Manners David (Orcid ID: 0000-0002-0046-0870)
Leong Tracy (Orcid ID: 0000-0002-1950-1505)

Lung cancer screening in Australia and New Zealand: the evidence and the challenge

Manners D[1], Dawkins P[2], Pascoe D[3], Crengle S[4], Bartholomew K[5], Leong TL[6,7,8]

1 St John of God, Perth, Western Australia, Australia
2 Department of Respiratory Medicine, Middlemore Hospital, Auckland, NZ
3 Royal Melbourne Hospital, Parkville, Victoria, Australia
4 Department of Preventative and Social Medicine, University of Otago, New Zealand
5 Planning Funding and Outcomes, Waitematã and Auckland District Health Boards, Auckland, NZ
6 Austin Health, Heidelberg, Victoria, Australia
7 Institute of Breathing and Sleep, Heidelberg, Victoria, Australia
8 University of Melbourne, Parkville, Victoria, Australia

Corresponding author:
Dr Tracy L Leong

Department of Respiratory and Sleep Medicine, Austin Health, 145 Studley Road, Heidelberg, VIC 3084

tracy.leong@austin.org.au

+61 438 852675

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Introduction

Lung cancer remains the leading cause of cancer mortality in Australia and New Zealand (NZ) with a five-year survival of 17% in Australia and 11% in NZ.[1] This is largely due to diagnosis occurring in advanced stages of disease. Targeted screening of individuals at highest risk of lung cancer aims to identify early stage disease which is more amenable to curative treatment. Previous policy recommendations in Australia and NZ have acknowledged the efficacy of lung cancer screening with low-dose computed tomography (LDCT) in clinical trials, but have advised against implementation.[2] However, recent developments have updated the evidence base of screening and shifted policy discussions regarding implementation.[3] This review provides latest international evidence and discusses implementation challenges in Australia and NZ.

Updating the evidence base of lung cancer screening

Benefits

In recent years, several randomised controlled trials of lung cancer screening have completed follow-up. The landmark U.S. National Lung Screening Trial (NLST) reported findings from over 53,000 individuals, aged 55-75, with a 30 pack-year smoking history who continued to smoke or stopped within 15 years.[4] Participants received three annual screenings with LDCT or chest radiography. The study demonstrated 20% (95%CI 6.8-26.7) relative reduction in lung cancer-specific mortality and 6.7% (95%CI 1.2-13.6) relative reduction in all-cause mortality in the LDCT group. Subsequently, the U.S. Preventative Services Task Force released a recommendation of targeted annual screening for lung cancer using LDCT.[5]

The final results of the largest European randomised controlled trial, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), were released in 2020.[6] This study included over 15,000 participants, aged 50-74, with a 15 pack-year current or less than 10 years cessation smoking history. Participants were randomised to receive LDCT or no screening at baseline, years 1, 3, and 5.5. At 10 years of follow-up, 24% (rate ratio [RR] 0.76, 95%CI 0.61-0.94) and 33% (RR 0.67, 95%CI 0.38-1.14) relative reductions in lung cancer associated deaths in males and females respectively, were observed in the

screening group compared with the control group. There was no difference in all-cause mortality (RR 1.01, 95% CI 0.92-1.11).

Additionally, a systematic review and meta-analysis of randomised controlled trials published until June 2019 confirmed that LDCT screening is superior to usual care in lung cancer survival. The magnitude of benefit of screening is, however, heavily dependent upon the risk profile of the target group.[7]

Harms

False-positive results are a potential harm of any screening modality, along with the resultant diagnostic work-up and complications thereof. In the NLST, the false-positive rate for LDCT was 27% in each of the first two rounds, decreasing to 16.8% in the third round.[4] While the majority of false-positive findings were followed with imaging modalities, 0.6% of resulted in an invasive diagnostic procedure and 0.06% experienced complications. In contrast, the NELSON study which utilised volumetric screening, showed a lower false-positive rate of 1.2% over all screening rounds and reduction in unnecessary diagnostic procedures.[6]

Overdiagnosis describes the detection of cancer through screening which would never have become symptomatic or been discovered otherwise, and may have consequences of provoking anxiety and potential for complications of unnecessary treatment. Utilising NLST data, Patz *et al.* estimated an upper boundary of overdiagnosis risk of 18.5%.[8] In comparison, the NELSON trial reported an overdiagnosis rate of 8.9-19.7%.[6]

Radiation exposure from CT imaging is often cited as a reason to minimise screening. Based on the assumptions of an average radiation dose of 1.5 mSv per LDCT and annual screening, Frank *et al.* estimated an excess cancer risk of 0.07% for males and 0.14% for females.[9] In context, Rampinelli *et al.* reported that radiation from 10 years of screening would induce one major cancer for every 108 screen-detected lung cancers.[10]

Cancer screening has the potential to widen health inequities. Despite high lung cancer incidence and mortality, there is a risk of low uptake in Indigenous and socioeconomically marginalised communities given the evidence of inequities of access and outcomes in other cancer screening programs.[11,12]

Context in Australia and NZ

Internal validity and external generalisation of these studies to the Australia and NZ context warrants critical review.

Cochrane reviews have judged the NLST study to be low risk of bias.[13] The NELSON protocol described random sequence generation and allocation concealment for randomisation and low incomplete outcome data which reduces bias.[6] However, measurement of the primary outcome changed during the study. The first 266 deaths were reviewed by a blinded committee. After a comparison showing a high rate of concordance between the committee's judgement and official cause of death, the remainder of primary outcomes were determined by official registry certificates. Potential bias may arise due to unblinding of the outcome by the physician completing the death certificate.

There may be limits to generalisability of these studies to Australian and NZ settings as exemplified by variation in study participants and outcomes between the NLST, NELSON, Queensland Lung Cancer Screening Study,[14] and general populations (Table 1). In the absence of an implementation pilot, the ongoing International Lung Screen Trial with Australian sites and a potential equity-focused screening trial in NZ will provide local screening expertise and data on these metrics.[15]

Changing the policy imperative

On World Lung Cancer Day 2019, Cancer Australia were invited to conduct an inquiry into the feasibility of lung cancer screening in Australia. Focus points included cost-effectiveness, target population, recruitment, and other areas of implementation concern.

Cost-effectiveness

Cost-utility analyses of LDCT screening report variable incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year (QALY) due to not only the underlying studies that quantify the various benefits (lung-cancer vs all-cause mortality reduction) and harms, but also due to variability in cost estimates, differences in types of costs included (e.g. lost productivity), and the choice of perspective (provider/patient vs societal). In addition, intangible effects, such as anxiety, are difficult to apply to numerical cost estimates.

International analyses report ICERs ranging from UK£8,466 for a one-off screen in the UKLS study[22] to US$81,000 in the NLST.[23] Villanti *et al*. estimated the cost per QALY in a cohort of high-risk subjects (≥30 pack-years) aged 50 to 64 undergoing annual screening for 15 years.[24] Their analysis yielded a cost-utility ratio of US$28,000 per QALY. This is in contrast to US$8,552 and US$53,000 per QALY for colonoscopy and biennial mammography respectively. The study concluded that cost-effectiveness of lung cancer screening was in line with other screening interventions and supported inclusion of LDCT screening for lung cancer in high-risk populations in clinical recommendations. Use of risk prediction models and smoking cessation programs have substantially improved cost-effectiveness estimates internationally.[25]

Australian studies have been contradictory. Prior to the NLST results, Manser *et al.* estimated that lung cancer screening in Australia could be cost-effective under ideal conditions.[26] Wade *et al.* utilised NLST data with Australian cost and survival data to estimate the cost per QALY-gained to be AU$233,000.[27] The large discrepancy between this estimate and the formal NLST cost-effectiveness analysis may be due to inclusion of all-cause mortality benefit and using a lifetime horizon in the NLST analysis.[23]

In NZ, a previous BODE^3 analysis has produced revised results showing that lung cancer screening is likely to be cost-effective for Māori.[3] The overall ICER was US$44,000 per QALY gained. Cost-effectiveness varied by socio-demographics, from US$21,000 for 70-74 year-old Māori females to US$60,000 for 55-59 year-old non-Māori males. An updated model using NELSON and NZ specific data concluded that lung cancer screening was cost-effective for all population groups in NZ.[28]

Target population

LDCT screening only reduces lung cancer-specific mortality in those with the highest risk. Recently released draft changes to U.S. eligibility criteria are based on age (50-80 years) and smoking history (20 pack-years with current smoking or cessation within 15 years).[29]

Risk prediction models, such as the $PLCO_{m2012}$, are more sensitive at detecting lung cancer than current eligibility criteria.[30] The $PLCO_{m2012}$ model with >1.5% eligibility threshold has been externally validated in a large Australian population with improved sensitivity (69.4% vs 57.3%) but reduced specificity (72.0% vs 75.2%) compared to current U.S. criteria.[31] Furthermore, recent analyses suggest that inclusion of ethnicity is required

within risk tools due to ethnic differences in risk of cancer at equivalent smoking exposures and differences in age at diagnosis.[32]

There is no evidence that screening lower risk individuals reduces lung cancer mortality. However, 72% of Australian ever-smokers have a preference for undergoing screening, which is related to perceived seriousness of lung cancer, and not eligibility status.[33] Limiting ad-hoc screening for those who do not meet eligibility criteria is critical to maximising benefits while minimising harms.

Recruitment

Current population-based cancer screening interventions systematically invite eligible individuals via direct contact using principles based on the Population Based Screening Framework in Australia[34] and the Quality Framework in NZ.[35] Eligible individuals are identified from administrative datasets based on age and sex only.

In contrast, there are no datasets that collect variables required for lung cancer screening eligibility assessment. In order for population-based recruitment to be implemented, individuals in the age-defined cohort would be invited to undergo assessment of lung cancer risk. Those meeting the eligibility criteria would progress to screening after a shared decision-making process. However, this approach is inefficient as only 10-14.5% of 55-74 years olds meet eligibility criteria.[36]

An alternative approach would be for General Practitioners (GPs) to identify high-risk individuals for screening. Potential benefits include leveraging strong patient-GP relationships to encourage screening; counselling concerned yet ineligible individuals against seeking screening; providing smoking cessation interventions; managing screen-detected incidental findings; and supporting cancer survivorship.[37] Such an approach will require educational support for primary care providers as Australian GPs are performing lung cancer screening in excess of current recommendations.[38] In NZ, current cancer screening programs utilising the GP invite approach are limited by ethnic inequities in participation and lack of a central population register. However, there is high quality primary care enrolment data which could form the basis of alternative lung cancer screening recruitment using opportunistic and invitation-based methods.

Access to specialist services

Processes to report CT scans will depend on infrastructure and workforce. While the use of existing scanners may be possible initially, there will be a need to purchase new infrastructure, including computer-aided diagnosis (CAD) software and mobile scanners to improve access in vulnerable populations.[39] The number of reporting radiologists required will depend upon the screening interval; use of CAD; uptake rate of screening within at-risk populations; and accreditation requirements for screen-reading. The potential for radiologist “burn-out" will need to be factored into longer-term workforce calculations.[40] Infrastructure and workforce requirements related to increased demand for PET-CTs and biopsies must also be addressed, and clear guidelines will be needed for the reporting and management of incidental findings on CTs.

Implementation of lung cancer screening will necessitate adequate provision of specialist services to diagnose and treat screen-detected lung cancers. In a large Victorian cohort of lung cancer patients, only 50% underwent surgery within the current recommended timeliness target of 42 days as set by the Optimal Care Pathways[41], similar concerns about timeliness to diagnostics and treatment exist in NZ.[42] Auckland and Waitematã District Health Boards in NZ are currently developing a readiness assessment tool to examine service level impacts. Equitable access to screening and downstream management for all populations is required, especially those living in regional/remote areas, Aboriginal and Torres Straight Islanders, Mãori, and people from non-English speaking backgrounds.

Consumer communication throughout the screening process

For screening-eligible individuals, the decision to undergo screening should be made with full understanding of potential benefits and harms. Funding for screening in the U.S. mandated the use of a patient decision aid (PtDA) as part of a shared-decision making process.[43] An Australian-developed lung cancer screening patient information tool, including PtDA, may reduce screening preference for lower-risk individuals and reduce decisional conflict among screening-eligible individuals.[44] Testing of shared-decision making approaches in high-risk populations, particularly Indigenous groups, will be important as will considerations of health literacy.

False-positive findings can cause adverse psychological effects including anxiety and stress. The associated disutility has a major impact on the cost-effectiveness of screening.[27] This is balanced by psychosocial benefit in screened individuals due to

reassurance provided by screening.[45] Patient information resources provided to screening participants, ideally tailored to nodule malignancy risk, need to be developed and tested prior to widespread screening implementation.

Conclusions

Lung cancer remains a significant health issue and there is high-quality evidence that screening high-risk individuals with LDCT improves outcomes. The next challenge is to implement screening in a cost-effective way that maximises benefits and minimises harms at individual and population levels. Given the disproportionate burden of lung cancer in Indigenous populations, it is critical that equity is considered in all facets of program development. In Australia and NZ, large government-funded lung cancer screening trials, similar to those that preceded breast and bowel cancer screening, will be essential.

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11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD × ADD

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Abstract

Lung cancer remains the commonest cause of cancer death in Australia and New Zealand. Targeted screening of individuals at highest risk of lung cancer aims to detect early stage disease, which may be amenable to potentially curative treatment. While current policy recommendations in Australia and New Zealand have acknowledged the efficacy of lung cancer screening in clinical trials, there has been no implementation of national programs. With the recent release of findings from large international trials, the evidence and experience in lung cancer screening has broadened. This article discusses the latest evidence and implications for Australian and New Zealand.

Table 1. Comparison of factors that may limit external generalisability of LDCT screening studies to the general population of Australia and NZ

Factor	NLST[4]	NELSON[6]	QLCSS[14]	Australian population	New Zealand population
European ethnicity	90.9%	Data not available	99.2%	62.3% total population[16]	74% total population[17]
Completed tertiary education	55%	Data not available	46.5%	16.1% total population[16]	18.8% total population 9.1% Māori population[18]
Screening adherence	95%	90% of male participants	96%	Total population coverage for: • Breast screening 55%[17] • Bowel screening 42%[17]	Total population coverage for: • Breast screening 70.8%[19] • Bowel screening 57.4% (round 1 pilot)[20]
Recruitment methodology	33 screening centres recruitment by direct mail-out and mass media	Population based recruitment by mail-out	General public recruitment by newspaper advertisement and press release	Breast cancer screening by central invitation[17] Bowel cancer screening by central invitation[17]	Breast cancer screening by central invitation[19] Bowel cancer screening by central invitation and population-based mail[20]
CT outside screening programme	4.3%	Data not available	4%	Data not available	Data not available
Mortality following thoracic surgery	1%	Data not available	Data not available	0.9%[21]	Data not available

NLST = National Lung Screening Trial; QLCSS = Queensland Lung Cancer Screening Study

Lung cancer screening in Australia and New Zealand: the evidence and the challenge

Manners D[1], Dawkins P[2], Pascoe D[3], Crengle S[4], Bartholomew K[5], Leong TL[6,7,8]

1 St John of God, Perth, Western Australia, Australia
2 Department of Respiratory Medicine, Middlemore Hospital, Auckland, NZ
3 Royal Melbourne Hospital, Parkville, Victoria, Australia
4 Department of Preventative and Social Medicine, University of Otago, New Zealand
5 Planning Funding and Outcomes, Waitematã and Auckland District Health Boards, Auckland, NZ
6 Austin Health, Heidelberg, Victoria, Australia
7 Institute of Breathing and Sleep, Heidelberg, Victoria, Australia
8 University of Melbourne, Parkville, Victoria, Australia

Corresponding author:
Dr Tracy L Leong

Department of Respiratory and Sleep Medicine, Austin Health, 145 Studley Road, Heidelberg, VIC 3084

tracy.leong@austin.org.au

+61 438 852675