



Feasibility of lung cancer screening in developing countries: challenges, opportunities and way forward

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Abstract: Lung cancer is the leading cause of all cancer deaths worldwide, comprising 18.4% of all cancer deaths. Low-dose computed tomography (LDCT) has shown mortality benefit in various trials and now a standard tool for lung cancer screening. Most researches have been carried out in developed countries where lung cancer incidence and mortality is very high. There is an increasing trend in lung cancer incidence in developing countries attributed to tobacco smoking and various environmental and occupational risk factors. Implementation of lung cancer screening is challenging, so organised lung cancer screening is practically non-existent. There are numerous challenges in implementing such programs ranging from infrastructure, trained human resources, referral algorithm to cost and psychological trauma due to over-diagnosis. Pulmonary tuberculosis and other chest infections are important issues to be addressed while planning for lung cancer screening in developing countries. Burden of these diseases is very high and can lead to over-diagnosis in view of cut off of lung nodule size in various studies. Assessment of high risk cases for lung cancer is difficult as various forms of smoking make quantification non-uniform and difficult. Lung cancer screening targets only high risk population unlike screening programs for other cancers where entire population is targeted. There is a need of lung cancer screening for high risk cases as it saves life. Tobacco control and smoking cessation remain the most important long term intervention to decrease morbidity and mortality from lung cancer in developing countries. There is no sufficient evidence supporting the introduction of population-based screening for lung cancer in public health services.

Keywords: Lung cancer; screening; developing countries; challenges; opportunities

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Introduction

Lung cancer is the most commonly diagnosed cancer type in the world with 2.094 million (11.6%) new cases of all diagnosed cancer cases with high mortality accounting for 1.8 million deaths (18.4%) in 2018. A total of 1,368,524 and 725,352 new lung cancer cases were reported in men and women respectively. The trend of lung cancer has changed over the decades but it is still a leading cause of death among men (1,2).

There is a rise in cases of lung cancer among women which is a major concern. Hungary is on the top of the list of lung cancer incidence among women, followed by other regions such as Northern America, Northern & Western Europe and Chile (3). Smoking, a major risk factor of lung cancer, accounts for about 85% of all lung cancers in current or former smokers (4), but this is changing now. Lung cancer cases among non-smoker females is becoming an important concern in developing countries (5,6).

Since most lung cancers are diagnosed at a late stage (7), lung cancer survival remains poor, not exceeding 15% at 5 years (8). Routine lung cancer screening is currently not recommended. Several studies have reported detection of lung cancer at an early stage with improved survival by making use of Low dose Computer Tomography in lung cancer screening. International Early Lung Cancer Action Program (I-ELCAP) results have shown a 10-year survival of 88% in patients with stage I lung cancer, which were identified during screening (9). A reduction of 20% was seen in deaths due to lung cancer in National Lung Screening Trial (NLST) with low dose computed tomography in comparison with chest radiograph. Three annual CT scans were conducted in NLST (10). Such outcomes demonstrate that lung cancer screening using CT can detect disease at a curable stage. It has been demonstrated that 90 percent of lung cancer cases can be attributed to smoking in developed countries, with the risk increasing with quantity and duration of smoking (11).

However, the epidemiology of lung cancer may be different in developing countries (12). While the prevalence of smoking (13), air pollution and environmental hazards (14) are considered to be significantly higher in developing countries, up to 30–40% of Asian lung cancer patients had never been smokers, in contrast to only 10% of patients in the United States (15).

Developing countries have a very high incidence of pulmonary tuberculosis and other chest infections (16–18). Therefore, misdiagnosis is a major concern (19–22).

Lung cancer screening is largely restricted to developed countries in spite of high prevalence of lung cancer cases even in developing countries. It is showing a rising trend because of tobacco use, environmental pollution along with various other factors. There are frameworks for cancer screening in many of the developing countries but lung cancer screening is not included in spite of high incidence of lung cancer. This may be attributed to lack of infrastructure, no willingness for screening among high risk population, fear of disease, over-diagnosis, continuum of care for treatment and psychological impact (23–25). Tobacco control and smoking cessation is the major focus as primary prevention, but it seems difficult to enforce the existing rules and policies. This review will give an overview of lung cancer screening methods, challenges in implementation, existing guidelines and recommendation, newer point of care technology in addition to specific problems of developing countries where patients with pulmonary tuberculosis and chest infections are very large in number.

Lung cancer: trend and mortality in developing countries

Incidence of lung cancer has significantly increased in last three decades and has a worrisome increase in developing countries. In 1990, incidence of lung cancer was high in the developed countries but now around every three cases out of five are being diagnosed in developing countries (1,26). As per GLOBOCAN 2018, 58.5% of all lung cancer cases were from Asia, followed by Europe and North America with 22.4% and 12.4% cases, respectively. This may be attributed to population of Asia region with prevalence of habit of smoking cigarette, Bidi, Hukka, indoor and outdoor air pollution (27,28). Mortality due to lung cancer is high among men and most deaths occurs in developing countries of Eastern Europe, Western Asia, Northern Africa, Eastern and South-Eastern Asia. Incidence rate among men is high in Micronesia followed by Eastern Europe and Eastern Asia. Lung cancer incidence in Chinese females is similar to developed countries (3).

Burden of lung cancer is very high in Asia with an estimated incidence of over 1.2 million cases and approximately 1.07 million deaths. Lung cancer incidence is on top of the list among males, but it ranks third in women after breast and cervical cancers in Asia (1). Highest incidence rate of lung cancer was reported in South Korea, China, Turkey, Singapore, Philippines (2,29). An estimated 774,323 new cases were reported in China with a mortality of 690,567 people (1). China accounts for almost half of

the total cases of lung cancer worldwide. Furthermore, the incidence of lung cancer in China is increasing, with more number of young lung cancer patients (30).

In India, lung cancer ranks fourth (5.9%) in overall cancer incidence and second among males, while it ranks third in mortality (8.82%) due to cancer after breast cancer and head & neck cancer (1). According to Population Based Cancer Registries Report 2016, incidence of lung cancer is higher in North-Eastern Region of India where incidence varies from 3.22–28.25 cases, followed by southern region, eastern region and northern regions. Incidence is low in western and central region as compare to other regions in India. Despite variation in incidence geographically, lung cancer is the leading cancer in many cancer registries in India (31,32), also the cases of non-smoking lung cancer in India is on the rise. Increase of lung cancer incidence in Indian women is another worrying trend (5,6).

In African continent, lung cancer is the fourth most common cancer among men with approximately 39,300 new lung cancer cases and an estimated mortality of approximately 37,700 people per year. Northern Africa has the highest incidence of Lung cancer cases in Africa. There is a wide variation in incidence and mortality across the African continent (1,33). In South Africa, a decrease in mortality among men while an increase was seen among women during the period of 1995–2006 (34).

In Latin America and Caribbean Region, 89,772 new lung cancer cases were estimated with 51,757 cases in men and 38,015 cases in women in the year 2018. It is the third common cancer in this region causing an estimated 81,384 deaths. In addition, the 5-year prevalence is low at 13.11% (1).

Lung cancer is common among men in countries of medium human development index (HDI), low income and low middle income countries, but the recent trends show an increase in lung cancer cases among women too. This may be attributed to second-hand smoke exposure, environmental pollution; household pollution (1,2,35–37). Apart from high incidence, mortality is very high too, accounting for around two third deaths in developing countries out of the total lung cancer deaths of which around 60.7% of deaths are in Asia alone (1).

Lung cancer screening

Screening is an effective method to detect cancer at an early stage. While there are regular screening recommendations for breast and cervical cancer, it is not the same in case of lung cancer (38). Most countries or organisations have

not framed any guidelines for lung cancer screening due to cost effectiveness and morbidity issues related to low-dose computed tomography (LDCT) (39). Various methods have been tried like chest radiography, sputum cytology, however, low dose computer tomography has been shown to be an effective screening modality for lung cancer.

Screening with chest radiography and sputum cytology

Lung cancer screening started in sixties when Brett published mass lung cancer screening research with approximately 55,000 men who were divided in two groups. Chest radiography was done biannually in test arm whereas chest radiograph was taken at starting and end of the study in control arm. There was no difference in mortality between test and control arms after three years of study period (40).

Three cooperative studies were conducted on lung cancer screening by National Cancer Institute, USA with Johns Hopkins Institute, Mayo Clinic and Memorial Sloan-Kettering Cancer Center to see the use of sputum cytology and chest radiograph in lung cancer screening. A total of 30,000 men participated in this study at 3 centers. In Mayo Clinic, half of the participants (screen group), were subjected to a dual-screen i.e., chest radiograph and sputum examination every 4 monthly for 6 years and another half were control. Participants were subjected to dual screen and chest radiography annually in each arm in Johns Hopkins and Memorial Sloan-Kettering. Participants who were screen negative at initial screening were followed up for 5 years or more. In Mayo Clinic study, chest radiograph detected lung cancer six times more when compared to sputum cytology, with a 5-year survival of 40% and 15% in screened and control groups respectively. This study could not show significant difference in mortality due to lung cancer like John Hopkins and Memorial Sloan-Kettering study where no benefit was seen in reducing lung cancer mortality by annual chest radiogram and sputum examination (41–45).

In PLCO randomised trial, 154,901 men and women aged 54–74 years were included from 1993–2001 at 10 screening centers. Chest radiograph was performed at the start of study followed by annual examination for three years. However, the results showed no reduction in lung cancer mortality (46).

Another study in Czechoslovakia compared the benefits of semi-annual lung cancer screening to 3-year interval screening with chest radiograph. Men aged 40–60 years who consumed 150,000 cigarettes or more in lifetime, current smoker were included in this study. Chest radiography

was done biannually in one arm for 3 years, while sputum examination was done at starting and end of the study in another arm. There was no significant difference in survival in both arms (47). Chest radiograph and sputum examination is not recommended for lung cancer screening as none of the studies have shown survival benefit. Additionally, adding sputum examination to chest radiograph for lung cancer screening is not useful (42-45,47).

LDCT

There are many studies where lung cancer screening was tried with low dose computed tomography. National Lung Screening Test (NLST) was largest landmark study on lung cancer screening which changed the screening guidelines for lung cancer by showing 20% reduction in mortality due to lung cancer using LDCT in comparison to chest radiograph. This USA study included 53,000 participants into two groups in which annual LDCT was done in one group while single chest radiograph was done in another group. Positive screening rate was higher in LDCT in comparison to chest radiograph with high rate of false positive cases (10).

NELSON trial (Dutch-Belgian Lung Cancer Screening Trial), the largest European trial with 15,822 participants aged 50–75 years with a history of smoking 15 or more cigarettes per day for 25 or more years or 10 or more cigarettes per day for 30 or more years, current smoker or former smoker who had quit smoking less than 10 year ago were included in this trial. In contrast to NLST, control group in NELSON study received no chest radiograph, while screening group was subjected to LDCT screening. Total 4 rounds of screening were done at 0, 1, 3 and 5.5 years (48). The protective value of LDCT screening was more pronounced in women than in men. Overall, mortality in high risk men and women decreased by 26% and 61% respectively by low dose CT scan over a period of 10 years (49).

Canada conducted its LDCT trial in 2000, which included current or former smokers aged 50–74 years with a history of 30 pack years or more. A total of 21 lung cancer cases were detected. The use of a sputum biomarker in addition to LDCT has increased the detection of lung cancer. Low dose CT has the benefit of detecting more lung cancer cases and has increased detection rate from 3% to 5% (50).

A pilot randomized control trial of comparing LDCT with chest radiograph was conducted in France in the year 2002. The screening was done at the start of the study, followed by annually screening for two year. This study included current or former smokers aged 50–75 years

consuming 15 or more cigarettes per day for 20 or more years. If LDCT detects nodules of size 5–10 mm, LDCT was repeated after three months to observe the changes. PET scan with or without histological examination was planned for nodules greater than 10 mm. A total of 765 participants were selected for randomization. It led to detection of 152 and 21 cases of non-calcified nodules on LDCT and chest radiograph, respectively, while 8 lung cancer cases were detected on LDCT out of 9 cases (51).

Lung cancer screening pilot trial in UK using LDCT was conducted in 2010. A total of 4,000 participants were divided into two arms. Participants aged 50–75 years, with a 5-year lung cancer risk of 5% or more based on Liverpool Lung project risk model were selected. One CT scan was performed at baseline and read by two experts who were supposed to record nodule size 3 mm or more in maximum diameter. Participants with nodule size of 10 mm or more on LDCT were referred to a local multidisciplinary team. Out of 1,994 participants who underwent LDCT, 42 were diagnosed with lung cancer. Only one LDCT screening in 5-years among population with lung cancer risk was found to be cost effective. Population based approach using validated risk assessment has the possibility to detect lung cancer at an early stage. It should however be noted that the prevalence of baseline lung cancer was high in UK trial in comparison to NLST (52).

A randomized control trial using LDCT was started in Denmark in 2004, in which a total of 4,104 participants aged 50–70 years, current smokers or minimum smoking history of 20 pack-years were randomised to two groups, the first with screening with five annual low dose CT scans and the second being no screening group. This trial reported no statistically significant effects on lung cancer mortality, but more number of early stage cancers (stages I, II and stage IIIa) were found in the screening group in comparison to the control group (53).

Japanese study using low dose CT scan was conducted in 1993 on 1,369 members of Anti-Lung Cancer Association (ALCA). Most of the members were men aged more than 50 years with smoking history of minimum 20 packs per year. LDCT was done once, twice, thrice and four times on 258, 318, 609 and 184 members respectively. This study concluded that low dose CT scan was better than chest radiography in the screening of lung cancer in high risk population (54).

There were trials using LDCT in Italy, South Korea, Germany & Taiwan and results are discussed in *Table 1* (51,55-62). There are many on-going trials on LDCT for lung cancer screening in developing countries listed in *Table 2*.

Table 1 Summary of landmark lung cancer screening trials

| Studies | Participants | Screening methods | Eligibility criteria | Outcome | Recommendation |
|------------|---|---|--|---|---|
| NLST | 53,454: LDCT arm, 26,722; CXR arm, 26,732 | LDCT annually for 3 years or one chest radiograph | Participants age between 50–75 years; 30-pack year smoking history; ≤15 years quitting smoking/current smoker | 20% reduction in mortality in comparison with chest radiograph | The cost effectiveness of LDCT must be attentively analysed. Use other studies for on molecular marker in blood, sputum and urine that help to select best suited participants for LDCT screening |
| NELSON | 15,792: test arm, 7,900; control arm, 7,892 | LDCT at baseline, than after 2 and 5.5 years. No chest radiograph | Participants age between 50–75 year; ≥15 cigarette/day for 25 years; ≥10 cigarette/day for 30 years; ≤15 years quitting smoking/current smoker | 26% reduction in mortality in men & 61% in women in over 10 years | This study is useful for further optimisation of the harm benefit ration of lung cancer screening program |
| UKLS Trial | 4,055: test arm, 2,028; control arm, 2,027 | One LDCT | Participants age between 50–75 years; 5-year lung cancer risk of 5% or more based on Liverpool Lung project risk model | More than 80% possibility to detect lung cancer in early stage. Prevalence of baseline lung cancer was high in UK trial in comparison with NLST | It is possible to detect lung cancer at early stage by which we can deliver potential curative treatment. Intervention would be cost effective |
| LSS | 3,318: LDCT arm, 1,660; CXR arm, 1,658 | LDCT and chest radiograph | Participants age between 55–74 years; 30-pack year smoking history; ≤10 years quitting smoking/current smoker | This study has established the feasibility of comparing annual spiral CT to chest X-ray for lung cancer screening | There is need of large study that focuses on compliance, screen positivity, diagnostic follow up |
| DLCST | 4,104: LDCT arm, 2,052; control arm, 2,052 | 5 annual LDCT | Participants age between 50–70 years; ≥20-pack year smoking history | No statistically significant effect of LDCT screening on lung cancer mortality | Over diagnosis could be a substantial problem associates with lung cancer screening. This study supports risk stratification with focus on age, smoking history and obstructive lung disease |
| LUSI | 4,052: MSCT arm, 2,029; control arm, 2,023 | 5 subsequent annual MSCT | Participants age between 50–69 years; ≥15 cigarette/day for 25 years; ≥10 cigarette/day for 30 years | Results indicate high recall rates in routine MSCT screening. Possible consequences for participants are more invasive than mammography | Screening must be strictly organise to be effective |
| DANTE | 2,450: LDCT arm, 1,264; other arm, 1,186 | Baseline chest radiograph and sputum cytology and 5 screening round with LDCT | Participants age between 60–74 years; ≥20-pack year smoking history; ≤10 years quitting smoking | No definitive finding of effectiveness to reduce mortality | They underline the importance of obtaining additional data for randomize trial with intervention free references before implementation of population screening |
| BRELT1 | 790: all participants underwent LDCT arm | LDCT | Participants age between 50–75 years; 30-pack year smoking history; ≤15 years quitting smoking/current smoker | Larger number of patients had positive scan in comparison with previous lung cancer screening studies | Supports the role of screening in population & patients with high incidence of granulomatous inflammation |

NLST, National Lung Screening Trial; NELSON, Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym-NELSON study); UKLS, UK Lung Cancer Screening; LSS, Lung Screening Study; DLCST, Danish Lung Cancer Screening Trial; LUSI, Lung Cancer Screening Intervention Trial; DANTE, Detection And Screening of early lung cancer with Novel imaging TEchnology; BRELT1, first Brazilian Lung Cancer Screening Trial; MSCT, multi slice computed tomography; CXR, chest X-ray.

Table 2 On-going lung cancer screening trial in developing countries

| Country | Study title | Sample size | Intervention | Criteria | Status |
|---------------|--|-------------|--|--|---------------------------------|
| Russia | Cohort study of low dose computed tomography for lung cancer screening in asymptomatic high-risk patients | 369 | LDCT | 55–75 years. ≥30 packs/year smoking history. ≤10 years quitting smoking. | Completed. Result not published |
| Taiwan, China | Low-dose computed tomography screening for lung cancer in relatives with family history of lung cancer | 1,102 | Three annual LDCT | 55–75 years. Relative of lung cancer patients | Completed. Result not published |
| China | Screening and diagnosing for early lung cancer in Shanghai communities with imaging procedures | 3,000 | CAD guided LDCT | 55–74 years with ≥30 packs/year smoking history and/or ≤15 years quitting smoking. Or ≥50 years with ≥20 packs/year smoking history and one additional risk factor. Or 35 years and one additional risk factor | Status unknown |
| China | Key technology in precision diagnosis and therapy for early stage lung cancer: a single arm clinical trial | 60,000 | Baseline LDCT followed by 2 biennial LDCT | 45–70 years. ≥20 packs/year smoking history. ≤15 years quitting smoking. Family history of malignant tumor. Occupational exposure to carcinogens. Long standing exposure: second hand smoke or cooking oil fumes | On-going |
| Taiwan, China | Low dose computed tomography screening study in non-smokers with risk factors for lung cancer in Taiwan | 12,000 | LDCT | ≤75 years. Never smoker or >15 years quitting smoking. Family history of lung cancer. Exposure to environmental tobacco smoke | On-going |
| China | Low-dose computed tomography for lung cancer screening in high risk asymptomatic patients: the Taiwan study | 600 | Baseline LDCT | 50–74 years. ≥30 packs/year smoking history. ≤15 years quitting smoking | Status unknown |
| Kazakhstan | Clinical trials on detection of lung cancer with non-invasive method based on DNA methylation of circulated tumor DNA, PBMC and T cells | 400 | DNA methylation of circulated tumor and PBMC DNA | ≥18 years | On-going |
| China | Evaluation of lung nodule and lung cancer detection with artificial intelligence assisted computed tomography among people living in North China: a prospective single-arm multicentre study of screening | 5,000 | AI assisted chest CT | ≥40 years. Yearly chest LDCT at least last 4 years up to 2017 | On-going |
| China | A study of the value of dynamic monitoring circulating tumor DNA in patients with lung cancer for post-operative evaluation, therapy response assessment, relapse prediction and defining molecular phenotypes | 1,500 | Detection of blood ctDNA using the second-generation sequencing technology | Patients with stage I–IV lung cancer who are eligible for surgery | On-going |
| China | Detection of early-stage lung cancer by using methylation signatures in circulating tumor DNA | 300 | ctDNA | ≥18D years with pulmonary nodule <30 mm found by LDCT | On-going |

CAD, computer aided diagnosis system; PBMC, peripheral blood mononuclear cell; ct, circulating tumor.

Screening in developing countries: existing programs & intervention

Though the burden of lung cancer is higher in developing countries, effective lung cancer screening program is not in place because of logistic issues. Several studies have been conducted worldwide for effective lung cancer screening methods (10,48-62). Most of these studies were conducted in developed countries and LDCT was used as standard lung cancer screening method. Several organisations have recommended use of LDCT in lung cancer screening for high risk population after mortality benefit of 20% shown in NLST study (10,63,64). But, cost of LDCT, risk of radiation, false positive finding and over-diagnosis make it difficult to implement at mass level (63). Considering the high incidence of lung cancer, China and Brazil conducted lung cancer screening trials using LDCT scans in 2014 and 2013–2014, respectively.

First Brazilian Lung Cancer Screening Trial (BRELT1) was conducted from January 2013 to July 2014. Around 4,030 participants showed interest but only 790 participants were taken in the program. Inclusion criteria for participants were same as NLST of USA with history of 30 packs-year smoking, current smoker or those who had quit smoking within last 15 years and aged between 55–74 years. The exclusion of large number of participants was because of lack of proper exposure of smoking (65). A LDCT was performed and pulmonary nodes more than 4 mm were taken as positive, similar to NLST trial. Positive findings were higher in BRELT1 (39.5%) in comparison to NLST (26%), but number of lung cancer cases found were almost similar in both studies. Though positive findings were higher in BRELT1, most of the large nodules had a very low suspicion of lung cancer in Brazil (65). Lung cancer screening is not recommended routinely in Brazil due to issues with applicability and effectiveness of LDCT. Incidence of granulomatous disease is high in Brazil and many pulmonary nodules may be attributed to tuberculosis and other chest infections (66).

In China, lung cancer screening trial was conducted by Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) in 2014 on 2,700 participants in three cities (67).

Screening challenges, opportunities & future research

Now, it is a well-established fact that screening for lung cancer with LDCT reduces mortality, a sign of relief in statement of three cooperative studies of Johns Hopkins

Institute, Mayo Clinic and Memorial Sloan-Kettering Cancer Center in USA, which showed no benefit from lung cancer screening with chest radiograph and sputum cytology in decreasing the mortality (45). But still there are no framework or guidelines for lung cancer screening in developing countries, with LDCT or other screening method, due to various constraints in implementing such program.

Symptoms of lung cancer and Tuberculosis are overlapping as fever, cough, expectoration, anorexia and weight loss are common to both but history of smoking, hoarseness of voice and SVC obstruction points towards a diagnosis of lung cancer. It is not quite uncommon that both tuberculosis and lung cancer are misdiagnosed due to radiological similarity (68), additionally patients with tuberculosis are at risk to develop lung cancer (69,70). There are a large number of pulmonary tuberculosis cases in developing countries and India reported an incidence of 204 per 100,000 cases in 2017 (71). It's always challenging and difficult to develop an effective lung cancer screening program in India in view of a large number of cases of pulmonary tuberculosis and other chest infections.

High false positive rate due to benign intrapulmonary lymph nodes or non-calcified granulomas, over-diagnosis and radiation exposure which leads to radiation induced cancer in long term are the harmful consequences of LDCT (10), and it remains the most critical issue with use of LDCT in lung cancer screening (72). Computer aided diagnosis (CAD) technique has high sensitivity in detecting lung cancer nodules with comparatively low specificity (73) and this system should be utilized in clinics for lung cancer screening. There is a decrease in false positive results in lung cancer screening with every millimetre increase in threshold nodule size (74). NLST, PLCO and other trial data showed that annual lung cancer screening reduced lung cancer mortality by 11–21% (range: 4.3–39.1% across various models) while biennial screening reduced only 6.5–9.6% lung cancer deaths. Triennial screening has limited scope in reducing lung cancer mortality. False positive results were increased with more frequent LDCT screening (75).

Over-diagnosis has been a problem in lung cancer screening, and ranges from 8.7–13.5% of screen detected lung cancer (75), but rate of over-diagnosis is low in LDCT in comparison to chest radiograph (10). LDCT has high sensitivity and specificity in detecting lung cancer among high risk smokers. Thus, selection of participants is the most important factor for cost effective and efficient screening program. Molecular Biomarker will be a value

addition for lung cancer screening and may reduce the cost of lung cancer screening (50) but more scientific research and validation is required to make it a point of care technology for high risk individuals.

Population based approach using validated risk assessment has the possibility to detect lung cancer at an early stage using LDCT as shown in UK trial. This approach can be utilized to reduce the cost of lung cancer screening (52). Selection of eligible population for lung cancer screening is always a challenge in developing countries in view of perception and stigma related to tobacco and smoking in the society. These are the barriers for high risk population to participate in lung cancer screening (76).

Conventional screening chest radiography in Lung cancer screening has shown no positive results in various studies (77,78), but use of digital chest radiography, with computer aided diagnostic technique and highly quantum-efficient detectors tools, to improve visualization of pulmonary structures (79-85) may, therefore, be a more better and sensitive screening tool in detecting lung cancer than conventional chest radiography. Lung cancer screening with chest radiography is difficult and missing lung cancer lesions by radiologists is not uncommon (86). Special training to read the chest radiograph for lung cancer screening can be beneficial (87). This is not only cost effective but also using digital radiograph may reduce mortality. Digital chest radiograph is easily accessible and cost effective method with low radiation exposure to participants. LDCT has a much higher sensitivity in lung cancer screening for the detection of small nodules, but lack of financial resources add difficulties in implementing lung cancer screening using LDCT.

Lung cancer mortality reduction among males in some developing countries can be attributed to anti-tobacco policies, which had shown trend of reduction in tobacco use and smoking, a major risk factor of lung cancer, with ban on smoking in public places & public transport and increased taxes on cigarettes and other tobacco products (34,88), but still lack of comprehensive policies on control of smoking and lack of guidelines on promotional advertisement and activates of tobacco products, can increase the lung cancer incidence in developing world, due to increased smoking and tobacco consumption, as reported in Global Youth Tobacco Survey from 1999–2008 (89-92).

Tobacco control and smoking cessation remain the most important long term intervention to decrease

morbidity and mortality from lung cancer in developing countries (93). There is a national framework for screening common cancers i.e., breast, cervical and oral cancers in India. Lung cancer is the most common cancer in males and its incidence is increasing further, but lung cancer screening is still not included in national framework in view of issues with availability of low dose CT scan and associated cost, also implicated is the high prevalence of pulmonary tuberculosis leading to over-diagnosis (38).

There is a need for aggressive research in lung cancer screening modalities for developing countries. There are many on-going trials for lung cancer screening in developing countries listed in *Table 2* (94). These trials have inclusion criteria of more than 30 years of smoking history, current or past smokers who had quit smoking within 10 or 15 years with variable age scales, with or without additional risk factors as history of occupational exposures of carcinogens, second hand smoke and household combustion of coal. These trials are focusing not only on LDCT based intervention, but also on newer modalities like molecular biomarkers, which may help in reducing the screening costs with high sensitivity and specificity, along with advantage of being non-invasive and easy to implement. End results of these trials will certainly help developing countries to adopt a lung cancer screening method, if there is a proven survival benefit.

Newer modalities in lung cancer screening

Positron emission tomography (PET)

PET is a propitious technique for lung cancer screening. Two studies evaluated the patients with non-calcified lung lesions more than 7 mm in diameter on annual low-dose CT followed by PET with fluorodeoxyglucose (FDG) (95,96).

In a study by Bastarrika *et al.*, FDG-PET correctly identified 19 of 25 indeterminate nodules. Sensitivity, specificity, positive predictive value and negative predictive value of using FDG PET for diagnosis of lung cancer were 69%, 91%, 90% and 71% respectively. Repeat CT was done after 3 months of negative FDG-PET, the negative predictive value was 100% (97). These results are promising but the obstacles to incorporation of FDG PET are cost and accessibility of FDG-PET. FDG-PET as a lung cancer screening tool needs to be validated in larger cohort studies.

Molecular biomarkers

Many research findings have demonstrated that, prior to lung cancer diagnosis, hypermethylation of gene promoters

remains present in exfoliated cells within sputum. Promoter of hypermethylation of multiple genes, especially p16 ink4a promoter and p53 mutation are shown to appear in chronic smokers or high risk group before the clinical evidence of lung cancer (98-101). Telomerase activity in sputum may be helpful in differentiating benign from malignant tumours (102).

Autofluorescence bronchoscopy (AFB)

This technique identifies the areas of epithelial thickness and hyper vascularity as abnormal fluorescence and helps to improve sensitivity to diagnose pre-invasive lesions, squamous dysplasia, carcinoma in situ (CIS) and early lung carcinoma when used simultaneously with conventional bronchoscopy. AFB has shown usefulness to adjunct conventional bronchoscopy for detecting intraepithelial neoplasms and CIS as shown in single center studies, 3 multicenter and 2 randomized clinical trials (103-107). However the specificity of AFB is too low to diagnose the pre-invasive lesions. New autofluorescence imaging (AFI) has been introduced to increase the specificity that can distinguish the pre-invasive lesion and benign tumour by colour (108).

Electronic nose

Many volatile organic compounds (VOCs), especially alkanes and benzene derivatives have been identified in breath of lung cancer patients. According to a research study, for stage 1 lung cancer, which had 22 breath VOCs, showed 100% sensitivity and 81.3% specificity. Patients with and without lung cancer can be distinguished by using this technique (109-111). Electronic nose has been successfully used in detection and analysis of VOCs in the food industry. Various studies reported the use of this tool for VOC pattern analysis to detect lung cancer with fairly high diagnostic accuracies (111-118). However, no large scale implementation studies using electronic nose have been reported.

Genomic and proteomic analysis of bronchoscopic samples

The advances that have been made in understanding the molecular mechanisms of NSCLC progression may open the door for improvement of current therapeutics and identification of novel targets (119). A proteomics is an approach that clarifies the molecular steps involved in lung cancer development. This technique differentiates the pre-invasive bronchial lesion from invasive bronchial lesion by the specific patterns of protein expression of the airway epithelium, however, large scale studies are required to prove its validity (120).

Breath print analysis

This technique captures a signature of the whole exhaled breath that consists of a large number of non-selective sensors combined in sensor arrays (121-123). These multiple sensor arrays produce a multidimensional output, after that it is analysed with pattern recognition techniques specific to multivariate data analysis.

Lung cancer screening guideline and recommendations

Various organizations have given recommendations for lung cancer screening and a few countries have guidelines related to it, but there is no guideline for lung cancer screening in developing countries. International Association for the Study of Lung Cancer (IASLC) issued statement for LDCT based Lung cancer screening after promising results of NELSON study, with a focus of identifying the high risk population and developing radiological guidelines of lung cancer screening program which can be implemented in developing countries (124,125). Japan Radiological Society and Japanese College of Radiology have issued guideline for persons over 50 year with smoking history of 30 pack years (126,127).

National Cancer Center, Saudi Arabia has issued guideline for Lung Cancer Screening with annual LDCT for person aged 55–77 years with more than 30 pack year smoking history or those who had quit smoking less than 15 years ago (128). Canada also has recommended LDCT based lung cancer screening for persons aged 55–74 years with more than 30 pack years smoking history, current smoker or had quit smoking for less than 15 years. There is no recommendation of chest radiograph for lung cancer screening (129). European Union has also issued a position statement for lung cancer screening in Europe (130).

In USA, many organizations have issued guidelines for lung cancer screening, highlighting the high risk groups, and also age and frequency of screening. After survival benefit in NLST, American Association for Thoracic Surgery, American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, American Lung Association, National Comprehensive Cancer Network, and US Preventive Service Task Force have recommended lung cancer screening for persons with smoking history of 30 pack year or more. But American Academy of Family Practice found insufficient evidence to recommend for or against screening (131-138). Details of guidelines and recommendations are listed in *Table 3*.

Table 3 Summary of lung cancer screening guidelines and recommendations

| Country/organisation | Eligible population group | Recommendation |
|--|--|--|
| Saudi Arabia | Person age between 55–74 years; smoking history: 30 packs/year or more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan, if finding normal or having nodule <5 mm in size; low dose CT in every 6 months, if having nodule 6–7 mm in size; refer to pulmonary surgeon, if having lung nodule >8 mm in size |
| Japan | Person age more than 50 years (with a Brinkman index >600) | Low dose CT annually |
| Canada | Person age between 55–74 years; smoking history: 30 packs/year or more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan up to 3 consecutive times; screening should only be carried out in a health care setting with expertise |
| American Academy of Family Practice | Evidence is insufficient to recommend for or against screening | |
| American Association for Thoracic Surgery | Category 1: person age between 55–79 years; smoking history more than 30 packs/year. Category 2: person age between 50–79 years; smoking history: 20 packs/year; additional comorbidity that produces a cumulative risk of developing lung cancer $\geq 5\%$ in 5 years. Category 3: long-term lung cancer survivors who have completed 4 years of surveillance without recurrence, and who can tolerate lung cancer treatment in order to detect second primary lung cancer until the age of 79 | Annual low dose CT scan; long-term lung cancer survivors should have annual low-dose computed tomography to detect second primary lung cancer until the age of 79 years |
| American Cancer Society | Person age between 55–74 years; smoking history 30 packs/year or more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan |
| American College of Chest Physician | Person age between 55–80 years; smoking history 30 pack/year or more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan |
| American College of Chest Physicians and American Society of Clinical Oncology | Person age between 55–74 years; smoking history 30 packs/year or more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan |
| US Preventive Services Task Force | Person age between 55–80 years; smoking history more than 30 packs per year; current smoker or quit smoking with in last 15 years | Annual low dose CT scan; screening should be discontinued once person has not smoked more than 15 years or having some health problems |
| American Lung Association | Person age between 55–77 years; no history of lung cancer; smoking history more than 30 packs/year; current smoker or quit smoking with in last 15 years | Annual screening with low dose CT up to 15 years |
| National Comprehensive Cancer Network | Category 1: person age between 55–74 years; smoking history more than 30 packs/year; current smoker or quit smoking with in last 15 years. Category 2: person age more than 50 years; smoking history more than 20 packs per year; at least one more risk factor other than second hand smoke | Annual low dose CT scan; if nodule more than 8 mm then PET/CT on 3-month follow up |

Conclusions

Incidence of lung cancer has significantly increased over the last three decades and has a worrisome increase in developing countries. LDCT has become the gold standard for lung cancer screening after survival benefits seen in NLST and NELSON studies. An effective lung cancer screening program is still a challenge in developing countries despite a high incidence of lung cancer. LDCT could be a good choice for screening, however, high cost of LDCT, large population size to be screened and low success rates of LDCT make it difficult to implement such a program. Also inadequate infrastructure, lack of human resources, low skilled manpower and lack of financial resources add further difficulties in adopting such a program. An Ideal Screening Method for developing countries should be easily and widely available, easy to perform and must be cost effective. High incidence of tuberculosis in developing countries further compounds the problem by adding to false positive cases during screening. There is a need to develop point of care technology for cost effective lung cancer screening in developing countries as lung cancer is going to be a major burden in coming years.

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Footnote

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