ORIGINAL ARTICLE

Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: the UKLS trial

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2018-212263).

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Received 27 June 2018
Revised 6 January 2019
Accepted 11 February 2019
Published Online First 26 April 2019

To cite: Marcus MW, Duffy SW, Devaraj A, *et al*. *Thorax* 2019;**74**:761–767.

ABSTRACT

Background Estimation of the clinical probability of malignancy in patients with pulmonary nodules will facilitate early diagnosis, determine optimum patient management strategies and reduce overall costs.

Methods Data from the UK Lung Cancer Screening trial were analysed. Multivariable logistic regression models were used to identify independent predictors and to develop a parsimonious model to estimate the probability of lung cancer in lung nodules detected at baseline and at 3-month and 12-month repeat screening.

Results Of 1994 participants who underwent CT scan, 1013 participants had a total of 5063 lung nodules and 52 (2.6%) of the participants developed lung cancer during a median follow-up of 4 years. Covariates that predict lung cancer in our model included female gender, asthma, bronchitis, asbestos exposure, history of cancer, early and late onset of family history of lung cancer, smoking duration, FVC, nodule type (pure ground-glass and part-solid) and volume as measured by semiautomated volumetry. The final model incorporating all predictors had excellent discrimination: area under the receiver operating characteristic curve (AUC 0.885, 95% CI 0.880 to 0.889). Internal validation suggested that the model will discriminate well when applied to new data (optimism-corrected AUC 0.882, 95% CI 0.848 to 0.907). The risk model had a good calibration (goodness-of-fit χ[8] 8.13, p=0.42).

Conclusions Our model may be used in estimating the probability of lung cancer in nodules detected at baseline and at 3 months and 12 months from baseline, allowing more efficient stratification of follow-up in population-based lung cancer screening programmes.

Trial registration number 78513845.

Key messages

What is the key question?
► To develop a lung cancer pulmonary nodule risk model which incorporates volumetric measurements.

What is the bottom line?
► The UK Lung Cancer Screening (UKLS) pulmonary risk model has excellent discrimination (area under the receiver operating characteristic curve 0.885, 95% CI 0.880 to 0.889) and has good calibration (goodness-of-fit χ[8] 8.13, p=0.42).

Why read on?
► The potential for the UKLS Nodule Risk Model is that it may be used in future national CT screening programmes, incorporating volumetric measurements to identify malignant pulmonary nodules.

INTRODUCTION

Lung cancer is the most common cause of cancer death in Europe and has the highest economic cost (€18.8 billion, 15% of overall cancer costs).[1] All respiratory illnesses in the UK costed £11.1 billion in 2014.[2] Despite recent improvements, thought to be related to improved resection rates, 5-year survival for all stages is only 13%, but >80% for patients with stage 1a disease.[3–5] The poor survival outcome is partly attributable to variation in resection rates but mainly due to late presentation of the disease when surgical resection or other treatment options are less effective.[6]

Low-dose CT (LDCT) is a viable screening tool for early lung cancer detection and mortality reduction. The USA-based National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality relative to chest X-ray screening.[7] The results of the ongoing Dutch-Belgian NELSON (Nederlands Leuvens Longkanker Screenings Onderzoek) trial and pooled European randomised controlled trials are awaited.[8] In the NLST and other (smaller) trials, over 20% of LDCT-screened participants had indeterminate lung nodules (ie, potentially cancerous, but of insufficient size to refer for treatment), and thus required further CT scans. Diagnostic stratification of indeterminate pulmonary nodules is currently based on radiological characterisation, including nodule diameter and/or volume and risk prediction models. Indeed two risk prediction models used sequentially are recommended in the latest British Thoracic Society (BTS) guidelines,[9] the Brock University model for nodules ≥300 mm^3 or ≥8 mm in diameter,[10] and where the risk is estimated at >10% the Herder model after positron emission tomography-CT.[11]

However, none of these models employ volumetry and all are for use at baseline. Nodule volumetry provides a more accurate assessment for baseline size and subsequent growth than diameter measurements.[12] Nodule volume is the preferred method for evaluation in the BTS guidelines and recommended as a more accurate method in the latest Fleischner Society guideline.[13] It appears in several diagnostic algorithms but is insufficient in isolation.[14 15] It is therefore crucial to improve

strategies to quantify the risk of malignancy in 'indeterminate nodules'. This allows participants in screening programmes to be simply returned to the next planned screen and patients to be reliably advised about the need for follow-up or referral for clinical work-up.

There is a growing recognition of the potential utility of risk models to predict lung cancer risk in patients with pulmonary nodules, thus allowing more subjects to be monitored with low-dose imaging rather than needing minimally invasive or invasive procedures.[16 17] The characteristics of pulmonary nodules detected on screening CT scans may determine optimum patient management strategies because risk-based selection of patients have been reported to precisely delineate the benefits and harms of screening by accommodating detailed information on lung cancer risk factors.[18] The aim of this study was to develop a model to predict the risk of lung cancer in screen-detected pulmonary nodules detected at baseline and at 3-month or 12-month interval CT screening.

METHODS

Study design and participants

The UK Lung Cancer Screening (UKLS) trial is a multicentre, randomised controlled pilot trial of LDCT screening versus standard care for the early detection of lung cancer in high-risk individuals.[15 19 20] The trial was registered with the International Standard Randomised Controlled Trial Register.

Primary care trust records were used to approach 247 354 individuals aged 50–75 years residing in specific healthcare areas (Liverpool, Knowsley, Sefton, Cambridgeshire, Peterborough and Bedfordshire) by letter to participate in the trial. The Liverpool Lung Project lung cancer risk prediction model (V.2) was used to calculate risk scores to identify those at high risk (≥5% over 5 years) of developing lung cancer.[21] A total of 4055 high-risk individuals were recruited and randomised, 2028 into the CT arm (of whom 1994 underwent a CT) and 2027 received usual care. At the time of reporting the UKLS identified 1.7% lung cancers at baseline, which was significantly higher than either the NELSON or NLST baseline data. This study presents the result of 1013 of the 1994 participants with at least one non-calcified lung nodule at baseline and at 3-month and 12-month repeat LDCT.

Thoracic CT scans

Details of the CT scans have been described previously.[20] Briefly, thoracic CT images were obtained from lung apices to bases, during suspended inspiration, in a single breath-hold and without the administration of intravenous contrast. Images were reconstructed at 1 mm thickness at 0.7 mm increments, using a moderate spatial frequency kernel reconstruction algorithm. Acquisition parameters (kVp and mAs) varied according to body habitus to achieve a CT dose index below 4 milliGray.

Reading methods

All CT scans were read using the 'LungCARE' (LungCARE, version Somaris/5 VB 10A, Siemens Medical Solutions) on the Syngo Siemens workstation, which provides a value for nodule size based on volume. To optimise sensitivity and specificity, all baseline CT scans were read by two thoracic radiologists at both local (Liverpool Heart and Chest Hospital or Papworth Hospital) and central (Royal Brompton Hospital) sites.[15] All discrepancies were resolved by a review from the third thoracic radiologist at the Royal Brompton site, and after reaching a consensus a letter outlining the results of the scan is sent to the participant and their general practitioner.[15]

Nodules: classification and management

The management of pulmonary nodules within the UKLS trial has been reported in detail in the full Health Technology Assessment report.[20] Four categories of nodules were reported (figure 1 provides the full details for solid, part-solid and pure ground-glass nodules [pGGN]): category 1: benign nodule <3 mm, diameter 15 mm^3; category 2: volume 15–49 mm^3, 3–4.9 mm); category 3 (volume 50–500 mm^3, 5–9.9 mm); and category 4 (volume >500 mm^3 or >10 mm). All categories 2, 3 and 4 nodules were included in this analysis. The number of nodules identified in each of the three categories is shown in table 1.

All of the nodules identified in the baseline scan were reanalysed in the follow-up CT scans at 3 and 12 months, except the malignant ones which had been resected. Thus, all of the UKLS-reported nodules at 3 or 12 months were originally matched with the baseline scan. Stable baseline nodules were only counted once, that is, at baseline; however, if a nodule developed new characteristics at 3 or 12 months, they were excluded from the analysis. Significant growth of nodules was defined based on their percentage change in volume and volume doubling time (VDT); that is, 25% increase in volume and VDT <400 days.

Readers identified up to a maximum of 20 non-calcified nodules per subject. Nodules were categorised as solid, part-solid or pGGN, and further classified into four categories based on the size reflecting their probability of being malignant, as depicted in table 2.[15] Solid nodule outline was also recorded as smooth, polylobulated, spiculated or irregular. Smooth was defined as a continuous regular outline. Lobulation was defined as areas of bulging of the lesion contour. Spiculation was defined as the presence of strands extending from the lung margin into the lung parenchyma. Irregular was defined as not smooth, polylobulated or spiculated. pGGN is defined as a nodule composed of a focal area of hazy increased lung opacity that does not obscure the underlying structures.[9] Whenever follow-up scans (at 3 or 12 months) were performed, the VDT of the solid nodule was calculated, in the cases where nodule segmentation was reliable at baseline and follow-up. In the UKLS, we used manual diameter for (1) ground-glass and part-solid nodules, (2) subpleural nodules, and (3) nodules where volumetry was recorded as being unreliable; these nodules were excluded from the analysis.

The diagnosis of lung cancer was made by histopathological examination of the resected specimen, otherwise it was based on radiological clinical diagnosis. Quality control of the specimen involved exchange of a representative H&E-stained section from all cases between reference thoracic pathologists at Liverpool and Papworth. This was accompanied where necessary by any immunolabelled sections used in the diagnosis and/or classification of lesion. Sections were blinded reviewed and responses were exchanged with appropriate discussion in case of discordance.

Statistical analyses

Descriptive statistics were obtained and compared by using the χ^2 test or the Fisher's exact test for categorical variables. Complete case analysis, that is, omitting covariates with missing data in regression models, could lead to bias.[22] Therefore, multiple imputation (MI) of missing data by chain equations was performed to impute missing data across multiple covariates simultaneously. The MI process was implemented in three steps: (1) imputation step, (2) analysis step and (3) pooling step.

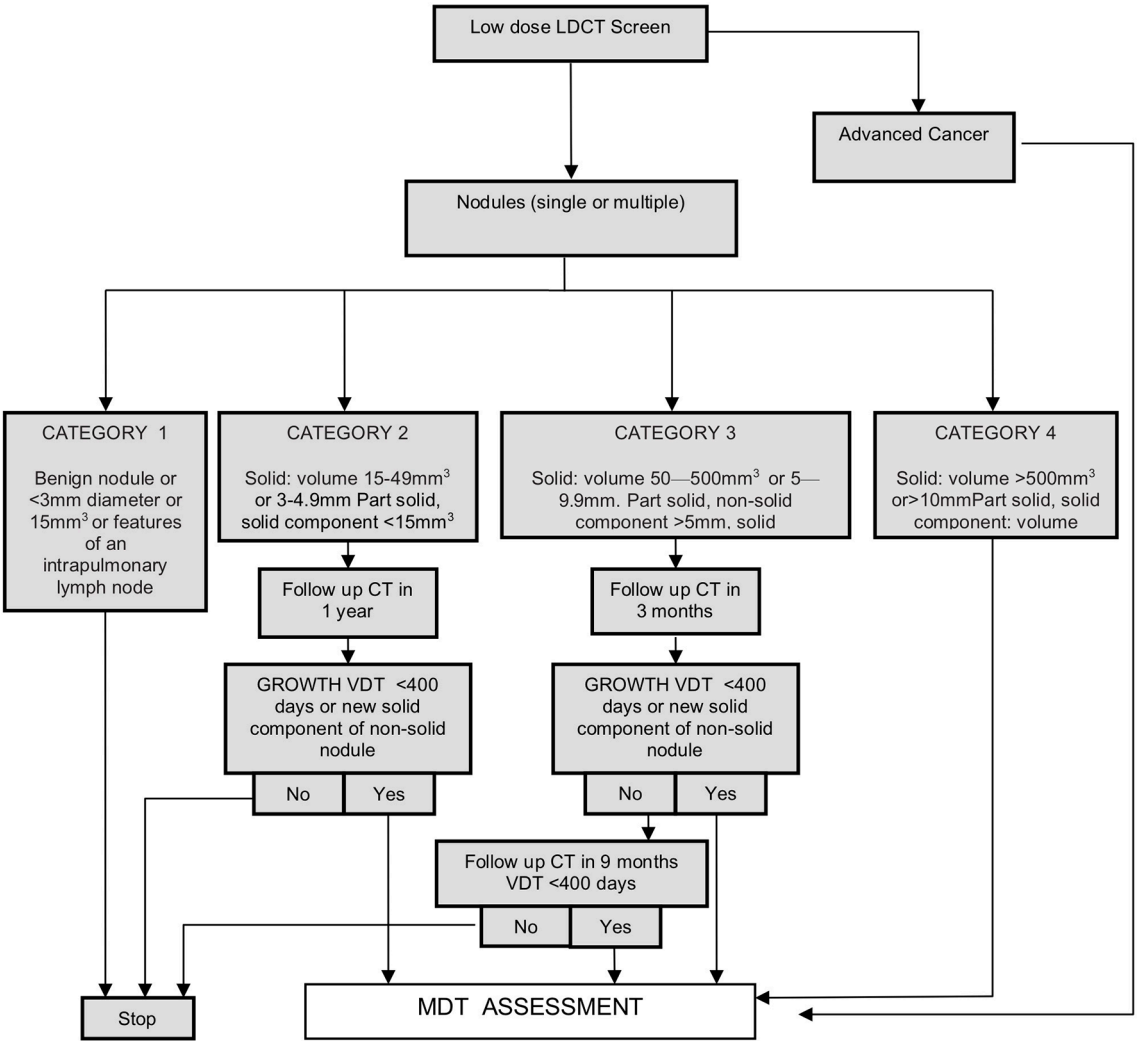

Figure 1 The UK Lung Cancer Screening nodule care pathway management protocol. Reproduced from Field *et al*.[20] LDCT, low-dose CT; MDT, multidisciplinary team; VDT, volume doubling time.

The results of the analyses were pooled by applying the Rubin's rules.[23] Graham *et al*[24] using simulations recommended the use of many more imputations than the classical recommendation of 3–5 imputations, so we used 20 imputations based on their recommendation. The results of the analyses with imputation of missing covariates were similar to that of complete case analyses (() online supplementary table S1). Multivariable logistic regression models were constructed to estimate the probability that lung nodules detected at baseline and at 3-month or 12-month LDCT screening were malignant. Variable selection was informed by the known and potential risk factors for lung cancer in the literature, clinical importance, confounding, collinearity, model stability and statistical significance. Variables considered for inclusion included age, gender, body mass index (BMI), history of respiratory diseases (asthma, bronchitis, emphysema, pneumonia, TB and COPD), exposure to asbestos, history of cancer excluding lung cancer, family history of lung cancer, previous CT scan, previous X-ray, FEV_1 and FVC. In addition, we also considered available nodular characteristics including nodular volume, nodule location, nodule type and nodule count (intrapulmonary lymph nodes were not included). VDT was assessed but insufficient data available for the UKLS risk model analysis. 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, a backward selection procedure with $p < 0.05$ was used to choose the covariates in the final multivariable model.[25] 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 χ^2 of the model.[25] The unit of analysis was undertaken on a per-nodule basis, and since some individuals had multiple nodules the variances of effect estimates were adjusted for data clustering within individuals using the Huber-White robust (sandwich) variance estimator.[26]

Non-linear effects of continuous variables were evaluated using fractional polynomials.[27] The performance of the multivariable model was quantified by assessing its discrimination and calibration. Discrimination (ability to classify correctly) was assessed using the area under the receiver operating characteristic curve

Table 1 Numbers of patients and nodules per UK Lung Cancer Screening nodule categories 2, 3 and 4

Nodule categories	Patients (n)	Nodules (n)
2	622	3065
3	333	1865
4	58	133

Table 2 Nodule: categories, morphology and management

Categories	Solid	Non-solid or part-solid	Management
Category 1	Nodules containing fat or with a benign pattern of calcification are considered benign. Nodules <15 mm^3 or if pleural or juxtapleural ≤3 mm. Including intrapulmonary nodules.		No future action taken.
Category 2	Intraparenchymal nodules with a volume of 15–49 mm^3. Pleural or juxtapleural nodules with a maximal diameter of 3.1–4.9 mm.	Nodules with a maximal non-solid component diameter <5 mm. Where there is a solid component, the component volume is <15 mm^3.	Follow-up CT scan at 12 months.
Category 3	Intraparenchymal nodules with a volume of 50–500 mm^3. Pleural or juxtapleural nodules with a maximal diameter of 5–9.9 mm.	Nodules with a maximal non-solid component diameter of 5–10 mm. Where there is a solid component, the component volume is 15–500 mm^3.	Follow-up CT scan at 3 months and 12 months.
Category 4	Intraparenchymal nodules with a volume of >500 mm^3. Pleural or juxtapleural nodules with a maximal diameter of ≥10 mm^3.	Nodules with a solid component with volume >500 mm^3.	Immediate referral to multidisciplinary team.

(AUC). Model calibration was evaluated using Hosmer-Lemeshow goodness-of-fit test, and the deviance and residual test.[28] The overall model performance was evaluated using the Brier score.[29] Bootstrapping techniques were used for internal validation of the model, and bootstrap samples were drawn 200 times with replacement.[30] Regression models were created in each bootstrap sample and tested on the original sample to obtain stable estimates of the optimism of the model, that is, how much the model performance was expected to decrease when applied in new data sets.[31–33] All analyses were performed using Stata V.14.2 and SAS V.9.4.

RESULTS

Of 1994 participants who underwent CT scan, 1013 participants had a total of 5063 lung nodules and 52 (2.6%) of the participants developed lung cancer during a median follow-up of 4 years. There were 979 category 1 patients who had no nodules reported as per the UKLS protocol. The mean age of the 1013 participants was 67.8±4.1 years. There was no significant difference between the age of participants with benign and malignant nodules. In subjects with malignant nodules, a greater proportion were female than in those with benign nodules (32.7% vs 26.4%). Participants with malignant nodules had longer smoking duration than participants with benign nodules (44.4±7.7 vs 41.3±10.3 years). COPD was more common in participants with malignant nodules compared with those with benign nodules (17.3% vs 2.5%). Patients with a malignant diagnosis had larger nodules than patients with benign nodules (p<0.0001). Furthermore, there were significant differences between FEV_1, FVC, volume, nodule counts and nodule types between benign and malignant nodules (table 3).

In univariate analysis, female gender (OR, 2.407; 95% CI 1.819 to 3.185), smoking duration (OR, 2.407; 95% CI 1.819 to 3.185), pneumonia (OR, 1.444; 95% CI 1.093 to 1.908), asthma (OR, 1.764; 95% CI 1.326 to 2.346), TB (OR, 2.026; 95% CI 1.514 to 2.710), COPD (OR, 2.062; 95% CI 1.549 to 2.744), family history of lung cancer, early onset (OR, 3.694; 95% CI 2.696 to 5.026) and late onset (OR, 2.062; 95% CI 1.508 to 2.820), BMI (OR, 0.963; 95% CI 0.933 to 0.994), FEV_1 (OR, 0.289; 95% CI 0.233 to 0.359), FVC (OR, 0.313; 95% CI 0.262 to 0.375), nodular volume (OR, 1.001; 95% CI 1.001 to 1.001), nodule counts (OR, 0.977; 95% CI 0.958 to 0.996), and pGGN type (OR, 3.106; 95% CI 1.674 to 5.764) were significantly associated with malignancy in a nodule.

Table 4 presents the final multivariate logistic regression model. Age, female gender, asthma, bronchitis, exposure to asbestos, previous malignancy, family history of lung cancer (early and late onset), smoking duration, FVC, nodule type (pGGN and pulmonary solitary nodule (PSN)), nodule location (upper vs middle or lower lobe) and nodular volume were included in the model. The model had very good discrimination with an AUC of 0.885 (95% CI 0.880 to 0.889; figure 2) and 0.882 (95% CI 0.848 to 0.907) by internal validation with bootstrap resampling and correction for optimism. The Hosmer-Lemeshow goodness-of-fit test demonstrated an excellent calibration: $\chi^2(8)$ 8.13, p=0.42. Likewise, the deviance (p=1.00) and Pearson goodness-of-fit (p=0.223) statistics indicate that the fitted model is appropriate. The overall model performance evaluated using the Brier score gives a p value of 0.034.

DISCUSSION

The clinical management of pulmonary nodules is challenging because of the need to distinguish benign and potentially malignant nodules. These challenges will become more widespread if LDCT national screening is introduced. In this study, we used data from the UKLS pilot trial to develop and internally validate a risk model for estimating the probability of lung cancer in pulmonary nodules detected using baseline and 3-month and 12-month data from baseline. Our model had very good discrimination, excellent calibration and overall model performance, and internally validated using bootstrapping.

An increasing number of malignancy risk prediction models have been proposed for categorising indeterminate pulmonary nodules. Some of these models may be subject to biases due to small sample size and retrospective study design.[34 35] However, some models have been evaluated and compared in external case series and some show good discrimination.[36–38] The two models with the highest accuracy were recommended for use in the BTS guidelines.[9–11]

Although our model gave values for discrimination and calibration comparable with the two models recommended in the BTS guidelines, we cannot directly compare it with these models because accuracy can vary considerably, within populations. However, our model can be easily incorporated into screening protocols 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. The model reported in this paper is novel, as it incorporates screen-detected nodule volume in the risk prediction calculation. Nodule volume is considered to be more accurate and reproducible than diameter measurements,[39] but its role in lung risk prediction models from clinical trial data has not

Table 3 Characteristics of UK Lung Cancer Screening screened participants with benign and malignant nodules

Characteristics	Benign nodules (n=961)	Malignant nodules (n=52)	P value
Mean age, (years)±SD	67.9±4.1	67.1±4.0	0.292
Gender			
Male	707 (73.6)	35 (67.3)	0.320
Female	254 (26.4)	17 (32.7)	
Smoking duration, (years)±SD	41.3±10.3	44.4±7.7	0.0229
Prior diagnosis of pneumonia*			
No	561 (58.4)	23 (44.2)	0.520
Yes	149 (15.5)	8 (15.4)	
Prior diagnosis of bronchitis†			
No	529 (55.0)	18 (34.6)	0.010
Yes	223 (23.2)	18 (34.6)	
Prior diagnosis of asthma‡			
No	603 (62.7)	26 (50.0)	0.201
Yes	126 (13.1)	9 (17.3)	
Prior diagnosis of TB§			
No	634 (66.0)	26 (50.0)	0.716
Yes	24 (2.5)	0 (0.0)	
Prior diagnosis of COPD¶			
No	605 (63.0)	25 (48.1)	0.080
Yes	109 (2.5)	9 (17.3)	
Occupational exposure to asbestos**			
No	526 (58.9)	29 (55.8)	0.269
Yes	366 (38.1)	14 (26.9)	
Prior diagnosis of malignant tumour††			
No	773 (80.4)	40 (76.9)	0.525
Yes	187 (19.5)	12 (23.1)	
Family history of lung cancer‡‡			
No	721 (75.0)	31 (59.6)	0.028
Early onset§§	93 (9.7)	10 (19.2)	
Late onset§§	146 (15.2)	11 (21.2)	
Body mass index (kg/m^2)	26.9±4.6	26.5±5.3	0.485
FEV_1 (L)	2.46±0.74	1.89±0.54	<0.0001
FVC (L)	3.49±0.92	2.63±0.67	<0.0001
Nodular volume (mm^3), median (IQR)	34.5 (21.0–70.5)	320.0 (49.5–1407.4)	<0.0001
Nodule counts	7.0±8.5	8.0±5.9	0.0193
Nodule location			
Upper	573	33	0.583
Middle or lower lobe	388	19	
Nodule type (solid as reference)			
Non-solid	947	49	0.023
Part-solid	4	3	

(a, b, c, d, e, f, g, h indicate the percentage of missingness in covariates).
Family history: early <60 years, late is 60 years and above.
*a=26%.
†b=22%.
‡c=24%.
§d=32%.
¶e=26%.
**f=7.2%.
††g=0.1%.
‡‡h=0.1%.
§§TB=prior diagnosis of tuberculosis

Table 4 Regression coefficients, OR (95% CI) and SE for covariates in the final model for the probability of lung cancer in pulmonary nodules

Covariates	β-coefficient	SE	OR (95% CI)	P value
Intercept	−2.2915	1.2921	–	0.076
Age (years)	−0.0257	0.0174	0.975 (0.942 to 1.008)	0.138
Gender (female)	0.5105	0.1653	1.666 (1.205 to 2.304)	0.002
Asthma	−0.7777	0.2093	0.459 (0.305 to 0.693)	<0.0001
Bronchitis	1.7616	0.2052	5.823 (3.894 to 8.704)	<0.0001
Asbestos exposure	0.5884	0.1855	1.801 (1.252 to 2.591)	0.002
Previous malignancy	0.5305	0.1824	1.699 (1.189 to 2.430)	0.004
Family history of cancer				
Early onset *	1.9985	0.2158	7.378 (4.834 to 11.262)	<0.0001
Late onset*	1.5724	0.2055	4.818 (3.220 to 7.209)	<0.0001
Smoking duration (years)	0.0565	0.0097	1.059 (1.038 to 1.078)	<0.0001
FVC (L)	−1.1693	0.1108	0.311 (0.250 to 0.386)	<0.0001
Nodule type (solid as reference)				
Non-solid	1.6396	0.3370	5.153 (2.662 to 9.976)	<0.0001
Part-solid	0.4919	0.2837	1.635 (0.938 to 2.852)	0.083
Nodule location				
Upper vs middle or lower lobe	−0.1799	0.1607	0.835 (0.610 to 1.144)	0.263
Nodular volume (mm^3)	0.000822	0.000186	1.001 (1.000 to 1.001)	<0.0001

Note: Multiple imputations used in this analysis.
*Family history: early <60 years, late is 60 years and above.

been previously been used. A previous effort has been made to develop pulmonary risk model incorporating volume in a small cohort from one centre, of 221 patients with a 37% malignancy. The coauthors provided three promising models, which correctly classified the predicted malignancy in 83%–88% of subjects.[40]

It can be hypothesised that nodule volume is superior to diameter at predicting malignancy because it is a parameter that reflects the size of the entire nodule.

Previous lung diseases such as asthma and bronchitis have been reported as risk factors for lung cancer.[41–43] In our study, asthma

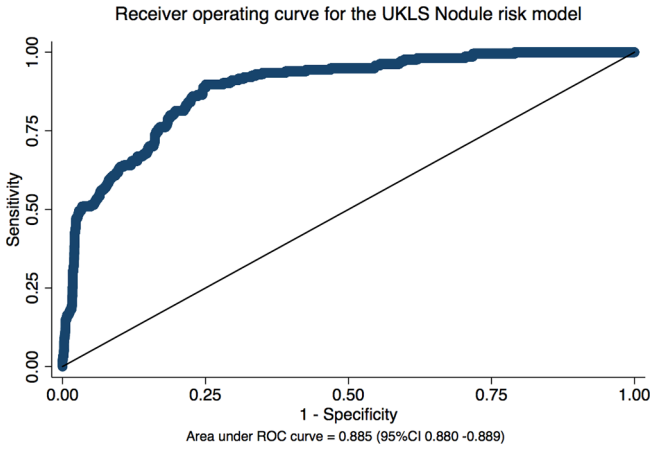

Figure 2 Receiver operating curve for the UKLS Nodule Risk Model. ROC, receiver operating characteristics; UKLS, UK Lung Cancer Screening.

and bronchitis were independent predictors of lung cancer in our final multivariable model. The reasoning why bronchitis was found to be significant but neither COPD or emphysema was significant may be explained by misclassification either when there is no disease or asthma is wrongly labelled as COPD. We are unable to confirm this from our data. A second reason is that our smoking data were relatively accurate, and there is some debate about whether COPD is a significant independent risk factor for lung cancer or merely a marker of smoking.[43] However, the protective association of asthma with nodule malignancy observed in our study suggests our source data were at least detecting true asthma, as asthma is not thought to be an independent risk factor for cancer. In a recent meta-analysis, asthma was associated with increased risk of lung cancer, but misclassification may have been operative here.[42] In contrast, our observation about bronchitis as an independent predictor of malignancy is in agreement with earlier studies in the literature.[41]

Other risk factors for lung cancer earlier described in the literature such as occupational exposure to asbestos, previous malignancy, family history of lung cancer, smoking duration and FVC were also significantly associated with lung cancer in this study.[21 44] Our observation that female gender is significantly associated with lung cancer is in agreement with the study by McWilliams *et al*[10] and also in the UK population.[43] Our observation that FVC is significantly inversely associated with lung cancer is supported by a recent study by Enomoto *et al*.[44] In their study, they reported that low FVC predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer. In addition, nodular characteristics such as pGGN type and nodular volume were independent predictors of lung cancer.

The strengths of our study include its study design, that is, a randomised trial, the large number of nodules relative to the participants, a UK socioeconomic representative population, the use of volumetry, and 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.[20]

A limitation of this study is that we did not include spiculation in our model because of the low number of nodules with this feature reported by UKLS radiologists and we were unable to examine the effect of VDT. A second limitation is that the model was developed from a cohort at a particularly high risk of lung cancer, which means there is a possibility that it will perform less well in populations at lower risk. Although the model was developed and internally validated using bootstrapping, a well-established method for internal validation that has been found to be superior to other internal validation techniques,[30] the ultimate test will be validation in an independent population.[33] In addition, the marked geographical variation in incidence rates of lung cancer warrants the evaluation of our model in geographically diverse populations. Another limitation is that we did not evaluate diameter in the model. However, while automated diameter measurements are available from volumetry applications, these measurements are not typically used in screening when reliable volume measurements are available.

Advancement in high-throughput methodologies and routine digitisation of medical records and their application in molecular and genetic epidemiological studies have expanded the potential for 'omic'-based risk prediction.[45] In this era of big data, advance statistical techniques, machine learning and deep learning methodologies will continue to emerge, so we therefore recommend future studies to explore the utilisation of these methodologies to integrate omics, imaging, and genetics with clinical and other phenotypic characteristics in order to produce robust predictive models that may expedite lung cancer in benign nodules.

In conclusion, we have developed and internally validated a risk model for estimating the probability of lung cancer in nodules detected at baseline and at 3 months and 12 months from baseline. The model is based on readily available, strong and plausible covariates that have been implicated in the aetiology of lung cancer. The application of the UKLS Nodule Risk Model has the potential to be used in both research and clinical setting, in CT screening studies using volumetric analysis. The application of our model in identifying nodules at high risk of developing lung cancer in a population-based screening programme needs further study.

Contributors MM and JF developed the concept and design of the probability of lung cancer in pulmonary nodules detected at baseline and associated repeat scans in the UKLS trial using nodule volumetry. AD provided expert advice on the radiological interpretation of the UKLS CT images. All of the authors contributed equally to developing and reviewing the manuscript.

Funding The study received funding from the National Institute for Health Research Health Technology Assessment (NIHR HTA) (reference number HTA 09/61/01).

Disclaimer The views and opinions expressed in this manuscript are those of the authors and do not necessarily reflect those of the Department of Health.

Competing interests JF reports grants from HTA, other from Epigenomics, other from Vision Gate, other from Nucleix and other from AstraZeneca, during the conduct of the study.

Patient consent for publication Not required.

Ethics approval The UKLS was approved by the National Information Governance Board, and ethical approval was given by the Liverpool Central Research Ethics Committee in 2010 (reference number 10/H1005/74).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We are committed, in principle, to data sharing with fellow researchers, and are currently drawing up operating procedures for this. We anticipate that the data will be stored securely in Liverpool and reasonable requests for data for further research will be accommodated, subject to compliance with regulations, maintaining the integrity of information governance and ensuring no loss of confidentiality on the part of the participants of the study. Requests that require considerable data manipulation and management on our part will need to be resourced by those requesting data.

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