Opportunities and challenges for implementation of cost-effective lung cancer screening

By Dr. Marianne Weber, Dr. Stephen Wade & Prof. Karen Canfell

In this article, we summarize the findings of our recent cost-effectiveness evaluation of lung cancer screening with low-dose computed tomography (LDCT) [1] in which we applied Australian health services costs and population-based survival data to the outcomes observed in the U.S. National Lung Screening Trial (NLST) [2] and assessed the impact of a range of screening scenarios on incremental cost effectiveness ratios (ICER) [1].

Our base case estimate was A$138,000 (± €87,000) per life-year gained and $233,000 (± €146,000) per quality-adjusted life year (QALY) gained.

Compared to an indicative willingness-to-pay threshold of A$30,000-50,000 (± €19,000 - € 31,500) lung screening is not yet likely to be cost-effective in Australia. Variation in base-case parameters resulted in ICER estimations that ranged from A$127,000 to A$509,000 (± €80,000 to €320,000) per QALY gained.

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Lung cancer is a major health problem worldwide [3], with tobacco smoking responsible for up to 85% of cases [4]. Although comprehensive investment in tobacco control is the most important long-term strategy for primary prevention, the full benefits of these interventions will not be realized for many years to come [5]. Lung cancer screening with LDCT has the potential to significantly reduce the lung cancer mortality burden, especially in countries with historically high smoking rates and effective tobacco control initiatives [6].

Lung screening of asymptomatic individuals using LDCT reduced the risk of lung cancer mortality in the U.S. National Lung Screening Trial (NLST) by the detection of cancerous pulmonary nodules when at an early, potentially curable stage [2]. Current- and ex- smokers (who quit within the past 15 years) aged 55-74 years, with a ≥30-pack-year smoking history and screened annually with LDCT over three years had a 20% (95% confidence interval [CI]: 6.8%–26.7%) lung cancer mortality benefit after six years of follow-up compared to those who received three annual chest x-rays [7]. The trial had a relatively favorable health economic evaluation, with an incremental cost effectiveness ratio (ICER) of US$81,000 per quality-adjusted life year (QALY) saved for LDCT screening [2].

Many organizations in high-income countries now recommend annual lung screening with LDCT using variations of the NLST eligibility criteria [8-13]. Outside the U.S., lung cancer screening has not been systematically introduced, in part because of uncertainty around cost-effectiveness and budget impact in different settings [12]. Health economic evaluations are dependent on the underlying assumptions required to translate trial results into a population-based setting, which are necessarily less reliable where evidence is lacking. Cost-effectiveness evaluations for the United Kingdom [14], Germany [15], Switzerland [16], New Zealand [17], Canada [18-20], and the United States [21] have since modelled the NLST strategy and/or outcomes within a population-wide setting, and have demonstrated similar variations in results to ours.

In our sensitivity analyses, the most cost-effective screening scenario was due to the inclusion of non-lung cancer deaths in the evaluation. The NLST reported a statistically significant, 6.7% (95% CI, 1.2-13.6) mortality benefit of LDCT screening on deaths from any cause (3.2% due to deaths other than lung cancer) [7]. Given the smoking history of those eligible for lung cancer screening, it is not surprising that LDCT imaging from the lower neck to the upper abdomen detects other smoking-related, clinically significant abnormalities (e.g., coronary artery calcification, chronic obstructive pulmonary disease) that when treated, has the potential to save additional lives [22].

However there is, as yet, no standard approach to the reporting and management of screen-detected incidental findings, which are common, and the definition of clinical relevance is left to the discretion of the radiologists [23]. Although we modelled the potential mortality benefit of treating incidental findings, we were not able to account for the potential harms and costs of overtreatment, which are still largely unknown. To what extent the treatment of incidental findings is likely to impact resource allocation and costs within the health system, and more specifically, the need for access to health services beyond the scope of a lung screening program, is also uncertain. We modelled a nominal cost of A$2000 (€1260) per incidental finding, with an estimate of one incidental finding in 19% of participants (based on a Canadian study [22]), which resulted in a more favorable cost-effectiveness estimate than modelling lung cancer outcomes alone. Given the current uncertainty around costs and management of incidental findings, health economic evaluations that focus on lung cancer mortality outcomes alone are likely to be more reliable, but will not capture the potential benefits of treating smoking-related comorbidity. This remains an area in need of further research.

"... Lung cancer screening is possibly a "teachable moment" for current smokers ... "

The least cost-effective scenario we estimated was due to the assignment of a high disutility weight to false-positive screening results. In the NLST, more than 20% of LDCT participants required follow-up after their first screen [7], however quality of life was not measurably affected by screening result. However, in the Netherlands-Leuvens screening trial (NELSON), clinically significant psychological distress was observed at two months post-screening among participants with an 'indeterminate result' requiring three months surveillance [24]. Thus, we modelled a hypothetical drop in utility for two months following a positive screen (i.e., 0 vs. 0.05; similar to sensitivity analyses in the NLST evaluation [2]) and the ICER estimate ($/QALY) more than doubled as a result. The difference between NELSON and NLST findings in terms of the psychological impact of positive results could potentially be due to differences in the nodule management protocol, differences in the tool used to assess distress, differences in the risk communication protocol, and/or differences in the degree of health literacy of trial participants. Local implementation trials that incorporate population-specific assessments of health literacy and effectiveness of risk communication strategies will identify ways to minimise unnecessary psychological distress in relation to screening, and maximise cost-effectiveness.

We found that varying the number of false-positives and the cost of follow-up had a greater impact on cost-effectiveness than varying the cost of lung cancer treatment itself, even after accounting for the increasing costs of newer therapies for advanced disease. The number and cost of false positive screens depends on the definition of a positive scan and the nodule management strategy employed. In the NLST, a positive screening result was defined as a non-calcified nodule with a longest diameter of ≥ 4 mm [7]. Studies of nodule management since the NLST have demonstrated that in a lung screening setting, the largest lung nodules are not necessarily the ones that are malignant [25]. Improved nodule management protocols such as the Brock (Pan Can) nodule malignancy risk calculator [25], which is an externally validated, predictive tool that incorporates a number of individualized patient and clinical factors [26-29], are likely to result in fewer false positives than that observed in the NLST. Indeed, the tool has been incorporated into the screening guidelines of the American College of Radiology (Lung-RADS [30]) and the British Thoracic Society [31]. However the optimal balance between positive predictive value and sensitivity for a screening population remains a topic of discussion [32].

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Our evaluation did not incorporate the potential mortality benefits that an adjunct smoking cessation intervention would have for current smokers, which has been shown to significantly improve cost-effectiveness [17, 19, 21, 33]. Lung cancer screening is possibly a "teachable moment" for current smokers, with evidence that quit rates are higher among screening participants than in the general population [34, 35]. In terms of cost-effectiveness, the additional benefits of a smoking cessation program for people aged 55 years and over will be dependent on the number of current smokers who participate in screening as well as the survival benefits that might be gained in this group. In Australia, like other high-income countries, the prevalence of smoking is now relatively low (12.2% in 2016 [36]) and the proportion of ex-smokers among lung cancer cases is expected to grow. Importantly though, long-term current smokers are now disproportionately represented in low socioeconomic, marginalized, and/or minority groups that are traditionally hard to reach [4, 37]. Recruitment of these population sub-groups to lung cancer screening programs is likely to be a challenge, and should be a focus of implementation studies [37]. Continued investment in tobacco control outside the context of a screening program will also remain a priority for these groups.

Recently, the results of the final round of the largest European lung screening trial, the Netherlands-Leuvens screening trial (NELSON) were announced [38]. Specifically, 7915 participants aged 50-74 years, who had smoked >15 cigarettes per day for more than 25 years or >10 cigarettes per day for more than 30 years, including those who quit within the past 10 years were randomized to LDCT screening or usual care [39]. After ten years of follow-up, there was a significant 26% (95% CI 9%-41%; p=0.003) lung cancer mortality benefit among men [38]. Cost-effectiveness evaluations that have modelled the NELSON trial eligibility criteria have had favorable outcomes [15, 16]. A cost-effectiveness evaluation directly based on data from the trial itself would potentially provide further momentum for lung screening protocol development and implementation in Europe. Our evaluation demonstrated that lung cancer screening with LDCT was unlikely to be cost-effective in Australia based on NLST outcomes. However, our analysis could be updated to reflect improvements in lung screening protocols since the NLST, including the use of risk prediction tools for defining eligibility criteria [40].

CONCLUSION

Ultimately, for countries like Australia with a lower indicative willingness-to-pay threshold than the U.S. and a relatively small population spread over a vast geographic area, favorable cost-effectiveness evaluations will need to be accompanied by budget impact analyses and well-designed local implementation studies to optimize recruitment and accessibility. The proven effectiveness of lung cancer screening and the large number of lung cancer deaths annually both in Australia and worldwide, means that optimizing lung cancer screening should be a research imperative.

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