Clinical practices to maximize early detection of non-small cell lung cancer (NSCLC) in never smokers

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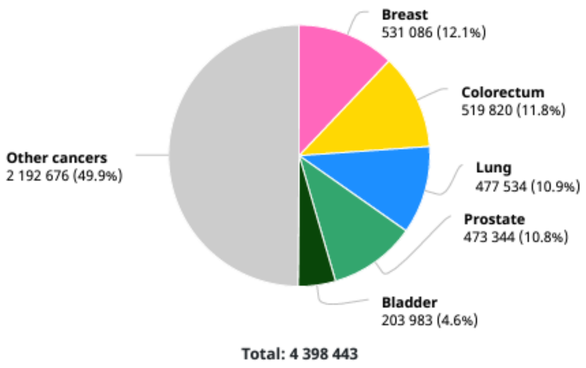
Introduction

Lung cancer (LC) is among the top leading causes of cancer deaths globally among both men and women. It is further divided into two types on a histological basis including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the predominant type comprising of 80% of patients and includes subtypes such as adenocarcinoma and squamous cell carcinoma. SCLC originates from neuroendocrine cells whereas adenocarcinoma originates from type II alveolar cells. NSCLC stems from gene mutations including epidermal growth factor receptor (EGFR), Kristen rats sarcoma viral oncogene homolog (KRAS), and anaplastic lymphoma kinase (ALK). SCLC presents with retinoblastoma protein 1 (RB1) deletion and tumor protein p53 (TP53) mutation.[1] SCLC grows, and spreads faster compared to NSCLC, making NSCLC less aggressive and is more common among the two subtypes. However, early identification of both is imperative to produce prolific results for the patients. Smoking is notoriously known for being the most common risk factor of LC that contributes towards increased mortality. However, LC is just as commonly diagnosed among non-smokers. In fact, LC in never smokers is the seventh most common malignant disease globally.[3] There were 17% of people in the US diagnosed with NSCLC between 2011 and 2013 compared to only 8.9% between 1990 and 1995.[2] There are several other risk factors besides smoking that can increase the risk of developing LC. Current guidelines to detect LC primarily encompasses population that is either currently smoking or were previous smokers and puts individuals at a disadvantage who may have been exposed to other risk factors. It is crucial to identify ways of incorporating at risk populations to detect LC in early stages and therefore, increase survival rate of those who are diagnosed with LC. Figure below indicates LC global burden of 10.9% in the year 2020 compared to other cancers.

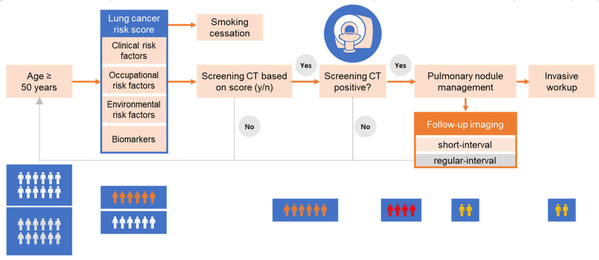


Current screening protocols for smokers and never-smokers

Current screening protocol according to the U.S. Preventive Services Task Force (USPSTF) recommends annual screening for LC with a low-dose computer tomography (LDCT) in ages 50 to 80 years with a 20-year smoking history, those who currently smoke, or those who quit within the last 15 years.[5] Meanwhile, USPSTF does not recommend any screening protocols for never smokers. Based on these criteria, individuals who are never smokers but do possess risk factors are ineligible to qualify for screening and thereby, increase their probability of developing lung cancer. It is crucial to identify patient population that is considered high-risk to meticulously develop screening guidelines that better streamline treatment protocol beginning with earlier diagnosis of LC.

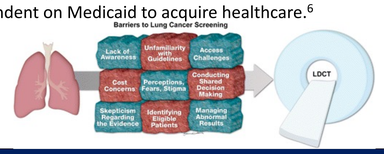
The primary purpose of screening for LC is threefold; to detect it early enough where it has not metastasized, to have an increased five-year survival rate upon diagnosis, and to produce positive patient outcomes. Screening efficacy is exhibited in many studies and this is supported by Collar et al stating a 24% reduced LC mortality in high-risk current and former smokers who received four rounds of LDCT compared to those who did not.[6] Corrales et al states that although screening reduces LC mortality in smokers, there is a clear research gap in studying LC screening in nonsmokers and its efficacy.[2] A study by Kang et al studied 12,176 patients who were never smokers, and screened them with LDCT, among which, 10% resulted in having lung nodules and 0.45% were diagnosed with LC. It evidently demonstrates some value in utilizing LDCT for never smokers.

Amongst many risk factors in never smokers, genetic factors are nonmodifiable and warrant criteria to screen patients who are susceptible. This entails those who particularly possess genomic mutations including EGFR, KRAS, and EML4-ALK that are found most frequently. Corrales et al found EGFR in 49.3% of never smokers who were diagnosed with LC.[2] Considering the statistics, patients screened for these mutations can have a therapeutical treatment that is individually tailored to them. Additionally, females are found to be at an increased risk among those who are diagnosed with LC and are never smokers. This is evident in a study by Infante et al which found 83% of women in that category.[7] However, both risk factors would not place an individual in a high-risk group qualifying for LDCT screening protocol. To further propagate the demand of screening for never smokers who are Asian females and have EGFR biomarkers, a study known as Female Asian Nonsmoker Screening Study (FANSS) was conducted in Chicago that resulted in LC detection rate of 1.5% and concluded the increasing population of nonsmokers with LC.[9] A study conducted in Taiwan (TALENT) detected 2.65% LC rate in never smokers among which 86.3% had stages 0-I.[10] This supports the need to expand LC screening eligibility since increased amount of never smokers are diagnosed with LC and granted that it is at an early age would infer positive health outcomes with early detection and improved prognosis.



Barriers to screening protocols for never smokers

- **Ineligibility for LC screening:** Due to the screening guidelines set by USPSTF, never smokers are ineligible for LC screening despite the known risks that have been discussed. Environmental exposures and genetic predispositions have made never smoking population susceptible to LC however, there are no conventions for early detection. Smoking history and age are the only factors that are currently considered during application of LDCT screening for LC.
- **Socioeconomic status (SES):** Lack of access to healthcare resources presents as one of the major hurdles in reaching LC screening. Studied LC trials failed to incorporate populations with racial and socioeconomical diversity. According to Sosa et al, 89.6% of participants in the National Lung Screening Trial (NLST) and Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trial were of White and higher SES.[11] This places populations in rural areas with low SES and decreased education level at lowered risk of acquiring LC screening.
- **Insurance coverage**: One of the biggest barriers to receive screening is the flawed healthcare system and lack of coverage by insurance, particularly for population who has limited number of resources. According to Collar et al, USPSTF is covered by private health plans and Medicare however, Medicaid coverage varies across states for LC prevention making those vulnerable who are solely dependent on Medicaid to acquire healthcare.[6]



Discussion

Based on global burden of LC among never smokers and their risk factors, it is imperative to incorporate that into clinical practice. Some of the most highly recognized risk factors include female gender, Asian descent, EGFR gene mutation, family history, and secondhand exposure to tobacco. Considering these, screening guidelines must address these risk factors and reach out to the population they reflect.

- To begin, **education** is key to raise awareness of LC amongst never smokers and discuss significance of LC screening, presence of susceptible risk factors, and ramifications one might face when diagnosed with LC. Not only must never smokers be educated, but clinicians must also be educated on susceptible populations.
- Risk factors such as environmental exposures including radon, asbestos, secondhand smoking comprise of persons who are restricted to neighborhoods due to **low SES**. Thus, implementation of screening in those areas is obligatory to contribute towards improved patient outcomes.
- Once screening protocols are developed, the following step includes application of those screening guidelines and patient adherence. Clinicians must **devise plans** that are tailored to each patient that fits into the category of high-risk population and then positively reinforce participation in screening protocols. This involves yearly screening of patients who qualify for aforementioned criteria and if successive screenings are negative, the plan can be altered to limit CT exposure.
- Screening has evidently proved to reduce risk in LC mortality and 6.7% reduction in all-cause mortality.[6] Thus, upon recognition of vulnerable population, appropriate screening must be held to record **baseline and follow up patients** consequently. In addition to establishing educational information and screening efforts, barriers to screening must also be mitigated to increase screening uptake and contribute towards early detection, LC reduction, and decreased mortality. There needs to be an effort made at all levels including patient, clinician, population, and policy.

Risk factors in never smokers

Although smoking is recognized as the most significant risk factor for developing LC, there are several other factors that increase one's susceptibility of being diagnosed with it. Epigenetic and genetic factors such as age, family history, secondhand smoking, radon exposure, asbestos exposure, domestic fuel smoke, human papillomavirus, mycobacterium tuberculosis, asthma and sarcoidosis are all capable of increasing one's likelihood of developing LC.[2,3] Considering these risk factors, screening protocols must incorporate this multitude of factors to increase early detection. According to CDC, 20,000 to 40,000 lung cancers are discovered among nonsmokers in the U.S. each year.[4] However, screening protocols are scarce that utilize risk factors that integrate never smokers.

Disadvantages of lung cancer screening in never smokers

Although LDCT for never smokers provides a striking benefit of early detection of lung cancer and thereby a decrease in lung cancer mortality, there are reasons identified why never smoking population is excluded from the screening guidelines. Exposing individuals with LDCT for screening measures who do not qualify with smoking history as the risk factor are at risk of increased exposure to radiation. This would ironically lead to them being susceptible of genetic mutations and development of cancer such as breast, thyroid, or even lung cancer. Additionally, upon screening of this population, if lung carcinoma is detected, patients would then go through psychological distress and invasive procedures including biopsies and surgeries which would cause them further harm than would the slow growing NSCLC. Furthermore, there have been many occurrences of false positive findings, overtreatment of indolent lesions, and excessive utilization of screening tools that have served more risks versus benefits to these patients.[7] To add to the costs of LC screening among never smokers, the cost to get the screening done is incredibly high and patients would not benefit from it despite of fitting the criteria for high-risk group. Thus, it is crucial to identify risk stratification in a strategic manner and determine risks versus benefits of each patient to produce the best individual outcomes.

Relevance

In 2020, LC caused around 1.79 million deaths globally.[3] Despite therapeutical and technological advancements, the reliability of treatment is dependent upon early detection of LC for most appropriate treatment measure. LC among never smokers is a public health concern as there has been an increased incidence as well as mortality among them. According to a microsimulation modeling U.S. data from 1964 to 2015 report by Kerpel-Fronius et al, the proportion of never smokers will increase and so will the deaths in those individuals caused by LC simultaneously by the year 2065.[3] Although the healthy people 2030 objective to reduce lung cancer death rate is improving, the objective to increase proportion of those screened for lung cancer has remained at baseline data indicating requirement of increased efforts.[8] Furthermore, the five-year survival rate of LC is only 23% suggesting early detection is essential to reach the healthy people 2030 objective which is 7.5% of population to be screened and death rate reduced by 25.1 per 100,000 by the year 2030.[8] Based on the facts presented, never smokers are inherently at risk of developing LC and there are no measures that can be taken by healthcare providers to decrease that risk, knowing one's enhanced risk factors. The population of never smokers will only increase in number with risk factors being constant requiring immediate research to develop screening guidelines that would reach the audience that are prone to barriers discussed, are considered high risk group, and have increased likelihood of developing LC.

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