Perspective

Lung cancer screening: screening frequency and lung cancer risk

Renee L. Manser[1,2]

[1]Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Parkville 3050, Victoria, Australia; [2]Department of Medical Oncology and Hematology, Peter MacCallum Cancer Centre, Parkville 3050, Victoria, Australia

Correspondence to: Dr. Renee L. Manser, MB, BS, FRACP, MSc, PhD. Respiratory Physician, Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Royal Parade, Parkville 3050, Victoria, Australia; Department of Medical Oncology and Haematology, Peter MacCallum Cancer Centre, Grattan Street, Parkville 3050, Victoria, Australia. Email: renee.manser@mh.org.au.

Comment on: Patz EF Jr, Greco E, Gatsonis C, *et al.* Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. Lancet Oncol 2016;17:590-9.

Abstract: Lung cancer is the commonest cause of cancer death worldwide. Along with primary prevention such as tobacco control, screening with low-dose computed tomography (LDCT) has the potential to reduce lung cancer mortality. Screening has already been implemented in some countries but national health authorities in many countries have yet to adopt lung cancer screening as a public health policy. Although there is evidence to support the effectiveness of LDCT screening in high-risk groups there are many challenges to implementing a cost-effective lung cancer screening program and there are still unanswered questions about how to most efficiently select high risk groups for screening, how to optimally manage lung nodules and how frequently to offer screening. A recent retrospective cohort analysis of data from the National Lung Screening Trial (NLST) provides some evidence to support the concept that annual screening might not be necessary for all participants in a lung cancer screening program. Individuals with a negative baseline LDCT result have been shown to have a lower incidence of lung cancer and reduced lung cancer mortality at follow up compared with all participants in baseline screening and the relative costs, benefits and harms of annual screening in this group may differ compared to those with a positive prevalence LDCT. Further research is needed to determine whether risk prediction models incorporating the findings of prevalence LDCT scans can be used to guide the frequency of subsequent screening in order to maximize the efficient use of resources and reduce the harms associated with screening.

Keywords: Lung cancer; screening; computed tomography; population screening

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Lung cancer is the commonest cause of cancer death worldwide (1). In recent decades there has been a steady improvement in survival for many cancers but improvements in lung cancer survival have not been as encouraging (2). Primary prevention including tobacco control is therefore a paramount public health strategy. Screening for the detection of early stage disease in asymptomatic individuals also has the potential to reduce lung cancer mortality. In 2013 a systematic review conducted by the US Preventive Services Task Force (USPSTF) concluded strong evidence shows that low-dose computed tomography (LDCT) screening can reduce lung cancer and all-cause mortality whilst acknowledging that the harms associated with screening must be balanced with the benefits (3). This conclusion is based largely on the results of the National Lung Screening Trial (NLST), a large, high quality, multicenter randomized controlled trial which showed a 20% reduction in lung cancer mortality with annual LDCT screening compared with chest X-ray screening in a population at high risk for lung cancer (4). The USPSTF recommends annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a

30 pack-year smoking history and currently smoke or have quit within the past 15 years (5). The Canadian Task Force on Preventive Health Care recommends screening for lung cancer with three consecutive annual low-dose CT scans among adults 55 to 74 years of age, with at least a 30 pack-year history of smoking, who smoke or who quit smoking within the previous 15 years (6). In line with the USPSTF recommendation, the Center for Medicare and Medicaid Services has approved coverage and reimbursement for lung cancer screening for individuals with the following characteristics: (I) ages 55 to 77 years; (II) asymptomatic (no signs of lung cancer illness); (III) a tobacco smoking history of at least 30 pack-years; and (IV) report current smoking or quit smoking within the past 15 years (7). In China national guidelines recommend annual lung cancer screening with LDCT for high risk individuals aged 50–74 years who have at least a 20 pack-year smoking history and who currently smoke or have quit within the past 5 years (8).

In other countries there is still a lack of acceptance for lung cancer screening as a public health policy (9,10). Many health authorities are continuing to evaluate emerging evidence on the effectiveness of screening in different settings and risk groups and cost-effectiveness at the local level. In Europe, the results of ongoing trials are likely to influence national health authorities and inform policy in the near future (11). For countries which have traditionally adopted a population based approach to screening one of the greatest challenges is to decide who should be targeted for screening and how high risk groups can be efficiently identified and recruited to screening programs. Other unanswered questions include how to optimally manage lung nodules and the optimal frequency and duration of screening and these questions may not all be directly evaluated in randomized controlled trials. Previous reviews have highlighted the fact that in low risk groups such as those without nodules on baseline screening annual screening may not be needed (12,13).

A recent retrospective cohort analysis of data from the NLST provides some data to support the concept that annual screening might not be necessary for all participants in a lung cancer screening program (14). In particular, Patz *et al.* found that participants in the LDCT screening arm of the NLST with a negative LDCT at baseline (prevalence screen) had a lower incidence of lung cancer and lung cancer mortality than did all participants who underwent prevalence screening (14). Similarly, in the Dutch-Belgian Lung Cancer Screening trial participants with negative prevalence scans (no nodules or nodules less than 50 mm^3) were reported to have a 5.5-year risk of lung cancer of only 1% (15). Lung cancer mortality has yet to be reported for this cohort however. Patz *et al.* proposed that one possible explanation for the relatively low risk of lung cancer death in participants with negative prevalence LDCT might be due to very slow growing tumors in this group (14). However this explanation seems unlikely and the relatively low lung cancer mortality is presumably largely related to the reduced incidence. In a recent analysis of the CT arm of the NLST, differences in survival for screen detected lung cancers which were classified according to the sequence of screening results, showed that lung cancer patients who developed a *de novo* nodule which proved to be cancerous (i.e., those with at least one negative CT screen prior to cancer diagnosis) had poorer survival outcomes compared to participants who had at least one positive screen prior to cancer diagnosis (16). The investigators postulated that this could be attributed to faster growing, more aggressive cancers that arose from a lung environment previously lacking in focal abnormalities (16).

Patz *et al.* have also suggested that indirect effects might explain the relatively low risk of lung cancer death in those with a negative prevalence LDCT screening result, however, it is difficult to speculate in depth about the basis for the findings. We do not have the details about what proportion of cancers arose at the site of previously detected lung nodules in the entire LDCT cohort of the NLST. One proposed mechanism is that those with a negative prevalence screen may not have developed the same degree of tobacco related lung injury (14). It is also plausible that the presence of 'benign' lung nodules represents an independent marker of risk and/or a precursor to disease. In the field of breast cancer screening several studies have found that individuals with benign, non-proliferative breast disease such as fibroadenoma or fibrosis have an increased risk of developing breast cancer at follow up, independent of other known risk factors (17,18). Large case series of resected pulmonary nodules demonstrate that benign nodules are commonly benign tumors (such as hamartomas) or granulomas, fibrosis, scar or inflammation (19,20). The association between chronic inflammation and the risk of cancer is well established (21). It has also long been postulated that focal pulmonary scarring may promote the development of lung cancer (22). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) the presence of scarring on baseline chest X-ray was associated with an increased risk for lung cancer in the ipsilateral but not contralateral lung and this risk remained elevated for 12 years after chest X-ray detection (23). The causal basis for this association warrants future research however it does support the concept that those with abnormal baseline imaging may warrant more frequent

or prolonged imaging follow up than those with normal baseline results (24).

Other work in the lung cancer screening field has also highlighted the potential role of LDCT as a biomarker for predicting lung cancer risk (25). Many diseases that are associated with an increased risk of lung cancer can be detected on LDCT including chronic obstructive pulmonary disease (COPD), emphysema, tuberculosis and diffuse fibrotic disease (25-29). Most research in this field has focused on the presence of emphysema on CT. A systematic review and meta-analysis of seven studies published in 2012 found that emphysema detected visually on CT was independently associated with an increased risk of lung cancer, although the association did not hold with automated emphysema detection (30). This association is also noted in the study reported by Patz *et al.* (14). In their Cox-regression model emphysema on the prevalence LDCT, history of self-reported COPD, age and smoking history were all predictors of lung cancer risk in the entire cohort who underwent prevalence LDCT screening and the subgroup with a negative result on the prevalence LDCT (14). In recent years morphological measurements in CT have been used to assess airway obstruction in COPD and these approaches have been evaluated in subgroups of participants in the Dutch-Belgian Lung Cancer Screening Trial (31-33). It is possible that measures of air trapping using quantitative imaging could provide information about lung cancer risk which is supplementary to that provided by spirometry (FEV1/FVC) (34).

To date there has been little published on the association between incidental interstitial lung abnormalities detected on screening LDCT and the risk of lung cancer. A recent analysis of prevalence LDCT scans in the Danish Lung Screening Trial found that early signs of emphysema and interstitial abnormalities were both more frequent among participants with lung cancer (35). In a small subgroup of participants in the CT arm of the NLST the incidence of interstitial lung abnormalities was reported to be nearly 10% however, this report did not include data on lung cancer incidence (36). In the future it might be possible to develop a comprehensive CT lung cancer risk profile based on the presence or absence of emphysema, features of airflow limitation, interstitial lung abnormalities, focal scarring and nodules. Evidence of prior tuberculosis exposure or markers of occupational exposures such as pleural plaques might also be relevant in some populations. However, such an approach will require large validation studies utilizing standardized assessments and reporting. Further post hoc analyses from the NLST and the Dutch-Belgian Lung Cancer Screening Trial may also provide useful insights. The incremental value of assessing specific radiological markers of lung cancer risk needs to be assessed given the potential for this approach to increase the cost of reporting scans.

The cost effectiveness of lung cancer screening with LDCT is dependent on the selection of high risk individuals for screening (37,38). Patz *et al.* have highlighted that the cost-effectiveness of annual low-dose CT is unclear in those with a negative prevalence LDCT and there is a need to weigh the potential harms from more intense screening versus the potential benefits (14). They performed a hypothetical analysis, assuming that the second round of screening (at 1 year) had not been carried out for any participants with a negative prevalence LDCT and reported that in this case the lung cancer mortality rate in those with a negative prevalence screen would increase from 185.2 per 100,000 person-years to 212.14 per 100,000 person-years (14). This estimated hypothetical lung cancer mortality is lower than that for the total cohort of participants who underwent prevalence LDCT screening. It is therefore possible that reducing the frequency of screening in those with a negative prevalence CT might not substantially reduce the effectiveness of screening overall although this has not been directly assessed.

Microsimulation modelling using 5 independent models and data from the NLST, the PLCO Screening trial; the Surveillance, Epidemiology, and End Results program; and the U.S. Smoking History Generator concluded that annual screening was more efficient than biennial or triennial screening (39). Further modelling studies have indicated that fewer stage 1A tumours might be detected with biennial and triennial screening strategies (40). In the same analysis it was also noted that the main differences between CT and chest X-ray sensitivity are found for early stages of lung cancer, particularly stage IA, and this difference may partly explain the difference in mortality between the CT and chest X-ray screening arms of the NLST (40). Increasing the duration between lung cancer screens may therefore reduce the effectiveness of screening. Adequately powered randomized controlled trials comparing annual with biennial screening have not been reported. One small randomized controlled trial did not find a difference in lung cancer mortality between annual and biennial screening arms however this study was underpowered and has a high risk of bias due to methodological limitations (41). Analysis of data from the first three rounds of screening in the Dutch-Belgian Lung Cancer Screening Trial showed that the proportion of advanced stage lung cancers was not significantly higher in the 2 years interval between the second and third screening rounds compared with the 1 year

screening interval between the first and second rounds of screening (42). However the proportion of advanced stage cancers was higher in the fourth round of screening (an interval of 2.5 years) compared with the earlier rounds of screening (43).

It is unlikely that sufficiently powered randomized controlled trials will be conducted in the future to directly compare different screening intervals, although in countries considering implementing lung cancer screening one approach could be to develop randomized controlled trials embedded in the implementation process which compare screening frequencies in a subgroup of participants judged at lower risk for lung cancer mortality based on the findings of the prevalence LDCT. As pointed out by Patz *et al.*, in the future, a detailed prediction model could be developed to individualize the frequency of screening based on clinical features and the findings on prevalence LDCT (14). This will require further data from large screened populations. Multiple risk prediction models based on demographic and clinical variables have been developed already which could be used to select high risk individuals for screening and this approach will improve the efficiency and cost-effectiveness of screening in the future (44-47). One model has been used prospectively to recruit participants to the United Kingdom Lung Cancer Screening trial (48). Targeted recruitment of high risk individuals for screening and modulation of the screening interval based on the results of prevalence LDCT scans are both important potential strategies to improve cost-effectiveness of screening and to minimize the harms associated with screening. The absolute benefit of screening is dependent on the underlying risk of lung cancer in the population being screened; however the harms of screening may not be related to the lung cancer risk so the balance of benefits and harms varies depending on the lung cancer risk profile of participants in a screening program (46,49). In addition, harms such as false positive diagnoses are often cumulative over successive screening rounds and therefore may increase with more frequent screening (50,51). Furthermore, recent evidence suggests that the risk of overdiagnosis is greater in those with a low risk of lung cancer compared with those with a higher risk, disproportionately increasing the potential harm from screening in those at low risk (52).

In conclusion the optimal screening interval for participants undergoing lung cancer screening with low-dose CT may vary depending on the underlying lung cancer risk and further research is needed to determine whether risk prediction models incorporating the findings of prevalence LDCT scans can be used to guide the frequency of subsequent screening scans in order to maximise the efficient use of resources and reduce the harms associated with screening.

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