



Prospects for cost-effective lung cancer screening using risk calculators

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Lung cancer is the most common cancer and greatest cancer killer worldwide (1). With up to 85% of lung cancers caused by tobacco smoke, it is a largely preventable disease (2). Since the US Surgeon General's report on the health hazards of smoking in 1967 (3), ongoing and comprehensive tobacco control has resulted in declining smoking and lung cancer rates in many high-income populations. Nevertheless, because of population growth and ageing, combined with the 20–30-year lag between population-level tobacco exposure patterns and changes in lung cancer mortality rates, the burden of lung cancer is likely to remain high for many years (especially in low-middle income countries). In countries with more recent trends for increased tobacco uptake, lung cancer mortality is continuing to rise and 40% of all lung cancers now occur in China and India (1). Primary prevention with sustained tobacco control is an effective long-term strategy for reducing the burden of lung cancer but there is potential to supplement tobacco control with interventions that might be effective in reducing mortality in the shorter term. Modelled predictions have suggested it could take more than 50 years to see an elimination of the smoking-related health burden in relation to tobacco-free endgame scenarios (4). Further, in many high-income countries, as smoking cessation rates increase, the lung cancer rates among former smokers become significantly higher than in current smokers, reflecting the irreversible genetic impact of tobacco smoking and a lifetime of continued elevated lung cancer risk (5). Thus, although primary prevention with sustained tobacco control is an effective long-term strategy for reducing the burden of lung cancer, the full benefits of these interventions will not be realised for many years to come, and,

in the interim, lung cancer screening might have potential to make a significant impact.

Lung cancer screening with low-dose computed tomography (LDCT) was demonstrated to reduce lung cancer mortality by 20% [95% confidence interval (CI): 6.8–26.7%] in the US National Lung Screening Trial (NLST) (6) and in a recent preliminary report, by 26% (95% CI: 9–41%) among men in the Netherlands-Leuven Screening Trial (NELSON) (7). Both trials had eligibility criteria determined by age (55–74 years) and smoking history, and both have underpinned favourable cost-effectiveness estimates (8–11). Many organisations in high-income countries are now recommending annual lung screening with LDCT using variations of the NLST eligibility criteria (i.e., those aged 55–74 years with a ≥ 30 -pack-year smoking history, including those who quit within the past 15 years) (12–17). Based on modelled analyses (18), the United States Preventive Services Task Force (USPSTF) recommended extending the age of screening up to age 80 years in this group (19). Outside the US, lung cancer screening has not been systematically introduced, in part because many questions remain with regard to cost-effectiveness in different settings, which will be influenced by the choice of target population (16).

Accurately identifying the target population for screening is also important for minimising harms, which include adverse psychological sequelae of screening, invasive follow-up testing and potential over-diagnosis of indolent tumours (20). Risk-targeted lung screening using individualised risk calculators that incorporate demographic and clinical factors in addition

to smoking history have been shown in some settings to have better predictive performance than the USPSTF eligibility criteria (21). One in particular, the PLCO_{m2012} (22), has been widely validated and is now recommended in the US National Comprehensive Cancer Network guidelines for lung cancer screening (21). While risk calculators are expected to increase screening efficiency, it has been unclear to what degree risk-targeted screening will improve cost-effectiveness.

Recently, Kumar and colleagues published a cost-effectiveness evaluation of risk-targeted LDCT lung screening by calculating cost-effectiveness ratios (CER; ratio of costs to benefits of LDCT *vs.* chest radiography) within groups defined by decile of lung cancer mortality risk in a re-analysis of the NLST data (23). NLST participants were assigned a level of risk using hazard ratios derived from a multi-state regression model. The regression model included factors identified as having predictive significance by the PLCO_{m2012} risk calculator (22). Broadly consistent with the original NLST findings, they concluded that 80% of screen-detected, lung cancer deaths could be averted by targeting the highest-risk 60%, and that the CERs varied from \$75,000 to \$53,000 per quality-adjusted life year gained in the lowest to the highest risk decile. In the current US setting, both these estimates would be considered likely to be cost-effective.

This analysis should be interpreted in context of a prior Canadian analysis which also found that risk-targeted lung cancer screening using the PLCO_{m2012} risk calculator could be cost-effective (24). Kumar and colleagues conclude that, *“Although risk targeting may improve screening efficiency in terms of early lung cancer mortality per person screened, the gains in efficiency are attenuated and modest in terms of life-years, QALYs, and cost-effectiveness”*. An alternate approach to this cost-effectiveness analysis would have involved calculation of the incremental cost-effectiveness of screening progressively larger populations defined by progressively lower thresholds of risk using the risk assessment tool. Such incremental analysis would then allow construction of a cost-effectiveness frontier curve, and after checking for dominated strategies, the calculation of incremental cost-effectiveness ratios (25). This alternative approach would be useful for informing policy, especially if paired with a budget impact study.

From a cost-effectiveness perspective, country-specific policy decision-making processes and conventions for health economic evaluations will contribute to the possibility of reaching different conclusions; notably many countries set a lower indicative willingness to pay threshold than that usually set in the US. Further, seemingly marginal gains in cost-effectiveness for individualised risk

estimated from a short-term trial that was terminated after three annual screens may translate into significant reductions in overall budget impact. Thus, depending on health system affordability, the variation in CERs reported by Kumar *et al.* across the spectrum of low to high risk is not insignificant and their demonstration of a cost-effectiveness gradient in relation to risk is an important finding. Furthermore, as they noted, the inclusion of the costs of chest X-ray in the calculation will mean that CERs may change in countries where chest radiography is not a part of routine care. Overall, further evaluation of the benefits and cost-effectiveness of risk-stratified lung screening in specific settings is warranted.

As they acknowledged, and as has been previously noted (26), an intrinsic limitation of Kumar *et al.*'s analysis is the restriction of risk assessment to participants meeting the NLST criteria. In a population setting, there will be lung cancer cases that meet the high-risk criteria from a risk calculator that do not meet the NLST criteria and therefore were not accounted for in Kumar *et al.*'s analysis. These include, in particular, people from low socioeconomic and minority groups, and/or those with a family history of lung cancer, because these factors are specifically part of risk assessment. Data from prospective studies of lung screening using risk calculators are accruing and can be used to inform both implementation and cost-effectiveness evaluations of risk-targeted screening within clinical settings (27,28). For example, the UK Lung Screening Trial uses the Liverpool Lung Project Prediction Model to determine eligibility and demonstrated that high-risk individuals could be recruited with a 2.1% lung cancer detection rate after a single screen, equivalent to the rate seen after three annual screens in the NLST (28). The extent of potential complexities related to implementation of risk-based eligibility criteria, and whether they outweigh the complexity of implementing USPSTF-like eligibility criteria is largely unknown and will also depend on the health system and recruitment strategy. Prospective studies will be required to assess these potential implementation complications.

Whether screening eligibility is based on individualised risk or simpler smoking and age criteria, achieving sufficient participation rates in a population-based screening program will be a significant challenge. In high-income countries where smoking rates are declining, long-term heavy smokers are now disproportionately represented in low socioeconomic, marginalised, and/or minority groups that are likely to be hard to reach (2,29). Furthermore, the target population for lung screening is only one of many factors that will determine the optimal level of cost-effectiveness of

any lung screening program. Economic evaluations based on NLST outcomes have identified other key factors that impact on cost-effectiveness including management of incidental findings, smoking cessation rates, and the potential for screening-related disutility (10,24,30,31). Ultimately, only implementation trials will reduce uncertainty in these areas and should be focused on effective recruitment strategies and accessibility to screening and treatment centres, evaluating effective risk communication to minimise anxiety around indeterminate and false positive screening results, adjunct smoking cessation interventions, quantifying the costs and outcomes of clinically relevant incidental findings, and adequately capturing quality of life outcomes in relation to screening and both lung and non-lung cancer related events. As these data accrue, microsimulation modelling studies that take into account dynamic changes in smoking behaviours across birth cohorts over time will be able to inform decision-making around the optimization of trade-offs between these drivers of screening efficiency (9-11,32).

Although many countries have delayed recommendations for lung cancer screening, the highly anticipated, favourable results of the final round of the NELSON trial may hasten investment in implementation, especially in Europe. Cost-effectiveness analyses for Canada have been favourable and implementation studies are underway (e.g., the Cancer Care Ontario study) (10,33). In Australia and New Zealand, early cost-effectiveness analyses based on NLST eligibility criteria have not been favourable (30,31), and will need to be updated over time as new data become available. Given that significant reductions in lung cancer mortality have now been demonstrated in two lung screening trials, across two different settings, reducing uncertainty around the implementation of lung screening in local health systems should be an immediate research priority. Overall, the full benefits of lung screening using risk-calculators for cost-effectiveness is yet to be demonstrated and is likely to be population specific.

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