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AMERICAN COLLEGE OF CHEST PHYSICIANS

Benchmarking Lung Cancer Mortality Rates in Current and Former Smokers*

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Study objectives: To develop and validate a model for estimating the risk of lung cancer death in current and former smokers. The model is intended for use in analyzing a population of subjects who are undergoing lung cancer screening or receiving lung cancer chemoprevention, to determine whether the intervention has altered lung cancer mortality.

Design/setting/patients: Model derivation was based on analyses of the placebo arm of the Carotene and Retinol Efficacy Trial. Model validation was based on analyses of three other longitudinal cohorts.

Measurements: Observed and predicted number of deaths due to lung cancer.

Results: In internal validation, the model was highly concordant and well calibrated. In external validation, the model predictions were similar to what was observed in all of the validation analyses. The predicted and observed deaths within 6 years were very similar when assessed in the Johns Hopkins Hospital trial of chest radiography and sputum cytology screening (176 predicted, 184 observed, p = 0.53), the Memorial Sloan-Kettering Cancer Center trial of chest radiography and sputum cytology screening (108 predicted, 114 observed, p = 0.57), and the National Health and Nutrition Evaluation Survey part I (24 predicted, 21 observed, p = 0.52).

Conclusions: The number of lung cancer deaths in a population of current or former smokers can be accurately predicted, making model-based evaluations of prevention and early detection interventions a useful adjunct to definitive randomized trials. We illustrate this potential use with a small example. *(CHEST 2004; 126:1742–1749)*

Key words: Cancer screening; CT; logistic models; lung cancer; risk assessment

Abbreviations: CARET = Carotene and Retinol Efficacy Trial; JHH = Johns Hopkins Hospital; LDCT = low-dose CT; MSKCC = Memorial Sloan-Kettering Cancer Center; NHANES = National Health and Nutrition Evaluation Survey

The newest hope for lung cancer screening, low-dose CT (LDCT), is being evaluated in a number of studies. Many of these studies,[1–3] such as the Early Lung Cancer Action Project, have annually screened current and former smokers with LDCT and tracked their outcomes, but have not included a contemporaneous control group. More recently, a large randomized trial called the National Lung Screening Trial has been launched, in which half of current and former smokers will be screened with LDCT, while the other half will serve as control subjects.[4]

It is generally accepted that the only valid end point for evaluations of cancer screening programs is cancer-specific mortality.[5] As such, most investigators agree that the randomized trial will produce a definitive estimate of the impact of screening, because it will allow the lung cancer mortality rate among individuals who are screened with LDCT to be directly compared with the lung cancer mortality rate of a similar group ("the controls") who are not screened with LDCT. Investigators disagree about studies that have not included a control group, in which stage at diagnosis and survival after diagnosis are the primary end points; in the context of a

screening program, changes in these measures may not be predictive of changes in cancer-specific mortality, due to phenomena such as "lead time" and "length time" bias.[6]

What has not been considered is whether this "gold standard" outcome for screening evaluation— the lung cancer mortality rate—can be examined in the groups who have been screened, to determine if this rate is lower than it would have been in the absence of screening. To perform such a comparison would require that the lung cancer mortality rate that would have occurred in the absence of screening could be accurately anticipated. In this article, we describe a model that can be used to calculate the expected number of lung cancer deaths that will occur within a population of current and former smokers in the absence of screening or prevention intervention.

There is precedent for using nonrandomized comparisons to evaluate the impact of screening strategies. Investigators[7–9] concluded that the Papanicolou test reduced the cervical cancer mortality rate when rates of cervical cancer incidence and mortality were reduced after introduction of the test. However, in these studies,[7–9] the magnitude of the screening impact was very large. In contrast, investigators[10,11] concluded that newborn screening for neuroblastoma did not reduce mortality from the disease by comparing neuroblastoma mortality rates in populations that were screened to other populations that had not been screened. Lung cancer differs from these examples in that investigators seek to demonstrate a more modest impact than that demonstrated for the Papanicolou test or for colonoscopy. However, lung cancer is also unusual in that the major risk factors—cigarette smoking and age—have a very strong impact on risk, and the degree of exposure is easily obtained from an interview.[12]

Materials and Methods

Our prediction model was derived on data collected from subjects enrolled in the Carotene and Retinol Efficacy Trial (CARET), a multicenter, randomized controlled study[13,14] that evaluated the impact of beta-carotene and vitamin A on lung cancer mortality. CARET enrolled two populations. There were 14,254 "heavy smokers" (men and women, aged 50 to 69 years), who had at least 20 pack-years of smoking exposure and were either current smokers or had quit within 6 years of enrollment. There were 4,060 "asbestos-exposed" men (aged 45 to 69 years, either current smokers or former smokers who quit within 15 years of enrollment), who had either radiologic evidence of asbestos exposure or a history of employment in a high-risk trade (primarily shipyard or construction work). All participants were randomized either to a placebo or to the intervention (30 mg/d beta-carotene and 25,000 IU/d retinyl palmitate). Enrollment in the pilot study began in 1985, full-scale recruitment began in 1988, and study accrual ended in September 1994. The interven-

tion was stopped in January 1996 after preliminary results revealed definitive evidence of no benefit and substantial evidence of possible harm.[14]

The data from CARET are highly appropriate for deriving our model. They are rich in subjects and events, and the risk factors and outcomes were evaluated and recorded scrupulously. Moreover, the population of subjects in CARET are relevant to our purposes, in that they are drawn from six geographically diverse areas of the United States (Seattle WA, Portland OR, Irvine CA, Baltimore MD, New Haven CT, San Francisco CA), they consist only of volunteers in a clinical trial of cancer prevention, and they possess the smoking risks that make them strong candidates for lung cancer screening and prevention.

Our approach to model development and initial testing paralleled that which we used to develop a model of an individual's risk of having lung cancer diagnosed.[12] First, the data in CARET were divided into separate person-time periods. The beginning of each time period was defined by date of an encounter with a study coordinator (either initial or follow-up), and the end of the time period was defined either by the date of the outcome (death due to lung cancer) or by the date of a censored event (subsequent follow-up encounter, death due to another cause, end of the data). These person-time periods were then coded as either commencing within 1 year of study entry, or commencing after that point. The data were dichotomized in this manner to capture any risk attenuation that was initially present among study entrants due to their being asymptomatic at the time of enrollment.

Our validation involved subjects in the following three cohorts (Table 1): the National Health and Nutrition Evaluation Survey (NHANES) I[6]; the Memorial Sloan-Kettering Cancer Center (MSKCC) randomized trial of chest radiograph and sputum cytology screening[15]; and the Johns Hopkins Hospital (JHH) randomized trial of chest radiograph and sputum cytology screening.[16] These validation cohorts were comprised of individuals who were eligible for and elected to enroll in longitudinal health studies, making them well suited to our purposes. There were also some shortcomings to the use of these cohorts. The NHANES I cohort is small, and the subjects were not asked about asbestos exposure; we assumed in our analyses that none of the subjects had been exposed to asbestos. The MSKCC and JHH cohorts included male subjects only; moreover, all subjects were screened for lung cancer in the context of the study. Because it is widely accepted that the screening interventions in these studies did not alter the lung cancer mortality rates, we assumed that the lung cancer mortality rates in these studies were similar to rates that would have been observed in the absence of screening.[6,15,16]

As in our earlier work, we only apply the model to subjects who are 50 to 75 years old at study entry, smoked 10 to 60 cigarettes per day when actively smoking, smoked for 25 to 60 years, and had quit smoking for no more than 20 years.[12] These restrictions are based on the number of lung cancer deaths observed among subjects with these characteristics in CARET, and also either parallel or are more liberal than the entry criteria of the majority of lung cancer screening and prevention studies.

To illustrate how the model might be used to evaluate single-arm studies of lung cancer screening, we applied the model to an ongoing single-arm study being conducted in Milan Italy, in which subjects have been annually screened with low dose CT. This study has been described in detail elsewhere.[3] The study began enrolling study subjects in 2000 with a prespecified plan for follow-up and cause-of-death ascertainment. Follow-up has been accomplished through annual follow-up scans, telephone contact of those subjects who did not appear for follow-up scans, and searches of death registries for the Lombardy region of Italy. Through these means, all but one of the study subjects had

Table 1—*Characteristics of Cohorts Used for Model Validation**

Variables	JHH	MSKCC	NHANES I
Parent cohorts			
Subjects	10,828	10,040	31,973
Years of enrollment	1974–1978	1974–1978	1971–1975
Validation cohorts			
Subjects	8,428	5,603	1,140
Median follow-up, yr	7.9	8.0	13.8
Male gender, %	100	100	67.5
Age, yr	57.1 (5.5)	57.4 (5.9)	59.9 (6.8)
Cigarettes per day	30.6 (11.1)	32.2 (11.2)	27.7 (12.9)
Years of smoking	37.8 (6.9)	37.2 (6.9)	38.8 (7.9)
Quit smoking at study entry, %	4.0	99.2	32.8
Asbestos exposed, %	7.3	5.6	Not available†
Lung cancer deaths within 6 yr	184	114	21

*Data are presented as No. or mean (SD) unless otherwise indicated.
†All individuals assumed to not have occupational asbestos exposure in modeling.

vital status ascertained in 2003 or 2004; the one outstanding subject had follow-up only through December 2001, at which point he was alive and free of a lung cancer diagnosis. For the 16 study subjects who died, 14 medical records were obtained and reviewed in order to assign cause of death. For the remaining two decedents, cause of death was ascertained through reviews of death certificates, the Lombardy cancer registry, and health population files. All subjects who died after a diagnosis of lung cancer were assigned lung cancer as a cause of death in our analysis.

Statistical Analysis

Model Development and Internal Validation: Cox proportional hazards regression was used to estimate the multivariable relations between the risk factors and the risk of lung cancer death. The proportional hazards assumption that the hazard ratios were constant over time was verified by tests of correlations with time and examination of residual plots. Continuous predictors (age, duration of quitting, duration of smoking, number of cigarettes smoked per day) were fit with restricted cubic splines to allow for nonlinear and nonmonotonic effects; the knots separated quartiles of the data. Sex, asbestos exposure, and study entry were treated as categorical variables. Model discrimination was assessed by the concordance index after tenfold cross-validation, a form of resampling that reduces the bias that is introduced when the model is tested on the data from which it was derived.[17–20] Internal calibration was assessed using a calibration plot. In this plot, the cohort was divided into 10 equally sized groups by level of predicted risk. Then, the observed probabilities of lung cancer death were compared to those predicted both in the empiric data, and after tenfold cross-validation.

External Model Validation and Applied Example: The number of lung cancer deaths predicted by the model was compared to the number of lung cancer deaths observed in the validation and Milan cohorts. For each individual and for each year of the study, we generated estimates of the probability of death from lung cancer. During the first year of the study, the individual's risk was based on their risk factors at the time of study entry, including the risk attenuation estimate, a factor included to reflect the lower immediate risk of death for individuals who are healthy enough to register in a clinical trial. In subsequent years, risk was calculated from incremented risk factors; age increased each year for all subjects, and years of smoking or years of quitting increased for individuals depending on their smoking status at entry. To determine the number of lung cancer deaths expected in each period, we summed the individual probabilities for those subjects who were still being followed up in that time period of the study. In other words, each individual contributed to the group estimate only over the duration of his or her follow-up.

The predicted and observed number of lung cancer deaths were compared in each of the studies individually; for the validation step, all three validation cohorts were combined. To test whether the numbers differed, we used the χ^2 test for Poisson distributed variables $[(O-E)]\hat{\ }2/E$. We also constructed a z-test, based on the binomial distribution, so that we could determine whether the inclusion of an additional variance term for the predicted probability of death for each individual in each time period reduced the estimates of statistical significance. The statistic was calculated from the following formula, where d_i denotes whether the subject died of lung cancer in the ith interval, and p_i is the probability of that event for that subject in that time interval. Each interval was either 1 year, or a portion of year in years when subjects had follow-up for less than that year.

$$z = \frac{\sum (d_i - p_i)}{\sqrt{\sum (p_i(1 - p_i) + \text{var}(p_i))}}$$

In our analyses, we found that the addition of the variance (var) of the probabilities to the denominator had no measurable effect on the statistical significance of the test, so the tests of significance and estimates of statistical power are based on the χ^2 test.

These analyses of the CARET data were approved by the Institutional Review Boards at the Fred Hutchinson Cancer Research Center, Seattle, WA, and MSKCC, New York, NY. Model development was conducted with appropriate software (S-Plus software, version 2000 Professional; Insightful; Seattle, WA) with additional functions (called Design).[17] Predicted and observed mortality curves were generated and compared with a statistical software package (STATA 8.1; StataCorp; College Station, TX). The model formula is available by request from the author.

RESULTS

Model Derivation

We analyzed the 8,825 subjects enrolled in the placebo arm of CARET, who had documented cur-

rent or former smoking history (7,292 subjects from the heavy smoking cohort; 1,533 subjects from the asbestos cohort). The characteristics of these subjects are listed in Table 2. Subjects contributed a total of 111,380 observational intervals, averaging 12.6 observational intervals (median, 13) per person, with a mean duration of 268 days per interval (median, 216 days; interquartile range, 122 to 366 days). As of February 25, 2002, the subjects had been followed up for 81,673 person-years, during which time 307 subjects died of lung cancer (lung cancer mortality rate of 376 per 100,000 person-years). Our multivariable regression yielded a 1-year model for an individual's risk of lung cancer death with a cross-validated concordance index of 0.72, and a cross-validated calibration plot consistent with excellent calibration (Fig 1).

Model Validation

In our comparisons between the projections of the model and the observed number of lung cancer deaths in our validation cohorts, the predictions very closely paralleled the observed number of lung cancer deaths in all of the studies individually and in the three studies combined. The observed numbers of deaths over 6 years of follow-up were 184 (176 predicted), 114 (108 predicted), 21 (24 predicted), and 319 (308 predicted) for the JHH, MSK, and

NHANES cohorts, and all three cohorts combined, respectively. In Figure 2, the accrued deaths are plotted against the cumulative expected number, using time of study registration as the time origin. In addition to the close empiric matching of observed and expected lung cancer deaths, we saw no statistical evidence that there were differences in the observed and expected number of lung cancer deaths either, with all p values > 0.50. This latter observation should be considered within the context of our statistical power. In the analyses involving all three cohorts combined, with 311 expected deaths within 6 years, we had $> 92\%$ power to detect true differences in excess of $\geq 20\%$. In the individual cohorts, the power was substantially less; for a difference of the same magnitude, the power in the JHH cohort was 74%, in the MSKCC cohort was 54%, and in the NHANES I cohort was 19%.

Applied Example

From the Milan cohort, there were 973 subjects who had risk factors within the range allowable for the model. From the time of their first LDCT scan, these subjects contributed 2,895 person-years of follow-up (mean follow-up time, 3.0 years; range, 0.3 to 3.9 years), during which time there were nine deaths from other causes, and five deaths due to lung cancer. In comparison, the model predicted that 7.3 lung cancer deaths should have occurred (Fig 3, $p = 0.40$). We present this finding for illustration purposes only, as this study has an insufficient follow-up duration and sample size to support drawing any conclusions about LDCT screening

Discussion

We developed a model to predict the number of lung cancer deaths that should occur in a cohort of current or former smokers in the absence of screening or prevention efforts. We then determined that the predictions from this model, which are based on the values of ascertainable risk factors from each subject, essentially match the actual number of lung cancer deaths that were observed in three separate validation cohorts. Because the model appears to predict accurately, it may be useful in evaluating findings from single-arm studies of screening and prevention, as we illustrated in a cohort of current and former smokers in an ongoing single-arm study of lung cancer screening.

We pursued this study because in lung cancer there are easily observable factors that very strongly predict the risk of this disease and death due to it (age and detailed smoking history). Our analyses were also justified by the availability of a large

Table 2—Characteristics of CARET Cohort Used for Model Development: Participants Were Enrolled During the Years 1988 Through 1994*

Variables	Subjects	Lung Cancer Deaths	All Deaths
All, No.	8,825	307 (3.5)	1,104 (12.5)
Heavy smoker cohort	7,292 (82.6)	249 (3.4)	852 (11.7)
Asbestos cohort	1,533 (17.4)	58 (3.7)	252 (16.4)
Age at entry, yr			
44–58	3,338 (37.8)	78 (2.3)	245 (7.3)
59–64	2,673 (30.3)	108 (4.0)	325 (12.2)
65–80	2,814 (31.9)	121 (4.3)	534 (19.0)
Sex			
Male	5,744 (65.1)	222 (3.9)	863 (15.0)
Female	3,081 (34.9)	85 (2.7)	241 (7.8)
Smoking status†			
Former	2,958 (33.5)	79 (2.7)	343 (11.6)
Current	5,867 (66.5)	228 (3.9)	761 (13.0)
Race			
White	8,198 (92.9)	284 (3.5)	1,009 (12.3)
Black	273 (3.1)	13 (4.8)	62 (22.7)
Hispanic	137 (1.6)	1 (0.7)	9 (6.6)
Asian/Pacific Islander	106 (1.2)	2 (1.9)	9 (8.5)
American Indian/Alaskan	69 (0.8)	3 (4.4)	9 (13.0)
Other/unknown	42 (0.5)	4 (9.5)	6 (15.8)

*Data are presented as No. (percentage of total).
†Ranges: cigarettes (1 to 90 per d); duration of smoking (1 to 63 yr); duration of quitting (0 to 51 yr).
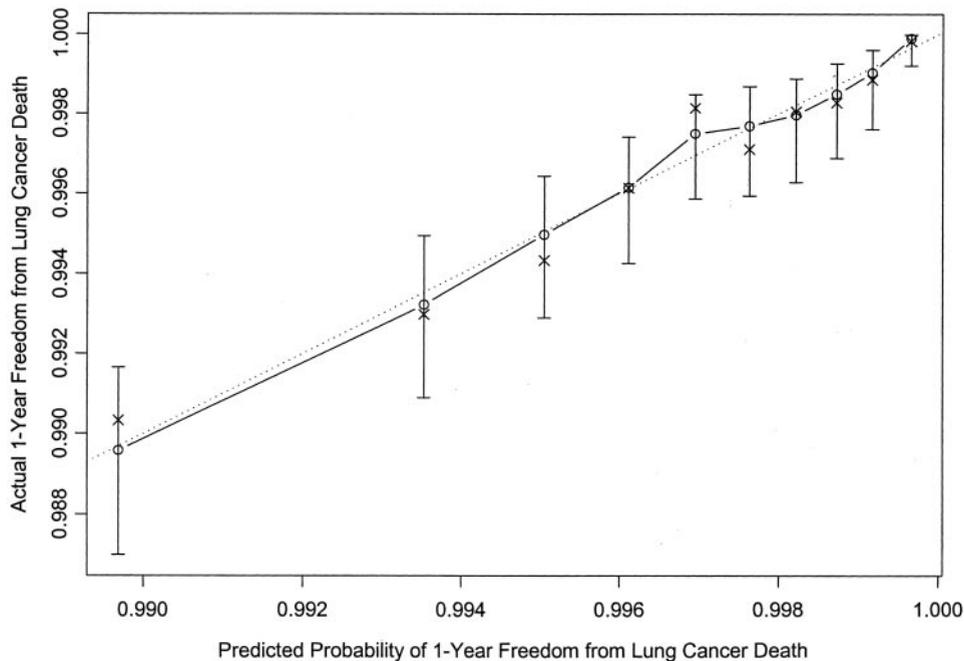
FIGURE 1. Calibration of the 1-year lung cancer mortality risk model by decile of risk. The figure demonstrates that the model predicts mortality rates accurately whether predicting for individuals at relatively low risk, some intermediate level of risk, or relatively high risk. The predicted and observed probabilities of lung cancer by each risk decile are graphed respectively on the horizontal and vertical axes. The dotted line indicates the reference line on which an ideal model would lie. Circles mark the intersection between the prediction of the model and the observed mortality. The Xs mark the intersection between the prediction of the model and the observed mortality after cross-validation. Vertical bars indicate 95% confidence intervals.

high-quality data set for model derivation (the data from CARET). In CARET, the population under study was similar to the highly selected populations that are included in trials of lung cancer screening (middle-aged and elderly people with a long-term smoking history who lack symptoms of lung cancer). Because this set of favorable circumstances are not applicable to any of the other common cancers, our approach may not be widely generalizable beyond lung cancer.

Investigators might consider applying our model to their studies of lung cancer screening or prevention if (and only if) their studies have the following features: (1) the characteristics and risk factors of all subjects are ascertained at study entry; (2) the outcomes of all subjects are determined, including those subjects who only inconsistently received the study intervention(s); and (3) all subjects who were asymptomatic at study entry are included in all analyses, even if they were discovered to have advanced lung cancer during the initial screening process. There may be many ongoing studies of LDCT that have these features, and these studies may collectively include tens of thousands of participants and person-years of follow-up. As such, these studies might be used to generate a preliminary

estimate of the impact of lung cancer screening with low-dose CT on lung cancer mortality, at least until more definitive results from the National Lung Screening Trial are available.[6,21]

We caution that evaluating outcomes of individuals in single-arm studies of screening or prevention using our model is an approach potentially susceptible to a variety of biases, some which affect all models, and some which are unique to our model. In general, a predictive model is typically less accurate in a new group of subjects than it is when originally described due to differences between the cohorts that were used to derive the model and the cohorts to which it is applied.[22,23] For our model, the cohort (CARET) that was used for derivation was assembled and evaluated during the late 1980s and early 1990s, and the cohorts used for evaluation were enrolled in studies more than a decade earlier. Cohorts enrolled in current studies of screening and prevention began smoking many years after the cohorts included in our derivation and validation cohorts, and may have been exposed to cigarettes with different nitrate and tar composition. Our model has not been sufficiently validated in women either, given that neither the JHH or MSKCC
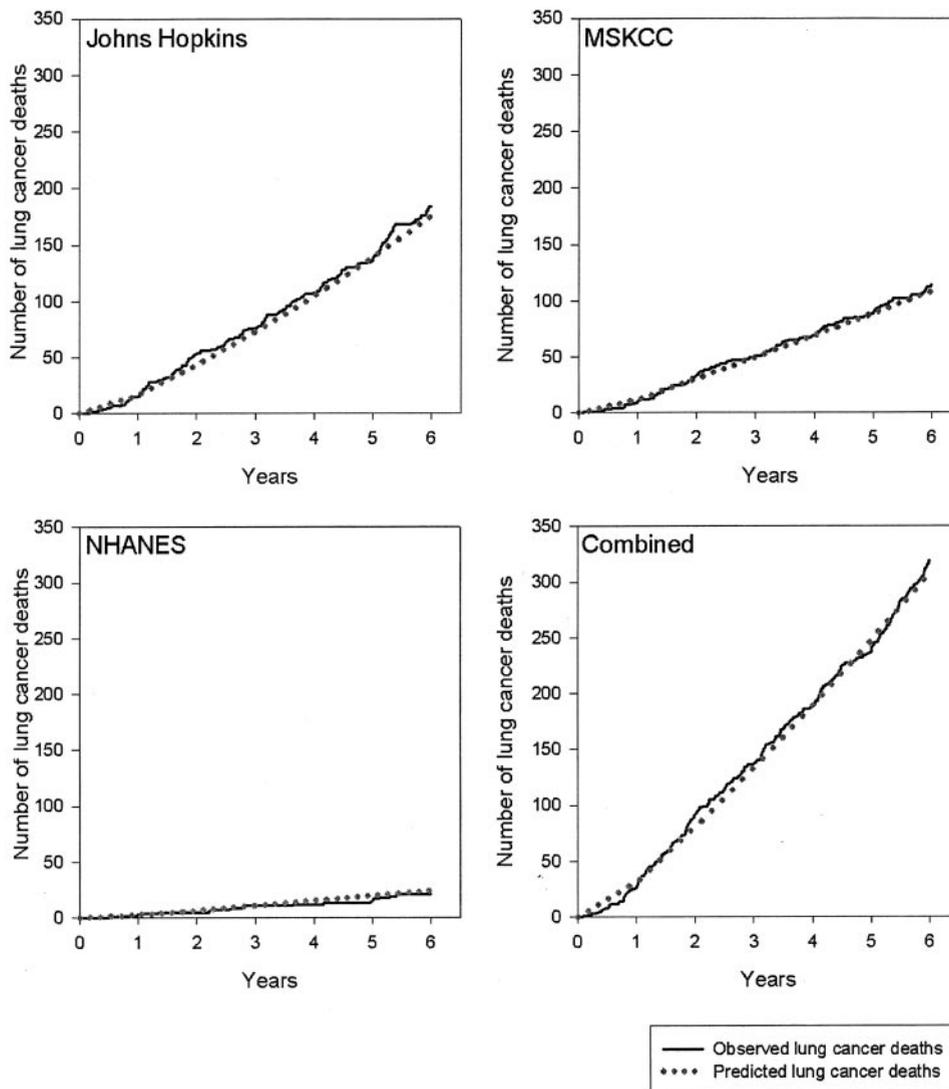
FIGURE 2. Predicted and observed lung cancer deaths over 6 years of follow-up from four analyses. These figures demonstrate that the predicted and observed number of lung cancer deaths are very close in (*top left*) the JHH cohort (8,428 individuals, 184 lung cancer deaths observed, 176 deaths predicted; p = 0.53); (*top right*) the MSKCC cohort (5,603 individuals, 114 lung cancer deaths observed, 108 deaths predicted; p = 0.57); (*bottom left*) NHANES I (1,140 individuals, 21 lung cancer deaths observed, 24 deaths predicted; p = 0.53); and (*bottom right*) all cohorts combined (15,171 individuals, 319 lung cancer deaths observed, 308 deaths predicted; p = 0.53).

studies enrolled women. With the rising incidence of the disease in women, this is an important shortcoming.[24]

Subjects enrolled in CARET and in our validation studies faced a competing risk of death due to causes other than lung cancer; in many cases, these causes of death (particularly cardiovascular death) are also closely linked to the risk factors that confer an excess risk of lung cancer death (*ie*, more advanced age, greater degree of smoking exposure). Medical progress has successfully reduced the risk of death due to many of these smoking-related diseases. As a result, in contemporary cohorts, the observed lung cancer mortality rate may actually be higher than it would have been at the time CARET was conducted. This phenomenon may cause the model to underpredict lung cancer mortality rates, so the direction of this bias will not cause studies of screening or prevention to appear falsely beneficial.

The excellent performance of our model in our validation analyses does suggest that this approach to the assessment of screening and prevention interventions should receive further consideration. Before being assessed in randomized studies, new therapeutic agents in cancer are evaluated by comparing the overall response rate of a group of subjects who
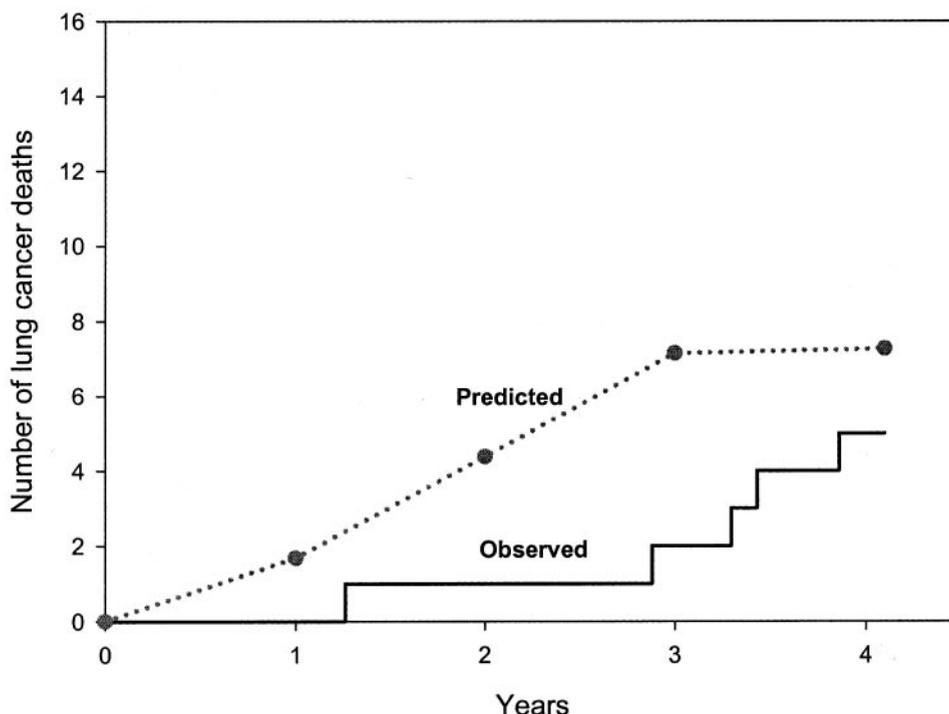
FIGURE 3. Predicted and observed lung cancer mortality in a study of LDCT screening conducted in Milan, Italy. These data are presented purely for the purpose of illustrating how the lung cancer mortality model could be applied to a study of screening for the purposes of evaluating lung cancer mortality among screened individuals. No conclusions can be drawn from this analysis about the efficacy of screening in reducing lung cancer mortality, due to the small sample size and incomplete follow-up of study subjects. The figure reflects data on 973 subjects, where five lung cancer deaths were observed, and 7.3 were expected (p = 0.40 for difference).

receive the new agent to the overall response rate of a set of historical controls; these latter individuals provide the "expected" response rate. In the evaluation of new screening and prevention strategies in lung cancer, this type of comparison has not been performed, because no suitable group of historical controls exists. Our statistical model of lung cancer mortality might be useful for evaluating lung cancer prevention and early detection strategies, because it provides an analog to "historical controls." The added advantage of our approach in this context is that each person serves as his or her control, an important feature when the risk of the disease varies broadly across subjects.

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