Risk prediction models in lung cancer: The methodology for identifying high risk individuals for future lung cancer computed tomography (CT) screening programs

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Screening for Lung Cancer

The results of the US National Lung Screening Trial (NLST) were published in 2011 and are considered a landmark event in lung cancer research (1). This randomized study of 53,454 individuals showed that computed tomography (CT) scans are able to reduce lung cancer mortality by 20 percent through early detection, although with important cost and morbidity due to overdiagnosis and treatment of benign nodules. (2) Several European lung cancer screening trials have also been initiated, with the largest being the NELSON trial in the Netherlands (3) and the plan is to pool data from a number of European trials (4). Clearly, screening tools that are able to identify lung cancers at an early stage have much potential to reduce the enormous burden on lung cancer mortality (5). There are now discussions on how implementation may be put in place across the world, within differing health care systems (6). The success of lung cancer screening will be dependent upon identifying populations at sufficient risk in order to maximize the benefit-to-harm ratio of the intervention.

The recommendation from the US Preventive Task Forces is based on the US NLST trial, includes screening all individuals between the ages of 55 and 80 with a smoking history of 30 pack-years or more (one pack-year is 20 cigarettes/day for one year or 10 cigarettes/day for two years, etc.) (7). An in-depth analysis of the NLST showed that there were significant differences in the number of lung cancer cases detected based on underlying risk, even though all participants had satisfied the criteria for participation in the study and were considered at high risk: 60 percent of participants at highest risk for lung-cancer death (quintiles 3 through 5) accounted for 88 percent of the prevented deaths, whereas the 20 percent of participants at lowest risk (quintile 1) accounted for only 1 percent of prevented lung-cancer deaths (8).

Risk Prediction Models

Thus, accurate selection of high-risk individuals for lung cancer screening requires robust methods for risk prediction (Fig. 1). The discriminative performance of a risk model depends

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Risk prediction modeling can contribute to two major questions that have been identified by the lung cancer CT screening community, prior to the implementation of lung CT screening programs:

1. Identification of individuals at a high risk of developing lung cancer by combining their lifestyle and clinical risks in order to select those individuals who are most likely to benefit from CT screening, while limiting possible harms, and maximizing its cost-effectiveness.

2. Many individuals have suspicious (indeterminate) nodules detected by CT scans. We need to develop risk models which will contribute to the radiological management of these “indeterminate” (suspicious) CT detected nodules to distinguish those individuals that need clinical follow-up, from those without clinical relevance, in future lung CT screening programs.

Current Lung Cancer Prediction Models

The lung cancer risk prediction models which have been developed include Bach (9), Spitz (10), LLP (11), and more recently the PLCO (12) and EPIC (13) model. These models were...
developed in Caucasian populations. Likewise, risk models for lung cancer have also been
developed in other ethnic groups and other lung cancer risk models have incorporated genetic
factors. The UK Lung Cancer Screening trial (UKLS) (14) has been the only RCT trial to date,
to select high-risk individuals from a population based study for a screening trial, utilizing a
validated risk prediction model (15). The data already analyzed from the UKLS population-
based approach will provide valuable information as to how to we should implement lung
cancer screening, if it becomes a national program.

**PLCO Risk Model**

The PLCO lung cancer risk model used prospective data from 70,962 control subjects
in the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO). Models were
built for the general population and a sub-cohort of ever-smokers. Logistic regression
models were used to model significant risk factors and the PLCO models demonstrated
high calibration and discrimination. The PLCO-M2012, was developed with fewer variables.
It used a simplified evaluation for non-linear effects, applied logistic regression modeling
to calculate the probability of developing lung cancer over a period of six years. They
evaluated the risk threshold for selecting individuals for screening and compared
the efficiency of the threshold with the US Preventive Services Task Force (USPSTF)
criteria for identifying screenees. (16). The PLCO-M2012 improved the sensitivity and
specificity of the selection of individuals for lung cancer screening over the UPSTF criteria,
however, a major limitation of the PLCO M2012 risk threshold for selecting
individuals for screening is that the evaluation was population specific and not based on
cost-effectiveness. The risk model is available on line at http://www.brocku.ca/lung-cancer-
risk-calculator.

**NLST and Cost Effectiveness**

Recently the cost effectiveness of this trial was reported as $81,000 per QALY gained (95
percent CI 52,000 to 186,000), which is considered to be cost effective within the USA medical
care system (17) but one of the major issues which has not been addressed is that the majority of
the CT screening trial monies were spent on individuals with no disease, for whom screening
would provide no health gain.

Kovalchik, et al. (8) calculated the number of lung-cancer deaths per 10,000 person-years that
were prevented in the NLST CT-screening group, compared to the chest x-ray group, and found
that they increased according to the risk quintile. Sixty percent of the NLST participants at
highest risk for lung-cancer death (quintiles 3 through 5) accounted for 88 percent of the
screening-prevented, lung-cancer deaths, while the 20 percent of participants at the lowest risk
(quintile 1) accounted for only 1 percent of prevented lung-cancer deaths. Thus, screening those
with the highest risk prevented the greatest number of deaths from lung cancer, which most
likely also inflated the NLST cost effectiveness data. Indeed, it is evident from the NLST’s
calculations that their ICER would have be at least halved, had screening been confined only to
those in the two highest-risk quintiles.
The Liverpool Lung Project (LLP) risk model was developed from a case-control study (11). Using a model-based approach, the LLP estimated the probability that an individual, with a specific combination of risk factors, would develop lung cancer within a five-year period (Fig. 2). In short, data from 579 lung cancer cases and 1157 age- and sex-matched, population-based controls were used. Conditional logistic regression models were used to model significant risk factors. Smoking duration, prior diagnosis of pneumonia, occupational exposure to asbestos, prior diagnosis of malignant tumor and early onset (<60 years) family history of lung cancer were significantly associated with lung cancer. The final multivariable model was combined with

![Fig. 2. Percentage of UKLS positive responders with a LLPv2 risk of equal or greater than 5 percent over five years, by individual year of age. This figure shows decision curves comparing the "net benefit" of using the LLP risk model for making screening decisions compared to alternative strategies such as "screen all," "screen none," "screen based on smoking duration," and "screen based on family history age of onset." Superior net benefit was observed for the LLP risk model across threshold probability ranging between 3 to 15 percent. The model’s relative utility in the LLP cohort was also highest across relevant threshold probabilities. Abbreviation: DCA –Decision Curve Analysis, EUELC –European Union Early Lung Cancer, LLPC – Liverpool Lung Prospective Cohort, RU- Relative Utility]

The Liverpool Lung Project

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age-standardized incident data to estimate the absolute risk of developing lung cancer. In another study, Raji, et al., evaluated the discrimination of the LLP risk model and demonstrated its predicted benefit for stratifying patients for CT screening by using data from three independent studies from Europe and North America (15). In this study, the LLP risk model performed better than smoking duration or family history alone in stratifying high-risk patients for lung cancer CT screening.

Utilization of LLP Risk Model on UKLS Screening Trial

The LLPv2 risk model (18) has been used to select high-risk individual in the United Kingdom Lung Screening (UKLS) (14). UKLS is a randomized, controlled trial of LDCT for lung cancer screening, following the Wald single-screen design. In short, the UKLS randomized subjects based on their ≥5 percent risk of developing lung cancer in the next five years (Fig. 3). Using this selection criterion shows that screening program can potentially be more cost-effective if it is limited to the high-risk segment of the population. A web version of the LLP risk model is available on www.MyLungrisk.org (19), which has now been updated to LLPv2.

Inclusion of SNPs in Risk Models

Much of lung cancer risk is explained by known epidemiological factors. Lung cancer risk prediction models have, therefore, tended to concentrate on these parameters (age, smoking, history of respiratory diseases, etc.) However, the current models are not perfect in terms of their discriminatory performance. In particular, it has been recognized that they have poor predictive accuracy in patients with early onset of lung cancer (20). The occurrence of lung cancer at a young age is more likely to be due to a genetic predisposition. There is potential to improve prediction of inter-individual risk by incorporating factors/markers associated with genetic variation. Initial attempts included 1) the incorporation of two markers of DNA repair capacity into the Spitz model (21), and 2) the incorporation of a genetic susceptibility polymorphism
(a SNP in SEZ6L) into the LLP model (22). Both incorporations enhanced prediction performance. However, the improvement was only modest in absolute terms, compared to the baseline models (ROC-AUC improvement ≤ 0.05) (21, 23).

**Risk Models to Evaluate "Indeterminate Nodules"

The basis of CT lung cancer screening is to identify lung nodules, which are at a level of suspicion whereby they are referred to a specialist clinical team for work-up and potential surgical intervention. It has been demonstrated that such nodules detected within screening trials are often very early stage disease and thus these patients have a very good clinical outcome. (2) However, nodules are common in the scans of many patients, and experienced radiologists using volumetric techniques can now measure these nodules and determine whether they are growing (3). The major clinical problem concerns nodules which are less than 10 mm in diameter or volume <500 mm³ and thus require potentially multiple repeat scans to determine the management.

The major issues in the implementation of CT screening for lung cancer are the definition of a positive result and the management of lung nodules detected on the scans. Williams, et al. (24) analyzed data from two cohorts of participants undergoing low-dose CT screening in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) and the British Columbia Cancer Agency (BCCA). Outcomes of all nodules were detected on baseline low-dose CT scans. Parsimonious and fuller multivariable logistic-regression models were prepared to estimate the probability of lung cancer. Their final parsimonious and full models showed excellent discrimination and calibration, with areas under the receiver-operating-characteristic curve of more than 0.90, even for nodules that were 10 mm or smaller in the validation set.

Recently the NELSON trial has provided a recommendation for calculating indeterminate nodule risk based on their own trial data which also included volumetric measurements (25). Data from the NELSON CT screening trial was utilized to quantify how nodule diameter, volume, and volume doubling time affect the probability of developing lung cancer within two years of a CT scan and based on this they proposed thresholds for management protocols.

They included all participants assigned to the screening group who had attended at least one round of screening, and whose results were available from the national cancer registry database. The NELSON group calculated lung cancer probabilities, stratified by nodule diameter, volume, and volume doubling time and did logistic regression analysis using diameter, volume, volume doubling time (VDT), and multi-nodularity as potential predictor variables. Then they assessed the management strategies based on nodule threshold characteristics for specificity and sensitivity, and compared them to the American College of Chest Physicians (ACCP) guidelines.

These authors demonstrated that small nodules (those with a volume <100 mm³ or diameter <5 mm) are not predictive for lung cancer. Immediate diagnostic evaluation is necessary for large nodules (>/= 300 mm³ or >/= 10 mm). Volume doubling time assessment is advocated only for intermediate-sized nodules (with a volume ranging between 100–300 mm³ or diameter of 5–10 mm). Nodule management protocols based on these thresholds performed better than the simulated ACCP nodule protocol.
Conclusion

The data from these trials has already started to change the management of indeterminate CT screen detected nodules, thus proving the power of “risk prediction modeling” in lung cancer, which will contribute to the methodology currently under discussion on “how to implement” lung cancer CT screening programs (26).

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