

ARTICLE

Impact of Tobacco Dependence in Risk Prediction Models for Lung Cancer Diagnoses and Deaths

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Abstract

Background: Stronger nicotine dependence is associated with greater lung cancer incidence and lung cancer death. This study investigates whether including nicotine dependence in risk prediction models for lung cancer incidence and mortality provides any important clinical benefits.

Methods: Smoking data were used from 14 123 participants in the American College of Radiology Imaging Network arm of the National Lung Screening trial. We added nicotine dependence as the primary exposure in two published lung cancer risk prediction models (Katki-Gu or PLCO-m2012) and compared four results: with no tobacco-dependence measure, with time to first cigarette, with heaviness of smoking index, and with Fagestrom test for nicotine dependence. We used a cross-validation method based on leave-one-out and compared performance using likelihood ratio tests (LRT), area under the curve, concordance, sensitivity and specificity for 1% and 2% risk thresholds, and net benefit statistics. Statistical tests were two-sided.

Results: All LRT results were statistically significant ($P \leq .0001$), whereas other tests were not, except that specificity statistically significantly improved ($P < .0001$). Because the LRT is asymptotically more powerful for testing for prediction gain, we conclude that both models were improved on a statistical level by adding dependence measures. The other performance statistics generally indicated that such gains were likely very small. Net benefit analysis confirmed there was no apparent clinical benefit for including dependence measures.

Conclusions: Although inclusion of dependence measures may not provide a clinical benefit when added to risk prediction models, nicotine-dependence measures should nonetheless be an integral tool for patient counseling and for encouraging tobacco cessation.

Lung cancer is responsible for the most cancer-related deaths in the United States and worldwide annually (1,2). This is because most patients have advanced stage disease at the time of diagnosis. Screening individuals at high risk for lung cancer with annual low-dose computed tomography has been shown in a large, randomized controlled trial to reduce mortality from lung cancer by 20% through early detection (3). The US Preventive Services Task Force has assigned lung cancer screening a Grade B recommendation, and it is a covered service by Centers for Medicare and Medicaid (4,5).

Eligibility criteria for lung cancer screening (LCS) involve only smoking status, age, and tobacco pack-year history. Although these are relatively simple criteria, the inclusion of other individual factors into a risk prediction model led to improved sensitivity and positive predictive value without changing specificity with the potential of improving screening efficiency (6). These risk calculators are being used during shared decision making to help patients eligible for LCS understand their individual risk for developing lung cancer (7). Further, risk prediction modeling has been used to demonstrate

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that never smokers would not achieve a risk threshold high enough to warrant screening (8).

Stronger nicotine dependence is associated with greater risk of lung cancer incidence and lung cancer death (9), and there has been interest in determining whether existing risk prediction models could be further improved by including this factor. For example, one recent study (10) incorporated time to first cigarette (TTFC), a surrogate for nicotine dependence, into an existing risk prediction model (11) to conclude that smokers who are less dependent have lower lung cancer incidence and death risk compared to those with stronger dependence; however, this model's predictive performance was not validated in an independent cohort. Moreover, area under the curve (AUC) was the only criteria used to assess the performance of the prediction model (10). We undertook this study to more broadly evaluate the impact of including nicotine dependence in risk prediction modeling for lung cancer incidence and mortality by comparing the relative performance of three nicotine-dependence measures in two existing prediction models and applying rigorous statistical evaluation of their comparative predictive performance.

Materials and Methods

This study was approved by the Medical University of South Carolina Institutional Review Board (IRB No. 00054733). This is analysis of secondary data collected from subjects in the American College of Radiology Imaging Network (ACRIN) arm of the National Lung Screening trial (NLST), a randomized controlled study.

Participants

The NLST enrolled 53 452 current and former (quit within 15 years) smokers ages 55–74 years with a minimum of a 30 pack-year cigarette smoking history (12). Participants were randomly assigned to three rounds of annual screening with LDCT or chest radiography. The ACRIN arm of the NLST ($n = 14\ 123$) was selected for analysis because this subset completed more detailed smoking questionnaires on variables of interest (eg, nicotine dependence) than the other NLST participants.

Outcomes

The clinical outcomes considered were lung cancer diagnosis and death due to lung cancer during the NLST study period (2002–2009).

Main Exposure

Tobacco dependence was estimated by three measures: Fagerstrom test for nicotine dependence (FTND), heaviness of smoking index (HSI), and time to first cigarette (TTFC). Total scores on the FTND range from 0 to 10, on the HSI from 0 to 6, and on TTFC from 0 to 3, with higher scores reflecting greater severity of nicotine dependence. These dependence metrics have been shown to predict both behavioral and biochemical indices of smoking (13–17).

Statistical Analysis

Prediction Models. We evaluated nicotine dependence as the primary exposure in two risk prediction models: lung cancer

incidence and lung cancer death described by Gu et al. (10) and Katki et al. (11) (referred to here as the Katki-Gu model), and lung cancer incidence described by Tammemagi et al. (6) (referred to here as PLCO-m2012). To be consistent with earlier models, we controlled for the same covariates as reported earlier. For the Katki-Gu models, logistic regression and Cox proportional hazards models were developed for each outcome. For the lung cancer diagnosis outcome, all comparison models included the screening group (radiography or computed tomography); age (log-transformed); sex; race or ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, or other); education (continuous; <12th grade, completed high school, post-high school education but no college, associate's degree, bachelor's degree, or graduate school); family history of lung cancer (0, 1, or 2 first-degree relatives with lung cancer); emphysema; body mass index (BMI; log-transformed); underweight body mass index (BMI ≥ 18.5 vs < 18.5); cigarettes per day (< 20 vs ≥ 20); smoking duration (continuous); pack-years (< 30 , 30–39, 40–49, or > 50); and years since quitting (log-transform of number of years quit + 1). The same parameterizations were used for all lung cancer mortality models, except smoking duration was log-transformed. For the PLCO-m2012 model, in addition to the primary exposure, we controlled for age (continuous); race or ethnicity (white, black, Hispanic, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander); education (six ordinal levels); BMI (continuous); chronic obstructive pulmonary disease (binary); personal history of cancer (binary); family history of cancer (binary); smoking status (current vs former); smoking intensity (average number of cigarettes per day, log transformed); duration of smoking (years); and smoking quit time (years).

Evaluating Prediction Performance. To evaluate whether inclusion of tobacco dependence measures in risk models improved their predictive performance, we compared four models: no tobacco-dependence measure (baseline model); with TTFC; with HSI; and with FTND. We used a wide range of methods for evaluating predictive performance to establish whether the dependence measures led to statistically significant improvements, to quantify the size of any such improvement, and to place the results in a clinical perspective.

For logistic regression models, we compared the dependence and baseline models using likelihood ratio tests (LRTs); receiver operator characteristic AUC; Brier scores (18); and decision curve analysis using net benefit (NB) statistics (19). We tested for a statistically significant improvement in AUC by the method outlined by DeLong et al. (20) and used 1000 bootstrap samples to estimate the change of AUC and its standard error based on the methods outlined by Pepe et al. (21). Predicted probabilities in all cases were based on leave-one-out cross-validation.

For Cox proportional hazards models, we evaluated model performance by LTRs and by comparing Uno concordance statistics, for which we tested whether there was a statistically significant difference between competing models by methods outlined by Uno et al. (22), and used 1000 bootstrap samples to estimate the difference in Uno concordance statistics and its standard error.

Finally, similar to Gu et al. (10), we tested for a statistically significant change in sensitivity and specificity for models with or without TTFC. Only patients from the radiography arm were included to avoid any bias from the beneficial effects of LDCT screening. Here we estimated the cumulative incidence from Cox proportional hazard models using methods described by Leisenring et al. (23); patients were assigned to screening if their estimated 5-year lung cancer risk exceeded standard risk thresholds (1% or 2%).

The NB for treatment is defined as

$$NB(p_t) = \frac{TP}{n} - \frac{FP}{n} \left(\frac{p_t}{1-p_t} \right)$$

,where n is the total number of patients, TP and FP are the number of true or false positives, and p_t is a risk threshold (19). NB could be viewed as the difference between the benefit for screening the correct group (true positives) and the weighted cost for screening the wrong group. Vickers and Elkin (19) discussed that NB is intended to examine whether a given test provides any clinical benefit and should not be considered a strict measure of predictive performance.

Our use of multiple methods to assess prediction performance will help ensure that our conclusions do not hinge on a single method. For example, several authors have warned that AUC can be insensitive to gains in predictive performance in some conditions (21,24). Assel et al. (25) pointed out limitations of the Brier score. Further, Pepe et al. (21) commented that there is substantial debate over how to most effectively measure such gains.

Model assumptions were assessed via residual plots. All statistical analyses were two-sided and performed with SAS 9.4_M4 software and SAS/STAT 14.2 (26).

Results

Demographic, clinical, and smoking history characteristics for the ACRIN population are provided in Table 1. The population had an average age of 61.6 years, was 45.0% female, and 91.4% non-Hispanic white. The mean smoking history was 55.9 pack-years, and 36.2% were current smokers throughout the study. When nicotine dependence was assessed by the FTND, HSI, and TTFC measures, 30.2%, 22.9%, and 33.8% fell into the very high dependence category, respectively. Table 2 provides hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CI) for the Katki-Gu lung cancer incidence and lung cancer mortality models in which nicotine-dependence measures were added as primary exposures. The very low dependence category serves as the reference in each case. For both outcomes, there was a positive trend overall in hazard ratios and odds ratios between the low and very high dependence categories. For example, for lung cancer incidence with low and very high dependence as measured by TTFC, the hazard ratios were 1.75 (95% CI = 1.17 to 2.62) and 2.22 (95% CI = 1.54 to 3.21), respectively. For lung cancer mortality, the corresponding hazard ratios were 2.34 (95% CI = 1.13 to 4.79) and 3.13 (95% CI = 1.61 to 6.07), respectively.

Table 3 provides the LRT results, AUC contrasts, Brier scores, and Uno concordance contrasts for the Katki-Gu and PLCom2012 models. Similar to the Table 2 results, LRT results for all tobacco-dependence measures are statistically significant regardless of the model; the largest P value was .0001. For the logistic regression models, in both outcomes, there is only a small gain in AUC when a nicotine-dependence measure was added, and none of these gains was statistically significant. The largest AUC gains were 0.007 ($P = .26$) for lung cancer death and 0.007 ($P = .13$) for lung cancer incidence. Only AUC results from bootstrap analysis are shown because these had the smallest standard errors. Similarly, the Brier scores were identical to at least the third statistically significant digit, indicating no improvement in predictive performance for any nicotine dependence measure. For the Cox proportional hazards models, there were no statistically significant improvements in Uno concordance statistics when any of the nicotine dependence measures were added to the model; the largest gain was 0.0130 ($P = .08$) for lung cancer death and 0.009 ($P = .12$) for lung cancer incidence [this

Table 1. Demographic and clinical characteristics of the ACRIN population*

Characteristics	No.(n = 14 123)
Lung cancer death, No. (%)	258 (1.8)
Lung cancer incidence, No. (%)	587 (4.1)
All-cause death, No. (%)	1038 (7.4)
Randomized to CT arm, No. (%)	7084 (50.2)
Age, mean (SD), y	61.6 (5.1)
Women, No. (%)	6354 (45.0)
Race/ethnicity, No. (%)	
Non-Hispanic white	12 912 (91.4)
Non-Hispanic black	820 (5.8)
Hispanic	187 (1.3)
Other	204 (1.4)
Married, No. (%)	8923 (63.2)
Education >12 y, No. (%)	9941 (70.4)
Pack years, mean (SD)	55.9 (23.7)
Age began smoking, mean (SD), y	17.3 (4.6)
Age quit smoking, mean (SD), y	55.1 (6.6)
Cigarettes per day, mean (SD)	28.0 (11.1)
Total years smoked, mean (SD)	40.3 (7.4)
Smoking status, No. (%)	
Current smoker throughout study	5107 (36.2)
Current smoker quit during study	1949 (13.8)
Restarted smoking during study	486 (3.4)
Former smoker throughout study	6581 (46.6)
FTND, No. (%)	
Very low dependence	1207 (8.6)
Low dependence	2572 (18.2)
Medium dependence	1830 (13.0)
High dependence	4249 (30.1)
Very high dependence	4265 (30.2)
HSI, No. (%)	
Very low dependence	1991 (14.1)
Low dependence	2337 (16.6)
Medium dependence	2903 (20.6)
High dependence	3653 (25.9)
Very high dependence	3239 (22.9)
Time to first cigarette, No. (%)	
>60 min	1840 (13.0)
31–60 min	2042 (14.5)
15–30 min	2266 (16.0)
6–14 min	3204 (22.7)
≤5 min	4771 (33.8)
Family history of lung cancer, No. (%)	
0 first-degree relatives	11 087 (78.5)
1 first-degree relative	2554 (18.1)
≥2 first-degree relatives	482 (3.4)
Emphysema diagnosis, No. (%)	1230 (8.7)
BMI, mean (SD), kg/m ²	27.8 (5.1)
Low BMI, <18.5 kg/m ² , No. (%)	164 (1.2)

*ACRIN = American College of Radiology Imaging Network; CT = computed tomography; BMI = body mass index; FTND = Fagestrom test for nicotine dependence; HSI = heaviness of smoking index; SD = standard deviation.

contradicts Gu et al. (10) results]. Only concordance results from bootstrap analysis are shown.

Table 4 provides the estimated changes in sensitivity and specificity when TTFC was added to the Cox proportional hazard models predicting lung cancer incidence. Risk thresholds for screening were fixed at 1% and 2% risk of 5-year cancer incidence. Sensitivity did not improve at either threshold when TTFC was added to the models, and no new cases were identified. Specificity improved from 5.96% to 9.1% ($P < .0001$) at the 1% threshold, and there were

Table 2. Risk of lung cancer outcomes for tobacco-dependence measures*

Model	Tobacco dependence level				
	Very low	Low	Medium	High	Very high
Lung cancer incidence hazard ratio (95% CI)					
TTFC	(Referent)	1.75 (1.17 to 2.62)	1.63 (1.09 to 2.42)	2.16 (1.49 to 2.13)	2.22 (1.54 to 3.21)
FTND	(Referent)	1.59 (1.02 to 2.47)	1.71 (1.09 to 2.70)	1.67 (1.09 to 2.56)	2.36 (1.53 to 3.64)
HSI	(Referent)	1.81 (1.25 to 2.61)	1.82 (1.27 to 2.61)	1.96 (1.37 to 2.81)	2.35 (1.62 to 3.41)
Lung cancer death hazard ratio (95% CI)					
TTFC	(Referent)	2.34 (1.13 to 4.79)	2.14 (1.05 to 4.35)	3.14 (1.61 to 6.13)	3.13 (1.61 to 6.07)
FTND	(Referent)	1.89 (0.87 to 4.10)	2.06 (0.93 to 4.54)	2.22 (1.05 to 4.68)	2.88 (1.35 to 6.13)
HSI	(Referent)	2.06 (1.11 to 3.84)	2.04 (1.11 to 3.74)	2.38 (1.30 to 4.33)	3.06 (1.66 to 5.65)
Lung cancer incidence odds ratio (95% CI)					
TTFC	(Referent)	1.73 (1.16 to 2.60)	1.62 (1.09 to 2.42)	2.16 (1.48 to 3.14)	2.20 (1.52 to 3.19)
FTND	(Referent)	1.56 (1.01 to 2.42)	1.70 (1.07 to 2.68)	1.65 (1.07 to 2.53)	2.32 (1.51 to 3.58)
HSI	(Referent)	1.78 (1.23 to 2.59)	1.83 (1.28 to 2.63)	1.96 (1.37 to 2.82)	2.35 (1.61 to 3.41)
Lung cancer death odds ratio (95% CI)					
TTFC	(Referent)	2.22 (1.11 to 4.45)	2.08 (1.04 to 4.12)	3.01 (1.58 to 5.76)	2.96 (1.56 to 5.62)
FTND	(Referent)	1.78 (0.85 to 3.77)	1.96 (0.91 to 4.20)	2.10 (1.02 to 4.31)	2.68 (1.29 to 5.55)
HSI	(Referent)	1.99 (1.09 to 3.64)	1.99 (1.10 to 3.59)	2.29 (1.27 to 4.11)	2.94 (1.62 to 5.35)

*CI = confidence interval; FTND = Fagestrom test for nicotine dependence; HSI = heaviness of smoking index; TTFC = time to first cigarette.

Table 3. Prediction performance statistics for lung cancer outcomes

Model	LRT P*	Mean AUC or concordance† (SE)	ROC or concordance contrast‡		Brier score§
			Mean diff. (SE)	P	
Lung cancer death (COXPH model, Katki-Gu model)					
Without TTFC	Referent	0.77 (0.024)	Referent	Referent	—
With TTFC	<.0001	0.79 (0.023)	0.013 (0.007)	.08	—
With FTND	.0001	0.78 (0.024)	0.009 (0.006)	.14	—
With HSI	<.0001	0.78 (0.024)	0.012 (0.007)	.10	—
Lung cancer death (Logistic regression, Katki-Gu model)					
Without TTFC	Referent	0.73 (0.019)	Referent	Referent	0.0177
With TTFC	<.0001	0.74 (0.019)	0.007 (0.006)	.26	0.0177
With FTND	.0001	0.73 (0.019)	0.002 (0.005)	.69	0.0177
With HSI	<.0001	0.73 (0.019)	0.006 (0.060)	.32	0.0177
Lung cancer incidence (COXPH model, Katki-Gu model)					
Without TTFC	Referent	0.71 (0.017)	Referent	ref	—
With TTFC	<.0001	0.72 (0.017)	0.009 (0.006)	.12	—
With FTND	<.0001	0.72 (0.017)	0.008 (0.005)	.16	—
With HSI	<.0001	0.72 (0.017)	0.009 (0.006)	.12	—
Lung cancer incidence (Logistic regression, Katki-Gu model)					
Without TTFC	Referent	0.68 (0.013)	Referent	Referent	0.0390
With TTFC	<.0001	0.69 (0.013)	0.007 (0.004)	.13	0.0390
With FTND	<.0001	0.69 (0.013)	0.005 (0.004)	.26	0.0389
With HSI	<.0001	0.69 (0.013)	0.006 (0.004)	.15	0.0390
Lung cancer incidence (Logistic regression, PLCO M2012 model)					
Without TTFC	Referent	0.69 (0.013)	Referent	Referent	0.0389
With TTFC	<.0001	0.70 (0.013)	0.006 (0.004)	.16	0.0389
With FTND	<.0001	0.70 (0.013)	0.004 (0.004)	.30	0.0389
With HSI	<.0001	0.70 (0.013)	0.005 (0.004)	.23	0.0389

*Likelihood ratio test two-side P values (χ^2 test). AUC = area under the curve; FTND = Fagestrom test for nicotine dependence; HSI = heaviness of smoking index; LRT = likelihood ratio test; ROC = Receiver Operating Characteristics Curve; SE = standard error; TTFC = time to first cigarette.

†Mean AUC or concordance for logistic regression and COXPH models, respectively. Bootstrap results reported.

‡Contrast two-sided P value from Wald statistic.

§Brier score reported for logistic regression models only.

216 additional patients estimated to avoid unnecessary screening out of 6879 noncases. At the 2% threshold, the improvement in specificity was not statistically significant, but 148 additional patients were estimated to avoid unnecessary screening.

Figure 1 provides the decision curve analysis results for both outcomes, in which the NB is plotted for plausible ranges of threshold probabilities, where the maximum threshold considered for lung cancer diagnosis or death was 5%. In Figure 1, the

Table 4. Change in sensitivity and specificity for lung cancer incidence (Katki-Gu model), radiography arm

Model	Screening threshold							
	1%		2%		1%		2%	
	Sensitivity, %	No. cases correctly screened	Sensitivity, %	No. cases correctly screened	Specificity, %	No. noncases correctly predicted	Specificity, %	No. noncases correctly predicted
Lung cancer deaths								
Model without TTFC	98.65	146	91.22	135	5.96	410	33.96	2236
Model with TTFC	98.65	146	88.51	131	9.10	626	34.66	2384
Change	0	0	-2.71	-4	3.14	216	0.70	148
P*	1		.29		<.0001		.07	
Lung cancer diagnosis								
Model without TTFC	98.54	270	89.78	246	6.04	408	34.37	2321
Model with TTFC	98.54	270	87.59	240	9.24	624	35.05	2367
Change	0	0	-2.19	-6	3.20	216	0.68	46
P*	1		.15		<.0001		.09	

*Two-sided P values from McNemar statistic (23). FTND = Fagestrom test for nicotine dependence; HSI = heaviness of smoking index; TTFC = time to first cigarette.

dashed line is the net benefit curve for screening all patients regardless of their risk level, and vertical lines at 1% and 2% indicate the standard screening thresholds. A vertical separation between the “without dependence” curve and “with TTFC” or “with FTND” results would indicate a benefit for including dependence in the models. Although there is clear benefit to screening overall, there is very little added benefit when dependence measures are included in the prediction models.

Discussion

Risk prediction modeling is increasingly used in medical decision making and can be useful in both population- and individual-based settings (27,28). In lung cancer screening in which large randomized trials are not likely to be repeated, modeling is a tool used to improve screening efficiency beyond the currently accepted eligibility criteria. Although risk-based screening is not currently recommended by professional society guidelines (29), the use of individualized risk calculations have been shown to improve patient understanding and informed decision making (28). Our study examined the inclusion of tobacco-dependence measures into a risk prediction model and has two important findings. First, we confirm that higher nicotine dependence is associated with an increased risk of developing and dying from lung cancer. Secondly, we found that the addition of dependence measures to the Katki-Gu or the validated PLCOm2012 model led to statistically significant improvements in the prediction of cancer incidence or death. However, the magnitude of such gains was very small, and it is important that they be placed in a clinical perspective, as we discuss below.

Our second finding requires further discussion because the predictive performance measures in Tables 3 and 4 could support opposing conclusions. In Table 3, the LRTs were all statistically significant, but the AUC contrasts, concordance contrasts, and Brier scores did not indicate any important improvements. In Table 4, sensitivity did not improve, but specificity gains at the 1% threshold were statistically significant, although the improved values of approximately 9% for both outcomes were still extremely poor. As shown by Pepe et al. (21), the LRT that tests for statistical significance of a dependence measure also tests

the null hypothesis for no improvement in prediction performance. Further, the LRT is asymptotically the most powerful test, particularly when compared to tests for changes in AUC. We can thus conclude that prediction models with nicotine-dependence measures have statistically significant better prediction performance. However, the magnitude of such improvement is quite small based on the tests for changes in AUC, concordance, Brier score, sensitivity, and specificity. The NB statistic and decision curve (Figure 1) are designed to provide a clinical perspective, and these indicate there is little apparent added benefit for including nicotine-dependence measures in the models. It should be noted that despite the NB conclusions, clinicians could reasonably judge that the gains in specificity are important enough to justify including dependence measures.

None of the above discussion negates the utility of tobacco dependence in patient counseling. Here we confirm previous work done that demonstrates higher nicotine dependence as an independent risk factor for lung cancer diagnosis and mortality (9). Tobacco-dependence assessments may serve as important tools to help identify those who may have a more difficult time in attempting or achieving tobacco cessation. Lung cancer screening is thought to present an opportunity for a teachable moment for current smokers where consideration of a cessation attempt and a treatment plan can be discussed. Tobacco treatment is an integral part of lung cancer screening and a component of an effective comprehensive lung cancer screening program. Smoking cessation counseling within lung cancer screening is also a requirement for reimbursement by the Centers for Medicare and Medicaid (5,30). Determining the level of dependence can assist both the patient and the provider in developing a treatment plan.

Our finding differs from a recently published study that showed a small but statistically significant improvement in the prediction of lung cancer incidence when TTFC was added to the Katki-Gu model; concordance improved by 0.0079 (95% CI = 0.0019 to 0.0138, $P = .0085$) (10). The authors noted that validation on an independent population had been left for future work, and the addition of cross validation and bootstrap methods in our approach may explain this difference (10,21,31). Although we similarly conclude that models with TTFC have superior predictive performance on a statistical level, our conclusion is based on the LRT results, and we use a wide range of

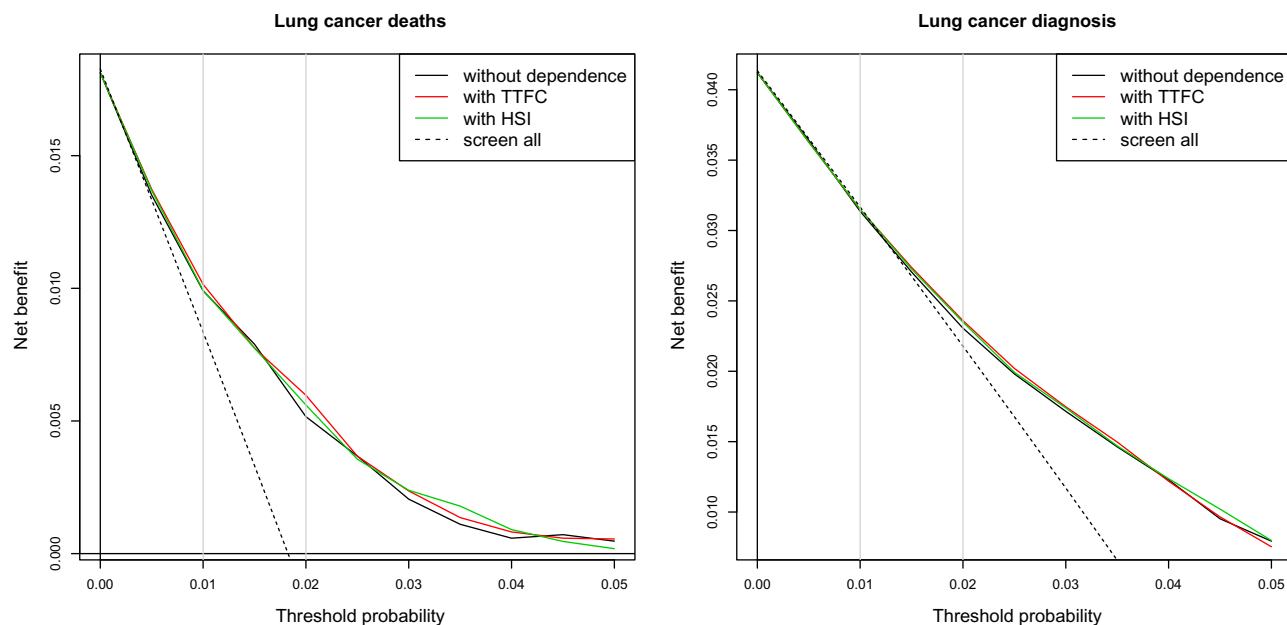


Figure 1. Decision curves for lung cancer screening, comparing lung cancer mortality and lung cancer incidence using the Katki-Gu models. HSI = heaviness of smoking index; TTFC = time to first cigarette

performance statistics to conclude that overall gains are most likely very small. We also use NB analysis to provide an additional clinical perspective that adding dependence measures to risk prediction models likely provides little additional clinical benefit.

Our analyses highlighted the many challenges involved in accurately assessing whether a new predictor can produce performance gains in established risk prediction models. Although the level of nicotine dependence is independently associated with the risk of developing and dying from lung cancer, inclusion of dependence measures into risk prediction models does not provide an apparent additional benefit at a clinical level. Nicotine-dependence measures should nonetheless be an integral tool for patient counseling and for encouraging tobacco cessation.

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Disclosures

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Notes

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MG, RW, and NT had full access to the study data and take responsibility for the integrity of the data and the accuracy of the analyses. MG and RW designed the study and led the analysis of the data. RW, MG, and NT drafted the manuscript. MG, RW, NT, and GS contributed to the interpretation and writing of the manuscript. All authors have approved the final draft.

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