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CISNET lung models: Comparison of model assumptions and model structures

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Abstract

Sophisticated modeling techniques can be powerful tools to help us understand the effects of cancer control interventions on population trends in cancer incidence and mortality. Readers of journal articles are however rarely supplied with modeling details.

Six modeling groups collaborated as part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) to investigate the contribution of US tobacco control efforts towards reducing lung cancer deaths over the period 1975 to 2000.

The models included in this monograph were developed independently and use distinct, complementary approaches towards modeling the natural history of lung cancer. The models used the same data for inputs and agreed on the design of the analysis and the outcome measures. This article highlights aspects of the models that are most relevant to similarities of or differences between the results. Structured comparisons can increase the transparency of these complex models.

Keywords

Lung cancer; population trends; tobacco control; modeling

1. Introduction

Sophisticated modeling techniques can be powerful tools to help us understand the effects of cancer control interventions on population trends in cancer incidence and mortality. When modeling studies arrive at discordant conclusions, however, gains in understanding can be compromised. Readers of journal articles are often supplied with few modeling details with which to parse out the root causes of differences in results.

The NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) was created to promote collaboration between independent modeling groups investigating similar questions. Six groups participated in the Smoking Base Case to investigate the contribution of US tobacco control efforts towards reducing lung cancer deaths over the period 1975 to

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2000. The results suggest that between a quarter and a third of all avoidable deaths from lung cancer were actually avoided as a result of the tobacco control efforts beginning in the mid-1950s.

The models included in this monograph were developed independently and use distinct, complementary approaches towards modeling the natural history of lung cancer. By using the same sources of data for inputs and agreeing on design of the analysis and uniform outcome measures, the modeling groups sought to collaboratively identify model features that contributed to variation in model results. Detailed comparisons can increase the transparency of these complex models.

This article highlights aspects of the models that are most relevant to similarities of or differences between the results of the Smoking Base Case analyses. Additional details for each model are available in other articles in this monograph^{1–6} and on the individual model profiles (www.cisnet.cancer.gov/profiles). Results of the main endpoint (changes in mortality trends and numbers of lung cancer deaths) are provided in Boer, et al., in this monograph.⁷

2. Methods

2.1 Rules for the Smoking Base Case

Each group in the CISNET lung consortium developed its model independently, according to its own primary purpose and using its own philosophy and techniques. For this article, the models developed by the six groups will be abbreviated by initials as follows:

- **E:** Erasmus MC;
- **F:** Fred Hutchinson Cancer Research Center (FHCRC);
- **M:** Massachusetts General Hospital-Harvard Medical School (MGH-HMS);
- **P:** Pacific Institute for Research and Evaluation (PIRE);
- **R:** Rice-M.D. Anderson;
- **Y:** Yale University.

The groups differed in their approaches to modeling lung cancer incidence, disease progression, symptomatic and/or screen detection, and lung cancer survival or mortality. They used different smoking cohort, cancer registry, and case-control datasets to estimate their model parameters. The central component of each model is a dose-response module that provides a quantitative description of the age-specific risks of lung cancer among never-smokers, continuing smokers and ex-smokers by smoking history and intensity. See Table I for an overview of the six models.

Common inputs were developed and used in the six CISNET lung models: competing mortality rates and smoking histories from three varieties of a common ‘smoking history generator’ (corresponding to the actual, worst case, and best case scenarios) are described in detail elsewhere in this monograph.^{8–10} The histories include detailed information on smoking behaviors, including smoking intensity and duration, and years since quitting for ex-smokers. As shown in Table I, some models simulate smoking in broad categories, while others simulate the smoking histories of every individual (possibly weighted) in the population. In addition to the smoking histories, shared data sources from U.S. vital statistics and a lung cancer screening trial were provided as standard inputs, but could be used in different ways by the different models.

As described by Feuer, et al. in this monograph,¹¹ all six models were used to predict US lung cancer mortality rates between 1975 and 2000 for ages 30 to 84 under three scenarios. Actual tobacco control (corresponding to observed smoking trends) was compared to two counterfactuals: the absence of tobacco control since the early 1950s based on a continuation of the smoking patterns that were present prior to the Surgeon General's Report of 1964, (worst case scenario) and complete cessation of all smoking in 1965 (best case scenario).

Standardized templates were developed, for both intermediate and main outcome metrics. Intermediate endpoints were predicted age-specific lung cancer mortality rates for the three population-level scenarios (observed, worst, and best case) and for seven hypothetical smoking histories among men born in the period 1921 to 1925. The hypothetical histories varied by ages at starting and stopping smoking and daily dose, from never having smoked (History VII) to continued smoking of 20 cigarettes per day (Histories II and IV). The main endpoints were 1) the fraction of lung cancer deaths that were avoided as a direct result of tobacco control activities; and 2) the fraction of total potential avoidable deaths that was actually realized by tobacco control efforts. Some models also estimated the numbers of lung cancer deaths that would have occurred under the two counterfactual cases as secondary endpoints. Rates by year are provided in Boer, et al., in this monograph and numbers of deaths are provided in a separate publication.

2.2 Overview of Model Similarities

All six groups have models able to investigate the question: "How does a given smoking history translate into lung cancer outcomes?" All the models can simulate a population and/or a specific cohort and generate predictions consistent with observed results, through some combination of input parameters and calibration. All models have the ability to vary inputs (smoking histories, other cause mortality risks) to examine the effect of policy options on population trends in lung cancer mortality.

The models are flexible enough to incorporate new data while retaining the ability to generate results consistent with older data. The models that focus on screening can extrapolate findings from past screening studies to predict results in different populations or as a result of different screening programs; these extrapolations are possible because the models simulate unobservable portions of natural history and do not require estimates of screening biases (lead-time, length-time, overdiagnosis) as inputs.^{12, 13}

2.3 Overview of Model Differences

Reflecting their original purposes, the models inherently focus on different aspects of the cancer control spectrum (Table I). The FHCRC CISNET-Model (F) was originally developed to investigate the biological relationship between smoking and lung cancer using the two-stage clonal expansion (TSCE) model as the central dose-response model, which estimates the effects of tobacco smoke on pre-malignant cell initiation and promotion, and malignant conversion. The Yale model (Y) was developed to understand the age-period-cohort structure of lung cancer incidence and mortality by separating the effects of aging (age), calendar year (period), and birth-year (cohort). The MGH-HMS Lung Cancer Policy Model (M) was originally developed to evaluate screening; it includes upstream events and a natural history model but emphasizes downstream events (i.e., mortality reductions from screening and early treatment). In Model (M), lung cancer mortality can vary with smoking history, once lung cancer has developed. The Erasmus MC MISCAN model (E) incorporates both a natural history model intended to evaluate screening and early treatment, as well as the TSCE model of cancer cell initiation and promotion fit to incidence, not mortality. The Rice/M.D. Anderson Lung Cancer Model (R) and the PIRE Smoking Base Case Model (P) also employ the TSCE model but differ from Models (F, Y) and (E) in other ways. Model

(R) integrates additional case-control data and Model (P) uses the TSCE model fit to mortality in a different cohort. Like Model (Y), Model (P) uses an aggregated group-level approach to evaluate lung cancer mortality trends.

The models complement each other by synthesizing available evidence in different ways. For example, some models use incidence or survival from SEER as calibration targets while others employ the same metrics as inputs. Several models use the same central TSCE stochastic model for relating smoking history to lung cancer development, but have different parameter estimates because the TSCE model can be calibrated to different cohorts and end points. The degree of detail with respect to specifying lung cancer types, stages, and sizes varies across the models, as does the explicit simulation of individual treatment modalities.

2.4 Details

2.4.1 Model Purposes and Structures—Four models (F, P, R, and Y) were originally developed to serve as effective tools for evaluating US population lung cancer trends. All four models use the biologically-based two-stage clonal expansion (TSCE) model, based on the paradigm of initiation, promotion and malignant conversion in carcinogenesis, originally developed to describe cancer incidence in human populations.^{14, 15} The TSCE has since been used for analyses of epidemiologic^{16–25} and toxicologic data^{26–29} and for risk assessment.^{29, 30}

Two models (F, R) relate individual smoking histories to the age-specific risk of lung cancer mortality. The FHCRC model (F) embedded the TSCE model in an age-period-cohort (APC) model and estimated period and cohort effects by calibration against lung cancer mortality in the US population over the period 1975–2000 (see Hazelton W, et al., in this monograph¹). The Rice-M.D. Anderson model (R) incorporated a second source of data for estimating the TSCE model parameters and did not use an APC approach to estimating mortality rates.

Two models (P, Y) are macro models that focus on evaluation of population trends by aggregating predictions over age groups for each year and gender, an approach that is distinct from the microsimulation models that simulate the experience of individuals that are then combined to represent a simulated population. The PIRE SBC model (P) applies the standardized smoking data on smoking prevalence, duration and intensity by age, year and gender to the TSCE model. The predictions are aggregated and compared to levels and trends in historical lung cancer deaths by gender over the years 1975 through 2000. The Yale Lung Cancer Model (Y) provides a flexible framework that can be used with alternative carcinogenesis models for the effect of cigarette smoking. The implementation Holford, et al. in this monograph⁶ makes use of a specified function for the TSCE model that is derived using summary exposure information for subgroups of the population; although not described in this monograph, the Yale model can also be used to calibrate rates derived from a microsimulation model to population rates. Calibration can be used to introduce temporal factors that correct for temporal effects that are not identified either by the carcinogenesis model or by the smoking history for the population.

Two groups (E, M) originally developed their models to evaluate screening, but these models can also be used to evaluate prevention or treatment interventions and ensuing population trends. The Erasmus MC MISCAN-lung Model (E) is an extension of the MISCAN simulation package for analysis of data from screening projects and for predicting effects of alternative screening policies. The MGH-HMS Lung Cancer Policy Model (M) is a microsimulation model of lung cancer development, growth, progression, detection, and survival. Both models employ the technique of stochastic microsimulation of life histories and detailed lung cancer progression models specifically intended for the evaluation of

screening. A life history starts with an assigned birth date and sex and values for risk factors (in particular, smoking histories). MISCAN-lung (E) uses the TSCE model for carcinogenesis^{14, 15} and a separate progression model. The TSCE model is not used in Model (M). In models E and M, lung cancer may develop and progress to clinical diagnosis, and may lead to lung cancer death if death from other causes does not occur sooner. In both models, individuals can develop multiple lung cancers of different histological types. Outputs include survival, screening effectiveness, lead time, overdiagnosis, and years of life lost due to lung cancer.

2.4.2 How the Models Used Smoking History Data—The smoking histories described in Burns et al. and Holford et al. in this monograph^{8, 10} were either used as individual-level histories or aggregated into categories.

Four models (E, F, M, and R) used individual-level histories. Based on sex and birth cohort, each simulated individual is assigned a smoking history (age initiated smoking, cigarettes per day while continuing to smoke, age at quitting if applicable). Age at other-cause death is also an output of the smoking history generator. (Rosenberg, et al., in this monograph⁹). (Likewise, if simulating participants in cohort or screening studies, individual histories would be based on observed characteristics recorded in the study.)

Two models (P, Y) used aggregated smoking histories that were adjusted to include censoring from deaths from lung cancer (see Rosenberg, et al., in this monograph, Appendix B). To model the effect of smoking on lung cancer mortality rates, these models regard the population as a mixture of nonsmokers, current and former smokers, with age-specific mortality rates calculated for smoking categories (defined according to the mean number of cigarettes smoked per day and the mean ages of smoking initiation and quitting).

2.4.3 Relationships Between Smoking and Lung Cancer—The TSCE model was used by most of the modeling groups (E, F, P, R, and Y) to govern the relationship between smoking and lung cancer, although groups used a variety of parameter estimates derived from fitting the TSCE model to different endpoints (incidence or mortality) in separate cohorts. The remaining group (M) used an independent probabilistic model, described below. A second-stage calibration of period and cohort terms was performed by some of the groups and is described separately, below.

2.4.3.1 TSCE model: The TSCE model is a stochastic model that represents the cellular processes of initiation, promotion, and malignant conversion during carcinogenesis.^{14, 15} These processes are assumed to be influenced by smoking through (possibly non-linear) dose-response relationships. Model calibration consists of estimating dose-response parameters that best represent the effects of individual smoking histories in relation to lung cancer incidence or mortality in a cohort.

Two groups (F, Y) used the TSCE model parameters estimated by calibrating to lung cancer mortality in the Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS) cohorts (see Hazelton W, et al., in this monograph^{1 and 25}). In prior publications,^{31–33} the FHCRC group (F) described likelihood-based methods for survival analysis.

The Erasmus MC (E) MISCAN-lung model includes the TSCE model for initiation and promotion fit to incidence rates in the NHS and HPFS obtained from a published analysis by the FHCRC group^{14, 15, 25} and a progression model unique to MISCAN-lung. The progression model consists of preclinical, preclinical screen-detectable, invasive, and clinical (diagnosed) lung cancer states. Tumor progression parameters were estimated by calibrating to lung cancer incidence observed in the SEER tumor registry and in the Mayo

Lung Project, a randomized controlled trial of lung cancer screening started by the Mayo Clinic in 1971.^{34, 35} All the modeling groups had a common set of de-identified data from MLP participant smoking histories and trial outcomes but the remaining groups did not calibrate to MLP data. MISCAN-lung distinguishes three lung cancer cell types, i.e. small cell, squamous cell and combined large cell and adenocarcinoma. AJCC stage classifications are reduced to two categories: 2- (I + II) and 3+ (III + IV).

The Rice Lung Cancer Model (R) used a combination of case-control data on risk factor exposures from M.D. Anderson and tabled incidence/mortality rate data from CPS-II (males) and NHS (females) cohorts to fit the TSCE model. The MD Anderson case-control study of lung cancer has collected data on over 6,000 matched cases and controls.^{36–38} In this study, detailed smoking histories, as well as data on other risk factors such as DNA repair capacity are being recorded. Lung cancer cases are matched with cancer-free controls on age (within 5 years), gender, ethnicity, and smoking status. The data on smoking histories is combined with incidence/mortality rate data from CPS-II and NHS to estimate the parameters of the TSCE model.

The PIRE SBC model (P) includes the TSCE model fit to CPS-II mortality (Levy, et al., in this monograph⁴). The predictions from the TSCE are then aggregated over age groups for each year and gender and the results are compared to levels and trends in historical lung cancer deaths by gender over the years 1995 through 2000. The predicted rates are regressed against historical lung cancer deaths (National Center for Health Statistics) to evaluate the predictions of the models and calibrate the models. The regressions allow for linear and non-linear deviations of the predictions of the TSCE models from historical lung cancer rates, as well as linear and non-linear trends unrelated to the predictions from the TSCE models. The calibration to historical lung cancer deaths from the predicted rates under the actual tobacco control scenario are applied to the no tobacco control and complete tobacco control scenarios.

2.4.3.2 Probabilistic model: The MGH-HMS (M) Lung Cancer Policy Model employs a probabilistic model of lung cancer development. Natural history parameters for this model were estimated by calibrating the LCPM predictions against observed outcomes, principally from tumor registries (the NCI's Surveillance, Epidemiology, and End Results, SEER).³⁹ The application of two engineering-based algorithms for calibration of the LCPM has been described.³⁹

In each LCPM cycle (month), individuals face risks of developing one of 5 histological types of lung cancer (adenocarcinoma, large cell, small cell, squamous cell or carcinoma, not otherwise specified (ICD-O-2 code 80103) according to 5 logistic equations that predict development of the first cancer cell. Bronchioloalveolar carcinoma (BAC) is modeled as a subset of adenocarcinoma. Individuals can develop up to 3 lung cancers. Risks are a function of current values of age, years of smoking, cigarettes per day, years since quitting, and alleles that confer a higher risk of lung cancer.^{40, 41} Each new lung cancer is assigned a growth parameter drawn from distributions specific for the 5 cell types of lung cancer and grows according to a Gompertz function. Another term allows cancers in smokers to exhibit accelerated growth, which translates to faster progression and increased lung cancer mortality risks. Smokers remain at increased risk of second and third lung cancer primaries, each of which can lead to lung cancer diagnosis and death. Lobe and location (central/peripheral) in the lung are assigned to each new cancer (varied by histology), according to published observations. Each month, primary lung cancers can spread to involve lymph nodes and/or metastasize to distant sites. The speed of progression varies greatly, however, so that some cancers would never be detected during life in the absence of screening.

Each month, individuals with distant metastases and/or a primary lung cancer may develop symptoms that result in lung cancer detection. Asymptomatic lung cancers and benign pulmonary nodules can be detected during a chest imaging exam (performed for reasons unrelated to lung cancer or as part of a screening program, depending on the scenario). Each individual's true and observed TNM stages (these do not necessarily match due to imperfect tests) are updated each month.

Individual-level lung cancer outcomes include age and stage at diagnosis, location in the lung and histological type, treatment provided and survival.

2.4.4 Incidence, Survival, and Mortality—Reflecting their different purposes (Table I), two models (E, M) are ‘deep’ models that simulate clinical events including disease detection (incidence) and survival as well as mortality, while the remaining groups (F, P, R, Y) – to date, less focused on screening – model at a broader level and focus on mortality.

The Erasmus MC (E) and MGH-HMS (M) models were originally developed to model screening scenarios.^{42, 43} Input variables for both models include characteristics of any screening program (e.g., eligibility criteria, periodicity, accuracy of the screening test) and of individuals (birth cohorts, participation rates). When asymptomatic lung cancers are found on a screening examination, the MGH-HMS (M) LCPM simulates cell type-specific (non-small cell vs. small cell) staging and treatment according to consensus practice guidelines. Treatment consists of either removal of the primary lung cancer (i.e., resection) or systematic therapy (see McMahon, et al., in this monograph³). Tumors which respond to systemic therapy are reduced in size, following conventional guidelines for solid tumors⁴⁴, thereby delaying disease progression. In the LCPM, once an individual has been staged as M1, median survival is as for stage IV in SEER, with exponential survival. Survival curves for earlier stages are predicted by the model using SEER survival curves for similar age/sex cohorts as calibration targets. The Erasmus MC (E) MISCAN-lung model used for these analyses does not specifically model treatment; the consequences of early detection of lung cancer by screening are simulated as a chance of shifting to a new survival distribution. Survival distributions for screen-detected lung cancers were estimated from SEER data by cell type and stage and could result in delayed lung cancer death, no change in time of death, or cure from lung cancer (i.e. dying at the time originally simulated for death from other causes). In both models (E, M), age-specific mortality rates are determined by the incidence, treatment (model M), and survival components and were not calibration targets.

The TSCE model as employed by the FHCRC, PIRE, Rice and Yale groups (F, P, R, Y) was calibrated to mortality rates in different cohorts as described above and in the individual articles detailing each model.^{1–6} The TSCE model includes a lag (generally 5 years) between the first malignant cell and death from cancer. Thus, there is no separate clinical detection event and therefore no incidence or survival rates are predicted. The groups differ in some respects; the FHCRC group prefers to work directly with Poisson likelihoods, whereas the Yale group prefers to work in the generalized linear model (GLM) framework.

2.4.5 U.S. Vital Statistics – Lung Cancer Mortality Rates—Differences in approach to mortality rates translated into different estimates for numbers of lung cancer deaths avoided. To compensate for limitations of the dose-response modules (see below), some groups (F, M, Y) chose additionally to calibrate their models to lung cancer deaths in the US population over the period 1975–2000 using cohort and period effects. The other groups using the TSCE model (E, P, and R) did not calibrate in a second step to the US population lung cancer mortality.

2.4.6 APC Models—Although cigarette smoking is recognized as the primary risk factor for lung cancer, mortality (and incidence) trends in the US are complex, and not fully understood. Comparing the CPS-I (covering the years 1959 through 1981) to the CPS-II (covering the years 1982 through 1988), the relative risks of lung cancer in smokers increased from 11.9 to 23.2 for men and from 2.7 to 12.8 for women.⁴⁵ While much of that change can be explained by the changes in cohort-related smoking habits, such as duration and intensity, a large portion of the difference is still unexplained.⁴⁵ Changes in the composition of cigarettes have been proposed as an explanation, but the evidence is mixed.⁴⁶

The central dose-response models used in the SBC analyses could not distinguish changing risks associated with smoking from those due to other risk factors (e.g., diet, radon, asbestos), which would be needed for a complete description of lung cancer mortality in the US.

To compensate for these effects, three groups (F, M, Y) used their models (with natural history parameters as estimated above and fixed) to simulate the U.S. population at the individual (F, M) or group (Y) level. Using an age-period-cohort (APC) model approach, each group fit their models to lung cancer mortality in the US (separately for males and females) over the period 1975–2000. Model (Y) estimated age, period, and cohort effects, but in models (F and M), the non-specific age effects of the APC models are replaced by the age effects from the natural history models calibrated as described above. This procedure of replacing the non-specific age effects in APC models with a parametric function of age eliminates the fundamental problem of non-identifiability of APC models (see, e.g.,^{47–50}). The cohort and period effects were estimated by maximizing a likelihood function that differed across the groups. The idea of embedding a multistage model in an APC model for analyses of registry data is not new. The FHCRC group has used this technique for analyses of incidence data for other tumors in the SEER registry (colon,^{21, 51} esophagus,²⁴ pancreas,⁵¹ and mesothelioma⁵²). In the earlier papers, notably, the TSCE model parameters were estimated simultaneously with period and cohort effects by fitting to registry data, whereas for the (F) CISNET model (like the other models that calibrated to US mortality, M and Y), the natural history parameters in the central smoking models (TSCE or probabilistic) were separately estimated in a first stage as described above and then kept fixed during estimation of the period and cohort parameters. The Yale Lung Cancer Model used a log-linear calibration function similar to that employed by Luebeck et al.²¹ to scale mortality rates from the TSCE model so that the TSCE estimates corresponded with population trends in lung cancer mortality observed in the US. As described in detail in Holford, et al., in this monograph,⁶ maximum likelihood estimates for age, period (calendar year) and birth cohort terms were derived as part of the scaling process.

The aggregation over age in the PIRE SBC (P) model described above is equivalent to estimating a period effect, distinct from the period and cohort effects estimated for models F, M, and Y.

3. Mapping Model Results to Model Structures and Assumptions

3.1 Intermediate Endpoints

3.1.1 Hypothetical Smoking Histories—Predicted age-specific mortality rates for men born in the period 1921 to 1925 are shown in Figure 2. The results are on an absolute scale and are direct comparisons of outputs from the 6 models. Note that the y-axis scales are not fixed; the differences between the model predictions for the never-smoker (History VII) in particular are magnified but represent a range between 0.04% and 0.16% at age 80. (It is not

possible to compare the model outputs to ‘truth,’ as the histories are hypothetical and unobserved.)

We observed few systematic patterns among the predictions but point out the following differences. Models (F and Y) used identical TSCE parameters (from fits to mortality rates in the HPFS and NHS cohorts) and give similar predictions. Model (E), which used parameters for the TSCE model derived from fits to incidence rates in the HPFS and NHS cohorts, generally predicted higher mortality rates than models F and Y (except for History II, which specified the earliest start age). The generally lower rates predicted by Model (P) are not a consequence of a different underlying assumption, but rather a consequence of using a different cohort for estimating TSCE parameters. Model (R), which incorporated smoking histories from a case control study, predicted lower mortality rates for histories of former smokers (Histories I, III, V, and VI), consistent with a relatively large potential gain from quitting smoking (see below). In model M, which did not use the TSCE model, relatively higher risks were faced by the smoker with the highest daily dose (History VI).

No obvious differences were apparent between models that used a second-step APC calibration (F, M, and Y) and models that did not (E, P and R). The degree of ‘jumpiness’ of a model’s predictions is a function of the specific approach to simulation. Stochastic models with defined numbers of simulated lifetimes (model M, for example) exhibit less-smooth curves than do the models with analytic mathematical formulas for the hazard functions (model F, for example). The results for women born in the period 1921 to 1925 with the same histories exhibited similar patterns.

3.1.2 U.S. Lung Cancer Mortality Rates—As discussed above, three groups (F, M, Y) performed the second-step APC calibration and as a consequence generated mortality rates close or identical to observed mortality rates (see Hazelton, et al., McMahon, et al., and Holford, et al. in this monograph^{1,3,6}). The groups that chose not to perform the second-step calibration (E, P, and R) nonetheless generated consistent predictions of main endpoints (see below).

3.2 Main Endpoints

Figure 3 shows the variation among the models for predictions of the potential lung cancer deaths avoided with complete tobacco control on the horizontal axis and the estimated number of lung cancer deaths actually avoided (realized) on the vertical axis. Numbers of deaths predicted by each model are provided in Boer, et al., in this monograph.⁷ Note that each point in Figure 3 represents the relative differences (across the whole population) between scenarios run by one model; the points in Figure 3 therefore reflect weighting of the absolute differences between model predictions for specific smoking histories that were apparent in Figure 2. In other words, two models that predicted different absolute mortality rates but placed the histories in the same rank-order could predict the same ratio. Several observations are worth noting in Figure 3. First, the models that performed the second-step calibration to US mortality are close together (between 2.45 and 2.55m potential and 0.70 to 0.82m realized), while the models that did not calibrate to US mortality unsurprisingly predicted a wider range of estimates for potential deaths averted (between 2.39 and 2.56m) but generated close estimates of realized deaths averted (between 0.79 and 0.89m). A combined estimate (giving equal weight to each of the six models) of the ratio of realized to potential would be 0.32. Models F, M, and Y (those that performed the second-stage calibration) would have an average predicted ratio of 0.30, indicating that calibration had little influence on the *ratio* of realized vs. potential lung cancer deaths avoided.

Some patterns noted in the hypothetical smoking histories (Figure 2) may translate to results in Figure 3. Model E predicted generally higher mortality rates in smokers and among the

highest gains (both realized and potential). Conversely, model P predicted generally lower rates in Figure 2 and low potential gains; predicted realized gains were intermediate relative to the other models. Translating model M's higher risks for the smoker with the highest daily dose (Figure 2) to gains from smoking cessation depends on the proportion of heavy daily smokers in the population.

4. Discussion

The Smoking Base Case analyses yielded insights into the impact of cigarette smoking on trends in lung cancer mortality and provided estimates from six independent models of the success of US tobacco control policies in avoiding lung cancer deaths. Six models that varied with respect to structure and parameter values generated consistent results: tobacco control efforts avoided one-third of the potential lung cancer deaths over the period 1975 to 2000, compared to cessation of smoking. Despite decades of evidence linking smoking and lung cancer,^{23, 25, 53–56} understanding the intricate biological relationship between smoking and lung cancer is still an active area of research, and there remain gaps in our knowledge about other causes of lung cancer.

Given the standardized inputs (smoking histories), variation in the predicted ratio (Figure 3) is an indication of the magnitude of uncertainty surrounding the relationship between a given smoking history and lung cancer death (Figure 2). An important caveat should be emphasized, however: the absolute results that compare each model versus the others (Figure 2) are less likely to match than the relative results that compare scenarios generated by each model separately (Figure 3). In other words, the points in Figure 3 are 'within-model' estimates of a ratio that could obscure systematic 'across-model' differences in absolute rates. Some of the variability is due also to heterogeneity in model structure and the number of specific events each model simulates between the appearance of a malignant cell and death. Some of the variability is due to the choice of cohort for calibration of the TSCE or probabilistic model. Further, the models that used the TSCE model had different predictions of the realized proportion. This apparently paradoxical result is likely due to a combination of factors, including calibration of the TSCE model to a range of cohorts and lung cancer endpoints, differences in level of aggregation (i.e., modeling at the individual-level or group level) and the different philosophies towards the second step calibration.

Several limitations should be made clear. These analyses were limited to mortality rates over the period 1975–2000. In some cases, mortality rates for all years have been used to calibrate the models, and thus no mortality rates were available for model validation. Mortality data are available for the entire US, but survival from cancer, including lung, is only available from SEER, which currently covers about 26% of the population. Lung cancer incidence for the entire US is not currently directly available.

Tobacco control efforts were treated as a single policy, when in fact a wide range of components were in place over time (clean air laws, taxes, media campaigns, health warnings, cessation treatment, youth access policies and advertising restrictions).

A limitation of the birth cohort and period effect calibration approach is that calibrating the total number of lung cancer deaths per year does not specifically distinguish how smoking and non-smoking risks may have varied separately over time, i.e., how period and cohort effects may have separately affected trends among smokers and non-smokers. For example, it has been suggested that lung cancer risks in never-smokers may be influenced by second hand smoke, air pollution, diet or the use of hormone replacement therapy.

The joint analysis undertaken here did not quantify lung cancer mortality rates by histology. Four major histopathologic types of lung cancer, all related to smoking, are recognized, but

the risks associated with smoking likely vary by histologic sub-type.^{57, 58} Consensus practice guidelines and even staging systems vary between the most aggressive form of the disease, small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC, comprised of large cell, squamous cell, and adenocarcinoma with or without bronchioloalveolar carcinoma features). Also, molecular markers and prognoses vary significantly even within one histology.^{59–62}

Comparative modeling can extract more insight from rich datasets and inform our understanding of the relationship between smoking and lung cancer. Despite heterogeneity in modeling approach, six independent groups agreed that US tobacco control policies were far from achieving the idealized goal of no further initiation and complete cessation of the use of tobacco. Lung cancer control policies should continue to emphasize cessation, as 1 in 5 Americans still smoke.⁶³

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Figure 1. Schematic of CISNET lung models, illustrating key events in a life history (indicated by the arrow from birth to death). Smoking histories and other cause death rates were shared components (left side), while cancer events were predicted by each of 6 models (right side).

Figure 2.
Each line represents the absolute mortality rate for a hypothetical history as simulated by one model.

Realized vs Potential Cumulative Lung Cancer Deaths Avoided
Through Tobacco Control:
US Population years 1975-2000

Figure 3.

Each point represents the relative differences between scenarios as simulated by one model.

Table 1

Key Differences and Similarities Across Models*

Abbreviation for this article	E	F	M	P	R	Y
Institution	Erasmus MC	FHCRC	MGH-HMS	PIRE	Rice-M.D. Anderson	Yale
Model Name	MISCAN lung	TSCE	Lung Cancer Policy Model	SBC Model	Rice Lung Cancer Model	Yale Lung Model
Original purpose*	Screening evaluation	Analysis of epidemiological data	Screening evaluation	Policy evaluation	Mortality risk due to smoking	Population trends and lung cancer
Unit of analysis/ smoking Histories	Microsimulation/ Individual	Microsimulation/ Individual	Microsimulation/ Individual	Macro-level/ Group	Microsimulation/ Individual	Macro-level/ Group
Simulation of Populations or Trials/Cohorts	Both	Both	Both	Populations	Both	Populations
Central dose response model*	TSCE	TSCE	Probabilistic/ logistic regressions	TSCE	TSCE	TSCE
Parameter source(s) [§]	NHS (F incidence), HPFS (M incidence), SEER (survival)	NHS (F mortality), HPFS (M mortality)	SEER (incidence, stage, size, type, survival)	CPS II (mortality)	MDA CCS (smoking histories), NHS (F mortality), CPS II (M mortality)	NHS (F mortality), HPFS (M mortality)
Natural history model features						
Histologic cell types	3 (SQ, AD+LC, SC)	No	5 (SQ, AD, LC, SC, OT)	No	No	No
Modeling of metastases	Implicit	Implicit	Explicit	Implicit	Implicit	Implicit
Tumor growth	No	n/a	Gompertz	n/a	n/a	n/a
Calibration to U.S. lung cancer mortality trends	n/a	PC	PC	P [^]	n/a	APC
Scope of cancer controls*						
Prevention	Yes	Yes	Yes	Yes	Yes	Yes
Screening	Yes	No	Yes	No	No	No
Treatment	Yes	No	Yes	No	No	No

* Descriptions refer to model versions used for analyses in this Monograph and (forthcoming) and do not reflect earlier published versions or subsequent extensions of individual models.

[§] See text for details on how sources were used (as inputs or as calibration targets).

[^] See text for description of regression model. For additional details about how parameters were estimated and supporting references for the models, Model Profiles are available at www.cancer.cisnet.gov/profiles or in the individual model descriptions in this monograph.

Abbreviations: TSCE, two-stage clonal expansion; SEER, Surveillance, Epidemiology, and End Results; NHS (F), Nurses' Health Study (Females); HPFS (M), Health Professionals Follow-up Study (Males); CPS, Cancer Prevention Study; MDA CCS, M.D. Anderson case control study; N/SCLC, Non-small cell and small cell lung cancer; AD, adenocarcinoma, SQ, squamous cell carcinoma; LC, large cell carcinoma; SC, small cell carcinoma; OT, other cell types; APC, age, period, and cohort terms; PC, period and cohort terms; P, period terms only.