

The potential for using risk models in future lung cancer screening trials

John K Field* and Olaide Y Raji

Address: Roy Castle Lung Cancer Research Programme, School of Cancer Studies, University of Liverpool Cancer Research Centre, 200 London Road, Liverpool, L3 9TA, UK

* Corresponding author: John K Field (j.k.field@liv.ac.uk)

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Abstract

Computed tomography screening for early diagnosis of lung cancer is one of the more potentially useful strategies, aside from smoking cessation programmes, for reducing mortality and improving the current poor survival from this disease. The long-term success of lung cancer screening will be dependent upon identifying populations at sufficient risk in order to maximise the benefit-to-harm ratio of the intervention. Risk prediction models could potentially play a major role in the selection of high-risk individuals who would benefit most from screening intervention programmes for the early detection of lung cancer. Improvements of developed lung cancer risk prediction models (through incorporation of objective clinical factors and genetic and molecular biomarkers for precise and accurate estimation of risks), demonstration of their clinical usefulness in decision making, and their use in future screening programmes are the focus of current research.

Introduction and context

Lung cancer is the most commonly diagnosed cancer worldwide and the leading cause of all cancer deaths [1,2]. The disease is diagnosed mostly at an advanced stage, when surgical resection is unlikely to be a treatment option, thus leading to poor survival rates [3]. The 5-year survival rate for all stages of lung cancer ranges from 6% in the UK [4] to 15% in the US, in contrast to a survival rate of about 70% for stage I lung cancer, suggesting that early diagnosis and treatment of the disease would vastly improve outcome and reduce mortality [5].

Computed tomography (CT) screening has been highlighted as one of the potential strategies for early diagnosis of lung cancer [6-9]. However, the lung cancer research community is eagerly awaiting results of various ongoing screening trials (Table 1) evaluating the potential benefit of CT screening [6]. For optimum cost-effectiveness, a population of individuals at sufficiently high risk of the disease needs to be identified so that the benefit-to-harm ratio of the screening can be maximized [10]. The need for

the selection of a high-risk population for lung cancer screening has renewed international interest in developing methods for the prediction of an individual's risk of developing lung cancer.

There are now a number of lung cancer risk prediction models, including those of Peto and colleagues [11], Bach and colleagues [12], Spitz and colleagues [13], and the Liverpool Lung Project (LLP) [14]. These models use a selection of data which includes the patient's self-reported information on epidemiological and clinical risk factors with local lung cancer incidence data to predict the individual's risk within a specified period. For example, the LLP risk model included information on the patient's smoking duration, prior diagnosis of pneumonia, asbestos exposure, previous diagnosis of a non-melanoma malignant tumour, and family history of lung cancer (using age of diagnosis in first-degree relatives). The individual's 5-year absolute risk of lung cancer was then estimated by combining the relative risk model with age- and gender-specific lung cancer incidence rates [14].

Table 1. Low-dose computed tomography randomized clinical trials for lung cancer screening

Country, study name	Patients receiving LDCT	Patients in control arm	Study design	Selection of participants	Report date	Publications
The Netherlands and Belgium, NELSON	8000 ^a	8000 ^a	LDCT versus no intervention	Smokers and ex-smokers with a history of >30 PKS	Recruitment completed Report 2015	[9,33]
Denmark, NELSON	2000 ^a	2000 ^a	LDCT versus no intervention	Smokers and ex-smokers with a history of >30 PKS	Recruitment completed Report 2015	[34]
Italy, Italung-CT	1500	1500	LDCT versus no intervention	Smokers and ex-smokers with a history of >30 PKS	Report 2005	[35]
DANTE	1276	1196	Chest X-ray and sputum cytology for all patients in year 1. LDCT versus yearly review.	Smokers with a history of >20 PKS	Report 2007	[36]
France, (pilot) Dépiscan	330	291	LDCT versus chest X-ray	Smokers (64%) and ex-smokers (36%)	Report 2006	[37]
USA, LSS feasibility study	1600	1658	LDCT versus chest X-ray	Smokers with a history of \geq 30 PKS	Report 2005	[38]
USA, NLST	26,500	26,500	LDCT versus chest X-ray	Smokers and ex-smokers with a history of \geq 30 PKS	Recruitment completed	[39,40]

^aPlanned recruitment. Pack years (PKS) = (packs smoked per day) \times (years as a smoker). DANTE, Randomized Study on Lung Cancer Screening With Low-Dose Spiral Computed Tomography; Dépiscan, Pilot Study to Evaluate Low Dose Spiral CT Scanning as a Screening Method for Bronchial Carcinoma; Italung-CT, Multicentric Randomised Clinical Trial for Lung Cancer Screening with Low-Dose CT; LDCT, low-dose computed tomography; LSS, Lung Screening Study; NELSON, Dutch-Belgian Randomised Lung Cancer Screening Trial; NLST, National Lung Screening Trial. Table modified and updated from Field & Duffy, *Br J Cancer* 2008 [6]. Copyright © 2008 Cancer Research UK.

Risk prediction models could be incorporated into the design, recruitment, and analysis of studies of lung cancer prevention programmes, potentially reducing the sample size required to achieve the desired statistical power for outcome benefit [12]. We recently discussed the potential use of the LLP risk model in the design of a CT screening trial and a population screening intervention programme in the event of positive results from the trial [15]. The results reveal that increasing the minimum 5-year absolute risk criterion of individuals to be selected in a screening trial from 1.5% to 2.5% reduces the required sample size by approximately one-third.

Recent advances

Ideally, the lung cancer community needs to be developing risk prediction models that embrace not only epidemiological parameters but also emerging genetic and molecular biomarkers [16] (Figure 1). Recently, three major genome-wide association studies in lung cancer identified genetic susceptibility genes strongly associated with lung cancer [17-19]. The promise of the expansion of genomic research is that many more biomarkers will be identified and validated in case control studies with specimens such as serum, plasma, bronchial lavage, induced sputum, or tissue. It is anticipated that the addition of these biomarkers or their combinations into existing risk models would improve the precision and accuracy of the predicted risks [16,20]. This has led to the recent quest to identify the best methodology for assessing improvements in risk models, which incorporate additional risk factors such as genetic biomarkers. The recent

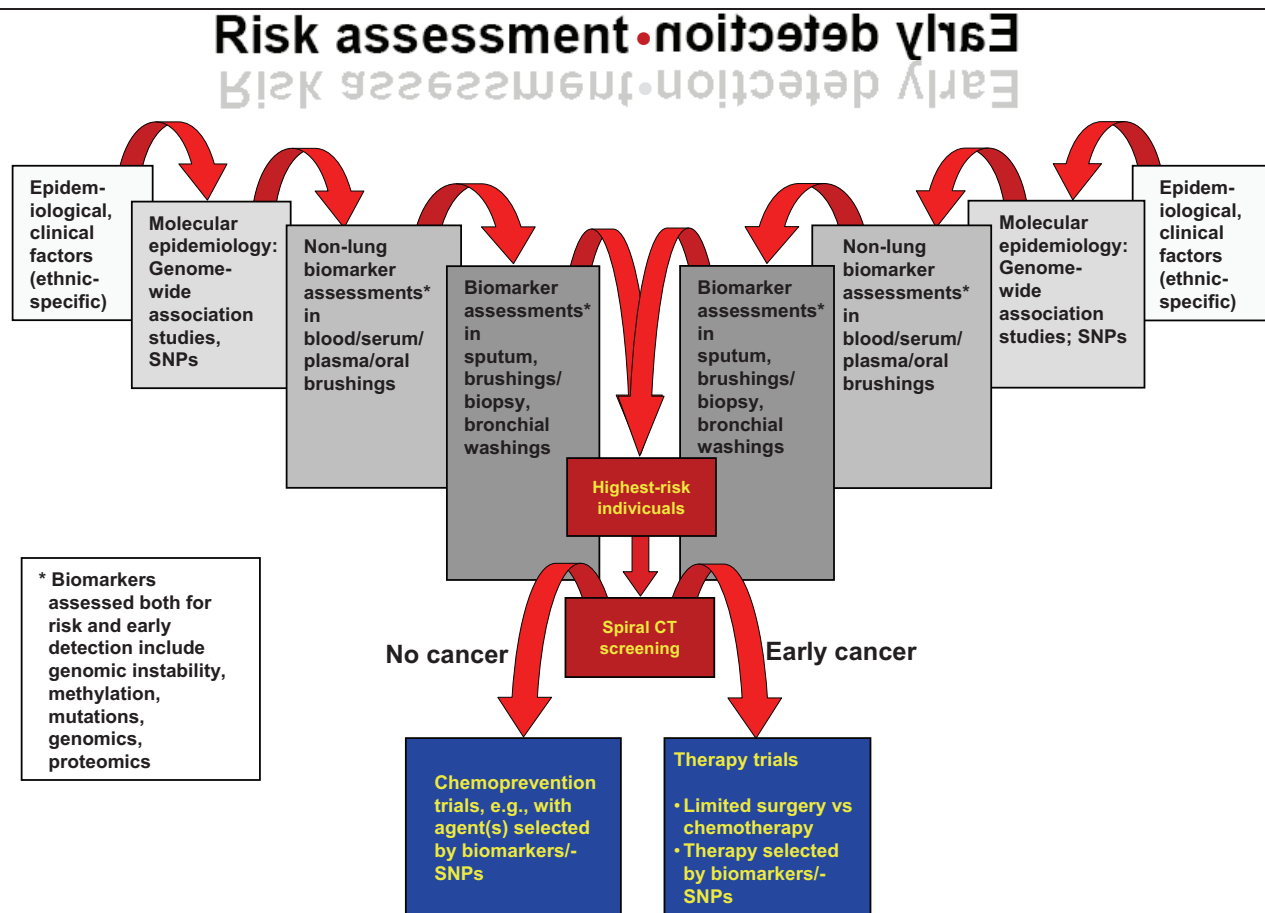
emergence of new methodologies such as decision curve analysis and relative utility of risk models has put assessment of risk model performance in clinical perspective rather than using pure statistical measure [21-24].

Recently, two specific respiratory risk factors have been highlighted in the development of lung cancer, that of pre-existing tuberculosis [25] and chronic obstructive pulmonary disease (COPD) [26]. The inclusion of these risk factors, particularly an objective COPD measurement (ratio of forced expiratory volume in 1 second to forced expiratory capacity, or FEV₁/FEC) and other validated clinical information, in place of self-reported responses to questionnaire data would alleviate the impact of recall bias on the estimated risks.

Implications for clinical practice

In recognizing the impact of late diagnosis of cancer, the Cancer Reform Strategy recently established a National Awareness and Early Diagnosis Initiative (NAEDI) with a view to continuously promote early diagnosis in the large majority of patients who present with symptoms [27]. The NAEDI-hypothesized pathways for late presentation include low awareness of the signs and symptoms of cancer among the public as well as delay occurring within primary care, which may be due to inadequate access to a decision tool that may assist general practices (GPs) to reassure or observe patients, request further investigations, or refer patients to specialist services. As a result, there are now plans to equip every GP within a period of 5 years with a computerized algorithm to predict cancer risk [28].

Figure 1. Lung cancer risk model decision cascade



Mirror images of shared aspects of the cascades of lung cancer risk assessment (left) and early detection (right) are shown. These cascades move from clinical and epidemiological assessments to molecular epidemiological assessments to biomarker assessments in non-lung samples and finally to biomarker assessments in lung samples. They merge in the middle with the identification of the highest-risk individuals who need computed tomography (CT) screening. Individuals with a positive CT scan will be entered into clinical workup and treatment protocols. Those with a negative CT scan are clearly at a high risk and should be considered for prevention research studies. SNP, single-nucleotide polymorphism. Image originally published in Field, *Cancer Prev Res* 2008 [16]. Copyright © 2008 American Association of Cancer Research.

Meanwhile, risk models need to be validated in different populations and demonstrated to be clinically useful for making decisions regarding patient treatment or clinical interventions before they can be acceptable as decision tools by clinicians [29,30]. This is rarely undertaken as only a few existing models, including those for lung cancer, have been validated in independent populations. The validation of the LLP risk model in data from three independent studies revealed promising results (unpublished data); the model displayed good clinical utility by performing better than all other alternative approaches for making decisions about whom to screen or not to screen for lung cancer.

The LLP risk model has been implemented in a feasibility study (funded by the Knowsley Primary Care Trust, UK)

in the primary care setting [31] and is being evaluated in other high-risk GP locations. The outcome of this study will provide important public health guidance as to how to identify individuals who are at risk of developing lung cancer prior to developing symptoms. Also, an assessment of the model in the UK Lung Cancer CT Screening Study (UKLS) trial [32] was successful; therefore, it has been recommended as a major tool in stratification of patients to be screened in the general population.

In conclusion, screening and other clinical interventions for prevention and early diagnosis of lung cancer would be cost-effective if targeted on patients at sufficient high risk. Risk models provide useful tools to stratify patients into high or low risk and provide counselling regarding level of risks, motivating changes in personal lifestyle.

Abbreviations

COPD, chronic obstructive pulmonary disease; CT, computed tomography; GP, general practice; LLP, Liver-pool Lung Project; NAEDI, National Awareness and Early Diagnosis Initiative.

Competing interest

The authors declare that they have no competing interests.

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