ORIGINAL ARTICLE

Lung Cancer Risk Prediction Models for Asian Ever-Smokers

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ABSTRACT

Introduction: Although lung cancer prediction models are widely used to support risk-based screening, their performance outside Western populations remains uncertain. This study aims to evaluate the performance of 11 existing risk prediction models in multiple Asian populations and to refit prediction models for Asians.

Methods: In a pooled analysis of 186,458 Asian ever-smokers from 19 prospective cohorts, we assessed calibration (expected-to-observed ratio) and discrimination (area under the receiver operating characteristic curve [AUC]) for each model. In addition, we developed the "Shanghai models" to better refine risk models for Asians on the basis of two well-characterized population-based prospective cohorts and externally validated them in other Asian cohorts.

Results: Among the 11 models, the Lung Cancer Death Risk Assessment Tool yielded the highest AUC (AUC [95% confidence interval (CI)] = 0.71 [0.67–0.74] for lung cancer death and 0.69 [0.67–0.72] for lung cancer incidence) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model had good calibration overall (expected-to-observed ratio [95% CI] = 1.06 [0.90–1.25]). Nevertheless, these models substantially underestimated lung cancer risk among Asians who reported less than 10 smoking pack-years or stopped smoking more than or equal to 20 years ago. The Shanghai models were found to have marginal improvement overall in discrimination (AUC [95% CI] = 0.72 [0.69–0.74] for lung cancer death and 0.70 [0.67–0.72] for lung cancer incidence) but consistently outperformed the selected Western models among low-intensity smokers and long-term quitters.

Conclusions: The Shanghai models had comparable performance overall to the best existing models, but they improved much in predicting the lung cancer risk of low-intensity smokers and long-term quitters in Asia.

Keywords: Lung cancer; Risk prediction model; Calibration; Discrimination; Asia; Cohort

Introduction

Despite remarkable advances in diagnosis and treatment, lung cancer still accounts for approximately 1.8 million deaths worldwide each year.[1,2] Most patients with lung cancer are diagnosed at an advanced stage, and their deaths generally occur within a year of diagnosis,[3] highlighting the urgent need for establishing effective public health strategies for early detection. Building on the success of the National Lung Screening Trial and the Dutch-Belgian Randomized Lung Cancer Screening Trial,[4,5] low-dose computed tomography (LDCT) has now been applied in many Western countries for lung cancer screening. In 2013, the U.S. Preventive Services Task Force (USPSTF) issued a guideline on lung cancer screening for people aged 55 to 80 years with more than or equal to 30 pack-years who currently smoked or quit within 15 years. This guideline was amended in 2021 to annual LDCT screening for either current smokers or recent quitters of less than 15 years who had a 20 pack-year smoking history.[6] Although

LDCT screening helps lower the chances of dying from lung cancer among high-risk individuals, many concerns are also raised because of uncertainty on the benefit-to-harm ratio and the possibility of false-positive results leading to unnecessary invasive procedures and complications.[7–9] In addition, overdiagnosis issues associated with LDCT screening have now drawn considerable attention and extensive discourse.[9–11] To address the existing concerns around LDCT screening, it is important to adopt a more rigorous approach to determine screening eligibility on the basis of a personalized lung cancer risk assessment that incorporates a more comprehensive smoking history and other potential risk factors.[12–15]

In the context of risk-based lung cancer screening, lung cancer prediction models were developed in the United States and Europe[15–25] and found to have superior performance in selecting at-risk Western individuals compared with the USPSTF guidelines. Nevertheless, a major knowledge gap remains—as these prediction models were validated almost exclusively in Western white populations, little is known about how well they operate outside of that context. No external validation was conducted in non-Western settings, particularly in Asian populations who have distinct smoking patterns (e.g., low-intensity smoking and late initiation) and background risk profiles (e.g., outdoor/household air pollution) from their Western counterparts.[26,27]

Asia has emerged as the major epicenter of lung cancer: more than 50% of lung cancers worldwide occur in Asian regions,[1,2] and LDCT screening has been increasingly implemented in many Asian countries. Meanwhile, personalized lung cancer risk assessment remains limited in Asia owing to the lack of validated tools applicable to identifying at-risk Asian populations. To address this knowledge gap and unmet need, we first conducted external validation of 11 Western lung cancer prediction models in Asia; the statistical performance (i.e., calibration and discrimination) of each model was assessed using 19 prospective cohorts within the Asia Cohort Consortium (ACC). Then, to better refine risk models for Asians, we developed new prediction models incorporating Asian-specific risk estimates on the basis of two well-characterized prospective cohorts and externally validated them in other ACC cohorts, both overall and stratified by major lung cancer risk factors.

Materials and Methods

Study Populations

We used deidentified, individual-participant data from 19 prospective cohort studies participating in the ACC (Table 1). Details of the ACC and participating cohorts have been described elsewhere.[26,27] Each cohort collected baseline and outcome data according to its study protocol approved by the Institutional Review Boards and ethics committees of the hosting institutes. Of the 857,070 study participants in these cohorts, we first excluded a total of 522,416 lifelong never-smokers. Individuals missing smoking status (n = 42,809), participants with unknown follow-up times (n = 2118), and those under 50 years old (n = 103,269) were further excluded. After these exclusions, 186,458 Asian ever-smokers aged above or equal to 50 years at enrollment remained in the data analysis. Participating cohorts provided detailed smoking information, including the number of cigarettes smoked per day, ages at starting and quitting smoking, total years of smoking and after quitting. Combining and cross-checking multiple smoking-related variables allowed us to extract highly complete smoking data; the missing rates of smoking-related variables were mostly less than 10%. In the previous ACC smoking-related research projects,[26–29] we found that smoking behaviors in Asia were tightly clustered with sex and birth cohorts in each country; therefore, missing smoking-related variables were imputed by sex- and birth cohort-specific median values stratified by current and former smoking in each cohort. For bidi smoking prevalent in South Asia, one bidi was assumed to be equivalent to a quarter of a cigarette considering the weight of tobacco flakes per bidi versus cigarette.[26] Our imputation protocols and data harmonization methods were established through the previous ACC projects analyzing more than one million Asians.[26–30] Incident lung cancer cases and deaths from lung cancer or other causes were ascertained through data linkages to local and national cancer registries and death certificates and active follow-up surveys.

Evaluation of Western Lung Cancer Risk Prediction Models

A total of 11 lung cancer risk prediction models were evaluated in this study, including the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012 ($PLCO_{M2012}$),[15] the Lung Cancer Risk Assessment Tool (LCRAT),[16] the Lung Cancer Death Risk Assessment Tool (LCDRAT),[16] the Bach Model (Bach),[17] the Pittsburgh Predictor (Pittsburgh),[18] the Liverpool Lung Project Risk Model (LLP),[19,20] the LLP version 2 (v2),[21] the LLPv3,[22] the LLP Incidence Risk Model (LLPi),[23] the Spitz model (Spitz),[24] and the Hoggart model (Hoggart).[25] Details of each model are summarized in Supplementary Table 1. All models provided publicly available risk parameters to estimate a cumulative risk for lung cancer incidence or mortality at a one-time point (one to 10 years). The number of risk factors varied from four (e.g., Hoggart) to more than 10 (e.g., LCRAT and

Table 1. Participating Cohorts in the Asia Cohort Consortium

Participating Cohorts	No. of Participants[a]	Baseline Survey	Follow-up Years[b]	Age at Baseline[c]	Men (%)	Current Smokers (%)	Smoking Pack-Years[c]		Eligible USPSTF[d]		No. of Lung Cancer	
							Men	Women	2013 (%)	2021 (%)	Cases[e] (N)	Deaths (N)
Chinese												
SMHS	24,069	2002-2006	11.5	60.0	100.0	84.2	27.7	N.A.	27.1	59.4	845	695
SWHS	1584	1997-2000	15.4	63.6	0.0	81.6	N.A.	14.7	14.4	25.3	85	76
SCHS	15,816	1994-2005	11.5	64.4	82.7	53.7	31.4	15.0	35.1	52.7	906	791
SCS	8485	1986-1989	20.4	57.9	100.0	89.2	26.9	N.A.	32.0	61.0	823	801
CBCSP	3451	1991-1992	14.0	57.6	98.9	85.0	24.5	6.8	28.3	68.9	N.A.	92
Japanese												
JACC	22,699	1988-1990	14.5	62.1	90.8	64.2	28.7	14.4	34.7	54.9	1021	910
Miyagi	11,414	1990-1990	19.5	57.5	91.3	72.4	34.7	17.1	37.9	70.2	811	445
Ohsaki	16,026	1996-1996	10.3	64.2	90.0	63.9	34.8	15.4	45.6	67.3	722	486
3Pref Miyagi	6610	1984-1984	7.4	62.0	83.3	67.7	36.6	18.5	38.6	67.3	125	94
3Pref Aichi	10,374	1985-1985	11.1	61.8	81.7	64.0	38.3	18.4	37.5	66.0	317	283
LSS (RERF)	12,255	1963-1993	16.3	60.6	78.8	88.1	30.2	12.1	47.2	74.2	N.A.	574
Takayama	8369	1992-1992	12.5	63.3	83.3	58.4	25.1	11.8	23.1	40.4	302	N.A.
Korean												
KMCC	5218	1993-2004	12.1	63.5	82.0	68.7	33.4	13.7	41.7	63.7	307	257
Seoul	4818	1992-1993	15.4	54.0	100.0	62.3	24.6	N.A.	16.3	56.8	N.A.	65
KNCC	8278	2002-	8.9	57.3	94.0	39.2	24.4	9.6	20.5	48.8	155	43
Namwon	3356	2004-2007	11.6	64.2	90.2	85.5	31.7	15.8	42.0	64.2	172	127
KCS	3101	1985-1985	12.5	67.4	71.1	91.0	40.5	15.2	49.9	63.3	124	103
Indian												
Mumbai	16,093	1991-1997	4.8	60.0	99.0	73.7	12.9	5.9	7.0	15.8	52	52
Iranian												
GCS	4442	2003-2008	11.1	59.5	93.5	54.7	20.7	7.8	18.5	37.1	54	47
Total	186,458	1963-2008	12.7	61.1	89.7	68.8	28.3	14.5	31.8	55.8	6821	5941

[a]Including participants who were eligible for the current analysis: current or former smokers aged 50 years or older at enrollment.
[b]Mean follow-up years from the date of study enrollment to the date of the last follow-up.
[c]Mean values of each variable.
[d]Eligibility for low-dose computed tomography screening: 2013 guideline included adults aged 55 to 80 years who have 30 pack-years smoking and currently smoke or have quit within the past 15 years and 2021 guideline included adults aged 50 to 80 years who have 20 pack-years smoking and currently smoke or have quit within the past 15 years.
[e]Included death certificate only cases, that is, lung cancer diagnosis at death.
3Pref Aichi, Three Prefecture Cohort Study Aichi; LSS, Life Span Study; 3Pref Miyagi, Three Prefecture Cohort Study Miyagi; CBCSP, Community-Based Cancer Screening Project; GCS, Golestan Cohort Study; JACC, Japan Collaborative Cohort Study; KCS, Kangwha Cohort Study; KMCC, Korea Multi-Center Cancer Cohort; KNCC, Korean National Cancer Center Cohort; Miyagi, Miyagi Cohort Study; Mumbai, Mumbai Cohort Study; N.A., not applicable; Namwon, The Namwon Study; Ohsaki, Ohsaki National Health Insurance Cohort Study; SCHS, Singapore Chinese Health Study; SCS, Shanghai Cohort Study; Seoul, Seoul Male Cohort Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; Takayama, Takayama study; USPSTF, United States Preventive Services Task Force.

LCDRAT), including demographics, smoking habits, personal and family histories of lung diseases and cancer beyond the USPSTF guideline. Most risk factors were available in all participating cohorts, except asbestos exposure and hay fever symptoms, which were assumed not to be exposed in our analyses.

Individual risks of developing or dying from lung cancer were calculated using the publicly available R package *lcmodels* (https://dceg.cancer.gov/tools/risk-assessment/lcmodels).[31] This R package uses the risk calculation procedures of nine risk models, including the $PLCO_{M2012}$ (6-y time horizon), LCRAT (5-y), LCDRAT (5-y), Bach (10-y), Pittsburgh (6-y), LLP (5-y), LLPi (8.7-y), Spitz (1-y), and Hoggart (1-y). For LLPv2 and LLPv3 models, risk estimates (5-y) were calculated directly using the updated parameters and the age-standardized lung cancer incidence data.[22]

Development of Asian Lung Cancer Risk Prediction Models

To develop lung cancer risk models better tailored to Asian populations, we fit two absolute risk models using data on Chinese ever-smokers within the Shanghai Men's and Women's Health Studies. The Shanghai lung cancer incidence model (Shanghai-LCM) and Shanghai lung cancer death model (Shanghai-LCDM) were each built on the basis of cause-specific proportional hazards models, taking into account the competing mortality hazard.[32] To make the prediction models more comparable to Western models and more applicable for LDCT screening, we truncated the follow-up time at 10 years. Events that occurred after 10 years of enrollment were treated as censoring. Thus, both Shanghai-LCM and Shanghai-LCDM were built to predict the 1- to 10-year cumulative risk of developing or dying from lung cancer, respectively. No significant violations of the proportional hazards assumption were found. Model parameters, coding, and the definitions of variables used for model building are given in the appendix (Supplementary Tables 2–4). The Shanghai models include the same predictors as the Western ones (LCRAT and LCDRAT) to facilitate cross-model comparison; data on these predictors are available from all participating Asian cohorts. Included predictors were sociodemographic factors (age, sex, and educational attainment), body mass index, history of chronic obstructive pulmonary disease, family history of lung cancer (number of lung cancer cases in first-degree relatives), and smoking history (smoking status, number of cigarettes smoked per day, total years smoked, pack-years of smoking, and years since smoking cessation). The linearity of associations for continuous variables was assessed by the best combination of their transformed values, such as linear, log, and square root. Other emerging risk factors, for example, cooking fuels and outdoor air pollution, were not considered as predictors because most ACC cohorts did not collect the relevant data. Internal validation was performed to correct overfitting in the prediction models with Harrell's bootstrap-based bias correction method.[33,34] External validation was conducted using individual participant data from the other 17 ACC cohorts, excluding the Shanghai Men's and Women's Health Studies.

Statistical Analysis

Model validity was assessed on the basis of calibration and discrimination. Calibration was evaluated as the ratio of expected (the number of events predicted by each model) to observed (the exact number of events within each time frame) lung cancer cases or deaths. Generally, expected-observed (E/O) ratios less than one indicate an underestimation of the risk, and those greater than one indicate an overestimation. The discriminative ability was evaluated by the area under the receiver operating characteristic curve (AUC) statistics ranging from 0.5 to 1.0—the AUC value of 0.5 indicates no discrimination, equivalent to random selection. For each model, we calculated E/O and AUC statistics using only the cases occurring within the corresponding time frame designated by each model, for example, for $PLCO_{m2012}$, we analyzed cases occurring within 6 years of enrollment. Given the potential inter-study variability, we first estimated cohort-specific statistics and then combined them with a random-effects model.[35,36] Calibration and discrimination were evaluated overall and by ethnic groups, smoking history, and other major risk factors for lung cancer. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.0.4, the *rms* package.

Results

Analytic Sample Across Each Participating Cohort

Among 186,458 Asian ever-smokers, 6821 incident lung cancer cases and 5941 deaths from lung cancer were ascertained during a mean follow-up of 12.7 years. The mean age at baseline was 61.1 years, and most study participants were men (89.7%), mirroring typical smoking patterns in Asia. The prevalence of current smoking was almost 70%. Male ever-smokers had an average of 28.3 pack-years of smoking, whereas female counterparts had a corresponding 14.5 pack-years. Only 32% of the study participants were deemed screening eligible according to the 2013 USPSTF criteria, but the amended 2021 recommendation designated approximately 56% as screening eligible (Table 1).

Baseline Characteristics

The baseline characteristics of the total study population are presented in Table 2. Among 128,340 Asians who currently smoked and 58,118 who stopped smoking, 1397 and 486 individuals developed lung cancer within five years of enrollment, respectively. In addition, a total of 1312 deaths from lung cancer were confirmed during this period. Of note, approximately 20% of Asian smokers reported less than 10 smoking pack-years during their lifetime (31.4% of former smokers and 14.4% of current smokers) and 25% of former smokers quit smoking more than or equal to 20 years ago. Approximately 75% of the current smokers diagnosed with having lung cancer met the new USPSTF screening criteria. Nevertheless, less than half of the quitters with lung cancer were eligible for LDCT screening, indicating that the USPSTF guidelines might not be practical enough to identify at-risk former smokers in Asia. When comparing individuals who developed incident lung cancer and those who did not (Supplementary Table 5), lung cancer cases had a higher likelihood of being older and current smokers, having a greater cumulative exposure to smoking, having a lower level of educational attainment, and having a history of lung disorders.

External Validation of Western Models in Asian Populations

Western models revealed moderate performance in discriminating lung cancer cases from noncases in Asian populations (Fig. 1). The highest AUC was observed for LCDRAT (AUC [95% confidence interval or CI] = 0.71 [0.67–0.74]), followed by LCRAT (0.69 [0.67–0.72]). Meanwhile, $PLCO_{m2012}$ was best calibrated (E/O [95% CI] = 1.06 [0.90–1.25]), followed by LLPv3 (1.09 [0.89–1.30]), Bach (1.48 [1.26–1.74]), LCRAT (1.55 [1.30–1.86]), Pittsburgh (1.56 [1.30–1.86]), and LCDRAT (1.67 [1.39–2.00]). Cohort-specific statistics for calibration and discrimination highlighted substantial variations across ethnicity and risk models (Supplementary Tables 6 and 7 and Supplementary Fig. 1). Overall, the $PLCO_{m2012}$, LCRAT, and LCDRAT seemed to yield relatively good performance in Asian populations. Nevertheless, these models substantially underestimated lung cancer risk among Asians who stopped smoking a long time ago (E/O [95% CI] for $\geq$20 y = 0.48 [0.34–0.78] for $PLCO_{m2012}$, 0.55 [0.39–0.76] for LCRAT, and 0.60 [0.38–0.95] for LCDRAT) or who reported low-intensity smoking (E/O [95% CI] for <10 pack-years and <10 cigarettes smoked per day = 0.19 [0.14–0.26] and 0.24 [0.18–0.33] for $PLCO_{m2012}$, respectively; Table 3). When comparing the average predicted versus observed cumulative incidence/mortality risks per 100,000 persons across the risk groups (quintiles), the $PLCO_{m2012}$ revealed a relatively high level of miscalibration in low-risk groups, whereas LCRAT and LCDRAT tended to have a high level of miscalibration in the high-risk groups (Supplementary Fig. 2).

Development and Validation of Shanghai Models

Model parameters and their coefficients for developing the Shanghai-LCM and Shanghai-LCDM are listed in Supplementary Tables 3 and 4. Age was the most critical risk factor for both lung cancer incidence and mortality. Lower education, higher smoking intensity, and family history of lung cancer were found to have significant positive associations with lung cancer outcomes, whereas body mass index and cessation years had significant inverse associations, all of which agree with the general patterns observed in Western models. Notably, in the Shanghai-LCDM, even less than 10 years of smoking held a great magnitude of the hazards of lung cancer deaths.

The Shanghai-LCM and Shanghai-LCDM had good internal validity, with AUCs of 0.78 and 0.80, respectively (Supplementary Table 8). In terms of external validity (Table 4), Shanghai models yielded marginal improvement in discrimination (AUC [95% CI] = 0.72 [0.69–0.74] for lung cancer death and 0.70 [0.67–0.72] for lung cancer incidence). An overall tendency toward overestimation was suggested in high-risk groups (Supplementary Fig. 3). Substantial variations in both calibration and discrimination were still detected across ethnicity and cohort, similar to those observed in Western models (Supplementary Table 9). Nevertheless, in contrast to the Western models, both Shanghai models yielded much more stable E/O ratios and AUCs among Asians with low-intensity smoking or long-term cessation: for less than 10 smoking pack-years and more than or equal to 20 years since quitting, E/O ratios ranged from 0.88 to 1.15 and AUCs ranged from 0.69 to 0.77 (Table 4). In addition, the average calibration for Chinese ethnicity was substantially improved (Supplementary Fig. 3).

Discussion

In 186,458 Asian ever-smokers from 19 prospective cohorts, most models developed in the United States and Europe had reasonable discriminatory ability and typical overestimation of lung cancer risk. The $PLCO_{m2012}$, LCRAT, and LCDRAT performed relatively better than other models overall, but poorly in predicting lung cancer risk among Asians who reported low-intensity smoking or who had quit smoking for prolonged periods. Although the Shanghai-LCM and Shanghai-LDCM performed comparably to the best Western models in general, their ability to predict the risk of low-intensity

Table 2. Baseline Characteristics of Ever-Smokers in Participating Cohorts

Characteristics	Total (N = 186,458)	Current Smokers (n = 128,340)	Former Smokers (n = 58,118)
Incident lung cancer cases,[a] *n*			
Within 1 y	381	269	112
Within 5 y	1883	1397	486
Within 6 y	2312	1715	597
Within 8.7 y	3485	2663	822
Within 10 y	4030	3098	932
Lung cancer deaths within 5 y, *n*	1312	965	347
Eligible subjects for screening,[b] (%)			
Among total participants, USPSTF 2013	31.8	37.4	19.3
Among lung cancer cases, USPSTF 2013	49.3	53.4	33.1
Among total participants, USPSTF 2021	55.8	66.1	33.0
Among lung cancer cases, USPSTF 2021	68.9	75.2	43.5
Age at baseline, y (%)			
50-59	47.6	52.3	37.2
60-69	36.8	35.4	39.7
≥70	15.7	12.3	23.0
Sex, (%)			
Men	89.7	88.9	91.5
Women	10.3	11.1	8.5
Smoking pack-years, (%)			
<10	19.7	14.4	31.4
10-19	20.4	19.0	23.7
20-29	16.3	16.3	16.3
30-39	22.2	26.5	12.7
≥40	21.3	23.8	15.8
Cigarettes smoked/d, (%)			
<10	19.8	19.8	19.7
10-19	33.6	34.8	30.9
20-29	33.9	34.2	33.3
≥30	12.7	11.2	16.1
Years since quitting, (%)			
<5	29.0	N.A.	29.0
5-9	18.1	N.A.	18.1
10-14	15.0	N.A.	15.0
15-19	12.9	N.A.	12.9
≥20	25.0	N.A.	25.0
Education, (%)			
No schooling or primary education	58.0	58.4	57.1
High school graduation	24.8	25.2	24.1
Associate degree or some college	7.5	7.8	6.7
University degree	8.6	7.9	10.1
Graduate school	1.1	0.8	1.9
Body mass index, (%)			
Underweight, <18.5	8.5	9.3	6.7
Normal, 18.5-24.9	68.6	70.0	65.8
Overweight, 25.0-29.9	20.7	18.7	24.9
Obese, ≥30.0	2.2	2.0	2.7
Disease history, (%)			
Cancer	1.8	1.4	2.7
Lung diseases	2.5	2.2	3.2
Family history of lung cancer,[c] (%)			
None	97.6	97.7	97.4
1	2.3	2.2	2.5
≥2	0.1	0.1	0.1

[a]Number of newly diagnosed lung cancer cases across the multiple time frames defined by lung cancer risk models.
[b]Eligibility for low-dose computed tomography screening according to the USPST guidelines.
[c]No. of family members with a history of lung cancer.
USPSTF 2013, United States Preventive Services Task Force 2013 Guideline; USPSTF 2021, US Preventive Services Task Force Guideline.

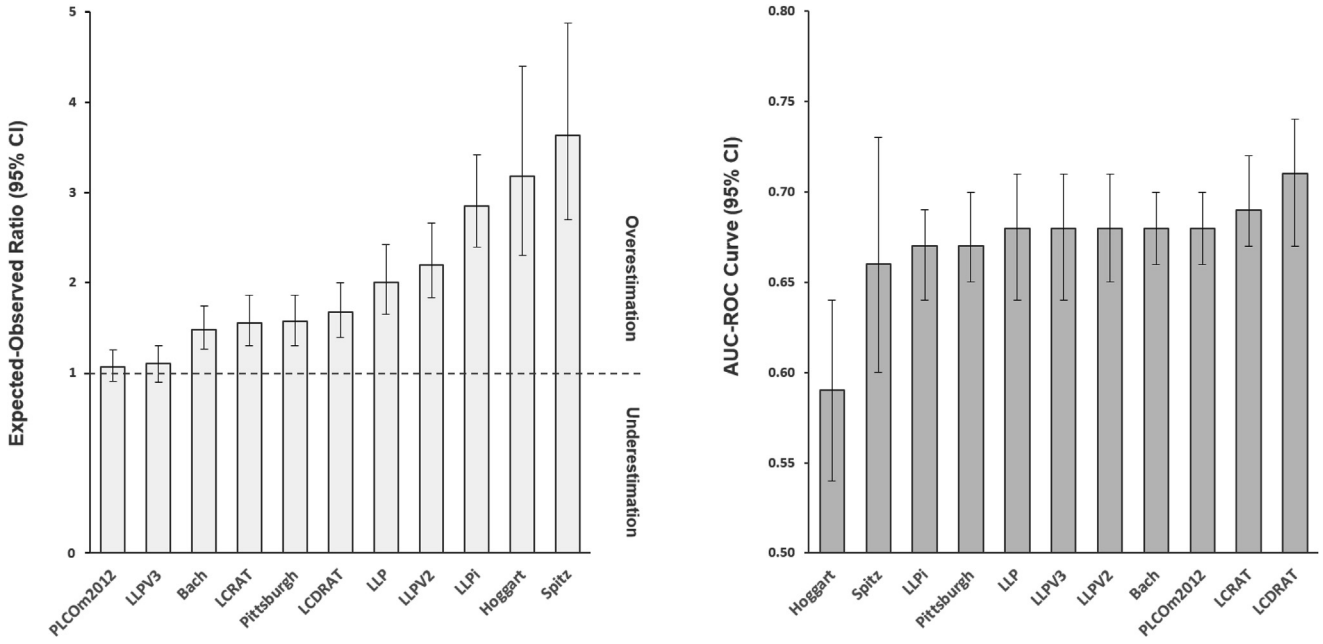

Figure 1. Calibration and discrimination of western lung cancer risk models in Asian populations. Expected-observed ratios less than 1 indicate underestimation of the risk and those greater than 1 indicate overestimation of the risk. The AUC value of 0.50 indicates no discrimination (equivalent to random selection). Error bars represent 95% confidence intervals. AUC-ROC curve, area under the receiver operating characteristic curve; Bach, Bach model; Hoggart, the Hoggart model; LCDRAT, Lung Cancer Death Risk Assessment Tool; LCRAT, Lung Cancer Risk Assessment Tool; LLP, Liverpool Lung Project Risk Model; LLPi, Liverpool Lung Project Incidence Risk Model; Pittsburgh, Pittsburgh Predictor; PLCOm2012, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012; Spitz, Spitz model.

smokers and long-term quitters in Asia was considerably enhanced. These findings indicate the importance of incorporating Asia-specific risk estimates into personalized lung cancer risk assessment to better implement risk-based LDCT screening in Asia.

Lung cancer risk prediction models are expected to better identify individuals most likely to benefit from LDCT screening than the USPSTF guideline, which is based solely on age and pack-years smoked.[12–16] The risk models evaluated in our study have been externally validated in the United States, United Kingdom, Europe, North America, and Australia,[13,20,31,37–41] revealing their complementary potential for implementing personalized LDCT screening. In Western populations, the $PLCO_{m2012}$, Bach, LCRAT, and LCDRAT models were generally found to be well calibrated and had moderate-to-good discriminatory power (AUCs mostly >0.70 up to >0.80).[13,20,31,37–41] Nevertheless, these models underperformed in some study populations, which might be due to differences in the variance of key model predictors (e.g., age and smoking characteristics) across the tested populations. Before our study, it was unclear whether Western models would perform well in Asians owing to their smoking patterns being distinct from those of their Western counterparts.[26,27] This issue had not yet been fully investigated, although Asia is the leading region outside of North America and Europe where LDCT screening has been actively implemented. The current study, the largest external validation in multiple Asian populations, revealed that Western models generally underperformed in identifying high-risk Asians who might benefit from LDCT screening (E/O ratios ranging from 1.05 to 3.62 and AUCs mostly <0.70). The $PLCO_{m2012}$, LCRAT, and LCDRAT models, having relatively good performance in Asian ever-smokers, still need to be refined, particularly for those with low-intensity smoking or long-term cessation.

The underperformance of Western models in Asians may be explained by the difference in the magnitude of the associations between predictors and lung cancer risk across Asian and Western countries. It is worth noting that even among individuals with similar smoking histories, the risk of developing or dying from lung cancer has been reported to be much lower in Asia compared with the West. Our previous analysis of more than 1 million Asians revealed that the overall risk estimates for lung cancer mortality attributable to tobacco smoking were comparable to those for Americans with low-intensity smoking.[27] The same is true when comparing Asian-Americans to European-Americans at the same level of smoking intensity.[42] The distinctive smoking patterns in Asia, such as low intensity, late initiation, bidi

Table 3. Calibration and Discrimination of Western Lung Cancer Risk Models: Stratified by Risk Factors

	Expected-to-Observed Ratio (95% CI)			AUC (95% CI)		
Stratification	$PLCO_{m2012}$	LCRAT	LCDRAT	$PLCO_{m2012}$	LCRAT	LCDRAT
Total study population	1.06 (0.90-1.25)	1.55 (1.30-1.86)	1.67 (1.39-2.00)	0.68 (0.66-0.70)	0.69 (0.67-0.72)	0.71 (0.67-0.74)
Ethnicity						
Chinese	0.73 (0.63-0.83)	1.19 (1.07-1.31)	1.07 (0.98-1.18)	0.69 (0.64-0.74)	0.70 (0.64-0.77)	0.70 (0.64-0.77)
Japanese	1.26 (1.05-1.51)	1.66 (1.35-2.06)	1.78 (1.42-2.24)	0.68 (0.64-0.73)	0.69 (0.65-0.73)	0.69 (0.65-0.74)
Korean	1.04 (0.62-1.76)	1.27 (0.76-2.12)	1.73 (1.14-2.63)	0.67 (0.64-0.71)	0.69 (0.66-0.72)	0.73 (0.67-0.80)
Indian	1.51 (1.13-2.02)	5.58 (3.95-7.89)	5.06 (3.39-7.55)	0.60 (0.52-0.69)	0.62 (0.53-0.72)	0.64 (0.55-0.75)
Iranian	1.63 (1.08-2.48)	2.58 (1.60-4.14)	1.94 (1.19-3.16)	0.70 (0.61-0.81)	0.75 (0.65-0.86)	0.75 (0.64-0.87)
Age, y						
50-59	1.09 (0.87-1.38)	1.72 (1.36-2.17)	1.55 (1.24-1.95)	0.68 (0.65-0.72)	0.67 (0.65-0.68)	0.66 (0.64-0.68)
60-69	0.90 (0.77-1.06)	1.40 (1.16-1.68)	1.48 (1.25-1.75)	0.65 (0.63-0.67)	0.65 (0.63-0.68)	0.67 (0.65-0.69)
≥70	1.37 (1.08-1.74)	1.66 (1.32-2.09)	1.77 (1.36-2.30)	0.69 (0.67-0.72)	0.70 (0.68-0.72)	0.72 (0.70-0.74)
Sex						
Men	1.07 (0.90-1.26)	1.52 (1.27-1.83)	1.59 (1.33-1.90)	0.68 (0.65-0.70)	0.68 (0.66-0.71)	0.69 (0.66-0.73)
Women	1.33 (0.90-1.97)	1.95 (1.47-2.60)	2.01 (1.38-2.91)	0.69 (0.59-0.82)	0.70 (0.62-0.80)	0.82 (0.75-0.89)
Smoking status						
Current	1.11 (0.93-1.33)	1.68 (1.39-2.03)	1.82 (1.48-2.23)	0.68 (0.66-0.70)	0.69 (0.66-0.72)	0.70 (0.67-0.74)
Former	0.86 (0.69-1.07)	1.12 (0.88-1.42)	1.09 (0.85-1.42)	0.68 (0.64-0.73)	0.65 (0.60-0.71)	0.70 (0.65-0.76)
Smoking pack-years						
<10	0.19 (0.14-0.26)	1.26 (0.84-1.88)	1.38 (0.83-2.28)	0.58 (0.54-0.63)	0.65 (0.59-0.71)	0.72 (0.66-0.78)
10-19	0.62 (0.49-0.77)	1.33 (1.02-1.75)	1.45 (1.10-1.90)	0.62 (0.58-0.67)	0.65 (0.60-0.71)	0.69 (0.61-0.78)
20-29	1.05 (0.84-1.31)	1.16 (0.97-1.39)	1.05 (0.84-1.31)	0.67 (0.63-0.72)	0.69 (0.63-0.76)	0.71 (0.65-0.77)
30-39	1.12 (0.89-1.41)	1.49 (1.19-1.86)	1.57 (1.23-2.01)	0.64 (0.60-0.69)	0.65 (0.58-0.72)	0.64 (0.58-0.72)
≥40	1.34 (1.11-1.63)	1.67 (1.38-2.02)	1.68 (1.36-2.08)	0.61 (0.58-0.65)	0.63 (0.59-0.67)	0.62 (0.56-0.68)
Cigarettes smoked/d						
<10	0.24 (0.18-0.33)	1.59 (1.18-2.15)	1.90 (1.30-2.76)	0.63 (0.58-0.69)	0.72 (0.64-0.80)	0.81 (0.76-0.86)
10-19	1.00 (0.80-1.24)	1.35 (1.11-1.64)	1.39 (1.16-1.67)	0.70 (0.66-0.73)	0.69 (0.65-0.73)	0.68 (0.63-0.72)
20-29	1.22 (1.03-1.46)	1.46 (1.23-1.73)	1.55 (1.28-1.88)	0.68 (0.64-0.72)	0.69 (0.65-0.73)	0.71 (0.66-0.78)
≥30	1.25 (1.02-1.54)	1.56 (1.26-1.94)	1.61 (1.27-2.03)	0.68 (0.60-0.76)	0.69 (0.62-0.76)	0.71 (0.63-0.80)
Years since quitting smoking						
<5	0.98 (0.76-1.27)	1.50 (1.11-2.03)	1.26 (0.91-1.77)	0.70 (0.65-0.75)	0.67 (0.60-0.74)	0.76 (0.69-0.83)
5-9	0.99 (0.78-1.27)	1.08 (0.84-1.40)	0.85 (0.67-1.09)	0.71 (0.63-0.80)	0.67 (0.56-0.81)	0.76 (0.68-0.84)
10-14	0.83 (0.64-1.07)	0.89 (0.66-1.19)	0.93 (0.70-1.24)	0.67 (0.57-0.78)	0.69 (0.55-0.81)	0.62 (0.51-0.76)
15-19	0.63 (0.48-0.83)	0.73 (0.56-0.94)	0.77 (0.51-1.15)	0.67 (0.58-0.78)	0.67 (0.57-0.78)	0.64 (0.52-0.80)
≥20	0.48 (0.34-0.78)	0.55 (0.39-0.76)	0.60 (0.38-0.95)	0.64 (0.55-0.73)	0.71 (0.64-0.79)	0.68 (0.59-0.77)
Education						
<High school graduation	1.10 (0.91-1.32)	1.52 (1.28-1.82)	1.55 (1.27-1.91)	0.67 (0.64-0.69)	0.68 (0.65-0.71)	0.70 (0.66-0.74)
≥High school graduation	0.86 (0.73-1.02)	1.35 (1.04-1.75)	1.52 (1.24-1.86)	0.70 (0.68-0.72)	0.71 (0.69-0.73)	0.68 (0.62-0.75)
Body mass index						
<18.5	1.03 (0.85-1.25)	1.53 (1.18-1.97)	1.81 (1.30-2.52)	0.65 (0.59-0.72)	0.68 (0.61-0.75)	0.67 (0.60-0.76)
18.5-24.9	1.02 (0.86-1.22)	1.50 (1.26-1.79)	1.52 (1.29-1.80)	0.68 (0.66-0.71)	0.69 (0.66-0.72)	0.70 (0.67-0.74)
≥25	1.09 (0.88-1.36)	1.57 (1.26-1.96)	1.57 (1.28-1.93)	0.70 (0.66-0.74)	0.66 (0.57-0.76)	0.74 (0.68-0.81)

AUC, area under the receiver operating characteristic curve; CI, confidence interval; LCDRAT, Lung Cancer Death Risk Assessment Tool; LCRAT, Lung Cancer Risk Assessment Tool; PLCOm2012, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012.

use, and extremely low prevalence of female smoking, might have an impact on shaping Asian-specific underlying risk for lung cancer. It is possible that Western risk models were unable to reflect the underlying risk in Asian populations appropriately, especially for those with low-intensity smoking or long-term smoking cessation, thus resulting in the observed poor performance. This possibility is supported by our findings that Shanghai models refitting risk estimates for Chinese enhanced predictive performance in Asians with low-intensity smoking or long-term cessation without adding additional predictors. In addition to smoking-related factors, we should also address other unique features in Asia. For instance, approximately 60% of our study participants fell into the lowest educational level, that is, no schooling or primary education only, which could

Table 4. Calibration and Discrimination of Shanghai Lung Cancer Risk Models[a]: Stratified by Risk Factors

	Expected to Observed Ratio (95% CI)		AUC (95% CI)	
Stratification	Shanghai-LCM	Shanghai-LCDM	Shanghai-LCM	Shanghai-LCDM
Total study population	1.55 (1.24-1.93)	1.80 (1.44-2.25)	0.70 (0.67-0.72)	0.72 (0.69-0.74)
Ethnicity				
Chinese	0.98 (0.89-1.08)	1.08 (0.85-1.38)	0.70 (0.65-0.76)	0.69 (0.63-0.77)
Japanese	1.70 (1.36-2.13)	1.97 (1.52-2.55)	0.70 (0.66-0.75)	0.71 (0.67-0.75)
Korean	1.20 (0.73-1.99)	1.72 (1.11-2.66)	0.69 (0.66-0.72)	0.75 (0.68-0.81)
Indian	4.24 (3.00-6.00)	4.39 (2.94-6.55)	0.64 (0.55-0.74)	0.65 (0.54-0.76)
Iranian	2.75 (1.71-4.42)	2.31 (1.41-3.77)	0.74 (0.64-0.84)	0.75 (0.65-0.85)
Age, y				
50-59	1.67 (1.27-2.19)	1.79 (1.37-2.33)	0.68 (0.64-0.71)	0.67 (0.64-0.71)
60-69	1.45 (1.15-1.82)	1.64 (1.31-2.05)	0.65 (0.62-0.67)	0.66 (0.64-0.68)
≥70	1.65 (1.27-2.14)	1.89 (1.40-2.54)	0.71 (0.69-0.73)	0.71 (0.68-0.75)
Gender				
Men	1.52 (1.22-1.89)	1.77 (1.43-2.18)	0.69 (0.66-0.71)	0.70 (0.67-0.73)
Women	1.85 (1.21-2.83)	1.78 (1.06-2.98)	0.76 (0.69-0.84)	0.84 (0.78-0.91)
Smoking status				
Current	1.58 (1.25-1.99)	1.88 (1.47-2.40)	0.70 (0.68-0.71)	0.71 (0.68-0.74)
Former	1.40 (1.09-1.79)	1.45 (1.13-1.87)	0.69 (0.65-0.74)	0.70 (0.60-0.81)
Smoking pack-years				
<10	0.88 (0.64-1.22)	1.15 (0.78-1.70)	0.70 (0.63-0.78)	0.77 (0.71-0.83)
10-19	1.36 (1.00-1.86)	1.65 (1.21-2.26)	0.69 (0.64-0.74)	0.72 (0.65-0.80)
20-29	1.52 (1.19-1.93)	1.53 (1.17-2.01)	0.71 (0.65-0.78)	0.72 (0.65-0.79)
30-39	1.45 (1.10-1.91)	1.71 (1.27-2.30)	0.66 (0.63-0.70)	0.67 (0.62-0.71)
≥40	1.64 (1.30-2.06)	1.73 (1.35-2.21)	0.64 (0.60-0.67)	0.67 (0.62-0.71)
Cigarettes smoked/d				
<10	1.15 (0.79-1.67)	1.66 (1.03-2.67)	0.71 (0.63-0.80)	0.81 (0.75-0.87)
10-19	1.52 (1.19-1.94)	1.77 (1.38-2.26)	0.70 (0.66-0.74)	0.69 (0.65-0.74)
20-29	1.48 (1.20-1.82)	1.67 (1.33-2.11)	0.69 (0.66-0.72)	0.70 (0.64-0.77)
≥30	1.53 (1.18-1.99)	1.69 (1.29-2.22)	0.69 (0.62-0.78)	0.73 (0.66-0.82)
Years since quitting smoking				
<5	1.58 (1.12-2.24)	1.55 (1.02-2.35)	0.63 (0.53-0.74)	0.68 (0.58-0.80)
5-9	1.28 (0.95-1.73)	1.01 (0.78-1.32)	0.76 (0.67-0.87)	0.83 (0.76-0.91)
10-14	1.09 (0.83-1.42)	1.11 (0.81-1.52)	0.66 (0.54-0.80)	0.68 (0.55-0.84)
15-19	1.08 (0.79-1.48)	1.02 (0.66-1.59)	0.73 (0.68-0.79)	0.74 (0.64-0.86)
≥20	0.88 (0.65-1.19)	0.94 (0.67-1.32)	0.70 (0.63-0.77)	0.69 (0.63-0.76)
Education				
<High school graduation	1.63 (1.32-2.01)	1.83 (1.45-2.32)	0.69 (0.66-0.72)	0.71 (0.68-0.74)
≥High school graduation	1.07 (0.79-1.44)	1.26 (0.95-1.68)	0.71 (0.69-0.74)	0.71 (0.66-0.77)
Body mass index				
<18.5	1.95 (1.49-2.56)	2.35 (1.75-3.17)	0.66 (0.58-0.75)	0.63 (0.55-0.72)
18.5-24.9	1.47 (1.20-1.81)	1.64 (1.33-2.03)	0.69 (0.67-0.71)	0.71 (0.68-0.73)
≥25	1.39 (1.04-1.84)	1.56 (1.15-2.12)	0.73 (0.67-0.79)	0.77 (0.70-0.84)

[a]External validation using individual participant data from 17 cohorts, excluding the SMHS and SWHS.
AUC, area under the receiver operating characteristic curve; CI, confidence interval; LCM, lung cancer incidence model; LCDM, lung cancer death model.

lead to higher E/O ratios (overestimation of risk) when applying Western models directly without refinement. Meanwhile, little variance in the main predictors—a narrow age range restricted to above 50 years old and clusters of men and normal weight—might explain in part the low AUCs we observed, considering that AUCs generally increase with more variance in the main predictors. Taken all together, the direct application of Western risk prediction models to Asians needs to be cautious and may possibly lead to inaccurate risk estimation and inferior discrimination.

When incorporating risk estimates from Shanghai cohorts into the risk models, predictive performance improved marginally overall, but greatly for Asians with low-intensity smoking or long-term cessation whose risks were not accurately estimated by Western models.

Despite the improvement, Shanghai models also have room to be refined for universal application to diverse Asian populations. Our previous studies revealed that each Asian country was experiencing the tobacco epidemic at a different stage, resulting in country-specific epidemiologic patterns of smoking.[26,27] Substantial differences in the population-attributable risk for lung cancer deaths owing to tobacco smoking have also been reported across different Asian settings.[27] These aspects of variation might cause the underperformance of Shanghai models in some ethnicities such as Indian and Iranian. Although it is possible that Shanghai models could not capture ethnic differences well, we should also acknowledge several practical limitations that might affect higher E/O ratios and lower AUCs in Indians and Iranians. Only one cohort was included from each of these countries and very few lung cancer cases and deaths (approximately 50 or less) were available per cohort. In addition, the Indian cohort had a much shorter mean follow-up time compared with other cohorts. These limitations might contribute to the poor performance of Shanghai models, including Western models, among Indians and Iranians. Further evaluations with sufficient statistical power are warranted to confirm how successfully Shanghai models predict future lung cancer risk in these diverse Asian ethnicities.

Very recently, lung cancer mortality risk prediction models targeted at Asian populations were developed using the China Kadoorie Biobank (149,832 Chinese ever-smokers and 330,283 never-smokers).[43] The Asian Lung Cancer Absolute Risk Models (ALARM) were built separately for never- and ever-smokers with consideration of two novel risk factors, that is, lung function (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC]) and cooking fuel exposure (excluded from the final model owing to the lack of improvement of model performance), collected in 10 regions in China. When fitted in the training (75%) data and internally validated in the holdout testing (25%) data, the ALARM had comparable discriminatory ability to LCDRAT but better calibration for a Chinese population, which is in line with our findings. Nevertheless, no external validation has been conducted yet in other Asian populations. Unfortunately, these models could not be evaluated in our study because of the unavailability of FEV_1/FVC in ACC cohorts. In fact, FEV_1/FVC data are rarely collected in population-based settings, including cohort studies, especially for healthy individuals without any apparent symptoms of lung disease. Whether the ALARM could improve the prediction of lung cancer mortality in non-Chinese Asian ethnicities remains unknown; however, this study suggests that adding clinical parameters can improve the predictive performance of models. Further research to develop more accurate lung cancer prediction models and justify their widespread utilization should also consider evaluating whether blood biomarkers could enhance risk prediction.[44]

To the best of our knowledge, this study is the largest investigation into the comparative performance of lung cancer risk models in multiple Asian populations. We evaluated 11 Western risk models and the newly developed Shanghai models by analyzing 19 prospective cohorts representing various Asian ethnicities. The Shanghai models improved predictive performance for low-intensity smokers and long-term quitters who were particularly prevalent in Asia but not captured well by Western models. Our findings provide additional support for applying personalized lung cancer risk assessment in LDCT screening in Asian countries. Nonetheless, our study has several limitations. First, some parameters, for example, asbestos exposure, history of hay fever, and cigar/pipe smoking, were unavailable in most participating cohorts and assumed not to be exposed—several Western models using pertinent information (i.e., Bach, Spitz, and LLP/LLPv2/LLPv3) might yield decreased E/O ratios to a certain degree. Second, data completeness and quality somewhat varied by cohort. Nevertheless, the impact of this limitation should be marginal because overall estimates remained consistent when comparing imputation analysis to complete case analysis (Supplementary Table 10). Third, approximately 90% of the study participants were men who were mostly recruited in the 1980s and 1990s. Thus, our findings might not be fully applicable to female ever-smokers or younger generations in Asia. In addition, the potential influence of the birth cohort cannot be ruled out owing to the broad range of baseline survey periods across the participating cohorts. Fourth, the newly developed Shanghai models used the same predictors as the Western models, which could limit the further improvement of model performance. Finally, measurement error and completeness of outcome ascertainment remain concerns, despite using validated questionnaires and standardized survey protocols for follow-up.

In conclusion, the $PLCO_{m2012}$, LCRAT, and LCDRAT had good predictive performance in Asian populations but performed poorly in predicting lung cancer risk for low-intensity smokers or long-term quitters in Asia. The latter limitation was overcome by the newly developed Shanghai models. Our findings suggest that Shanghai models may facilitate the identification of at-risk Asians who are more eligible for LDCT screening and the implementation of personalized lung cancer risk assessment in Asia. Furthermore, our findings indicate that it is imperative to develop preventive strategies for individuals who are at high risk but fall outside the current LDCT screening criteria to reduce their potential

risk of developing or dying from lung cancer and to more equitably disseminate the benefits of LDCT screening.

CRediT Authorship Contribution Statement

Xiao-Ou Shu and Hilary A. Robbins: Conception and design, Financial support.

Sarah K. Abe, Md. Shafiur Rahman, Md. Rashedul Islam, and Eiko Saito: Administrative support.

Prakash C. Gupta, Akiko Tamakoshi, Woon-Puay Koh, Yu-Tang Gao, Ritsu Sakata, Ichiro Tsuji, Reza Malekzadeh, Yumi Sugawara, Jeongseon Kim, Hidemi Ito, Chisato Nagata, San-Lin You, Sue K. Park, Jian-Min Yuan, Myung-Hee Shin, Sun-Seog Kweon, Sang-Wook Yi, Mangesh S. Pednekar, Takashi Kimura, Hui Cai, Yukai Lu, Arash Etemadi, Seiki Kanemura, Keiko Wada, Chien-Jen Chen, Aesun Shin, Renwei Wang, Yoon-Ok Ahn, Myung-Hee Shin, Heechoul Ohrr, Habibul Ahsan, Paolo Boffetta, Kee Seng Chia, Keitaro Matsuo, You-Lin Qiao, Nathaniel Rothman, Manami Inoue, Daehee Kang, and Xiao-Ou Shu: Provision of study materials or patients.

Prakash C. Gupta, Akiko Tamakoshi, Woon-Puay Koh, Yu-Tang Gao, Ritsu Sakata, Ichiro Tsuji, Reza Malekzadeh, Yumi Sugawara, Jeongseon Kim, Hidemi Ito, Chisato Nagata, San-Lin You, Sue K. Park, Jian-Min Yuan, Myung-Hee Shin, Sun-Seog Kweon, Sang-Wook Yi, Mangesh S. Pednekar, Takashi Kimura, Hui Cai, Yukai Lu, Arash Etemadi, Seiki Kanemura, Keiko Wada, Chien-Jen Chen, Aesun Shin, Renwei Wang, Yoon-Ok Ahn, Myung-Hee Shin, Heechoul Ohrr, Habibul Ahsan, Paolo Boffetta, Kee Seng Chia, Keitaro Matsuo, You-Lin Qiao, Nathaniel Rothman, Manami Inoue, Daehee Kang, and Xiao-Ou Shu: Collection and assembly of data.

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Data Sharing Statement

Data access can be through permission from the Asia Cohort Consortium only; please find more details on https://www.asiacohort.org/about/workingwith/index.html and send any inquiries to the Asia Cohort Consortium Coordinating Center at cc@asiacohort.org.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology at www.jto.org* and at https://doi.org/10.1016/j.jtho.2023.11.002.

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