CHEST

POINT:

Should Lung Cancer Screening Be Expanded to Persons Who Don't Currently Meet Accepted Criteria Set Forth by the CHEST Guidelines on Lung Cancer Screening? Yes

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PODCAST

ABBREVIATIONS: CHEST = American College of Chest Physicians; LDCT = low-dose CT; NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial

The identification of a 20% lung cancer mortality reduction attributable to annual screening with low-dose CT imaging[1] is the most profound advance in the war against cancer in a generation. The relatively simple but powerful impact of early detection in lung cancer has the potential to save 12,000 to 15,000 lives per year in the United States alone.[2,3] No other cancer intervention or therapy comes close to this impact of converting cancer victims to cancer survivors.

The American College of Chest Physicians (CHEST) published their guidelines in 2013.[4] Although the guidelines did endorse screening with low-dose CT imaging for patients aged 55 to 74 years with at least a 30 pack-year smoking history, they recommended against lung cancer screening for any other individuals who may be at risk of lung cancer. An anticipated update of the CHEST guidelines is imminent but is likely to be similar in its narrow inclusion criteria for lung cancer screening.

Of course, the source of the CHEST criteria is straightforward: it is simply the inclusion criteria selected by the investigators of the National Lung Screening Trial (NLST). However, to disapprove of lung cancer screening for any other individuals implies that there are no other patient populations at a risk for lung cancer similar to those included in the NLST.

Most other guideline groups have not been as rigid as the CHEST in translating the outcomes of the NLST into recommendations for lung cancer screening. The United States Preventive Services Task Force recommends lung cancer screening for a similar group of patients but up to age 80 years rather than age 74 years.[5] The Centers for Medicare & Medicaid Services provides coverage for Medicare beneficiaries up to age 77 years.[6] Both the National Comprehensive Cancer Network (NCCN) and the American Association for Thoracic Surgery guidelines recommend consideration of additional risk factors beyond age and smoking history to identify additional individuals who may be of a similar risk of lung cancer to those studied within the NLST.[7,8] In addition, the most recent NCCN update provides further guidance with references to lung cancer risk calculators and threshold levels of risk that extend beyond those criteria studied in the NLST.[9]

Limiting lung cancer screening to the population studied in the NLST is intellectually simple; it is the only randomized trial evidence showing a benefit of screening. However, it is also lacking in a real-world perspective of what can and cannot be demonstrated in a randomized trial, and in not considering decades of peer-reviewed evidence of additional risk factors for lung cancer. A pure evidence-based medicine world view will be satisfied that CHEST guidelines only recommend screening for those patients identical to those studied in the NLST. A clinical pragmatist will be concerned about the inequity of denying preventive health services for other individuals who may have a similar risk of lung cancer but do not fit the NLST inclusion criteria.

As important as the NLST was, it is critical to recognize what this study did do, as well as what it did not do. What the NLST did do was to show a reduction in lung

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cancer mortality in patients at high risk for developing lung cancer. What the NLST did not do was define risk factors for lung cancer, or the limits of "high risk." As a clinical trial, the NLST investigators needed to be practical and simple in their design of an enormous randomized trial that ultimately enrolled > 53,000 individuals. Reasonably, the investigators settled on just two variables (age and smoking history) to have easily identifiable inclusion criteria that could be applied to a large population in a multi-institutional study.

Although the randomized trial data from the NLST are a critical foundation for guidelines and policy, they are not sufficient for defining eligibility criteria because we know there are individuals who do not meet NLST inclusion criteria but have a similar risk of lung cancer. NCCN guidelines consider whether there could be individuals with a risk of lung cancer similar to those studied in the NLST based on other known risk factors for lung cancer.[8] The working principle is that if individuals with a qualitatively similar risk can be identified, one could reasonably extrapolate a similar benefit of having access to early detection through lung cancer screening. The expert panel for the NCCN guidelines recognized that this assessment was qualitative, rather than quantitative, and was based on lower level evidence than that from the NLST randomized trial. However, there was consensus to consider the full spectrum of lung cancer

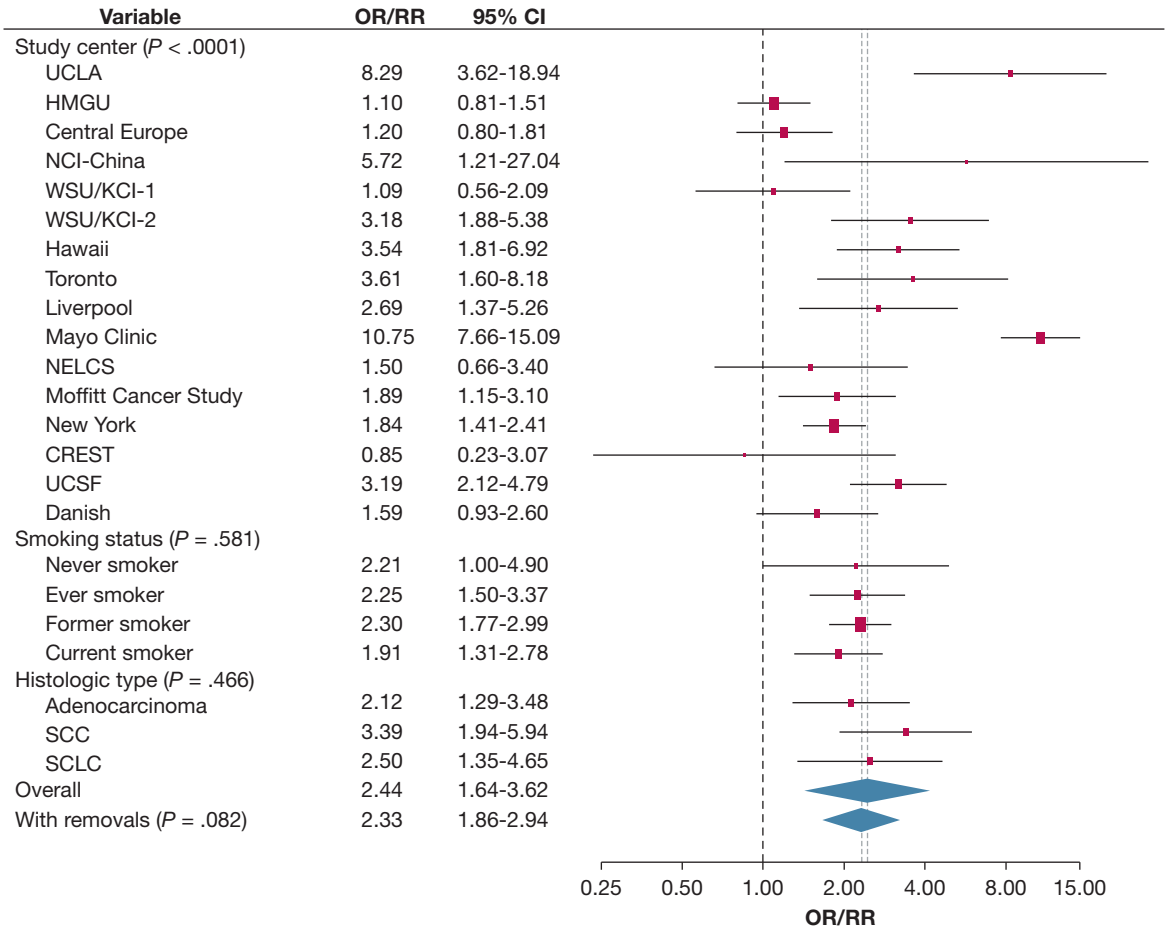

Figure 1 – *OR of lung cancer in individuals with emphysema. Results from a pooled analysis of emphysema as a risk factor for the development of lung cancer, International Lung Cancer Consortium, 1984-2011. The graph shows a forest plot of the association between emphysema and lung cancer risk by study center, smoking status, and histologic type. Models adjusted for age, sex, and pack-years of smoking. P values are from a test for heterogeneity across studies or across subgroups. "With removals" represents removal of the Mayo, Central Europe, HMGU, WSU/KCI-2, and UCLA studies. See Table 1 for published references. CREST = CREST (Cancer of the Respiratory Tract) Biorepository; Danish, Danish Diet, Cancer, and Health Study; HMGU = Helmholtz Center Munich; KCI = Karmanos Cancer Institute; Liverpool = Liverpool Lung Project; NCI = National Cancer Institute; NELCS = New England Lung Cancer Study; New York = New York Multicenter Study; RR = relative risk; SCC = squamous cell carcinoma; SCLC = small cell lung cancer; Toronto = Samuel Lunenfeld Research Institute; UCLA = University of California, Los Angeles; UCSF = University of California, San Francisco; WSU = Wayne State University; WSU/KCI-1 = Family Health Study; WSU/KCI-2 = study of women's lung cancer epidemiology. (Reprinted from Brenner et al,[13] by permission of Oxford University Press.)*

risk when creating guidelines for the purposes of health-care equity, to maximize the potential benefit of lung cancer screening, and to avoid disenfranchising or harming individuals who are at high risk for lung cancer but excluded from the benefits.

A comprehensive review of established risk factors for lung cancer is beyond the scope of this article. Those risk factors frequently cited include occupational exposure (eg, asbestos), family history, cancer history, and certain lung diseases (eg, emphysema, pulmonary fibrosis).

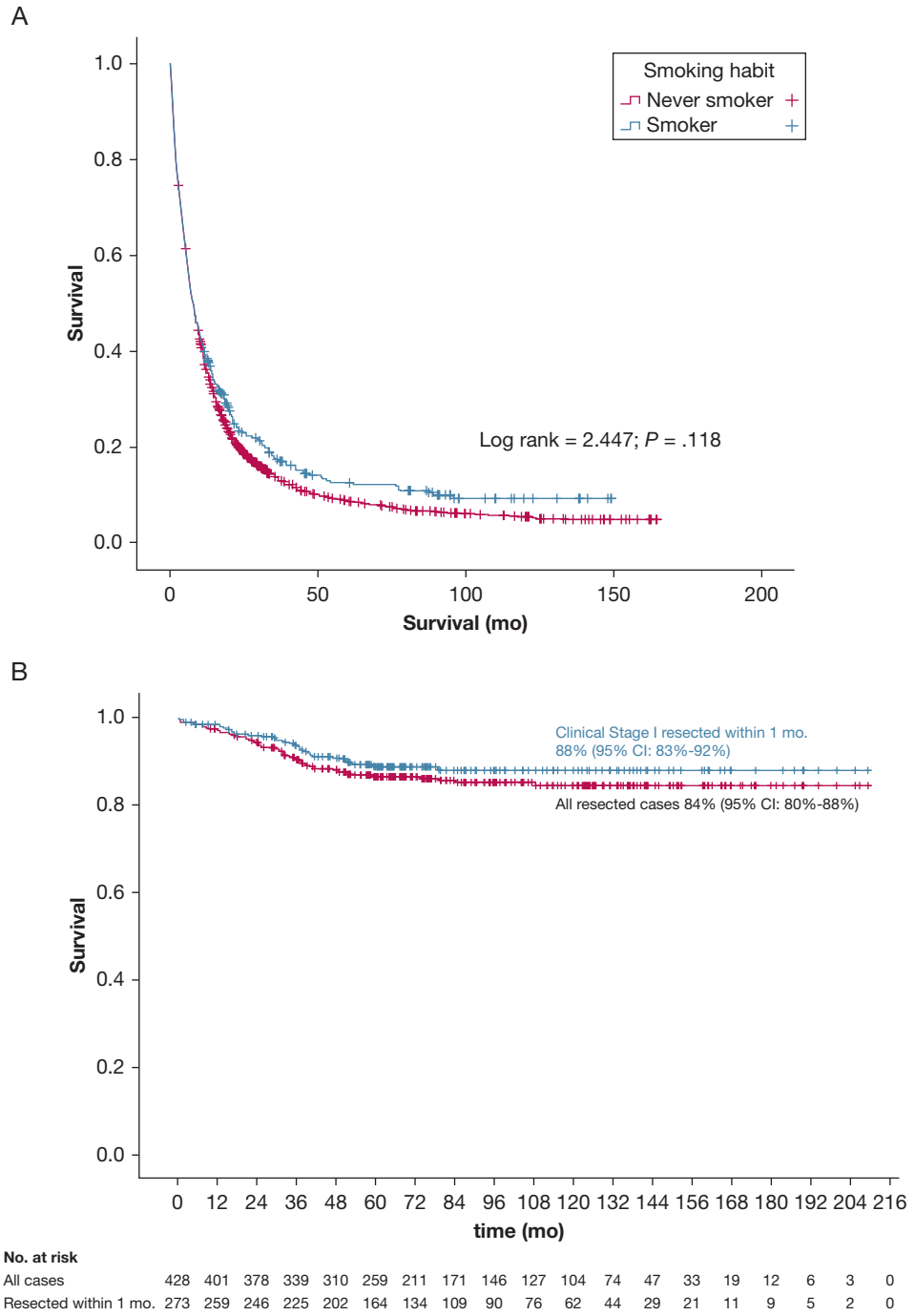

Figure 2 – *A, Representative overall lung cancer survival curve. (Reprinted from Parente Lamelas et al,[15] Copyright (2014), with permission from Elsevier.) B, Lung cancer survival in screened detected lung cancer in the International Early Lung Cancer Action Project (I-ELCAP). (Reprinted from Flores et al,[16] Copyright (2014), with permission from Elsevier.)*

A number of online lung cancer risk calculators have also been developed, and each of these include lung cancer risk factors beyond the age and smoking history variables used in the CHEST guideline.[10-12] If only one of these risk factors (eg, emphysema) is chosen, pooled data demonstrate a 2.3 OR for the development of lung cancer in patients with an emphysema diagnosis, independent of their smoking history (Fig 1).[13] A 70-year-old patient with a 25 pack-year smoking history and emphysema therefore has roughly two times the lung cancer risk of a 70-year-old patient with a 30 pack-year smoking history and without emphysema. However, in this example, CHEST guidelines deny lung cancer screening to the higher risk patient while recommending screening for the lower risk patient. This scenario is the paradox of limiting consideration for lung cancer screening to only those patients studied within the NLST.

The well-established lung cancer screening group at Lahey Clinic has examined their patient population and outcomes stratified according to whether they fit the NLST inclusion criteria (identical to CHEST guideline recommendations) and those who do not fit the strict criteria but would be included under the consideration of extended risk factors as recommended by NCCN guidelines.[3] Twenty-six percent of the Lahey Clinic patients were screened due to the inclusion of other risk factors by the extended NCCN criteria. This group of patients had an identical rate of cancer detection between the two groups. This retrospective analysis seems to validate the concept that there is a cohort of individuals with risk factors for lung cancer that are similar to those studied in the NLST, yet not supported for lung cancer screening within the CHEST guidelines.

The mortality of lung cancer remains staggering, responsible for more cancer deaths than breast, colon, prostate, and pancreas cancer combined. The overall survival rate of 18%[14] is dismal, largely due to the advanced stage of disease at diagnosis (Fig 2A).[15] However, the survival curve for those with a screen-detected lung cancer is essentially inverted, with a 5-year survival of 84% (Fig 2B).[16] Early detection through lung cancer screening is a game-changer, and it is important to assure that high-risk patients are not denied access to care.

It is certainly important to require a high level of evidence to help frame guidelines and policy, particularly for preventive services such as lung cancer screening. However, it is naive and myopic to believe that the inclusion criteria of the NLST define the only population at high risk of lung cancer and to rigidly adhere to recommending only that group for screening under the principal that these are the only patients in whom sufficient evidence for benefit exist. Although well intended, this view takes adherence of "evidence-based" to an extreme, and to an extreme that has the potential to harm individuals who are at high risk of developing lung cancer, yet would not be candidates for screening and early detection according to CHEST guidelines.

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