



衛生防護中心
Centre for Health Protection

Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)

Recommendations on Prevention and Screening for Lung Cancer For Health Professionals

Local epidemiology

Lung cancer is the most common cancer in Hong Kong. In 2020, there were 5,422 newly diagnosed cases (3,252 men and 2,170 women), accounting for 15.9% of all new cancer cases.^{1,2} The median age at diagnosis was 70 for men and 68 for women.¹ The overall age-standardised incidence rate (ASIR)* of lung cancer was 31.0 per 100,000 standard population with the rates being 39.3 and 23.5 for male and female, respectively.^{1,2} Lung cancer is also the leading cause of local cancer death. A total of 3,910 persons (2,526 men and 1,384 women) died from lung cancer in 2020, comprising 26.4% of all cancer deaths.^{1,2} The age-standardised mortality rate (ASMR)* of lung cancer was 20.0 per 100,000 standard population with the rates being 28.1 and 12.5 for male and female, respectively.^{1,2} Over the past two decades, the overall ASIR and ASMR of lung cancer for both sexes had a downward trend.



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*Rates are standardised to the Segi's World Standard Population (1960).

2. While lung cancer is usually asymptomatic until it has reached an advanced stage, some lung cancers are aggressive in nature and hence the treatment outcome is generally poor. Lung cancer survival remains low, with the 5-year survival rate ranging from 10% to 20% in most countries.³ In Hong Kong, more than half of the lung cancer patients (58.5%) in 2020 were diagnosed at stage IV whereas 16.0% were diagnosed at stage I.¹ Adenocarcinoma was the most common histological type, accounting for 58% of all lung cancer cases, followed by squamous cell carcinoma (8%) and small cell carcinoma (4.5%).¹

Risk factors

3. Tobacco smoking is the most important risk factor for developing lung cancer. The International Agency for Research on Cancer (IARC) classified tobacco smoking as Group 1 carcinogen (i.e. carcinogenic to humans).⁴ The risk of developing lung cancer associated with cigarette smoking is dose-dependent and increases markedly with the total amount of cigarettes smoked, duration and age of initiating smoking. There is no safe level of tobacco exposure. The more a person smokes, the greater the risk of developing cancer. Epidemiological evidence show that current smokers are up to 22 times more likely to develop lung cancer in their lifetime compared to non-smokers.⁵

4. Other risk factors for developing lung cancer include increasing age, exposure to secondhand smoke (also known as environmental tobacco smoke or passive smoking), occupational exposure to carcinogens (e.g. radon, asbestos), outdoor and indoor air pollution, previous lung diseases (e.g. chronic obstructive pulmonary disease), and family history of lung cancer (particularly with a first-degree relative).^{4,6,7,8,9}

Primary prevention

5. Avoidance or cessation of tobacco smoking is the most effective strategy to prevent lung cancer. Smoking cessation at any age is beneficial to the health of all smokers. After 10 years of quitting smoking, the risk of lung cancer falls to about half of that of a smoker.¹⁰ A community-based prospective cohort study with a medium follow-up of almost 30 years found that heavy smokers who quit smoking within the past five years had a 39.1% lower risk of lung cancer than current smokers; yet their risk remains more than threefold higher than never-smokers even after quitting for 25 years.¹¹

6. The Government has been strengthening tobacco control measures through legislation, enforcement, publicity, education, smoking cessation services, and taxation. Currently, the Department of Health, Hospital Authority and non-governmental organisations provide smoking cessation services, including hotline, counselling, medications, Chinese medicine and acupuncture. Of note, Hong Kong has achieved a remarkable reduction in the local smoking prevalence[†] from 11.1% in 2010 to 9.5% in 2021, marking the first time on record that the percentage dropped to a single digit level.^{12,13}

7. Eliminating or reducing secondhand smoke exposure at home, in the workplace, and in other public settings can reduce the risk of lung cancer among never-smokers. In Hong Kong, statutory smoking ban covers all indoor workplaces, public places and many outdoor places. Moreover, avoiding or reducing exposure to known carcinogens in occupational setting by following recommended occupation safety practices (e.g. wearing protection gears) can reduce the risk of developing lung cancer.

[†] Prevalence of daily conventional cigarette smoking among all persons aged 15 and over.

Lung cancer symptom awareness

8. There are usually no noticeable symptoms in the early stages of lung cancer. Common symptoms include chronic cough, haemoptysis, recurrent respiratory infections, shortness of breath, chest pain, hoarseness, unexplained tiredness and weight loss. Although most of these symptoms may be caused by other medical conditions, it is important for individuals to seek medical attention promptly when they first notice any symptoms or changes because delayed diagnosis may contribute to poorer outcomes. Healthcare professionals should also be vigilant of warning signs and symptoms of lung cancer.

Evidence for lung cancer screening

9. Screening will potentially lead to early detection of lung cancer at a more curable stage, hence better treatment outcome and reduce the likelihood of dying from lung cancer. Chest X-ray (CXR), sputum cytology, and low-dose computed tomography (LDCT) are three screening modalities that have been or being studied in multiple randomised controlled trials (RCTs) and studies.

Screening with chest X-ray and sputum cytology

10. Early in the 1970s, several RCTs in the United States (US) and Europe evaluated the effectiveness of screening with CXR, with or without sputum cytology, among male heavy smokers; their results showed no reduction in lung cancer mortality among the screened participants.^{14,15,16,17} In 1993, the large well-designed Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) examined the effectiveness of annual CXR screening in 154,901 participants aged 55-74 years.¹⁸ After 13 years of follow-up, there was no demonstrable benefit of annual CXR screening on lung cancer mortality

reduction or stage shift.¹⁸ Overseas guidelines recommend against using CXR alone or in combination with sputum cytology to screen for lung cancer.

Screening with low-dose computed tomography

11. On the other hand, two large and sufficiently powered RCTs, namely, the US-based National Lung Screening Trial (NLST) and the Dutch-Belgian Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) Trial have shown that screening with LDCT can detect lung cancer at an earlier stage and reduce lung cancer death.^{19,20,21,22,23,24}

12. Low-dose computed tomography has high sensitivity for detecting lung cancer among high risk individuals. As reported in the second screening round of the NLST, the sensitivity of LDCT was 93.0%, the specificity was 83.9%, the positive predictive value (PPV) was 5.2%, and the negative predictive value (NPV) was 99.9%.²⁵ The NELSON reported for the three screening rounds combined with a 2-year follow-up, the sensitivity of LDCT was 84.6%, the specificity was 98.6%, the PPV was 40.4%, and the NPV was 99.8%.²⁶ The apparent difference in the PPV reported in these two RCTs is likely to have stemmed from the discrepant definitions of positive results adopted across the two studies.

13. The NLST is so far the largest RCT, enrolling 53,454 participants who were randomly assigned to screen with either LDCT or CXR annually for 3 years between 2002 and 2004.¹⁹ The NLST used age and smoking history as inclusion criteria and defined those aged 55 to 74 years who were current smokers with a ≥ 30 pack-year[‡] smoking history or former smokers who had quit smoking within the past 15 years as eligible participants.¹⁹ Diameter-based approach is used to assess the nodule and define the CT scans (i.e. any

[‡] Pack-year = number of packs of cigarettes per day multiplied by number of years smoked

non-calcified nodule $\geq 4\text{mm}$ was interpreted as a positive screening result). After a median follow-up of 6.5 years, compared with CXR group, LDCT group yielded a 20% relative reduction in lung cancer mortality (95% confidence interval [CI] 6.8-26.7, $p=0.004$).¹⁹ The number needed to screen (NNS) with LDCT to prevent one lung cancer death was 320.¹⁹ An extended follow-up analysis of NLST subjects after a median follow-up of 12.3 years continued to show a favorable NNS of 303 to prevent one lung cancer death (relative risk [RR] 0.92, 95% CI 0.85-1.00, $p=0.05$) in the LDCT arm (versus CXR arm), which was similar to the original analysis and indicated that the originally reported lung cancer reduction in the LDC arm versus the CXR arm was sustained.²²

14. The NELSON is the second largest trial after the NLST to assess whether volume-based LDCT screening reduces lung cancer mortality among 15,792 high-risk participants.²⁴ Current smokers (or former smokers who had quit ≤ 10 years ago) between the ages of 50 and 75, and had smoked ≥ 15 cigarettes per day for >25 years or ≥ 10 cigarettes per day for >30 years were considered as high-risk participants.²⁴ They were randomised to undergo four rounds of LDCT screening at baseline, year 1, year 3, and year 5.5 or no screening.²⁴ The NELSON trial classified screening results as negative, indeterminate or positive based on presence of nodule and volume (a solid nodule with a volume of $>500\text{mm}^3$ as positive). Participants with initial indeterminate results underwent follow up screening to classify their final screening result based on nodule volume doubling time. At 10 years of follow up, the results found that compared with no screening, LDCT screening achieved a significant 24% lung cancer mortality reduction in men (95% CI 0.61-0.94, $p=0.01$) and non-significant 33% reduction in women (95% CI 0.38-1.14).²⁴

15. In addition to the mortality reduction, screening with LDCT could detect higher proportions of lung cancers at an earlier stage. In the NLST study, when comparing three annual screening rounds with LDCT to CXR, there were

a relative increase of 46% (RR 1.46, 95% CI 1.33-1.61) in detection of early-stage lung cancers and a reduction of 29% (RR 0.71, 95% CI 0.65-0.77) in detection of late-stage disease.²⁷ Similarly, the NELSON trial reported that compared to control group, substantially more stage I lung cancers (58.6%) and less stage IV lung cancers (9.4%) were diagnosed in the LDCT group.²⁴

16. Several LDCT screening RCTs were also conducted in Europe; however, these trials had a smaller sample size and some might have insufficient statistical power to assess lung cancer mortality benefits.^{28,29,30,31,32,33}

Potential harms of screening with low-dose computed tomography

17. Notwithstanding the benefits in reducing lung cancer mortality and detecting early-stage disease, LDCT screening can cause harms, including false-positives, over-diagnosis, radiation exposure, and some mild and short-term psychological distress. Substantial false-positives findings may lead to unnecessary follow-up investigation (including imaging) and invasive procedures (such as biopsy and bronchoscopy). Though uncommon, there is a risk of major complications or death associated with these invasive procedures. As reported in the NLST, the average false-positive rate per screening round was 23.3%.¹⁹ Among LDCT screened participants with false-positive results, 1.7% received invasive procedures and 0.1% experienced complications.^{21, 34} Though the NELSON trial reported false-positive rate of 1.2%, it reported indeterminate rate of 19.7% at baseline which requiring follow up.²⁴

18. Screening may find lung cancer that would not have become clinically significant and led to death in a person's lifetime if left untreated. The NLST estimated an 18.5% probability (95% CI 5.4%–30.6%) that any lung cancer detected by LDCT (vs. CXR) was an over-diagnosis (i.e. indolent tumour) after 6.4 years of follow-up,³⁵ but it decreased to 3% with the extended follow-up of

11.3 years.²² In the NELSON trial, the over-diagnosis rate was 19.7% with 4.5 years' follow-up after the final screening round and dropped to 8.9% when extending the follow-up to 5.5 years.²⁴ Over-diagnosis rate seems to be affected by the duration of follow-up and decreases over time.

19. As estimated in the NLST, each participant might receive an average of 8 mSv of radiation over three years (including both screening and diagnostic examination), and approximately one cancer death per 2,500 people screened may be induced by radiation exposure.³⁶ Nevertheless, the benefit of LDCT screening in preventing lung cancer deaths substantially outweighs its radiation risk.

20. The NLST showed that short-term and long-term health-related quality of life (HRQoL) and state anxiety did not significantly differ across participants with false-positives, significant incidental findings or negative screening results, but did find significantly lower HRQoL and higher state anxiety for those who screened true-positive.³⁷ Participants in the NELSON trial experienced an increase in lung-cancer-specific distress for a short term after receiving an indeterminate result.³⁸ Healthcare professionals should inform individuals undergoing LDCT screening the benefits and potential harms, as well as the implication of all possible results and the distress induced.

Overseas recommendations and practice on lung cancer screening for high-risk populations

21. Some authoritative medical organisations overseas recommend lung cancer screening by LDCT for high-risk groups which are defined by age and smoking history, but their eligibility criteria and screening interval vary. Screening recommendations in some selected countries or regions are summarised in **Annex**.

Local research on lung cancer screening

22. There are as yet no local studies on the effectiveness, cost-effectiveness and benefits-versus-harms of LDCT screening in individuals at high risk. Moreover, there is also no locally validated risk assessment tool to characterise individuals at high risk of lung cancer or set any risk threshold for screening. Although overseas studies generally consider that LDCT screening is cost-effective when targeted to high-risk populations; their findings may not be directly applicable to local context.

23. The Department of Medicine of The University of Hong Kong is currently conducting a LDCT screening study, which is part of the International Lung Screening Trial (ILST). The ILST is a multi-centre prospective cohort study recruiting 4,500 aged 55-80 current or former smokers, who meet 2013 USPSTF criteria[§] and/or PLCOm2012 risk^{**} of $\geq 1.51\%$ within 6 years of screening from nine screening sites including Hong Kong, Canada, Australia and the United Kingdom, with the aim to compare the predictive accuracies of these two screening selection criteria.³⁹ The ILST study is ongoing.

Summary

24. Collective evidence from two large, high-quality and sufficiently powered RCTs (NLST and NELSON) showed that LDCT detects early-stage disease and reduces lung cancer mortality among individuals who are at high risk

[§] In 2013, the United States Preventive Services Task Force (USPSTF) recommended annual screening for lung cancer with LDCT for 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.

^{**} PLCOm2012 is a modified lung cancer risk prediction model using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Risk variables include age, education, smoking history (current smoking, intensity, duration, time since quitting for former smokers), body mass index, history of COPD, personal history of cancer, and family history of lung cancer.

for lung cancer. LDCT screening can cause potential harms, especially when false-positive findings lead to unnecessary follow-up investigations and invasive procedures. Many national health authorities in Asia and the West recommend LDCT screening for persons at high risk of lung cancer with variations in screening criteria and screening intervals. In Hong Kong, no study has measured effectiveness, cost-effectiveness and potential benefit-versus-harm of LDCT screening in the local setting. The impact of an LDCT screening programme for lung cancer to the local healthcare system has not been well studied.

25. Cigarette smoking is the single biggest risk factor for developing lung cancer. Lung cancer screening is not an alternative for quitting smoking. Smoking cessation or never start smoking remains the best way to prevent lung cancer.

Conclusion

26. There is insufficient local data to establish definitive local screening criteria or recommend any population-based LDCT screening programme for lung cancer for persons at increased risk. Nonetheless, it is considered appropriate to inform local doctors and persons at increased risk about the latest evidence from scientific literature and overseas recommendations to facilitate them in making informed decisions. Based on overseas literature,

- Smoking history: more than 20-30 pack-year and who either currently smoke or have quit for not more than 10-15 years
- Usual starting and finishing age for screening: 50-55 years and 74-80 years respectively
- Screening interval: most commonly performed annually or biennially

Applicability of these overseas criteria and evidence in the local population remains to be further investigated.

27. The CEWG would periodically review the latest evidence and developments in LDCT screening for lung cancer, and update the recommendations as appropriate.

Revised recommendations by CEWG

28. Taking into consideration the latest international scientific evidence and local actual situation, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) revised the recommendations on lung cancer screening which were endorsed by the Cancer Coordinating Committee at its 18th meeting on 12 June 2023. The CEWG's revised recommendations serve as general reference for doctors to provide individualised advice on lung cancer screening in local population:

<p>1. Primary prevention is the most important strategy for reducing the risk of developing lung cancer. Current smokers should quit smoking and non-smokers should never start smoking.</p>
<p>For asymptomatic population at average risk</p>
<p>2. Routine screening for lung cancer (including chest X-ray, sputum cytology, or low-dose computed tomography (LDCT)) is NOT recommended for asymptomatic persons at average risk.</p>
<p>For asymptomatic persons at increased risk</p>
<p>3. There is currently insufficient data to assess the benefit vs harm and cost-effectiveness of LDCT screening and its associated criteria such as target groups and optimal screening protocol in the local setting. Based on overseas literature, asymptomatic persons with heavy smoking history (i.e., more than 20-30 pack-year and who either currently smoke or have quit for not more than 10-15 years) that put them at increased risk of lung cancer may benefit from LDCT screening. In the majority of overseas recommendations, the usual starting and finishing age for screening is 50-55 years and 74-80 years respectively, and screening is most commonly performed annually or biennially. Since the local applicability of these criteria has not been sufficiently characterised, persons with heavy smoking history are advised to discuss with their doctors the benefits and harms (including false-positive findings and potential follow up investigations) of LDCT screening before making an informed and individualised decision.</p>
<p>4. Screening for lung cancer with chest X-ray or sputum cytology is NOT recommended.</p>

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Annex

Recommendations on lung cancer screening in some selected countries or regions

Country/Region/ Organisation	Year	Target population	Recommendations
UK National Screening Committee ⁴⁰	2022	People aged 55 to 74 identified as being at high risk of lung cancer	LDCT screening
Australian Medical Services Advisory Committee ⁴¹	2022	Adults aged 50 to 70 years with ≥ 30 pack-year smoking history who currently smoke or have quit within the past 10 years	Biennial LDCT screening
Taiwan Guideline on LDCT Lung Cancer Screening ⁴²	2022	(1) Individuals aged 50 to 74 years who have more than a 30 pack-year smoking history, and currently smoke or have quit within the past 15 years	<ul style="list-style-type: none"> If first LDCT screening result negative, rescreen every 1-2 years until quit smoking for >15 years
		(2) Individuals aged 50 to 74 years with family history of lung cancer among first-degree relative	<ul style="list-style-type: none"> If affected relative was diagnosed at age <50, start screening at age <50 Rescreen every 2-5 years, depend on doctor's recommendations
United States Preventive Services Task Force ³⁴	2021	Adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years	Annual LDCT screening
China Guideline for the Screening and Early Detection of Lung Cancer, National Health Commission ⁴³	2021	Individuals aged 50 to 74 years who qualify as high risk for lung cancer, including <ol style="list-style-type: none"> with at least a 30 pack-year smoking history, who smoke or have quit within 15 years; Exposure to passive smoking: have been living or working with smoker for ≥ 20 years; Previous diagnosis of COPD; Occupational exposure to carcinogens for at least one year; Family history of lung cancer among first-degree relative 	Annual LDCT screening
Academy of Medicine, Singapore ⁴⁴	2019	High risk groups: <ol style="list-style-type: none"> Individuals aged between 55 to 74 who have smoked ≥ 30 pack years and are continuing to smoke Individuals aged between 55 to 74 who have smoked ≥ 30 pack years but quit <15 years ago 	Annual LDCT screening
Canadian Task Force on Preventive Health Care ⁴⁵	2016	Adults aged 55 to 74 years with at least a 30 pack-year smoking history, who smoke or quit smoking less than 15 years ago	Annual LDCT screening up to three consecutive years
National Cancer Center, Korea ⁴⁶	2015	<ol style="list-style-type: none"> High-risk smoking groups aged 55 to 74 years, with at least 30 pack-year smoking history and current smokers; Former smokers who quit smoking within 15 years 	Annual LDCT screening
Japan Radiological Society and the Japanese College of Radiology ⁴⁷	2013	High-risk group (aged ≥ 50 years with a Brinkman index* ≥ 600) *number of cigarettes smoked per day x number of years of smoking	LDCT screening

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