Should We Expand Eligibility for Low-Dose CT Scans?

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Editorial

Lung cancer is the deadliest and the most preventable cancer related death. Each year, the North American Association of Central Cancer Registries (NAACCR) annual report releases the trends for the most common cancers in the United States. From 2011-2015, lung cancers remained the leading cause of cancer related deaths in men and women and accounted for an estimated 1,690,000 deaths globally in 2015 alone [1,2]. In the most recent NAACCR report, the five-year survival rate for Stage I lung cancer (which includes lung and bronchus cancer) was 55.1%. If diagnosed at Stage IV, the survival rate dropped to 4.2%. The most troubling statistic is that only 20.7% of cases were diagnosed at Stage I, while 43.6% were diagnosed at the more fatal Stage IV [1].

Even with a significant decrease in smoking, lung cancer has maintained the second highest incidence rate of all cancer diagnoses [1]. The current screening guidelines issued by multiple organizations including The American Cancer Society (ACS), The National Comprehensive Cancer Network (NCCN), and The American Association for Thoracic Surgery's (AATS) follow the parameters of the National Lung Screening Trial (NLST), and are most relevant for individuals at high risk for lung cancer due to cigarette smoking. While the correlation between smoking and cancer is undoubtedly the single greatest determinant in developing cancer, this familiarity heuristic towards tobacco may be blindsiding us. Current studies show that the etiology of nearly 25% of lung cancers are not attributed to smoking and further studies show that lung cancers in never-smokers (individuals who have smoked less than 100 cigarettes in their lifetime) are the 7th most common malignancy worldwide [3-5]. Given this prevalence, it may be necessary to include other variables in addition to tobacco related risks in future guidelines.

The ACS screening guidelines are based upon the NLST data. The findings of NLST were conclusive; annual Low-Dose Computed Tomography (LDCT) screenings reduced lung cancer specific mortality by more than 20% [6]. However, the NLST inclusion criteria (and therefore current ACS screening guidelines), only opened the study to those between 55 and 74 years old, those with a history of at least 30-pack years, and former smokers who had quit within the last 15 years [7]. The NCCN has established two high-risk groups, one that is identical to the ACS guidelines, and a second high-risk group that contains people 50 years and over with 20-pack years or more of cigarette smoking, and have at least one additional risk factor (other than second-hand smoke) [8]. The AATS guidelines expand the screening opportunity of the NCCN by increasing the screening age through the eighth decade of life, and recommend continuation of screening beyond 15 years of smoking abstinence [9]. While both the NCCN and AATS recommendations have included additional risk factors for screening, their guidelines are still predominantly based on tobacco use.

The United States Preventive Services Task Force's (USPSTF) recommendation (also based on the NLST trial) requires commercial insurance coverage for individuals between 55-80 with a minimum 30 pack-year history of cigarette smoking and that the individual has smoked within the preceding 15 years [10]. For those covered by Medicare and Medicaid, the Centers for Medicare and Medicaid Services (CMS) somewhat reluctantly agreed to recommend lung cancer screening CT for individuals between 55 and 77 who meet smoking history requirements (30 pack-years) [10]. CMS eligibility also includes provisions to add lung cancer screening counseling and a shared decision making (the use of a qualified individual who can outline the risks and benefits of screening) before enrollment in a LDCT screening program. Additionally, CMS requires inclusion in an approved clinical registry that contains reporting from all lung cancer CT scans, not just Medicare beneficiaries [10].

Additional analyses of the NLST data by Pinksky et al. [11] highlighted demographic differences between subpopulations including evidence that women and underserved minorities develop lung cancer at a younger age and with less smoking intensity. The incidence of lung cancers being

diagnosed in very young, particularly women never-smokers, has been observed in increasing frequency and additional studies of early onset lung cancer is being performed [12,13]. NAACCR data was used to show a slightly higher incidence rate among women non-smokers than non-smoking men, and a complete reversal in the overall lung cancer incidence rates in women compared to men [13]. Across multiple ethnic groups, age groups and smoking histories, women are being diagnosed with lung cancer at a higher rate than men [13]. Nearly 25% of all lung cancer cases worldwide, and in 53% of women who develop lung cancer, tobacco smoking is not directly attributed as the cause [3]. It is clear that critical risk factors unrelated to tobacco are being missed and that current guidelines are excluding individuals that need to be screened.

Collection of data for younger adults through the required clinical registry reporting is limited due to the lack of insurance coverage for screening. Such cases are no longer anecdotal and we do not adequately understand increasingly important non-tobacco risk factors. Some are genetic, such as individuals carrying inherited EGFR gene mutations called T790M [12]. This underlies at least part of the significance of family history of early onset lung cancer, i.e. those before age 60. To date, this risk factor has been identified and studied in lung cancer patients. Prospective identification of T790M remains limited but it does highlight the potential to identify increasingly specific risk factors that, in combination, would be as powerful for selection of high risk individuals for screening to further reduce lung cancer mortality [12]. As we identify new risk factors, it is also important to recognize shortcomings to screen individuals who are eligible even under the current guidelines.

Lung cancer screening penetration in populations that meet current guidelines is very low. Su et al. [14] studied lung cancer screening in an underserved population with insured patients and found that only 33 out of 175 eligible participants who had established a relationship with a PCP and were eligible for screening based on the USPSTF guidelines, went on to receive LDCT screenings that preceded their diagnosis of lung cancer. This study was completed in a major metropolitan screening center in the Northeast, and we believe that it is fair to consider that the screening penetration is less than 10% in populations with lower rates of insurance. It is with certainty that there are discrepancies and biases to those who are getting sent, and followed up on, for lung cancer screening. Survival is significantly decreased for those that did not receive early screening [1]. This poses a risk for those that are underserved, vulnerable, and have low health competency. Barriers to care such as poor access, time constraints, language discordance, and socioeconomic factors could be limiting the success of screening this population [14]. Underserved vulnerable populations require greater education and supportive services such as smoking cessation programs.

One possible supplement to the future of lung cancer screening guidelines includes the use of lung cancer risk prediction models. Accounting for and analyzing an individual's personal factors including: familial history of cancer, environmental/occupational exposures, previous lung conditions and potentially clinically collected data, could help identify smokers and non-smokers who are at high risk while lowering downstream costs. Some of these models have already identified these potential risk factors. Gray et al. [15] preformed a systematic review of lung cancer prediction models and found that there are currently 25 distinct models for determining an individual's risk of developing lung cancer. Some of the

epidemiological models have been extensively validated, including the Liverpool Lung Project (LLP) and the Prostate, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Between these two trials, a total of 10 non-smoking risk factors where included as variables. These risk factors fell under the categories of personal factors such as family history of cancer, environmental/occupational exposures and previous lung conditions. Other epidemiological plus clinical assessment models went on to include clinically collected variables such as the presence of a single nucleotide polymorphism, Body Mass Index (BMI), physical activity, and fasting glucose. Most notably, "the (PLCOM2012) model had a better prediction rules performance than the NLST, so applying this model…could offer an improvement in selective screening trials" [16]. After further studies and careful validation, the use of these prediction models could provide a cost-effective method for patients and physicians to determine who should begin annual LDCT screenings.

Seven years after the results of the NLST were reported, lung cancer continues to be the deadliest cancer worldwide. This begs the question if we need to improve screening education and recruitment, expand to a larger cohort using newer techniques such as mathematical modeling, or both. Annual LCDT screening has been a great first step to improving survival, but when 43.6% of individuals still being diagnosed with late stage disease, our current policies are not sufficient. We need to increase smoking cessation programs, raise awareness about annual lung cancer screenings, and conduct further studies to concretely identity the potential risk factors that are contributing to disease in non-smokers. In addition, we need to study and eliminate the screening guideline disparities which benefit older heavy smokers and ignore women and minorities who get cancer with less smoking and at a younger age.

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