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ERASMUS MC (LUNG)

Important note: This document will be updated periodically. 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.

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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.

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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. Detailed information is available for each specific parameter.

Component Overview

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

- Population Component
- Risk Factors Component
- Smoking Generator Component
- Natural History Component
- Screening Component

Output Overview

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Specific implementations

- Smoking Base Case14Mar06 describes the 14 March 2006 version of our model assumptions for the Smoking Base Case.
- Smoking Base Case16Feb09 describes the 16 February 2009 version of our model assumptions for the Smoking Base Case.

Key References

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

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MODEL PURPOSE

SUMMARY

This document describes the purposes of the MISCAN-lung model and the types of questions it was designed to answer.

PURPOSE

The MISCAN-lung model is intended to simulate population trends in lung cancer for comprehensive surveillance of the disease and to estimate the impact of cancer-control interventions (smoking, diet, screening).

Comprehensive surveillance of population trends in lung cancer

The model is primarily intended to simulate observed trends in incidence and mortality from lung cancer in the U.S. population in order to investigate to what extent observed trends can be explained by (earlier) trends in exposure to risk factors, in particular smoking and diet.

The model is also intended to project trends in lung cancer incidence and mortality to years of (future) observation not yet reported. Where the simulation of observed trends concentrates on exposure to risk factors, future trends may be influenced also by trends in screening and therapy.

Evaluation of interventions

The model can simulate the effects of different intervention scenarios in order to compare results in terms of population trends as well as health outcomes, including life years lost due to lung cancer.

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MODEL OVERVIEW

SUMMARY

This document provides an overview of purpose and background of the MISCAN-lung model for lung cancer surveillance and offers a brief description of the model.

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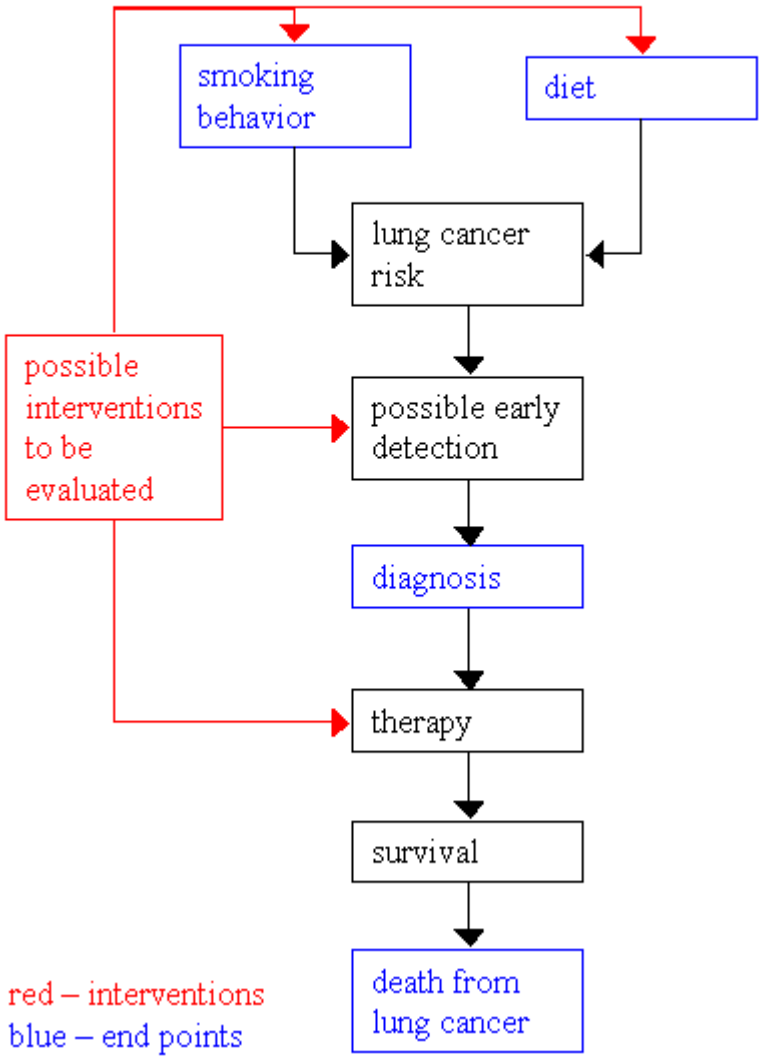
PURPOSE

The MISCAN-lung model is primarily intended for surveillance of population trends in lung cancer and secondarily for evaluation of interventions, particularly concerning smoking and screening.

MISCAN-lung includes the complete lung cancer chain of events, from behavior- and diet-related risk factors to death from lung cancer (see Figure 1) in order to facilitate evaluation of the influences on population trends and of effects of interventions.

Figure 1. Chain of events to be evaluated for surveillance and interventions that could contribute to the elimination of lung cancer.



Causal chain

BACKGROUND

Lung cancer is a major health problem in the United States, even though the age-adjusted incidence and mortality rates of lung cancer have been decreasing each year,

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since around 1992, by an average of 1.8% for men and 0.6% for women. It is generally assumed that most of this population trend is due to changes in smoking behavior but this assumption is so far not quantified and there are no good tools to predict future trends other than extrapolating observed trends.

Risk factors

Exposure to tobacco smoke is by far the most serious risk factor for cancer of the lung and bronchi. An estimated 87% of lung cancer deaths in 2003 are attributable to active smoking. Other risk factors include exposure to second-hand smoke (passive smoking); radon (a naturally occurring air pollutant); asbestos; and diet.
In addition to tobacco, poor dietary quality has been related to lung cancer. Expert consensus suggests that as much as 20-30% of lung cancers are attributable to a poor quality diet.

There is an intricate relationship between exposure to risk factors and resulting risk of lung cancer. Generally, this relationship is described by empirical studies as a relative or excess risk among those exposed to a risk factor with respect to those who were not exposed, or as a comparison between different levels of exposure. Very few report on possible mechanisms that explain the timing from exposure to expression. There is general agreement that exposure to tobacco smoke leads to a very strong increase in risk for lung cancer and that the time from exposure to lung cancer can be several decades.

Multistage Carcinogenesis

The concept of multistage carcinogenesis provides a possible explanation of the long duration from exposure to expression. Carcinogenesis proceeds through at least the following stages:

Initiation: Initiation is the process in which a single somatic cell undergoes non-lethal, but heritable, mutation. The initiated cell can escape cellular regulatory mechanisms.
Promotion: Promotion is the process in which the initiated cell is exposed to a tumor promoter that causes phenotypical clonal expansion. Tumor promoters are either external or internal stimuli and stimulate growth of initiated cells.
Malignant conversion: During malignant conversion or transformation, cellular growth is further deregulated. Like initiation, this step requires genetic alteration.
Progression: During this stage, cellular growth is further deregulated and proceeds uncontrolled. Progression is probably the most complex stage, because both acquired genetic and phenotypic alterations occur, and cellular expansion is rapid.

The first quantitative mechanistic model concerning carcinogenesis was published by Armitage and Doll (1954). Subsequent models incorporate new knowledge concerning multistage carcinogenesis, such as the clonal expansion occurring during the promotion stage. Dr. Moolgavkar at the Fred Hutchinson Cancer Research Center is at the forefront of this model development.
The Moolgavkar model summarizes the promotion stage in a single step and agrees very well with observed epidemiological evidence. However, current versions of the Moolgavkar model do not account for the progression stage in any detail. This stage is particularly important for evaluation of early detection of (lung) cancer.

Early detection

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Since neither primary prevention nor treatment has had a satisfying impact on lung cancer incidence or mortality, secondary prevention (screening of asymptomatic individuals) remains a topic of great interest. Because lung cancer is usually diagnosed based on symptoms, the disease is usually so far advanced that curative therapy is not possible. Screening has the potential to detect lung cancer at earlier stages, when survival rates are considerably higher.

It is anticipated that new technology for lung cancer screening, particularly CT screening, will make it possible to better detect aggressive cancers early enough to be curable. Improved screening has the potential to prevent thousands of lung cancer deaths annually.

Diagnosis and therapy

New lung cancer therapies unfortunately have not had a substantial impact on mortality so far. Most clinical trials did not show major improvements in survival, and population-based survival from a diagnosis of lung cancer has improved only slightly over the past few decades.

However, there is a striking variation in the treatment of lung cancer that raises concerns about disparities in the care of patients of different racial/ethnic groups and advanced age. Several population-based studies have found that black and Hispanic patients are less likely to undergo potentially curative surgical resection for early stage non-small cell lung cancer than white patients, even when controlling for differences in comorbid illness and age. In addition to these variations according to patients' racial/ethnic background, many studies have demonstrated a marked decline in the use of curative treatments with increasing patient age.

Model Description

The system that is modeled

MISCAN-lung models a human population consisting of individual life histories, in which lung cancer may develop.
The life histories consist of (see Figure 2):

- Exposure to risk factors, particularly smoke and diet.
- Carcinogenesis as influenced by risk factors.
- Timing of diagnosis of lung cancer.
- Net survival from lung cancer.
- Influence of screening on time of diagnosis and death.

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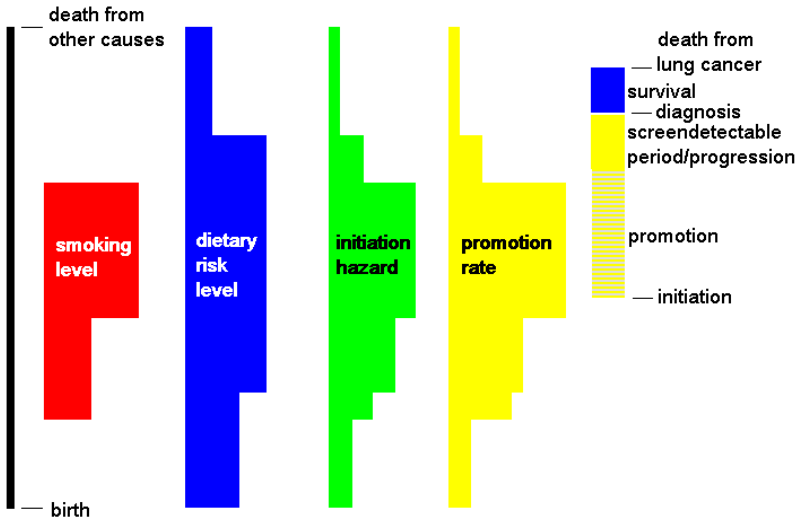
Figure 2. Risk model – sample life history



Risk model

Individual life histories are created with events drawn from probability distributions. A life history starts with a birth date and assigning gender/ethnicity. Age of death from causes other than lung cancer is determined from a life table without this specific disease. Then the birth date and gender/ethnicity dependent smoking history is generated, i.e. starting age, stopping age and smoking intensity in between those time points. Likewise, time points are determined at which dietary risk changes. The steps in risk level are combined. The corresponding age-specific risk factors are applied to modify the initiation hazard and promotion and malignant transfer rates in the multistage carcinogenesis model. As a result, a malignant nodule may appear which, after progression to a clinically diagnosed lung cancer (see Natural History Component), leads to lung cancer death. (In this sample, before the projected time of death from other causes.) During progression, the tumor is assumed to be screen-detectable.

General modeling methodologies

We apply the technique of microsimulation of individual life histories in order to constitute a relevant population. The life histories are constructed stochastically by drawing events and development rates from probability distributions in order to

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reproduce distributions of personal characteristics over the population.

We developed two modules of MISCAN-lung model: smoking history generator module for Smoking Base Case (SBC) calculations and Mayo Lung Project (MLP) module, which is also used to analyze data collected from the Mayo CT screening trial (MCT). The first module uses the smoking history generator provided by NCI to determine probability of exposure to risk factors and subsequently, its impact on lung cancer development, survival, and mortality from other causes. The second module uses the smoking history data and screening data derived from the MLP or MCT to determine the effect of smoking and screening on lung cancer development and survival. The model profile applies to both modules in general. However, descriptions regarding screening only apply to the MLP module. At places where the two modules differ, apart from screening, descriptions of both modules are provided.

The primary unit of analysis
MISCAN-lung based estimates and comparisons with observations will be primarily on population level.

Inputs
Probability distributions for

- Time of birth.
- Exposure to risk factors;
- Influenced by exposure to risk factors:
  - Age of death from causes other than the disease of interest;
  - Initiation of carcinogenesis;
  - Promotion or clonal expansion;
  - Malignant transformation.
- Cell type of lung cancer;
- Influenced by cell type and early detection:
  - Progression to clinical lung cancer;
  - Dwelling times by preclinical stage of lung cancer;
  - Stage distribution at diagnosis;
  - Net survival from lung cancer, also influenced by stage at diagnosis.
- Compliance with screening.
- Sensitivity of screening test for detection of preclinical cancer.
- Consequences of screen-detection.

Outputs

- Incidence of lung cancer by stage and cell type, mortality from lung cancer and from other causes, life years in disease states.
- Exposure to screening-tests and test results.

Important limitations of the model

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- The most obvious limitation of the model concerns the limitations in knowledge that inform the model, which regards uncertainty in parameter estimates as well as in correct interpretation and structural composition of the model.
- The model has a limited amount of detail, particularly when modeling cancer characteristics.
- The chain of events modeled concentrates on biology and medical interventions in the disease; behavioral interventions e.g. to reduce exposure to tobacco smoke are only included in the model as their effect on exposure.

CONTRIBUTORS

The MISCAN-lung model is an extension of the MISCAN model, which has been developed at the Department of Public Health of Erasmus MC, Rotterdam, the Netherlands with contributions of several people.

The MISCAN-lung model includes the influence of risk factors. It has been developed by:
Rob Boer with contributions of:
Shin-Yi Wu, Haijun Tian, Lu Shi, Marjolein van Ballegooijen, Bill McCarthy, Barbara Berman
programmer of MISCAN extensions:
Floris van Maanen
consultants:
Robert Figlin, Jennifer Malin (until 2004)

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ASSUMPTION OVERVIEW

SUMMARY

This document describes the assumptions used in the MISCAN-lung model.

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BACKGROUND

A comprehensive model for lung cancer surveillance requires assumptions concerning the following aspects:

- Demography.
- Risk factor exposure.
- Risk factor exposure-effect relationships.
- Preclinical lung cancer.
- Screening.
- Clinical lung cancer.
- Lung cancer survival.
- Mortality from causes other than lung cancer.

The model aspects that are directly observable require the least model specific assumptions. Demography and mortality from other causes are generally observed quite accurately. However, when mortality from other causes needs to be distinguished by exposure to risk factors, e.g. smoking status, which is not directly observed in the U.S. population, there is already need for specific model assumptions.

Clinical lung cancer and its survival can be observed directly. However, often direct observations of survival as well as exposure to risk factors are not available. Therefore relevant assumptions are needed.

Exposure to risk factors is directly observable, but observation of the long term effects of such exposure is much more difficult. Therefore, surveillance of trends in recent history still requires data on exposure to risk factors of several decades earlier when observations were not made. This void can only be resolved by making some extrapolations from more recent observations.

The most typical assumptions for our model concern the aspects: Risk factor exposure-effect relationships, preclinical lung cancer, and screening where interpretation of observations takes place through (formal or informal) model assumptions.

ASSUMPTION LISTING

Demography

Demography assumptions focus on the population characteristics including gender, race/ethnicity, and age distribution.

Our model does not assume any entry or exit from the population due to migration. This is generally not a problem when studying a research cohort but to some extent it is

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when studying a geographically defined dynamic population.

The primary purpose of our model is to study population trends in a geographically defined dynamic population, viz. the U.S. population. As long as we study a limited time period during which the population does not change substantially due to migration, and when risk factor exposure is measured retrospectively, e.g. by contemporary survey on smoking history, then the problem of migration is very limited: We simulate a births distribution that (in conjunction with modeled mortality) reproduces the demography during the period of the study. The simulated births will not accurately represent actual birth statistics in the U.S. but rather concern births of people who are alive in the U.S. during the study period. In the model, at times long before the period of interest in the study, the simulated population will then be larger than the actual U.S. population.

Risk factor exposure

In general we rely on self-reported exposure to risk factors, which tends to be not very accurate, and on a limited number of questions to characterize exposure history. Therefore, we should assume that there is a substantial amount of uncertainty concerning risk factor exposure. In a non-linear system, such as the effects of risk factors on lung cancer risk, this uncertainty may lead to incorrect estimates but an investigation into this potential problem did not show inaccuracies that would lead to faulty inference in our project.[1]

Risk factor exposure-effect relationships

We adapted the Moolgavkar model on multistage carcinogenesis[2,3] for use within our existing MISCAN microsimulation model.
Validation of the original Moolgavkar model for smoking and lung cancer is described elsewhere.[3]
Our adaptation for microsimulation concerns the very early stage: The Moolgavkar model assumes that , after initiation of a stem cell, there is a stochastic process where an initiated cell can form an additional initiated cell, differentiate, or die. The vast majority of initiations does not lead to a clone of initiated cells with any slight chance of malignant transformation. In a microsimulation model this would imply the need to simulate many initiations that only die out within a quite limited period of time, adding a lot of computing time with no effect on risk projections. Therefore, our model only simulates initiations that grow out to a clone of initiated cells that is large enough to have surpassed the stage in which stochastic death or differentiation of individual cells can lead to the end of the whole clone.

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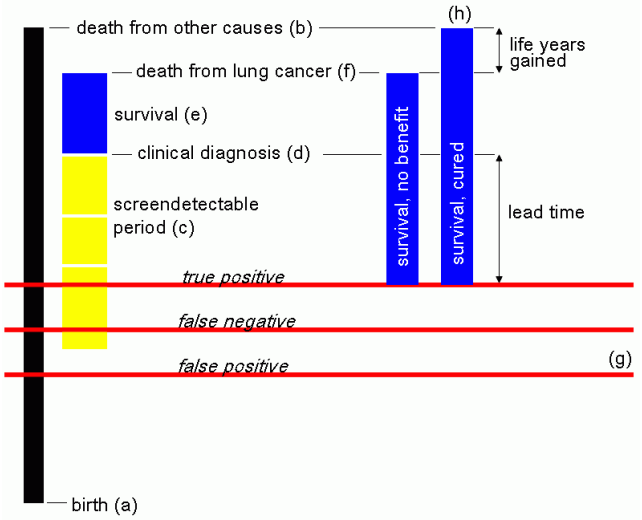
Preclinical lung cancer

Although risk factors can influence all stages of the TSCE model, it is generally assumed that the stage of progression from malignant transformation to clinical cancer is not influenced as strongly by risk factors as the earlier stages of carcinogenesis.
We replaced the progression part of the TSCE model with a natural history model of lung cancer. (see **Natural History Component**)
We assumed a model structure for preclinical lung cancer that is similar to model structures that we have used for the evaluation of screening of other cancers.[4,5,6,7,8,9]
The model assumes that (at least during the screen-detectable period) lung cancer is one of three cell types: squamous cell, adeno/large cell, or small cell carcinoma and that it progresses from preclinical stage I-II to clinical diagnosis in stage I-II ,or to preclinical stage III-IV and then to clinical diagnosis in stage III-IV.

Of the four main cell types in which lung cancer is generally categorized, we joined adenocarcinoma and large cell carcinoma because we considered that there may be a nonnegligible probability of adenocarcinoma developing into large cell carcinoma during the
screen-detectable period.

Screening

Figure 3. Screening model – sample life history



Screening Model

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(a) Distribution of births over calendar time. (b) Distribution of death from other causes over age. (c) Distribution of start of screen-detectable preclinical period over age. Dwelling time distributions of each preclinical disease state. Transition probabilities to diagnosis versus progression to next preclinical disease state. (d) Age specific incidence depends on distribution of start of screen-detectable preclinical period and dwelling time distributions of preclinical disease states. Stage distribution depends on transition probabilities to diagnosis versus progression to next preclinical disease state. (e) Net survival distribution from diagnosis to death from lung cancer. (f) Mortality from lung cancer depends on incidence, survival and mortality from other causes. (g) Screening defined by times of screening, compliance (two possible mechanisms for timing/compliance), and sensitivity and specificity of screening test. (h) Effect of early detection can be defined by several mechanisms such as probability by screen-detected stage of extending life from death of lung cancer to death of another cause.

We assume a preclinical lung cancer may be detected by screening, depending on the screening-test. The screening-test is assumed to have a probability of systematic error, in which a preclinical cancer will always be missed due to personal, lesion, or test moment factors. If a preclinical cancer is not missed by systematic error, then it has a probability to be detected depending on the sensitivity of the screening-test. The sensitivity of a screen-test varies by the stage (I-II or III-IV) and type (squamous cell, adeno/large cell, or small cell) of the cancer development.
When a screening is offered, some people will accept it while others will not. In our model we assume that the reach of screening is determined by two factors: 1) whether a screening is a first screening or a repeated screening in a trial, and 2) whether the person attended or missed the previous screening.
There are several possibilities to simulate the consequences of early detection of lung cancer by screening, the most important of which are: no change in time of death; cure from lung cancer (defined by dying at the time originally simulated for death from causes other than
lung cancer); or a new survival distribution. As mentioned in section "Lung cancer survival" below, we currently have two alternative assumptions for MLP and MCT: maintain the cell type and stage specific survival curves for screen-detected cases so that any improvement just results from detection in an earlier stage, or assume 40% cure of screen-detected stage II cancer.

Clinical lung cancer
According to the multistage carcinogenesis model, after malignant conversion occurs,

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cellular growth is further deregulated and proceeds uncontrolled. This period in carcinogenesis development can further be divided into preclinical lung cancer and clinical lung cancer. As previously described, preclinical lung cancer can only be screen-detected, but clinical lung cancer can be both screen-detected and clinically detected. Our model structure for clinical lung cancer is similar to the model structures described in section "Preclinical lung cancer" above in order to correspond with the SEER registry; that is, the model assumes that lung cancer is one of three cell types: squamous cell, adeno/large cell, or small cell carcinoma and that it progresses from preclinical stage I-II to clinical stage I-II, or to preclinical stage III-IV and then to clinical stage III-IV. The clinical detectability is determined by the carcinogenesis model, and the lung cancer survival is described below in section "Lung cancer survival".

Lung cancer survival

After clinical diagnosis we assume a net survival distribution based on SEER by stage category and cell type. In reality the studied population (e.g. the U.S. population) may have a different survival distribution than observed in SEER but we expect that any such differences have a relatively small effect on mortality.

Survival after screen-detection can be modeled in different ways. For the MLP module we made two different sets of tentative assumptions:

- In case of screen-detection a new survival distribution is started that follows the same survival distribution by cell type and by stage category as when clinically diagnosed but the survival curve, starting from the date of early diagnosis, possibly concerns an earlier stage category with a more favorable survival.
- Persons with a screen-detected lung cancer in stage I-II that would be fatal in the situation without screening, receive a probability of 40% of not dying from lung cancer (therefore dying from other causes at a later time), and all other cases die at the same time and from the same cause as in the situation without screening. This assumption gives a reasonably close similarity of observed and modeled survival in MLP.

Mortality from causes other than lung cancer

We assume that death from lung cancer and death from other causes are independent, and modeled two ways of mortality from other causes. In our MLP module, mortality from causes other than lung cancer is assumed to depend on exposure to risk factors. We assume a Gompertz distribution in case of constant exposure to risk factors where both the exponential growth rate in the Gompertz hazard model and the immediate hazard itself can depend on concurrent exposure to risk factors. By this mechanism smokers, for example, can have a higher relative risk of mortality from other causes, including a gradual moderation of the increased relative risk when quitting smoking. Alternatively, in the smoking history generator module, mortality from other causes is governed by the smoking history generator (developed by NCI), which gives the probability of death from other causes for each year and each birth cohort by smoking status.

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PARAMETER OVERVIEW

SUMMARY

This document provides an overview of the parameters used to quantify the MISCAN-lung model for lung cancer surveillance.

BACKGROUND

The MISCAN-lung model uses four types of parameters:

- Demography parameters.
- Risk factors parameters.
- Natural history parameters.
- Screening parameters.

Currently, treatment parameters have not been modeled but they will be considered in the near future.

PARAMETER LISTING OVERVIEW

Demography Parameters

1. Births:
   a. Number of birth cohorts;
   b. Distribution of the population among the birth cohorts;
   c. For each birth cohort parameters of its birth table to give the period of dates of birth within the birth cohort;
   d. For each birth cohort the parameters of its life table.
5. Stratification of birth cohorts by gender and race/ethnicity.
6. Mortality from other causes, either as:
   a. Parameters for the exponential growth rate of the hazard and the baseline hazard for death from other causes, and the dose effect relationships of risk factors on that exponential growth rate and immediate hazard;
   b. When mortality from other causes is governed by the smoking history generator: the probability of death from other causes for each year and each birth cohort by smoking status.

Risk Factors Parameters

1. Number of risk factors: smoking and/or diet, with option of additional risk factor.
2. Number of risk levels for each risk factor.
3. Risk exposure (e.g., smoking, diet risk) over time at different risk levels.
4. Hazards of multistage carcinogenesis as the dose effect relationships of risk factors on initiation, promotion, and malignant transformation.

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Natural History Parameters

1. Parameters for the cell type distribution of lung cancer.
2. Parameters for the stage distribution of lung cancer.
3. Parameters for the initiation, promotion, and malignant transformation of lung cancer.
4. Parameters for duration distribution of screen-detectable disease states after malignant transformation.
5. Parameters for the transition probability from each stage.
6. Parameters for net survival from lung cancer after clinical diagnosis by stage of the cancer.

Screening Test Parameters

1. Parameters for screening policy, e.g., timing and dissemination of screening (e.g. start age, end age, screening interval, adherence to screening).
2. Sensitivity of a screening test.
3. Systemic error of a screening test.
4. Parameters for consequence of screening after screen-detected diagnosis:

    a. Probability of dying from other causes due to early detection by screening;
    b. Survival benefit due to early detection by screening.

3. Parameters for an individual's screening behavior/adherence:

    a. Probability of screening acceptance by screening type (initial vs. repeat screening);
    b. Probability of screening acceptance by previous screening acceptance.

Summary table

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The following table summarizes parameter name, validation criteria, and its use for lung cancer surveillance in the MISCAN-lung model.

Parameters	Validation	Surveillance
DEMOGRAPHY		
Births:	Reproducing age distribution of the study cohort.	Reproducing age distribution of U.S. population.
Stratification:	Distribution over gender and race/ethnicity as in study cohort.	Distribution over gender and race/ethnicity of U.S. population.
Mortality from other causes:	Correlation between durations, rate ratios of concurrent smoking for mortality hazard and increase rate of hazard in Gompertz distribution reproducing rate ratios of CPS.	--
RISK FACTORS		
Smoking exposure over time:	Reconstructed from smoking history at enrollment in study.	Reconstructed from U.S. survey data.
Dietary risk over time:	Assuming average dietary risk distribution unless dietary history is available in study data.	Reconstructed from U.S. survey data.
Hazards of multistage carcinogenesis - Dose effect relationships:	Reproducing dose effect relationships estimated with the Moolgavkar model from CPS I and II, British Doctors Cohort and Nurses' Health Study.	--
NATURAL HISTORY		
Cell-type distribution of lung cancer:	Reproducing distribution over squamous cell; adeno + large cell; and small cell carcinoma in the study cohort.	Reproducing distribution over squamous cell; adeno + large cell; and small cell carcinoma in SEER.
Stages of lung cancer:	Reproducing distribution over stage II or earlier and stage III or later in the study cohort, where available in control group.	Reproducing distribution over stage II or earlier and stage III or later in SEER.
Duration distribution of screen-detectable disease states:	Based on earlier model based estimates from screening studies including the Mayo Clinic Trial.	--
Transitions from each stage:	Based on stage distribution of lung cancer in unscreened study cohort after preclinical phase.	Based on clinical stage distribution of lung cancer in SEER.
Net survival from lung cancer:	Based on SEER disease-specific survival.	--
SCREENING		
Test sensitivity:	Based on earlier model based estimates from screening studies including the Mayo Clinic Trial.	--
Timing of screening:	As reported from the study.	As reported from surveys.
Consequence of screening:	Based on expert opinion and a range based on confidence limits for improvement of prognosis model parameters for screening trial data.	--

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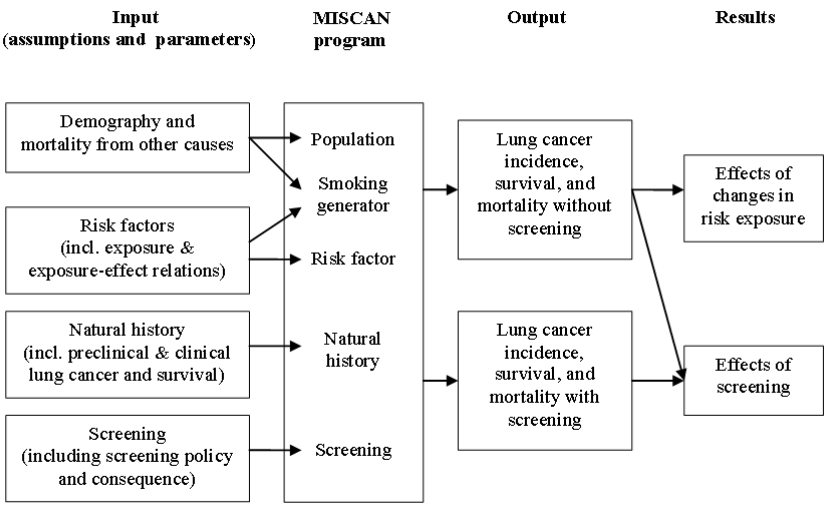
COMPONENT OVERVIEW

SUMMARY

An overview of the five major components in the MISCAN-lung model for lung cancer surveillance.

OVERVIEW

The MISCAN-lung model contains five primary components: population, risk factors, smoking generator, natural history, and screening.



Components overview

COMPONENT LISTING

The MISCAN-lung model consists of five major components.

1. **Population Component**: This component simulates a population of individual life histories, according to the demography and mortality from other causes assumptions and their parameters. Each individual in the population consists of a date of birth and an age of death.
2. **Risk Factors Component**: This component simulates how risk factors (such as smoking and diet) influence the hazard growth rate of lung cancer according to the exposure and exposure-effect relationships assumptions (see Assumption Overview) and their parameters (see Parameter Overview).
3. **Smoking Generator Component**: This component takes data from NCI's smoking generator and simulates the smoking history of an individual and deaths from other causes. In case this component is activated, it replaces the first risk factor in the *risk factors component* and the simulation of deaths from other causes in the *population component*.

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4. **Natural History Component**: Subsequently, the *natural history* part of MISCAN-lung simulates separate lung cancer histories (natural histories) for each individual life history. The initiation, promotion, malignant transformation, and progression of lung cancer are generated according to an individual's exposure to risk factors (smoking and diet). The development of lung cancer into different cell types and stages is governed by the natural history assumptions (see Assumption Overview) and their parameters (see Parameter Overview). The survival of a person, once a preclinical lesion has developed into clinical lung cancer, depends on the cancer cell type and stage of disease. The life history of each person is altered according to the natural history that is simulated for that person. If he or she dies from lung cancer before he or she dies from other causes, his/her death age is adjusted accordingly.
5. **Screening Component**: After simulating the natural history if screening were absent, the *screening component* makes detection of preclinical lung cancer possible. Timing of screenings can follow an invitational schedule or an opportunistic pattern. Screening in the model potentially affects early stages (I and II) of all preclinical lung cancer, resulting in either a cure or a new survival upon screen-detection. The effectiveness of screening depends on the screening assumptions (see Assumption Overview) and their parameters (see Parameter Overview).

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POPULATION COMPONENT

SUMMARY

This document gives a description of how the simulated population is modeled.

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OVERVIEW

The model simulates a dynamic population by generating births according to a distribution over calendar time, e.g. the relative sizes of birth year bins of persons in a specified study.
Stratification on the basis of specific subpopulation characteristics is possible.
The general population model includes mortality from other causes that can depend on exposure to risk factors.
However, in the Smoking Base Case, mortality from other causes is determined by the *smoking history generator* (see Smoking Generator Component).
Thus, a population consists of individuals whose life histories in the absence of lung cancer begin with a date of birth and end on a date of death from other causes.

QUANTITATIVE DESCRIPTION

The MISCAN-lung code is an individual-based microsimulator. Life histories are determined by random draws from probability distributions (Monte Carlo simulation) for allocation to categories (e.g. birth year cohort) or selecting time to event (e.g. death from other causes).

POPULATION DYNAMICS

The MISCAN-lung code models the population by simulating individuals from birth to death from disease or death from other causes. Distribution across birth year bins must be defined at input. Age distributions in specific calendar years can be computed at output.

RECURRENCE

During the life history of an individual person multiple clones of malignant cells may be created, which each will progress through various states of disease from preclinical to clinical lung cancer. (Also see Risk Factors Component and Natural History Component.)

DISEASE DISTRIBUTION

In the MISCAN-lung model the lung cancer stages I and II are combined into stage 2-, and the stages III and IV into 3+.
Three lung cancer cell types are distinguished, i.e. small cell carcinoma, squamous cell carcinoma, and combined adeno / large cell carcinoma.
Upon creation of a malignant nodule (clone of malignant cells) the decision about cell type is made according to clinically observed fractions. (Also see Natural History Component.)

RELEVANT ASSUMPTIONS

See sections

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- Demography;
- Preclinical lung cancer;
- Clinical lung cancer;
- Lung cancer survival;
- Mortality from causes other than lung cancer;

in Assumption Overview.

Relevant Parameters

See **Demography** and **Natural History** parameters in Parameter Overview.

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RISK FACTORS COMPONENT

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SUMMARY

This document describes how MISCAN-lung models carcinogenesis and the influence of risk factors on this process.

OVERVIEW

Multistage carcinogenesis

The multistage carcinogenesis model as developed by Moolgavkar et al.[1,2] consists of the following stages:

- Initiation of stem cells: One or more mutations result in an initiated cell that partially escapes growth control.
- Clonal expansion of initiated cells: The single initiated cell develops into a clone of initiated cells.
- Malignant transformation: Each of the initiated cells in an expanding clone can acquire further mutational changes leading to a malignant cell.
- Progression to diagnosis: Malignant cells develop into a symptomatic cancer.

An initiated cell multiplies at a fairly high rate, but there is an almost as high rate of cell death or differentiation. The latter implies, similarly to cell death, the end of the malignant potential of the cell. The model assumes that multiplication and death/differentiation are stochastic processes; therefore, the large majority of clones die out because there happened to be one more cell death/differentiation than reproduction of initiated cells. These clones contribute practically nothing to the cancer risk. A relatively small number of clones of initiated cells succeeds in growing to a substantial size, by which it is unlikely to die out. These clones follow a slow but sure path to containing a large number of initiated cells, making it more likely that one of the initiated cells undergoes malignant transformation.

Each cell in a clone of initiated cells has a hazard of malignant transformation. Because the clones increase in numbers of initiated cells, the hazard of malignant transformation in a clone increases over time. At a certain moment the number of cells is so large that the stochastic element doesn't play a significant role any more. A constant rate of generation of new initiated cells implies that the growth of an expanding clone is exponential. Because they are the clones that produce more initiated cells than cell deaths or differentiations, the clones that lead to cancer grow faster during the earlier stage of development. That implies that the time distribution from initiation to malignancy has a clear mode, which is generally estimated to be at a distance of several decades.

After malignant transformation, there is a stage of progression of the cancer until it is developed far enough to be diagnosed.

Contrary to the original Moolgavkar model, MISCAN-lung disregards the clones of initiated cells that die out early in their development. The shape of the distribution of

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the period of clonal expansion to malignant transformation determines that in the first several decades of their lives people rarely get cancer. There is a steep increase in risk of cancer by age that reflects mainly the steepness of dwelling time distribution of clonal expansion to malignant transformation. When most of the clones that were initiated very early in life have come through as cancer, the slope of increase in cancer risk levels off. Hence the slope of increase in cancer risk at higher ages reflects to large extent the increase in the rate of initiation.

Risk Factors

Risk factors can influence initiation, clonal expansion (promotion), malignant transformation, and progression.

If a risk factor influences the rate of initiation, it will take a very long time before there is a substantial influence on cancer incidence because the stage of clonal expansion must be passed through before becoming a cancer.

If e.g. the rate of clonal expansion is reduced by half, then the rate of malignant transformation starts decreasing immediately. The subsequent period of progression from malignant cell to diagnosed cancer makes the influence on cancer incidence somewhat less immediate.

A change in a risk factor that leads to e.g. a reduction by half of the rate of malignant transformation has a more immediate effect on malignant transformation, but in the end only postpones the appearance of cancer by one doubling time of a clone of initiated cells; if the doubling time of cancer incidence is less than the doubling time of a clone of initiated cells, the rate ratio for malignant transformation decreases over time since change of the risk factor.

It is generally assumed that the stage of progression from malignant transformation to clinical cancer is not influenced as strongly by risk factors as the earlier stages of carcinogenesis.

Implementation of the Risk Factors Model

Input parameters

1. Parameters for carcinogenesis in absence of risk factors

For each stratum the model specification consists of:

- The number of cells that start an initiated close. This is generally larger than 1 in order to adjust for the higher initial growth rate of surviving clones.
- Basic rate of initiation.
- Basic rate of proliferation of a clone of initiated cells, also called: promotion.
- Basic rate of malignant transformation.
- Basic growth rate of cancer, also called: progression.

2. Risk Factors

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MISCAN-lung can model up to 5 different explicit risk factors, each with up to 10 levels of exposure. For each stratum and risk factor the model specification consists of:

- The probability of starting at a risk level (thus, up to 10 probabilities of exposure intensity).
- The probability matrix of transition from the current level of exposure to the next risk level.
- For each current risk level:
  - The dwelling time distribution to first change of risk level.
  - The dwelling time distribution to second change of risk level.
  - The dwelling time distribution to third or later change of risk level.

Alternatively, the model for exposure to the first risk factor (= smoking) can be replaced by the smoking history generator (see Smoking Generator Component).

3. Dose effect relationships

For each risk factor and each level of exposure the model specification consists of the factor by which the rates of initiation, promotion, malignant transformation, and progression are adjusted at the time of exposure to the given level of the given risk factor.

Computation

The life history is split up into segments during which there is no change in the level of exposure to any of the risk factors. For each of these segments, the adjustment factor resulting from exposure to all of the risk factors is determined and applied to the rates of initiation, promotion, malignant transformation, and progression.
The rate of initiation of new clones is constant during each segment of constant risk factor exposure and is adjusted when exposure changes.
The current clone size, c is initiated with the specified number of cells that start an initiated clone.
The time to malignant transformation is determined iteratively as follows:
The proliferation rate of the clone of initiated cells, given current exposure to risk factors, is p; and the malignant transformation rate per initiated cell is m.
Let u be a draw from the standard uniform distribution.
Then it is determined if the following period of time is shorter than the length, l of the current segment of constant exposure to risk factors:

$$\{ln[c \times m - ln(1-u) \times ln(p)] - ln(c) - ln(m)\}/ln(p)$$

If so, then the time of malignant transformation is reached; if not, the clone size is updated to the value at the end of the current segment of constant exposure to risk factors: c becomes $c \times p^l$

The iterations are repeated for subsequent segments of constant exposure to risk factors until the moment of malignant transformation or the maximum life span is reached.

Progression from malignant transformation to clinical diagnosis and time from birth to death from causes other than lung cancer are determined similarly.

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REFERENCES:

[1] Moolgavkar, S.H., Knudson, A.G. "Mutation and cancer: A model for human carcinogenesis." in J Natl Cancer Inst 1981; 66: : 1037-1052

[2] Hazelton, W.D., Clements, M.S., Moolgavkar, S.H. "Multistage carcinogenesis and lung cancer mortality in three cohorts." in Cancer Epidemiol Biomarkers Prev. 2005; 14: 5: 1171-81

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SMOKING GENERATOR COMPONENT

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SUMMARY

This document describes how data from the NCI's Smoking History Generator Application is used within the MISCAN-lung model.

OVERVIEW

The Smoking History Generator Application has been developed by NCI staff for the CISNET program, based on NHIS data on the U.S. population.
The original MISCAN-lung model structure for determining exposure to the first risk factor (i.e. smoking) was replaced to accommodate the optional use of data from the Smoking History Generator. Those data are provided in tables, which can be read by the MISCAN-lung code to produce appropriate random smoking histories for the individual persons simulated.

The onset of smoking is determined by a table of probability to start smoking by single year of age, 5-year birth cohort, gender and race (i.e. whites or all races). Cessation of smoking is determined by a similar table.
The smoking intensity is modeled as cigarettes per day (cpd). First, placement in one of five smoking intensity categories is determined by a table with a probability distribution over 5 categories (from light to heavy smoker) by age of initiation. Subsequently, the number of cigarettes smoked per day is determined using a table of cpd by year of birth, age, race and gender, and smoking intensity category.

It is assumed that, once a smoker has been assigned to an intensity class, this level of exposure will remain constant unless the person quits smoking altogether.

For *never* and *current* smokers, the time of *death from causes other* than lung cancer is determined from a table of other cause death probabilities by race and gender, year of birth, age, and smoking status (never or current) and intensity (5 categories for current smokers).
For *former* smokers, the difference between the 'current' and 'never' probability for the person is multiplied by the following excess risk formula,

$$exp[(-0.1711+0.00102\times cpd+0.00171\times QuitAge)\times(YearsQuit)^{1.08}]$$

and added to the 'never' probability to obtain the 'former' probability.
A thus generated smoking history can be treated as usual input to the risk factors model (see Risk Factors Component) in order to continue simulation of the development of lung cancer.

ADDITIONAL REMARKS

For the Smoking Base Case, the functionality of the Smoking History Generator application has been extended in 2009 by NCI staff.

- Birth years 1890-1900 were added to the tables.

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- Table data were supplied for the counterfactual (No Tobacco Control) scenario, next to those for the actual (Tobacco Control) scenario.

The additional tables were used just like the original ones in MISCAN-lung.

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NATURAL HISTORY COMPONENT

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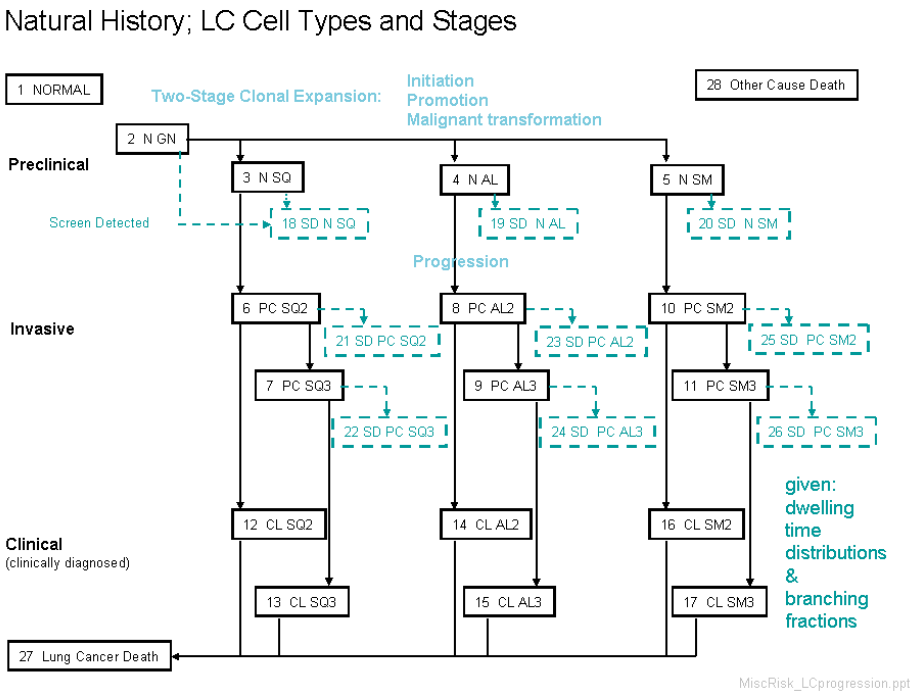
SUMMARY

This document gives a description of the model processes responsible for generating the natural history of disease.

OVERVIEW

The model simulates a network of disease states (Figure 4) categorized by the following dimensions: cell type (squamous cell, adeno/large cell, and small cell carcinoma); stage (stage I-II and stage III-IV); and clinical status (preclinical, clinically diagnosed, and screen-detected).

FIGURE 4:



Natural History

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Natural History Model

(Figure 4) After initiation of cells in normal state (1) and promotion and malignant transformation of generic nodules (2), nodular fractions of squamous cell carcinoma (SQ), adeno plus large cell carcinoma (AL) and small cell carcinoma (SM) appear in states (3), (4) and (5), respectively. This process is governed by the parameters of the multistage carcinogenesis model. Lung cancer cell type distribution corresponds with clinically observed fractions.

Further progression through preclinical states (6-11) occurs, where stage 2- (= I-II) and stage 3+ (= III-IV) cancers may develop. Progression continues to clinically detectable cancers in states (12-17), which may result in the person's death from lung cancer upon entering state (27).

Branching and dwelling time

Branching fractions and dwelling time distributions determine the time-course of the state of the progression model. Three types of dwelling time distributions are used to describe the duration of the stay in one compartment until transition to the next compartment. They are:

- Weibull distribution, characterized by a mean value and a shape parameter;
- Piecewise linear distribution, consisting of a set of (time point, probability of transition before this time point) data;
- Fixed duration, i.e. transition after a fixed period of time.

Death from other causes

The simulated person may die from causes other than lung cancer, i.e. entering state (28), if this event –at a projected time point which was determined during an earlier step in the model– occurs before progression through the natural history has finished.

Screening

Screening, if performed, may detect cancers in preclinical states (2-11), which means transfer to corresponding screen-detected states (18-26). No further transition is modeled.

Disease Stages

The disease stages 2- and 3+ are distinguished as described in the above section "Natural History Model". As is shown in Figure 4, a stage 2- tumor may become a stage 3+ tumor. At transition time it is decided whether the nodule continues in the next model state as a stage 2- or stage 3+ tumor. Such branching takes place according to a fixed fraction parameter (model input).
Time until transition from one state to the next one in the model is determined from random draws from given dwelling time distributions.

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Disease growth

Tumor size is NOT a quantity monitored in MISCAN-lung. Once malignant transformation has occurred, by which a generic nodule appears in state 2 (Figure 4), tumor progression continues by stochastic state transitions according to given dwelling time distributions and branching fractions.

It is assumed that the tumor is detected (clinical diagnosis) the moment the nodule, now identified as either squamous cell or small cell or adeno/large cell carcinoma, enters one of the clinical states (12 through 17 in Figure 4).

Disease evolution

See section **Disease growth** above.

Regression

So far, the possibility of tumor regression has NOT been modeled in MISCAN-lung. Only irreversible progression is modeled, which can be influenced by adapting the dwelling time distributions in the various states.

Relevant Assumptions

See **Assumption Listing** in Assumption Overview.

Relevant Parameters

See **Natural History** parameters in Parameter Overview.

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SCREENING COMPONENT

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SUMMARY

This document describes the processes in the model that are responsible for generating screening dissemination and detection of disease.

OVERVIEW

The screening component simulates the screening program for lung cancer and its effects.

DISEASE DETECTION MECHANISM

Preclinical lung cancer can pass through a number of disease states before clinical diagnosis. Each of these states has a dwelling time distribution. If a screening takes place during the phase of preclinical lung cancer, there is a probability of detection of the cancer by the screening test that depends on stage and cell type. This probability is called test sensitivity.

A screening examination may consist of more than one (up to three) screening-tests. In case of simple model assumptions, the probability of a positive test result is taken to be independent of the results of the same tests in previous screens, and also independent of the results of other tests applied in the same or in previous screenings.

Systematic errors from screening-tests can occur for any of the following reasons:

- Person: For example, it is possible that a person has always had a positive sputum test result in lung cancer screening.
- Lesion: For example, a lesion can be missed systematically because the screening-test is less sensitive for some lesions that for others.
- Test moment: For example, in lung cancer screening it is possible that a particular sputum cytology test yields a negative result because no material from any of the malignant lesions was present in the sputum at the moment of the test.

It should be noted that both dwelling time distributions and sensitivity are generally estimated from screening data. Therefore, the dwelling time distribution for lung cancer states concerns disease that is in principle screen-detectable and does not start at the time one single cell or an arbitrary low tumor size is present.

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Screening Dissemination

Each stratum (*) may have its own definition of exposure to screening, which can be used to specify a relation between e.g. lung cancer risk and uptake of screening.

A typical screening policy is defined by the ages at which persons will be invited for screening and the year from which this policy is implemented. At first invitation a simulated person attends with a given probability. The age at first invitation is not always the first invitation age of the program because the person may be older when the program starts. At the subsequent invitations for screening the probability of a person attending depends on attendance to the previous screening. In general we have observed that the percentage of people who accepted the previous invitation and is again attending a subsequent screening is around 60 higher than that of people who did not show up at the previous invitation.

Alternatively, timing of screenings can be defined as the age distribution of receiving the first screening; a probability to receive a second screening and the interval distribution to that second screening; and the interval distribution to subsequent screenings depending on the length of the previous interval.

(*) A stratum as a subset of the modeled population that can have a different birth table (to define cohorts), life table, exposure to risk factors, risk-effect relationships, and screening participation.

Type / Detection Interaction

Test sensitivity can depend on tumor cell type.

Stage / Detection Interaction

Test sensitivity can depend on disease stage.

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Length Bias

When sensitivity is constant during the preclinical cancer period, at first screening, screen-detected cancers will be found on average halfway their preclinical period. Therefore, the lead-time is on average half of their preclinical period. This implies that cancers with a long preclinical period tend to have a longer lead-time. Because of the longer duration of possible detection by first screenings, first-screening-detected cases tend to have longer dwelling times than the average cancer. When the dwelling time distribution is exponential, then the average lead-time of cases detected at first screening will be the same as the average dwelling time of the average cancer, despite the fact that among the screen-detected cases the average lead-time is only half of their dwelling time.
This phenomenon causes an extra long lead-time effect on survival from screen-detected cases.
At repeat screenings (unless after a very long interval) there will be relatively fewer cancers detected with long dwelling times but the average lead-time will be longer than half of their dwelling time.

Another possible length-time effect concerns a possible correlation between preclinical dwelling time and survival from clinical diagnosis. MISCAN-lung can explicitly model such an effect but our current models do not do this.

Detail

For each simulated initiation, an anatomical site may be generated, for instance central versus peripheral location in the lung.

Positive test results can change the course that the disease would take without screening. There are two ways of specifying the consequences of screen-detection: as modifications relative to the original course of the disease, or as a new course independent of the original course.

When defining consequences as modification relative to the original course of the disease, the model accounts for the effects of lead-time due to early detection of cancer and for diagnoses of cancer that would not have occurred without screening (often called overdiagnosis or extra incidence). The moment of death from disease can be delayed, and the probability distribution of the length of the delay should be specified. Important special cases of delay are complete cure (infinite delay) and no change (zero delay).

Defining consequences as an independent further course of the disease consists of specifying a new survival distribution from time of screen-detection.

Another possible consequence of screen-detection is a probability of (surgery) mortality at the time of diagnosis and treatment.

Relevant Assumptions

See section **Screening** under **Assumption Listing** in Assumption Overview.

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RELEVANT PARAMETERS

See **Screening Test** parameters in Parameter Overview.

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OUTPUT OVERVIEW

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SUMMARY

This section describes the outputs generated by the MISCAN-lung model for lung cancer.

OVERVIEW

The output of the MISCAN-lung program consists of the simulated events (e.g., the number of cases diagnosed, number of cases missed by screening, and mortality from the disease and from other causes) and person time (e.g., the life years lost due to the disease and life years with the disease). Most output is given by calendar year and disease state. The output is stored in data files to enable further calculations with the simulated results.

The MISCAN-lung model simulates among others the outputs for the Smoking Generator and Screening Base Cases. The output on screening effects are limited to the case in which the Mayo Lung Project (MLP) module is activated.

OUTPUT LISTING

The MISCAN-lung model produces output data in files, which can be processed further to yield the final outputs of the model. (E.g. using Microsoft Excel or a statistical package like SAS or SPSS.)

The main outputs of MISCAN-lung are:

1. Lung cancer (LC) incidence;
2. Mortality (Lung Cancer and Other Causes);
3. Survival/life years in disease states;

by time, stage, cell type, and demographics.

Because our model is a microsimulation model, we can also produce the following outputs:

4. Age groups required in the output;
5. Lead time;
6. Overdiagnosis;
7. Individual life history;
8. Simulated screening tests and test results.

The outputs in the base case analyses include:
Smoking Base Case

1. Prevalence of lung cancer in 1986 by age groups in the range 30-84 y.
2. Age-adjusted lung cancer incidence rate by calendar year (1975-2000).
3. Age-adjusted lung cancer mortality rate by calendar year (1975-2000) and by smoking status.

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4. Smoking prevalence by calendar year (1975-2000).
5. Smoking attributable lung cancer mortality.

Screening Base Case

6. Number of invitations for screen-tests and opportunistic screen-tests for each year.
7. Number of positive and negative test results per preclinical state and per year.
8. Total number of life years, life years lost due to cancer, number of specific deaths and non specific deaths.
9. Number of screenings that prevented cancer by year of screening.
10. Number of screenings that detected cancer early by year of screening.
11. Number of life years gained due to screening by year of screening.

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RESULTS OVERVIEW

SUMMARY

Describes the general results for lung cancer obtained from MISCAN and MISCAN-lung model output. (Before 2008.)

OVERVIEW

This document describes results of MISCAN & MISCAN-lung on calibration and validation, and results concerning Base Case analyses. (Before 2008.)

(The MISCAN model does NOT include the Risk Factors Component of MISCAN-lung.)

RESULTS LIST

1. Calibration

For the Base Case analyses we calibrated the MISCAN model to common inputs on:

- Cancer incidence per 100,000 (SEER 1975-1979) by age group;
- Cell type prevalence (SEER) by age group;
- Stage distribution (SEER) by age group;
- Relative survival by stage, cell type, and age group;

Calibration was done on cancer incidence, prevalence and stage and cell type distribution of cancers. MISCAN reproduces the base case inputs well. Only lung cancer incidence, prevalence, and mortality in the older age groups (> 70 years) differ significantly.

2. Model Validation by Simulation of Mayo Lung Project - flat screen X-ray screening

We have tried to estimate a model of screening for lung cancer from the Mayo Clinic randomized trial on lung cancer screening that started around 1975. The Mayo Lung Project[1,2,3,4,5,6] was a randomized controlled trial designed to detect lung cancer at a curable stage. Screening tests included chest X-rays, 3-day pooled sputum cytology studies, and lung-health questionnaires. These tests were given to a study population of 9,211 male outpatients with a negative first screening for lung cancer and high risk for the disease. Both trial arms (intervention and control) received a first screening and the intervention arm continued to receive screenings every four months for six years. Lung cancer diagnoses were followed up to 30 June 1983 and mortality was followed up to 31 December 1996. The trial was successful in detection of early lung cancer but not in prevention of lung cancer mortality.

Four models (Models A, B, C, D) were developed before we had access to the data set of the Mayo Clinic trial. Model A assumes that screening test sensitivity is 100% and the sojourn time has an exponential distribution from the time of becoming screen-detectable to the time of clinical diagnosis without screening. Model B adjusted model A by assuming three times longer sojourn times and fitted the test sensitivity to the detection rate at first screening again. Model C adjusted model B by assuming the possibility of a systematic negative screening result. Finally, we constructed Model D,

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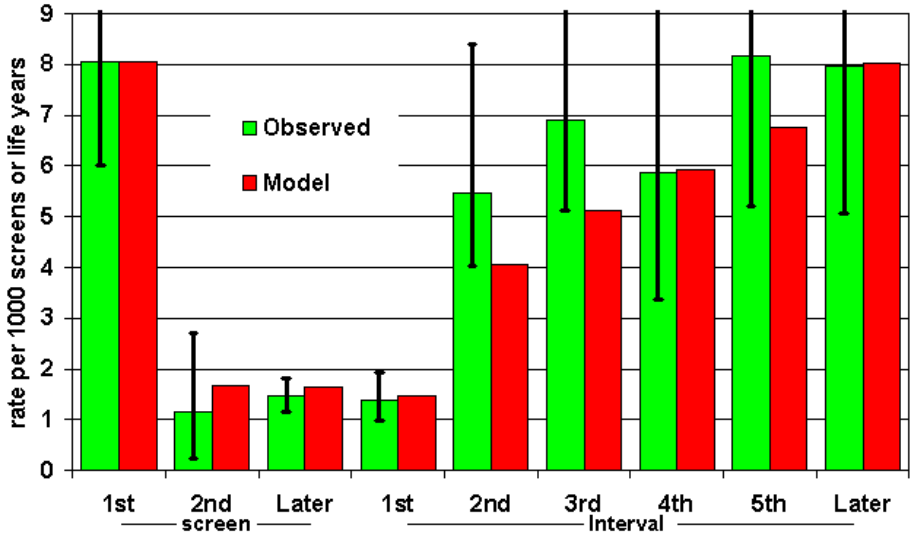
which is in agreement with observed interval cancer incidence.

We then applied an automatic fit procedure based on the Nelder and Mead method (or amoeba) by simultaneously adjusting model parameters until best agreement with observed data was reached[7]. We fitted the modeled onset of preclinical screen-detectable disease so that incidence in a situation without screening agrees with incidence observed in SEER. Subsequently, we fitted the screen-detectable sojourn times, test sensitivity and a relative lung cancer risk of the trial to the results from the Mayo Clinic trial. Starting from the best fit, we further investigated to what extent indolent cancers give a better explanation of observed data. In addition, we tested the design of the study to test the randomization of the study.

The best model fit so far has good agreement with observed data. Figure 8 compares screen-detected rates and interval cancer incidence of the intervention group and Figure 9 of the control group. Although the interval cancer incidence in the intervention group still looks low in comparison with observed data, this does not reach a threshold of statistical significance of 5% and therefore can be regarded as due to random noise. We found that even our best model fit predicts lower rates of interval cancer incidence of adeno carcinoma/large cell lung cancer. That appears to be consistent with an assumption of overdiagnosis of adeno carcinoma due to screening. The simulated results show that there are systematic missed lesions in either preclinical stage 2- and preclinical stage 3+. Our model also predicts that indolent cancers are not a serious issue in the Mayo Clinic trial. Finally, our model predicts higher cancer incidence in the study group compared to the control group, which provides evidence against the randomization of the trial.

Figure 8. Screen-detection rates per 1000 screens and interval cancer incidence per 1000 life years of the intervention group



cancers MLP intervention

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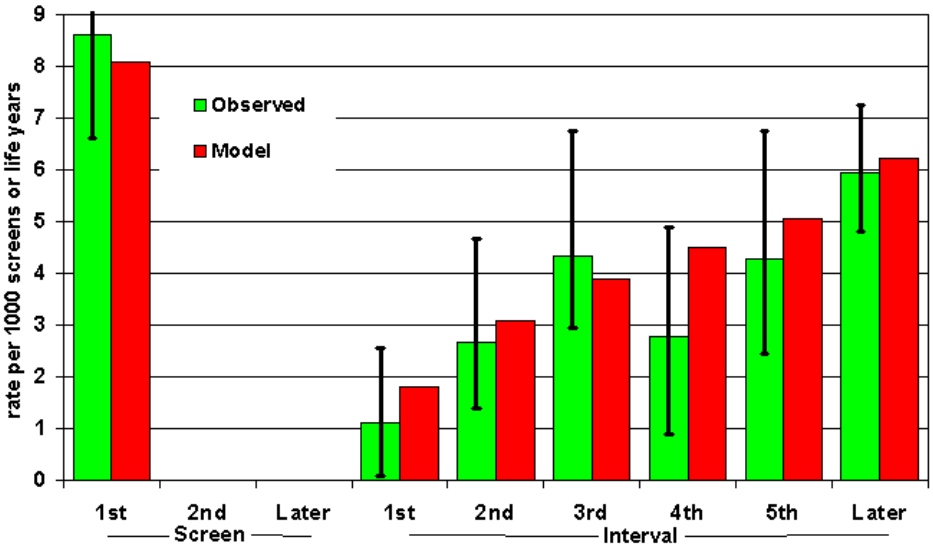
Figure 9. Screen-detection rates per 1000 screens and interval cancer incidence per 1000 life years of the control group



cancers MLP control

The model results presented above are produced by the MISCAN model as *before* inclusion of the risk factors model based on the Moolgavkar model on multistage carcinogenesis[8,9,10,11,12]. We have designed a model for the Mayo Clinic trial that includes the risk factors model where the risk of lung cancer is predicted based on smoking history as reported by trial participants instead of based on a fit of the age effect on SEER data and an elevated risk due to high smoking prevalence in the trial population. This MISCAN-lung model is still too tentative to present its results here but we have concluded that the model predicts background incidence very well. Because of similarity of the screen-detectable phase of the disease in both models, we expect that this model will closely reproduce the results as presented above but it will provide additional opportunity to study screening results by smoking history.

3. Model Validation by Simulation of CT Screening

We simulated the Early Lung Cancer Action Project (ELCAP)[13,14,15,16,17,18] for validation concerning low dose CT screening by comparing observed data from ELCAP to the results of the MISCAN simulation. ELCAP is a non-comparative observational study that is designed to evaluate baseline and annual repeat screening by low dose CT in 1,000 individuals with higher risk of lung cancer. The baseline screening found that among the whole study population, a positive result (defined as 1-6 non-calcified nodules) was found three times more commonly on low-dose CT than on CRX (23% [95% CI 21-26] vs 7% [5-9]). In the whole study population, malignant tumors were found four times more frequently on low-dose CT than on CRX; and stage I tumors were detected six times more frequently on low-dose CT than on CRX (2.3% [1.5-3.3] vs 0.4% [0.1-0.9])[13,14,17]. The initial findings on repeat screening found that

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annual repetition of CT screening is sufficient to minimize interval cancers[15,17].

We have begun to adapt the x-ray screening model for simulating the ELCAP. The distinct characteristic of the ELCAP is that there is detailed information on tumor size; thus, it is possible to study the relationship between tumor size and curability of lung cancers. Currently, ELCAP is limited because there are not enough cancer cases yet. Our simulation model is not limited by number of cancer cases and therefore is able to achieve the study goal even if there are not yet real data available. We take this into account in our development of the model by assuming more disease states, which influence the size of the tumor. Since ELCAP is designed to compare the screening by low dose CT and chest radiographs, we introduced two screening policies to represent these two kinds of tests.

4. Simulations of CT Screening in the Mayo CT Project

...UNDER CONSTRUCTION...

5. Smoking Base Case: Effects of Anti-Smoking Campaigns on lung cancer mortality

...UNDER CONSTRUCTION...

Also refer to the specific implementations:

- Smoking Base Case14Mar06
- Smoking Base Case16Feb09

which describe the assumptions used in two versions of our model for the Smoking Base Case.

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SMOKING BASE CASE14MAR06

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Summary

This document describes the MISCAN-lung model assumptions for the Smoking Base Case, from which we submitted the results to the CISNET program on 14 March 2006.

The Smoking Base Case involved four models: white males and white females, and including and excluding smoking effects on lung cancer risk.

Demography

The birth table used describes the probability distribution of being born before the start of the calendar year:

Birth Table	
Calendar Year	**Cumulative Probability**
1901	0
1906	0.0514
1911	0.1081
1916	0.1678
1921	0.23
1926	0.2942
1931	0.3551
1936	0.4108
1941	0.468
1946	0.5367
1951	0.6214
1956	0.7163
1961	0.8173
1966	0.9157
1971	1

Mortality from causes other than lung cancer is governed by the Smoking History Generator provided for the Smoking Base Case by NCI staff (see Smoking Generator Component).

Disease States

The disease model includes the following disease states:

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Disease States	
	Normal, No Known Lung Cancer
Preclinical	Squamous Cell, Stage II-
	Squamous Cell, Stage III+
	Adeno/Large Cell, Stage II-
	Adeno/Large Cell, Stage III+
	Small Cell, Stage II-
	Small Cell, Stage III+
Clinical	Squamous Cell, Stage II-
	Squamous Cell, Stage III+
	Adeno/Large Cell, Stage II-
	Adeno/Large Cell, Stage III+
	Small Cell, Stage II-
	Small Cell, Stage III+
Screen-Detected	Squamous Cell, Stage II-
	Squamous Cell, Stage III+
	Adeno/Large Cell, Stage II-
	Adeno/Large Cell, Stage III+
	Small Cell, Stage II-
	Small Cell, Stage III+
End States	Death from Lung Cancer
	Death from Other Causes

Risk Factors Model

The model includes exposure to one risk factor: cigarette smoking. The exposure to this risk factor is governed by the Smoking History Generator, provided for the Smoking Base Case by NCI staff (see Smoking Generator Component).

Based on the current smoking status over the course of the life history, the model assumes the following parameters for the development of lung cancer:

When not smoking: Clones of initiated cells start at a size of 200 cells; the rate of initiation is 0.007015 per year; the exponential growth rate of the clones of initiated cells is 0.0751; and the rate of malignant transformation to lung cancer is $1.403 \cdot 10^{-7}$. These base rates are derived from CPS I[1].

When smoking, the when-not-smoking rates are multiplied by the following factors, depending on the dose expressed in cigarettes per day:

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Rate ratios by smoking dose relative to when not smoking			
Cigarettes per Day	**Initiation**	**Promotion**	**Malignant Transformation**
	4.532	1.323	4.532
	4.532	1.541	4.532
	4.532	1.688	4.532
	4.532	1.806	4.532
	4.532	1.907	4.532
	4.532	1.997	4.532
	4.532	2.078	4.532
	4.532	2.153	4.532
	4.532	2.223	4.532

The assumptions for the risk factor model are based on[1].

Preclinical lung cancer

Of the malignant transformations that are generated, 35.7% become squamous cell carcinoma, 44.0% adeno or large cell carcinoma, and 20.3% small cell carcinoma.

Dwelling times [in years] and stage distribution				
Cell type	**Constant lag time from malignant transformation to screen-detectable preclinical cancer**	**Mean dwelling time in preclinical stage I-II**	**Mean dwelling time in preclinical stage III-IV**	**Percentage clinical diagnosis in stage I-II**
Squamous	7.2 years	1.36	2.82	29.2%
Adeno/Large	8.2 years	1.36	2.82	30.0%
Small	5.9 years	0.39	1.11	9.4%

The assumptions on dwelling times for preclinical disease states are based on our model estimates of the Mayo Lung Project[2].

Survival from lung cancer

Survival from lung cancer is modeled as a probability of long term cause specific survival, and for the remaining cancers, a Weibull distribution for the time from clinical diagnosis to death from lung cancer. This cause specific cancer survival is superseded if death from causes other than lung cancer is earlier than death from lung cancer.

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Survival from lung cancer				
			Weibull distribution for time from clinical diagnosis to lung cancer death	
Cell type	**Stage at diagnosis**	**Long term survival**	**Mean**	**Shape**
Squamous	I-II	0.180	2.419	0.573
Squamous	III-IV	0.060	0.752	0.641
Adeno/ Large	I-II	0.290	4.783	0.676
Adeno/ Large	III-IV	0.050	0.674	0.607
Small	I-II	0.080	1.049	0.727
Small	III-IV	0.010	0.507	0.738

Screening

The four models for the Smoking Base Case did NOT include any screening.

Model variants

The models for white males and white females are only different with respect to the exposure to cigarette smoking as determined by the Smoking History Generator (see Smoking Generator Component).

The models for no smoking effect are only different from the specification above with respect to the table "Rate ratios by smoking dose relative to when not smoking" where the rate ratios are all 1.

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SMOKING BASE CASE16FEB09

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Summary

This document describes the MISCAN-lung model assumptions for the Smoking Base Case, from which we submitted the results to the CISNET program on 16 Feb 2009.

The Smoking Base Case involves four populations: white males, white females, all races males and all races females and considers the U.S. population aged 30-84 y in the calendar years 1975-2000. Three tobacco control scenarios are evaluated, i.e. actual tobacco control (TC), no tobacco control (NTC counterfactual) and complete tobacco control (CTC counterfactual, assuming everybody stopped smoking in 1965).

Demography

Birth tables used describe the probability distribution of being born before the start of a specific calendar year.

The original range of birth years comprised 1900-1970 in five-year bins. As this leads to an incomplete age range (30-84) in the calendar years 1975-1984, the range of birth years was later extended to include 1890-1900 (for all races only).

The birth tables are based on U.S. population data[1]. For the extended birth year range, small adjustments were made by trial and error to improve agreement between the age distributions as calculated by MISCAN-lung for the calendar years 1975, 1986 and 2000 and the age distributions observed in the U.S. all races male and female populations in those years[2].

Birth Table					
Calendar Year	Cumulative Probability				
	Original		Extended		
	Whites	All races	All races	male	female
1891	0	0	0	0	0
1896	0	0	0.0548	0.0449	0.0465
1901	0	0	0.1095	0.0969	0.0957
1906	0.0619	0.0615	0.1643	0.1517	0.1503
1911	0.1241	0.1233	0.2193	0.2122	0.2063
1916	0.1906	0.1887	0.2776	0.2704	0.2650
1921	0.2578	0.2545	0.3362	0.3290	0.3224
1926	0.3253	0.3212	0.3956	0.3866	0.3816
1931	0.3872	0.3824	0.4501	0.4400	0.4360
1936	0.4419	0.4368	0.4985	0.4884	0.4849
1941	0.4977	0.4924	0.5480	0.5379	0.5358
1946	0.5645	0.5585	0.6069	0.5979	0.5968
1951	0.6476	0.6406	0.6800	0.6710	0.6698
1956	0.7373	0.7305	0.7600	0.7510	0.7505
1961	0.8324	0.8267	0.8457	0.8367	0.8377
1966	0.9212	0.9187	0.9276	0.9218	0.9227
1971	1	1	1	1	1

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Mortality from causes other than lung cancer is governed by the data tables of the Smoking History Generator Application (see Smoking Generator Component) provided for the Smoking Base Case by NCI staff.

Estimation of U.S. population size for the counterfactual scenarios of No Tobacco Control and Complete Tobacco Control.

For persons of a certain age, a, in a given year, yr, the expected number of lung cancer deaths, $D(a, yr)$, can be calculated from the model results (number of simulated lung cancer deaths, $Ds(a, yr)$; size of simulated population, $Ns(a, yr)$ and the actual U.S. population size, $N(a, yr)$:

$$D(a, yr) = \frac{Ds(a, yr)}{Ns(a, yr)} \times N(a, yr)$$

The latter quantity is known from observations for the actual tobacco control scenario in the U.S. but not for the two counterfactual scenarios as the latter never happened in reality.
Therefore, the population size in the case of for instance complete tobacco control, $N_{cc}(a, yr)$, is estimated as follows:

$$N_{cc}(a, yr) = \frac{Ns_{cc}(a, yr)}{Ns(a, yr)} \times N(a, yr)$$

where $Ns_{cc}(a, yr)$ is the population size resulting from the simulation of the complete tobacco control scenario.
Under this scenario, the estimated number of lung cancer deaths, $D_{cc}(a, yr)$, becomes:

$$D_{cc}(a, yr) = \frac{Ds_{cc}(a, yr)}{Ns_{cc}(a, yr)} \times N_{cc}(a, yr) = \frac{Ds_{cc}(a, yr)}{Ns(a, yr)} \times N(a, yr)$$

where $Ds_{cc}(a, yr)$ is the number of simulated lung cancer deaths under the complete tobacco control scenario.
Similar reasoning holds for the no tobacco control scenario.

Disease States
The disease model includes the following disease states:

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Disease States	
Normal, No Known Lung Cancer	
Preclinical	Squamous Cell, Stage II-
Squamous Cell, Stage III+	
Adeno/Large Cell, Stage II-	
Adeno/Large Cell, Stage III+	
Small Cell, Stage II-	
Small Cell, Stage III+	
Clinical	Squamous Cell, Stage II-
Squamous Cell, Stage III+	
Adeno/Large Cell, Stage II-	
Adeno/Large Cell, Stage III+	
Small Cell, Stage II-	
Small Cell, Stage III+	
Screen-Detected	Squamous Cell, Stage II-
Squamous Cell, Stage III+	
Adeno/Large Cell, Stage II-	
Adeno/Large Cell, Stage III+	
Small Cell, Stage II-	
Small Cell, Stage III+	
End States	Death from Lung Cancer
Death from Other Causes	

Risk Factors Model

The model includes exposure to one risk factor: cigarette smoking. The exposure to this risk factor is governed by the data tables of the Smoking History Generator Application, provided for the Smoking Base Case by NCI staff (see Smoking Generator Component). MISCAN-lung reads those tables to produce appropriate random individual smoking histories for the simulated persons.

Based on the current smoking status over the course of the life history, the model assumes the following parameters for the development of lung cancer:

When NOT smoking: Clones of initiated cells start at a size of 80 or 30 cells for males or females, respectively; the rate of initiation is 0.024 or 0.036 per year; the exponential growth rate of the clones of initiated cells is 0.0973; and the rate of malignant transformation to lung cancer is $7.58 \cdot 10^{-8}$. These base rates are derived from HPFS or NHS for males or females, respectively[3].

When smoking, the when-not-smoking rates are multiplied by the following factors, depending on the dose expressed in cigarettes per day:

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Rate ratios by smoking dose relative to when not smoking						
Cigarettes per Day	Males			Females		
	Initiation	Promotion	Malignant Transformation	Initiation	Promotion	Malignant Transformation
	1.0	1.1810	1.7804	1.0	1.2322	1.3026
	1.0	1.3208	2.2976	1.0	1.4116	1.5031
	1.0	1.4186	2.6437	1.0	1.5371	1.6373
	1.0	1.4987	2.9206	1.0	1.6400	1.7446
	1.0	1.5685	3.1575	1.0	1.7295	1.8365
	1.0	1.6311	3.3675	1.0	1.8099	1.9179
	1.0	1.6885	3.5578	1.0	1.8835	1.9917
	1.0	1.7418	3.7329	1.0	1.9519	2.0596
	1.0	1.8157	3.9735	1.0	2.0467	2.1528

The assumptions for the risk factors model are based on[4] and the newer data from[3].

Preclinical lung cancer

Of the malignant transformations that are generated, 35.7% become squamous cell carcinoma, 44.0% adeno or large cell carcinoma, and 20.3% small cell carcinoma.

Dwelling times [in years] and stage distribution				
Cell type	Constant lag time from malignant transformation to screen-detectable preclinical cancer	Mean dwelling time in preclinical stage I-II	Mean dwelling time in preclinical stage III-IV	Percentage clinical diagnosis in stage I-II
Squamous	0.01	1.36	2.82	29.2%
Adeno/Large	0.01	1.36	2.82	30.0%
Small	0.01	0.39	1.11	9.4%

The assumptions on dwelling times for preclinical disease states are based on our model estimates of the Mayo Lung Project[5].

Survival from lung cancer

Survival from lung cancer is modeled as a probability of long term cause specific survival, and for the remaining cancers, a Weibull distribution for the time from clinical diagnosis to death from lung cancer. This cause specific cancer survival is superseded if death from causes other than lung cancer is earlier than death from lung cancer.

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Survival from lung cancer				
Weibull distribution for time from clinical diagnosis to lung cancer death				
Cell type	**Stage at diagnosis**	**Long term survival (fraction)**	**Mean (y)**	**Shape**
Squamous	I-II	0.180	2.419	0.573
Squamous	III-IV	0.060	0.752	0.641
Adeno/Large	I-II	0.290	4.783	0.676
Adeno/Large	III-IV	0.050	0.674	0.607
Small	I-II	0.080	1.049	0.727
Small	III-IV	0.010	0.507	0.738

Screening

The MISCAN-lung models for the Smoking Base Case do NOT include any screening.

Model variants

The models for the various population categories are only different with respect to the exposure to cigarette smoking as determined from the data tables of the Smoking History Generator Application (see Smoking Generator Component).The data tables provided cover the Tobacco Control and No Tobacco Control scenarios. The Smoking History Generator Application includes an option to calculate smoking histories in case of Complete Tobacco Control, when nobody smokes after the start of a given year (e.g. 1965).

As MISCAN-lung computes its own sets of smoking histories, for the scenario of Complete Tobacco Control we amended the data tables ourselves: the probabilities to start smoking in or after 1965 were set to zero; the probabilities to stop smoking in or after 1965 were set to one; the corresponding smoking intensities were set to zero cpd; and the probabilities of death from other causes in that time period were set equal to those for never smokers.

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