LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence

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Abstract

Identification of high risk individuals will facilitate early diagnosis, reduce overall costs and also improve the current poor survival from lung cancer. The Liverpool Lung Project prospective cohort of 8760 participants aged 45-79 years, recruited between 1998 and 2008, were followed annually through the hospital episode statistics until 31 January 2013. Cox proportional hazards models were used to identify risk predictors of lung cancer incidence. C-statistic was used to assess the discriminatory accuracy of the models. Models were internally validated using bootstrap method. During mean follow-up of 8.7 years, 237 participants developed lung cancer. Age (hazard ratio [HR] 1.04; 95%CI, 1.02-1.06), male gender (HR 1.48; 95% CI:1.10-1.98), smoking duration (HR 1.04; 95%CI 1.03-1.05), COPD (HR 2.43; 95%CI 1.79-3.30), prior diagnosis of malignant tumour (HR 2.84; 95%CI 2.08-3.89) and early onset of family history of lung cancer (HR 1.68;95%CI 1.04-2.72) were associated with the incidence of lung cancer. The LLPi risk model had a good calibration (goodness-of-fit $\chi^2 7.58$, $P=0.371$). The apparent C-statistic was 0.852 (95% CI 0.831-0.873) and the optimism-corrected bootstrap resampling C-statistic was 0.849 (95% CI of 0.829–0.873). The LLPi risk model may assist in identifying individuals at high risk of developing lung cancer in population-based screening programmes.
Introduction

Lung cancer is the leading cause of cancer-related death worldwide with mortality rate exceeding that of prostate, breast and colon cancer combined (1). It has one of the poorest survival outcomes of any cancer because a vast majority of patients are diagnosed at an advanced stage when surgical resection or other treatment options are less effective (2). The National Lung Screening Trial (NLST) showed that lung cancer screening with low-dose computed tomography (LDCT) reduced lung cancer mortality by 20% (3). In practice, the success of any lung cancer screening program will depend on successful identification of individuals at high risk. Risk prediction models have been recognised as a method of identifying individuals at high risk of developing lung cancer (4, 5). Identification of individuals at high risk will facilitate early diagnosis, reduce overall costs and also improve the current poor survival from lung cancer.

To date, most risk prediction models for lung cancer were developed in case control studies (6-9). Case-control studies are proficient in studying dynamic populations where follow-up is difficult, are usually less expensive and are less time consuming, but may be plagued by biases and cannot study the incidence of a disease (10-13). Cohort studies though time consuming and expensive, offer the methodological advantage of direct calculation of incidence rate and can demonstrate the temporal sequence between exposure and outcome (14, 15).

We previously developed the LLP risk model from the LLP case-control study and validated it in three independent populations (16). Covariates such as prior history of respiratory diseases and prior diagnosis of malignant diseases have been reported as risk factors for lung cancer (16, 17). Clinical covariates in the previous case-control model were based on un-validated self-reported questionnaire responses (18). However, in the newly developed model reported in this article, clinical covariates were confirmed in the Hospital Episode Statistics (HES) database. HES is the national statistical data warehouse for the National Health Service (NHS) that includes clinical and administrative information.
about the care provided to NHS patients who live, or are treated in England (19). The aim of the current study was to use baseline data from the LLP population-based cohort to develop and validate a risk prediction model for lung cancer incident.

Materials and Methods

Study Population

This study was performed as part of the Liverpool Lung Project. The objectives, methods, rationale, and study design have been described previously (18). In short, 8760 randomly selected healthy subjects aged 45-79 years were recruited between 1998 and 2008 and followed annually for lung cancer and mortality outcomes through the Office for National Statistics (ONS), public health England (the North West Cancer Intelligence Service), and hospital case-note review until 31 January 2013.

Data Collection and Extraction of Risk Factors

A standardised questionnaire was used to collect self-reported information on demographic and socioeconomic economic characteristics, medical history, family history of cancer, history of tobacco consumption and lifetime occupational history. Information on age, gender, smoking duration, marital status, education level, family history of lung cancer, prior history of other cancers and prior history of non-malignant lung disease such as asthma, chronic obstructive pulmonary disease (COPD), pneumonia, bronchitis, emphysema, tuberculosis and exposure to asbestos was extracted from the questionnaire. Smoking duration was measured in years; ever smoker was defined as someone who had smoked at least 100 cigarettes in their lifetime and a current smoker was defined as a participant who reported smoking within 12 months of the date of the interview. Marital status was reported as single, married, living together, widowed, divorced/separated or other. Education was classified as high school and below and greater than high school and recorded as “yes” or “no”. Family history of
lung cancer included age at onset in a first-degree relative (none, early [<60 years], or late [>60 years]). Previous history of cancer (except melanoma) was coded as “yes” or “no”. Information on prior history of non-malignant lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), pneumonia and tuberculosis were coded “yes” or “no” and diagnosis was corroborated in the HES database prior to their recruitment into the study. Asbestos exposure was determined based on the documentation of participant’s employment history in asbestos-related occupation or industry and was coded “yes” or “no”. The study protocol was approved by the Liverpool Research Ethic Committee and all research participants provided written, informed consent in accordance with the Declaration of Helsinki.

Statistical analyses

Descriptive statistics were obtained and compared by using Chi-square test or Fisher’s exact test for categorical variables and t-tests for normally distributed variables, between participants who developed lung cancer (n=237) and those who did not (n=8523) at the end of the follow-up period. Cox proportional hazards model was used to develop a multivariable model for lung cancer risk and to compute hazard ratios (HR) and corresponding confidence intervals (CI) after testing the proportional hazards assumption with the un-scaled and scaled Schoenfeld residuals (20). Follow-up duration was used as the time axis in the model. For participants that developed lung cancer, follow-up time started from baseline visit, till the date of diagnosis of lung cancer. For participants without incident lung cancer, the follow-up duration was counted from the baseline visit till death, withdrawal, loss to follow-up or 31 January 2013. Five percent of the 8760 participants had missing data; we therefore performed complete case analysis because the characteristics of participants with missing data were largely similar to those of participants with complete observed data. Martingale residuals were used to determine the best function of all covariates (21). The multivariable model was built in two phases.
First, all covariates with \( P \leq 0.10 \) in the univariate analyses were considered for inclusion in the multivariable model. Second, backward selection procedure with \( P < 0.05 \) was used to choose the covariates in the final multivariable model (22). Covariates eliminated were re-entered in the final multivariable model with adjustment for the remaining significant covariates to ensure that no omitted covariate significantly reduced the log likelihood chi-square of the model (23). The performance of the multivariable model was quantified by Harrell’s concordance (C) statistics which is analogous to the receiver operating characteristics (ROC) curve for binary data with confidence interval estimates using jackknife resampling method (24). A C-statistic can be interpreted as the probability that the model predicts a higher risk of lung cancer for those who actually developed lung cancer compared with those that did not develop lung cancer over the follow-up time (25). Model calibration was evaluated using the omnibus Grønnesby-Borgan goodness-of-fit test. Bootstrapping techniques were used for internal validation of the model (26, 27) and bootstrap samples were drawn 200 times with replacement. Regression models were created in each bootstrap sample and tested on the original sample to obtain stable estimates of the optimism of the model, i.e. how much the model performance was expected to decrease when applied in new datasets (28-30). All analyses were performed using STATA® version 13.1 (StataCorp LP, College Station, Texas) and SAS® statistical software version 9.3 (SAS Institute, Cary, North Carolina).

Results

Overall, 8760 participants aged 45-79 recruited between 1998 and 2008 were included in this study and 237 participants (2.7%) developed lung cancer during a mean follow-up of 8.7 years. Table 1 depicts the baseline characteristics of the study population stratified by incident lung cancer status. Lung cancer incidence was higher in older participants, men and also in participants with longer smoking duration, participants with prior history of pneumonia, asthma, tuberculosis, COPD,
emphysema and bronchitis. Furthermore, the percentage of lung cancer incidence was higher in participants with; family history of lung cancer and prior diagnosis of malignant tumour.

In univariate analysis, age, male gender, smoking duration, prior diagnosis of pneumonia, asthma, COPD, emphysema, bronchitis, prior diagnosis of malignant tumour and family history of lung cancer were significantly associated with the risk of developing lung cancer. In addition, we also performed analyses that adjusted all potential confounders in Table 1 for smoking duration. There was a significant increase in risk with age both before (HR=1.08, 1.06-1.09) and after adjusting for smoking duration (HR=1.05, 95% CI 1.03-1.07). Male gender was significantly associated with the incidence of lung cancer both before (HR 1.55, 95%CI 1.20-2.01) and after (HR=1.51, 95%CI 1.16-1.97) adjusting for smoking. Participants with a prior history of asthma had a significant increase in risk before adjustment (HR=1.53, 95%CI 1.12-2.09) but not after (HR=1.25, 0.91-1.71). Participants with a prior history of COPD had a significant increase in risk both before (HR=5.13, 95%CI 3.85-6.84) and after adjustment (HR=2.75, 2.03-3.72). Prior diagnosis of malignant tumour increased risk before (HR=4.18, 95%CI 3.15-5.55) and after adjustment (HR=3.09, 95%CI 2.33-4.11). Family history of lung cancer with early onset (<60 years) increased risk with marginal significantly before (HR=1.56, 95%CI 0.98-2.48) but not after adjustment (HR=1.38, 95%CI 0.87-2.20) for smoking. Education, a measure of socio-economic status was protective against lung cancer before (HR=0.58, 95%CI 0.43-.0.79) for low education (high school and below) and (HR=0.28, 95%CI 0.16-.0.49) for higher education (greater than high school) while only higher education was protective against lung cancer after adjusting for smoking (HR=0.53, 95%CI 0.30-0.95). No significant effect was observed on marital status, occupational exposure to asbestos, pneumonia, bronchitis, emphysema and tuberculosis on lung cancer risk after adjustment for smoking duration. Ever smokers (HR=24.1, 95%CI 10.74-54.3) were at higher risk than never smokers. Fitting smoking duration as a continuous covariate and in 10- and 20 years interval revealed a steady increase in lung cancer risk. There was also a steady increase in risk with increasing smoking pack-years and the average amount smoked, although in neither case was it
as large as that with smoking duration. A significant dose-response effect was also observed for the amount of cigarettes ($P<0.001$), smoking duration ($P<0.001$) and smoking pack-years ($P<0.001$).

Table 2 presents the final multivariate Cox-regression model. Age (HR= 1.04, 95% CI 1.02-1.06), male gender (HR=1.48, 95%CI 1.10-1.98), Smoking duration (HR= 1.04, 95% CI 1.03-1.05), COPD (HR= 2.43, 95%CI 1.79-3.30), prior diagnosis of malignant tumour (HR=2.84, 95%CI 2.07-3.89) and family history of early onset of lung cancer (HR=1.68, 95%CI 1.04-2.72) significantly increased the risk of developing lung cancer. The LLPi model for incident lung cancer had good discrimination C-statistic 0.852(95%CI 0.832-0.873) (Figure 1) and 0.849 (95% CI of 0.829–0.870) by internal validation with bootstrap resampling and correction for optimism. The Grønnesby-Borgan goodness-of-fit test demonstrated overall good calibration $\chi^2 7.58, P=0.371$. A standard test of the proportional hazard (PH) assumption for the model for each covariate using scaled Schoenfeld residuals showed that the PH was not violated.

Using the equation under Table 2, the absolute risk of lung cancer within a mean follow-up period of 8.7 years was calculated. The LLPi risk model was used to estimate the absolute risk of developing lung cancer for three hypothetical individuals with diverse risk profile. First, the absolute risk of a woman aged 65 with 37 years smoking history and a history of COPD diagnosis with a late onset family history of lung cancer (aged >60 at diagnosis) and no other risk factors is calculated as

$$\hat{P} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{p} \beta_i x_i - \sum_{i=1}^{p} \beta_i x_i\right)} = 9.9\%$$

(see details of the formula under Table 2). Second, the absolute risk of a man aged 67 without a smoking history but with an early onset family history of lung cancer (aged <60 at diagnosis) and a prior diagnosis of cancer is 6%. Third, the absolute risk of a man aged 73 who has smoked for 59 years and also had an early onset (aged <60 at diagnosis) family history of lung cancer is 29%.
Discussions

In this study, we developed and internally validated the LLPi risk model for incident lung cancer in the LLP population cohort. Age, male gender, smoking duration, prior history of COPD, prior diagnosis of malignant tumour and family history of early onset of lung cancer (< 60 years) were significant risk factors. The C-statistic of the LLPi risk model and the bias corrected bootstrap resampling were very similar: 0.852 (95%CI 0.832-0.873) and 0.849 (95% CI of 0.829–0.870) respectively. The average difference known as the degree of optimism was 0.003 which indicates that the LLPi can discriminate well between patients with lung cancer and population controls. A model such as the LLPi with a high discrimination and good calibration is expedient for counselling and population-based screening programmes.

To date, several risk prediction models have been developed in population-based cohort data with variable discrimination presented as ROC AUC or C-statistic (Table 3). Bach et al. used prospective cohort data for smokers in the Carotene and Retinol Efficacy Trial (CARET) to develop their model that included age, gender, smoking history and exposure to asbestos as predictors (31). The model was externally validated in the alpha-tocopherol, beta-carotene cancer prevention (ATBC) study control arm with a C-statistic of 0.69 (32,33). The Prostate, Lung, Colorectal and Ovarian cancer screening (PLCO) used prospective data to build two risk prediction models for the general population (model 1) and a sub-cohort of ever-smokers (model 2) (34). The bootstrap optimism corrected ROC AUC were 0.857 and 0.805 respectively. External validation of the models was performed in the PLCO intervention arm with AUC ROC of 0.841 and 0.784 for models 1 and 2 respectively (34). Park et al., developed a risk model in a large population-based cohort study of Korean men with a C-statistic of 0.864 (95%CI 0.860-0.868) (34). External validation of their model produced a C-statistic of 0.871 (95%CI 0.867-0.876) (35). Hoggart et al. used prospective data from the European Prospective Investigation into Cancer (EPIC) to build a predictive model for lung cancer (36). Using smoking information alone, their model had an AUC ROC of 0.843 (95% CI 0.810-0.875). External validation of
the Bach model using the same data gave an AUC ROC of 0.775 (95% CI 0.737-0.813) (36). In another study, Tammemagi et al. modified the PLCO model 1 and 2 to ensure applicability to National Lung Screening Trial (NLST) (37). The newly developed model PLCO M2012 utilised data from PLCO control groups of individuals who had ever smoked and validated the model in the PLCO intervention group of smokers, NLST participants, and in the PLCO intervention group stratified according to whether or not they met the NLST criteria. The AUC of their model was 0.803 in the developmental dataset and 0.797 in the validation dataset (37).

Although the LLPi had a high C-statistic with magnitude comparable to the aforementioned models, its interpretation is not directly comparable with these models because the differences in distributions of covariates can affect performance statistics (38). However, the LLPi model will be more directly applicable for use in primary care setting because it included readily available, strong and plausible covariates that have been implicated in the aetiology of lung cancer from our own and numerous other case-control and cohort studies.

Previous lung diseases including COPD (emphysema, bronchitis), tuberculosis, pneumonia (39) and asthma (40) have been reported as risk factors for lung cancer. In our study, we also examined the association between COPD, emphysema, bronchitis, pneumonia, tuberculosis and asthma on lung cancer. COPD was the only significant covariate in our final multivariable model. The association between COPD and lung cancer we found in our study was consistent with the result from two earlier meta-analyses (17, 39). In contrast, emphysema, bronchitis, pneumonia, asthma and tuberculosis were not significantly associated with lung cancer in our final multivariate model. A plausible explanation for this observation is the small numbers of participants with these respiratory conditions in our study compared to the pooled analysis of 16, 17 and 39 studies for asthma, and other respiratory diseases in the aforementioned meta-analysis respectively. In addition, occupational exposure to asbestos was a risk factor for lung cancer in the LLP risk model (8). However, in this present study, occupational exposure to asbestos was not a risk factor for lung cancer. This
observation may be attributed to the fact that only one of the 237 individuals that developed lung cancer was exposed to occupational asbestos. Twenty three participants had missing data on occupational exposure to asbestos and 213 participants that also developed lung cancer were not exposed to asbestos (Table 1). Thus occupational exposure to asbestos cannot be included in the model because our study population does not have adequate sample of such individuals. Another plausible explanation for this observation is reporting bias and/or misclassification as there is no means of validating the asbestos exposure other than as reported by participant. This is not the case with the medical conditions that may be validated using HES.

Strengths of our study include: its prospective design; the large number of participants; long follow-up period; the population-based setting and that detailed information on the main risk factors (such as smoking and family history of lung cancer) was ascertained by closely supervised trained interviewers, using standardised questionnaires. In addition, information bias was prevented by complete documentation of lung cancer incidence (by the Office for National Statistics (ONS), the North West Cancer Intelligence Service, and hospital case-note review) and comorbidity data that were corroborated using the HES database. Furthermore, unlike in case-control studies, we were able to easily compute the absolute risk estimates for each combination of risk factors from Cox regression.

Although the LLPi model demonstrated good discrimination and calibration, more work is needed to test the applicability of the model in diverse populations, including those from diverse geographic regions. Because of marked geographical differences in incidence rates, evaluation of the LLPi risk model in high and low risk areas is necessary. Advancement in high throughput methodologies and their application in molecular and genetic epidemiological studies have expanded the potential for ‘omic’-based risk prediction (41). Genome-wide association studies have identified inherited susceptibility patterns for lung cancer at different loci (42-44) and several methylation (45-47) and microRNA biomarkers (48-51) associated with lung cancer have been identified. It is anticipated that many more DNA polymorphism and biomarkers will be developed. Due to fewer opportunities to
access biomaterials from large prospective cohort studies, most current biomarkers are used mainly for diagnosis, but their value in risk prediction have not been widely explored (41). We therefore recommend future studies to explore the contribution of genetic polymorphism, methylation and microRNA in combination with clinical and epidemiological factors on lung cancer risk.

In conclusion, we have developed and internally validated the LLPi risk model based on readily available, strong and plausible covariates that have been implicated in the aetiology of lung cancer from our own and numerous other case-control and cohort studies. The application of LLPi risk model in identifying individuals at high risk of developing lung cancer in population-based screening programmes needs further study.
References


Table 1: Distribution of baseline characteristics stratified by lung cancer status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incident lung cancer (n=237)</th>
<th>No –incident lung cancer (n=8523)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>66.0 (7.2)</td>
<td>61.5 (8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>137 (57.8)</td>
<td>4052 (47.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>100 (42.2)</td>
<td>4471 (52.5)</td>
<td></td>
</tr>
<tr>
<td>Mean Smoking duration (SD)</td>
<td>39.9 (14.3)</td>
<td>18.9 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior diagnosis of pneumonia</td>
<td></td>
<td></td>
<td>0.066</td>
</tr>
<tr>
<td>No</td>
<td>186 (83.0)</td>
<td>6971 (87.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (17.0)</td>
<td>1022 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of asthma</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>No</td>
<td>173 (77.2)</td>
<td>6687 (83.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (22.8)</td>
<td>1310 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of tuberculosis</td>
<td></td>
<td></td>
<td>0.674</td>
</tr>
<tr>
<td>No</td>
<td>216 (96.4)</td>
<td>7745 (96.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (3.6)</td>
<td>246 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of COPD</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>90 (47.6)</td>
<td>5196 (82.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99 (52.4)</td>
<td>1094 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>203 (90.6)</td>
<td>7718 (96.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (9.4)</td>
<td>277 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>135 (60.3)</td>
<td>5890 (73.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89 (39.7)</td>
<td>2103 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>0.017*</td>
</tr>
<tr>
<td>Single</td>
<td>17 (7.6)</td>
<td>725 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>133 (59.4)</td>
<td>5187 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Living together</td>
<td>3 (1.3)</td>
<td>202 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>44 (19.6)</td>
<td>958 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>27 (12.1)</td>
<td>897 (11.2)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>0 (0.0)</td>
<td>15 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Occupational exposure to asbestos</td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>No</td>
<td>213 (99.5)</td>
<td>7877 (99.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (0.5)</td>
<td>68 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of malignant tumor</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>154 (65.0)</td>
<td>7193 (89.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70 (29.5)</td>
<td>805 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school and below</td>
<td>201 (93.9)</td>
<td>6728 (84.3)</td>
<td></td>
</tr>
<tr>
<td>Greater than high school</td>
<td>13 (6.1)</td>
<td>1256 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Family history of lung cancer</td>
<td></td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>No</td>
<td>179 (75.5)</td>
<td>6940 (81.4)</td>
<td></td>
</tr>
<tr>
<td>Early onset (&lt;60 years)</td>
<td>20 (8.4)</td>
<td>484 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Late onset (≥60 years)</td>
<td>38 (16.0)</td>
<td>1099 (12.9)</td>
<td></td>
</tr>
</tbody>
</table>

a= Numbers do not add up to total due to missing data; * P values were derived from Fisher’s Exact test.
Abbreviations: SD=Standard deviation; COPD= chronic obstructive pulmonary disease.
Based on the Cox model, the probability of developing lung cancer at an average of 8.7 years of follow-up is defined by the formula:

\[
P = 1 - S_0(t)^\exp\left(\sum_{i=1}^{P} \beta_i x_i - \sum_{i=1}^{P} \beta_i \bar{x}_i\right)
\]

\(S_0(t)\) = the baseline survival at mean value 8.7 years;
\(\beta_i\) = the estimated regression coefficient,
\(x_i\) = the value of the covariate;
\(\bar{x}_i\) = the corresponding mean for continuous covariates or proportion for categorical covariates;
\(P\) = the number of covariates.

Using the equation described above, the probability of developing lung cancer during the mean follow-up period of 8.7 years was calculated. This can be illustrated by considering a man diagnosed with lung cancer at the aged of 50, with 30 years smoking history and a known history of COPD and no other risk factors. The estimated risk based on the LLPi model is:

\[\sum_{i=1}^{P} \beta_i x_i = 0.036(50) + 0.391(1) + 0.043(30) + 0.890(1) + 1.044(0) + 0.521(0) + 0.071(0) = 4.371\]

\[\sum_{i=1}^{P} \beta_i \bar{x}_i = 0.521(61.65) + 0.391(0.478) + 0.043(19.42) + 0.890(0.185) + 1.044(0.106) + 0.521(0.058) + 0.071(0.129) = 3.556\]

\[
P = 1 - S_0(t)^\exp\left(\sum_{i=1}^{P} \beta_i x_i - \sum_{i=1}^{P} \beta_i \bar{x}_i\right)
\]

\[= 1 - 0.9728386^{\exp(4.371-3.556)} = 0.060 = 6.0\%
\]

*Mutually adjusted baseline survival probability at 8.7 years \(S_0(t) = 0.9728386\)
Table 3 Risk prediction model developed in prospective population-based cohort

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Bach (31)</th>
<th>PLCO (34)</th>
<th>PLCO\textsubscript{M2012} (37)</th>
<th>EPIC (36)</th>
<th>Park (35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors included in model</td>
<td>Age, sex, asbestos exposure, and smoking duration, duration of abstinence (if applicable) and average amount per day (while smoking).</td>
<td>Age, socioeconomic status (education), BMI, family history of lung cancer, COPD, recent chest X-ray and smoking status, pack-year, duration and time since quitting smoking (if applicable).</td>
<td>Age, race/ethnic group, education, BMI, COPD, personal history of cancer, family history of lung cancer and smoking-related factors (status, intensity, duration and quit time).</td>
<td>Age, smoking intensity (measured by average number of cigarettes smoked per day), age started smoking and smoking duration.</td>
<td>Age, smoking exposure (status and intensity), age at smoking initiation, BMI, physical activity and fasting glucose level.</td>
</tr>
<tr>
<td>Discriminatory power in modelling population</td>
<td>0.72</td>
<td>0.86 (for all subjects); 0.81 (for ever-smokers)</td>
<td>0.80</td>
<td>0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>Discriminatory power in populations for external validation</td>
<td>0.69 (32); 0.66 (33)</td>
<td>0.84 (for all subjects); 0.78 (for ever-smokers only)</td>
<td>0.80</td>
<td>0.78</td>
<td>0.87</td>
</tr>
<tr>
<td>Strength</td>
<td>First lung cancer risk model.</td>
<td>Use of spline function in modelling; High discriminatory power.</td>
<td>Major classic risk factor included; high discriminatory power.</td>
<td>Large population; high discriminatory power.</td>
<td>Very large population; high discriminatory power.</td>
</tr>
<tr>
<td>Weakness</td>
<td>Moderate discriminatory power; smoker population only.</td>
<td>Healthy volunteer effect may limit external generalisation</td>
<td>Smoker population only.</td>
<td>Based on only age and smoking-related factors.</td>
<td>Men only; missing some other classical risk factors.</td>
</tr>
</tbody>
</table>

Abbreviations: PLCO = Prostate, Lung Colorectal and Ovarian cancer screening trial; EPIC = European Prospective Investigation into Cancer and Nutrition; BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease
Figure 1 Performance of the LLPi risk model: C-statistic

C-statistic 0.852 (95% CI 0.831-0.873)
Cancer Prevention Research

LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence

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