PROFESSIONAL GUIDELINES

LUNG CANCER SCREENING IN SINGAPORE

CHAPTER OF RESPIRATORY PHYSICIANS

JANUARY 2025

ACADEMY OF MEDICINE
SINGAPORE

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1. PURPOSE AND DEVELOPMENT OF THE GUIDELINE

In our journey towards a healthier Singapore, the Ministry of Health has adopted a Healthier SG strategy. One of the key focus areas is to reduce disease burden and morbidity through cancer screening. Lung cancer has the highest cancer mortality rate among Singaporean men and the third highest cancer mortality rate among Singaporean women. It is the third most common cancer in Singapore.[1]

In March 2019, "Report of the Screening Test Review Committee", Academy of Medicine Singapore, classified lung cancer screening as a category 2 screening recommendation, where screening is effective in high-risk population and not for the general population.[2] Hence a shared decision-making between the clinician and the at-risk individual is required before lung cancer screening with low-dose computer tomography scan (LDCT) is performed.

The aim of this guideline in Singapore is to provide guidance to clinicians about screening for lung cancer. A shared decision-making process between the clinician and the individual relating to the potential benefits and harms should occur prior to lung cancer screening with LDCT. In addition, clinicians should have access to high quality lung cancer screening service and treatment centers. Smoking cessation is a key priority for current smokers and must be an integral component of any lung cancer screening service.

The Chapter of Respiratory Physicians of the College of Physicians, Academy of Medicine Singapore ('the Chapter'), initiated the formation of a workgroup to develop the guidelines. Chapter member representatives from each healthcare cluster were invited to be part of the workgroup. Inputs from the members of the Chapter of Respiratory Physicians, Chapter of Radiology and Chapter of Family Physicians were included in the development of the guidelines to ensure that the guidelines are practical for implementation nationally.

2. SELECTING INDIVIDUALS FOR SCREENING

Recommendations
• Lung cancer screening with annual low dose CT thorax may be offered to individuals aged 50 to 80 years, with a ≥20 pack year smoking history, who currently smoke or had quit smoking ≤15 years ago. • Currently, screening should not be offered to non-smokers. • Annual screening should be discontinued once the individual has quit smoking for more than 15 years, becomes medically unfit or unwilling to undergo invasive evaluation or anti-cancer treatment.

Two large randomized controlled trials, namely the National Lung Screening Trial (NLST)[3] and the NELSON trial,[4] have demonstrated significant mortality benefit of annual low dose computer tomography (LDCT) of the thorax screening for lung cancer. Hence in March 2019, the "Report of the Screening Test Review Committee", Academy of Medicine Singapore, recommended LDCT screening for individuals, aged 55-74 years, with a ≥30 pack year smoking history, who are currently smoking or had quit smoking ≤15 years ago, as a category 2 recommendation, where screening is effective in high-risk population and not for the general population[2].

Subsequently, a Cochrane review[5] provided further evidence that LDCT screening resulted in a reduction of lung cancer-related and all-cause mortality in at-risk populations. A systematic review, which examined cost-effectiveness studies on lung cancer screening, showed that LDCT screening was cost-effective.[6] Based on a comprehensive review of the evidence from 233 studies,[7] the U.S. Preventive Services Task Force updated the screening inclusion criteria to include adults aged 50 to 80 years, who have a ≥20 pack-year smoking history, and currently smoke or have quit smoking within the past 15 years." The Chapter thus recommends that screening with annual LDCT be offered to individuals aged 50 to 80 with a ≥20 pack year smoking history, who currently smoke or had quit smoking ≤15 years ago. Screening should be discontinued once the individual has quit smoking for more than 15 years, becomes medically unfit, or unwilling to undergo invasive evaluation or anticancer treatment.

These studies, that have demonstrated a lung cancer-specific and all-cause mortality benefit, were performed in individuals who are at-risk for lung cancer, determined by smoking and age criteria. Screening only individuals at-risk is important to ensure that the screened population has a higher prevalence of cancer, especially when screening

involves potential harms to screened individuals. Screening only at-risk individuals therefore improves the efficiency and cost effectiveness of the screening service, while avoiding the harmful effects of screening individuals with lower risk of lung cancer.[8] Some studies have also used lung cancer risk prediction algorithms (i.e. the Prostate Lung Colorectal and Ovarian (PLCO)[9] and Liverpool Lung Project (LLP)[10] models) to select the 'high-risk' populations[11] for screening. While these could further improve identification of the most at-risk population, they can be challenging to apply practically to screening services. Hence the Chapter recommends adopting the age and smoking criteria to select at-risk individuals who should be considered for lung cancer screening in Singapore.

The Chapter acknowledges that selecting the population for screening using only age and smoking criteria in Singapore could miss a significant proportion of individuals with lung cancers. These individuals could be either outside of the recommended age criteria or has light or no prior smoking history.[12] In Asia, this is particularly pertinent as the proportion of lung cancers that would be missed, using only the age and smoking criteria, is higher than Western populations, particularly in Asian female never-smokers.[13] As a result, several Asian lung cancer screening studies have investigated screening services to include never-smokers and younger patients, but the lung cancer prevalence in these studies were variable and low.[14] There is evidence, however, to suggest that inclusion of other potential risk factors, such as family history of lung cancer, in addition to the age criteria in non-smokers, could enhance lung cancer detection, as shown in the TALENT study which achieved a baseline lung cancer prevalence of 1.4%.[15] Of note, to date, there is no definitive evidence to demonstrate mortality benefit of screening never-smokers. Moreover, many of the lung cancers occurring in never-smokers, are typically subsolid lesions, which may be more indolent and may never lead to death. In the TALENT study, 19% of detected cancers were reported to be pre-invasive (adenocarcinoma in-situ) lesions. Detecting such cancers could seemingly improve survival from lung cancer, although this may be attributed to lead time bias, where cancer is diagnosed at an earlier time point but time of death is not impacted by screening. Hence screening this population could lead to overdiagnosis of cases.[16]

Given the potential harms of screening, the Chapter is of the opinion that recommending lung cancer screening to never-smokers is currently premature, and

should not be performed outside of research context. This recommendation could evolve with time. The presence of family history as a screening criterion could be considered in the future if further local research provides evidence for it.[17] In addition, the availability of biomarkers, that may be applied as a pre-screening test on a wider population, to better define the at-risk individual, could determine future screening criteria. At this time, such a biomarker has not been identified.

3. BENEFITS OF SCREENING

Recommendations
• Clinicians must deliver smoking cessation interventions to current smokers who are reviewed for screening. • Clinicians should make use of the opportunity during screening to diagnose and treat conditions such as chronic obstructive pulmonary disease and ischemic heart disease.

Lung cancer remains the leading cause of cancer-related deaths in males and the third leading cause of cancer-related deaths in females in Singapore. Unfortunately, lung cancer is often diagnosed at advanced stages, i.e., stages III and IV. This translates to the low 5-year relative survival rates in both males (17.9%) and females (33.2%).[1,18]

Lung cancer screening in Singapore is currently limited and carried out in an opportunistic manner, with no local data on efficacy or cost effectiveness for our population. However, there are multiple large trials globally that have shown a mortality benefit with screening using LDCT.[3,19–43] The National Lung Screening Trial (NLST) in the United States had demonstrated that LDCT screening had resulted in a relative reduction in mortality from lung cancer by 20%. This means that for every 1000 individuals who was screened with LDCT, 18 people died from lung cancer in comparison to 21 people who died in the non-LDCT screened group. In other words, for every 1000 at-risk individuals who were screened with LDCT, there were 3 fewer deaths. Hence, the number needed to screen (NNS) was 323 at-risk individuals to prevent one lung cancer death following 3 rounds of annual LDCT screening, with a follow up period of 6.5 years. Moreover, there was a 6.7% reduction in the rate of all-cause mortality in the LDCT group.[19] The NLST had thus form the basis for the US Preventive Services Task Force in making their recommendations for lung cancer screening in the US for at-risk individuals. This mortality benefit has subsequently

been corroborated by other studies. The Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trial,[4] involving 15,789 participants in Europe, showed a 24% (95% CI, 6-39%) reduction in lung cancer mortality with LDCT compared with chest radiograph. Subsequently, a Cochrane review[5] and metanalysis of 8 trials with a total of 91,122 participants found that there was a 21% reduction in mortality with LDCT compared to control groups of no screening or screening with chest radiograph (relative risk 0.79, 95% confidence interval 0.72 to 0.87). The Cochrane review concluded "the current evidence supports a reduction in lung cancer-related mortality with the use of low dose CT for lung cancer screening in high-risk populations." In summary, lung cancer screening benefits the at-risk individual through detection of lung cancer at early stages that is amenable to curative treatment for improved survival.

The benefits of a lung cancer screening service have also been shown to provide opportunities in the diagnosis of lung conditions such as chronic obstructive pulmonary disease (COPD), a respiratory condition afflicting smokers with significant morbidity and mortality. In addition, incidental detection of coronary calcification, could lead to diagnosis of ischemic heart disease (IHD). The earlier detection of conditions such as COPD and IHD are important case finding opportunities to deliver treatment of these conditions earlier and prevent complications.[44,45] This could be a possible reason for improved all-cause mortality outcomes demonstrated in LDCT screening studies.

A lung cancer screening service importantly results in opportunities to engage smokers in smoking cessation interventions. This is further elaborated in "Effective Screening Setting".

4. HARMS OF SCREENING

Lung cancer screening could lead to harms and unintended consequences. These should be counselled and informed to individuals during the shared decision-making process prior to LDCT cancer screening.

4.1 False Positive Results

A false positive result is defined as any result that could lead to additional evaluation that did not lead to a cancer diagnosis. These evaluations could include repeat LDCT prior to the next annual LDCT screen, PET (Positive Emission Tomography) CT scan,

biopsy and surgical interventions. There are many studies documenting false positive rates from lung cancer screening services with a wide range of 7.9% to 49.3% for the initial LDCT screen.[3,20,24,27,28,30,39,40,46–60] The wide range is largely contributed by varying definition of a positive result, such as nodule size cut offs (e.g. 4mm vs 5mm vs 6 mm), nodule characteristics and nodule volume-doubling time. For example, in NLST, a cut of ≥ 4mm was used to define a positive result. The false positive rate in NLST 26.3%, 27.2% and 15.9% for the baseline, year 1 and year 2 LDCTs respectively.[61] In NELSON, lung nodules requiring repeat interval CT were regarded as 'indeterminate' rather than positive and indeed the majority of these nodules as later were proved to be benign. The suggested cut off to define a positive result is beyond the scope of this guideline and we suggest that the approach to the evaluation of pulmonary nodules in Asia needs to be re-addressed incorporating emerging evidence.

False positive results lead to increase frequency of CT scans, increase in invasive procedures (e.g., needle biopsy, bronchoscopy, thoracoscopy, mediastinoscopy and thoracotomy) and an increase in complications resulting from the invasive procedures. For example, in the NLST, 1.7% of those screened resulted in an invasive procedure, leading to a complication rate of 0.1% of all who were screened (0.03% major, 0.05% intermediate and 0.01% minor complications). The 60-day mortality post invasive procedure of all who were screened was 0.007%.[61] Stringent protocols for managing lung nodules can again ensure these risks are minimised in those with benign nodules.

4.2 Overdiagnosis of lung cancer

Overdiagnosis from lung cancer screening is defined as diagnosing lung cancer in an individual that would not have become clinically apparent or significant if the individual had not been screened. These types of lung cancer detected from screening could be so slow growing that they would not result in any medical problems prior to death from other causes. Several studies have examined overdiagnosis in lung cancer screening and is estimated to range from 0% to 67.2%.[62–66] Overdiagnosis inadvertently leads to invasive procedures and their complications. Management of lung nodules and avoiding invasive tests and surgery unless there is clear evidence of growth is another way to reduce overdiagnosis and harms from overtreatment. Another consideration is selecting the appropriate at-risk individuals for screening to minimise the effects of overdiagnosis.

4.3 Radiation Risk

The radiation dose associated with 1 LDCT ranges from 1.0-1.7mSv for LDCTs performed in Singapore healthcare context, with the dose likely to be lower with time as technology advances. To provide some perspective, a CXR is associated with 0.1 mSv of radiation. Moreover, most individuals are typically exposed to naturally occurring background radiation. In Singapore, the background radiation is about 0.1 microSv per hour[67] and the typical amount of radiation exposure for a commercial airplane flight is about 2 microSv per hour.[68] Based on the radiation dose associated with LDCT, performing LDCTs for an individual enrolled in a lung cancer screening service would lead to an excess lifetime cancer risk of approximately 0.02% and 0.05% for a male and female smoker respectively. However, the baseline cancer risk of an individual has been reported to range from 0.8-2.2%.[69] Hence the risk-benefit ratio with regards to radiation risk is favourable for the at-risk individual who is enrolled into a lung cancer screening service.

4.4 Psychosocial harms

There are several studies that have been performed to evaluate anxiety, depression, distress and general health-related quality of life.[52,70–77] These studies have shown that although individuals enrolled into a LDCT screening service did not have any increased psychosocial harms comparatively over a 2-year period, these individuals do experience distress and anxiety in the short term, especially when the results of a LDCT yields an indeterminate or positive result that would require further evaluation or closer surveillance.

4.5 False negatives results

A false negative result from LDCT screening service refers to the LDCT result that incorrectly indicates that there is no lung cancer when it is present. The magnitude of this harm is small, as the sensitivity of LDCT in detecting lung cancer is estimated at 97%.[78] A false negative may occur because of errors in detection, interpretation and screening protocol.[21,33,79–84] Errors in detection and interpretation may occur for centrally located and endobronchial lesions, lesions that mimic lung fibrosis, linear or stripe-like opacities, occult mediastinal or hilar nodal enlargement or lesions presenting as peri-cystic nodularity or cyst wall thickening. Protocol errors are related to nodule management and screening interval protocols.[33,79,82] Errors from nodule

management protocol may result, for example, from not following up a small lung nodule with its size below the cut off for a positive result. This protocol directed stipulated lower size threshold is however important to minimize false positive results and its antecedent harms as described. Similarly, protocolised screening intervals for lung nodule surveillance balances the importance of minimizing unnecessary recalls and scans versus the risk of developing an interval lung cancer. Computer aided detection programs can help to enhance reporter sensitivity thereby reducing the false negative rate, though may do so at the expense of an increased false positive rate.[85] Artificial intelligence systems are also currently being widely researched as a means to improve reading accuracy and predict future lung cancer risk.[86,87] Of note, the LDCT screening result may indeed be truly negative, but a rapidly growing, so called “interval” lung cancer, could develop between planned repeated LDCT scans. It is important to counsel the individual that although studies on lung cancer screening have shown better mortality outcomes for individuals selected for screening, there will be individuals enrolled in the screening service who will die from lung cancer.

4.6 Incidental Findings

Incidental findings are findings on LDCT that are unrelated to the primary reason for identifying lung cancer. Although these findings are usually clinically insignificant, some findings can potentially affect the health outcomes of the individual. Common incidental findings include cardiopulmonary findings such as emphysema and coronary calcifications and extra-cardiopulmonary findings such as adrenal nodules breasts nodules and thyroid nodules. Some of these findings are regarded as a positive effect of screening that could result in earlier diagnosis and management such as COPD and IHD. Findings such as nodules and lesions noted in adjacent organs on the LDCT, could lead to further imaging tests, evaluation and referrals to relevant specialties. Hence, protocols should be optimised to ensure avoidance of unnecessary evaluation and referrals. While the approach to managing these incidental findings is beyond the scope of this guidelines, we recommend the consensus statements on reporting, communication and management of incidental findings from the American College of Radiology Incidental Findings Committee.[88]

5. SHARED DECISION-MAKING

Recommendations
• Individuals identified for screening must be informed and counselled on the benefits and harms of LDCT screening. • Individuals must be informed on the implications of a positive finding. • Individuals should be counselled and have access to information that is congruent with the individual's level of health literacy. • Screening should not be offered to individuals who are unwilling to consider, and/or are medically unfit, to undergo invasive evaluation and anticancer treatment.

The Chapter recommends that individuals who have been identified for screening be counselled on the benefits and harms of LDCT screening as well as the implications of a positive finding.

Communicating complex medical statistics and risk is challenging, but evidence suggests that individuals wish to be informed about these risks.[89–91] Informing individuals helps to prepare them for repeated screening rounds and other tests that may follow the baseline LDCT. This can help to reduce anxiety for LDCT tests with positive or indeterminate results.[92] Overburdening and confusing individuals must be avoided. Hence, information needs to be delivered appropriately according to the individual's health literacy. Specifically, individuals from lower socioeconomic or educational backgrounds tend to be disproportionately affected by lung cancer.[93] Engaging this group is crucial to ensure equitable access to lung cancer screening. Decision control preferences are recognized to vary, and caution must be heeded to avoid a 'one-size fits all' approach.[94] Several written, visual and audiovisual resources have been developed[95] to facilitate the shared decision-making process.

In addition to the inclusion criteria for selecting at-risk individuals, the clinician should review the co-morbidities and willingness of the individual to ensure that the necessary evaluation and treatment can be performed if a positive finding is detected.

Individuals who have decided with their clinician to proceed with LDCT screening should understand that this is a journey rather than a one-off investigation. For individuals with a normal LDCT result, they should continue with annual LDCT screening, while focusing on quitting smoking for all current smokers. Individuals

should also understand that a positive finding could lead to additional investigations such as CT scans and invasive biopsies.

6. EFFECTIVE SCREENING IMPLEMENTATION

Recommendations
• Lung cancer screening services should systematically identify at-risk individuals when they access the healthcare system for lung cancer screening through a shared decision-making process. • Screening services must include smoking cessation services. • There should be access to multidisciplinary teams in the management of screen-detected lung nodules. • Performance measures should be developed and monitored for quality improvement of systematic screening of high-risk individuals. • A lung cancer screening service registry should be developed to systematically track lung cancer screening outcomes, harms and benefits of screening to inform clinical practice.

6.1 Identifying at-risk individuals

At-risk individuals should be identified in a systematic manner when they access the healthcare system. At-risk individuals who are seen at the Primary Care setting, be it a review of their Health Plan, acute or chronic medical conditions, should be identified and engaged on lung cancer screening. There are also opportunities to engage at-risk patients who are hospitalized or seen at the hospital outpatient clinics. In addition, at-risk individuals who are already enrolled into a smoking cessation service, should be identified for lung cancer screening through a shared decision-making process.

6.2 Smoking Cessation Services

Numerous guidelines have recommended integration of smoking cessation with a lung cancer screening service.[96–98] Lung cancer screening may represent a 'teachable' moment given that approximately half enrolled in screening were current smokers. Moreover, the finding of a positive result on LDCT have been reported to increase quit rates.[99,100] The combination of smoking cessation services with LDCT screening may double the reduction in lung cancer specific mortality and overall mortality, thus amplifying the benefits gained and cost effectiveness of screening.[101,102] The overall benefits of smoking cessation go beyond early lung cancer detection, including

mitigating the effects on other smoking-related diseases like COPD and cardiovascular disease.

Methods for delivering smoking cessation include telephone, internet-based resources, written information pamphlets and face to face consults.[103] Combination of both counselling and pharmacotherapy have been recommended to be employed as it is more effective than when used in isolation.[104] However, the most effective method within the context of a lung cancer screening service remains uncertain and it needs to be tailored to the individual, taking into consideration access to existing health resources and platforms where these methods would be delivered.

6.3 Multidisciplinary teams

Having access to multidisciplinary team (MDT) in accredited medical centres comprising of pulmonologists, radiologists, cardiothoracic surgeons, oncologists and pathologists is essential for a successful lung cancer screening service.[97] Pulmonologists with experience in lung nodule management play an essential role in screen-detected lung nodule evaluation and minimise the rate of invasive workup for benign disease. Whilst the vast majority of nodules can be conservatively managed, close collaboration between specialties is needed to ensure timely workup and management of suspicious screen-detected lung nodules especially when surgery is being considered.[105] Due to higher burden of tuberculosis in Asia including Singapore, non-surgical biopsy may be preferred to confirm malignancy before definitive surgical management to avoid futile surgical intervention.[106] Hence, the MDT should include expertise from interventional radiology and interventional pulmonology to safely sample suspicious lung nodules via percutaneous lung biopsy or bronchoscopic lung biopsy. Complication rates arising from unnecessary invasive workups must be minimised, otherwise they risk negating the overall benefit of lung cancer screening.[105]

6.4 Performance Measures

An effective service should have key performance measures in place and monitored for quality improvement. These could include adherence to screening criteria, shared decision-making process, false positive rates and resulting biopsies, as well as stage of cancer at diagnosis. In addition, specifically for LDCT, quality standards with respect to image acquisition, image reporting, nodule evaluation and incidental findings management should be developed and adhered to.

6.5 Resource Allocation

For a screening service to be implemented effectively, resource allocation for key stakeholders is required to ensure that the service is sustainable. Resources should be dedicated to promote a healthy lifestyle, encourage a health prevention mindset and nudge individuals into adopting the right behavior leading to smoking cessation and undergoing appropriate cancer screening. Hence, LDCT screening for lung cancer could be considered for inclusion into the Screen for Life National Screening Program[107] in Singapore once there is cost effectiveness evidence in Singapore.

Based on experience in other countries where lung cancer screening has been adopted nationwide, the uptake has been shown to be universally poor with variable adherence rates.[108] Lung cancer screening with upfront or downstream costs to the individual (e.g. in the evaluation of lung nodules) is a deterrent to embarking on the lung cancer screening journey. This is particularly a challenge to those from more socioeconomically deprived backgrounds who are often at-risk individuals with the highest risk from lung cancer and is an important consideration when designing and implementing a lung cancer screening service.

6.6 Lung Cancer Screening Service Registry

Developing a lung cancer screening service registry in Singapore is crucial to inform stakeholders on the quality of LDCT lung cancer screening service. The registry would be important to ensure that the harms and benefits are monitored, reported regularly to inform clinical practice, and measured against peer and registry benchmarks.

7. FUTURE DIRECTIONS

Lung cancer screening in Singapore is currently physician dependent. Recommendations for lung cancer screening are based on age and smoking criteria. However, there is a proportion of individuals in Singapore who are non-smokers presenting with advance lung cancer that will be missed currently. Local studies are being conducted to further refine the inclusion criteria for effective lung cancer screening service in Singapore, specifically looking at family history of lung cancer as well as potential biomarkers.[17] Moving forwards, we should also focus on the appropriate use of technology and artificial intelligence for the interpretation of

LDCTs,[109–118] detection of lung nodules and differentiating benign form malignant lung nodules.

8. CONCLUSION

As Singapore embarks on its Healthier SG journey, with a shift in focus towards health promotion and early disease detection, it is anticipated that lung cancer screening would be of interest to the population and the medical community given that it is the 3rd most cancer in Singapore, presenting often at advance stages with high death rates. Lung cancer screening with LDCT can reduce lung cancer mortality in at-risk individuals but also comes with its harms and unintended consequences, necessitating the importance of a shared decision-making between physician and the individual prior to embarking on the lung cancer screening journey. It is thus timely for this professional guidance to provide key recommendations so that individuals enrolled into a screening service would reap the benefits while mitigating the harms and unintended consequences of lung cancer screening.

9. REFERENCES

(1) Singapore Cancer Registry Annual Report 2020. (2022).

(2) Report of the Screening Test Review Committee. (2019).

(3) Aberle, D. et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. New England Journal of Medicine 365, 395–409 (2011).

(4) de Koning, H. J. et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. New England Journal of Medicine 382, 503–513 (2020).

(5) Bonney, A. et al. Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. Cochrane Database of Systematic Reviews (2022) doi:10.1002/14651858.CD013829.pub2.

(6) Grover, H. et al. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. Lung Cancer 170, 20–33 (2022).

(7) Jonas, D. E. et al. Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force. vol. Synthesis No. 198 (Rockville, MD: Agency for Healthcare Research and Quality, 2021).

(8) Kovalchik, S. A. et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 369, 245–54 (2013).

(9) Tammemagi, C. M. et al. Lung cancer risk prediction: Prostate, lung, colorectal and ovarian cancer screening trial models and validation. J Natl Cancer Inst 103, 1058–1068 (2011).

(10) Cassidy, A. et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer 98, 270–6 (2008).

(11) ten Haaf, K. et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 14, 1–24 (2017).

(12) Wang, Y. et al. Trends in the Proportion of Patients With Lung Cancer Meeting Screening Criteria. JAMA 313, 853 (2015).

(13) CH, L. et al. Characteristics of Singapore lung cancer patients who miss out on lung cancer screening recommendations. Singapore Med J (2022) doi:10.11622/SMEDJ.2022039.

(14) Triphuridet, N. et al. Low-Dose Computed Tomography (LDCT) Lung Cancer Screening in Asian Female Never-Smokers Is as Efficacious in Detecting Lung Cancer as in Asian Male Ever-Smokers: A Systematic Review and Meta-Analysis. Journal of Thoracic Oncology 18, 698–717 (2023).

(15) Yang, P. PS01.02 National Lung Cancer Screening Program in Taiwan: The TALENT Study. Journal of Thoracic Oncology 16, S58 (2021).

(16) Gao, W., Wen, C. P., Wu, A. & Welch, H. G. Association of Computed Tomographic Screening Promotion With Lung Cancer Overdiagnosis Among Asian Women. JAMA Intern Med 182, 283–290 (2022).

(17) Lim, D. W. & Lai, G. G. SingapOre Lung cancer Screening Through Integrating CT with other biomarkErs (SOLSTICE) Study (NCT05724264). ClinicalTrials.gov.

(18) Ang, Y. L. E. et al. Lung Cancer in Singapore. Journal of Thoracic Oncology vol. 16 906–911 Preprint at https://doi.org/10.1016/j.jtho.2020.11.020 (2021).

(19) NLST Research Team & Gatsonis, C. The National Lung Screening Trial: Overview and Study Design 1 National Lung Screening Trial Research Team. Radiology 258, 243 (2011).

(20) de Koning, H. J. et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. New England Journal of Medicine 382, 503–513 (2020).

(21) Infante, M. et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. Am J Respir Crit Care Med 191, 1166–1175 (2015).

(22) Infante, M. et al. A randomized study of lung cancer screening with spiral computed tomography: Three-year results from the DANTE trial. Am J Respir Crit Care Med 180, 445–453 (2009).

(23) Infante, M. et al. Lung cancer screening with spiral CT: Baseline results of the randomized DANTE trial. Lung Cancer 59, 355–363 (2008).

(24) Saghir, Z. et al. CT screening for lung cancer brings forward early disease. The randomised Danish lung cancer screening trial: Status after five annual screening rounds with low-dose CT. Thorax 67, 296–301 (2012).

(25) Wille, M. M. W. et al. Results of the randomized danish lung cancer screening trial with focus on high-risk profiling. Am J Respir Crit Care Med 193, 542–551 (2016).

(26) Paci, E. et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 72, 825–831 (2017).

(27) Gohagan, J. K. et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer 47, 9–15 (2005).

(28) Gohagan, J. et al. Baseline Findings of a Randomized Feasibility Trial of Lung Cancer Screening With Spiral CT Scan vs Chest Radiograph: The Lung Screening Study of the National Cancer Institute. Chest 126, 114–121 (2004).

(29) Doroudi, M., Pinsky, P. F. & Marcus, P. M. Lung cancer mortality in the Lung Screening Study feasibility trial. JNCI Cancer Spectr 2, (2018).

(30) Becker, N. et al. Randomized Study on Early Detection of Lung Cancer with MSCT in Germany: Results of the First 3 Years of Follow-up After Randomization. Journal of Thoracic Oncology 10, 890–896 (2015).

(31) Becker, N. et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol 138, 1475–1486 (2012).

(32) Becker, N. et al. Lung cancer mortality reduction by LDCT screening—Results from the randomized German LUSI trial. Int J Cancer 146, 1503–1513 (2020).

(33) Horeweg, N. et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol 15, 1342–1350 (2014).

(34) Zhao, Y. R. et al. NELSON lung cancer screening study. Cancer Imaging 11, (2011).

(35) Walter, J. E. et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 17, 907–916 (2016).

(36) Xu, D. M. et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer 54, 177–184 (2006).

(37) Kovalchik, S. A. et al. Targeting of Low-Dose CT Screening According to the Risk of Lung-Cancer Death. New England Journal of Medicine 369, 245–254 (2013).

(38) Pinsky, P. F., Church, T. R., Izmirlian, G. & Kramer, B. S. The National Lung Screening Trial: Results stratified by demographics, smoking history, and lung cancer histology. Cancer 119, 3976–3983 (2013).

(39) Aberle, D. R. et al. Results of the Two Incidence Screenings in the National Lung Screening Trial. New England Journal of Medicine 369, 920–931 (2013).

(40) Pinsky, P. F., Gierada, D. S., Hocking, W., Patz, E. F. & Kramer, B. S. National Lung Screening Trial Findings by Age: Medicare-Eligible Versus Under-65 Population. Ann Intern Med 161, 627–633 (2014).

(41) Tanner, N. T. et al. Racial differences in outcomes within the National Lung Screening Trial: Implications for widespread implementation. Am J Respir Crit Care Med 192, 200–208 (2015).

(42) Schabath, M. B. et al. Differences in Patient Outcomes of Prevalence, Interval, and Screen-Detected Lung Cancers in the CT Arm of the National Lung Screening Trial. PLoS One 11, (2016).

(43) Black, W. C. et al. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. J Thorac Oncol 14, 1732–1742 (2019).

(44) Ruparel, M. et al. Evaluation of cardiovascular risk in a lung cancer screening cohort. Thorax 74, 1140–1146 (2019).

(45) Tisi, S. et al. Detection of COPD in the SUMMIT Study lung cancer screening cohort using symptoms and spirometry. European Respiratory Journal 60, (2022).

(46) Church, T. et al. Results of Initial Low-Dose Computed Tomographic Screening for Lung Cancer. New England Journal of Medicine 368, 1980–1991 (2013).

(47) Kinsinger, L. S. et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. JAMA Intern Med 177, 399–406 (2017).

(48) Sverzellati, N. et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. Eur Radiol 26, 3821–3829 (2016).

(49) Yip, R., Henschke, C. I., Yankelevitz, D. F. & Smith, J. P. Screening for lung cancer: Alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases. Radiology 273, 591–596 (2014).

(50) Henschke, C. I., Yip, R., Yankelevitz, D. F. & Smith, J. P. Definition of a Positive Test Result in Computed Tomography Screening for Lung Cancer. Ann Intern Med 158, 246–252 (2013).

(51) Crucitti, P., Gallo, I. F., Santoro, G. & Mangiameli, G. Lung cancer screening with low dose CT: experience at Campus Bio-Medico of Rome on 1500 patients. Minerva Chir 70, 393–399 (2015).

(52) Field, J. K. et al. The UK lung cancer screening trial: A pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess (Rockv) 20, 1–146 (2016).

(53) van Klaveren, R. et al. Management of Lung Nodules Detected by Volume CT Scanning. New England Journal of Medicine 361, 2221–2229 (2009).

(54) Tsushima, K., Sone, S., Hanaoka, T. & Kubo, K. Radiological diagnosis of small pulmonary nodules detected on low-dose screening computed tomography. Respirology 13, 817–824 (2008).

(55) Henschke, C. I., Yankelevitz, D. F., Libby, D. M., Pasmantier, M. W. & Smith, J. P. Survival of Patients with Stage I Lung Cancer Detected on CT Screening The International Early Lung Cancer Action Program Investigators* A bs t r ac t. New England Journal of Medicine 17, 1763–71 (2006).

(56) Swensen, S. J. et al. CT Screening for Lung Cancer: Five-year Prospective Experience. Radiology 235, 259–265 (2005).

(57) Henschke, C. I. et al. CT screening for lung cancer: Assessing a regimen's diagnostic performance. Clin Imaging 28, 317–321 (2004).

(58) Chung, K. et al. Lung-RADS Category 4X: Does It Improve Prediction of Malignancy in Subsolid Nodules? Radiology 284, 264–271 (2017).

(59) Wilson, D. O. et al. The Pittsburgh lung screening study (PLuSS): Outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med 178, 956–961 (2008).

(60) Pinsky, P. F., Bellinger, C. R. & Miller, D. P. False-positive screens and lung cancer risk in the national lung screening trial: Implications for shared decision-making. J Med Screen 25, 110–112 (2018).

(61) Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. New England Journal of Medicine 365, 395–409 (2011).

(62) Veronesi, G. et al. Estimating Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. Ann Intern Med 157, 776–784 (2012).

(63) Heleno, B., Siersma, V. & Brodersen, J. Estimation of Overdiagnosis of Lung Cancer in Low-Dose Computed Tomography Screening: A Secondary Analysis of the Danish Lung Cancer Screening Trial. JAMA Intern Med 178, 1418–1420 (2018).

(64) Patz Jr, E. F. et al. Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. JAMA Intern Med 174, 269–274 (2014).

(65) Thalanayar, P. M., Altintas, N., Weissfeld, J. L., Fuhrman, C. R. & Wilson, D. O. Indolent, potentially inconsequential lung cancers in the Pittsburgh Lung Screening Study. Ann Am Thorac Soc 12, 1193–1196 (2015).

(66) Young, R. P. et al. Airflow limitation and histology shift in the National Lung Screening Trial: The NLST-ACRIN cohort substudy. Am J Respir Crit Care Med 192, 1060–1067 (2015).

(67) Environmental Radiation Monitoring. (2023).

(68) Ying-jin Feng et al. Estimated cosmic radiation doses for flight personnel. Space Med jinn Eng (Beijing) 15, 265–269 (2002).

(69) Kauczor, H. U. et al. ESR/ERS white paper on lung cancer screening. Eur Radiol 25, 2519–2531 (2015).

(70) Gareen, I. F. et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. Cancer 120, 3401–3409 (2014).

(71) Kaerlev, L., Iachina, M., Pedersen, J. H., Green, A. & Nørgård, B. M. CT-Screening for lung cancer does not increase the use of anxiolytic or antidepressant medication. BMC Cancer 12, (2012).

(72) Rasmussen, J. F., Siersma, V., Pedersen, J. H. & Brodersen, J. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). Lung Cancer 87, 65–72 (2015).

(73) Van Den Bergh, K. A. M. et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: The NELSON trial. European Respiratory Journal 38, 154–161 (2011).

(74) Aggestrup, L. M., Hestbech, M. S., Siersma, V., Pedersen, J. H. & Brodersen, J. Psychosocial consequences of allocation to lung cancer screening: A randomised controlled trial. BMJ Open 2, (2012).

(75) Byrne, M. M., Weissfeld, J. & Roberts, M. S. Anxiety, Fear of Cancer, and Perceived Risk of Cancer following Lung Cancer Screening. Medical Decision Making 28, 917–925 (2008).

(76) Van Den Bergh, K. A. M. et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). Br J Cancer 102, 27–34 (2010).

(77) Dunn, C. E. et al. The role of screening expectations in modifying short–term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. Patient Educ Couns 100, 1572–1579 (2017).

(78) Guo, L. et al. Accuracy of baseline low-dose computed tomography lung cancer screening: a systematic review and meta-analysis. Chin Med J (Engl) 136, 1047–1056 (2023).

(79) Xu, D. M., Yip, R., Smith, J. P., Yankelevitz, D. F. & Henschke, C. I. Retrospective review of lung cancers diagnosed in annual rounds of CT screening. American Journal of Roentgenology 203, 965–972 (2014).

(80) Gierada, D. S. et al. Interval lung cancer after a negative CT screening examination: CT findings and outcomes in National Lung Screening Trial participants. Eur Radiol 27, 3249–3256 (2017).

(81) Devaraj, A. Missed cancers in lung cancer screening – more than meets the eye. Eur Radiol 25, 89–91 (2015).

(82) Veronesi, G. et al. Diagnostic Performance of Low-Dose Computed Tomography Screening for Lung Cancer over Five Years. Journal of Thoracic Oncology 9, 935–939 (2014).

(83) Mascalchi, M. et al. Initial LDCT appearance of incident lung cancers in the ITALUNG trial. Eur J Radiol 83, 2080–2086 (2014).

(84) Scholten, E. Th. et al. Computed tomographic characteristics of interval and post screen carcinomas in lung cancer screening. Eur Radiol 25, 81–88 (2015).

(85) Zhao, Y. et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. Eur Radiol 22, 2076–2084 (2012).

(86) Mikhael, P. G. et al. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. Journal of Clinical Oncology 41, 2191–2200 (2023).

(87) Cellina, M. et al. Artificial Intelligence in Lung Cancer Screening: The Future Is Now. Cancers (Basel) 15, (2023).

(88) Munden, R. F. et al. Managing Incidental Findings on Thoracic CT: Mediastinal and Cardiovascular Findings. A White Paper of the ACR Incidental Findings Committee. Journal of the American College of Radiology 15, 1087–1096 (2018).

(89) Hersch, J. et al. Women's views on overdiagnosis in breast cancer screening: a qualitative study. BMJ 346, f158 (2013).

(90) Waller, J., Douglas, E., Whitaker, K. L. & Wardle, J. Women 's responses to information about overdiagnosis in the UK breast cancer screening programme: A qualitative study. BMJ Open 3, e002703 (2013).

(91) Ruparel, M., Quaife, S., Baldwin, D., Waller, J. & Janes, S. Defining the information needs of lung cancer screening participants: A qualitative study. BMJ Open Respir Res 6, 1–9 (2019).

(92) Crothers, K. et al. Patients' Attitudes Regarding Lung Cancer Screening and Decision Aids. A Survey and Focus Group Study. Ann Am Thorac Soc 13, 1992–2001 (2016).

(93) Public Health England and Cancer Research UK. Cancer by Deprivation in England Incidence, 1996-2010 Mortality, 1997-2011. (2014).

(94) Bonfield, S. et al. Preferences for Decision Control among a High-Risk Cohort Offered Lung Cancer Screening: A Brief Report of Secondary Analyses from the Lung Screen Uptake Trial (LSUT). MDM Policy Pract 8, (2023).

(95) Ruparel, M. et al. Impact of a lung cancer screening information film on informed decision-making: A randomized trial. Ann Am Thorac Soc 16, 744–751 (2019).

(96) Mazzone, P. J. et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest 160, e427–e494 (2021).

(97) Kauczor, H. U. et al. ESR/ERS statement paper on lung cancer screening. European Respiratory Journal 55, (2020).

(98) Krist, A. et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 325, 962–970 (2021).

(99) Brain, K. et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening trial. Thorax 72, 912–918 (2017).

(100) Joseph, A. M. et al. Lung Cancer Screening and Smoking Cessation Clinical Trials SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. Am J Respir Crit Care Med 197, 172–182 (2018).

(101) Tanner, N. T. et al. The association between smoking abstinence and mortality in the national lung screening trial. Am J Respir Crit Care Med 193, 534–541 (2016).

(102) Villanti, A. C., Jiang, Y., Abrams, D. B. & Pyenson, B. S. A Cost-Utility Analysis of Lung Cancer Screening and the Additional Benefits of Incorporating Smoking Cessation Interventions. PLoS One 8, (2013).

(103) Rankin, N. M., McWilliams, A. & Marshall, H. M. Lung cancer screening implementation: Complexities and priorities. Respirology vol. 25 5–23 Preprint at https://doi.org/10.1111/resp.13963 (2020).

(104) Fiore, M. et al. A Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update. A U.S. Public Health Service Report. American Journal of Preventive Medicine vol. 35 158–176 Preprint at https://doi.org/10.1016/j.amepre.2008.04.009 (2008).

(105) Arenberg, D. Update on screening for lung cancer. Translational Lung Cancer Research vol. 8 S77–S87 Preprint at https://doi.org/10.21037/tlcr.2019.03.01 (2019).

(106) Bai, C. et al. Evaluation of Pulmonary Nodules: Clinical Practice Consensus Guidelines for Asia. Chest 150, 877–893 (2016).

(107) Enhanced Screen for Life. (2023).

(108) Jemal, A. & Fedewa, S. A. Lung Cancer Screening With Low-Dose Computed Tomography in the United States—2010 to 2015. JAMA Oncol 3, 1278–1281 (2017).

(109) Sahiner, B. et al. Effect of CAD on Radiologists' Detection of Lung Nodules on Thoracic CT Scans: Analysis of an Observer Performance Study by Nodule Size. Acad Radiol 16, 1518–1530 (2009).

(110) Armato III, S. G., Giger, M. L. & MacMahon, H. Automated detection of lung nodules in CT scans: Preliminary results. Med Phys 28, 1552–1561 (2001).

(111) Li, Q. Recent progress in computer-aided diagnosis of lung nodules on thin-section CT. Computerized Medical Imaging and Graphics 31, 248–257 (2007).

(112) Roos, J. E. et al. Computer-aided detection (CAD) of lung nodules in CT scans: radiologist performance and reading time with incremental CAD assistance. Eur Radiol 20, 549–557 (2010).

(113) Suzuki, K., Armato III, S. G., Li, F., Sone, S. & Doi, K. Massive training artificial neural network (MTANN) for reduction of false positives in computerized detection of lung nodules in low-dose computed tomography. Med Phys 30, 1602–1617 (2003).

(114) Arimura, H. et al. Computerized scheme for automated detection of lung nodules in low-dose computed tomography images for lung cancer screening. Acad Radiol 11, 617–629 (2004).

(115) Beigelman-Aubry, C., Raffy, P., Yang, W., Castellino, R. A. & Grenier, P. A. Computer-aided detection of solid lung nodules on follow-up MDCT screening: Evaluation of detection, tracking, and reading time. American Journal of Roentgenology 189, 948–955 (2007).

(116) Beyer, F. et al. Comparison of sensitivity and reading time for the use of computer-aided detection (CAD) of pulmonary nodules at MDCT as concurrent or second reader. Eur Radiol 17, 2941–2947 (2007).

(117) Jankowski, A. et al. Pulmonary nodule detection on MDCT images: evaluation of diagnostic performance using thin axial images, maximum intensity projections, and computer-assisted detection. Eur Radiol 17, 3148–3156 (2007).

(118) Rubin, G. D. et al. Pulmonary Nodules on Multi–Detector Row CT Scans: Performance Comparison of Radiologists and Computer-aided Detection. Radiology 234, 274–283 (2005).

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PUBLISHED: 15 OCTOBER 2024

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