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Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

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The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

Racial Disparities in Lung Cancer: Here and Now…

By Christopher S. Lathan, MD, MS, MPH

Over the past 30 years, there has been a preponderance of research describing racial disparities in cancer care, and lung cancer is no exception.[1,2,3] Indeed, because of its major impact on morbidity and mortality, lung cancer has been well studied in this regard.[4-9] Lung cancer is the leading cause of cancer mortality for both men and women in the United States. It is estimated that there will be 159,480 deaths from lung cancer in the year 2013.[10]

African American men have the highest incidence and mortality rates of lung cancer in the United States.[11] Unfortunately, even though lung cancer survival for both African Americans and whites has improved over the past 40 years as smoking rates have fallen, African American men continue to have higher rates of lung cancer incidence and mortality than white men.[11] The incidence of lung cancer for other ethnic groups (Asian Americans, Native Americans, and Non-Black Hispanics) tends to be lower than that for whites.[12]

There are many causes of racial disparities in lung cancer incidence and mortality. They include access to care, cultural differences, and communication difficulties with providers leading to refusal of care, biological differences, as well as the systemic and structural effects of racial exclusion.[1,2,13] Of increasing concern is the possibility that disparities will worsen with the dawn of targeted therapy and personalized medicine in lung cancer.[14,15] The move to molecularly targeted therapy in non-small cell lung cancer (NSCLC) has been an important advance. However, access to targeted therapy could have a significant impact on survival. There is increasing evidence that access to molecular diagnostic tests and targeted therapy are limited, depending on the geographic region. In the rush to improve lung cancer treatment, there has been little focus on disseminating these new therapies to members of vulnerable communities.

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Tobacco

The amount of tobacco smoked does not appear to be the cause of lung cancer incidence and mortality differences between African Americans and whites.[11] Smoking rates for both groups have decreased dramatically, with rates now approximately 26% for black men and 23.5% for white men. This difference is essentially negligible after accounting for age and socioeconomic status (SES).[16,17] Black women and white women continue to have similarly low smoking rates.

The high incidence of lung cancer among African Americans, in addition to the aggressive targeting of African Americans by tobacco manufactures, have prompted many to focus on factors that enhance smoking cessation campaigns.[18,19] Studies demonstrate that low income and education levels adversely affect smoking cessation attempts. African Americans more frequently underestimate the link between cancer and tobacco smoking when compared to white smokers.[20]

Investigators have also examined exposure to cigarette additives, such as menthol, as a potential explanation for the increased incidence of lung cancer in African Americans. The evidence for a role of additives is, as of yet, inconclusive.[17,21] It has also been suggested that there may be differences in tobacco smoke metabolism between blacks and whites, but there is no conclusive data to support this hypothesis at this time. Further studies of tobacco carcinogenesis are needed to determine the role that tobacco smoke metabolism plays in creating racial disparities in lung cancer.

Socioeconomic status

Low SES is associated with higher smoking rates across all races.[17,22,23] However, nothing illustrates the complexity of studying racial disparities in lung cancer more than evaluating the role of SES. Studies of SES reveal a "double jeopardy" phenomenon: low income increases the risk associated with tobacco use, and it also increases the risk of dying from lung cancer, presumably from lack of appropriate treatment.[24,25]

Previous work has demonstrated that SES is often directly related to the stage of cancer at the time of presentation. Patients of lower SES with lung cancer are more likely to be diagnosed with advanced disease than patients of higher SES. This adversely affects treatment choices and other processes of care.[26] Similar research has shown that patients of lower SES receive poor-quality treatment, both in the United States and in the United Kingdom.[27,28] Nonetheless, health care systems that provide universal access have been shown to attenuate racial and ethnic disparities in lung cancer treatment.[29,30] This finding further supports the important role of income and access to care in explaining observed racial disparities in lung cancer outcomes.

Diagnosis and treatment

As for most solid tumor cancers, the stage of presentation is closely associated with survival for lung cancer. The majority of patients with lung cancer, regardless of their race, present with advanced disease. Early stage lung cancer is usually discovered incidentally,[31] and it makes up only 14-16% of the total cases of lung cancer.[32] Failure to use curative modalities in even a small subset of potentially curable patients is a public health problem, one that affects African Americans disproportionately.[33] African Americans are nearly 50% less likely to receive surgery for early stage NSCLC when compared to white patients.[4] The reasons for this difference in lung cancer treatment have not been fully elucidated, though it has been suggested that increased comorbid disease in African American men,[29] differences in patient preferences due to mistrust and prevalent beliefs,[34] poor physician and patient communication,[35] and access to care[7,28,30,36] may all contribute to the problem.

Of increasing importance in lung cancer treatment is the quality of the diagnostic specimens. Lung cancer treatment now, more than ever, is guided by the histologic and molecular characteristics of the tumor.[14,37-40] Inadequate tumor samples (eg, those amenable only to cytological evaluation) can make it challenging to select the appropriate therapy. African American patients were found in one study to be less likely to undergo invasive staging procedures for lung cancer.[6] This has the potential to exacerbate already existing treatment disparities, because more tissue is needed for molecular testing in order to evaluate the patient's eligibility for targeted therapy.

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Targeted therapy is now an option for a sizable number of lung cancer patients, but there has been little research on racial disparities in the use of targeted agents for lung cancer.[14,15,41-48] Given the disparities seen in every other treatment modality, however, it seems likely that targeted therapy will also be a source of treatment differences related to race and class. At this time, few studies have evaluated the frequency of somatic mutations related to lung cancer in African Americans. Therefore, the question of disparities in the use of targeted agents for lung cancer in the underserved population remains unexplored. Even allowing for advances made with targeted therapy, surgery for early stage disease is the only treatment modality that can potentially cure lung cancer, and it is here that the disparities in treatment have their maximum effect.

Summary

Differential outcomes by race and SES continue to remain an important and timely issue in the study of lung cancer.[6-8,17,22,49-55] Not only do these racial and SES disparities affect survival in early stage disease, but it is likely they will also impact the survival of patients with advanced disease, especially as innovations continue in the areas of personalized medicine and adjuvant and maintenance therapy.[15,56-58] In addition, the role of screening for lung cancer[59-61] has not been fully resolved, but pilot programs should include underserved patient populations, or they will run the risk of exacerbating existing disparities.

The idea that equal treatment can lead to equal outcomes is important. In a review of clinical trial data from the Southwest Oncology Group, Albain and colleagues found that for patients in clinical trials, there were no survival differences for lung cancer related to race after adjusting for confounders.[62] This finding is similar to work done by Blackstock et al.[29] in small cell lung cancer clinical trials. They discovered that even though African-American patients were more likely to present with worse comorbid disease and lower performance status, they had the same survival rate as their white counterparts if they received similar treatment. These studies suggest that equal treatment can lead to equal outcomes, even when patients present with advanced lung cancer and comorbid disease. Certainly, we cannot make great strides in lung cancer treatment if we continue to leave the most vulnerable patients behind.

As targeted therapies become more widely used, it is important to ensure that all lung cancer patients benefit equally from these treatment advances. Otherwise, the very patients who are most affected by lung cancer will continue have inferior access to the most effective therapies.

Disclosures

Dr. Lathan submitted an ICMJE Disclosure Form to ***Lung Cancer Frontiers***. He reports no relationships with any companies or organizations whose products or services are discussed in this article.

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Information: gotoper.com

15th World Conference on Lung Cancer

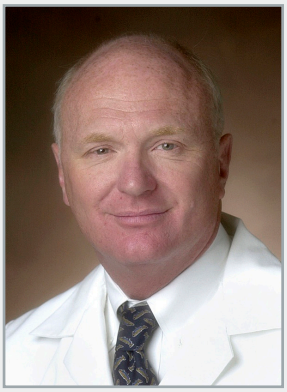
October 27-30, 2013

Sydney, Australia

Information: 2013worldlungcancer.org

Selections from the Peer-Reviewed Literature

By York E. Miller, MD, Deputy Editor



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American Cancer Society lung cancer screening guidelines

Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, Etzioni R, Flowers CR, Scott Gazelle G, Kelsey DK, Lamonte SJ, Michaelson JS, Oeffinger KC, Shih YC, Sullivan DC, Travis W, Walter L, Wolf AM, Brawley OW, Smith RA.
CA Cancer J Clin 2013; 63:106-17.

ABSTRACT: Findings from the National Cancer Institute's National Lung Screening Trial established that lung cancer mortality in specific high-risk groups can be reduced by annual screening with low-dose computed tomography. These findings indicate that the adoption of lung cancer screening could save many lives. Based on the results of the National Lung Screening Trial, the American Cancer Society is issuing an initial guideline for lung cancer screening. This guideline recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30-pack-year smoking history and who currently smoke or have quit within the past 15 years. A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation.

EDITORIAL COMMENT: Prior to the report in 2010 of the results of the National Lung Screening Trial (NLST), which demonstrated a 20% reduction in lung cancer mortality in the computed tomography (CT) screening arm compared to the chest radiograph arm, no major organizations recommended CT screening for lung cancer. Since that time, a number of major professional organizations with an interest in lung cancer have made formal statements in favor of discussing lung cancer screening with patients meeting the NLST entry guidelines, provided that this service can be offered in facilities with high-volume, high-quality programs in lung cancer screening, diagnosis, and treatment. Organizations supporting this now include the American College of Chest Physicians, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the American Thoracic Society, and the American Association for Thoracic Surgery. In this informative and comprehensive review of the evidence for and ramifications of CT screening for lung cancer, the American Cancer Society provides similar guidelines supporting a discussion of screening with apparently healthy patients aged 55 to 74 years who have at least a 30 pack-year smoking history and who currently smoke or who have quit within the past 15 years. A process of informed and shared decision making with a clinician that

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includes consideration of the potential benefits, limitations, and harms of low-dose CT (LDCT) screening for lung cancer is advocated. The importance of carrying out screening in a setting with a high-volume, high-quality program in imaging, diagnosis, and treatment is emphasized. Screening outside of this situation is discouraged.

One concern about the implementation of LDCT screening is that smokers may feel that screening lessens the need for smoking cessation. Fortunately, current evidence suggests that this is not the case; in fact, abnormal findings on LDCT may increase smoking cessation. All agree that smoking cessation efforts need to be emphasized to patients considering CT screening. A limitation of LDCT screening is that it does not guarantee that death from lung cancer will be avoided. Potential harms include anxiety associated with abnormal test results, additional imaging, and biopsy testing for false positive results. The false positive rate for LDCT is very high, with over 39% of subjects having at least one abnormal CT over a 3-year period. The NLST was conducted largely in academic centers with expertise in CT scanning and diagnostic workup. The rate of invasive procedures among participants who were determined not to have lung cancer was 2.7%, and serious complications were low among patients without lung cancer (0.06%) but higher in those with lung cancer (11.2%). The potential harm from radiation associated with LDCT screening is considered to be small and will decrease with improvements in technology. There is little information on the financial implications of the introduction of LDCT screening for lung cancer, and this area is not discussed. Currently, few health insurance programs cover the cost of LDCT screening. The United States Preventive Services Task Force is planning to issue a statement on LDCT screening in 2014; if this is also supportive, insurance coverage may become less of a barrier.

Selection criteria for lung-cancer screening

Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, Chaturvedi AK, Silvestri GA, Riley TL, Commins J, Berg CD. *N Engl J Med* 2013; 21; 368:728-36.

BACKGROUND: The National Lung Screening Trial (NLST) used risk factors for lung cancer (e.g., ≥30 pack-years of smoking and <15 years since quitting) as selection criteria for lung-cancer screening. Use of an accurate model that incorporates additional risk factors to select persons for screening may identify more persons who have lung cancer or in whom lung cancer will develop.

METHODS: We modified the 2011 lung-cancer risk-prediction model from our Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to ensure applicability to NLST data; risk was the probability of a diagnosis of lung cancer during the 6-year study period. We developed and validated the model (PLCOM2012) with data from the 80,375 persons in the PLCO control and intervention groups who had ever smoked. Discrimination (area under the receiver-operating-characteristic curve [AUC]) and calibration were assessed. In the validation data set, 14,144 of 37,332 persons (37.9%) met NLST criteria. For comparison, 14,144 highest-risk persons were considered positive (eligible for screening) according to PLCOM2012 criteria. We compared the accuracy of PLCOM2012 criteria with NLST criteria to detect lung cancer. Cox models were used to evaluate whether the reduction in mortality among 53,202 persons undergoing low-dose computed tomographic screening in the NLST differed according to risk.

RESULTS: The AUC was 0.803 in the development data set and 0.797 in the validation data set. As compared with NLST criteria, PLCOM2012 criteria had improved sensitivity (83.0% vs. 71.1%, P<0.001) and positive predictive value (4.0% vs. 3.4%, P=0.01), without loss of specificity (62.9% and. 62.7%, respectively; P=0.54); 41.3% fewer lung cancers were missed. The NLST screening effect did not vary according to PLCOM2012 risk (P=0.61 for interaction).

CONCLUSIONS: The use of the PLCOM2012 model was more sensitive than the NLST criteria for lung-cancer detection.

EDITORIAL COMMENT: The NLST selection criteria were fairly simple: a 30 pack-year or greater smoking history, current or former smokers who had quit for less than 15 years, and patients in fairly good health who were between 55 and 74 years of age. More sophisticated risk models, based on readily obtained clinical features, have been developed to include age, level of education, race, body mass index, family history of lung cancer, history of chronic obstructive lung disease, chest radiography in the past 3 years, smoking status

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(current or former), tobacco exposure in pack-years, years of smoking, and time since quitting. This group of investigators developed one such model based on lung cancer diagnoses in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial control group and then applied their risk model and the NLST entry criteria to the PLCO intervention group, adjusting the threshold criteria so that equal numbers of the PLCO intervention group would be criteria-positive for each model. Comparing the NLST criteria to the new PLCO model for selecting persons who received a diagnosis of lung cancer, the sensitivity improved from 71.1% to 83.0% ($P < 0.001$), specificities were similar (62.7% and 62.9%), and the positive predictive value improved from 3.4% to 4.0% ($P < 0.01$). Six hundred seventy-eight lung cancers were diagnosed in the PLCO intervention group, which was used to compare the two risk models. Using NLST criteria, 482 patients were criteria-positive (screening would have been recommended) and 196 were criteria-negative (screening not recommended). Using the new model, 563 were criteria-positive and 115 were criteria-negative. The analysis was conducted so that the fraction of participants who would have had screening recommended was the same for both risk models. Thus, it appears that more efficient risk models than the NLST criteria can be applied to patient populations under consideration for LDCT screening for lung cancer, with the result that more lung cancers would be diagnosed in the same sized screened population. These more efficient risk models are more complex, however, and would require computer analysis, either on software in physician offices or online.

The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK

Pirie K, Peto R, Reeves GK, Green J, Beral V for the Million Women Study Collaborators. *Lancet* 2013; 381:133-41.

BACKGROUND: Women born around 1940 in countries such as the UK and USA were the first generation in which many smoked substantial numbers of cigarettes throughout adult life. Hence, only in the 21st century can we observe directly the full effects of prolonged smoking, and of prolonged cessation, on mortality among women in the UK.

METHODS: For this prospective study, 1.3 million UK women were recruited in 1996-2001 and resurveyed postally about 3 and 8 years later. All were followed to Jan 1, 2011, through national mortality records (mean 12 woman-years, SD 2). Participants were asked at entry whether they were current or ex-smokers, and how many cigarettes they currently smoked. Those who were ex-smokers at both entry and the 3-year resurvey and had stopped before the age of 55 years were categorised by the age they had stopped smoking. We used Cox regression models to obtain adjusted relative risks that compared categories of smokers or ex-smokers with otherwise similar never-smokers.

FINDINGS: After excluding 0.1 million women with previous disease, 1.2 million women remained, with median birth year 1943 (IQR 1938-46) and age 55 years (IQR 52-60). Overall, 6% (66,489/1,180,652) died, at mean age 65 years (SD 6). At baseline, 20% (232,461) were current smokers, 28% (328,417) were ex-smokers, and 52% (619,774) were never-smokers. For 12-year mortality, those smoking at baseline had a mortality rate ratio of 2.76 (95% CI 2.71-2.81) compared with never-smokers, even though 44% (37,240/85,256) of the baseline smokers who responded to the 8-year resurvey had by then stopped smoking. Mortality was tripled, largely irrespective of age, in those still smoking at the 3-year resurvey (rate ratio 2.97, 2.88-3.07). Even for women smoking fewer than ten cigarettes per day at baseline, 12-year mortality was doubled (rate ratio 1.98, 1.91-2.04). Of the 30 most common causes of death, 23 were increased significantly in smokers; for lung cancer, the rate ratio was 21.4 (19.7-23.2). The excess mortality among smokers (in comparison with never-smokers) was mainly from diseases that, like lung cancer, can be caused by smoking. Among ex-smokers who had stopped permanently at ages 25-34 years or at ages 35-44 years, the respective relative risks were 1.05 (95% CI 1.00-1.11) and 1.20 (1.14-1.26) for all-cause mortality and 1.84 (1.45-2.34) and 3.34 (2.76-4.03) for lung cancer mortality. Thus, although some excess mortality remains among these long-term ex-smokers, it is only 3% and 10% of the excess mortality among continuing smokers. If combined with 2010 UK national death rates, tripled mortality rates among smokers indicate 53% of smokers and 22% of never-smokers dying before age 80 years, and an 11-year lifespan difference.

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INTERPRETATION: Among UK women, two-thirds of all deaths of smokers in their 50s, 60s, and 70s are caused by smoking; smokers lose at least 10 years of lifespan. Although the hazards of smoking until age 40 years and then stopping are substantial, the hazards of continuing are ten times greater. Stopping before age 40 years (and preferably well before age 40 years) avoids more than 90% of the excess mortality caused by continuing smoking; stopping before age 30 years avoids more than 97% of it.

EDITORIAL COMMENT: During the 1970s, it was widely believed that women were largely resistant to the adverse health consequences of tobacco smoking, as it was not possible to estimate the effects of smoking and smoking cessation until a generation of adult smokers had fully traversed a lifespan. In the UK, women born in the 1940s were the first generation to take up tobacco smoking in substantial numbers. In 1996-2001, participants were recruited into the Million Women Study in Britain. Subjects were queried in regard to lifestyle, medical history, sociodemographic factors, and smoking habits at study entry, year 3, and year 8, and mortality were ascertained. While the results of the study are not qualitatively surprising, this report provides interesting quantitative data. At a 12-year follow up, the mortality rate ratio among those smoking at baseline compared with never-smokers was 2.76. Deaths from chronic lung disease and lung cancer had strikingly increased relative risks of 35.3 and 21.4, respectively. There was a strong, linear relationship between lung cancer death risk and daily cigarette consumption. Smoking cessation had clear benefits, both in terms of overall and lung cancer specific mortality. Stopping at ages 25-34 reduced all-cause and lung cancer mortality relative risks to 1.05 and 1.84, while stopping later (ages 35-44) had definite, but smaller, benefits, with all-cause and lung cancer mortality relative risks of 1.20 and 3.34. These relative risks increased further in women who stopped at ages 45-54 to 1.56 and 5.91, respectively. The overall message from this report is optimistic; it is clearly beneficial to stop smoking — the earlier the better. We have known this at least since the 1970s, but we now have quantitative data to share with our female patients.

Disclosures

Dr. Miller submitted an ICMJE Disclosure Form to ***Lung Cancer Frontiers***. He reports that he has grants/grants pending from LUNGevity Foundation, National Cancer Institute (NCI), Gift of Life and Breath Foundation, and the Department of Veterans Affairs. He has a patent/patent pending with the University of Colorado. He has received travel expenses/accommodations from the International Association for the Study of Lung Cancer, LUNGevity Foundation, and NCI.

Lung Cancer Frontiers Editorial Board

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