{k_n\}$ is

$$S_{\{k_n\}}(t_{n-1}, t_n; Z_n(t)) = F(t_n, t_n; Z_n(t)) / F(t_{n-1}, t_{n-1}; Z_n(t)) \quad (13)$$

To include left-truncation, the equations are again solved from $s = 0$ to $s = t_e$, where t_e is the time of entry into the study. The survival, conditioning on left truncation, is

$$S_{\{k\}}(t_e, t; Z_n(t)) = F(t, t; Z_n(t)) / F(t_e, t_e; Z_n(t_e)). \quad (\text{Survival, left-truncation}) \quad (14)$$

The hazard for a continuous observation k occurring at time t_n is evaluated by solving the system of ODEs on each time interval beginning at $s = 0$ and ending at $s = t_n$, including offsets for negative outcomes of scheduled observations that may occur at prior time points t_n' , with

$$\lambda_k^n(t_n; Z_n(t_n)) = H(t_n, t_n; Z_n(t_n)). \quad (\text{Continuous hazard}) \quad (15)$$

The hazard for a scheduled observation of type k' occurring at time t_n is evaluated using Equation 9 in the limit $\Delta t \rightarrow 0$ as the difference in survival $F(t_n, t_n; Z_n(t))$ evaluated

backward from shortly before t_n at $t_n - \Delta t$ and at $t_n + \Delta t$ beginning evaluation shortly after the observation time, conditional on survival until t_n . Evaluation at time $t_n - \Delta t$ has no offset on equations *C* and *D*. However, survival beginning right after the event time at $t_n + \Delta t$ includes the Dirac delta function for scheduled observation k' , creating an offset in equations *C* and *D* as shown by Equation 12. This is equivalent to beginning with differing boundary conditions at $s = 0$ reflecting the effect of the observation at t_n , e.g.

$$\begin{aligned} & \lambda_{k'}^n(t_n; Z_n(t_n)) \quad (\text{Scheduled hazard}) \\ &= 1 - \lim_{\Delta t \rightarrow 0} [S_{k' \{k\}}(t_n + \Delta t, t_n + \Delta t; Z_n(t_n)) / S_{\{k\}}(t_n - \Delta t, t_n - \Delta t; Z_n(t_n))] \\ &= 1 - S_{k' \{k\}}^+ / S_{\{k\}}^- \end{aligned} \quad (16)$$

where for scheduled observation k and continuous observations $\{k\}$,

$$\begin{aligned} S_{\{k\}}^- &\equiv F(t_n, t_n; Z_n(t)) \{C(0, t_n) = 1; D(0, t_n) = \sum_{\{k\}} \xi_k(t - t_n) (z_k - 1)\} \\ S_{k' \{k\}}^+ &\equiv F(t_n, t_n; Z_n(t)) \{C(0, t_n) = \exp(-\xi_{k'}(z_{k'} - 1)); \\ &D(0, t_n) = \exp(-\xi_{k'}(z_{k'} - 1)) \sum_{\{k\}} \xi_k(t - t_n) (z_k - 1)\}. \end{aligned}$$

Hazards are also conditioned by earlier positive outcomes, and by external cure processes. Suppose that an individual is diagnosed with lung cancer at time t_n' (through observation type k'). The hazard for subsequent lung cancer death ($k = 2$) is conditioned on the prior lung cancer diagnosis given the probability of cure ($\text{prob}_{\text{cure}}$),

$$\begin{aligned} & \lambda_{2(\text{cure})}^n(t; Z_n(t) | \delta_{n'} = 1) \\ &= \lambda_2^n(t; Z_n(t)) / [\lambda_{k'}^n(t_n'; Z_n(t_n')) * (1 - \text{prob}_{\text{cure}})] \\ & \text{(LC death hazard conditioned on diagnosis with possibility of cure)} \end{aligned} \quad (17)$$

with $(k' = 1)$ representing CT diagnosis and $(k' = 2)$ incidental diagnosis.

3.3 The multivariate likelihood

The multivariate likelihood [41] is formulated as the product of survivals on time interval $(t_{n-1}, t_n]$ with observations or censoring events n , $n = 1, \dots, N_i$ at times t_{ni} for subjects i , $i = 1, \dots, I$. Positive outcomes are represented by $\delta_{ni} = 1$ and negative outcomes or censoring by $\delta_{ni} = 0$. The individual likelihood over all time intervals N_i including follow-up until end of the study at $t = t_{N_i}$ is

$$\begin{aligned} \mathcal{L}_i(t) &= \prod_{n=1}^{N_i} \left([\lambda_{k_{ni}}^n(t_{ni}; Z_n(t_{ni}))]^{\delta_{ni}} \prod_{k \in \{k_n\}} \exp \left[- \int_{t_{(n-1)i}}^{t_{ni}} \lambda_k^n(t; Z_n(t)) dt \right] \right) \\ &= \prod_{n=1}^{N_i} \left([\lambda_{k_{ni}}^n(t_{ni}; Z_n(t_{ni}))]^{\delta_{ni}} S_{\{k_n\}}(t_{n-1}, t_n; Z_n(t)) \right). \end{aligned} \quad (18)$$

The individual likelihood is conditioned on entry into the study at time t_e using

$$\mathcal{L}_i = \mathcal{L}_i(t) / \mathcal{L}_i(t_e) \quad (19)$$

The cohort likelihood is composed of a product of individual likelihoods,

$$\mathcal{L} = \prod_i^I \mathcal{L}_i \quad (20)$$

3.4 Alternative exposure-response models for smoking and for enhanced clonal expansion during gestation

During preliminary model development, we assumed that smoking may independently influence the pre-malignant and malignant clonal expansion rates, and the two mutation rates, using non-linear exposure-response relationships of the same form as in Equation 1. Likelihood ratio tests indicated that only the pre-malignant clonal expansion rate is significantly influenced by smoking exposure-response. Thus we simplified the model by keeping only the smoking dose-response on pre-malignant clonal expansion, as shown in Equation 1.

For some cancer types, it is thought that a large fraction of early onset cases may be due to an early mutation of a stem cell that becomes clonally expanded during gestation, or during normal childhood growth. As described in the Discussion, we tried alternative models with a gestational effect, and a childhood effect, with the gestational effect having an improved likelihood. (However, the improvement was only marginally significant). To model this, we introduce a new parameter p_{20} .

$$\begin{aligned} g_1(t) &= p_3 * p_{20}, \quad (\text{for } 0 < t \leq 1) \quad (\text{Gestational effect in year 1}), \\ g_1(t) &= p_3 * (1 + p_4 * z_s^{p_5}(t)) \quad (\text{for } t > 1) \quad (\text{Smoking at rate } z_s(t)). \end{aligned} \quad (21)$$

The gestational effect increase the premalignant clonal expansion rate during the first year of life. Maximum likelihood estimates for the gestational effect are $p_{20} = 3.3652$ along with a slightly different value for the background premalignant clonal expansion rate $p_3 = 0.17524$ for males, and $p_{20} = 4.9783$ with $p_3 = 0.19629$ for females.

3.5 Assumptions about stem cells in normal and cancerous lung tissue

We assume both lungs in an individual contain 10^8 normal pulmonary stem cells [42, 43], as discussed in detail in the SM section. There are approximately 800 gm of lung tissue in both lungs [44, 45]. Assuming a similar density of malignant stem cells in solid tumor, and a solid tumor density of about 1 gm/cm^3 , we estimate there are about $\rho = 1.25 * 10^5$ tumor stem cells/cm³.

3.6 Choosing observation parameters

The probability that an individual has a negative outcome for a scheduled observation (or the approximate probability of no positive event during a unit time interval for a hazard) is the collective probability for no event, given the number of malignant cells at the time (or average number during the unit time interval for a hazard). For example, if we assume there are $n_2(t)$ malignant stem cells at time t , then this negative outcome probability is approximately

$$S_k(t) \approx (1 - \xi_k(t))^{n_2(t)}. \quad (22)$$

$S_k(t)$ defines the observation sensitivity as a function of malignant cell number, or tumor size (as illustrated in Figure 2).

If we assume the detection probability is significantly greater than zero (specifically, larger than ε) only when there are a large number of malignant cells ($n_2 \gg 1$), this can be simplified as $-\log(S_k^{-1}) = n_2 \log(1 - \xi_k) \approx -n_2(\xi_k + \xi_k^2/2 + \dots) \approx -n_2\xi_k$, since $\xi_k \ll 1$ for $n_2 \gg 1$ with $\varepsilon < S_k(t) \leq 1$. Thus

$$\xi_k \approx \log(S_k^{-1})/n_2. \quad (23)$$

The number of cells in a tumor with volume equivalent to a solid sphere of diameter d_k is

$$n_2 = \rho * \frac{4}{3} \pi \left(\frac{d_k}{2}\right)^3. \quad (24)$$

Substituting this in the formula above, we calculate observation parameter ξ_k necessary to produce a 50% probability of detection ($S_k = 0.5$) during a scheduled observation (or within a unit time interval for a hazard) as

$$\xi_k \approx \frac{\log(2)}{\frac{4}{3} \rho \pi \left(\frac{d_k}{2}\right)^3}. \quad (25)$$

If we know from other sources that the median detection diameter has a specific value d_k and ρ is known, this allows calculation of ξ_k . Alternatively, if d_k is not known, then ξ_k may be estimated by maximum likelihood, which also provides an estimate of d_k through this relationship. Thus using $\rho = 1.25 * 10^5$, we calculate $\xi_2 = 6.129 * 10^{-9}$ for incidental detection (in the absence of screening) of a tumor averaging about 3 cm in diameter during a given year, and $\xi_3 = 1.655 * 10^{-10}$ for lung cancer death at median 10 cm tumor diameter. The 3 cm effective diameter at incidental diagnosis lung cancer and 10 cm diameter at death is based on data from Geddes [34].

4.0 Results

Maximum likelihood estimates for parameters of the longitudinal multistage observation model were calculated using Equations 18–20 through a joint analysis of CARET and PLuSS data, with results shown in Table 2. Two-sided 95% credibility intervals (CI)s for all parameters in the lung cancer pathway were calculated using MCMC methods. CARET data are most important in relation to estimation of model parameters for lung cancer incidence and mortality in the absence of screening (parameters p_1 – p_{10}). The joint optimization included CT screening data from PLuSS, which allows estimation of the fraction of indolent nodules for CT screening (p_{11}), and the diagnostic sensitivity for CT screening as a function of cancer diameter (diameter of sphere with equivalent volume as the tumor) (modeled as p_{12}) (See Figure 2a,b). A cohort effect (set equal to one for CARET) was estimated separately for males and females in PLuSS and other CT screening cohorts as parameter p_{13} . Other-cause mortality was also modeled for each cohort (p_{14} – p_{19}).

4.1 Longitudinal multistage observation model calibration

We began by assuming a slightly more general model than shown in Figure 1, with separate non-linear (power law) smoking exposure-response functions that influenced both (pre-malignant and malignant) clonal expansion rates (p_3 and p_8) and both mutation rates (p_1 and p_6) in the lung cancer pathway. Maximum likelihood testing of this “full model” to CARET data for lung cancer incidence and mortality in the absence of screening with, or without, each of these smoking exposure-response terms indicated that there was only one significant

smoking exposure-response function for males and females, consisting of a sub-linear effect on clonal expansion of pre-malignant cells (p_4 , p_5). All subsequent modeling utilized smoking exposure-response affecting only the pre-malignant clonal expansion rate (See Equation 1, Figure 1, and Table 2).

Subsequent calibration was done in a joint analysis of data from CARET and PLuSS. With long follow-up in CARET (median mortality follow-up of 10.1 years), the fit to incidence and mortality indicated that there were significantly fewer observed lung cancer deaths than expected if there were no cure, delayed mortality due to treatment, or shifting of the “missing” lung cancer deaths to other-cause mortality due to lung cancer morbidity or misclassification.

Comparison of observed and model expected lung cancer incident cases and deaths in CARET by study year show a significant deficit for both observed outcomes during the first three study years. Effects of healthy entry bias are apparent in the ramping-up of cases in CARET during the first few years of study follow-up, with 9 female and 10 male incidental cases in year 1, 25 female and 27 male cases in years 1–2, and 168 female and 256 male cases during all (10.1 years median) follow-up. This is consistent with selection bias for subjects tending to be healthy at study entry. The healthy entry was modeled as a fictitious screen that was assumed to occur one year prior to study entry. The healthy entry effect was estimated as a negative outcome for observation ($k = 0$), where sensitivity depends on nodule size. At 50% sensitivity, the estimated threshold (p_{10}) was estimated as being 0.64 cm (0.62 cm, 0.81 cm) diameter.

Estimates of parameters for CT screening are also based on PLuSS data, as there was no CT screening in CARET. The diagnostic sensitivity was estimated for CT using the individual screening dates in PLuSS and records of the diagnosed cancers detected by CT. We also tested to see if there were significant differences in diagnostic sensitivity between baseline and subsequent annual CT screens, under the assumption that more easily identifiable lung cancers may be preferentially detected at baseline screen, and diagnosis of more difficult to diagnose tumors delayed until further growth at subsequent annual screens. Likelihood ratio tests indicated that a single diagnostic sensitivity (p_{12}) was sufficient. During the joint analysis, we also estimated cohort effects (p_{13}), setting the cohort effect equal to one for CARET. The estimated cohort effect for PLuSS males is 1.08 (0.99, 1.17), and for females is 1.11 (1.00, 1.23).

We began the joint calibration to CARET and PLuSS data, starting with the assumption that there are no indolent cancers ($\delta_2 = 0$). We found however, that there were significantly more cancers diagnosed by CT than is consistent with the longitudinal model process for the lung cancer pathway. Without indolent cancers, fits to the pattern of diagnoses by follow-up year were unacceptable. A likely explanation for this discrepancy is that some cancers diagnosed by CT are indolent, or slowly progressing. Thus we estimated the relative fraction of indolent cancers ($p_{11} = \delta_2$) using a Gompertz growth process that allows indolent nodules to be detected by CT, but limits their growth so that they are unlikely to contribute to symptomatic diagnosis or death.

With these refinements, the likelihood-based calibration of the longitudinal model provides excellent fits to CARET for lung cancer incidence, lung cancer mortality, and other-cause mortality for both genders, and combined CT and incidental diagnosis in PLuSS, as validated using χ^2 statistics comparing observed and expected cases in annual risk bins for each outcome. We also compared χ^2 values for the model predictions for lung cancer diagnosis in CARET with identical binning using the (20 parameter) Bach model for lung cancer diagnosis, using identical restrictions on the CARET data as used in developing the

Bach model [38]. The χ^2 values indicate that both models provide good fits to the CARET data.

4.2 Similarities and differences by gender

Likelihood ratio tests indicate smoking exposure-response parameters do not differ significantly between genders. Thus we utilize common values for both genders (See Figure 1 and parameters p_4 and p_5 in Table 2). Similarly, common parameters were found for the malignant cell death rate (p_7), healthy entry effect (p_{10}), and CT detection sensitivity for CT screens (p_{12}).

We found significant differences between genders for the remaining parameters, with males having higher first and second mutation rates (p_1 and p_6) and malignant cell clonal expansion rate (p_8) than females. Females have a higher pre-malignant cell death rate (p_2), pre-malignant clonal expansion rate (p_3), combined rate for cure or delayed mortality and transition to other-cause mortality after lung cancer diagnosis (p_9), indolent cancer fraction (p_{11}) and cohort effect (p_{13}).

4.3 CT diagnosis of indolent and aggressive cancers

We estimated that the effective tumor diameter at 50% sensitivity (p_{12}) for lung cancer diagnosis is 0.60 cm (0.54 cm, 0.64 cm). (See Table 2).

The estimated sensitivity for CT diagnosis as a function of tumor size is shown in Figure 3. We assume indolent and aggressive cancers have the same CT diagnostic sensitivity curves as a function of tumor size. Figure 2a,b shows cumulative incidental and CT diagnosis in CARET (black lines) and PLuSS (blue lines) for females and males, respectively. The stair-step lines represent observed cumulative lung cancer detection probabilities, calculated as one minus the Kaplan-Meier survival. The solid lines represent expected cumulative diagnostic probabilities from the longitudinal model. For PLuSS, the blue dashed lines represent the cumulative aggressive lung cancers. The area between the dashed and solid lines represents indolent lung cancers. Expected lung cancer detection in PLuSS, in the absence of screening, is shown by blue dash-dot lines. Expected incident cases for PLuSS males and females, in the absence of CT, are above those for CARET (due to the cohort effect and slightly heavier smoking among males in PLuSS).

Table 3 shows observed and expected cumulative CT and incidental lung cancer diagnoses for females and males in CARET, PLuSS, NYU, and Moffitt. CARET only had incidental diagnosis, with the table showing a good fit between observed and expected cases.

Cumulative lung cancer diagnoses in PLuSS, NYU, and Moffitt include CT diagnosed indolent and aggressive lung cancers, along with incidental cancers. (See Table 3). Most CT screening in PLuSS occurred at baseline and year 1. The first year of follow-up includes effects of the baseline CT screen, while years 1–2 include baseline and first annual CT. The estimated overdiagnosis due to detection of indolent nodules at the end of year 2, after most CT screening ended, is 7.0% (4.9%, 11.7%) for males and 33.0% (26.9%, 36.9%) for females (See Table 3). We also estimated that, due to earlier detection by CT (lead time) and limited follow-up, that an additional 2.2% (2.0%, 2.4%) of all diagnosed cancers among females and 7.1% (6.7%, 8.0%) among males would not have been diagnosed based on symptoms, in the absence of CT screening.

4.4 Lung cancer mortality

Observed and expected cumulative lung cancer deaths are shown in Table 4. We find the healthy entry effect has a larger influence on reducing CARET lung cancer mortality than

lung cancer incidence during the first few years of follow-up, as seen in Tables 3 and 4. Calibration between observed and expected lung cancer deaths in CARET for males and females is good. However, when we held the cure rate fixed at the value determined by calibration to CARET data, the CT screening trials generally have fewer observed lung cancer deaths than expected. In all CT screening cohorts combined, there were 45 observed lung cancer deaths, with 78.0 expected. After correcting for the cohort effect, this suggests a 42% reduction in lung cancer deaths compared to the unscreened CARET population. These results appear somewhat larger than the reports of a 20% reduction of lung cancer deaths in NLST, a randomized controlled trial comparing CT screening and x-ray detection [6].

4.5 Other-cause mortality

The longitudinal model also includes an effective model of other-cause mortality (See bottom of Figure 1). This requires six parameters, with two used for smoking exposure-response. Total other-cause mortality is calculated as a combination of expected cases from the other-cause model and excess other-cause mortality following incidence, as described above. No particular meaning should be assigned to the rates in the other cause mortality pathway.

4.6 Apparent cure or delayed mortality rates in CARET

Estimates from CARET of the combined rate (p_3) of apparent cure or delayed mortality and excess other-cause mortality following lung cancer diagnosis are 12.6% for males, and 21.1% for females. Among CARET males, there were 19 observed other-cause deaths after lung cancer diagnosis, with 4.4 expected; and for CARET females, there were 6 observed and 2.1 expected. After adjusting for excess other-cause deaths after incidence, the apparent cure or delayed mortality rates are 13.7% (12.0%, 14.0%) for males and 25.7% (24.1%, 26.7%) for females.

5.0 Discussion

The primary finding of this study is that, particularly among females, more lung cancers are diagnosed through CT screening, and are histologically confirmed as lung cancers, than should be “in the pipeline” based on calibration to incidence and mortality in the absence of screening. The model results indicates that this excess is primarily due to the presence of indolent cancers. We assume in modeling indolent cancers that initial growth kinetics are the same as for aggressive lung cancers, but that growth occurs through a Gompertz process, limiting the tumors to a size detectable by CT but unlikely to contribute to symptomatic diagnosis or death. Thus we assume that the indolent fraction does not contribute to lung cancer incidence or mortality. From these assumptions, we are unable to distinguish if some or all of the indolent cancers are temporarily held in check and may become aggressive later, or if they are permanently growth arrested.

Interestingly, we find significant gender differences in lung cancer progression. Approximately 33% of the CT detected cancers diagnosed among females during baseline and first annual CT screens are indolent, while we estimate approximately 7% are indolent among males. Similarly, we find an apparent cure or delayed mortality rate for females in CARET that is approximately twice that for CARET males.

For both genders, a higher proportion of indolent cancers are diagnosed at baseline CT, compared with subsequent annual CTs, as shown in Table 3. This is consistent with accumulation of indolent cancers that may be diagnosed at first CT, with fewer indolent cancers growing to diagnosable size at subsequent screens. The estimates of 7–35% fraction of indolent cancers (depending on gender and screening period) appears consistent with

other estimates of approximately 25% or more of radiographically diagnosed lung cancers being over-diagnosed, with higher estimates expected for CT screening [9].

Biological implications of the differences in lung cancer progression between males and females may be inferred from the MLEs of model parameters in Table 2. The MLEs indicate that males have higher mutation rates, but lower pre-malignant and malignant clonal expansion rates than females. The pre-malignant cell doubling time in the absence of smoking is 3.92 years for males, and 3.54 years for females. Smoking exposure-response parameters are the same for both genders, contributing the same relative increase in pre-malignant clonal expansion rates for both genders of 12% for 10 cig/day, 14% for 20 cig/day, and 16% for 40 cig/day, compared to non-smoking periods for males and females. The high pre-malignant cell death rates and small clonal expansion rates indicate that 99.4% of pre-malignant clones in non-smoking males and females eventually become extinct. For newly mutated malignant cells, we expect 97.6% will become extinct among males, and 96.8% among females. MLE estimates for the mean malignant stem cell doubling time are approximately 63.1 days for males, and 50.6 days for females. The estimated malignant stem cell cycle time is about once every 1.6 days. These rates generally agree with clinical data reported by Hall [51], where tumor doubling times for six primary lung cancers averaged 66 days, with 80% of the values falling between 18 and 200 days, and observed cell cycle times range from 1 to 5 days. However, our model doubling times are toward the short end of the range of estimates of median lung cancer doubling time from other studies [9, 34]. Our faster doubling time estimates relate primarily to the timing of diagnosis and death due to aggressive cancers, and may thus be explained as due to our separate analysis of aggressive and indolent cancers.

We note that a biological switch from malignant to indolent status would require a 3% increase in the malignant cell death rate, or similar decrease in the malignant cell division rate.

The methods developed here allow likelihood based estimation of the diagnostic contributions of aggressive and indolent cancers that may occur in the course of successive CT screens, along with symptomatic diagnoses, lung cancer mortality, and other cause mortality. We used biologically-based longitudinal modeling methods that include a stochastic observation process and conditioning of the probability for a positive or negative outcome on prior observation outcomes and smoking history. These methods allow estimation of screening sensitivities as a function of nodule size, and cellular kinetics which generate a stochastic sojourn time distribution (the time between when cancers are first screen detectable and when symptomatic diagnosis would occur).

Other methods have been used previously to estimate the effects of multiple cancer screens. Likelihood-based statistical methods were developed by Day and Walter [52] for joint estimation of parameters for screening sensitivity and sojourn-time distribution, which they applied for analysis of data for breast cancer screening. Biologically-based methods have been developed by Jeon, et al. [20] for simulation of the effects of multiple screens, using mathematical expressions for the size distribution of screen-detectable pre-malignant lesions, and applied for analysis of the benefits of up to two colonoscopies on the lifetime risk of colorectal cancer. Other models were used to estimate overdiagnosis in relation to prostate cancer [53] and the contributions of aggressive and indolent cancers in screening for ovarian cancer [54].

Current limitations of the longitudinal multistage observation model include calibration only to total lung cancer incidence and mortality (not by subtype), and lack of a treatment effect by which early diagnosis may impact lung cancer deaths. We expect that estimates of the

clonal expansion rate for malignant cells would likely change if treatment effects were modeled. However, we do not expect this would have much influence on estimates for the indolent fraction, since estimation of the indolent fraction depends primarily on the cumulative incidence curve, and not on survival.

We made a number of sensitivity analysis of our modeling assumptions. Comparison of residuals between observed and model-expected lung cancer cases among young age groups suggested that the model may be slightly improved by a non-constant clonal expansion rate beginning at birth. Thus we developed two alternative models with separate rates for pre-malignant clonal expansion (see Equation 21) during the first year of life (which we call a gestational effect) or during the first 15 years of life (a childhood effect). We found the alternative model with a gestational effect shows marginally significant improvement over no effect, with a better likelihood than for the childhood effect. A gestational effect is sometimes called a “jackpot” effect, since a few individuals have mutations which are clonally expanded during infancy, markedly increasing risk later in life [55, 56]. The gestational effect model is specified by substituting $p_3 = 0.17524$ for males and using a new parameter p_{20} to increase p_3 by a factor of 3.3652 during year one for males; and substituting $p_3 = 0.19629$ and increasing p_3 by a factor of 4.9783 during year one for females. This alternative model suggests that the gestational effect is rather small, accounting for approximately 2.7% of lung cancers among CARET females, and 1.7% among males. The gestational effect makes almost no difference in the estimates for the fractions of indolent nodules detectable by CT or in CT detection sensitivities that are presented here.

Although Table 1 indicates that all study populations have similar smoking profiles, experience indicates that there are almost always significant differences between study populations that may be associated with selection criteria, geographic, social, occupational, and temporal factors. We included a cohort effect (parameter p_{14}) to adjust for these factors, which we set equal to 1 in CARET and estimated for PLuSS and the other screening cohorts. The CARET study began approximately a decade before the CT trials, changes in cigarette manufacture and improvements in detection and treatment may contribute to differences in risk. The Moffitt study included an early entry cohort in which subjects were required to have COPD, whereas this requirement did not apply to the late entry cohort.

All follow-up in CARET, PLuSS, and Moffitt consisted of active cohort follow-up combined with National Death Index follow-up for mortality. However, the NYU cohort only used active cohort follow-up. The model was developed using CARET and PLuSS data, both with high follow-up rates - the 6-year follow-up rate for mortality in CARET was 98.5%, and for PLuSS was 100%. We plan to do further validation of the longitudinal model against other populations.

6.0 Conclusions

In summary, we find that approximately 33% of lung cancers diagnosed among females by the second year of CT screening appear to be indolent, in contrast to approximately 7.0% among males. This conclusion is based on analysis of longitudinal data for lung cancer incidence, CT screening, lung cancer mortality, and other-cause mortality. We also found that the apparent cure or delayed mortality rate for CARET females is approximately twice that for males. Taken together, these results suggest that there may be immunological or other biological differences between genders that produce a higher fraction of indolent lung cancers among females than males, or a higher probability that females switch from aggressive to indolent status during lung cancer progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

We develop a longitudinal multistage model of lung cancer incidence, computerized tomography (CT) diagnosis of indolent and aggressive cancers, lung cancer mortality, and other cause mortality.

The longitudinal multistage model utilizes a new stochastic observation process.

Indolent lung cancers make a significant contribution to CT diagnosis.

There are significant gender differences in the proportion of indolent lung cancers detected by CT.

Figure 1.

Longitudinal multistage observation model, including a lung cancer pathway (top) and an effective other-cause mortality pathway (bottom). The longitudinal data used for model calibration consist of individual smoking histories and variable combinations of sequential events, or observations. The lung cancer pathway includes three cell populations (circles), with $j=0$ representing a deterministic number of normal stem cells, and two stochastic stages ($j=1$ and $j=2$) representing populations of pre-malignant and malignant cells, respectively. Pre-malignant and malignant cells undergo stochastic birth at rates α_j , death or differentiation at rates β_j , and mutation at rates $\mu_{j,j+1}$ (with mutation modeled as an asymmetric cell division process), and observations at rates ξ_k . Observation probabilities in the lung cancer pathway (boxes labeled $k=0, \dots, 3$) are related to the size of the malignant cell population ($j=2$), and also to the indolent cell population ($j=2'$) for CT screening. Survivals and hazards for CT screen detection and histological confirmation of lung cancer ($k=1$), lung cancer incidence ($k=2$), and lung cancer mortality ($k=3$) are conditioned on subjects being healthy at study entry ($k=0$) and on prior observations. Symbols δ represent a fraction of states or observations, with δ_2 representing the indolent fraction of lung cancers that are detectable by CT and histologically confirmed as lung cancers while not contributing to lung cancer incidence or death during follow-up; δ_3 is the “missing” fraction of expected lung cancer deaths that do not occur due to apparent cure, treatment related delay of death beyond end of follow up, or excess other-cause mortality after lung cancer incidence; δ_4 is the sub-fraction of previously diagnosed lung cancers that (due to morbidity or misclassification) contribute to excess other-cause mortality instead of lung cancer mortality. The other-cause mortality pathway is separate from the lung cancer pathway. However, individual deaths occur through a competition between these pathways. Similar notation is used for the other-cause mortality pathway with $k=4$ representing other-cause death, but with effective rates that are not interpretable in terms of cell kinetics. The p_i ($i=1, \dots, 19$) label model parameters which are estimated from likelihood-based fitting to cohort data (See Table 2).

a) CARET and PLuSS male lung cancer detection

b) CARET and PLuSS female lung cancer detection

Figure 2.

Figure 2ab Cumulative lung cancer detection probability among a) females and b) males in CARET (black) and PLuSS (blue). The observed lung cancer incidental diagnosis probability in CARET (black stair-step line) is calculated as one minus the Kaplan-Meier survival curve. The expected lung cancer incidental diagnosis probability for CARET (black thick line) is calculated from the longitudinal model and the individual smoking histories in CARET. There is good agreement between observed and expected incidental diagnosis as a function of years since study entry. Observed lung cancer diagnosis in PLuSS combines CT diagnosis with incidental diagnosis (blue stair-step line); and expected lung cancer diagnosis in PLuSS from CT and incidental detection (blue thick line) is calculated from the longitudinal model including indolent and aggressive tumors. Again, the observed diagnosed cases in PLuSS are in reasonably good agreement with model predictions based on smoking histories (compare blue thick and stair-step lines). Note, however, that CT screening in PLuSS contributes to a rapid increase in diagnosed lung cancer cases during the first several years of follow-up (when most CT screening occurred in PLuSS) compared to the gradual

increase in CARET. In subsequent years, diagnosed cases in PLuSS and CARET remain nearly parallel (when most CT screening in PLuSS was finished), indicating that incidental rates in CARET and PLuSS are similar, but differ slightly as estimated by the cohort effect (parameter p_{13}). The nearly constant vertical offset of the diagnosed cases in PLuSS provides an indication that indolent tumors are diagnosed by CT that would not be detected incidentally. However, the model indicates that CT has a beneficial effect in providing earlier detection of aggressive cancers (blue dashed line) compared with no CT detection (dot-dash blue line) in PLuSS.

Comparison of model CT and incidental diagnostic sensitivity

Figure 3.

Comparison of model diagnostic sensitivity for CT (solid line) and incidental diagnosis (dashed line) as a function of the equivalent tumor diameter. The equivalent tumor diameter is defined as the diameter of a sphere with volume equal to the tumor volume. Tumor volume is calculated based on the expected number of malignant stem cells, as discussed in Section 3.3. The CT diagnostic sensitivity for lung cancer diagnosis is estimated based on PLuSS data. Maximum likelihood estimates suggest that lung cancers are diagnosed by CT with 50% sensitivity at a diameter of approximately 0.61 cm. The mean tumor size at incidental detection is assumed to be 3 cm equivalent tumor diameter, based on data compiled by Geddes [34]. The detection probabilities ($1 - S_k$) are plotted as a function of diameter d_k for observation type k , using Equations 22 and 24.

Table 1

Characteristics of study populations*

Variable	control arm	CT trial	CT trial	late entry	early (COPD)
No. of subjects	6,878	3,642	1,021	387	290
Male total (%)	3,797 (55.2)	1,872 (51.4)	476 (46.6)	206 (53.2)	169 (58.3)
Female total (%)	3,081 (44.8)	1,770 (48.6)	545 (53.4)	181 (46.8)	121 (41.7)
Age at entry mean (STD)	58.3 (5.5)	59.4 (6.8)	56.6 (9.7)	59.6 (7.8)	63.2 (8.3)
Smoke years mean (STD)	38.6 (7.1)	39.9 (7.6)	33.5 (10.7)	36.9 (9.2)	40.5 (10.2)
Pack years mean (STD)	49.1 (20.4)	50.0 (21.8)	44.2 (23.4)	55.2 (26.1)	62.2 (26.3)
Cig/day mean (STD)	25.6 (9.5)	25.1 (9.7)	26.6 (10.7)	30.5 (11.8)	31.4 (12.1)
Current smokers (%)	4,743 (69.0)	2,192 (60.2)	560 (54.8)	207 (53.5)	148 (51.0)
Former smokers (%)	2,135 (31.0)	1,450 (39.8)	421 (41.2)	180 (46.5)	142 (49.0)
Quit years mean (STD)	3.3 (1.7)	5.7 (3.9)	14.9 (10.7)	13.9 (13.2)	13.6 (16.3)
Person years at risk for detection	67,359	15,035	2,165	674	856
Male total (%)	36,386 (54.0)	7,651 (50.9)	817 (37.7)	357 (53.0)	503 (58.7)
Female total (%)	30,972 (46.0)	7,384 (49.1)	1,348 (62.3)	316 (47.0)	353 (41.3)
All lung cancers diagnosed	424	105	20	10	20
Male total (%)	256 (60.4)	54 (51.4)	5 (25.0)	3 (30.0)	15 (75.0)
Female total (%)	168 (39.6)	51 (48.6)	15 (75.0)	7 (70.0)	5 (25.0)
CT screens/subject (STD)	-	2.2 (0.6)	3.2 (2.4)	2.7 [†] (0.8)	3.9 [†] (1.4)
Total number of CT screens	-	8,059	3,766	1,044 [†]	1,122 [†]
Diagnosis < 9 mo after CT	-	64	14	10	19
Male total [yrs. 0-4]	-	35 [18.8,8.1,0]	4 [3.0,0.1,0]	3 [3.0,0.0,0]	15 [9.2,2.2,0]
Female total [yrs. 0-4]	-	29 [19.5,5.0,0]	10 [3.0,1.4,2]	7 [5.1,0.1,0]	4 [3.0,0.1,0]
Person years at risk for death	67,964	15,412	2,200	1,411	1,530
Male total (%)	36,704 (54.0)	7,849 (50.9)	829 (37.7)	754 (53.4)	886 (57.9)
Female total (%)	31,259 (46.0)	7,563 (49.1)	1,371 (62.3)	658 (46.6)	644 (42.1)
Lung cancer deaths	313	31	3	4	7
Male total (%)	196 (62.6)	16 (51.6)	2 (66.7)	2 (50.0)	5 (71.4)
Female total (%)	117 (37.4)	15 (48.4)	1 (33.3)	2 (50.0)	2 (28.6)

Variable	CARET cohort control arm	PLuSS CT trial	NYU CT trial	Moffitt CT trial	
				late entry	early (COPD)
other-cause deaths	938	128	11	6	26
Male total (%)	618 (65.9)	89 (69.5)	7 (63.6)	3 (50.0)	17 (65.4)
Female total (%)	320 (34.1)	39 (30.5)	4 (36.4)	3 (50.0)	9 (34.6)

Abbreviations: STD=standard deviation; COPD=chronic obstructive pulmonary disease.

* Excludes subjects with 5 or more years record of asbestos exposure.

[†] Assumes compliance with study protocol.

Longitudinal multistage observation model parameters

Table 1: The longitudinal multistage observation model includes a lung cancer pathway and an effective other-cause mortality pathway. Estimated model parameters are labeled by symbols p_i , $i = 1, \dots, 20$. Six parameters in Common column) represent cell kinetic rates in the lung cancer pathway that were indistinguishable between males and females based on likelihood ratio tests. Lung cancer mutation rates are labeled $\mu_{i,j+1}$, cell division rates as α_j , cell death or differentiation rates as β_j , and observation rates as ξ_k . Subscripts j represent cell type (or stage) and k the observation type. Cell types include normal stem cells ($j=0$), pre-malignant cells ($j=1$), and malignant cells ($j=2$). We assume there are a deterministic number $N_0 = 10^8$ of normal stem cells in both lungs combined. Pre-malignant and malignant cells undergo stochastic birth and death processes, with the clonal expansion rate being $\gamma_j = \alpha_j - \beta_j$. Smoking exposure-response affects the clonal expansion rate for pre-malignant cells. Aggressive lung cancers are modeled as undergoing exponential growth, while indolent cancers are modeled using Gompertz growth, making them detectable by CT but unlikely to cause symptoms or death. All observation processes are related to the expected size of the malignant cell population. Observation types include being healthy at study entry ($k=0$), CT screening ($k=1$), lung cancer incidence ($k=2$), and lung cancer death ($k=3$). A cohort effect multiplicatively modifies the entire lung cancer pathway. All rates have units of $[\text{yr}^{-1}]$. Other-cause mortality is modeled using similar methods, but the effective rates are not assigned meaning.

Table 2

Parameter	Effect	Maximum likelihood estimates (MLE)s and Markov Chain Monte Carlo 95% Credibility Intervals (MCMC 95% CIs)					
		Common parameters		Male-specific parameters		Female-specific parameters	
		MLE	(MCMC 95% CI)	MLE	(MCMC 95% CI)	MLE	(MCMC 95% CI)
Longitudinal lung cancer pathway							
CARET calibration							
$p_1 = \mu_{01}$	First mutation rate			0.24721 E-07	(0.24063–0.25321 E-07)	0.14453 E-07	(0.14050–0.14630 E-07)
$p_2 = \beta_1$	Pre-malignant cell death rate			27.435	(27.211–29.923)	33.937	(33.092–38.037)
$p_3 = \gamma_1$	Pre-malignant clonal expansion (CE) base			0.17691	(0.17498–0.17738)	0.19589	(0.19336–0.19681)
$p_4 = \gamma_{11}$	Smoking D-R coeff. pre-malignant CE	0.06913	(0.06795–0.08018)				
$p_5 = \gamma_{12}$	Smoking D-R power pre-malignant CE	0.22745	(0.19833–0.25505)				
$p_6 = \mu_{12}$	Second mutation rate			0.26886 E-06	(0.24765–0.29429 E-06)	0.15267 E-06	(0.13040–0.17871 E-06)
$p_7 = \beta_2$	Malignant cell death rate	160.360	(148.78–175.92)				
$p_8 = \gamma_2$	Malignant cell CE rate			4.0131	(3.7439–4.2096)	4.9992	(4.4658–5.3079)
$p_9 = \delta_3$	Apparent cure or excess OCM (fraction)			0.13748	(0.11972–0.13999)	0.25697	(0.24130–0.26738)
$p_{10} = d_0$	Healthy entry - effect threshold (cm)	0.64482	(0.62314–0.80587)				
PLuSS calibration							
$p_{11} = \delta_2$	Indolent pathway (relative fraction)			1.5888	(1.0757–2.8580)	9.7774	(6.8751–12.1368)
$p_{12} = d_1$	CT diagnostic sensitivity threshold (cm),	0.60669	(0.53909–0.63593)				
p_{13}	Cohort effect for PLuSS (CARET = 1.0)			1.1560	(1.0976–1.1877)	1.2339	(1.1872–1.2601)
Other-cause mortality pathway (effective model)				Male-specific parameters		Female-specific parameters	

Parameter	Effect	Maximum likelihood estimates (MLE)s and Markov Chain Monte Carlo 95% Credibility Intervals (MCMC 95% CIs)	
CARET calibration			
$p_{14} = \mu_{34}$		0.11609 E-07	0.65909 E-07
$p_{15} = \beta_4$		22.120	31.963
$p_{16} = \gamma_4$		0.21742	0.12112
$p_{17} = \gamma_{41}$	Smoking D-R coeff. for OCM	0.09853	0.08950
$p_{18} = \xi_{42}$	Smoking D-R power for OCM	0.31198	0.33041
$p_{19} = \xi_4$		0.19799 E-07	0.27671 E-07
PLuSS calibration			
$p_{14} = \mu_{34}$		0.84757 E-07	0.79665 E-07
$p_{15} = \beta_4$		33.208	28.877
$p_{16} = \gamma_4$		0.11849	0.10387
$p_{17} = \gamma_{41}$	Smoking D-R coeff. for OCM	0.08042	0.09650
$p_{18} = \gamma_{42}$	Smoking D-R power for OCM	0.32849	0.32978
$p_{19} = \xi_4$		0.26899 E-07	0.27562 E-07

Abbreviations: D-R=exposure-response; CE=clonal expansion; OCM=other-cause mortality; sens.=sensitivity.

Cumulative incidental and CT lung cancer diagnosis

Table 3

Variable	CARET			PLuSS			NYU			Moffitt CT trial		
	control arm			CT trial			CT trial			late entry		
	obs	exp	obs	exp	obs	exp	obs	exp	obs	exp	obs	exp
Female - year 1 (includes baseline CT for PLuSS, NYU, and Moffitt)												
All diagnoses	9	8.9	19	17.1	4	4.3	5	1.9	3	1.0		
Excess diag. lim. Fol-Up	-	-		4.8	1.4			0.6		0.3		
Overdiagnosis - indolent	-	-		6.0	1.6			0.2		0.2		
Indolent %	-	-		35.0%	37.3%			11.5%		21.4%		
Malignant (non-indolent)	-	-		11.1	2.7			1.7		0.8		
Malignant without CT	9	8.9		6.3	1.3			1.1		0.5		
Female - years 1-2 (baseline and 1st annual CT for PLuSS, NYU, and Moffitt)												
All diagnoses	25	22.1	29	28.7	4	7.5	6	4.7	4	2.5		
Excess diag. lim. Fol-Up	-	-		3.7	1.8			1.0		0.4		
Overdiagnosis - indolent	-	-		9.4	2.7			1.1		0.9		
Indolent %	-	-		33.0%	35.8%			22.6%		34.3%		
Malignant (non-indolent)	-	-		19.2	4.8			3.7		1.7		
Malignant without CT	25	22.1		15.5	3.0			2.7		1.4		
Female - all years (includes all CT screens in PLuSS, NYU, and Moffitt)												
All diagnoses	168	169.8	51	52.4	15	15.0	7	7.6	5	5.9		
Excess diag. lim. Fol-Up	-	-		1.1	3.2			0.1		0.1		
Overdiagnosis - indolent	-	-		11.9	5.0			1.8		2.0		
Indolent %	-	-		22.7%	33.4%			23.4%		33.2%		
Malignant (non-indolent)	-	-		40.5	10.0			5.8		3.9		
Malignant without CT	168	169.8		39.3	6.8			5.7		3.9		
Male - year 1 (includes baseline CT for PLuSS, NYU, and Moffitt)												
All diagnoses	11	9.5	17	16.2	4	1.9	3	1.1	9	2.9		
Excess diag. lim. Fol-Up	-	-		9.3	1.1			0.5		1.3		
Overdiagnosis - indolent	-	-		1.2	0.1			0.0		0.1		

Variable	CARET		PLuSS		NYU		Moffitt CT trial	
	control arm		CT trial		CT trial		late entry	
	obs	exp	obs	exp	obs	exp	obs	exp
Indolent %	-	-	-	7.1%	-	7.1%	-	3.4%
Malignant (non-indolent)	-	-	-	15.1	-	1.7	-	2.8
Malignant without CT	11	9.5	-	5.8	-	0.6	-	1.5
Male - years 1-2 (baseline and 1st annual CT for PLuSS, NYU, and Moffitt)								
All diagnoses	28	28.6	27	27.4	4	3.3	3	2.5
Excess diag. lim. Fol-Up	-	-	-	8.2	-	1.4	-	0.9
Overdiagnosis - indolent	-	-	-	1.9	-	0.2	-	0.1
Indolent %	-	-	-	7.0%	-	7.5%	-	4.3%
Malignant (non-indolent)	-	-	-	25.4	-	3.0	-	2.4
Malignant without CT	28	28.6	-	17.3	-	1.6	-	1.5
Male - all years (includes all CT screens in PLuSS, NYU, and Moffitt)								
All diagnoses	256	257.4	54	54.1	5	6.5	3	3.7
Excess diag. lim. Fol-Up	-	-	-	3.8	-	2.2	-	0.2
Overdiagnosis - indolent	-	-	-	2.7	-	0.5	-	0.2
Indolent %	-	-	-	5.0%	-	7.5%	-	4.8%
Malignant (non-indolent)	-	-	-	51.4	-	6.0	-	3.6
Malignant without CT	256	257.4	-	47.6	-	3.8	-	3.4

Table 4

Cumulative lung cancer deaths

Variable	CARET		PLuSS		NYU		Moffitt		CT trial	
	obs	exp	obs	exp	obs	exp	late entry	obs	exp	early (COPD)
Females										
Year 1	3	1.4	0	1.0	0	0.2	1	0.2	0	0.1
Years 1–2	8	9.7	3	6.9	0	1.3	2	1.2	1	0.6
Years 1–3	20	19.7	6	13.9	0	2.3	2	2.4	2	1.1
Years 1–4	30	30.3	12	19.8	0	3.1	2	3.3	2	1.7
Years 1–5	40	41.5	15	23.4	0	3.7	2	3.4	2	2.2
Years 1–6	47	53.1	15	24.2	1	4.1	2	3.4	2	2.5
All years	117	116.5	15	24.2	1	4.1	2	3.4	2	2.5
Males										
Year 1	3	0.7	1	0.5	0	0.0	1	0.0	0	0.1
Years 1–2	10	10.0	2	6.1	1	0.5	1	0.5	3	1.6
Years 1–3	19	26.6	6	16.0	1	1.2	2	1.4	4	4.2
Years 1–4	40	44.8	13	24.3	1	1.7	2	2.0	4	6.8
Years 1–5	62	64.2	16	29.4	2	2.0	2	2.1	5	9.5
Years 1–6	83	84.5	16	30.7	2	2.2	2	2.1	5	11.1
All years	196	195.3	16	30.7	2	2.3	2	2.1	5	11.2
Total (males + females)										
All years (obs/exp %)	313	311.8	31	54.9	3	6.4	4	5.5	7	13.7
	100%		56.5%		46.9%		72.7%		51.1%	