FLEXKB DOCUMENT
Version: HI.001.01132012.83639
Document generated: 01/13/2012

MGH Institute for Technology Assessment

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

READERS GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

- Smoking History Generator Component
- Population Component
- Incidence Component
- Natural History Component
- Screening Component
- Treatment Component
- Survival Mortality Component

Output Overview

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.

Further Reading

These topics will provide a intermediate level view of the model. Consider these documents if you are interested gaining in a working knowledge of the model, its inputs and outputs.

Advanced Reading

These topics denote more detailed documentation about specific and important aspects of the model structure

MODEL PURPOSE

SUMMARY

This document provides a brief overview of two versions of the Lung Cancer Policy Model (LCPM) as of the time this model profile was archived. The Summary Of Versions table lists differences between the single cohort and dynamic cohort versions of the model and provides examples of their uses to date. The Model Overview gives more detail and links to model components.

PURPOSE

The original single-cohort LCPM was designed to evaluate the effectiveness, costs, and cost-effectiveness of helical computed tomography (CT) screening for lung cancer in the U.S. The single-cohort model can also be used to evaluate both future screening technologies and advances in treatment effectiveness.

The LCPM was designed to reproduce observed lung cancer incidence and survival rates in a specified cohort, in the absence of screening. A screening component allows comparison of mortality rates in the same cohorts under multiple scenarios, e.g., no screening versus screening. Individual-level outputs include the probability of false positive screening tests. A notable limitation of the current model is that individuals are simulated as receiving care consistent with clinical practice guidelines.

A dynamic-cohort Population LCPM was developed to evaluate U.S. population trends in incidence and mortality.

CATEGORIES

Core Docs

MODEL OVERVIEW

SUMMARY

This document provides an overview of the lung cancer simulation model developed by researchers at the MGH Institute for Technology Assessment/Harvard Medical School.

PURPOSE

The Lung Cancer Policy Model (LCPM) was originally designed to evaluate screening programs in a specified cohort. When we originally joined CISNET (as an Affiliate group), the LCPM did not simulate populations. The Population LCPM was developed with CISNET funding and was used to participate in the Smoking Base Case. See Summary Of Versions for an overview of the differences between the versions.

Designed to evaluate the effectiveness, costs, and cost-effectiveness of helical computed tomography (CT) screening for lung cancer in the U.S., the LCPM will inform screening decisions prior to completion of ongoing trials, address limitations of published cost-effectiveness analyses of lung cancer screening and offer an opportunity to evaluate both future screening technologies and advances in treatment effectiveness.

BACKGROUND

An effective means of reducing mortality from lung cancer, the leading cause of cancer death in the U.S., is urgently needed. Unfortunately, even a sharp reduction in current smoking rates -- an obvious first step -- would not eliminate lung cancer in the near term: a former smoker's risk for lung cancer remains elevated for decades after smoking cessation. To date, no screening program has been demonstrated effective at reducing lung cancer mortality.

Ongoing trials of helical CT screening will contribute critical information on effectiveness, but debates over past cancer screening trials (e.g.,[1]) should remind us that publication of completed trial results is unlikely to eliminate uncertainty about the effectiveness of lung cancer screening.

Advances in screening technologies, staging examinations, and therapies are being made simultaneously, yet conducting controlled trials on all of these aspects at once is simply not feasible. The comprehensive modeling approach used in the LCPM, however, permits an evaluation of all three inter-related areas. Specifically, modeling can be used to: 1) estimate effects of several combined screening, workup, and treatment strategies; 2) interpret and reconcile the results of different screening trials; 3) evaluate the potential effects of improved adherence to staging and treatment guidelines; and 4) determine the effect that improvements in staging and treatment might have on screening effectiveness. Finally, by including costs as well as effectiveness outcomes, our model will provide information concerning the relative cost-effectiveness of interventions spanning the spectrum from screening to treatment, and thereby provide information which is useful to physicians, policy makers, legislators and the public.

Model Description

The LCPM is a state-transition model, analyzed as Monte Carlo to allow for individual heterogeneity in risk factors and event rates. Individuals can move through 5 possible states: general population, follow-up, diagnosis & staging, treatment & survival, and dead. Please see the Component Overview and links provided for further details.

The model employs a lifetime time horizon and a cycle length of one month to capture the short survival times of late-stage lung cancers and to allow for a wide variety of event recurrence frequencies. The model was populated with individuals in an age-, race-, gender-, and calendar year-specific cohort representative of the U.S. in terms of smoking history (Population Component).

Inputs include national survey data for assigning smoking histories, type-specific distributions of doubling times for lung cancers (Natural History Component), rates of thoracic imaging exams performed for reasons unrelated to lung cancer, and response rates of treatments.

Outputs include estimation of incident cancers (Incidence Component), stratified by age, type, and stage, as well as mortality by detected stage and treatment (Survival Mortality Component). Calibration to observed incidence and stage-specific survival curves from the NCI SEER tumor registry allowed estimation of parameters governing unobservable events, such as development of the first cancerous cell and of metastasis. Some endpoints from CT screening trials and other literature sources describing clinical experience were used as secondary calibration targets. Validation of the model was performed by reproducing observed results of a past lung cancer screening trial and cohort studies. See Calibration Validation Results for a summary of model calibration and validation.

As with any model, simplifying assumptions were made (Assumption Overview). Increasing complexity of the model must be balanced against the number of parameters that can be estimated using available data; calibration and validation can show that model outputs are consistent with observed data, but do not guarantee that the model accurately represents the underlying biology. The model currently omits radon and second-hand smoke exposure, two known risk factors for lung cancer.

Contributors

Pamela M. Mc Mahon, PhD
Chung Yin Kong, PhD
G. Scott Gazelle, MD, MPH, PhD

Categories

Core Docs

References:

[1] Gøtzsche, P. C., Nielsen, M. “Screening for breast cancer with mammography” in Cochrane Database of Systematic Reviews 2006; 4

ASSUMPTION OVERVIEW

SUMMARY

This document discusses key assumptions underlying the Lung Cancer Policy Model (LCPM) and their possible implications. See the linked Component documents for context and further details.

BACKGROUND

The LCPM is a comprehensive model of lung cancer development, detection, treatment, and survival. Unlike a stage-shift model, the LCPM's underlying natural history model does not require estimates of Screening Biases (eg lead-time) as model inputs. To estimate parameters governing unobservable events (e.g., timing of metastasis), we calibrated to multiple endpoints in observed data (see Calibration Details). Using the calibrated model, we can simulate a screening program and generate estimates of the screening biases as model outputs.

Archived versions of this document will remain as technical appendices for publications, but newer versions of this document will reflect updates and refinements. Like the Coronary Heart Disease Policy Model developed by Dr. Milton Weinstein (a Co-Investigator on the LCPM) and colleagues[1,2], the LCPM was designed to be a model with a long lifespan.

The LCPM does not rely on data from a single trial to inform the parameter estimates (but rather incorporates trial data as they emerge), so can be used to evaluate screening in populations not included in ongoing trials, and can address the 'moving target' problem of improved test sensitivity (e.g., CT resolution), as well as other late-breaking topics, such as treatment interventions.

ASSUMPTION LISTING

Population Component Assumptions

- To allow for undetected lung cancers in the cohort, each individual is first 'regressed' to age 20 and assumed to be free of lung cancer. Upon entering the general population state, he can develop one or more lung cancers as he ages and acquires his (known[3,4]) smoking exposure. Two procedures insure that the cohort still reflects the U.S. population upon reaching the cohort age: 1) individuals face no competing risks of death until reaching the cohort age; and 2) any individual who dies of lung cancer prior to reaching the cohort age is re-started at age 20 with the same smoking history. Aggressive cancers that would have been fatal at ages younger than the cohort age are thus appropriately removed.
- In the single cohort LCPM, all current smokers after 1990 face a 3% annual chance of quitting, based on estimates of 2.5% to 3.2%.[5,6] Cessation rates in the Population LCPM rely on the Smoking History Generator.

- Smoking histories in the single cohort LCPM did not incorporate the tendency of beginning smokers to gradually increase the number of cigarettes smoked per day. The Smoking History Generator used in the Population LCPM more closely approximates such smoking behavior influences the apportioning of lung cancer risk across the population (see Natural History, below) and alters the proportion of individuals in a cohort eligible for screening.

Natural History Component Assumptions

- The risk of developing a lung cancer is modeled using a tolerance model: increasing age, smoking exposure, and genetic susceptibility contribute to risks of developing one of 5 histologic types of lung cancer.
- A person can develop a maximum of 3 cancers in a lifetime, of any of the 5 types.
- The growth rate assigned to each cancer is drawn from a distribution specific to the histologic type, is assumed to decrease with increasing size, and was allowed to vary by smoking status during model calibration.
- Disease progression is modeled through monthly probabilities of involvement of lymph nodes and development of distant metastases. Progression risks are functions of characteristics of existing cancers (location, volume, doubling time, and type), nodal status, and random individual variation.
- Incidence of benign lesions varies with age and geographical region but not with smoking history. Few benign lesions exhibit cancer-like growth.
- The proportion of mixed adenocarcinoma/BAC that is pure BAC (bronchioloalveolar carcinoma) was estimated via calibration, not taken from the literature.

Incidence Component Assumptions

- Benign lesions and asymptomatic lung cancers can be detected incidentally during a thoracic imaging exam performed for an unrelated reason (non-screening). Risks of incidental imaging are functions of age, gender, and geography. Sensitivity varies with size and location and was estimated during calibration.
- Symptom detection can occur via symptoms from the largest primary cancer, by distant metastases, or both.
- Incidence rates reported in SEER reflect a negligible rate of lung cancer screening in the population.

Follow Up Component and Workup And Staging Component Assumptions

- Lesions suspicious for lung cancer (from symptoms or incidental detection) are biopsied if over a minimum diameter or followed with serial high-resolution CT exams (even in the absence of screening).
- Lesions that exhibit no detectable growth after 2 years of follow-up are assumed to be benign and to require no further surveillance. Reflecting clinical practice, a proportion of benign lesions are diagnosed as benign on the basis of a high-resolution CT (a proxy for modeling calcification patterns).

- Biopsy-confirmed malignancies are clinically staged based on guidelines recommended by the National Comprehensive Cancer Network (NCCN).

Treatment Component Assumptions

- Treatments are assigned following NCCN guidelines.
- Effectiveness of systemic treatments are based on probabilities of complete or partial response. See below for relationship of treatment effectiveness to survival.
- Effectiveness of resection depends on the existence of undetected second lung cancers and/or occult metastases.

Survival Mortality Component Assumptions

- Survival is a function of both underlying disease state and treatment received (which itself depends on the accuracy of staging). Patients with M1 (stage IV or ES) cancers are assigned exponential survival, based on observed median survival rates[7]. (Observed stage-specific survival rates[7] for patients with M0 cancers are used as calibration targets, not inputs.)
- Once a patient is diagnosed as stage IV, survival is as observed in SEER (by age, decade, race, gender, and cell type).

CATEGORIES

Core Docs

REFERENCES:

[1] Weinstein, MC, Coxson, PG, Williams, LW, Pass, TM, Stason, WB, Goldman, L "Forecasting coronary heart disease incidence, mortality, and cost: The Coronary Heart Disease Policy Model" in American Journal of Public Health 1987; 77: : 1417-1426

[2] Hunink, MGM, Goldman, L, Tosteson, ANA, Mittleman, MA, Goldman, PA, Williams, LW, Tsevat, J, Weinstein, MC "The recent decline in mortality from coronary heart disease, 1980-1990" in JAMA 1997; 277: 7: 535-542

[3] Massey, JT, Moore, TF, Parsons, VL, Tadros, W "Design and Estimation for the National Health Interview Survey, 1985-94" in Vital Health Statistics, Series 2, No. 110 1989;

[4] U.S. Department of Health and Human Services, National Center for Health Statistics, "The National Health and Nutrition Examination Survey III Data file 1988-1994." in Public Use Data file Series 11 1997;

[5] Centers for Disease Control "Smoking Cessation During Previous Year Among Adults -- United States, 1990 and 1991" in Morbidity and Mortality Weekly Report 1993; 42: 26: 504-507

[6] The Commit Research Group "Community Intervention Trial for Smoking Cessation (COMMIT): II. Changes in Adult Cigarette Smoking Prevalence" in Am J Public Health 1995; 85: : 193-200

[7] Surveillance Research Program, National Cancer Institute, "Surveillance, Epidemiology, and End Results (SEER) Program Seer*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2004 Sub (1973-2002 varying)" in Seer*Stat software version 6.1.4 2005;

PARAMETER OVERVIEW

SUMMARY

This document provides an overview of the major classes of parameters in the LCPM, and provides links to parameter documents.

BACKGROUND

Most natural history parameters were estimated by calibration. The NCI's SEER registry was the primary data source for calibration targets. In the absence of screening, the model should accurately predict observed tumor registry (SEER) incidence by year, age, sex, and race. Characteristics of incident cancers predicted by the model should also correspond to observed distributions of cell types, stages, and sizes, and stage-specific survival rates for M0 cancers should be accurately predicted. Additional calibration targets were defined from the literature (see Calibration Details and Output Overview).

PARAMETER LISTING OVERVIEW

1. Unobservable parameters define unobservable events: development of lung cancer, disease progression, and symptom detection. Note that the actual values of many of these parameters are not meaningful outside the context of the LCPM (although their relative magnitudes may reveal insights into biology). Of more interest are outputs of the model, such as estimates of Screening Biases.

See Parameters Natural History and Natural History Component for details.

2. Uncertain parameters were those for which literature estimates provided ranges of values. Categories of uncertain parameters included test characteristics, operative mortality rates for interventions, response rates for systemic therapies, and probabilities of clinical events such as wedge biopsy of a growing pulmonary lesion.

See Parameters Test Performance and Parameters Treatment for details.

3. Structural parameters were fixed during calibration, but included for future analyses. These included a parameter to allow simulation of African-American cohorts. Additional structural parameters are described in their relevant model components.

The Assumption Overview describes major assumptions underlying the LCPM.

4. Other parameters include estimates of costs and weights for adjustments in quality of life due to lung cancer diagnosis and treatment (to allow estimation of cost-effectiveness ratios; see Results Overview).

CATEGORIES

Core Docs

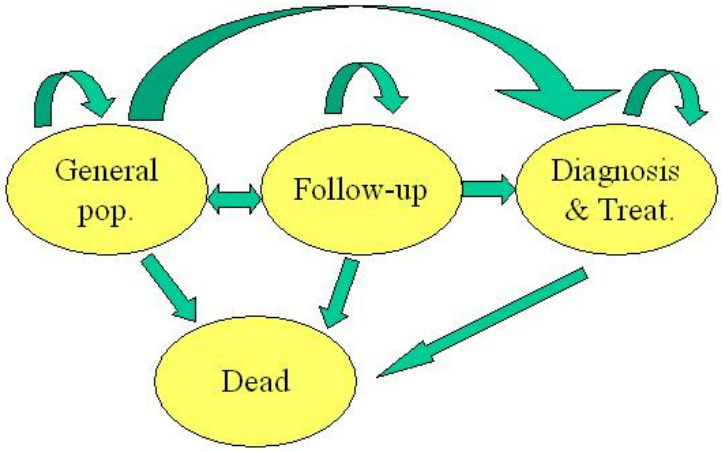
COMPONENT OVERVIEW

SUMMARY

This document describes typical sequences of component processes for a hypothetical individual simulated by the LCPM.

OVERVIEW

Persons start the model in the general population state.
See schematic.



Each month, persons in the general population state face competing risks of death from causes other than lung cancer.[1] While in the general population state, benign pulmonary nodules and lung cancers can develop, and lung cancers can grow, progress to nodal involvement and/or distant metastases, or cause symptoms. Additionally, persons face risks of undergoing non-screening thoracic imaging exams for reasons unrelated to lung cancer (e.g., for trauma). In a screening scenario, persons can undergo screening if they are eligible for the specific program and adherent to the screening protocol.

Persons with small incidentally detected lesions undergo sequential imaging exams in the follow up state.

Larger incidentally detected lesions, lesions exhibiting growth on serial imaging exams, and symptomatic cancers are sent for work up and staging.

Once the diagnosis of lung cancer is made, the cancer is staged, and the person moves to the treatment and survival state.

In the next section, we provide available links to component processes for each of the states indicated above.

Component Listing

General population

The Natural History Component is included, as well as the Screening Component and the Incidental Imaging Component.

Follow-Up

In the Follow Up Component, incidentally-detected nodules smaller than the cutoff threshold are managed expectantly with periodic high-resolution CT exams. While a patient is being followed up, he also cycles through the Natural History Component.

Work-up and Staging

In a single cycle (one month), workup and staging tests are used to establish both the presence of lung cancer as well as the extent of disease progression. See the Workup And Staging Component. Patients also cycle through the Natural History Component.

Treatment and Survival

In addition to the Treatment Component and the Survival Mortality Component, the Natural History Component is also included here. This allows for development of second lung cancers as well as disease progression of existing primary cancers or occult metastases.

See the Assumption Overview for key assumptions and links to parameter documents from the corresponding component documents.

Categories

Core Docs

REFERENCES:

[1] McMahon, P. M., Zaslavsky, A. M., et al. "Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis" in Medical Decision Making 2006; 26: : 497-511

SMOKING HISTORY GENERATOR COMPONENT

SUMMARY

The smoking history generator (SHG) is a shared precursor micro-simulation model that produces cohort-specific smoking histories and deaths due to causes other than lung cancer as inputs for the dose-response models used by members of the CISNET lung cancer consortium.

OVERVIEW

The core SHG software was parameterized using three tobacco control scenarios to produce the requisite input data for the models. The first, called the actual tobacco control (ATC) scenario, is a quantitative description of actual smoking behaviors of males and females born in the United States between 1890 and 1984. The second, called no tobacco control (NTC), is a quantitative description of predicted smoking behaviors of males and females in the United States under the assumption that tobacco control efforts starting mid-century had never been implemented. The third, called complete tobacco control (CTC), is a quantitative description of predicted smoking behaviors of males and females in the United States under the assumption that tobacco control activities yielded perfect compliance, with all cigarette smoking coming to an end in the mid-sixties. The ATC scenario used inputs derived directly from observed data in the National Health Interview Surveys (NHIS) and the Substance Abuse and Mental Health Services Administration (SAMHSA) National Survey on Drug Use and Health. The NTC scenario used inputs derived by extrapolating from trends in the observed histories before 1954, i.e., before any tobacco control in the decade leading up to the publication of the Surgeon General's Report in 1964. The CTC scenario was simulated by setting cessation rates to one (i.e., transferring all current smokers to former smokers) and allowing no further initiation starting in 1965 while using the observed values in earlier years.

DETAIL

The SHG accepts parameters supportive of the three tobacco control scenarios described above (see Table SGH-I below). The ATC scenario uses initiation, cessation and smoking intensity (CPD) rates directly derived from the NHIS and SAMHSA datasets. The NTC scenario uses initiation and cessation rates derived by fitting an age-

period-cohort model to the ATC rates upto 1954, i.e., before the apperance of any tobacco control measures, and by projecting those into the future maintaining them consistent with the patterns observed in 1954. The CTC scenario uses initiation and cessation rates identical to those of the ATC scenario upto 1965, and then sets the cessation rates equal to one and the initiation rates equal to zero, i.e., all smokers are forced to quit in 1965, and no new smokers are allowed to appear thereafter. All scenarios use smoking dependent other cause mortality (OCD) rates derived from several sources as mentioned above.

Computational process in the usage of the SHG

The CISNET SHG is implemented in C++ and consists of a single simulation class, that receives file system paths to five parameter files, four integer pseudorandom number generator (PRNG) seeds, and an optional immediate smoking cessation year parameter. The SHG simulation class employs four independent random selection processes that are implemented via a class-based wrapper of the Mersenne Twister PRNG.[1]

Here we briefly describe the outline for computational process in the usage of the SHG:

1. **Initialization**
    a. Load input data
    b. Initialize random number streams
3. **Start Simulation**
    a. Validate inputs
    b. Determine Initiation Age (if any)
    c. Determine Cessation Age (if any)
    d. Compute cigarettes smoked per day (CPD) vector for those who initiate
        1. Determine smoking intensity group (based on initiation age)
        2. Determine CPD based on smoking intensity and age at initiation
        3. Determine uptake period and attenuate CPD during uptake period
        4. Generate CPD vector from initiation to cessation or simulation cutoff
    e. Compute other cause of death (OCD) age
5. **Write individual outputs**
6. **Loop simulation if repeats are specified**

RELEVANT PARAMETERS

The SHG utilizes input data from several sources: the NHIS data from 1965 to 2001, the SAMHSA data, the Berkeley mortality database cohort life-tables, the National Center for Health Statistics (NCHS), the Cancer Prevention Study I and II (CPS-I and CPS-II), and the Nutrition follow-up studies sponsored by the American Cancer Society. The NHIS and the SAMHSA datasets provide estimates for prevalence of never, former (by years quit) and current smokers by age and year, and data on smoking intensity (in terms of the average number of cigarettes smoked per day (CPD)). These data were used to create implicit initiation and cessation rates. Using the average initiation rate, the SHG is able to determine the likelihood that a never smoker becomes a smoker. For those individuals that are smokers, the cessation rates are used to determine the likelihood that a smoker becomes an ex-smoker. The Berkeley life-tables, combined with smoking prevalence estimates from NHIS and the relative risks of death for smokers and former smokers in comparison to never smokers from CPS-I and CPS-II, are used to produce the probability of death from causes other than lung cancer based on age, sex, birth cohort, and smoking status. Table SHG-I summarizes the input source for the SHG for the three CISNET tobacco control scenarios.

Table SHG-I

Inpupt	**ATC**	**NTC**	**CTC**
Initiation rates	NHIS	Derived	Derived (no new smokers after 1965)
Cessation rates	NHIS	Derived	Derived (all smokers quit in 1965)
CPD[1]	NHIS,SMAHSA		
OCD[2]	Berkely life-tables, NCHS, NHIS, CPS-I, CPS-III, Nutrition Follow-up studies		
Birth year (1890-1984)	User Defined		
Gender (Male/Female)	User Defined		
Race (All race)	User Defined		

[1] Cigarettes smoked per day,[2]Other Cause of Death

ATC: actual tobacco control, NTC: no tobacco control, CTC: complete tobacco control.

To simulate life histories for individuals using the SHG, for any given run, the following parameters must be provided:

Table SHG-II

Parameter	Valid Values
Seed value for PRNG used for Initiation, Cessation, OCD[1], Smoking intensity quintile	Integer from -1 to 2147483647 (A value of -1 uses the clock time as the seed)
Race	0 = All Races
Sex	0=Male, 1=Female
Year of Birth	Integer from 1890 to 1984
Immediate Cessation year[2]	0 or Integer from 1910 to 2000
Repeat[3]	Integer >1 (number of times to repeat simulation)
File paths to Initiation,Cessation, OCD, Smoking intensity quintile and CPD[4] data files	As derived from NHIS depending on the scenario

[1]Other cause of death, [2] This variable is set to 0 except for CTC scenario. To apply immediate smoking cessation for CTC scenario, the year for immediate cessation must be supplied to the simulator. If the year value supplied is 0, immediate cessation will not be used in the run. If a year value is supplied, immediate cessation will occur on January 1st of year provided. [3]Key is optional and can be excluded. If the Repeat value is included and is not a vector value, each set of parameters will be repeated by the amount specified. If the Repeat value is included and is a vector value, the repeat value will pertain to the value set that it corresponds to. [4]Cigarettes smoked per day.

Dependent Outputs

The inputs of the SHG are used to simulate life histories (up to age 84) for individuals born in the United States between 1890 and 1984. These life histories include a birth year, and age at death from causes other than lung cancer, conditioned on smoking histories. For each simulated individual, the generated life histories include whether the individual was a smoker or not and, if a smoker, the age at smoking initiation, the smoking intensity in cigarettes per day (CPD) by age, and the age of smoking cessation. Smoking relapse, the probability that a former smoker starts smoking again, is not modeled. Table SHG-III summarizes the output of the SHG. Fig. SHG-1 shows two examples of smoking histories simulated by the SHG; a) an individual born in 1910 who begins smoking at age 17, quits at age 56 and dies at age 67 due to causes other than lung cancer, and b) an individual born in 1920 who begins smoking at age 22 and dies at age 53 due to causes other than lung cancer.

Table SHG-III

Table SHG-III

Initiation Age	Age at smoking initiation
Cessation Age	Age at smoking cessation
OCD[1] Age	Age at death from cause other than lung cancer
Smoking History	Smoking intensity quintile (5 quintiles ranging from light to heavy smoking), Yearly smoking dose (CPD[2])

[1]Other cause of death, [2]Cigarettes smoked per day.

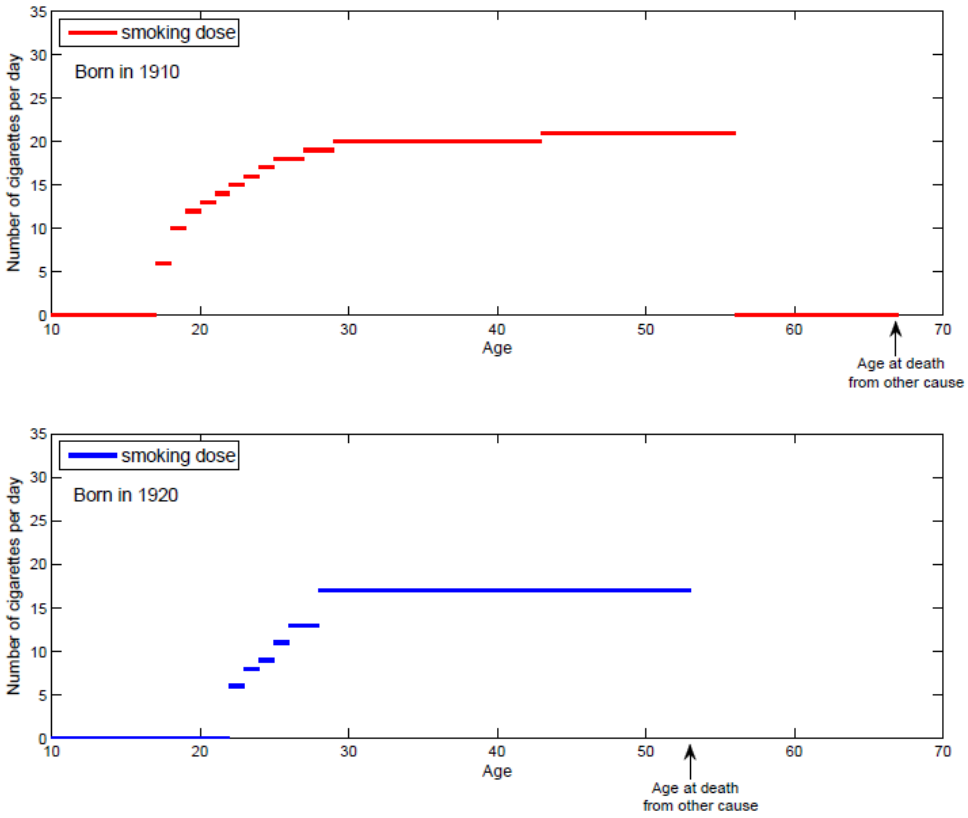


Figure SHG-1: Examples of the SHG-Generated Events

Simulation results by the SHG can be formatted in four different ways:

1. Text (formatted, human readable text depicting smoking history);
2. Tab Delimited Data (plain text, suitable for post-processing);
3. Annotated text-based timeline (visual representation in text);
4. XML (plain text, suitable for parsing). The outputs from the SHG are made up of individual life histories, each of which includes the following variables: birth year, age of smoking initiation, the corresponding smoking intensity (CPD) by age, age of smoking cessation, and age at death from causes other than lung cancer, conditioned on smoking histories.

REFERENCES:

[1] Matsumoto M., Nishimura T. "Mersenne twister: a 623-dimensionally equidistributed uniform pseudo-random number generator." in ACM Transactions on Modeling and Computer Simulation 1998; 8: 1: 3-30

POPULATION COMPONENT

SUMMARY

This document describes both the original single cohort LCPM and the Population LCPM. See Summary Of Versions for an overview of how the versions compare to each other.

OVERVIEW

The population component defines the initial characteristics of the population entering the LCPM for a given simulation. This is the first component in the modeling process. Once each individual in the population is initiated, the individual moves to the general population state (see Component Overview).

Initial characteristics assigned to each hypothetical person include gender, race, ethnicity, age, and smoking history. Smoking history includes current status, age at smoking initiation (if applicable), age at smoking cessation (if applicable), and cigarettes per day. In the single-cohort LCPM, the cigarettes smoked per day is assumed constant for cycles in which the individual is a current smoker. In the Population LCPM, cigarettes per day could vary over time.

Additional characteristics include an indicator for genetic susceptibility to lung cancer (see Natural History Component).

Simulations begin in a specified calendar year, so that:
1) the proportions of ethnicities and the prevalence of smoking is representative of the cohort being simulated, and
2) the model-predicted incidence rates can be compared to the corresponding SEER data (see Incidence Component).

QUANTITATIVE DESCRIPTION

The LCPM is a state transition (Markov) model, analyzed as Monte Carlo (i.e. it simulates life histories of individuals). The possible states are described in the Component Overview. The model uses a lifetime time horizon and a cycle length of one month to capture the short survival times of late-stage lung cancers and to allow for a wide variety of event recurrence frequencies.

POPULATION DYNAMICS

The original version of the LCPM is a single-cohort model. Individuals enter the model in specified calendar years, however, and carry appropriate smoking histories (informed by national survey data).

The Population LCPM simulates multiple birth cohorts to generate annual incidence and mortality rates.

Recurrence

The LCPM does model recurrence, via either clinical detection of (previously) occult metastases or by development of a new primary lung cancer. Each individual in the LCPM can develop up to 3 lung cancers (of any of 5 cell types), and up to 3 benign lesions. See the Natural History Component and the Survival Mortality Component.

Disease Distribution

We model the risks of developing each of the 5 cell types of lung cancer (adenocarcinoma/BAC, large cell, small cell, and squamous, as well as other) as independent, conditional on risk factors. (In other words, we do not assign a distribution of lung cancer histologies to the population.)

Detail

Approximately 10% of lung cancers occur in life-long non-smokers and SEER data are not stratified by smoking history. Therefore, the LCPM is populated with entire age, race and gender cohorts, representative of the U.S. in terms of smoking history. Smoking history includes current status, age at smoking initiation (if applicable), age at smoking cessation (if applicable), and cigarettes per day.

An indicator for genetic susceptibility to lung cancer (see Natural History Component) is assigned randomly.

Single cohort LCPM

The single-cohort LCPM simulates cohorts of white males and females aged 50, 60 or 70 in 1990. Cohorts entered the model in calendar year 1990 for calibration to SEER data from 1990 to 2000. Joint distributions of ethnicity and geographic region of the U.S. were derived from the 1990 Census. Ethnicity (Hispanic/non), region of the country, and smoking history were assigned to each individual.

Using the 1990 National Health Interview Survey we fit a multinomial logistic model to estimate the proportion of each smoking status using the predictors age, sex, race, ethnicity, and region. Data from the third National Health and Nutrition Examination Survey fielded in 1988-1994, were used to estimate normal distributions of ages of starting and stopping smoking and the average number of cigarettes smoked per day, conditional on smoking status, age group, and ethnicity. Cigarettes per day was assumed constant for cycles in which the individual is a current smoker.

Trial populations can also be simulated - see Screening Component.

Population LCPM

The Population LCPM uses the Smoking History Generator common to all CISNET lung groups. The Smoking History Generator allows for beginning smokers to 'ramp up' the number of cigarettes per day and yields a wider range of accumulated pack-years than the smoking histories used for the single cohort model described above.

Relevant Assumptions

See the Assumption Overview.

Relevant Parameters

Inputs

As described above, smoking histories for the single cohort LCPM were derived from the NHIS and NHANES, large sample surveys that yielded precise estimates of cigarettes per day and ages of starting and stopping smoking. For the same 6 cohorts in 1990, the Smoking History Generator yields a wider range of pack-years.

Impacts of Smoking History Inputs

Smoking is the strongest risk factor for lung cancer, so even small variations in smoking histories will influence lung cancer outcomes. To assess the downstream effects of the observed differences between the smoking histories from the original single cohort LCPM and those from the Smoking History Generator, we used the Smoking History Generator to provide ages of starting/stopping smoking and cigarettes per day and re-calibrated the model, allowing effects of smoke-years, cigarettes per day, and age to vary from their original estimates. We identified a parameter set that apportioned the lung cancer risk across smokers differently. See Parameters Natural History for further details.

Relevant Components

The Population Component is necessary to specify the characteristics of the cohort entering the LCPM. Different cohorts will have different lung cancer risks and therefore outcomes.

Dependent Outputs

All outputs will be affected by the characteristics of the population being simulated. Heavier smokers, for instance, will have higher rates of lung cancer death and possibly poorer outcomes from treatment. Characteristics (e.g., doubling times, sizes) of detected lung cancers will also vary across input populations. See the Output Overview document.

Relevant Results

See the Results Overview for a summary of relevant results from the single cohort LCPM and Population LCPM.

INCIDENCE COMPONENT

SUMMARY

To be counted as an incident case, a lung cancer must first develop, then be detected (by any of several possible modalities) and finally be diagnosed.

This document describes how the LCPM counts incident lung cancers and provides links to descriptions of components that involve development of cancer, detection, and diagnosis.

OVERVIEW

In the LCPM, we model the development of lung cancers, followed by tumor growth and metastasis (see Natural History Component). An individual with undetected lung cancer remains in the general population state (see Component Overview).

After the last individual in a cohort is simulated, we essentially count up the numbers of cancers in various categories. We count as incident cancers only cancers that were diagnosed during the patient's lifetime. Incident cancers are further categorized by stage, size, type, etc.

Non-screening scenarios:

Lung cancer can be diagnosed symptomatically (either the primary cancer obstructing an airway or from distant metastases) or asymptomatically (found incidentally during a thoracic imaging exam performed for unrelated causes - see Relevant Components, below).

Age-specific incidence rates are calculated and then compared to observed data.

Screening scenarios:

Cancers may also be detected by screening (see Screening Component). The model tracks the mode of detection of each cancer.

DISEASE RISK

For each of the 5 lung cancer cell types, we estimate a logistic function to predict monthly risks of developing a cancer. For each cancer type, we estimated independent coefficients for age, age squared, cigarettes per day, years of smoking, and years since quitting. There is also a randomly-assigned indicator for increased genetic risk (equivalent to HR=2). See Natural History Component.

To account for observed birth cohort trends in lung cancer risks and allow for differences in baseline risk by gender, we added a term that modifies the monthly risk of lung cancer development (all cell types), stratified by gender. See Calibration Details.

Impact of Screening

As described above, we do distinguish between incidence in the absence of screening vs. the presence.
We calibrate to SEER (no screening) and validate with screening trial data (with screening).

Detail

Development of cancer

Further details on the way the LCPM simulates development of cancer is provided in the Natural History Component.

Detection of cancer

Three modes of detection are possible in the LCPM:

1. Symptoms of previously undiagnosed lung cancers (either the primary cancer or distant metastases) can prompt detection. See the Symptom Detection Component.

2. During each cycle spent in the general population, persons may undergo imaging exams (thoracic CT, or CXR) performed for reasons unrelated to screening for lung cancer. See the Incidental Imaging Component.

3. Screen detection can occur in eligible individuals, in scenarios which include screening. See Screening Component.

Diagnosis of cancer

In the LCPM, a diagnosis of lung cancer is required before a person transitions into the Treatment Component. Diagnosis is operationalized by a biopsy that returns a specific diagnosis of lung cancer. Biopsies and staging both occur in the one-month Workup And Staging Component.

Relevant Assumptions

For the single-cohort LCPM, we used national survey data (NHIS, NHANES) to assign smoking histories to the individuals in the cohort (see Population Component), and calibrate to SEER data for incidence.

- If the SEER registries are not representative of the US, calibration to SEER data may yield biased parameter estimates.
- The smoking histories used for the single-cohort LCPM do not reflect the tendency of individuals to increase their smoking intake over time (i.e., light smokers become heavy smokers), which overestimates the pack-years accrued. This could have resulted in biased estimates of the cumulative dose-response relationship between smoking and lung cancer risk.

Also see the Assumption Overview.

Relevant Parameters

This component relies most directly on the natural history parameters (see Natural History Component and the Symptom Detection Component).

However, parameters in other components can influence the incidence rates, such as patterns of imaging examinations (and their test characteristics) in the general population (see the Incidental Imaging Component) and whether screening is occurring (see the Screening Component).

Relevant Components

The incidence component operates after the last individual in a simulated cohort 'dies.' It does not contain any other components, per se, but merely functions as a bookkeeping component.

Components that influence the predicted incidence rates include the Natural History Component, as well as the Follow-up, Workup And Staging Component and the Incidental Imaging Component.

Dependent Outputs

Most outputs of interest will depend on the Incidence component, including incidence rates and therefore mortality rates.

Relevant Results

See Calibration Validation Results for a description of outputs from the LCPM after calibration and validation and links to specific outputs.

Natural History Component

Summary

This document describes various aspects of the model processes responsible for generating the natural history of lung cancer. Benign pulmonary nodules are described in the Benign Component.

Overview

The natural history component occurs in every cycle of the model, so that new lung cancers may develop (and existing lung cancers grow and progress) throughout life.

The Population Component initiates the population entering the LCPM and therefore precedes the natural history component. The natural history component has sub-components for lung cancer development, disease (tumor) growth, disease progression, and symptom detection. All of the sub-components are described below and/or in linked documents.

Approximately 6% of patients with lung cancer develop more than one primary tumor, and only half of synchronous multiple primaries are the same type. Therefore, we model up to three cancers per person, of any of the 4 main types of lung cancer, plus a 5th type to represent Carcinoma, Not Otherwise Specified (ICD-O-2 code 80103). We modeled pure bronchioloalveolar carcinoma (BAC) as a subset of adenocarcinoma +/- some BAC, reflecting their differences yet typically mixed histology and misclassification.[3]

Disease Stages

A 'true' disease stage is assigned based on the individual's simulated disease characteristics (tumor size, nodal involvement, distant spread). This true stage is updated every cycle. See Details, below. An observed disease stage is also assigned, based on the individual's 'true' disease characteristics and the results from any diagnostic or staging tests performed. Observed and true stages may not match if a cancer is undiagnosed or mis-staged by a false test result.

Disease growth

We assume continuous Gompertz tumor growth, assigning a growth parameter for each new cancer that is drawn from distributions specific for the 5 cell types of lung cancer. We also include a term to allow cancers in smokers to exhibit accelerated growth. See Details, below and Parameters Natural History.

Stage Transition Trends

No temporal trends are imposed on stage transitions.

Disease evolution

One birth cohort parameter is changed over calendar time:

To account for observed birth cohort trends in lung cancer risks and allow for differences in baseline risk by gender,[6] we added a term that modifies the monthly risk of lung cancer development (all cell types), stratified by decade of birth and gender. See Calibration Details.

Remaining natural history parameters are not changed over (calendar) time. (Smoking histories do change over time, however, so will influence lung cancer trends.)

Regression

The model assumes an irreversible (in the absence of resection) progression of lung cancer disease stages. The speed of progression varies greatly, however, so that some cancers would never be detected during life in the absence of screening. The growth of BACs was truncated at a maximum diameter of 1 cm (detectable by X-ray).

Detail

Lung Cancer Development

The LCPM employs a simple 'tolerance' model of cancer development (so-called because cancer may only develop after an individual's tolerance to risk factors has been exceeded).

The monthly probability of developing the first malignant cell of cancer type k = 1-5 is a logistic function with a type-specific intercept and type-specific coefficients for age, age^2, years of cigarette exposure (smoke-years, SY), average number of cigarettes smoked per day (cigarettes per day, CPD), and the years since quitting (YSQ) smoking, if applicable. We also allow for random individual variation (highrisk, a proxy for genetic susceptibility), constant for all 5 types.

A logistic model produced nearly as high an R^2 goodness-of-fit statistic as a two-stage model[7] (R^2 of 0.61 and 0.67, respectively) in a comparison of 5 models for lung cancer's dose-response to tobacco,[8] and studies of case control data showed good fit using a logistic function to predict lung cancer (all types combined).[9] The MVK 2-stage model[7] models each initiated cell as growing instantaneously into a malignant tumor after a fixed period of time,[10] an assumption that precludes size-dependent sensitivity of imaging exams.

Lung Cancer Characteristics and Growth

Indicators are assigned to each new cancer for cell type, size (initial diameter of 0.01 mm), lobe in the lung, and central or peripheral location (varied by type).

In each cycle, the diameter and volume of existing cancers (and any growing benign lesions) are incremented according to a Gompertz function for tumor growth. Consistent with biological mechanisms of tumor growth (e.g., angiogenesis and necrosis of the tumor core), tumor doubling times decrease as the volume asymptotes to its maximum possible.

Mean doubling times for large, small, and squamous cell cancers were estimated from the literature (see Table Growth Parameters) and used to derive distributions of growth rate parameters. Distributions of growth rate parameters for adenocarcinoma/ BAC and "other" cell types were estimated via calibration.

A modification term (estimated during calibration) allows slower growth rates in non-smokers.

Lung Cancer Progression

Disease progression of an existing lung cancer can occur via nodal involvement and distant metastasis. Risks of disease progression depend on characteristics of any cancers present, and random individual variation that allows for more or less aggressive cancers, given a cancer's size and growth rate.

For each individual, 8 threshold volumes are drawn randomly from distributions for each nodal stage (N1, N2, N3) and for distant spread (M1), stratified by cell type (NSCLC/SCLC). Threshold volumes are adjusted to allow variation by growth rate. In each cycle, development of metastases and involvement of lymph nodes (N1, 2, 3) occurs if and only if the current volume of the largest cancer is greater than the corresponding adjusted threshold volume.

Symptom Detection

Each month, individuals with distant metastases and/or a primary lung cancer may develop symptoms that result in lung cancer detection. A person with symptom-detected cancer begins the following cycle in the Workup And Staging Component. See Symptom Detection Component for details.

Relevant Assumptions

Lung Cancer Development

The probabilities of developing each cancer type are assumed independent, conditional on the covariates (see Relevant Parameters, below). Each month >age 20, only one cancer can develop. Because the monthly probabilities are on the order of 10E-7, bias resulting from development of more than one cancer type is negligible.

Lung Cancer Growth

After Spratt, a maximum possible tumor size of 277 mm is assumed (this is consistent with the largest reported size of 201-300mm diameter in the SEER*Stat database for 60-64 year old white males, 1990-1994). As a simplification, we assume equal growth in all directions (i.e., spherical), allowing only one diameter to be tracked. The growth of BACs was truncated at a maximum diameter of 1cm.

Lung Cancer Progression

By definition, BACs do not progress. Because AJCC stage T3 cancers (i.e., cancers with extension into adjacent organs) represent only about 5% of NSCLC, we modeled tumor stage as T1 (≤3cm) or T2+ (>3cm). Involvement of lymph nodes (stages N0, N1, N2, and N3) dictates treatment options, so nodal status is modeled explicitly (but not specific nodes within each stage). Once distant spread (M1) has occurred, survival is poor, so explicit modeling of types of metastases was assumed to be unnecessary. As hypothesized for breast cancer, growth rate is related to the probability of metastasis. To reflect observed variations in propensity to metastasize for each histological type, adenocarcinomas are often more indolent, while small cell lung cancers develop metastases earlier. We assume that lymph nodes typically (but not always) become involved before distant spread occurs.

Lung Cancer Symptom Detection

We assume that peripheral cancers must be at least 10mm in diameter to cause symptoms. Central cancers have a smaller minimum diameter, because they are more likely to obstruct airways. We assume that metastases from SCLC cause symptoms faster than metastases from NSCLC. Benign nodules and lymph node involvement do not cause symptoms that result in lung cancer detection.

Relevant Parameters

The parameters in the Natural History Component are informed by calibration (see Calibration Details and Parameters Natural History).

Relevant Components

The Natural History Component occurs in every cycle, so can be thought of as a sub-component of the major states in the LCPM (see Component Overview for schematic).

Sub-components in the Natural History Component are described above or in linked documents:
lung cancer development, lung cancer growth, lung cancer progression, Symptom Detection Component, and Benign Component.

Dependent Outputs

The natural history component primarily determines the lung cancer incidence rate, as well as the type and stage distributions of incident cancers. The natural history component also primarily determines the survival rates of incident cancers, in conjunction with the Treatment Component.

The particular staging, work-up, and follow-up algorithms used in a scenario will also influence the stage distribution and rate of incident cancers, as well as the stage-specific survival rates (see the Workup And Staging Component). And the rates of thoracic imaging exams performed for reasons unrelated to screening (Incidental Imaging Component) will also influence incidence rates, although to a lesser extent than the natural history components.

Relevant Results

See the Results Overview for a description of the outputs from the base case LCPM.

REFERENCES:

[1] Raz, D J, He, B, Rosell, R, Jablons, D M "Current concepts in bronchioloalveolar carcinoma biology" in Clin Cancer Res 2005; 12: : 3698-3704

[2] Travis, W D, Garg, K, Franklin, W A, et al. "Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma" in J Clin Oncol 2005; 23: : 3279-3287

[3] Jackman, DM, Chirieac, LR, Janne, PA "Bronchioloalveolar carcinoma: A review of the epidemiology, pathology, and treatment." in Sem Respir Crit Care Med 2006; 26: : 342-352

[4] Jemal, A, Chu, K, Tarone, R "Cancer Surveillance Series: Recent trends in lung cancer mortality in the United States." in J Natl Cancer Inst 2001; 93: : 277-283

[5] Zheng, T, Holford, TR, Boyle, P, et al. "Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989" in Cancer 1994; 74: : 1556-1567

[6] Wakelee, HA, Chang, ET, Gomez, SL, et al. "Lung cancer incidence in never smokers" in J Clin Oncol 2007; 25: : 472-478

[7] Moolgavkar, S. H., Knudson, A. G., Jr. "Mutation and cancer: a model for human carcinogenesis" in J Natl Cancer Inst 1981; 66: 6: 1037-52

[8] Puntoni, R., Toninelli, F., Zhankui, L., Bonassi, S. "Mathematical modelling in risk/ exposure assessment of tobacco related lung cancer" in Carcinogenesis 1995; 16: 7: 1465-71

[9] Rachet, B., Siemiatycki, J., Abrahamowicz, M., Leffondre, K. "A flexible modeling approach to estimating the component effects of smoking behavior on lung cancer" in J Clin Epidemiol 2004; 57: 10: 1076-85

[10] Tan, W. Y., Zhang, L.-J. "Stochastic modeling of carcinogenesis: state space models and estimation of parameters" in Discrete and Continuous Dynamical Systems - Series B 2004; 4: 1: 297-322

SCREENING COMPONENT

SUMMARY

This document describes the processes in the model responsible for screen-detection of asymptomatic lung cancers.

OVERVIEW

Note that during model calibration (to SEER registry data), the screening component was turned off.

To define a screening program, we can specify eligibility in terms of age and pack-year histories, as well as screen frequencies and probabilities of adherence to recommended screenings.

To reproduce results from a particular screening study (e.g., for validation), the model is populated with simulated trial participants and the screening component is turned on.

An individual with a positive screening exam proceeds in the next cycle to either the Follow Up Component or the Workup And Staging Component. The particular scenario being modeled determines which of these components a person will transition into.

DISEASE DETECTION MECHANISM

Lung cancer detection can occur in one of 4 ways: 1) by symptom detection of distant metastases, as a function of the time since metastases developed, varied by N/SCLC; 2) symptom detection of the primary cancer as a function of size and location; 3) by incidental detection of an asymptomatic lung cancer on a chest imaging exam performed for unrelated reasons; and 4) by a screening exam (imaging or biomarker), in a scenario with screening operating.

For any imaging exam, the probability of detection of asymptomatic cancers is a function of size, location (peripheral/central) and test characteristics.

SCREENING DISSEMINATION

For screening exams, individuals are screened if they are both 1) eligible for the screening program being modeled and 2) adherent, which is currently assigned randomly according to the population-wide probability of adherence.

The probability of incidental (non-screening) imaging exams is a function of age, region of the U.S., and race. See Incidental Imaging Component. Temporal trends in these background rates have not yet been explicitly incorporated.

Type / Detection Interaction

The probability of detection on an imaging exam is a function of nodule size (and therefore growth rate, indirectly) and location: central lesions are less likely to be detected. Both growth rate and the proportion central vs. peripheral vary by cell type. See the Natural History Component.

Stage / Detection Interaction

As stated above, the probability of detection of a pulmonary lesion on an imaging exam is a function of nodule size and location (central/peripheral) and the test characteristics of the imaging exam. Nodal involvement and distant metastases are not detected on a screening imaging exam so do not influence screen detection (but do of course influence symptom-detection - see the Natural History Component).

Length Bias

Slower-growing lesions persist in the asymptomatic state and are therefore more often 'available' to be screen-detected, on average, than faster-growing lesions. The probability of detection on an imaging exam is a function of lesion size (and therefore growth rate, indirectly). The growth rate varies by cell type. See the Natural History Component.

On average, lung cancers detected on annual screening exams would be expected to have longer doubling times (i.e., slower growth rates) than interval-detected lung cancers. Note that a small, slow-growing lung cancer may be referred for follow-up serial CT exams; if no growth is detectable over a two-year period, the cancer would be incorrectly diagnosed as benign.

See Screening Biases for background information on lead-time, length-time and overdiagnosis biases.

Detail

Parallel random number generation allows simulation of the same individuals in screening vs. non-screening scenarios. This allows us to compare the outcomes of individuals in the two scenarios, as well as the mean life expectancy across a cohort, for a better understanding of the range of individual outcomes attributable to screening.

When simulating a specific screening study, individual-level data from the study (if available) is used to populate the LCPM with a cohort similar to the study participants. See Protected Health Information.

Relevant Assumptions

We assume that nodal involvement and distant metastases are not detected on a screening imaging exam. See also the Assumption Overview.

Relevant Parameters

To enable simulation of screening, one parameter is set in the input file (intervention = 1 for screening, vs. 0 for no screening), and additional parameters define eligibility (based on pack-years of smoking exposure, years since quitting, and age), adherence rates, and screening frequency (modality, frequency, maximum number of screens, and follow-up algorithm).

Sensitivity and specificity of the screening exam also affect the efficacy of the screening program. See Parameters Test Performance.

Indicators record screen results and cancers detected.

Relevant Components

Under a screening scenario, individuals in the general population state are screened if they are 1) eligible, and 2) adherent. Persons in the Follow Up Component, the Workup And Staging Component, and the Treatment Component are not screened.

Screening will increase the rate of detection of lung cancer in a population and therefore impact the Incidence Component. Similarly, by detecting a lung cancer earlier, screening can alter the treatment a patient would receive in the Treatment Component.

Dependent Outputs

Because screening detects asymptomatic cancers, prevalence and incidence rates depend on the screening program in place (if any), as do stage distributions and cell types.

To date, we have used outputs from simulations of two single-arm screening studies to calibrate certain endpoints, to validate the LCPM, and to predict outcomes from hypothetical control arms.

Relevant Results

The Mayo Clinic conducted a single-arm study of helical CT screening for lung cancer in current and former smokers. Using data provided by the Mayo Clinic (see Protected Health Information), we replicated the trial population by bootstrapping demographics and smoking histories from individual records. One endpoint (baseline prevalence) was used to calibrate the proportion of adenocarcinoma that was BAC (see Natural History Component). Remaining endpoints were reserved for use as validation endpoints.

See the validation section of Calibration Validation Results for a link to a description of validation of the LCPM using the LSS study endpoints.

See the Results Overview for analyses of screening programs.

TREATMENT COMPONENT

SUMMARY

This document describes how treatment after diagnosis is modeled.

OVERVIEW

To enter the treatment component, patients must have been diagnosed with lung cancer in the Workup And Staging Component. Treatment is modeled as occurring in the month(s) after reaching the 'treatment and survival' state. Patients remain in this state until death (from any cause). See also the Survival Mortality Component.

Treatment consists of either removal of the primary lung cancer (i.e., resection) or systematic therapy. Tumors which respond to systemic therapy are reduced in size (diameter), following conventional guidelines for solid tumors.[1]

TREATMENT DISSEMINATION

Treatment is assigned based on the diagnosed stage and type (NSCLC/SCLC). We currently assume all patients receive care according to consensus guidelines (e.g., National Comprehensive Cancer Network, NCCN).

We are in the process of adding a 'usual care' option that more closely approximates observed practice patterns. The usual care option will allow us to explicitly vary treatments with calendar year, which will be particularly important in the Population LCPM.

TREATMENT EFFICACY

Treatment effectiveness is incorporated as follows: a person with no occult metastases whose primary cancer is resected is assigned competing risks consistent with a person of the same smoking history – not stage I survival from SEER. On the other hand, if occult metastases are present in a person who undergoes resection for an apparent stage I cancer, the metastases continue to develop as before. (The presence of undetected micro metastases is likely the cause of the poor observed survival after "curative" resection in many patients.)

If a second, undetected primary tumor remains (in a non-resected lobe), metastasis can occur. Note that removal or sampling nodes at resection can result in re-assigning stage at diagnosis, but provides no survival benefit.

For systemic therapies, we use probabilities of partial and complete responses as published in the literature (see Parameters Treatment). A response results in a reduction of the size(s) of existing lung cancer(s), and thereby may delay disease progression.

We do model adverse effects of screening and treatment. Operative mortality can occur during resection, mediastinoscopy, or VATS, in diseased or non-diseased persons (iatrogenic deaths are tracked). We have not yet incorporated complications (e.g., pneumothorax) or quality of life.

Detail

The default Treatment Component simulates all patients as receiving guideline care.

Only individuals assigned the status of operative candidate were eligible for surgical resection, regardless of stage. To account for patients who were not operative candidates, we estimated proportions of SEER cases who were NSCLC stage I and II and either refused surgery or had contraindications.

As observed in clinical practice, a small proportion of operative candidates with stage LS (limited stage) SCLC underwent resection, with the remaining patients receiving chemoradiation.

Operative candidates with NSCLC stages I through IIIa were assigned resection, with the remainder and all stage IIIb cases receiving chemoradiation.

Stages IV (NSCLC) and ES (SCLC) were assigned chemotherapy.

See Parameters Treatment.

Relevant Assumptions

Death from lung cancer is unlikely to occur without detection of metastases (due to symptoms or otherwise), so we assume that once metastases are detected (by symptoms or any modality), survival is as observed in SEER for stage IV-detected cancer. We estimated cause-specific (net) survival for cases diagnosed as stage IV in the years 1990 – 2000, stratified by 10-year age group, race, and gender. Net survival (i.e., in absence of other causes) was used because persons face competing risks elsewhere in the model.[2]

Median survival of stage IV lung cancer is uniformly less than one year, so survival for M1 (stages IV or ES) is modeled as exponential.

See also the Assumption Overview.

Relevant Parameters

Parameter values that define treatment efficacy are probabilities of complete or partial response, using the definition of complete as no visible cancer at 4 week follow-up and partial as ≥30% decrease in diameter.[1] Probabilities of complete and partial responses vary by type, with estimates taken from the literature. A cancer that partially responds to therapy is decreased in diameter by 30%, and a cancer that completely responds to therapy is reduced to 1.5mm diameter, or below the 2mm detection threshold assumed for helical CT.

Based on the new diameter, an adjusted 'time since cancer developed' is calculated, retaining the original growth parameter, alpha. The new 'time since cancer developed' is used to increment growth in all future cycles.

To account for observed differences in growth rates of cancers pre- and post-therapy, we include a parameter that allows faster-growing cancers (cancers with a parameters over a specified cutoff) to be more or less likely to respond to therapy. These parameters were initially set to values that conferred no effect (probabilities of response vary by cell type and treatment) but were varied during calibration.

See Parameters Treatment.

Relevant Components

Treatment assignment occurs as the final step in the Workup And Staging Component (i.e., after the stage at diagnosis is assigned). The treatment itself is the first step in the Treatment and Survival state.

The sensitivity and specificity of the staging algorithm influences the treatment assignment. The specific treatment assigned and the treatment's effectiveness both influence the survival rate.

Dependent Outputs

Survival by stage is dependent on the treatment assigned and the treatment's effectiveness. For example, assigning systemic therapy instead of resection to a patient with resectable disease will result in a shorter survival time.

Further, the sensitivity and specificity of the staging algorithm (Parameters Test Performance) influence the treatment assignment. For example, if the staging tests performed on a hypothetical patient miss the involvement in a contralateral node, the individual will be understaged and receive an inappropriate treatment.

Mortality rates are calculated as a secondary output, based on age at death among lung cancer patients.

Incidence rates, on the other hand, depend on neither the treatment assigned nor the treatment effectiveness.

Relevant Results

See Output Overview and Results Overview.

REFERENCES:

[1] Therasse, P, Arbuck, SG, Eisenhauer, EA, Wanders, J, Kaplan, RS, Rubinstein, L, Verweij, J, Van Glabbeke, M, van Oosterom, AT, Christian, MC, Gwyther, SG "New guidelines to evaluate the response to treatment in solid tumors" in Journal of the National Cancer Institute 2000; 92: : 205-216

[2] McMahon, P. M., Zaslavsky, A. M., et al. "Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis" in Medical Decision Making 2006; 26: : 497-511

Survival Mortality Component

Summary

This document describes how lung cancer survival is modeled and describes estimation of both lung cancer-specific and other-cause mortality.

Overview

Once a hypothetical patient is diagnosed with lung cancer, he or she moves into the 'treatment and survival state', and remains there until death. The Treatment Component precedes the Survival Mortality Component.

The patient can die from any cause while in this state. Relative risks of each cause of death are a function of underlying disease state, treatment received, any surveillance performed, age, gender, race, and smoking history.

Survival Estimation Covariates

Lung cancer-specific survival for patients diagnosed at stages I-III (i.e., M0) is based on the true, underlying disease stage and the treatment assigned. Stage-specific survival for patients with M0 cancers is a calibration target for the LCPM, not an input. See Calibration Details and below.

Once a person is diagnosed (by symptoms or any modality) as stage IV (i.e., M1), lung cancer specific survival is assumed exponential. Cell-type (N/SCLC) specific median survival by age, gender, and race group was estimated from SEER for appropriate calendar years as inputs.

Survival after clinical detection

Same as above.

Screen Detection Benefit

Screening may detect cancers that have not yet metastasized.

Mortality Reduction

Resection of an early-stage cancer is curative if 1) no occult metastases remain and 2) no additional lung cancers arise. The person is subject to competing mortality risks appropriate to his/her age and smoking history (see below).

Resection of an early-stage cancer in a patient with occult metastases does not confer a survival benefit.

Mortality rates are calculated after the last individual in a simulation run 'dies', and are merely counts of lung cancer deaths by age at death, divided by the population at risk. Mortality rates are therefore completely dependent on the incidence and survival rates, and are merely an additional way to present the same information.

Other Cause Mortality

The Population LCPM assigns other cause mortality according to estimates from the Smoking History Generator, a common input for the lung cancer models in CISNET.

The original single-cohort LCPM assigns other-cause mortality risks using results from an independently-conducted analysis. We developed a Bayesian evidence synthesis model to estimate cause-specific mortality rates stratified by age, sex, race, and smoking status.[1] We combined three data sources: 1) individual survey data on smoking status, demographics, and date and cause of death; 2) population data on numbers of deaths by cause; and 3) cohort study estimates of smoking-related mortality risks, correcting for known inconsistencies between two of the data sources. Risks of heart disease and other causes (i.e., non-lung cancer, non-heart disease) are used as inputs for the LCPM.

Leadtime

Stage-specific survival is not an input, but rather a calibration target (see Calibration Details and Output Overview).

Estimates of lead, length, and overdiagnosis biases (see Screening Biases) are outputs of the model, obtained by simulating the same cohort with and without screening.

Detail

If a patient undergoes curative resection of an early stage lung cancer and harbors no occult metastases, the patient is assigned competing mortality risks appropriate for his or her age, gender, race, and smoking status.

If a patient undergoes resection of an early stage lung cancer but does harbor occult metastases, the metastases continue to develop as before, and can cause symptoms. Once symptomatic, the person is assigned a stage IV survival as above.

Patients who undergo systemic therapies may respond to the therapy, which results in a reduction in the size of the primary lung cancer(s), and therefore a reduction in the monthly probability of disease progression (see Natural History Component).

Relevant Assumptions

See the Assumption Overview, the Treatment Component and the Natural History Component.

Relevant Parameters

See Parameters Treatment for values of parameters that govern effectiveness of treatment and influence survival rates.

Relevant Components

See the Treatment Component and the Natural History Component.

Dependent Outputs

Stage-specific survival is dependent on this component (Calibration Survival1). Incidence rates, however, are not dependent on this component.

Relevant Results

See Results Overview and Output Overview for more information on calibration and validation outputs.

References:

[1] McMahon, P. M., Zaslavsky, A. M., et al. "Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis" in Medical Decision Making 2006; 26: : 497-511

OUTPUT OVERVIEW

SUMMARY

This document describes the types of outputs generated by the LCPM.

OVERVIEW

See Results Overview for a summary of how the various outputs are used for calibration, validation, predictions, and analyses.

Some general categories of outputs include:

incidence rates;
characteristics of incident cancers;
survival and mortality rates;
screening test results;
effectiveness of screening tests;
estimation of screening biases.

OUTPUT LISTING

Within each general category, some examples of specific outputs include:

incidence rates;
Age-specific incidence rates, by gender, race, and calendar year (used as calibration endpoints for model development; see Calibration Incidence1)
Age-adjusted incidence rates (predictions from the Population LCPM)

characteristics of incident cancers;
Size, type and stage distributions of incident cancers (used in Calibration Size Type Stage1 as calibration endpoints for model development)

survival and mortality rates;

Survival curves by type (SCLC vs. NSCLC) and stage at diagnosis (used in Calibration Survival1 as calibration endpoints for model development)

Mortality rates (used in Validation Cohort Studies1 as validation endpoints, in comparison to published cohort studies)

Age-adjusted mortality rates (used in Calibration USMortality1 as calibration endpoints for the Population LCPM)

screening endpoints;

Estimation of effectiveness of screening (see Results Overview for publications)

Reproduction of observed endpoints in the LSS screening trial (used in Validation Lung Screening Study1 as validation endpoints)

Screening trial endpoints:

-stage shift

-number of surgeries (appropriate and inappropriate)

-number of invasive work-up procedures (appropriate and inappropriate)

estimation of screening biases

By simulating both screened and unscreened scenarios, the model estimates lead-time, length-time, and overdiagnosis (see Screening Biases).

CATEGORIES

Core Docs

RESULTS OVERVIEW

SUMMARY

This document will discuss results from the LCPM and provide links to published evaluations of lung cancer control interventions.

OVERVIEW

We see simulation as a tool for integrating data from national sources such as SEER with individual-level data from screening trials. By synthesizing available evidence, we can impute unobserved results.
This is conceptually similar to the 'borrowing strength' idea from Bayesian statistics. Extrapolating from available data allows us to pose a wide range of interesting questions regarding cancer control interventions in a wider variety of populations than represented in trials.

Results from the LCPM have been used to calibrate and validate the model, and evaluate screening programs, smoking cessation programs, and treatments. Additional types of results could include estimation of natural history parameters.

RESULTS LIST

CALIBRATION AND VALIDATION

See Calibration Validation Results for results of calibration and validation.

Kong CY, Mc Mahon PM, Gazelle GS. Calibration of Disease Simulation Models Using an Engineering Approach. Value in Health. 2008 In Press. See Calibration Methods Research for a description of this evaluation of advanced engineering methods used for calibration of the LCPM.

SCREENING EVALUATIONS

McMahon PM, Kong CY, Johnson BE, Weinstein MC, Weeks JC, Kuntz KM, Shepard JA, Swensen SJ, Gazelle GS. Estimating Long-term Effectiveness of Lung Cancer Screening in the Mayo CT Screening Study. Radiology. 2008 Jul;248(1):278-87. Epub 2008 May 5. PMID: 18458247 [Pub Med - as supplied by publisher]

See also Validation Lung Screening Study1 for results from simulating the CT-screened arm of the LSS study.

McMahon PM, Kong CY, Weinstein MC, Tramontano AC, Cipriano LE, Johnson BE, Weeks JC, Gazelle GS. Adopting helical CT screening for lung cancer: potential health consequences during a 15-year period. Cancer. 2008 Dec 15;113(12):3440-9. PMID: 18988293 [Pub Med - indexed for MEDLINE]
See Index Supplement Cancer for information that might be helpful for readers of this analysis.

An evaluation of the cost-effectiveness of helical CT screening for lung cancer is underway and will be described in a future results document.

Treatment Evaluations

Evaluations of specific treatments (ablation, other) will be described in future results documents.

Population Trends

Trends in lung cancer incidence and mortality under various scenarios (e.g., the Smoking Base Case) will be described in future results documents.

Categories

Core Docs

SUMMARY OF VERSIONS

Summary of differences and similarities between the original single cohort LCPM (v.1) and the Population LCPM (v.2).

Original single cohort LCPM (v.1)

*Used for published screening evaluations and to document calibration methods.[1,1,2]
*Smoking histories for U.S. cohorts were derived from survey data, as described in the Population Component.
*Competing mortality risks are stratified by smoking status, age group, race, and sex.[3]
*Natural history parameter values are described in Parameters Natural History.
*Calibration targets for birth cohort terms were age-specific incidence for 5 cohorts in 1990 (males aged 50 and 70, and females aged 50, 60, and 70).
*Calibration targets for period terms - not applicable.

Population LCPM (v.2)

*Used for all analyses in Risk Analysis Monograph and Moolgavkar, et al. (forthcoming)
*Smoking histories for U.S. cohorts and competing mortality risks by smoking status, age, and sex were from the shared smoking history generator (cite Chapter 3 and the Smoking History Generator Component.
*Natural history parameter values consistent with a stronger relationship between years of smoking and lung cancer risk; weaker relationship between cigarettes per day and lung cancer risk; greater benefit from quitting. See also Calibration Details.
*Calibration targets for birth cohort and period terms were age-adjusted mortality rates for US population 1975-2000

Similarities

Calibration targets for natural history parameters (excluding birth cohort and period terms) were age-specific incidence rates for cohort of white males aged 60 in 1990, and cell, stage, and size distributions as described previously (cite) and in Calibration Details.

REFERENCES:

1No Reference found for: McMahon, 2008

2No Reference found for: Kong, 2009

3 McMahon, P. M., Zaslavsky, A. M., et al. "Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis" in Medical Decision Making 2006; 26: : 497-511

CALIBRATION VALIDATION RESULTS

SUMMARY

This document summarizes the calibration of the LCPM and validation to additional endpoints.

RESULT TYPE

Other

OVERVIEW

Calibration and validation results indicate no immediately obvious departure from observed data, lending credence to simulations of hypothetical scenarios (i.e., those that extrapolate past observed data).

Many limitations of the LCPM are common to all studies employing simulation models. Tradeoffs must be made between increasing complexity and practical limits on the number of unknown parameters that can be identified using available data. A 'deep' model like the LCPM has more complexity (which allows us to evaluate different workup algorithms) than a 'shallow' statistical model that estimates transition probabilities (e.g., stage I to stage II), but at the cost of greater risk of identifiability problems. To reduce the risk of identifiability issues biasing results, we continue to select additional calibration targets, refine calibration approaches, remove parameters where possible, and identify additional sources of data for inputs and validation.

METHODS

See the Population Component and Calibration Details for descriptions of calibration of the original single cohort LCPM and the more recent Population LCPM.

For both the single cohort LCPM and the Population LCPM, birth cohort terms were estimated.

RESULT

FIT TO CALIBRATION TARGETS

Primary Targets, Derived from SEER

The single cohort LCPM produced a good fit to incidence by age for cohorts of 50-, 60-,

and 70 year-old whites (Calibration Incidence1). We also achieved good fits to size, type, and stage distributions (Calibration Size Type Stage1). The best-fitting set slightly overestimated ≥3-year survival for NSCLC stages I and II (Calibration Survival1). This overestimation is due to our assumption that all patients underwent guideline staging and treatment; many patients represented in SEER did not receive guideline treatments. Survival of patients with limited stage small-cell lung cancer was accurately predicted.

The Population LCPM produced a good fit to age-adjusted lung cancer mortality rates over the period 1975 to 2000 (see Calibration USMortality1).

Secondary Targets, Derived from Cohort Studies and Literature

The single cohort LCPM predicted annual mortality rates per 100,000 non-smokers and lung cancer-specific mortality ratios for current (vs. never) smokers (by 5-year age group) that agree with observed data (Calibration Cohort Study1).

The LCPM predicted lung cancer outcomes in non-smokers and in autopsy studies that agreed with published findings (Calibration Non Smokers Autopsy1).

Validation

Validation is documented here (Validation Cohort Studies1 and Validation Lung Screening Study1).

Discussion

After calibration and validation of the LCPM, the model could be used to evaluate screening programs.

Because screening is not part of usual clinical practice, most lung cancers in the SEER registry were diagnosed on the basis of symptoms. The SEER calibration targets used to inform estimates of incidence and survival were therefore supplemented with screening trial data to refine estimates regarding noninvasive BACs, which appear with greater frequency in screening studies.

Conclusion

The LCPM generates outputs consistent with multiple data sources. Predictions from the model regarding the effectiveness of screening or other interventions are however extrapolations beyond available data, and are subject to all assumptions built in to the model.

Relevant Assumptions

The base case assumption that all individuals receive guideline care is necessary, given the lack of data on staging practices in the US. However, this assumption likely yields fewer understaged patients and therefore higher survival for early-stage cancers than in SEER data used for calibration.

See also Assumption Overview.

Relevant Parameters

Calibration was used to estimate unobservable parameters (e.g., those that govern metastasis). See Parameters Natural History for details.

Relevant Outputs

See Output Overview.

SCREENING BIASES

Screening trial results are affected by several well-known biases that make interpretation of results challenging.[3,4] A test that detects earlier-stage disease, will, by definition, prolong observed survival times (lead-time bias). Assuming some individual heterogeneity in disease progression rates, periodic screening will preferentially detect slowly progressing cases, simply because such cases persist longer in the asymptomatic state (length-time bias). The extreme of length-time bias, overdiagnosis refers to both screen detection of cases that would not have caused symptom detection or death (i.e., without screening, the person would die of competing causes, unaware of the presence of the disease) and to detection of pseudo-disease (e.g., cases with a self-resolving clinical course).[6]

REFERENCES:

[1] Reich, J. M. "Improved survival and higher mortality: the conundrum of lung cancer screening.[see comment]." in Chest 2002; 122: 1: 329-37

[2] Black, W. "Overdiagnosis: An underrecognized cause of confusion and harm in cancer screening [Editorials]" in Journal of the National Cancer Institute 2000; 92: 16: 1280-1282

[3] Patz, E., Goodman, P., et al. "Screening for lung cancer [Review]" in New England Journal of Medicine 2000; 343: 22: 1627-1633

[4] Eddy, D. "Screening for lung cancer." in Annals of Internal Medicine 1989; 111: : 232-237

[5] Woods, William G., Gao, Ru-Nie, Shuster, Jonathan J., Robison, Leslie L., Bernstein, Mark, Weitzman, Sheila, Bunin, Greta, Levy, Isra, Brossard, Josee, Dougherty, Geoffrey, Tuchman, Mendel, Lemieux, Bernard "Screening of infants and mortality due to neuroblastoma" in N Engl J Med 2002; 346: 14: 1041-1046

[6] Schilling, Freimut H., Spix, Claudia, Berthold, Frank, Erttmann, Rudolf, Fehse, Natalja, Hero, Barbara, Klein, Gisela, Sander, Johannes, Schwarz, Kerstin, Treuner, Joern, Zorn, Ulrich, Michaelis, Joerg "Neuroblastoma screening at one year of age" in N Engl J Med 2002; 346: 14: 1047-1053

CALIBRATION DETAILS

OVERVIEW

Calibration was used to estimate values of unobservable natural history parameters and uncertain parameters (those for which literature estimates provided ranges of values). Each unique combination of model inputs (tables, distributions, and scalar values) is referred to as a parameter set. A combination of grid search and simulated annealing was used to identify the parameter set that minimized the total sum of squared errors between model output and 8 primary calibration targets. Of the 25 parameter sets with the best fit to the primary calibration targets, we chose the set with the best fit to 5 secondary calibration targets. Extensive debugging was performed throughout model development and prior to final calibration.

CALIBRATION TARGETS

Primary: Age-specific incidence, cell type, stage, and size distributions of incident cancers, survival curves (4 stages).
Secondary: Autopsy data, mortality in never-smokers, percent symptomatic at detection, lung cancer mortality.

Please see Calibration Methods Research for information on a comparison of calibration approaches.

ORIGINAL SINGLE COHORT LCPM

We chose a large cohort (white males aged 60 in 1990) as the initial calibration cohort, setting the birth cohort term to 1.0 (reference group). Once calibration to this large cohort was completed, the same parameter set was used to generate incidence by age predictions for cohorts of 50 and 70-year old white males and 50, 60, and 70-year old white females. To account for observed birth cohort trends in lung cancer risks and allow for differences in baseline risk by gender,[1,2,3] we added a term that modifies the monthly risk of lung cancer development (all cell types), stratified by gender. The birth cohort term was adjusted in these cohorts such that the LCPM generated observed age-specific incidence rates. See Population Component for a description of smoking histories used in the single cohort LCPM and[4] for a description of other cause mortality rates, and how these differed from inputs for the Population LCPM.

Population LCPM

The Population LCPM assigns smoking histories and other cause (non- lung cancer) mortality risks from the Smoking History Generator that is common to all CISNET lung models that simulate populations. The Population LCPM was re-calibrated to the same calibration targets used for the original single cohort LCPM (see below) to generate a revised parameter set ("version 2") that assigns a stronger dose-response relationship between years of smoking (duration) and lung cancer risk. The effect of cigarettes per day (dose) is correspondingly lower in the "version 2" parameter set. See Parameters Natural History for further details on smoking parameters and differences in birth cohort terms between parameter sets (versions 1 and 2).

Targets

See Output Overview for links to comparisons of targets and outputs from the calibrated LCPM.

Defining Ranges for Unobservable Natural History Parameters

See Natural History Component and Parameters Natural History. During calibration, some parameter values could be ruled out as implausible, after consultation with clinical experts and past research. For example, the intercept terms were ordered to reflect observed risks of each cell type among non-smokers. Lung cancer risks increase with age and SY and decrease with YSQ. SY has the strongest effect on development of small cell cancers, and the effect of YSQ was weakest for adenocarcinoma. The amount of BAC as a proportion of adenocarcinoma was varied from 0 to 0.4[5,6] and estimated to be 0.2.

Initial values of symptom detection parameters were selected so that the cumulative probability of symptom detection from (true) distant metastases was nearly 1.0 by 3 years, i.e., very few patients had asymptomatic/undetected metastases at 3 years after diagnosis, but it was not impossible. By comparison, the estimated growth duration of metastases was 3.8 years (faster growth than the primary tumor) in a published breast cancer model. Initial values of the intercept term and coefficient on tumor volume for symptom detection of primary cancers were chosen so that once a cancer passed the threshold size, the probability of symptom detection increased slowly to yield lung cancers of similar sizes as those observed in SEER. Adenocarcinomas were assumed to be less aggressive than SCLCs.

Defining Ranges for Uncertain Parameters

We classified parameters as uncertain if literature estimates provided ranges of values. During calibration, test characteristics were allowed to vary because verification bias likely affects many published sensitivity and specificity values. See Parameters Test Performance and Parameters Treatment for details.

Results

See Calibration Validation Results for model calibration and validation.

References:

[1] Jemal, A, Chu, K, Tarone, R "Cancer Surveillance Series: Recent trends in lung cancer mortality in the United States." in J Natl Cancer Inst 2001; 93: : 277-283

[2] Wakelee, HA, Chang, ET, Gomez, SL, et al. "Lung cancer incidence in never smokers" in J Clin Oncol 2007; 25: : 472-478

[3] Zheng, T, Holford, TR, Boyle, P, et al. "Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989" in Cancer 1994; 74: : 1556-1567

[4] McMahon, P. M., Zaslavsky, A. M., et al. "Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis" in Medical Decision Making 2006; 26: : 497-511

[5] Raz, D J, He, B, Rosell, R, Jablons, D M "Current concepts in bronchioloalveolar carcinoma biology" in Clin Cancer Res 2005; 12: : 3698-3704

[6] Crestanello, J. A., Allen, M. S., Jett, J. R., Cassivi, S. D., Nichols, F. C., 3rd, Swensen, S. J., Deschamps, C., Pairolero, P. C. "Thoracic surgical operations in patients enrolled in a computed tomographic screening trial" in Journal of Thoracic & Cardiovascular Surgery 2004; 128: 2: 254-259

FOLLOW UP COMPONENT

As described in the Incidental Imaging Component, patients with incidentally detected nodules suspicious for lung cancer are triaged according to the size of the nodule. Patients with nodules over the threshold diameter are sent to the Workup And Staging Component.

In sensitivity analyses of a manuscript in press, we examined scenarios where nodules smaller than a cutoff size (e.g., 4mm diameter) are ignored, with patients returning to the general population.

Smaller nodules are followed-up with serial high-resolution CT exams (even in the absence of screening), with a specified periodicity (see below) over 24 months. Detection of new small nodules re-starts the 24-month follow-up sequence. Nodules that exhibit no detectable growth (see below) after 2 years of follow-up are diagnosed as benign;[1] detectable growth on any subsequent imaging exam is considered sufficient to cause suspicion for lung cancer.

Structural Parameters in the Follow Up Component
(See Parameter Overview for definition):
1) A threshold (or 'cutoff') diameter of 8mm was used and is generally in agreement with a low (5%) biopsy rate for 4-9mm nodules in a recent trial[2].
2) Depending on the scenario, follow-up could occur with a fixed periodicity of 1, 3, 6, 12, and 24 months[3] or be managed according to the size of the largest nodule found (similar to published algorithms from CT screening trials)[4].
3) For the base case, the minimum detectable growth on sequential exams was 2mm[1].
4) An estimated 50% of growing nodules are excisionally biopsied using VATS (video-assisted thoracic surgery).

REFERENCES:

[1] Benjamin, MS, Drucker, EA, McLoud, TC, Shepard, JO "Small pulmonary nodules: detection at chest CT and outcome" in Radiology 2002; 226: : 489-493
[2] Pinsky, P. F., Marcus, P. M., Kramer, B. S., Freedman, M., Nath, H., Kvale, P., Reding, D. "Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen" in Cancer 2005; 103: 1: 157-163
[3] Rubins, JB, Rubins, HB "Temporal trends in the prevalence of malignancy in resected solitary pulmonary lesions" in Chest 1996; 109: : 100-103
[4] Swensen, S., Jett, J., et al. "Screening for lung cancer with low-dose spiral computed tomography" in American Journal of Respiratory and Critical Care Medicine 2002; 165: : 508-513

Workup And Staging Component

Summary

This document describes the one-month cycle during which a patient with a pulmonary nodule suspicious for lung cancer undergoes clinical workup to establish a diagnosis of cancer or benign histology. Patients with cancer then undergo staging tests to establish the extent of disease progression.

Overview

Clinical algorithms for workup and staging are modeled explicitly, so that differences in patient management strategies can be compared.

Patients enter this component if they have a pulmonary nodule suspicious for lung cancer, detected by any modality and large enough to be biopsied. Patients with incidentally detected nodules smaller than the threshold go to the Follow Up Component.

Biopsy-confirmed malignancies are clinically staged (in the same cycle) based on practice guidelines from the National Comprehensive Cancer Network (NCCN, version 2000, for calibration to 1990-2000) and assigned both TNM and AJCC stages.

Patients whose pulmonary nodules are definitively diagnosed as benign start the next cycle in the general population state. Patients with a diagnosis of lung cancer begin the next cycle in the Treatment Component.

Detail

Patients presenting with symptom-detected cancers undergo biopsy to establish the histological type and a high-resolution CT examination to stage lymph nodes and determine tumor size, if not already known.

All patients undergo one high-resolution CT examination to determine calcification pattern and/or stage lymph nodes, per NCCN guidelines.

An estimated 50% of patients with N0/1 and evidence of primary tumor growth on CT are sent for excisional biopsies using VATS (video-assisted thoracic surgery). Non-operative candidates and remaining N0/1 patients undergo biopsy of the primary tumor (bronchoscopy for central nodules and TTNA for peripheral nodules).

Patients with clinically evident enlarged mediastinal lymph nodes (N2/3 on CT) undergo mediastinoscopy, which can establish a diagnosis of lung cancer and provide staging information. Patients with negative mediastinoscopy results are treated as N0/1.

Relevant Assumptions

The assumption that all patients undergo staging tests in accordance with consensus practice guidelines is a limitation of the current LCPM. Many publications have demonstrated that a large proportion of lung cancer patients do not receive guideline treatments, but information on staging practices in the U.S. is limited.

Our assumption of guideline staging, which is often more invasive/aggressive than usual care, will result in higher survival rates for earlier staged cancers, because patients with more advanced disease (and lower survival) will be correctly identified and categorized into later stages.

Relevant Parameters

Sensitivity and specificity of the diagnostic and staging tests will influence patient trajectories through this state (Parameters Test Performance).

Other input parameters define the scenario being simulated. For example, we will have the flexibility to simulate either guideline or usual care staging patterns.

Relevant Components

The Workup and Staging Component includes sub-components specific for NSCLC and SCLC, which have different characteristics and therefore different staging systems.

A "Usual Care" version of the staging component is in development and will be available for comparison to guideline staging.

Dependent Outputs

Distributions of stage at diagnosis and survival outputs rely on this component. Natural History and Incidence do not depend on this component.

Relevant Results

Size, Type and Stage Distributions of Incident Cancers (Calibration Size Type Stage1)

Survival Curves for NSCLC and SCLC (Calibration Survival1)

PARAMETERS NATURAL HISTORY

See the Natural History Component and Calibration Details for explanations of the way the LCPM models lung cancer natural history and how the unobservable parameters were estimated. This document contains additional detail not already provided.

LUNG CANCER DEVELOPMENT

The logistic model for development of a lung cancer was described in the Natural History Component. There are type-specific parameters for the effects of age and smoking history. We assume that beta_highrisk = ln(2), equivalent to a HR of 2 for individuals positive for the susceptible genotype, independent of age, gender, smoking status and pack-years. As a candidate 'susceptibility' genotype, we model the combined genotype of GST P1 (GG) and p53 (Arg/Pro or Pro/Pro) to occur with an estimated population frequency of 4.7% (no linkage).[1] The amount of BAC as a proportion of adenocarcinoma was varied from 0 to 0.4 during calibration and was estimated to equal 0.2.

As described in Calibration Details, values of smoking-related natural history parameters differ between the original single cohort LCPM and the Population LCPM.

LUNG CANCER LOCATION

Each newly-developed lung cancer is assigned a location, with indicators for the specific lobe in the lung and central/peripheral location. Most lung cancers occur in upper lobes, and the proportion central varies by cell type (more SCLC are central compared to adenocarcinomas).

LUNG CANCER GROWTH

See Table Growth Parameters. Lung cancers was assumed to grow 2-fold faster in smokers, although the difference may be due at least in part to 'type mix', i.e., non-smokers are more likely to develop slow-growing adenocarcinomas.[2,3,4] The growth of BACs was truncated at 1.0 cm diameter (detectable by CXR). For non-BACs, we assumed a maximum possible tumor size of 27.7 cm,[5] consistent with the largest reported size of 20.1-30.0cm diameter in the SEER*Stat database.

Lung Cancer Progression

Mean (SD) unadjusted threshold volumes for SCLC ranged from 0.61 (0.65) ml for N1 involvement to 4.07 (4.13) for N3 involvement and 4.71 (4.14) for distant metastases. Corresponding unadjusted threshold volumes for NSCLC ranged from 3.34 (4.09) ml for N1 involvement to 3.8 (4.64) for N3 involvement and 2.62 (3.18) for distant metastases. Adjustments were then estimated via calibration to allow the propensity to progress to vary by cell type and be correlated with the growth parameter assigned to the person's cancer. Note that the final estimated volume at metastasis development is an output of the model and will vary across populations that differ in terms of age, smoking history, and scenario (e.g., whether screening is in place).

Symptom Detection

See the Symptom Detection Component. The cumulative probability of symptom detection from (true) distant metastases was over 95% by 3 years (all cell types combined). By comparison, the estimated growth duration of metastases was 3.8 years in a breast cancer model.[6] Treatment with targeted therapies (eg, erlotinib) will influence the rate of symptom detection from metastases.

References:

[1] Miller, D. P., Liu, G., et al. “Combinations of the variant genotypes of GSTP1, GSTM1, and p53 are associated with an increased lung cancer risk” in Cancer Research 2002; 62: : 2819-2823

[2] Usuda, K., Saito, Y., et al. “Tumor doubling time and prognostic assessment of patients with primary lung cancer” in Cancer 1994; 74: : 2239-2244

[3] Song, P, Sekhon, HA, Jia, Y, Keller, JA, Blusztajn, JK, Mark, GP, Spindel, ER “Acetylcholine is synthesized by and acts as an autocrine growth factor for small cell lung carcinoma” in Cancer Research 2003; 63: : 214-221

[4] Hasegawa, M, Sone, S, Takashima, S, Li, F, Yang, Z-G, Maruyama, Y, Watanabe, T “Growth rate of small lung cancers detected on mass CT screening” in British Journal of Radiology 2000; 73: : 1252-1259

[5] Spratt, J. S., Spratt, J. A. “Growth Rates” in Cancer of the Breast 2002;

[6] Koscielny, S, Tubiana, M, Valleron, A-J “A simulation model of the natural history of breast cancer” in British Journal of Cancer 1985; 52: : 515-524

PARAMETERS TEST PERFORMANCE

Diagnostic test characteristics (sensitivity and specificity) determine the probabilities of detection and/or diagnosis of lung cancers or benign lesions.

PULMONARY NODULES

Sensitivities of imaging examinations for peripheral pulmonary nodules are input from tables indexed by diameter of the lesion. Sensitivities for a central lesion of the same diameter were assumed to be 25% lower than those for peripheral lesions. We derived sensitivities from the literature to test during calibration.

COMPUTED TOMOGRAPHY (CT)

Helical CT was estimated to have a sensitivity of 0.63 for 1-4mm peripheral nodules, 0.77 for 4-8mm peripheral nodules, and 1.0 for peripheral nodules >8mm. High-resolution CT was assumed to have equivalent sensitivity for detecting presence of a nodule as helical CT (by size), but to have greater resolution for calcification patterns. As in clinical practice, an estimated 11% of benign nodules are diagnosed by high-resolution CT as benign on the basis of calcification pattern (not explicitly modeled). CT could occur in several components: Incidental Imaging Component, Workup And Staging Component, Screening Component, and during surveillance for recurrent disease in the Survival Mortality Component.

CHEST X-RAY (CXR)

The sensitivity of CXR was estimated to be approximately 25% to 50% of that of helical CT, and to be less than 1.0 at 16mm. The minimum detectable size was assumed to be 7.5mm. CXR could occur in the Incidental Imaging Component.

Specificity for both helical CT and CXR is assumed to be 0.98 (per person, or 0.997 per nodule). Specificity of high-resolution CT for pulmonary nodules was assumed to be 1.0.

STAGING EXAMINATIONS

COMPUTED TOMOGRAPHY

High-resolution CT was estimated to have a sensitivity for nodal involvement of 0.63 (average of N1, N2/3) and a specificity of 0.6.[1,2]

BRONCHOSCOPY

Sensitivity of bronchoscopy is defined as the probability of establishing a definitive diagnosis on the basis of cells recovered from the nodule. The sensitivity increases with increasing size of the nodule. For cancer, the sensitivity is 5% for nodules less than 20mm diameter, 20% for nodules 20-29mm diameter, and 48% for nodules 30-40mm diameter. Establishing a specific diagnosis (of the many possible) for a benign nodule is more difficult; the sensitivities are lower for benign nodules of the same size.[3] Bronchoscopy was assumed to have a sensitivity of 0.5 for malignant nodal involvement.[4]

MEDIASTINOSCOPY

Sensitivity of mediastinoscopy for cancer in patients with enlarged lymph nodes is estimated at 0.92 (range, 0.88, 0.94),[2,5] and operative mortality is estimated at 0.3%.[5] Reflecting common practice of not initiating therapy without pathological proof of lung cancer, we assume perfect specificity for mediastinoscopy.[5]

TTNA

The sensitivities of trans-thoracic needle aspiration (TTNA) for malignancy and benign diagnoses were indexed by the size of the nodule, informed by literature estimates.[6,7,8]

VATS

VATS is assumed to have perfect accuracy at identifying malignant vs. benign disease and to include sampling or removal of nodes for confirmation of stage (perfect sensitivity and specificity). VATS had an operative mortality of 0.5%.[9]

METASTASES

A generic test for staging metastases (i.e., those not diagnosed on the basis of symptomatic presentation) is modeled with perfect specificity. Sensitivity for metastases was estimated during calibration; we tested functions of time since metastases developed and constant values of 0.4 to 0.5 derived from published sensitivities for bone scintigraphy and brain/bone MRI.[10,11]

OMITTED TESTS

We omitted sputum cytology due to its low sensitivity relative to bronchoscopy and positron emission tomography (PET) staging because it was uncommon during our calibration period (1990 to 2000).

REFERENCES:

[1] Beadsmoore, C. J., Screaton, N. J. "Classification, staging and prognosis of lung cancer" in European Journal of Radiology 2003; 45: 1: 8-17

[2] McLoud, TC, Bourgouin, PM, Greenberg, RW, Kosuik, JP, Templeton, PA, Shepard, JO, Moore, EH, Wain, JC, Mathesen, DJ, Grillo, HC "Bronchogenic carcinoma: Analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling" in Radiology 1992; 182: : 319-323

[3] Weinberger, SE "Differential diagnosis and evaluation of the solitary pulmonary nodule" in UpToDate 2004; version 12:

[4] Mandel, J, Weinberger, SE "Overview of non-small cell lung cancer staging" in UpToDate 2005; version 13:

[5] Esnaola, NF, Lazarides, SN, Mentzer, SJ, Kuntz, KM "Outcomes and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer" in JCO 2002; 20: 1: 263-273

[6] Tan, BB, Flaherty, KR, Kazerooni, EA, Iannettoni, MD "The solitary pulmonary nodule" in Chest 2003; 123: 1: 89S-96S

[7] Li, H, Boiselle, PM, Shepard, JO, Trotman-Dickenson, B, McLoud, TC "Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules" in American Journal of Radiology 1996; 167: : 105-109

[8] Wallace, MJ, Krishnamurthy, S, Broemeling, LD, Gupta, S, Ahrar, K, Morello, FA, Hicks, ME "CT-guided percutaneous fine-needle aspiration biopsy of small (less than or equal to 1-cm) pulmonary lesions" in Radiology 2002; 225: : 823-828

[9] Detterbeck, FC, Rivera, MP "Clinical presentation and diagnosis" in Diagnosis and Treatment of Lung Cancer 2001;

[10] Pope, RJE, Hansell, DM "Extra-thoracic staging of lung cancer" in European Journal of Radiology 2003; 45: 1: 31-38

[11] Earnest, Franklin, Ryu, Jay H., Miller, Gary M., Luetmer, Patrick H., Forstrom, Lee A., Burnett, Omer L., Rowland, Charles M., Swensen, Stephen J., Midthun, David E. "Suspected non–small cell lung cancer: Incidence of occult brain and skeletal metastases and effectiveness of imaging for detection—Pilot Study" in Radiology 1999; 211: 1: 137-145

PARAMETERS TREATMENT

Eligibility for Surgery

Individuals were randomly assigned as ineligible for surgical resection based on proportions of NSCLC stage I and II (all ages) cases that did not undergo surgery (where the reason was documented). Surgery was explicitly contraindicated for 5.6%, and offered but refused in 2.1% of cases. (Estimated from public release files using SEER*Stat 4.2.3 software.) We allow a small proportion (base case 13%, SEER-Medicare) of LS to be resected, reflecting the minority of cases which present with localized SCLC.

Resection

Effectiveness of resection is incorporated as follows: a person with no occult metastases whose single primary cancer is resected is assigned competing risks consistent with a person of the same smoking history – not stage I survival from SEER. However, if a second, undetected primary tumor remains (in a non-resected lobe), lung cancer can recur (see Natural History Component). The presence of undetected micro metastases is likely the cause of the poor observed survival after "curative" resection in many patients.[1] Removal of (or sampling from) nodes at resection can result in re-assigning stage at diagnosis, but provides no survival benefit.[2] The base case operative mortality rate for lobectomy is estimated at 4%[3] (value in sensitivity analysis, 3%). No increase in mortality due to late (post-30 day) effects of surgery (e.g., infection) was modeled.

Systemic Therapies

Parameter values that define efficacies of chemotherapy and radiotherapy are the probabilities of complete or partial response, using the definition of complete as no visible cancer at 4 week follow-up and partial as greater than or equal to a 30% decrease in diameter.[4] Probabilities of complete and partial responses vary by histologic type, with estimates taken from the literature. A cancer that partially responds to therapy is decreased in diameter by 30%, and a cancer that completely responds to therapy is reduced to 1.5mm diameter,[4] or below the 2mm detection threshold assumed for helical CT. Based on the new diameter, an adjusted 'time since cancer developed' is calculated and used to increment growth in all future cycles, retaining the original growth parameter alpha (Table Growth Parameters). To account for differences in growth rates of cancers pre- and post-therapy, we included parameters (estimated during calibration) that allowed faster-growing cancers to be more or less likely to respond to therapy.

Surveillance

Surveillance for recurrent lung cancer is modeled as helical CT at 6, 12, 24, 36, 48, and 60 months.[5]

REFERENCES:

[1] Spira, A, Ettinger, DS "Multidisciplinary management of lung cancer" in New England Journal of Medicine 2004; 350: : 379-392

[2] Smythe, W. R., American College of Chest Physicians "Treatment of stage I non-small cell lung carcinoma" in Chest 2003; 123: 1 Suppl.: 181S-187S

[3] Bach, PB, Cramer, LD, Schrag, D, Downey, RJ, Gelfand, SE, Begg, CB "The influence of hospital volume on survival after resection for lung cancer" in New England Journal of Medicine 2001; 345: : 181-188

[4] Therasse, P, Arbuck, SG, Eisenhauer, EA, Wanders, J, Kaplan, RS, Rubinstein, L, Verweij, J, Van Glabbeke, M, van Oosterom, AT, Christian, MC, Gwyther, SG "New guidelines to evaluate the response to treatment in solid tumors" in Journal of the National Cancer Institute 2000; 92: : 205-216

[5] Korst, Robert J., Gold, Heather T., Kent, Michael S., Port, Jeffrey L., Lee, Paul C., Altorki, Nasser K. "Surveillance computed tomography after complete resection for non-small cell lung cancer: Results and costs" in Journal of Thoracic and Cardiovascular Surgery 2005; 129: 3: 652-660

INCIDENTAL IMAGING COMPONENT

During each cycle spent in the general population, persons may undergo imaging exams (thoracic CT, or CXR) performed for reasons unrelated to screening for lung cancer.

We fit generalized linear models to insurance claims data from 1999. Increasing age predicted higher likelihood of both CT and CXR (p
Imaging results are compared to results of prior imaging exams, if available. Persons with no detected nodules or exclusively stable nodules return to the general population. Persons with newly detected nodules undergo follow-up and are managed according to the size of the largest nodule found. Persons with nodules large enough for biopsy start the next cycle in the Workup And Staging Component. If the new nodule is smaller than the threshold diameter, the person begins the following cycle in the Follow Up Component. A threshold diameter of 8mm was used as a proxy for clinical practice and is generally in agreement with a low (5%) biopsy rate for 4-9mm nodules in a recent trial.[1]
See Parameters Test Performance for details on test characteristics of imaging examinations.

REFERENCES:

[1] Pinsky, P. F., Marcus, P. M., Kramer, B. S., Freedman, M., Nath, H., Kvale, P., Reding, D. "Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen" in Cancer 2005; 103: 1: 157-163

SYMPTOM DETECTION COMPONENT

Symptom detection can occur via symptoms from the primary cancer or from distant metastases.

Each month, individuals with distant metastases and/or a primary lung cancer (but not those with exclusively benign nodules) may develop symptoms that result in lung cancer detection and begin the following cycle in the Workup And Staging Component. The probability of symptom detection from primary cancers varies by location (central cancers have a greater propensity to cause symptoms, given size) and cell type (NSCLC vs. SCLC) and is a logistic function of the size of the largest cancer. We assume the minimum diameter for peripheral cancers to cause symptoms is 10mm, approximately the size at which airways are obstructed. The probability of symptom detection from metastases is a logistic function of the months since metastases developed (varied by NSCLC vs. SCLC).

Symptom detection parameters were estimated during calibration (see Calibration Details). The most relevant calibration targets included the proportion of lung cancers detected via symptomatic presentation, the stage and type distributions of incident cancers, and survival by type and stage at diagnosis. The background rate of chest imaging in the population (Incidental Imaging Component) will also influence the symptom detection rates.

See also the Assumption Overview.

BENIGN COMPONENT

The benign component occurs in every cycle of the model, so that benign lesions may develop throughout life. Benign lesions may also spontaneously resorb (e.g., due to clearing an infection).

To incorporate the costs and risks of follow-up procedures for benign lesions, the natural history model allows up to 3 benign lesions (with no regard for histological type) per person.

Overview

Using a polynomial fit to raw Mayo CT screening trial prevalence data, we estimated the average number of benign lesions per person, by age. Cumulative incidences of one or more benign lesions were converted to age-specific annual probabilities of developing new lesions (ages 35 to 68) and of existing lesions regressing (after age 68). For simulations of Mayo CT participants, therefore, prevalence of benign nodules was as observed in the study.

We estimate that 3% of benign nodules exhibit growth, and assign these lesions doubling times consistent with adenocarcinomas. Non-growing benign lesions are modeled as appearing fully formed in the previous month, consistent with a range of biological mechanisms (e.g., pleural effusion, edema, and infection).

Each benign lesion's location (i.e., specific lobe) was assigned based on a study of (n=185) nodules from the Mayo Clinic, which stratified by right/left. An indicator for central/peripheral is randomly assigned. Size (diameter) was derived from the Mayo Clinic data, expressed as a lognormal distribution (mean = 0.9, variance 0.36).

Assumptions

Solidly calcified lesions are not considered suspicious for lung cancer, and are ignored.

The probability of developing benign lesions is assumed independent of smoking history; no significant correlations were observed between any of the smoking factors and numbers of lesions in the Mayo CT data; and to our knowledge, no literature sources refute this observation.

Extrapolating from Mayo CT study data on prevalence of benign nodules

The base case LCPM incorporates no regional variation in the prevalence of benign nodules. Infection with histoplasmosis is a common cause of small (less than 3mm diameter) benign nodules.[1] Histoplasmosis rates vary geographically, with nearly 100% prevalence in persons residing in the major river valleys of the central U.S.[1] The Mayo Clinic (Rochester, MN) is not in an area of the highest histoplasmosis rates.

REFERENCES:

[1] Gurney, J., Dewey, J. "Pulmonary histoplasmosis" in Radiology 1996; 199: : 297-306

TABLE GROWTH PARAMETERS

Natural History Parameters

Distribution of alpha parameters (rate of decay of growth rate) used in the Gompertz equation for lung cancer growth, and doubling times (in days) for lung cancers at various sizes (cm diameter), by cell type.

Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

Cell type	Distribution of alpha parameter	Mean (SD) DT at 0.5cm	Mean (SD) DT at 1.0cm	Mean (SD) DT at 1.5cm
Adenocarcinoma/BAC	logN(-7.765, 0.5504)	187(160)	227(194)	260(222)
Large cell	logN(-6.59942, 0.68862)	61(61)	74(74)	85(85)
Small cell	logN(-5.44357, 0.611485)	19(16)	23(20)	26(23)
Squamous cell	logN(-6.6111, 0.7935)	65(72)	79(87)	90(100)
Other	logN(-6.714, 0.6634)	67(66)	81(80)	93(92)

Notes: 'Other' refers to NSCLC not otherwise specified.

COMMENTS

The alpha parameters above are inputs for the LCPM. Thus the DTs shown are for all lung cancers at the specified size (*both diagnosed and undiagnosed*) and are **not** stratified by smoking history or stage.

See Parameters Natural History and Natural History Component for details.

PROTECTED HEALTH INFORMATION

The LCPM study's protocols for use of human subject data underwent expedited review (secondary use of medical records) and was approved by the human subjects institutional review board as compliant with HIPAA guidelines.

De-identified records (including demographics, smoking histories, and screen results) from two studies were provided to our institution for model calibration and validation.

- 1,520 current and former smokers aged 50-85 years participating in a Mayo Clinic study of annual CT screening for early detection of lung cancer[1]. Participants signed informed consent waivers approved by the Mayo Clinic institutional review board before enrollment in the screening study. Transfer of the de-identified data was approved by both institutions' human subjects review boards and was exempt from further informed consent requirements.

- 3,318 current and former smokers aged 55-74 years participating in the Lung Screening Study (LSS, a pilot study for the National Lung Screening Trial) of annual CT or CXR screening for early detection of lung cancer[2]. Transfer of the de-identified data was exempt from further informed consent requirements.

REFERENCES:

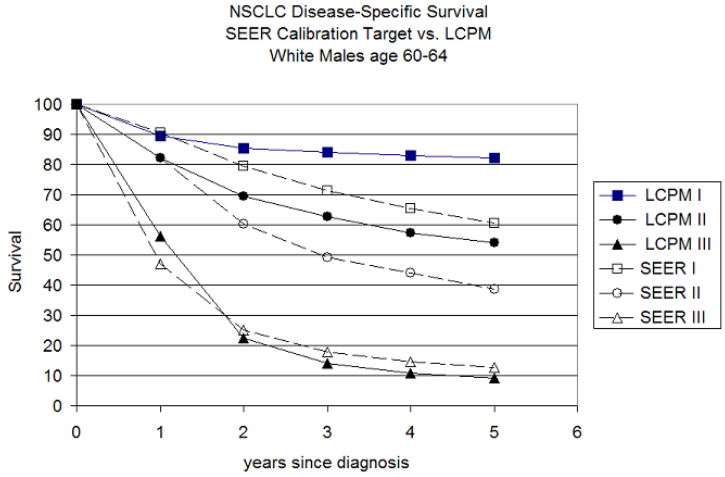
[1] Swensen, S., Jett, J., et al. "Screening for lung cancer with low-dose spiral computed tomography" in American Journal of Respiratory and Critical Care Medicine 2002; 165: : 508-513

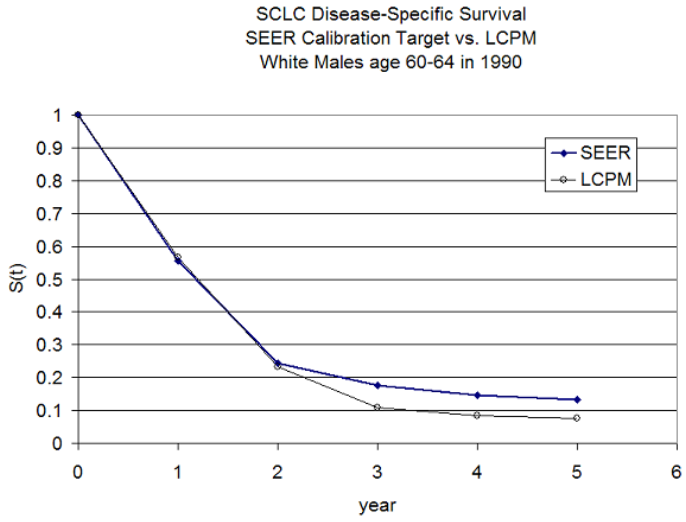
[2] Gohagan, J., Marcus, P., Fagerstrom, R., Pinsky, P., Kramer, B., Prorok, P., Writing Committee, Lung Screening Study Research Group "Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute" in Chest 2004; 126: 1: 114-21

CALIBRATION SURVIVAL1

CALIBRATION ENDPOINTS - SURVIVAL CURVES FOR NSCLC AND SCLC

Notes: Our use of published estimates for response rates from systemic therapies and our assumption that all patients underwent guideline staging and treatment may be irreconcilable with observed survival used for calibration targets, because many patients represented in SEER did not receive guideline treatments. Defining survival calibration targets that vary by treatment as well as stage, or by finer gradations of stage (i.e., T1N0M0 vs. T1N1M0) would address this limitation (ongoing work).

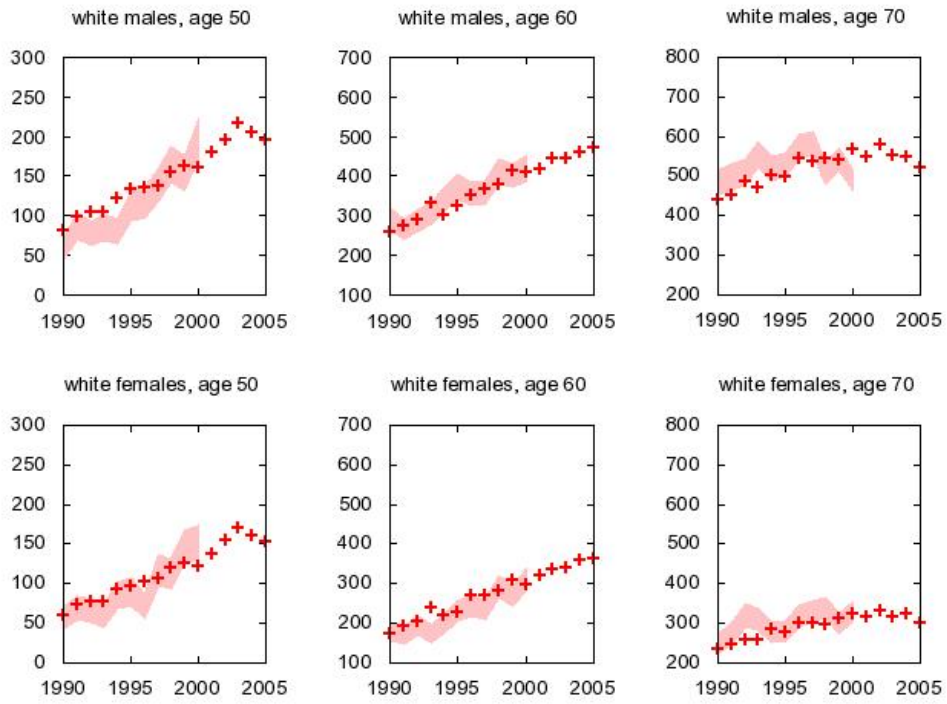




CALIBRATION INCIDENCE1

LUNG CANCER INCIDENCE FROM THE SINGLE COHORT LCPM VS. SEER

Age- (in single years), gender-, race-, and calendar year-specific lung cancer incidence rates, derived from SEER*Stat case listing files and counts of populations at risk from the NCI. Shown are incidence rates of all lung cancer types combined, for cohorts of whites.
Shaded regions are acceptance windows (95% CIs) around SEER calibration targets; crosses indicate LCPM output.



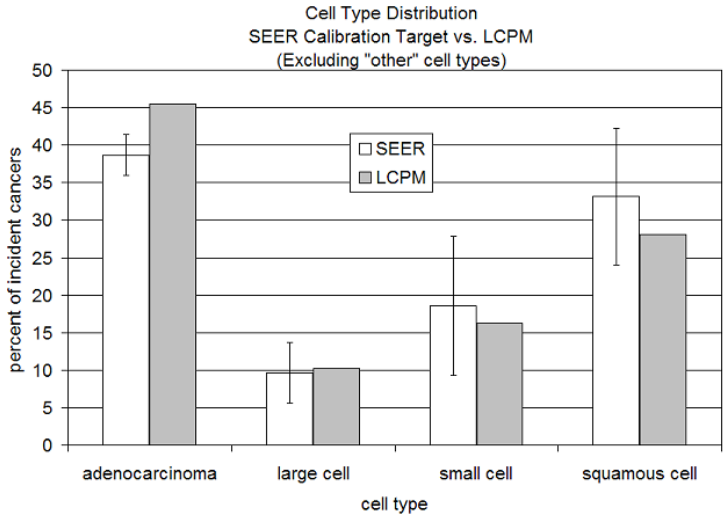
The Population LCPM (see Summary Of Versions for differences between the Population and single cohort LCPM models) was calibrated to the same reference cohort (60 year-old males).

Calibration USMortality documents calibration of period and cohort terms for the Population LCPM.

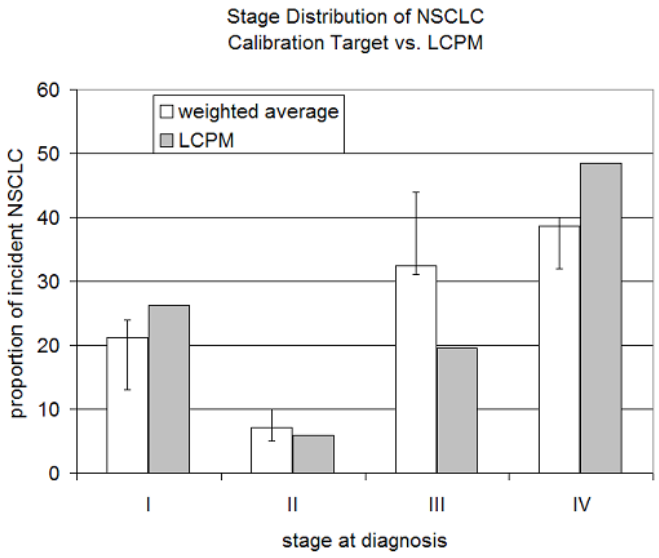
CALIBRATION SIZE TYPE STAGE1

SIZE, TYPE, AND STAGE DISTRIBUTIONS OF INCIDENT CANCERS; LCPM VS. SEER

The LCPM predicted a mean size of incident cancers of 29mm, vs. 38mm in SEER.



Calibration to type distribution of incident lung cancers, white males 60-70 years; 1990-2000.
Derived from SEER-Stat case listing files, stratified by gender, race, calendar decade, and 10-year age group.

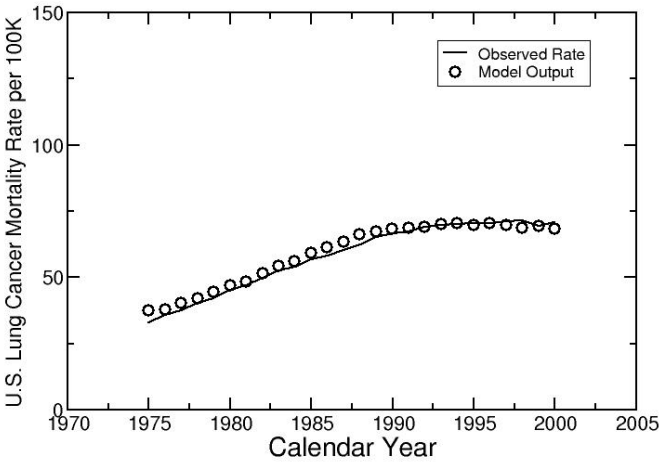


Calibration to stage distribution of incident lung cancers, white males 60-70 years; 1990-2000.

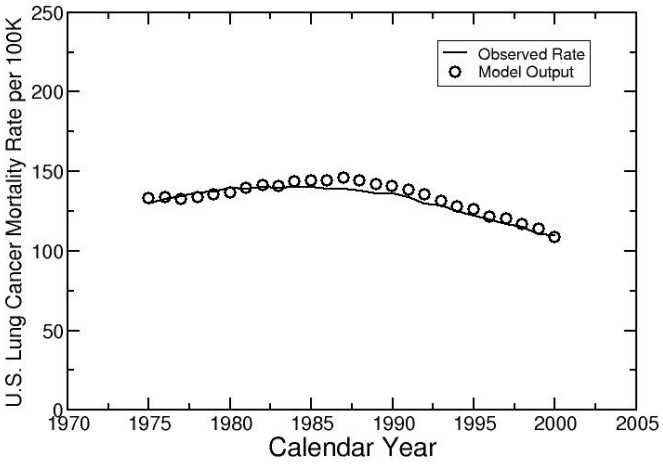
NB stratified by NSCLC and SCLC. Derived from a weighted average of 3 studies (all genders, all races) and SEER data (stratified by gender, race, decade, and age group).

CALIBRATION USMORTALITY1

Calibration plots from the Population LCPM.



Age-adjusted lung cancer mortality rates over the period 1975 to 2000. Model output vs. observed. All Races, Males



Age-adjusted lung cancer mortality rates over the period 1975 to 2000. Model output vs. observed. All Races, Females

VALIDATION LUNG SCREENING STUDY1

LCPM Populated with Lung Screening Study Population in Presence of Screening

Endpoint		Study result[2]	LCPM
participants with:	positive baseline CT screen	20.5%	20.9%
	lung cancer at baseline CT screen	1.9% (95% CI, 1.2%, 2.6)	1.2%
prevalent lung cancers that were:	adenocarcinoma	63% (n=16/30)	73.7%
	small cell	3%	3.1%
	NSCLC, NOS	10%	6.0%
prevalent lung cancers that were:	stage I	53% (n=16/30)	67.1%
	stage II	10%	8.0%
	stage III	20%	18.6%
	stage IV	10%	6.3%
	unstaged	7%	n/a
diameter of prevalent lung cancers:	median (mean, SD)	18mm (27, 23)	10mm (14.6, 8.4)
patients with prevalent lung cancers:	mean cigarettes/day (SD)	27.7 (9.3)	32.4
	mean years of smoking (SD)	47.3 (4.8)	50.3
	proportion male	0.57	0.58
	participants with lung cancer detected at screen #2	0.57% (n=8/1398)	0.29%

Notes: LCPM-predicted endpoints calculated from 250,000 simulated participants. Endpoints not provided in references were calculated directly from study data (see Protected Health Information). CI = confidence interval; SD = standard deviation; positive CT screen defined as detection of at least one non-solidly calcified pulmonary nodule at least 4mm in diameter. Retrospectively identified nodules not included in prevalence estimate. Adenocarcinoma includes bronchioloalveolar carcinoma (BAC) and mixed adenocarcinoma/BAC.

REFERENCES:

[1] Gohagan, J., Marcus, P., Fagerstrom, R., Pinsky, P., Kramer, B., Prorok, P., Writing Committee, Lung Screening Study Research Group "Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute" in Chest 2004; 126: 1: 114-21

[2] Gohagan, J. K., Marcus, P. M., Fagerstrom, R. M., et al., "Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer" in Lung Cancer 2005; 47: 1: 9-15

CALIBRATION METHODS RESEARCH

This note is for readers of *"Calibration of Disease Simulation Model Using an Engineering Approach"*,
Value in Health, Early View, February 2009
Chung Yin Kong, Pamela M. Mc Mahon, G. Scott Gazelle

Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

Kong, et al. compare approaches for calibration of the LCPM using an earlier model version that included only 4 lung cancer cell types. Since completion of the work described in this article, we have added a 5th cell type ('Other', represented by ICD-O-2 code 80103) to both the Natural History Component and the calibration targets for age-specific incidence lung cancer incidence.

ABSTRACT

Objectives: Calibrating a disease simulation model's outputs to existing clinical data is vital to generate confidence in the model's predictive ability. Calibration involves two challenges: 1) defining a total goodness-of-fit score for multiple targets if simultaneous fitting is required; and 2) searching for the optimal parameter set that minimizes the total goodness-of-fit score (i.e., yields the best fit). To address these two prominent challenges, we have applied an engineering approach to calibrate a microsimulation model, the Lung Cancer Policy Model (LCPM).
Methods: First, eleven targets derived from clinical and epidemiological data were combined into a total goodness-of-fit score by a weighted-sum approach, accounting for the user-defined relative importance of the calibration targets. Second, two automated parameter search algorithms, Simulated Annealing (SA) and Genetic Algorithm (GA), were independently applied to a simultaneous search of 28 natural history parameters to minimize the total goodness-of-fit score. Algorithm performance metrics were defined for speed and model fit.
Results: Both search algorithms obtained total goodness-of-fit scores below 95 within 1,000 search iterations. Our results show that SA outperformed GA in locating a lower goodness-of-fit. After calibrating our LCPM, the predicted natural history of lung cancer was consistent with other mathematical models of lung cancer development.
Conclusion: An engineering-based calibration method was able to simultaneously fit LCPM output to multiple calibration targets, with the benefits of fast computational speed and reduced need for human input and its potential bias.

INDEX SUPPLEMENT CANCER

This document is intended as a guide to this Model Profiler for readers of "Adopting helical CT screening for lung cancer: Potential health consequences over a fifteen-year period" Mc Mahon PM, Kong CY, Weinstein MC, Tramontano AC, Cipriano LE, Johnson BE, Weeks JC, Gazelle GS.

C. 2008 Dec 15;113(12):3440-9.

PMID: 18988293 />

OVERVIEW

A description of the model structure, major components, and purpose is available in the Model Overview

INPUT PARAMETERS AND SOURCES

Test characteristics and mortality risks are described in Parameters Test Performance

Treatment effects and mortality risks are described in Parameters Treatment

Natural history parameters are described in Parameters Natural History

Smoking histories were derived from survey data as described in the Population Component

ASSUMPTIONS

The Assumption Overview describes the major assumptions underlying the LCPM and their possible implications.

Omissions from current LCPM that may influence the estimate of screening effectiveness:

Harms and benefits from incidental detection of other diseases (e.g., other cancers) found at screening

Increased lung cancer risks from radiation doses during screening or follow-up CT

examinations
(Brenner, D.J., Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology, 2004. 231(2): p. 440-5)

Tumor seeding of surgical or biopsy site, which is mainly described in case studies (eg Raja and Bessman, JCO 2003) and is thought to be a rare event

Explicit modeling of late surgical mortality
(Handy JR, Jr., Asaph JW, Skokan L, et al. Chest 2002; 122:21-30 and Toker, et al., Eur J Cardio-Thoracic Surg 2004;25:515-519)
In these studies, a small minority of 'late' (>30 day) post-resection deaths were due to late surgical mortality (1 infection/16 late deaths in Handy, et al., and 5 late surgical mortality death/51 total late deaths in Toker, et al.). A higher proportion of late mortality was due to cancer progression (7/16 in Handy and 16/51 in Toker), which the LCPM models explicitly as a cause of post-operative death. Other-cause deaths due to respiratory failure and heart disease are to a large extent captured by the increased competing mortality risks faced by smokers in the LCPM.

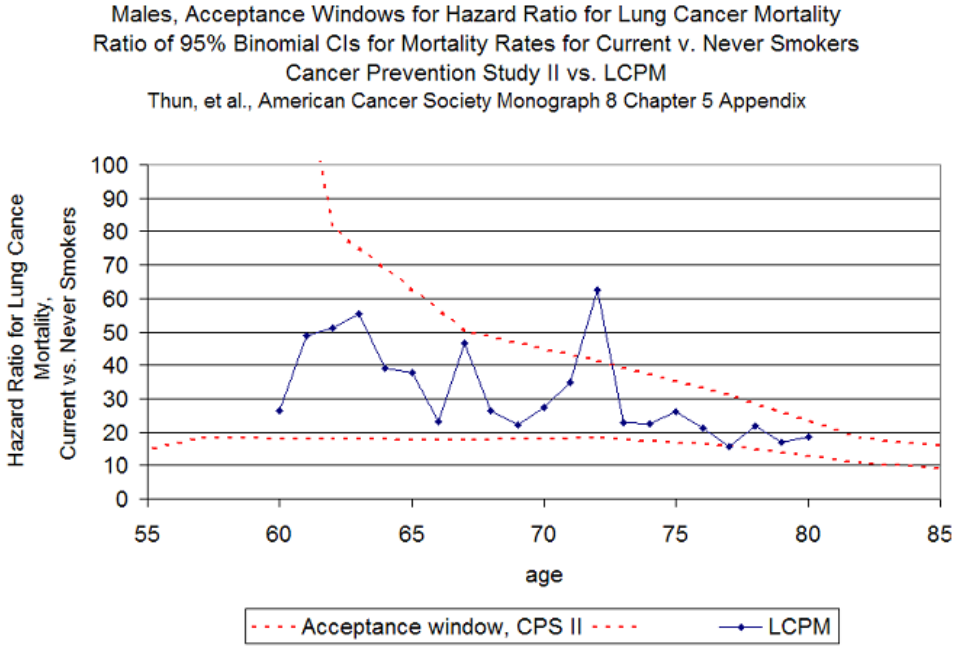
Economic consequences (costs) and influence of screening on quality of life (QALYs) were not considered in this analysis.

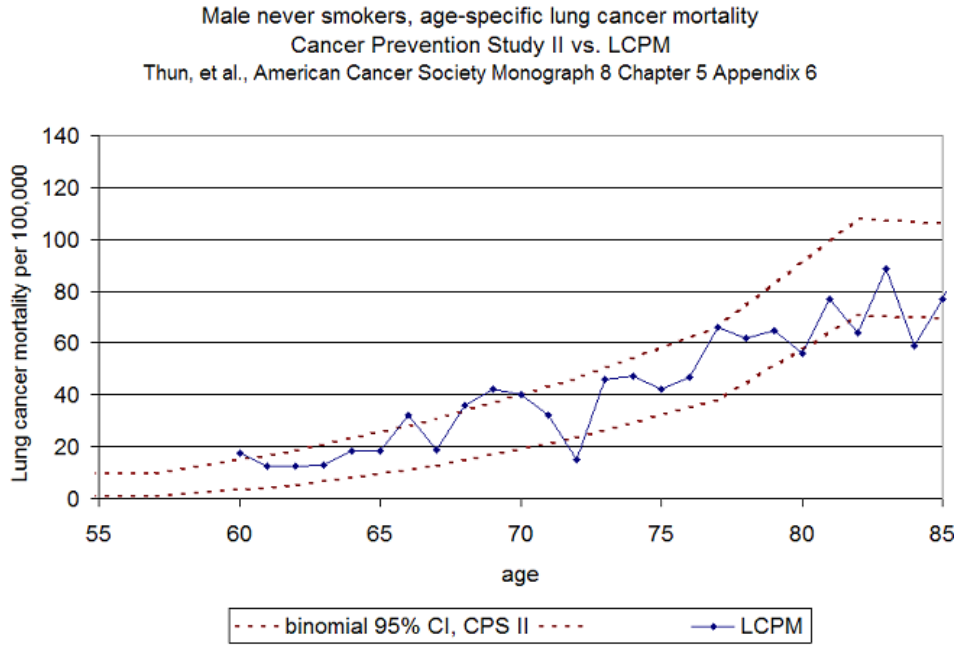
CALIBRATION COHORT STUDY1

SECONDARY CALIBRATION TARGETS - COHORT STUDY

Two targets were derived from an earlier (1980s) cohort study[1] with a highly selected population (i.e., volunteers with the American Cancer Society or their friends) that experienced only 70% of the all-cause mortality in the general U.S. population[2].

The LCPM predicted annual mortality rates per 100,000 non-smokers and lung cancer-specific mortality ratios for current (vs. never) smokers (by 5-year age group) that agree with observed data[1].





REFERENCES:

[1] Thun, M. J., Myers, D. G., et al. "Chapter 5. Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II. National Cancer Institute, Smoking and Tobacco Control, Monograph 8:" 1997;

[2] Flanders, W. Dana, Lally, Cathy A., Zhu, Bao-Ping, Henley, S. Jane, Thun, Michael J. "Lung Cancer Mortality in Relation to Age, Duration of Smoking, and Daily Cigarette Consumption: Results from Cancer Prevention Study II" in Cancer Research 2003; 63: 19: 6556-6562

CALIBRATION NON SMOKERS AUTOPSY1

LUNG CANCER IN NON-SMOKERS

The LCPM predicted a percentage of non-smokers among lung cancer cases of 5.4%, in the range of reported values of 2% to 15%[1,2]. As expected, the model predicted a lower proportion of SCLC cases among non-smokers (4.3%) than among all lung cancer cases (18%)[3].

LUNG CANCER DETECTED AT AUTOPSY

Estimates of rates of undetected ("surprise") lung cancers at autopsy range from 0.34% to 55%[4,5,6,7,8,9,10,11,12]. Furthermore, autopsy techniques varied in unknown ways and there was no way to correct for potentially large biases due to unreported variability in age ranges and case mix (especially smoking prevalence and the selection bias inherent in autopsy series)[13]. Assuming that all lung cancers >15mm diameter would be diagnosed on autopsy, the LCPM (in the absence of screening) predicts a 3.6% autopsy surprise rate, in the reported range.

REFERENCES:

1 Capewell, S., Sankaran, R., et al. "Lung cancer in lifelong non-smokers" in Thorax 1991; 46: : 565-568

2 Beadsmoore, C. J., Screaton, N. J. "Classification, staging and prognosis of lung cancer" in European Journal of Radiology 2003; 45: 1: 8-17

3 Damber, L., Larsson, L.-G. "Smoking and lung cancer with special regard to type of smoking and type of cancer. A case-control study in north Sweden." in British Journal of Cancer 1986; 53: : 673-681

4 Gobbato, F, Vecchiet, F, Barbierato, D, Melato, M, Manconi, R "Inaccuracy of death certificate diagnosis in malignancy" in Human Pathology 1982; 13: 11: 1036-1038

5 Saracci, R. "Problems with the use of autopsy results as a yardstick in medical audit and epidemiology" in Quality Assurance in Health Care 1993; 5: 4: 339-44

6 Mollo, F, Bertoldo, E, Grandi, G, Cavallo, F "Reliability of death certificates for different types of cancer: an autopsy survey" in Pathology Research and Practice 1986; 181: : 442-447

7 Stenbäck, F, Päivärinta, H "Relation between clinical and autopsy diagnoses, especially as regards cancer" in Scandinavian Journal of Social Medicine 1980; 8: : 67-72

8 Engel, LW, Strauchen, JA, Chiazze Jr., L, Heid, M "Accuracy of death certification in an autopsied population with specific attention to malignant neoplasms and vascular disease" in American J Epidemiol 1980; 111: 1: 99-112

9 Delendi, M, Riboli, E, Peruzzo, P, Stanta, G, Cocchi, A, Gardiman, D, Sasco, AJ, Giarelli, L "Comparison of diagnoses of cancers of the respiratory system on death certificates and at autopsy" in Autopsy in Epidemiology and Medical Research, International Agency for Research on Cancer 1991;

10 Sternby, NH "The role of autopsy in cancer registration in Sweden, with particular reference to findings in Malmö" in Autopsy in Epidemiology and Medical Research, International Agency for Research on Cancer 1991;

[11] Chan, CK, Wells, CK, McFarlane, MJ, Feinstein, AR “More lung cancer but better survival: Implications of secular trends in "necropsy surprise" rates” in Chest 1989; 96: 2: 291-296

[12] Manser, R.L., Dodd, M., Byrnes, G., Irving, L. B., Campbell, D. “Incidental lung cancers identified at coronial autopsy: implications for overdiagnosis of lung cancer by screening” in Respir Med 2005; 99: : 501-507

[13] Agency for Healthcare Research and Quality, Department of Health and Human Services, “The autopsy as an outcome and performance measure” in Evidence Report/Technology Assessment No. 58 2002;

KEY REFERENCES

(1999) Marketscan Database,

Agency for Healthcare Research and Quality, Department of Health and Human Services, (2002) The autopsy as an outcome and performance measure in *Evidence Report/Technology Assessment No. 58*,

American Cancer Society (2001) Lung Cancer Resource Center in *American Cancer Society*,

American Cancer Society (2005) Cancer Facts and Figures in *American Cancer Society*,

Baba, Y., Takahashi, M., et al. (1998) Cost-effectiveness decision analysis of mass screening for lung cancer in *Academic Radiology* 5:2 Suppl, p S344-346

Bach, PB, Cramer, LD, Schrag, D, Downey, RJ, Gelfand, SE, Begg, CB (2001) The influence of hospital volume on survival after resection for lung cancer in *New England Journal of Medicine* 345, p 181-188

Bain, Chris, Feskanich, Diane, Speizer, Frank E., Thun, Michael, Hertzmark, Ellen, Rosner, Bernard A., Colditz, Graham A. (2004) Lung cancer rates in men and women with comparable histories of smoking in *J Natl Cancer Inst* 96:11, p 826-834

Barbone, F., Bovenzi, M., et al. (1997) Cigarette smoking and histologic type of lung cancer in men in *Chest* 112, p 1474-1479

Beadsmoore, C. J., Screaton, N. J. (2003) Classification, staging and prognosis of lung cancer in *European Journal of Radiology* 45:1, p 8-17

Beckles, M. A., Spiro, S. G., et al. (2003) Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes in *Chest* 123:1 Suppl, p 97S-104S

Benjamin, MS, Drucker, EA, McLoud, TC, Shepard, JO (2002) Small pulmonary nodules: detection at chest CT and outcome in *Radiology* 226, p 489-493

Black, W. (2000) Overdiagnosis: An underrecognized cause of confusion and harm in cancer screening [Editorials] in *Journal of the National Cancer Institute* 92:16, p 1280-1282

Capewell, S., Sankaran, R., et al. (1991) Lung cancer in lifelong non-smokers in *Thorax* 46, p 565-568

Caro, J., Klittich, W., et al. (2000) Could chest X-ray screening for lung cancer be cost-effective? in *Cancer* 89:11 Suppl, p 2502-2505

Centers for Disease Control (1993) Smoking Cessation During Previous Year Among Adults -- United States, 1990 and 1991 in *Morbidity and Mortality Weekly Report* 42:26, p 504-507

Chan, CK, Wells, CK, McFarlane, MJ, Feinstein, AR (1989) More lung cancer but better survival: Implications of secular trends in "necropsy surprise" rates in *Chest* 96:2, p 291-296

Chirikos, T., Hazelton, T., et al. (2002) Screening for lung cancer with CT: a preliminary cost-effectiveness analysis in *Chest* 121, p 1507-1514

Clare, S., Nakhlis, F., et al. (2000) Molecular biology of breast cancer metastasis: the use of mathematical models to determine relapse and to predict response to chemotherapy in breast cancer [Review] in *Breast Cancer Research* 2:6, p 430-435

Collins, M., Barry, M. (1996) Controversies in prostate cancer screening: Analogies to the early lung cancer screening debate. in *Journal of the American Medical Association* 276:24, p 1976-1979

Crestanello, J. A., Allen, M. S., Jett, J. R., Cassivi, S. D., Nichols, F. C., 3rd, Swensen, S. J., Deschamps, C., Pairolero, P. C. (2004) Thoracic surgical operations in patients enrolled in a computed tomographic screening trial in *Journal of Thoracic & Cardiovascular Surgery* 128:2, p 254-259

Damber, L., Larsson, L.-G. (1986) Smoking and lung cancer with special regard to type of smoking and type of cancer. A case-control study in north Sweden. in *British Journal of Cancer* 53, p 673-681

Delendi, M, Riboli, E, Peruzzo, P, Stanta, G, Cocchi, A, Gardiman, D, Sasco, AJ, Giarelli, L (1991) Comparison of diagnoses of cancers of the respiratory system on death certificates and at autopsy in *Autopsy in Epidemiology and Medical Research, International Agency for Research on Cancer*,

Detterbeck, FC, Rivera, MP (2001) Clinical presentation and diagnosis in *Diagnosis and Treatment of Lung Cancer*,

Diederich, S., Wormanns, D., et al. (2002) Screening for early lung cancer with low-dose spiral CT: Prevalence in 817 asymptomatic smokers. in *Radiology* 222, p 773-781

Earnest, Franklin, Ryu, Jay H., Miller, Gary M., Luetmer, Patrick H., Forstrom, Lee A., Burnett, Omer L., Rowland, Charles M., Swensen, Stephen J., Midthun, David E. (1999) Suspected non–small cell lung cancer: Incidence of occult brain and skeletal metastases and effectiveness of imaging for detection—Pilot Study in *Radiology* 211:1, p 137-145

Eddy, D. (1989) Screening for lung cancer. in *Annals of Internal Medicine* 111, p 232-237

Engel, LW, Strauchen, JA, Chiazze Jr., L, Heid, M (1980) Accuracy of death certification in an autopsied population with specific attention to malignant neoplasms and vascular disease in *American J Epidemiol* 111:1, p 99-112

Esnaola, NF, Lazarides, SN, Mentzer, SJ, Kuntz, KM (2002) Outcomes and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer in *JCO* 20:1, p 263-273

Feig, S. A. (2005) Screening mammography controversies: resolved, partly resolved, and unresolved in *Breast Journal* 11:1 Suppl., p S3-6

Flanders, W. Dana, Lally, Cathy A., Zhu, Bao-Ping, Henley, S. Jane, Thun, Michael J. (2003) Lung Cancer Mortality in Relation to Age, Duration of Smoking, and Daily Cigarette Consumption: Results from Cancer Prevention Study II in *Cancer Research* 63:19, p 6556-6562

Gobbato, F, Vecchiet, F, Barbierato, D, Melato, M, Manconi, R (1982) Inaccuracy of death certificate diagnosis in malignancy in *Human Pathology* 13:11, p 1036-1038

Gohagan, J. K., Marcus, P. M., Fagerstrom, R. M., et al., (2005) Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer in *Lung Cancer* 47:1, p 9-15

Gohagan, J., Marcus, P., Fagerstrom, R., Pinsky, P., Kramer, B., Prorok, P., Writing Committee, Lung Screening Study Research Group (2004) Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute in *Chest* 126:1, p 114-21

Gurney, J., Dewey, J. (1996) Pulmonary histoplasmosis in *Radiology* 199, p 297-306

Gøtzsche, P. C., Nielsen, M. (2006) Screening for breast cancer with mammography in *Cochrane Database of Systematic Reviews*:4,

Gøtzsche, P., Olsen, O. (2000) Is screening for breast cancer with mammography justifiable? in *The Lancet* 355:9198, p 129-134

Harris, J. E. (1989) Trends in Smoking-Attributable Mortality, Chapter 3. Reducing the Health Consequences of Smoking, 25 Years of Progress: A Report of the Surgeon General., p 117-169

Hasegawa, M, Sone, S, Takashima, S, Li, F, Yang, Z-G, Maruyama, Y, Watanabe, T (2000) Growth rate of small lung cancers detected on mass CT screening in *British Journal of Radiology* 73, p 1252-1259

Health and Human Services (1997) The National Health and Nutrition Examination Survey III Data file 1988-1994. in *Public Use Data file Series 11*,

Health and Human Services (1990) The Health Benefits of Smoking Cessation,

Henschke, C., McCauley, D. , et al. (1999) Early Lung Cancer Action Project: Overall design and findings from baseline screening in *Lancet* 354:9173, p 99-105

Henschke, C., Naidich, D., et al. (2001) Early Lung Cancer Action Project: Initial findings on repeat screening in *Cancer* 92, p 153-159

Humphrey, L. L., Teutsch, S., et al. (2004) Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. Preventive Services Task Force.[see comment] in *Annals of Internal Medicine* 140:9, p 740-53

Hunink, MGM, Goldman, L, Tosteson, ANA, Mittleman, MA, Goldman, PA, Williams, LW, Tsevat, J, Weinstein, MC (1997) The recent decline in mortality from coronary heart disease, 1980-1990 in *JAMA* 277:7, p 535-542

International Early Lung Cancer Action Program, I., Henschke, C. I., et al. (2006) Survival of patients with stage I lung cancer detected on CT screening.[see comment] in *New England Journal of Medicine* 355:17, p 1763-71

Jackman, DM, Chirieac, LR, Janne, PA (2006) Bronchioloalveolar carcinoma: A review of the epidemiology, pathology, and treatment. in *Sem Respir Crit Care Med* 26, p 342-352

Jemal, A, Chu, K, Tarone, R (2001) Cancer Surveillance Series: Recent trends in lung cancer mortality in the United States. in *J Natl Cancer Inst* 93, p 277-283

Kaneko, M., Kusumoto, M., et al. (2000) Computed tomography screening for lung carcinoma in Japan in *Cancer* 89:11 Suppl., p 2485-8

Knudsen, A. B., McMahon, P. M., Gazelle, G. S. (2007) Special Series (Cost): Use of modeling to evaluate the cost-effectiveness of cancer screening programs in *Journal of Clinical Oncology* 25:2, p 203-208

Korst, Robert J., Gold, Heather T., Kent, Michael S., Port, Jeffrey L., Lee, Paul C., Altorki, Nasser K. (2005) Surveillance computed tomography after complete resection for non-small cell lung cancer: Results and costs in *Journal of Thoracic and Cardiovascular Surgery* 129:3, p 652-660

Koscielny, S, Tubiana, M, Valleron, A-J (1985) A simulation model of the natural history of breast cancer in *British Journal of Cancer* 52, p 515-524

Kramer, B. S., J. K. Gohagan, et al. (1999) Cancer Screening: Theory and Practice. in *Basic and Clinical Oncology*,

Kubik, A. K., Parkin, D. M., et al. (2000) Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment in *Cancer* 89:11 Suppl., p 2363-8

Li, H, Boiselle, PM, Shepard, JO, Trotman-Dickenson, B, McLoud, TC (1996) Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules in *American Journal of Radiology* 167, p 105-109

Mahadevia, P., Fleisher, L., et al. (2003) Lung cancer screening with helical computed tomography in older adult smokers in *Journal of the American Medical Association* 289:3, p 313-322

Mandel, J, Weinberger, SE (2005) Overview of non-small cell lung cancer staging in *UpToDate* version 13,

Manser, R.L., Dodd, M., Byrnes, G., Irving, L. B., Campbell, D. (2005) Incidental lung cancers identified at coronial autopsy: implications for overdiagnosis of lung cancer by screening in *Respir Med* 99, p 501-507

Marcus, P. M., Bergstralh, E. J., et al. (2006) Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis.[see comment] in *Journal of the National Cancer Institute* 98:11, p 748-56

Marcus, P., Bergstralh, E., et al. (2000) Lung cancer mortality in the Mayo Lung Project: Impact of extended follow-up in *Journal of the National Cancer Institute* 92:16, p 1308-1316

Marshall, D., Simpson, K., et al. (2001) Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort in *Lung Cancer* 32:3, p 227-236

Marshall, D., Simpson, K., et al. (2001) Economic decision analysis model of screening for lung cancer in *European Journal of Cancer* 37:14, p 1759-1767

Massey, JT, Moore, TF, Parsons, VL, Tadros, W (1989) Design and Estimation for the National Health Interview Survey, 1985-94 in *Vital Health Statistics, Series 2, No. 110,*

Matsumoto M., Nishimura T. (1998) Mersenne twister: a 623-dimensionally equidistributed uniform pseudo-random number generator. in *ACM Transactions on Modeling and Computer Simulation* 8:1, p 3-30

McLoud, TC, Bourgouin, PM, Greenberg, RW, Kosuik, JP, Templeton, PA, Shepard, JO, Moore, EH, Wain, JC, Mathesen, DJ, Grillo, HC (1992) Bronchogenic carcinoma: Analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling in *Radiology* 182, p 319-323

McMahon, P. M., Zaslavsky, A. M., et al. (2006) Estimation of mortality rates for disease simulation models using Bayesian evidence synthesis in *Medical Decision Making* 26, p 497-511

Miettinen, O., Henschke, C. (2001) Commentary on Drs. Patz, Black, and Goodman's viewpoint in *Radiology* 221, p 598-599

Miettinen, O., Henschke, C. (2001) CT screening for lung cancer: coping with nihilistic recommendations [Viewpoint] in *Radiology* 221, p 592-596

Miller, D. P., Liu, G., et al. (2002) Combinations of the variant genotypes of GSTP1, GSTM1, and p53 are associated with an increased lung cancer risk in *Cancer Research* 62, p 2819-2823

Mizuno, T., Masaoka, A., et al. (1984) Comparison of actual survivorship after treatment with survivorship predicted by actual tumor-volume doubling time from tumor diameter at first observation in *Cancer* 53, p 2716-2720

Mollo, F, Bertoldo, E, Grandi, G, Cavallo, F (1986) Reliability of death certificates for different types of cancer: an autopsy survey in *Pathology Research and Practice* 181, p 442-447

Moolgavkar, S. H., Knudson, A. G., Jr. (1981) Mutation and cancer: a model for human carcinogenesis in *J Natl Cancer Inst* 66:6, p 1037-52

Mountain, C. F. (1997) Revisions in the International System for Staging Lung Cancer.[see comment] in *Chest* 111:6, p 1710-7

Naruke, T., Goya, T., et al. (1988) The importance of surgery to non-small cell carcinoma of lung with mediastinal lymph node metastasis in *Annals of Thoracic Surgery* 46:6, p 603-10

Nathan, M., Collins, V., et al. (1962) Differentiation of benign and malignant pulmonary nodules by growth rate in *Radiology* 79, p 221-232

National Cancer Institute (2002) National Lung Screening Trial,

National Cancer Institute (2002) Database: Incidence - SEER 9 Regs Public-Use,

National Center for Health Statistics National Health Interview Survey,

Oreskes, N., Shrader-Frechette, K., et al. (1994) Verification, validation, and confirmation of numerical models in the earth sciences in *Science* 263, p 641-646

Patz, E., Black, W., et al. (2001) Commentary on Drs. Miettinen and Henschke's viewpoint in *Radiology* 221, p 597

Patz, E., Black, W., et al. (2001) CT screening for lung cancer: Not ready for routine practice [Viewpoint] in *Radiology* 221, p 587-591

Patz, E., Goodman, P., et al. (2000) Screening for lung cancer [Review] in *New England Journal of Medicine* 343:22, p 1627-1633

Pinsky, P. F., Marcus, P. M., Kramer, B. S., Freedman, M., Nath, H., Kvale, P., Reding, D. (2005) Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen in *Cancer* 103:1, p 157-163

Pope, RJE, Hansell, DM (2003) Extra-thoracic staging of lung cancer in *European Journal of Radiology* 45:1, p 31-38

Press, W. H., Teukolsky, S. A., et al. (2002) Numerical Recipes in C++: The Art of Scientific Computing,

Prorok, P., Andriole, G., et al. (2000) Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial in *Controlled Clinical Trials* 21, p 273S-309S

Puntoni, R., Toninelli, F., Zhankui, L., Bonassi, S. (1995) Mathematical modelling in risk/exposure assessment of tobacco related lung cancer in *Carcinogenesis* 16:7, p 1465-71

Rachet, B., Siemiatycki, J., Abrahamowicz, M., Leffondre, K. (2004) A flexible modeling approach to estimating the component effects of smoking behavior on lung cancer in *J Clin Epidemiol* 57:10, p 1076-85

Ramsey, S. D., McIntosh, M., et al. (2000) Simulation modeling of outcomes and cost effectiveness in *Hematology - Oncology Clinics of North America* 14:4, p 925-38

Ransohoff, D. F., Harris, R. P. (1997) Lessons from the mammography screening controversy: can we improve the debate? in *Annals of Internal Medicine.* 127:11, p 1029-34

Raz, D J, He, B, Rosell, R, Jablons, D M (2005) Current concepts in bronchioloalveolar carcinoma biology in *Clin Cancer Res* 12, p 3698-3704

Reich, J. M. (2002) Improved survival and higher mortality: the conundrum of lung cancer screening.[see comment]. in *Chest* 122:1, p 329-37

Ries, L., Eisner, M., et al. (2002) SEER Cancer Statistics Review, 1973-1999,

Rivera, M., Detterbeck, F., et al. (2001) Epidemiology and classification of lung cancer. Diagnosis and Treatment of Lung Cancer: An evidence-based guide for the practicing clinician
,

Rubins, JB, Rubins, HB (1996) Temporal trends in the prevalence of malignancy in resected solitary pulmonary lesions in *Chest* 109, p 100-103

Saracci, R. (1993) Problems with the use of autopsy results as a yardstick in medical audit and epidemiology in *Quality Assurance in Health Care* 5:4, p 339-44

Schilling, Freimut H., Spix, Claudia, Berthold, Frank, Erttmann, Rudolf, Fehse, Natalja, Hero, Barbara, Klein, Gisela, Sander, Johannes, Schwarz, Kerstin, Treuner, Joern, Zorn, Ulrich, Michaelis, Joerg (2002) Neuroblastoma screening at one year of age in *N Engl J Med* 346:14, p 1047-1053

Smythe, W. R., American College of Chest Physicians (2003) Treatment of stage I non-small cell lung carcinoma in *Chest* 123:1 Suppl., p 181S-187S

Sone, S., Li, F., et al. (2001) Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner in *British Journal of Cancer* 84:1, p 25-32

Song, P, Sekhon, HA, Jia, Y, Keller, JA, Blusztajn, JK, Mark, GP, Spindel, ER (2003) Acetylcholine is synthesized by and acts as an autocrine growth factor for small cell lung carcinoma in *Cancer Research* 63, p 214-221

Sox, H. (2002) Screening mammography for younger women: Back to basics in *Annals of Internal Medicine* 137:5 (Part 1), p 361-362

Spira, A, Ettinger, DS (2004) Multidisciplinary management of lung cancer in *New England Journal of Medicine* 350, p 379-392

Spratt, J. S., Spratt, J. A. (2002) Growth Rates in *Cancer of the Breast*,

Stenbäck, F, Päivärinta, H (1980) Relation between clinical and autopsy diagnoses, especially as regards cancer in *Scandinavian Journal of Social Medicine* 8, p 67-72

Sternby, NH (1991) The role of autopsy in cancer registration in Sweden, with particular reference to findings in Malmö in *Autopsy in Epidemiology and Medical Research, International Agency for Research on Cancer*,

Strauss, G., Gleason, R., et al. (1997) Screening for lung cancer: Another look; A different view in *Chest* 111:3, p 754-768

Surveillance Research Program, National Cancer Institute, (2005) Surveillance, Epidemiology, and End Results (SEER) Program Seer*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2004 Sub (1973-2002 varying) in *Seer*Stat software version 6.1.4*,

Swensen, S. J., Jett, J. R., et al. (2005) CT Screening for Lung Cancer: Five-year Prospective Experience in *Radiology* 235:1, p 259-265

Swensen, S., Jett, J., et al. (2002) Screening for lung cancer with low-dose spiral computed tomography in *American Journal of Respiratory and Critical Care Medicine* 165, p 508-513

Swensen, S., Jett, J., et al. (2003) Lung cancer screening with CT: Mayo Clinic experience in *Radiology* 226:3, p 756-761

Swensen, S., Viggiano, R., et al. (2000) Lung nodule enhancement at CT: multicenter study in *Radiology* 214, p 73-80

Takashima, S., Sone, S., et al. (2003) Indeterminate solitary pulmonary nodules revealed at population-based CT screening of the lung: Using first follow-up diagnostic CT to differentiate benign and malignant lesions in *American Journal of Radiology* 180, p 1255-1263

Tan, BB, Flaherty, KR, Kazerooni, EA, Iannettoni, MD (2003) The solitary pulmonary nodule in *Chest* 123:1, p 89S-96S

Tan, W. Y., Zhang, L.-J. (2004) Stochastic modeling of carcinogenesis: state space models and estimation of parameters in *Discrete and Continuous Dynamical Systems - Series B* 4:1, p 297-322

Taylor, K. L., Shelby, R., et al. (2004) Quality of Life and Trial Adherence Among Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in *J Natl Cancer Inst* 96:14, p 1083-1094

The Commit Research Group (1995) Community Intervention Trial for Smoking Cessation (COMMIT): II. Changes in Adult Cigarette Smoking Prevalence in *Am J Public Health* 85, p 193-200

Therasse, P, Arbuck, SG, Eisenhauer, EA, Wanders, J, Kaplan, RS, Rubinstein, L, Verweij, J, Van Glabbeke, M, van Oosterom, AT, Christian, MC, Gwyther, SG (2000) New guidelines to evaluate the response to treatment in solid tumors in *Journal of the National Cancer Institute* 92, p 205-216

Thun, M. J., Myers, D. G., et al. (1997) Chapter 5. Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II. National Cancer Institute, Smoking and Tobacco Control, Monograph 8:,

Travis, W D, Garg, K, Franklin, W A, et al. (2005) Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma in *J Clin Oncol* 23, p 3279-3287

U.S. Department of Health and Human Services, National Center for Health Statistics, (1997) The National Health and Nutrition Examination Survey III Data file 1988-1994. in *Public Use Data file Series 11*,

Usuda, K., Saito, Y., et al. (1994) Tumor doubling time and prognostic assessment of patients with primary lung cancer in *Cancer* 74, p 2239-2244

Wakelee, HA, Chang, ET, Gomez, SL, et al. (2007) Lung cancer incidence in never smokers in *J Clin Oncol* 25, p 472-478

Wallace, MJ, Krishnamurthy, S, Broemeling, LD, Gupta, S, Ahrar, K, Morello, FA, Hicks, ME (2002) CT-guided percutaneous fine-needle aspiration biopsy of small (less than or equal to 1-cm) pulmonary lesions in *Radiology* 225, p 823-828

Weinberger, SE (2004) Differential diagnosis and evaluation of the solitary pulmonary nodule in *UpToDate* version 12,

Weinstein, M. C., O'Brien, B., et al. (2003) Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR Task Force on Good Research Practices-Modeling Studies in *Value in Health* 6:1, p 9-17

Weinstein, MC, Coxson, PG, Williams, LW, Pass, TM, Stason, WB, Goldman, L (1987) Forecasting coronary heart disease incidence, mortality, and cost: The Coronary Heart Disease Policy Model in *American Journal of Public Health* 77, p 1417-1426

Winton, T., Livingston, R., et al. (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer in *New England Journal of Medicine* 352:25, p 2589-2597

Wisnivesky, J., Mushlin, A., et al. (2003) The cost-effectiveness of low-dose CT screening for lung cancer in *Chest* 124, p 614-621

Woods, William G., Gao, Ru-Nie, Shuster, Jonathan J., Robison, Leslie L., Bernstein, Mark, Weitzman, Sheila, Bunin, Greta, Levy, Isra, Brossard, Josee, Dougherty, Geoffrey, Tuchman, Mendel, Lemieux, Bernard (2002) Screening of infants and mortality due to neuroblastoma in *N Engl J Med* 346:14, p 1041-1046

Zheng, T, Holford, TR, Boyle, P, et al. (1994) Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989 in *Cancer* 74, p 1556-1567