Winter 2012 | NO 47

National Jewish Health®
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Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

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Lung Cancer in Women:
Differences in Epidemiology, Biology, and Therapy

By Jyoti D. Patel, MD

Women's cancers, such as breast cancer and gynecologic malignancies, have received substantial attention and research funding in the recent past. However, lung cancer is the leading cause of cancer mortality in women worldwide, having surpassed breast cancer in American women in 1987[1] (***Figure 1***). Almost twice as many women in the United States will die from lung cancer than from breast cancer in 2011.[2] There has been an alarming increase in lung cancer incidence in women over the last half century, and it is estimated that this trend will not significantly reverse until well after this decade.

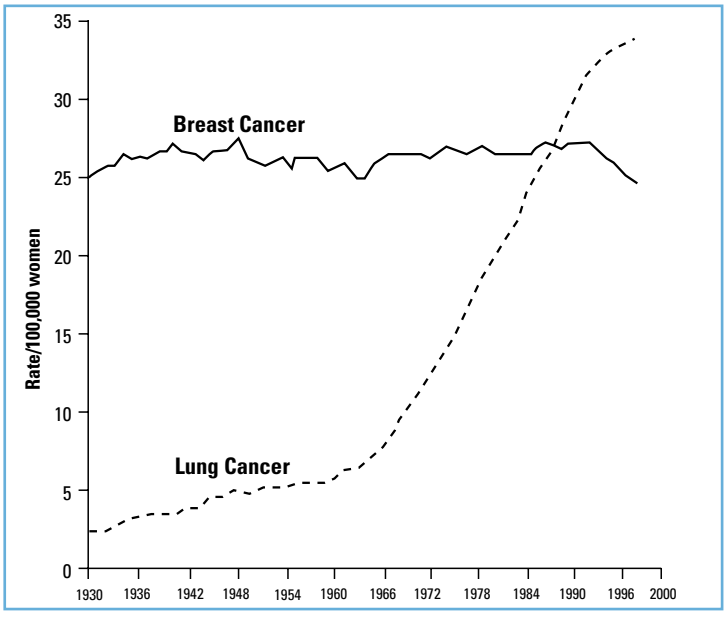

Figure 1. Age-adjusted death rates for lung cancer and breast cancer among women, United States, 1930-1997.[1] Lung cancer is the leading cause of cancer death among US women, far surpassing breast cancer for the past three decades.

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Epidemiology

The rise in lung cancer mortality among American women, accompanied by a concurrent decrease in lung cancer death rate among American men, has significantly altered patient demographics for this disease. Although lung cancer historically affected primarily men, the male to female incidence ratio has narrowed dramatically, from 3.65 in 1975 to 1.13 in 2009, as the incidence rate in men declined and the rate in women continued to rise.[3] While much of the changing epidemiology is directly attributable to tobacco use, it is becoming increasingly clear that the risks for specific types of lung cancer, the relationship between smoking and lung cancer, as well as the response to treatment may not be the same for both sexes.

Although many men and women who have never smoked develop lung cancer, smoking is the overwhelming cause of lung cancer. Of patients with lung cancer, 85-90% are former or current tobacco users. When examining smoking trends in women, causality in the rise of lung cancer over the past century is clearly evident. The prevalence of smoking among women was 18% in 1935 with a peak of 33% in 1965.[4] Following the increase in tobacco use from the 1930s, mortality from lung cancer in women increased by 600% from 1930 to 1997. The age-adjusted lung cancer death rate rose in parallel to the smoking rate among women, with the curves separated by about 30 years. This separation reflects the latency period between smoking and death from lung cancer.

After decades of steady increase, the lung cancer death rate in women declined slightly last year by 0.9%.[5] This is likely due to a slow decline in cigarette use by women over the past decades. However, almost a fifth of US women smoke today, despite all that is known about the devastating effects of tobacco consumption. Even more concerning is that the US Centers for Disease Control and Prevention (CDC) estimates that 15% of teenage girls use tobacco products.[6] Although death rates in women have seemingly plateaued, with a drop of nearly 1% in the past year, there is potential for the absolute number of women dying from lung cancer to increase as the "at risk" population ages. This is particularly true for the generation of women who were born in the 1960s and who continue to smoke.

Risk

There remains some controversy over whether women who smoke are at higher risk for developing lung cancer than male smokers. Risch et al. examined the odds ratio for lung cancer in patients with a 40 pack-year smoking history and found a ratio of 27.9 in women compared with 9.6 in men.[7] Zang and Wynder performed a hospital-based, case control study and reported that female smokers had a 1.5-fold higher estimated relative risk for developing lung cancer than male smokers with similar tobacco exposure.[8] In 2004, Henschke and Miettinen showed that the risk of developing lung cancer for women was 2.7 times the risk for men, when controlling for smoking history.[9] In 2005, a study based on the national Surveillance, Epidemiology and End Results (SEER) registry suggesting that women are more susceptible to tobacco carcinogens was published.[3]

There are, however, several other trials that found no difference in the relative risk of lung cancer between the sexes. Bain et al. analyzed cohort data from the Nurses' Health Study of Women and the Health Professional Follow-up Study of Men, and found that women have no greater susceptibility to lung cancer than men.[10] The American Cancer Society performed two cancer prevention studies, one assessing cancer risk between 1959 and 1965, and the second one between 1982 and 1986 (CPS-1 and CPS-II). Both demonstrated an increased risk for lung cancer in smoking men compared with smoking women.[11] The Carotene and Retinol Efficacy trial was a large, randomized lung cancer prevention trial that sought to derive a lung cancer prediction model (the Bach model). It analyzed data from 18,172 subjects, and its model revealed no clear association between sex and lung cancer risk.[12] At this juncture, the weight of the evidence suggests that there is little difference in risk, and that current efforts should focus upon the growing body of evidence showing that the biology of the disease differs between the sexes.

Other factors may contribute to differences in lung cancer biology between the sexes. Environmental tobacco smoke accounts for thousands of lung cancer deaths worldwide among nonsmokers, primarily women. A nonsmoking woman has a 24% greater risk of lung cancer if she lives with a smoker.[13] Molecular differences in the tumor between smokers and nonsmokers suggest some causative factors could be exposure to asbestos, radon, arsenic, and soot. A controlled study in Taiwan

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found a higher risk of lung cancer among women exposed to heated cooking oil without a fume extractor.[14] Human papillomavirus (HPV) is known to be associated with many types of cancer, and it is possible that HPV plays a role in the development of lung cancer.[15] Taiwanese researches reported a higher prevalence of HPV 16/18 among nonsmoking female lung cancer patients, compared with males, and suggested an association between HPV and lung cancer.[16] They further examined blood HPV DNA and found that the prevalence rate of HPV 16/18 in lung cancer cases was significantly higher than in controls without cancer.[17]

Hormonal Impact

A growing body of data suggests that sex hormones play a role in lung cancer. Estrogens participate in tumorigenesis at many levels: they may act as ligands to estrogen receptors, activating cellular proliferation pathways; they may undergo metabolic activation to reactive intermediates resulting in the formation of DNA adducts; or they may cause oxidative damage. The estrogen receptor ER-β regulates lung development, in particular, alveolar formation and surfactant homeostasis, and has been shown to correlate with the expression of Phase I/II carcinogen-metabolizing enzymes.[18,19] In lung tumors, an over expression of ER-β has been observed, more commonly in tumors from nonsmokers (53.5%) than in smokers (36.6%) ($p<0.04$). Among nonsmokers, ER-β expression was reported more frequently in women than in men.[20]

Several large randomized studies suggest that estrogen plus progestin therapy is associated with an increased risk of lung cancer.[21-23] Furthermore, other work suggests that exogenous estrogen may have a detrimental impact on the natural history of disease if lung cancer does develop.[24] Moore et al. analyzed the SEER database to evaluate the influence of menopausal status on outcomes in lung cancer. They classified 14,676 women and divided them into premenopausal and postmenopausal groups, and they compared them with men from similar age groups. The results indicated that for pre- vs. post-menopausal women, there was more extensive disease and adenocarcinoma histology; more extensive surgical procedures (pneumonectomies vs. lobectomies) at every stage of disease ($p<0.0001$); and a greater likelihood of receiving radiotherapy (58% vs. 48%; $p<0.0001$). While premenopausal women and younger men had similar mortality, postmenopausal women had fewer lung cancer-related deaths compared with older men.[25]

Histology

There is a consistent difference in the distribution of histologic types of lung cancer between men and women. Women proportionally have more adenocarcinoma and less squamous cell carcinoma compared to men. Part of the difference is related to smoking behavior, but estrogen may also influence the histologic and molecular features of lung cancer. Furthermore, genetic variation between men and woman is present in some genes that encode carcinogen-metabolizing enzymes. Carcinogens from smoke exert biologic effects through the formation of DNA adducts in lung tissue. They are metabolized and detoxified in two pathways by two classes of enzymes. Phase I enzymes produce reactive intermediates, and phase II enzymes neutralize these intermediates into water-soluble conjugates, which undergo urinary excretion. Higher levels of the gene product of the principal phase I enzyme gene, *CYP1A1*, has been noted in female smokers than in male smokers.[26] There are also differences in oncogene expression (*p53, K-ras*) and DNA repair capacity between men and women that may further contribute to differences in lung cancer biologic behavior.[27,28]

Response to Treatment

Although the incidence of lung cancer is high in women and continues to rise, women have a better survival outcome than do men regardless of stage or tumor histology. For example, in an analysis from the SEER and Medicare databases for 1991-1999 that studied the outcomes of almost 19,000 patients with stage I and II non-small cell lung cancer (NSCLC), the 5-year survival was 46% in women and 38% in men.[29] In patients with early disease, multiple studies have shown better outcomes from surgery, radiation and trimodality therapy in women.[30-32] A meta-analysis of five randomized, phase III, advanced NSCLC chemotherapy trials showed that women had a higher response rate to chemotherapy (42% vs. 40% in men, $p=0.01$) and longer survival than men (median 9.6 vs. 8.6 months, $p=0.002$).[33] It was noted, however, that the longer survival in women was only seen in patients with adenocarcinoma (test for interaction, $p=0.006$). The reasons for the consistent improvements in survival are likely multifactorial and need further study.

Certainly, sex-related differences in lung cancer gene mutations (*EGFR* mutations) may be responsible for some of

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the treatment outcome disparities between men and women, as patients with some *EGFR* tyrosine kinase mutations not only have improved survival from a prognostic standpoint, but they are also more responsive to drugs such as gefitinib and erlotinib. It is also possible that hormonal influences, though protective for most of one's life, can either accelerate the transition of a preneoplastic lesion to an overt malignancy or promote growth once malignancy is evident.

Lung cancer deaths would decline significantly if fewer people smoked, since almost 90% of lung cancer cases are attributable to smoking. With nearly 94 million current and former smokers in the US, screening for lung cancer appears to be the best current strategy for reducing the toll of this disease. As survival is directly related to the stage of lung cancer at the time of presentation, strategies for screening have been explored for some time. However, until the National Lung Screening Trial (NLST) was performed, not a single one of the randomized control trials of screening included women. Recently, the NLST demonstrated a significant reduction in disease-specific, relative mortality (20%) in high risk patients who underwent lung cancer screening.[34] In this trial of 53,454 persons, 41% of the subjects in both arms were female. We will await mature results of this study, but it appears that the survival benefits of screening are evident, regardless of gender.

Today, smoking rates remain unacceptably high, despite all that is known about the negative health effects of tobacco smoke. The prevalence of smoking is highest among young girls and the less educated. Tobacco marketing has been directed to young women with themes such as independence, and they include models who are generally athletic, thin, and beautiful. Some tobacco companies, even today, continue to design cigarette lines especially for women.

Lung cancer has reached epidemic proportions in women, and it is the leading cause of cancer death in women as well as men. Although is appears unlikely that women have greater risk for developing lung cancer than men, it is clear that the histologic spectrum differs between the sexes and that molecular differences do exist. Significant areas for future study include not only the epidemiology of lung cancer and smoking trends among women, but also a more thorough study of the complex interplay between carcinogens, susceptibility, and sex-specific influences that have led to the epidemic of lung cancer in women. This information could affect the way patients who smoke are screened and evaluated and the way smoking cessation and lung cancer prevention programs are directed. Finally, we must not allow a similar situation to occur in some countries of Asia and Africa, where young women are now increasingly addicted to tobacco.

Disclosures

Dr. Patel reported to *Lung Cancer Frontiers* no significant conflicts of interest with any companies or organizations whose products or services are discussed in this article.

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Selections from the Peer-Reviewed Literature

By Heidi Roberts, MD, FRCPC

***Heidi Roberts, MD, FRCPC**, is a new member of the Editorial Board of **Lung Cancer Frontiers**. Dr. Roberts is Professor of Radiology at the University of Toronto, Toronto, Canada. She serves as Section Head of Chest Imaging for the Joint Department of Medical Imaging of University Health Network/Mt. Sinai Hospital and Women's College Hospital, and is the Site Director for Medical Imaging at Women's College Hospital. Dr. Roberts is the principal investigator for the Toronto site in the International Early Lung Cancer Action Program (I-ELCAP), and in the Pan-Canadian Lung Screening Study. Her research interests include computed tomography (CT) screening for lung cancer, characterization of lung nodules, and prognostic assessment of advanced lung cancers using contrast-enhanced, dynamic CT.*

Following the favorable results from the National Lung Screening Trial (NLST) – the disease-specific mortality benefit following lung cancer screening with low-dose computed tomography (CT) – we can expect that screening CT scans in high-risk individuals will become much more mainstream. The anticipated growing number of thin-slice screening CT scans will result in the detection of numerous lung nodules requiring characterization, while at the same time the pool of reading radiologists is unlikely to change.

As such, tools are needed to help with risk assessment, beyond age and smoking history, to limit the number of people screened, to help with the characterization of indeterminate pulmonary nodules, and to minimize the morbidity from overly aggressive diagnostic procedures and radiation exposure from follow-up imaging.

The following recently published papers utilize and analyze different computer assisted detection (CAD) algorithms for the assessment of lung cancer risk and nodule characterization.

Quantitative CT assessment of emphysema and airways in relation to lung cancer risk

Glerada DS, Guniganti P, Newman BJ, Dransfield MT, Kvale PA, Lynch DA, Pilgram TK. *Radiology* 2011; 261:950-9.

PURPOSE: To determine whether quantitative computed tomographic (CT) measurements of emphysema and airway dimensions are associated with lung cancer risk in a screening population.

MATERIALS AND METHODS: Institutional review board approval and informed consent for the use of deidentified images were obtained. In this retrospective study, CT scans were analyzed from 279 participants in the CT screening arm of the National Lung Screening Trial who were diagnosed with lung cancer and 279 participants who were not diagnosed with lung cancer after a median follow-up period of 6.6 years. Quantitative CT measurements of emphysema and right upper lobe apical segmental and subsegmental airway dimensions, and multiple patient history-related variables, were compared between the two groups. Significant variables were tested in multivariate models for association with lung cancer by using multiple logistic regression.

RESULTS: The emphysema index of percentage upper lung volume less than -950 HU had the strongest association with lung cancer (mean, 10.7% [standard deviation, 13.5] in patients vs. 7.2% [standard deviation, 10.4] in control subjects; $P < .001$), but the relationship was weak ($R(2) = 0.015$, $P < .001$, $c = 0.57$). No CT measures of emphysema had an association with lung cancer independent of the patient medical history variables. Airway dimensions were not associated with lung cancer.

CONCLUSION: Quantitative CT measurements of emphysema but not airway dimensions were only weakly associated with lung cancer, demonstrating no potential practical value for clinical risk stratification.

EDITORIAL COMMENT: This paper addresses the utility of CAD for determining lung cancer risk. More specifically, the authors assess whether CT measurements of emphysema and

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airway dimensions are associated with lung cancer risk in a screening population.

Currently, lung cancer risk is defined based on age and smoking history. This is a simple assessment, but it results in a large percentage of any population in the Western world that would need to be screened. More sophisticated risk prediction models include detailed information about the individual's medical, occupational, and family history. Since airflow obstruction caused by COPD is associated with lung cancer risk, as is the presence of chronic inflammation in response to cigarette smoking, the authors attempted to quantify these pathophysiological features on CT scans, by quantifying emphysema and airway wall measurements in the upper lobes. A commercially available software package was used for emphysema quantification, and an open source image analysis program for the airway measurements. CT scans from 279 NLST participants who were diagnosed with lung cancer, and 279 control subjects without lung cancer, were analyzed.

The authors performed quantitative CT measurements of emphysema and right upper lobe apical segmental and subsegmental airway dimensions. They found that a history of COPD or emphysema was more strongly associated with lung cancer than quantitative emphysema, and airway dimensions were not associated with lung cancer.

In summary, these factors demonstrate no potential practical value for the inclusion of emphysema and airway CAD for risk stratification. This implies that different parameters are needed to improve risk assessment in the population, for example, spirometry, biomarkers, etc., and future research is needed in this area.

No benefit for consensus double reading at baseline screening for lung cancer with the use of semiautomated volumetry software

Wang Y, van Klaveren RJ, de Bock GH, Zhao Y, Vernhout R, Leusveld A, Scholten E, Verschakelen J, Mali W, de Koning H, Oudkerk M. *Radiology* 2012; 262:320-6.

PURPOSE: To retrospectively evaluate the performance of consensus double reading compared with single reading at baseline screening of a lung cancer computed tomography (CT) screening trial.

MATERIALS AND METHODS: The study was approved by the Dutch Minister of Health and ethical committees. Written informed consent was obtained from all participants. The benefit of consensus double reading was expressed by the percentage change in cancer detection rate, recall rate, number of additional nodules detected, and change in sensitivity and specificity in 7557 participants. The reference standard was a retrospective analysis of the serial CT scans performed in participants diagnosed with lung cancer during a 2-year period after baseline. Semiautomated volumetric software was used for nodule evaluation. McNemar tests were performed to test statistical significance. In addition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated and 95% confidence intervals (CIs) constructed.

RESULTS: Seventy-four cases of lung cancer were qualified as detectable at baseline. Compared with single reading, consensus double reading did not increase the cancer detection rate (2.7%; 95% CI: -1.0%, 6.4%; P = .50) or change the recall rate (20.6% vs. 20.8%, P = .28), but led to the detection of 19.0% (1635 of 8623; 95% CI: 18.0%, 19.9%, P < .01) more nodules. The sensitivity, specificity, PPV, and NPV were 95.9% (71 of 74), 80.2% (6001 of 7483), 4.6% (71 of 1553) and 99.9% (6001 of 6004) for single reading and 98.6% (73 of 74), 80.0% (1497 of 7483), 4.6% (73 of 1570), and 99.9% (5986 of 5987) for consensus double reading, respectively.

CONCLUSION: There is no statistically significant benefit for consensus double reading at baseline screening for lung cancer with the use of a nodule management strategy based solely on semiautomated volumetry.

EDITORIAL COMMENT: This paper focuses on the characterization of lung nodules as benign or malignant, and addresses the utility of CAD for nodule characterization with radiologists' double read.

Experience from double reading comes from mammography screening studies, in which a substantial difference in the interpretations of mammograms, and their recommendations, has been published repeatedly, and in which double reading has been shown to positively impact cancer detection rate. Given the prospect of millions of people at risk for lung cancer who would potentially get a CT scan if screening were widely

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recommended, the requirement for double reading would have a huge impact on the implementation, workflow, and cost-effectiveness of lung cancer screening.

This study was set in Belgium and was part of the Dutch-Belgian multicenter randomized controlled low-dose CT lung cancer screening trial (the NELSON trial). A large number (n=7,557) of baseline lung cancer screening CT scans were double read.

The first reader was one of the local readers at one of the four screening sites. Subsequently, the second reading was done at the central site by one of two central radiologists who were not blinded to the results of first reading. Both readers used the same software running on a digital workstation (Leonardo; Siemens Medical Solutions, Erlangen, Germany) for image interpretation. Based on semiautomated volumetry, the outcome of the screening test was positive if any non-calcified nodule on a CT scan had a solid component larger than 500 mm^3 (> 9.8 mm in diameter) and indeterminate if the volume of the largest solid nodule or the solid component of a partial-solid nodule was between 50 and 500 mm^3 (4.6–9.8 mm in diameter) or more than 8 mm for nonsolid nodules. Otherwise, the test was negative.

Only a non–statistically significant increase in cancer detection rate (2.7%; two of 74) and early stage cancer detection rate (1.3%; one of 74) by consensus double reading was observed. However, insufficient power led the authors to conclude that there is no evidence that the performances of the two readings were different.

These results are quite fortunate for a potential implementation of lung cancer screening with CT. The authors conclude that, after weighing the advantages and the cost of consensus double reading, consensus double reading in lung cancer screening is not required if a nodule management strategy based on semiautomated volumetry is used.

Doubling times and CT screen detected lung cancers in the Pittsburgh Lung Screening Study (PLuSS)

Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, Weissfeld J. *Am J Respir Crit Care Med* 2012; 185:85-9.

BACKGROUND: As CT screening for lung cancer becomes more widespread, volumetric analyses including doubling times, of CT screen detected lung nodules and lung cancers may provide useful information in the follow-up and management of CT detected lung nodules and cancers.

METHODS: We performed volumetric and doubling time analysis on 63 non-small cell lung cancers detected as part of the Pittsburgh Lung Screening Study using a commercially available VITREA 2 workstation and VITREA VITAL nodule segmentation software.

RESULTS: Doubling times (DT) were divided into 3 groups - rapid (DT < 183 days), typical (DT 183 - 365 days) and slow (DT > 365 days). Adenocarcinoma/bronchioloalveolar carcinoma (AC/BAC) comprised 86.7% of the slow DT group compared to 20% of the rapid DT group. Conversely, squamous cell cancer comprised 60% of the rapid DT group compared to 3.3% of the slow DT group. Twenty eight of 42 (67%) prevalent and 2 (10%) of 21 non-prevalent cancers were in the slow DT group, ($p < .0001$, Fisher's Exact Test). Twenty-four (75%) of 32 prevalent and one (9%) of 11 non-prevalent adenocarcinomas were in the slow DT group ($p < .0002$, Fisher's Exact Test).

CONCLUSION: Volumetric analysis of CT detected lung cancers is particularly useful in AC/BAC. Prevalent cancers have a significantly slower DT than non-prevalent cancers and a higher % of AC/BAC. These results should impact the management of indeterminant lung nodules detected on screening CT scans.

EDITORIAL COMMENT: Similar to the publication above, this paper focuses on the issue of lung nodule volumetry, and emphasizes its application for the follow-up of lung nodules. Whereas the publication by Wang et al. focuses on lung nodules, this publication focuses on screen-detected lung cancers.

Using a commercially available workstation with a (different than above) nodule segmentation software, the authors analyzed the volumetric doubling times (DTs) in CT screen-detected lung cancers of different cell types. The authors also differentiated between prevalent cancers (cancers visible, possibly in retrospect, as a nodule on an initial or baseline screening CT) and non-prevalent cancers (cancers not visible on the initial screening CT but newly visible on a follow-up CT performed for any reason).

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The DT of a total of 63 screen-detected, non-small cell lung cancers was analyzed. The authors found a wide range of DTs and slower DT in prevalent cancers, the majority of which were ACs. The slower DT in prevalent cancers would be expected, since the non-prevalent cancers had grown from nothing to detectability between the two CT scans. New nodules not previously seen on prior CT scans are more likely to be cancer than indeterminate nodules of unknown duration. The authors found that such a volumetric analysis is particularly useful in ACs and BACs. Adenocarcinoma/bronchioloalveolar carcinoma and prevalent cases had longer DTs, or equivalently, AC/BAC and prevalent detection characterized cases with slow DT.

As far as prevalent nodules (i.e., nodules of unknown duration) are concerned, their data suggest that following those nodules for two years may be inadequate. However, the authors suggest that one can hypothesize that in slow-growing, prevalent nodules suggestive of ACs, there is the potential for overdiagnosis and a more conservative approach might be warranted.

This publication again underscores the utility of CAD and volumetric analysis for the management of indeterminate lung nodules detected on screening CT scans.

In conclusion, the papers discussed above suggest that radiology, in general, and lung cancer screening specifically will not be able to avoid the use of CAD. Computer assisted detection for risk assessment and nodule characterization are assessed in the publications, but another important indication for CAD is nodule detection. It has to be emphasized that the use of CAD does require certain protocol adherences. Many factors can affect the accuracy of volumetric measurements, especially for small (<10 mm) nodules, including the technical features of the CT scanner, the reconstruction thickness and algorithm, and the type of analytical software. In addition, inter-scanner and inter-institutional comparison data is limited. Moreover, radiologists must be aware that while CAD does improve accuracy, it also invariably affects workflow and increases reading time. A seamless integration of CAD in the reading workstations is required for an efficient integration and overall benefit.

Disclosures

Dr. Roberts reported to *Lung Cancer Frontiers* no significant conflicts of interest with any companies or organizations whose products or services are discussed in this article.

Lung Cancer Meetings and Symposia

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