



## **Cancer Expert Working Group on Cancer Prevention and Screening**

### **Recommendations on Prevention and Screening for Lung Cancer For Health Professionals**

#### **Local epidemiology**

1. Lung cancer ranked the second in cancer incidence in Hong Kong in 2014, after being overtaken by colorectal cancer for two consecutive years. It was the most common cancer in men and the third commonest cancer in women. A total of 4,674 lung cancer cases were recorded, accounting for 15.8% of all newly diagnosed cancer cases, with 3,014 cases in males and 1,660 cases in females. The median age at diagnosis was 70 for male and 69 for female respectively. The age-standardised incidence rates (ASIR) were 49.7 for male and 24.3 for female per 100,000 standard population of the respective sex.<sup>1</sup>

2. Locally, lung cancer was the leading cause of death from cancer in men and women, accounting for 4,031 deaths in 2015, which constituted 28.2% of all registered cancer deaths. The age-standardised mortality rates (ASMR) of lung cancer were 40.5 for male and 18.4 for female per 100,000 standard population of the respective sex.<sup>2</sup> After adjusting for population ageing, both the ASIR and ASMR for both sexes have shown a downward trend in the past three decades. More information on lung cancer statistics can be found at the Centre for Health Protection (CHP) website: [www.chp.gov.hk/en/content/9/25/49.html](http://www.chp.gov.hk/en/content/9/25/49.html).

3. Despite the decrease in the ASIR and ASMR of lung cancer in Hong Kong, the ASIR and ASMR in males were higher than those in many Western countries (e.g. United Kingdom (UK), Australia, etc.) in 2012.<sup>3</sup>

#### **Risk factors**

4. Tobacco smoking, including second-hand smoke, classified by the International Agency for Research on Cancer (IARC) of the World Health Organization as Group I carcinogen, is the most important risk factor for lung cancer.<sup>4</sup> Globally, smoking is responsible for over 71% of all lung cancer deaths.<sup>5</sup> All forms of tobacco are carcinogenic.

The risk of 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, and decreases with time since quitting. A systematic review of 287 studies found that as compared to never smokers, current smokers were 8.43 times as likely to have lung cancer while ever smokers were 5.5 times.<sup>6</sup> The Tobacco Atlas reported that for persons who smoke 10 or fewer cigarettes per day, their life expectancy is on average 5 years shorter and lung cancer risk is up to 20 times higher than in never smokers.<sup>7</sup>

5. While tobacco use accounts for the vast majority of lung cancer cases, other established risk factors include:<sup>4, 8</sup>

(a) Air pollution, including outdoors and indoors<sup>4</sup>

The IARC classified outdoor air pollution and particulate matter in outdoor air pollution as carcinogenic to humans (Group 1 carcinogen) and found sufficient evidence to conclude that exposure to outdoor air pollution and its particulate matter causes cancer of the lung. It has been estimated that about 15% of all lung cancer cases worldwide is attributable to outdoor air pollution.<sup>9</sup>

(b) Exposure to radon gas (a radioactive gas emanates from rocks and soils that may accumulate into the foundations of buildings)<sup>4</sup>

(c) Occupational exposure from inhalation of certain chemicals or substances, such as asbestos, arsenic, chromium and nickel, etc.<sup>4</sup>

(d) Radiation exposure<sup>4</sup>

(e) Arsenic in drinking water<sup>8</sup>

(f) Pharmacological doses of beta-carotene (in smokers only)<sup>8</sup>

The risk of lung cancer is much higher among smokers who are concomitantly exposed to polluted air and vapours that contain the above carcinogens.

6. In addition, family history of lung cancer has been noted to be a risk predictor of lung cancer, especially in persons aged below 50.<sup>10</sup> Persons with weakened immunity, such as people with AIDS/HIV infection or organ transplant recipients, are associated with increased risk of getting lung cancer.<sup>11</sup>

### **Primary prevention**

7. Smoking cessation or avoidance of smoking is the most effective measure for preventing lung cancer.<sup>8, 12</sup> Smoking cessation at any age is beneficial to health of all smokers. An individual's risk of lung cancer would drop by about half that of a smoker 10

years after quitting smoking.<sup>9</sup> A prospective study of one million women in the UK found that former smokers who stopped smoking at about 30 and 40 years of age had their risk of dying from lung cancer reduced by 97% and 90%, respectively.<sup>13</sup>

8. Avoiding or reducing exposure to known carcinogens such as asbestos, radon and radiation in occupational setting by following recommended occupational safety practices (such as wearing protective gears) would result in a decrease in the risk of developing lung cancer.

9. A World Cancer Research Fund (WCRF) International systematic review and meta-analysis observed an inverse association between fruit and vegetable consumption (up to 400g/day) and lung cancer risk, but it is difficult to exclude residual confounding by smoking.<sup>14</sup> Despite the potential protective effect by diet rich in fruits and vegetables, smoking cessation remains the most important intervention to reduce the risk of lung cancer.

### **Early detection**

10. In the early stages, lung cancer usually has no noticeable symptoms. Symptoms of lung cancer include persistent cough, haemoptysis, recurrent or persistent chest infections, hoarseness, chest discomfort or pain when coughing or taking a deep breath, loss of appetite and weight, and fatigue. Individuals with suspicious symptoms should seek medical assessment and investigation promptly.

### **Screening**

11. Screening for lung cancer aims to identify asymptomatic persons having early stage disease so that early treatment can be offered. Currently, three screening modalities are being used to different extents, namely chest X-ray, sputum cytology and low-dose computed tomography (LDCT, sometimes known as low-dose CT).

12. To increase the yield of any screening test, screening is generally offered to those considered at high risk of developing the disease. As tobacco smoking is the biggest single risk factor for lung cancer, screening is often considered for individuals with a significant history of heavy smoking [measured in ‘pack-years’ = number of packs of cigarettes smoked per day x number of years smoking].

## **Effectiveness of lung cancer screening**

13. In the United States (US), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial comparing annual screening by chest X-ray with usual care (no screening) found no reduction in lung cancer mortality (mortality relative risk [RR] 0.99, 95% confidence interval [CI] 0.87 – 1.22) after 13 years of follow-up.<sup>15</sup>

14. Cochrane review of nine trials with a total of 453,965 participants found that screening with chest X-ray or sputum cytology did not reduce lung cancer mortality. On the other hand, screening with LDCT was found in one large trial<sup>16</sup> to reduce lung cancer deaths among high risk smokers and former smokers.<sup>17</sup>

15. The National Lung Screening Trial (NLST) was a very large-scale randomised controlled trial conducted in the US involving 53,454 current smokers or former smokers within the past 15 years aged 55 to 74 years with at least 30 pack-years of smoking. The sensitivity and specificity for LDCT were 93.8% and 73.4% respectively, whereas 73.5% and 91.3% for chest X-ray respectively.<sup>18</sup> This trial showed a 20% reduction in lung cancer mortality with LDCT screening and a 6.7% reduction in all-cause mortality compared to those screened with chest X-ray.<sup>16</sup> Screening with LDCT was found to prevent the greatest number of deaths from lung cancer among participants in the highest-risk group and prevented very few deaths in the lowest-risk group.<sup>19</sup>

16. In the NLST, two annual screening rounds with LDCT resulted in a decrease in the number of advanced-stage lung cancers diagnosed and an increase in the number of early-stage cancers diagnosed, as compared with chest X-ray.<sup>20</sup> Similarly, another systematic review conducted in Canada found that screening with LDCT detected significantly more cases of early-stage lung cancer (8 more per 1000 people screened) and significantly fewer late-stage cases (4 fewer per 1000 people screened) when compared with chest X-ray.<sup>21</sup>

17. Several trials on LDCT screening are ongoing in the UK (United Kingdom Lung Cancer Screening trial)<sup>22</sup> and Europe (e.g. Dutch Belgian randomised lung cancer screening trial (NELSON),<sup>23</sup> Danish Lung cancer Screening Trial,<sup>24</sup> etc). Although these studies have recruited smaller samples than the NLST and used different screening intervals and follow-up approaches, the pooled results would provide valuable information on implementation of LDCT screening programme in Europe in the future.<sup>25, 26</sup>

## **Potential harms of screening with Low-dose computed tomography (LDCT)**

18. The NLST showed that 96.4% of the positive screening results in the LDCT screened group were false positive. Although uncommon, there is a possibility of complications or death arising from follow-up investigations and procedures. The rate of at least one complication was 1.4% after a diagnostic evaluation procedure for a positive screening test among the LDCT screened group.<sup>16</sup>

19. The NLST estimated that 18.5% of all lung cancer detected by LDCT was indolent tumours which may not cause clinical symptoms, resulting in over-diagnosis.<sup>27</sup> Another retrospective screening study in Italy found that slow-growing or indolent cancer comprised about 25% of incident cases of lung cancer found by LDCT.<sup>28</sup>

20. Excess cancer risks related to radiation from LDCT is another concern in lung cancer screening. Radiation exposure associated with LDCT ranged from 0.61 to 1.5 mSv per scan.<sup>29</sup> The risk for radiation-induced lung cancer depends on the age at which a person starts screening and the amount of cumulative radiation received. The NLST predicted that approximately one cancer death per 2500 persons screened may be caused by radiation exposure.<sup>30</sup>

21. The effect of LDCT screening on quality of life or psychological distress remains uncertain due to limited data on this area. However, there might be some potential detriments due to anxiety, costs and harms associated with false-positive screening results and over-diagnosis.<sup>30</sup>

## **Cost-effectiveness of screening with LDCT**

22. As estimated in the NLST, screening with LDCT would cost US\$81,000 per quality-adjusted life-year (QALY) gained and the corresponding incremental cost-effectiveness ratios (ICERs) were US\$52,000 per life-year gained. However, the ICERs varied widely in subgroup and sensitivity analyses with different assumptions. The ICERs were lower among women, those aged 60-69, current smokers (as compared with former smokers). Therefore, the cost-effectiveness of LDCT screening much depends on the screening criteria such as gender, age group, smoking status, and how the screening is implemented etc.<sup>31</sup>

23. A study made use of the Cancer Risk Management Model to evaluate the cost-effectiveness of LDCT screening for lung cancer within the Canadian health care system. It is estimated that annual screening of current and former smokers aged 55-74 years and with 30 pack-year smoking history (same protocol as the NLST) saved 51,000 QALY, and had an incremental cost-effectiveness ratio of CAD\$52,000 per QALY. When combining LDCT screening with a smoking cessation programme, it would improve the quit rate by 22.5% and lower the incremental cost-effectiveness ratio to CAD\$24,000 per QALY, which appears to be more economically attractive.<sup>32</sup>

**Local considerations**

24. As yet, there has not been any local study on the effectiveness of lung cancer screening for persons at increased risk. There is also no consensus on the local definition of increased risk, the screening modality or protocol for population at increased risk.

25. Current state of evidence shows that there is adequate evidence to recommend against screening with chest x-ray and sputum cytology in high risk population as they do not reduce lung cancer mortality. Although there is emerging evidence to support screening with LDCT for individuals at high risk, a number of issues have not been resolved, including substantial false-positive screening results, over-diagnosis and uncertainty over cost-effectiveness.

26. Primary prevention remains the fundamental strategy to reduce the burden of lung cancer in Hong Kong. Efforts should continue to focus on tobacco control and supporting smoking cessation.<sup>22</sup>

27. After taking into consideration local epidemiology, emerging scientific evidence, local and overseas screening practices, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) has fine-tuned the recommendations on lung cancer screening in June 2016 as follows:

<i>For general population or high risk populations</i>	
1.	Routine screening for lung cancer with chest X-ray or sputum cytology is not recommended.
2.	There is insufficient evidence to recommend for or against lung cancer screening by low dose computed tomography (LDCT) in asymptomatic persons or for mass screening.

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