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Review Article

Lung cancer screening in India: Preparing for the future using smart tools & biomarkers to identify highest risk individuals

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There is a growing burden of lung cancer cases in India, incidence projected to increase from 63,708 cases (2015) to 81,219 cases (2025). The increasing numbers are attributed to smoking (India currently has nearly 100 million adult smokers) and environmental pollution. Most patients present with advanced disease (80-85% are incurable), causing nearly 60,000 annual deaths from lung cancer. Early detection through lung cancer screening (LCS) can result in curative therapies for earlier stages of lung cancer and improved survival. Annual low-dose computerized tomography (LDCT) is the standard method for LCS. Usually, high-risk populations (age>50 yr and >20 pack-years of smoking) are considered for LCS, but even such focused screening may be challenging in resource-limited countries like India. However, developing a smart LCS programme with high yield may be possible by leveraging demographic and genomic data, use of smart tools, and judicious use of blood-based biomarkers. Developing this model over the next several years will facilitate a structured cancer screening programme for populations at the highest risk of lung cancer. In this paper, we discuss the demographics of lung cancer in India and its relation to smoking patterns. Further, we elaborate on the potential applications and challenges of bringing a smart approach to LCS in high-risk populations in India.

Key words Artificial intelligence - biomarkers - high-risk population - India - low-dose CT scans - lung cancer - screening

Lung cancer is the leading cause of cancer mortality across the globe and is primarily related to tobacco smoking. However, non-smoking lung cancers have increased in the last two decades, possibly due to air pollution[1,2]. Large trials have shown that lung cancer screening (LCS) can reduce mortality in high-risk populations of smokers. Low-dose computerized tomography (LDCT)-based screening and smoking cessation counselling form the basis of LCS recommendations in the United States, Canada, parts of Europe, Japan, and South Korea. Other nations, such as China and India, despite having the highest burdens, are yet to adopt LDCT for LCS. The number of new cancer cases among adults aged >60 is expected to increase by 75.2 per cent and deaths by 82.8 per cent by 2040[3].

This manuscript attempts to define the burden of lung cancer in India and outline challenges in implementing a population-wide LCS programme.

Unlike earlier reviews, which focus on summarizing the challenges, we delve into potential solutions for implementing an LCS programme. Population-level data, smart (artificial intelligence (AI)-based) tools, and point-of-care blood-based biomarkers that inform LDCT screening may result in a leaner yet comprehensive LCS programme.

The problem of lung cancer in India

Lung cancer is the most common cancer among Indian males, and the number of cases in India is expected to rise from 63,807 in 2015 to 81,219 cases in 2025[4] and it accounts for eight per cent of cancer-related mortality[5]. Most patients present in advanced stages, not amenable to curative therapy, resulting in high disease-specific mortality rates of 80-90 per cent. The numbers for incidence and mortality are derived from cancer registries that receive input from tertiary care hospitals, which do not reflect those who may not be registered at the time of arrival into a tertiary cancer care centre because they are too sick to be treated.

There is an unequal distribution of lung cancer burden across India. According to Population Based Cancer Registries Report 2016, the northeastern States have the highest incidence of lung cancer. As per the National Cancer Registry Programme, the age-adjusted incidence of lung cancer varies between 4.6 (Wardha) to 38.8 (Aizawl) per 100,000 males, and 1 (Barshi) to 37.9 (Aizawl) per 100,000 females. The incidence is lower in the western and central regions[6,7], a variation that could be partly explained by the differences in smoking patterns in these regions. The overall smoking prevalence in India is estimated to be 18.9 per cent, varying from 16.2 per cent (Kerala) to 72 per cent (Mizoram)[8]. Lung cancer affects Indian males more than females, though the female (non-smoker) lung cancer incidence is increasing[9]. These trends are similar to other Asian countries, such as China.

Taken together, the prevalence of lung cancer in India is lower than that in the West, but the median age at diagnosis is lower by a decade, with a high mortality-to-incidence (MIR) ratio contributed to by many factors, including advanced-stage of cancer at diagnosis, a sicker patient and reduced access to therapies.

'Arguments' against lung cancer screening in India

Screening using LDCT reduces mortality from lung cancer in high-risk populations. Arguments against LCS in India are: (*i*) lung cancer is not a 'major' problem, incidence in India is lower than in developed countries, (*ii*) India does not have the 'heavy smoking' population that forms the basis of screening studies, (*iii*) high prevalence of TB and resultant false positives on LDCT dilute the value of an ideal screening test, (*iv*) real risk of overdiagnosis, given the high prevalence of medical co-morbidities that may result in competing mortality before death from lung cancer, and (*v*) lack of resources such as access to CT scanners and an organized infrastructure required for an efficient LCS programme. Other challenges include provider and patient-related diagnostic delays and problems with patient selection, which have been addressed in a more recent review in this area[10].

Points in favour of considering lung cancer screening in India: 'Counterpoints' to the above 'arguments'

Lung cancer is not a 'major' problem in India: The age-standardized rate (ASR) of lung cancer is estimated at 5.4/100,000 males. However, the incidence is higher (15-20/100,000) in some urban areas. The incidence is lower than that in Eastern Europe (40-50/100,000) and the US (30/100,000), but contemporary trends show an increase in lung cancer rates. A 13 per cent increase in lung cancer is projected in India over the next decade[11]. Therefore, while the incidence of lung cancer is lagging behind that in Western countries, there is a real threat of this changing over the next decade, necessitating a framework of a practical and India-specific LCS programme.

India does not have the 'heavy smoking' population that forms the basis of screening studies: The proponents of LCS base their recommendations on studies demonstrating a reduction in lung cancer and all-cause mortality in high-risk (highest prevalence of smoking) populations. Most screen-detected cancers are Stage I and are cured by surgery or radiation. Implementing LCS leads to more stage I and fewer stage IV cases without a change in the overall incidence of lung cancer, thus negating the possibility of overdiagnosis[12]. In a meta-analysis, Passiglia *et al*[13] studied 88,497 individuals enrolled in LCS trials and identified the following: (*i*) a reduction of lung cancer–related mortality (13-20%), (*ii*) a significant increase of early-stage tumour diagnosis (2.8X), (*iii*) a significant decrease of late-stage tumour diagnosis (25% fewer), (*iv*) a significant increase of resectability rate, (*v*) a nonsignificant reduction of all-cause mortality, (*vi*) a

significant increase of overdiagnosis rate (38%; indolent cancers or competing mortality factors), and (*vii*) non-significant differences in lung cancer–related mortality by sex.

There are 267 million tobacco users in India[14], the highest number after China. As per the Global Adult Tobacco Survey 2 (GATS2), there are 100 million tobacco smokers in the country in India, mostly (73 million) hailing from rural areas. Almost 80 per cent of them smoke daily, and another 29.7 million are ex-smokers. Thus, India has a burden of nearly 130 million adults who have smoked tobacco at some point in time in their lives. The traditional definition of pack-years is not readily applicable to India, given that the numbers of cigarettes/*bidis* vary per pack and selling loose cigarettes is a prevalent practice. The surveys conducted by GATS2 inferred that the mean number of cigarettes smoked per day by a daily tobacco user was 6.8, and the mean number of *bidis* smoked per day by a daily user was 15.1. Taken together, about 100 million individuals can be deemed 'high-risk'. Due to the lower nicotine content in *bidis*, the equivalent pack years for *bidis* are 43 *bidis* per day for one year[15]. However, we cannot attribute the carcinogenic effects to nicotine alone as *bidis* require stronger puffs and have higher carbon monoxide per puff. Also, there is variation in the profile of *bidi* users (males, lower socioeconomic strata, older age) when compared to cigarette users, which may impact cancer incidence[16].

Aside from the tobacco-use heterogeneity, there is a significant increase in non-smoking-related lung cancers in India. In a large north Indian study, nearly 44 per cent of new lung cancers were noted in non-smokers[17]. The reasons for this are unclear. Similar demographics in Taiwan prompted a population-wide study (TALENT) of LDCT in non-smokers that demonstrated a lung cancer rate of 2.6 per cent, with the majority, >70 per cent, being Stage I[18]. However, this approach might have a significant lag time and overdiagnosis bias. Such an LDCT-based approach is not currently recommended for non-smokers. But we need to revisit this concept in the Indian context, considering the high burden of air pollution in many of the heavily populated Indian cities and the earlier cited increasing incidence of lung cancers among non-smokers in the country. Carefully constructed prospective longitudinal studies, considering environmental and social determinants of health, may be necessary to inform LCS in the non-smoking population.

High prevalence of tuberculosis (TB) and resultant false positives on LDCT dilute the value of an ideal screening test: Granulomatous disease such as TB is still rampant in India, particularly in rural areas, where tobacco smoking is most prevalent. TB-related findings can give rise to false positives in LDCTs and unnecessary invasive testing. While there is no direct report of the impact of TB on LCS from India, a recent paper from Brazil, another low-middle-income country (LMIC), showed that the positive predictive value of LCS and lung cancer incidence in the LDCT group was similar to that reported from the National Lung Screening Trial (NLST), despite having a higher incidence of granulomatous disease[19]. Others have also shown that the presence of radiological sequelae of tuberculosis was not associated with a positive LDCT scan[20]. In a study from Chandigarh, India, LDCT in a TB-endemic region (n=221), 33.5 per cent of participants had a positive result after the first round of screening, and 1.8 per cent were diagnosed as having lung cancer (unpublished data), which is comparable with similar data from other countries[5].

Taken together, these data, small numbers not with standing, reveal that the presence of prior granulomatous disease, including TB, may not be a significant confounding factor. However, these need validation in larger studies. Importantly, these studies reveal a consistent percentage of lung cancers detected (between 1-2%) as in the NLST and other large randomized controlled trials (RCTs) and a similar number of Stage 1 NSCLCs. Standardization of radiological reporting and prospective follow-up will further reduce false positives and build a better model for screening the highest-risk individuals.

Lack of resources such as access to CT scanners and lack of an organized infrastructure required for an efficient LCS programme: The resources needed for LCS as advocated by the West may be a significant ask. Let us consider the resources required to set up a comprehensive LCS programme using the USPSTF recommendations.

Workforce requirement for traditional lung cancer screening, by the numbers: Resourcing an LCS requires significant infrastructure and workforce. The scan itself is performed on a standard CT machine. However, the radiation dose is lower at 1.4 millisieverts (mSv) compared with 7mSV for a diagnostic CT of the chest; the LDCT scan is quick and completed in less than 5 min; however, these scans may compete

with time slots for patients who need diagnostic scans, straining resources. It is estimated that a lung cancer navigator who works with the primary care physician is necessary to keep track of high-risk individuals who are sent for LCS. On an average, one navigator is required for 1000 high-risk individuals (to provide counselling, shared decision making, referral to a smoking cessation programme, coordinating with a multidisciplinary lung nodule clinic, and follow up of indeterminate nodules as per established guidelines and tracking patients yearly, in addition to facilitating timely referral to cancer services in the event of lung cancer detection). The workforce includes radiologists, radiology technicians, pulmonologists, interventional radiologists, thoracic surgeons, nurse coordinators, radiation and medical oncologists and data managers. The programme requires a dedicated program manager to oversee personnel and maintain quality audits and controls.

Requirements for setting up a Lung cancer screening programme in India: A broad LCS programme for India will be cost-intensive and resource-prohibitive. Therefore, it is crucial to consider a programme targeting the highest-risk individuals. We will consider this in the following manner: (*i*) scale, (*ii*) optimizing opportunistic prevention and screening, (*iii*) optimizing incidental nodule diagnostic pathways, (*iv*) using robust algorithms to identify highest risk individuals, (*v*) incorporation of digital aids for CT reading, (*vi*) judicious incorporation of blood-based biomarkers, and (*vii*) incorporation of 'Smart Tools' across the programme.

(i) Scale: Implementing LCS in India without overcoming local barriers is impractical. Identifying 1-2 regions with high lung cancer and smoking prevalence to pilot test solutions should be part of the initial strategy. The specified population will require in-depth data collection on lung cancer incidence and demographics over the previous five-years. Registry data and GATS2 data for the region can then be combined to identify individuals with incident lung cancer who used tobacco. The scope of this demographic data will define the number of navigators needed to serve the population for tobacco cessation counselling and referral to a comprehensive LCS programme. Currently, primary care physicians in regional hospitals provide initial care and education on non-communicable diseases in general (this includes oral cavity, breast, and cervical cancer). One such innovative model is the Tata Digital Nerve Center (DiNC) model, which seeks to decentralize care, empower the rural primary care centres, and refer back to centralized resources for complex care, including cancer (*https://www.tcs.com/corporate-social-responsibility/empowerment/known-citizen-drive-DiNC*).

Such a model will provide both accurate data on lung cancer prevalence and tobacco use patterns and provide opportunistic screening and primary prevention through a decentralized model.

Resources: LDCTs do not require specialized CT scanners. However, adequate numbers of scanners will be required to provide dedicated CT scanner time to facilitate LCS. The availability of CT scanners and the cost of an LDCT may impact uptake. Regarding health infrastructure, Organization for Economic Co-operation and Development (OECD) data from 2021 show that in the US, there were 43 CT scanners/million population, higher than the OECD average of 26[21]. In India, there are 31 scanners/million population[22]. However, these are disproportionately located in urban areas. The LDCT reads must follow specific templates for LCS, which can add to the radiologist's workload. In a study of human resources required for a given high-risk population, we noted that with increasing numbers of the population at risk to be screened, there was an exponential increase in nurse navigators, primary care physicians and radiologists necessary to complete the proximal parts of the steps involved in LCS. Based on this, developing a systems-focused tool for modelling LCS resource needs is essential to accurately determine capital needs, including CT machines, information technology infrastructure and personnel, including radiologists, pulmonologists, thoracic surgeons, radiation, and medical oncologists. Given the concentration of most physicians in urban areas, these can present unique challenges in India. Development of AI-aided LCS may assist in reducing the frequency of LCS and sending only the highest risk nodules detected on baseline LDCTs to downstream steps requiring interventional radiology/pulmonary and surgery/radiation oncology. Such algorithms need to be specific to India to allow for personalized LCS. The factors affecting the uptake of LCS in seven countries have been reviewed by Poon *et al*[23] pointing to the factors other than infrastructure and resources required, which include prioritization from a public health standpoint, education, and outreach for both physicians and high-risk individuals[23].

(ii) Optimizing opportunistic prevention and screening: Opportunistic LCS can occur when an individual presents for a yearly health examination, a screening mammogram, PAP smear or colonoscopy. At the time of these visits, if the individual fulfils the proposed criteria for LCS, they may be referred to an organized LCS programme. Such opportunistic screening identified lung cancers in women presenting for a yearly mammogram[24,25]. 'Opportunistic' LCS also occurs when individuals present for CT scans for other respiratory or non-respiratory-related indications. In this instance, the results have been met with variable success[26]. However, such a program can pose significant challenges, particularly if a well-defined clinical pathway that triages the patient from 'abnormal nodule' in the incidental chest CT to diagnosis and therapy is absent. Clinical pathways wherein the radiologists alert the primary care provider of an incidental suspicious lung nodule may be useful[27]. These patients need to be directed to a robust multi-disciplinary lung nodule programme to avoid unnecessary thoracotomy or other invasive procedures and be followed on a dedicated navigator dashboard according to defined criteria, such as the updated Fleischner criteria[28] for incidental nodule management.

(iii) Optimizing nodule diagnostic algorithm: One of the challenges in a screening programme is the appropriate approach to screen-detected nodules. Fewer than four per cent of nodules detected in the NLST were malignant, so a mechanism of identifying and tracking indeterminate nodules is paramount to the success of LCS.

Though the lung imaging, reporting and data system (lung-RADS) introduced in 2015 represented an important step in reducing uncertainty in reporting, it still requires a human interface and trained radiologists[29]. Computer-aided diagnostic techniques can simultaneously improve nodule detection and reduce the number of nodules that require interpretation by a radiologist. In a decentralized model, this can reduce the number of nodules requiring further evaluation, including biopsies[30]. Another potential application of technology is cloud-based computerized systems, which have reduced the variability across sites in positivity rates[31]. Radiomics has shown promise in lung nodule evaluation, which can be incorporated into the initial studies[32].

(iv) Using robust algorithms to identify at-risk individuals: Current LCS trials target individuals who are at the highest risk based on their tobacco use history. For example, the NLST identified individuals between 55-74 yr with at least 30- pack years of smoking history[33]. The revised US Preventive Services Task Force (UPSTF) criteria expanded this in 2021 to include a 20-pack-year smoking history for LCS. Even with these revised criteria, just over half of the African American patients would qualify for LCS, whereas 3/4th of white patients would qualify. Simply changing the criteria to numbers of years smoked (>20 yr of smoking) reduced this disparity, such that over 80 per cent of both ethnic groups qualified for LCS[34]. Similar personalized risk models may be necessary in India to identify patients at risk for lung cancer to reduce disparities among urban, rural, and ethnic groups.

The most popular form of smoked tobacco in India is in the form of *bidis*, and the traditional definitions of 'pack-years' may not be feasible. Other predisposing factors may play a role (*e.g.*, air pollution and exposure to PM[35]. In the Indian context, indoor air pollution due to cooking stoves using biomass fuels like wood, dung, or crop residues has been associated with the risk of lung cancer in women[36,37]. However, there are currently no guidelines to identify populations eligible for LCS other than the widely used (albeit imperfect) metric of the pack-year. A modified algorithm based on the duration and intensity of tobacco smoking, air pollution, and occupational exposure will need to be considered.

(v) Identifying blood-based biomarkers to aid early diagnosis/screening: A robust, validated point-of-care blood test would be most valuable in resource-constrained countries, such as India and other LMICs. However, such tests will need to be cost-effective, have a high positive predictive value, and be rigorously tested prospectively with longitudinal follow-up to demonstrate a reduction in lung cancer-related mortality. Current 'liquid biopsy' testing includes the study of circulating tumour cells, cell-free DNA (cfDNA), circulating tumour (ctDNA), miRNA, exosomes and tumour-educated exosomes (TEX). A single blood tube may provide data on several biomarkers at once and allow for a comprehensive risk readout based on genomic, epigenomic and proteomic biomarkers. A complete discussion of the pros and cons of each of these blood biomarkers is beyond the scope of this paper, but this subject is reviewed comprehensively by Freitas *et al*[38]. Such blood-based biomarkers may be complementary to the LDCT screen[39].

Compared to genomic aberrations involving changes in the sequence of the DNA, epigenetic regulation affects the function of a particular gene[40]. The most well-studied of these epigenetic phenomena is DNA methylation, characterized by the reversible addition of a methyl group (CH3) to cytosine in DNA to form 5-methyl cytosine. Aberrant methylation patterns (hypomethylation or hypermethylation) are a hallmark of carcinogenesis, occurring early and across the genome, resulting in genomic instability. These epigenetic changes are remarkably distinct across organ types, enabling some recent technologies in this space. Currently, several competing platforms are using early epigenetic changes to detect cancers; one of these involves detecting methylation changes across the genome in the form of a multi-cancer detection test that includes lung cancer, reviewed recently by Constantin *et al*[41]. The purported specificity of GRAIL is >95 per cent with a false positive of less than one per cent. Other methylation-based tests of plasma markers like Lung Epi-check have shown promising results with high sensitivity (87.2%) and specificity (64.2%) in diagnosing early lung cancers. They could be a potential biomarker for screening lung cancer[42]. None of these platforms have long-term follow up of positive tests. Therefore, it is safe to say that these platforms require more rigorous and longitudinal testing in various populations before being adopted into clinical practice.

MicroRNAs (miRNAs) usually have 19-22 nucleotides involved in gene regulation and are very stable in circulation. With just 2 miRNAs, lung cancer patients can be differentiated from individuals without cancer[43].However, validation studies are required. Studies combining promising miRNAs and LDCT may increase detection rates[44]. The role of autoantibody-based biomarkers for screening is evolving. Early CDT-lung test, an ELISA-based detection of seven autoantibodies in peripheral blood, followed by a CT scan has shown promise[45]; but the sensitivity for early lung cancers was only 21 per cent and may need to be combined with LDCT.

Taken together, several blood-based biomarker platforms in the multi-cancer early detection space are being evaluated across the world in disparate populations. They may serve as a good adjunct to current screening practices and could be incorporated as a study tool to eventually identify the highest-risk individuals who might benefit from radiographic screening.

Comprehensive database: First, one requires comprehensive data on incident lung cancers in a large population. This could be done by linking cancer registries (maintained by the Indian Council of Medical Research), electronic medical records, imaging data, pathology, types of therapies received and date of death from lung cancer. This data would need to be meticulously collected and curated with specific accounting for missing data and replacing those patients without complete data. These data would be stored in a central database and must be 'cleaned', audited and maintained by an arms-length group. Another goal would be to develop natural language processing within this programme–training complex, transformer-based language models on the vast corpus of unstructured clinical text, fine-tuning to oncology language, and then performing concept extraction to unlock the information hidden within free text- an example of a learning health system. Read-outs would inform who gets lung cancer, what the 5-year survival is, and whether the currently recommended screening practice makes sense. Further details about these cancers could be obtained with patient consent to obtain their records in conjunction with pathology and radiological data. Patients may directly consent to biological samples individually or through screening 'fairs' where educational activities such as smoking cessation are emphasized.

Prospective data collection system: Second, setting up a prospective data collection system in a defined population that gets primary care in a specific village/ city. The control group will be those without cancers. Besides demographic data and environmental exposure, comprehensive data elements should include germline sequencing. Biological samples will be required after obtaining informed consent. These samples must be collected uniformly, stored, curated, and evaluated for genomic and epigenomic alterations. An incident diagnosis of lung cancer would entail somatic sequencing of the lung cancer. The pay-off would occur in 5-10 yr to build a unique risk assessment model that is India-specific. This would be similar to the UK-biobank, a large prospective study of individuals aged 40 to 70 yr at assessment. The persons who attended assessment centres between 2006 and 2010 contributed blood samples for genotyping and blood analysis and answered questionnaires about medical history and environmental exposures. In the years since assessment, health outcome data for these individuals

(*e.g.*, cancer diagnoses) have been accruing through UK national registries and hospital records. Third, demographic and clinical data should be extended and combined with a multi-omics platform, including genomics, epigenomics and proteomic results, to bring together several data sources for training of machine learning risk prediction models.

(vi) Incorporation of 'Smart Tools': At each step of the LCS programme, smart tools developed by Artificial Intelligence (AI) can aid in the workflow, as reviewed by Gandhi *et al*[46]. This could start from risk stratification models that are unique for India, available on a provider-facing interface to screen high-risk individuals, use of AI algorithms such as SYBIL to ascertain the medium-term risk of lung cancer from single baseline LDCT[47], ascertain genomics of newly diagnosed lung cancers from imaging or initial pathology slides[48,49], and use of advanced radiomic algorithms that can inform prognosis following radiotherapy for early stage lung cancers[50].

At present, we have little information about the usefulness of lung cancer screening in India. There is only one prospective study by Singh *et al*[5]. However, this is a single-arm study with only 253 participants. Nevertheless, the results could shed important preliminary information that may inform future longitudinal studies.

Conclusions

Lung cancer incidence and mortality are on the rise, and in India, most patients present at an advanced stage. Lack of adequate infrastructure, larger population, high incidence of granulomatous lesions, and changing etiological factors dilute LDCT as a valid screening tool. Opportunistic screening, optimizing lung nodule detection algorithms and identifying at-risk individuals with the incorporation of various biomarkers with LDCT, aided by artificial intelligence, should be explored for a successful screening programme to reduce mortality. Judicious use of blood-based biomarkers could be incorporated into the screening algorithm for longitudinal data collection and to inform a learning system. Funding for such a program must come from the government and industry partners. The data infrastructure will need to reside in a centre for informatics; the stakeholders will be required to be organized with built-in redundancies in the system and arm's length ombudsmen to allow for scientists to use the data generated to inform best practices. Eventually, one could envisage a scenario wherein a combination of tools can be used to inform lung cancer screening that is most specific and sensitive and that can be administered with optimized resources.

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References

1 Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, *et al.* Air Pollution, Genetic factors, and the risk of lung cancer: A prospective study in the UK Biobank. *Am J Respir Crit Care Med* 2021; *204* : 817-5.

2 Berg CD, Schiller JH, Boffetta P, Cai J, Connolly C, Kerpel-Fronius A, *et al.* Air pollution and lung cancer: A review by international association for the study of lung cancer early detection and screening committee. *J Thorac Oncol* 2023; *18* : 1277-89.

3 Kalita M, Devaraja M, Saha I, Chakrabarti A. Global burden of cancer pattern in 2020 & prediction to 2040 among older adults. *Indian J Med Res* 2023; *160* : 397-406.

4 Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. *Indian J Med Res* 2022; *156* : 598-607.

5 Singh N, Agrawal S, Jiwnani S, Khosla D, Malik PS, Mohan A, *et al.* Lung cancer in India. *J Thorac Oncol* 2021; *16* : 1250-66.

6 Asthana S, Patil RS, Labani S. Tobacco-related cancers in India: A review of incidence reported from population-based cancer registries. *Indian J Med Paediatr Oncol* 2016; *37* : 152-7.

7 Mohan S, Asthana S, Labani S, Popli G. Cancer trends in India: A review of population-based cancer registries (2005-2014). *Indian J Public Health* 2018; *62* : 221-3.

8 Nath A, Sathishkumar K, Das P, Sudarshan KL, Mathur P. A clinicoepidemiological profile of lung cancers in India - results from the National Cancer Registry Programme. *Indian J Med Res* 2022; *155* : 264-72.

9 Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George K, *et al.* Epidemiology of lung cancer in India: Focus on the differences between non-smokers and smokers: a single-centre experience. *Indian J Cancer* 2012; *49* : 74-81.

10 Vora A, Balamugesh T, Behera D, Kumar P, Tiwaskar M, Mehta P, *et al.* Screening for lung cancer in India: Expert opinion statement. *J Assoc Physicians India* 2024; *72* : e1-e16.

11 International Agency for Research on Cancer. World Health Organization. *Global cancer observatory: Cancer today*. Available from: *https://gco.iarc.fr/today/en*, accessed on December 18, 2024.

12 Vachani A, Carroll NM, Simoff MJ, Neslund-Dudas C, Honda S, Greenlee RT, *et al.* Stage migration and lung cancer incidence after initiation of low-dose computed tomography screening. *J Thorac Oncol* 2022; *17* : 1355-64.

13 Passiglia F, Cinquini M, Bertolaccini L, Del Re M, Facchinetti F, Ferrara R, *et al.* Benefits and harms of lung cancer screening by chest computed tomography: A systematic review and meta-analysis. *J Clin Oncol* 2021; *39* : 2574-85.

14 Tata Institute of Social Sciences. Ministry of Health and Family Welfare. Government of India. *Global Adult Tobacco Survey 2 GAT2 India 2016-17*. Available from: *https://ntcp.mohfw.gov.in/assets/document/surveys-reports-publications/Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017.pdf*, accessed on December 18, 2024.

15 Datta R, Singh S, Joshi A, Marwah V. Concept of BIDI years: Relevance to the perioperative period. *Lung India* 2022; *39* : 337-42.

16 Mbulo L, Palipudi KM, Smith T, Yin S, Munish VG, Sinha DN, *et al.* Patterns and related factors of bidi smoking in India. *Tob Prev Cessat* 2020; *6* : 28.

17 Batra U, Nathany S, Jose JT, Sharma M, Mehta A, Bansal A. Lung Metrics India: Molecular epidemiology and testing patterns in 4,773 non squamous NSCLC patients. *Ann Oncol* 2022; *33* : S106-S107.

18 Chang GC, Chiu CH, Yu CJ, Chang YC, Chang YH, Hsu KH, *et al.* Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: A prospective cohort study. *Lancet Respir Med* 2024; *12* : 141-52.

19 dos Santos RS, Franceschini JP, Chate RC, Ghefter MC, Kay F, Trajano AL, *et al.* Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? results from the first Brazilian lung cancer screening trial (BRELT1). *Ann Thorac Surg* 2016; *101* : 481-6; discussion 487-8.

20 Triphuridet N, Henschke C. Landscape on CT screening for lung cancer in Asia. *Lung Cancer (Auckl)* 2019; *10* : 107-24.

21 OECD. *Health at a glance 2021*. Available from: *https://doi.org/10.1787/ae3016b9-en*, accessed on March 1, 2024.

22 Tadia VK, Gupta SK, Satpathy S, Gupta AK, Arya SK. Utilization review of imaging equipment: An insight into CT Scanning. *Medico-legal Update* 2021; *21* : 1224-52.

23 Poon C, Wilsdon T, Sarwar I, Roediger A, Yuan M. Why is the screening rate in lung cancer still low? A seven-country analysis of the factors affecting adoption. *Front Public Health* 2023; *11* : 1264342.

24 Kuhl CK. Whether forced marriage or loving union, marrying breast and lung cancer screening practices would help prevent death from lung cancer. *JAMA Netw Open* 2022; *5* : e2237647.

25 Titan AL, Baiu I, Liou D, Lui NS, Berry M, Shrager J, *et al.* Eligibility for lung cancer screening among women receiving screening for breast cancer. *JAMA Netw Open* 2022; *5* : e2233840.

26 Linehan V, Harris S, Bhatia R. An Audit of opportunistic lung cancer screening in a Canadian province. *J Prim Care Community Health* 2021; *12* : 21501327211051484.

27 Hammer MM, Kapoor N, Desai SP, Sivashanker KS, Lacson R, Demers JP, *et al.* Adoption of a closed-loop communication tool to establish and execute a collaborative follow-up plan for incidental pulmonary nodules. *AJR Am J Roentgenol* 2019; *212* : 1077-81.

28 Bueno J, Landeras L, Chung JH. Updated Fleischner society guidelines for managing incidental pulmonary nodules: Common questions and challenging scenarios. *Radiographics* 2018; *38* : 1337-50.

29 Martin MD, Kanne JP, Broderick LS, Kazerooni EA, Meyer CA. Lung-RADS: Pushing the limits. *Radiographics* 2017; *37* : 1975-93.

30 Huang P, Park S, Yan R, Lee J, Chu LC, Lin CT, *et al.* Added value of computer-aided CT image features for early lung cancer diagnosis with small pulmonary nodules: A matched case-control study. *Radiology* 2018; *286* : 286-95.

31 Hwang EJ, Goo JM, Kim HY, Yi J, Yoon SH, Kim Y. Implementation of the cloud-based computerized interpretation system in a nationwide lung cancer screening with low-dose CT: Comparison with the conventional reading system. *Eur Radiol* 2021; *31* : 475-85.

32 Xu Y, Lu L, E LN, Lian W, Yang H, Schwartz LH, *et al.* Application of radiomics in predicting the malignancy of pulmonary nodules in different sizes. *AJR Am J Roentgenol* 2019; *213* : 1213-20.

33 National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; *365* : 395-409.

34 Potter AL, Xu NN, Senthil P, Srinivasan D, Lee H, Gazelle GS, *et al.* Pack-year smoking history: An inadequate and biased measure to determine lung cancer screening eligibility. *J Clin Oncol* 2024; *42* : 2026-37.

35 Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, *et al.* Outdoor particulate matter exposure and lung cancer: A systematic review and meta-analysis. *Environ Health Perspect* 2014; *122* : 906-11.

36 Kurmi OP, Arya PH, Lam KB, Sorahan T, Ayres JG. Lung cancer risk and solid fuel smoke exposure: A systematic review and meta-analysis. *Eur Respir J* 2012; *40* : 1228-37.

37 Smith KR, Mehta S. The burden of disease from indoor air pollution in developing countries: Comparison of estimates. *Int J Hyg Environ Health* 2003; *206* : 279-89.

38 Freitas C, Sousa C, Machado F, Serino M, Santos V, Cruz-Martins N, *et al.* The role of liquid biopsy in early diagnosis of lung cancer. *Front Oncol* 2021; *11* : 634316.

39 Fahrmann JF, Marsh T, Irajizad E, Patel N, Murage E, Vykoukal J, *et al.* Blood-based biomarker panel for personalized lung cancer risk assessment. *J Clin Oncol* 2022; *40* : 876-83.

40 Holliday R. The inheritance of epigenetic defects. *Science* 1987; *238* : 163-70.

41 Constantin N, Sina AA, Korbie D, Trau M. Opportunities for early cancer detection: The rise of ctDNA methylation-based pan-cancer screening technologies. *Epigenomes* 2022; *6* : 6.

42 Gaga M, Chorostowska-Wynimko J, Horváth I, Tammemagi MC, Shitrit D, Eisenberg VH, *et al.* Validation of Lung EpiCheck, a novel methylation-based blood assay, for the detection of lung cancer in European and Chinese high-risk individuals. *Eur Respir J* 2021; *57* : 2002682.

43 Asakura K, Kadota T, Matsuzaki J, Yoshida Y, Yamamoto Y, Nakagawa K, *et al.* A miRNA-based diagnostic model predicts resectable lung cancer in humans with high accuracy. *Commun Biol* 2020; *3* : 134.

44 Pastorino U, Boeri M, Sestini S, Sabia F, Milanese G, Silva M, *et al.* Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. *Ann Oncol* 2022; *33* : 395-405.

45 Sullivan FM, Mair FS, Anderson W, Armory P, Briggs A, Chew C, *et al.* Earlier diagnosis of lung cancer in a randomized trial of an autoantibody blood test followed by imaging. *Eur Respir J* 2021; *57* : 2000670.

46 Gandhi Z, Gurram P, Amgai B, Lekkala SP, Lokhandwala A, Manne S, *et al.* Artificial intelligence and lung cancer: Impact on improving patient outcomes. *Cancers (Basel)* 2023; *15* : 5236.

47 Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, *et al.* Sybil: A validated deep learning model to predict future lung cancer risk from a single low-dose chest computed tomography. *J Clin Oncol* 2023; *41* : 2191-2200.

48 Liu W, Shen N, Zhang L, Wang X, Chen B, Liu Z, *et al.* Research in the application of artificial intelligence to lung cancer diagnosis. *Front Med (Lausanne)* 2024; *11* : 1343485.

49 Xu H, Usuyama N, Bagga J, Zhang S, Rao R, Naumann T, *et al.* A whole-slide foundation model for digital pathology from real-world data. *Nature* 2024; *630* : 181-8.

50 Huynh E, Coroller TP, Narayan V, Agrawal V, Hou Y, Romano J, *et al.* CT-based radiomic analysis of stereotactic body radiation therapy patients with lung cancer. *Radiother Oncol* 2016; *120* : 258-66.

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