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The Forum for Early Diagnosis and Treatment of Lung Cancer

Takefumi Komiya, MD, PhD

Phillip A. Dennis, MD, PhD

Takefumi Komiya, MD, PhD *is a Clinical Fellow in the Medical Oncology Branch of the National Cancer Institute and the National Institutes of Health, Bethesda, MD. He completed his medical residency at Howard University, Washington, DC. His research interests include mutational analysis, chemotherapy, and chemoprevention strategies for lung cancer.*

Phillip A. Dennis, MD, PhD*, is the Director of Thoracic Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Director of the Department of Oncology at Johns Hopkins Bayview Medical Center, Baltimore, MD. His research interests include the role of the PI3K/Akt/mTOR pathway in lung tumorigenesis, as well as lung cancer chemoprevention. He is a member of the Oncology Section of the* ***Lung Cancer Frontiers*** *Editorial Board.*

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A Better Future for Lung Cancer Chemoprevention

By Takefumi Komiya, MD, PhD and Phillip A. Dennis, MD, PhD

Lung cancer is the leading cause of cancer death in men and women in the United States, as well as worldwide, and approximately 85% of cases are attributable to cigarette smoking.[1] Even after smoking cessation, the relative risk of lung cancer for a former smoker remains permanently elevated. As a result, preventive measures have been explored to lower lung cancer incidence. Cancer chemoprevention is defined as the use of natural or pharmacological interventions to reverse, suppress, or prevent the initial phase of carcinogenesis or progression to invasive carcinoma.[2] Chemoprevention has been successful in some types of cancer (e.g., breast cancer),[3] but it has been less so in lung cancer, despite relatively easy identification of the at-risk population.

Early Failures in Lung Cancer Prevention

Several large, expensive, randomized Phase III clinical trials have reported no benefit of chemoprevention in reducing lung cancer risk. Many of these early trials utilized beta-carotene.[4-6] The Beta-Carotene Cancer and Retinol Efficacy (CARET) Trial, a placebo-controlled trial in 18,000 men and women with a history of cigarette smoking, compared a combination of beta-carotene and retinyl palmitate with placebo. This study demonstrated a 28% higher lung cancer incidence and a 17% higher total mortality in the combination supplementation arm.[4] The Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention study, another placebo-controlled trial, randomized 29,000 Finnish male smokers to receive beta-carotene, vitamin E, both supplements, or neither supplement for an average of six years. This study also showed an 18% increased lung cancer incidence at 18 months in men who received beta-carotene, although these agents had no effect on lung cancer mortality.[5] The Physician's Health Study, a placebo-controlled trial that enrolled both never and current/former smokers in the US, then randomized participants to beta-carotene or placebo, showed no benefit or harm in the incidence of malignancy

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or death from all causes.[6] A recent meta-analysis of large beta-carotene trials (including these three studies) showed an increased risk of lung cancer in current smokers taking beta-carotene (OR=1.24; 95% CI=1.10-1.39).[7] The failure of these studies has caused investigators and funding agencies to revisit the criteria used to plan chemoprevention studies, because the rationale for these early studies was based only on epidemiological observations, not mechanistic studies.

Promising Early Phase Trials

The transformation of chemoprevention trials to smaller scale, early phase studies based on mechanistic, preclinical animal studies that utilize intermediate endpoints has led to new successes. Instead of lung cancer incidence and mortality, intermediate markers associated with improved outcomes have been chosen as study end points, including histological improvement in premalignant, dysplastic bronchial lesions that develop as a result of smoking. The most notable recent success has been with iloprost, a prostacyclin analog.

The arachidonic pathway is critical for lung tumorigenesis, and its inhibition by overexpression of prostacyclin synthase or administration of iloprost prevents lung carcinogenesis in preclinical models.[8-9] Keith and colleagues recently reported results from a double-blind, randomized, Phase II placebo-controlled trial of oral iloprost in current or former smokers with central airway endobronchial dysplasia.[10] Rigorous, blinded pathologic review using an extensive scoring system based on WHO pathology classification allowed the investigators to use changes in endobronchial histology as an intermediate marker. This study failed to meet its primary endpoint, which was a change in average histology score in all patients after six months of treatment. However, subset analysis demonstrated that in former smokers, iloprost decreased endobronchial dysplasia, as shown by improvement in average histology scores (0.41 units better), worst histology scores (1.1 units) and dysplasia index (12.5%). Of note, no significant difference was observed in current smokers. The results of this trial are promising, but they need to be validated in future trials to determine whether a change in these indices reflects a meaningful decrease in carcinogenesis.

Most chemoprevention trials have focused on endobronchial dysplastic lesions in central airways that are precursor lesions for squamous cell carcinoma of the lung. However, the most common histological type of lung cancer is adenocarcinoma, which commonly arises in peripheral airways. Veronesi et al. investigated peripheral lung lesions as an intermediate endpoint in a randomized, double-blind, Phase IIb trial of the inhaled steroid budesonide.[11] Serial, low-dose CT scans were used to evaluate peripheral lung lesions, and CT-detected lung nodules in current and former smokers were evaluated before and 12 months after intervention. Per person analysis of the primary endpoint showed no significant difference in the shrinkage of lung nodules by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria between the two arms, whereas per lesion analysis showed budesonide was associated significantly with nodule regression. Interestingly, there was a non-significant trend toward regression of non-solid and partially solid nodules with budesonide treatment. Non-solid and partially solid nodules are likely to be atypical adenomatous hyperplasic lesions and adenocarcinoma *in situ*, formerly known as bronchioloalveolar carcinoma; both are known precursors of adenocarcinoma.[12]

Advances in understanding the basic mechanisms of carcinogenesis has led to identification of new therapeutic targets as well as new molecular endpoints. For example, epigenetic changes, such as DNA methylation in promoter regions, are involved in initiation and progression of human cancers. Several studies have investigated whether methylation signatures have a diagnostic or prognostic role in evaluation of clinical samples. Promoter methylation status of *p16* and *CDH13* genes in both non-small cell lung cancer (NSCLC) and mediastinal lymph nodes was significantly associated with postsurgical relapse in early stage NSCLC cases (OR=15.5).[13] Although the use of promoter methylation status as an intermediate endpoint in secondary prevention trials in the post-surgery setting to prevent second lung cancers seems promising, it needs further validation for primary prevention studies.

PI3K/Akt/mTOR Signaling Pathway Inhibitors

The PI3K/Akt/mTOR pathway is an important signal transduction pathway that regulates protein synthesis, metabolism and cell survival (PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin). Activation of the PI3K/Akt/mTOR pathway contributes to formation, maintenance and therapeutic

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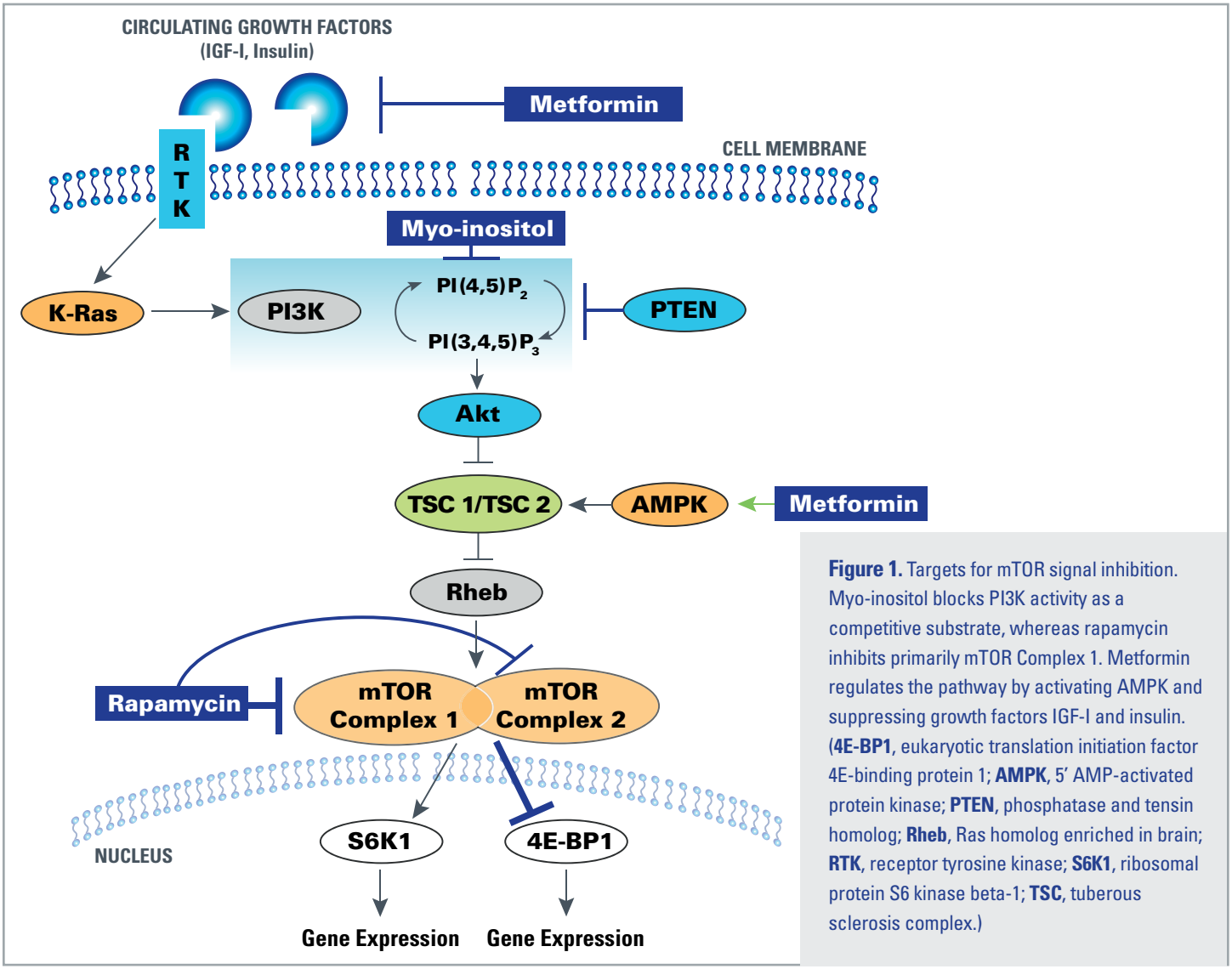

Figure 1. Targets for mTOR signal inhibition. Myo-inositol blocks PI3K activity as a competitive substrate, whereas rapamycin inhibits primarily mTOR Complex 1. Metformin regulates the pathway by activating AMPK and suppressing growth factors IGF-I and insulin. (**4E-BP1**, eukaryotic translation initiation factor 4E-binding protein 1; **AMPK**, 5' AMP-activated protein kinase; **PTEN**, phosphatase and tensin homolog; **Rheb**, Ras homolog enriched in brain; **RTK**, receptor tyrosine kinase; **S6K1**, ribosomal protein S6 kinase beta-1; **TSC**, tuberous sclerosis complex.)

resistance of lung cancer. Activation of Akt confers a poor prognosis in patients with NSCLC, especially those with early stage disease, and premalignant lesions in smokers have increased PI3K-related gene expression signatures and Akt activation.[14] Inhibitors of the PI3K/Akt/mTOR signaling pathway (***Figure 1***) have been used successfully to prevent lung tumorigenesis in K-Ras driven, tobacco carcinogen-induced lung cancer mouse models .[15-16] Because several inhibitors of the pathway are well studied and approved by the US Food and Drug Administration (FDA), the chemopreventive potential of these agents is worth exploring. These agents include myo-inositol, rapamycin, and metformin.

Myo-inositol is an isomer of glucose that is equivalent to the head group of phosphatidylinositol, the basic substrate for PI3K. Dietary myo-inositol has chemopreventive activity in several mouse models and is well tolerated. A recent Phase I trial of myo-inositol in heavy smokers showed increased regression of dysplastic lesions.[17] Post hoc analysis revealed that activation of Akt was observed more frequently in dysplastic lesions than in hyperplastic/metaplastic lesions. Myo-inositol significantly reduced activation of Akt in dysplastic lesions.[18] Using the same specimens, another group demonstrated that PI3K expression signatures were activated in cytologically normal appearing cells in smokers, suggesting PI3K is activated in the airway before malignant

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transformation of the cells. Further analysis showed that smokers who had regression of dysplastic lesions had decreased PI3K activity in the dysplastic area after treatment with myo-inositol.[19] These studies support further testing of myo-inositol and indicate that measuring PI3K-related gene expression could be a potential intermediate endpoint in future chemoprevention trials.

Rapamycin is an orally available inhibitor of mTOR that is approved by the FDA to prevent rejection of renal transplants.[20] Transplant patients taking rapamycin, as opposed to other immunosuppressive agents, have lower rates of cancer, which supports its use in cancer prevention. Preclinical data show that rapamycin is highly effective in inhibiting tobacco carcinogen-induced lung tumorigenesis, as well as other types of cancer in mouse models. Other advantages of rapamycin for clinical testing as a chemopreventive agent for lung cancer include the fact that drug levels can be readily monitored in clinical laboratories so that dosing can be easily adjusted.[21] Disadvantages of rapamycin include possible long-term sequelae of immunosuppression and potential promotion of tumorigenesis through feedback activation of Akt. Nonetheless, the body of evidence supports further evaluation of rapamycin in chemoprevention trials.

Metformin is a well-tolerated, commonly prescribed, FDA-approved anti-diabetic drug that inhibits mTOR through a mechanism distinct from rapamycin.[22] Epidemiologic evidence in diabetics taking metformin suggests a markedly reduced risk of many types of cancer, including lung cancer.[23-24] Preclinical studies in mouse models of smoking-related lung cancer show that metformin decreases lung tumor burden at clinically achievable drug concentrations. Its mode of action in these systems seems to involve inhibition of circulating growth factors such as insulin-like growth factor I (IGF-I) and insulin, as opposed to direct inhibition of mTOR.[25] Despite uncertainty over its mechanism of action and dosing in non-diabetic patients, chemoprevention trials in high-risk smokers are planned.

Future Directions

Despite a dismal past, recent studies of lung cancer chemoprevention show renewed promise. The shift to clinical trial designs that utilize intermediate markers (e.g., bronchial dysplasia) and employ well-tolerated drugs that target known pathogenic steps in lung tumorigenesis will make it easier to identify early successes and failures. Demonstrating that an intermediate biomarker is modulated by a drug that is well tolerated, and evidence of regression of premalignant lesions, will support the implementation of larger, definitive clinical trials with cancer prevention as an end point.

Disclosures

Dr. Komiya and Dr. Dennis submitted ICMJE Disclosure Forms to ***Lung Cancer Frontiers***. No significant conflicts of interest exist 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 Javier J. Zulueta, MD

***Javier J. Zulueta, MD**, is Associate Professor of Medicine, Director of the Respiratory Medicine Service, and Senior Consultant at the University Clinic, University of Navarra School of Medicine, in Pamplona, Spain, where he established the Service of Respiratory Medicine in 1998. He heads the Early Lung Cancer Detection Program at the University Clinic. His research interests include early lung cancer detection and the relationship between lung cancer and COPD. He also has a special interest in endobronchial ultrasound and electromagnetic navigational bronchoscopy. He is a member of the Pulmonary Section of the **Lung Cancer Frontiers** Editorial Board.*

Emphysema detected on computed tomography and risk of lung cancer: A systematic review and meta-analysis

Smith BM, Pinto L, Ezer N, Sverzellati N, Muro S, Schwartzman K.
Lung Cancer, March 19, 2012 [Epub ahead of print].

BACKGROUND: Studies exploring the association between emphysema detected on chest computed tomography (CT) and lung cancer have yielded mixed results. Our objective was to systematically review the evidence for this association.

METHODS: We searched MEDLINE, EMBASE and the Cochrane Library for the terms "lung cancer", "emphysema" and "computed tomography" without language restriction. Bibliographies were also reviewed and authors contacted for additional information. Human studies in which CTs were performed and assessed for emphysema and in which subjects were evaluated systematically for lung cancer were included. Qualitative synthesis of evidence was performed followed by pooling of effect estimates using a random-effects model.

RESULTS: Of 187 citations, 7 were included in the qualitative synthesis and 5 in the meta-analysis. Three studies assessing emphysema visually observed an association with lung cancer, independent of smoking history and airflow obstruction. Three studies using densitometry to detect emphysema found no association with lung cancer. Another study directly comparing automated and visual emphysema detection techniques found only the latter to associate with lung cancer. Among 7368 subjects included in the meta-analysis, 2809 had emphysema on CT and 870 were diagnosed with lung cancer. The pooled adjusted odds ratio for lung cancer in the presence of emphysema on CT was 2.11 (95% CI 1.10-4.04); stratification by detection method yielded OR of 3.50 (95% CI 2.71-4.51) with visually detected emphysema and 1.16 (95% CI 0.48-2.81) with densitometric emphysema.

CONCLUSION: Systematic literature review shows emphysema detected visually on CT to be independently associated with increased odds of lung cancer. This association did not hold with automated emphysema detection.

EDITORIAL COMMENT: Over the last ten years, numerous publications have addressed the risk profiles of individuals participating in low-dose computed tomography (LDCT)-based lung cancer screening trials. Currently, among the most debated issues in this field is whether emphysema observed on LDCT, and/or airways obstruction detected by spirometry or CT airway analysis, are factors that can be used to select higher-risk individuals for screening.

This systematic review and meta-analysis clarifies to a significant degree some of the conflicting results previously published. Many epidemiologic studies in the past reported significant associations between COPD and lung cancer risk, but none addressed emphysema as an independent variable. This can now be done, thanks to the availability of high-resolution lung imaging, even when using LDCT. The review includes seven publications in a quantitative synthesis, and five in a meta-analysis. The common thread between these studies is that those that assessed emphysema visually found a significant association between emphysema and lung cancer, whereas those that employed automated, quantitative assessment using software-determined densitometry, did not.

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Interestingly, one of the studies included compared both methodologies head to head and found the same difference. This review and meta-analysis has limitations, because the number of studies included is small, but a total of 7,368 individuals were included in the meta-analysis, 2,809 of whom had emphysema, and 870 of whom were diagnosed with lung cancer.

Why the qualitative assessment of a radiologist carries more weight than sophisticated software programs that automatically quantify emphysema is unknown. The authors speculate that software quantification may be too sensitive to distinguish significant emphysema associated with increased lung cancer risk from more subtle emphysema. This will have to be addressed in future studies. Whether emphysema will be used as a risk factor to select high-risk candidates for lung cancer screening is still an open question. However, these results should be taken into account when designing future screening studies with emphysema as a variable.

Lung cancer screening

Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, Klippenstein D, Lackner RP, Leard L, Leung AN, Massion PP, Meyers BF, Munden RF, Otterson GA, Peairs K, Pipavath S, Pratt-Pozo C, Reddy C, Reid ME, Rotter AJ, Schabath MB, Sequist LV, Tong BC, Travis WD, Unger M, Yang SC. *J Natl Compr Canc Netw* 2012;10:240-65.

EDITORIAL COMMENT: For decades, and as a consequence of early negative screening trials using chest radiography, all official guidelines, including those from the US Preventive Services Task Force, have either not recommended or recommended against lung cancer screening in any form. The National Comprehensive Cancer Network (NCCN), which gathers experts from top cancer centers around the world, just published the first clinical guidelines that recommend lung cancer screening using LDCT for high-risk individuals. This is a major milestone in the battle against one of the most frequent causes of death in the world. The guideline recommendations are based on the recently published National Lung Screening Trial (NLST) results. The main conclusion of the guidelines is that lung cancer screening using LDCT in certain high-risk individuals is beneficial and results in a reduction in lung cancer mortality.

A few comments regarding the recommendations are warranted. The first figure in the guidelines summarizes the indications for screening based entirely on NLST data. Screening is recommended (category 1 evidence) for individuals ≥55 years of age, with a ≥30 pack-year smoking history, and who quit smoking <15 years prior to screening. Screening is also recommended (category 2B evidence) for slightly younger individuals (≥50 years) with ≥20 pack-years of smoking and an additional risk factor other than second-hand smoke exposure. An individual in this last category without an additional risk factor would not be eligible for screening, according to the guidelines.

Are these limits and thresholds reasonable? For one, they are the only criteria that have been tested in a randomized, controlled trial. Thus, it makes sense that in order to make category 1 recommendations, the NCCN panel had to use the design of the NLST for their conclusions. However, ignoring high quality, descriptive data from non-randomized, controlled studies, such as the International Early Lung Cancer Action Program (I-ELCAP), can limit the usefulness of protocols and work-up algorithms. For example, the limitation to three years of screening is completely arbitrary. The NLST investigators had to limit the duration of yearly screening for practical reasons, but not because any evidence suggested that three years of screening is superior to four or more. On the contrary, plenty of data from other screening regimens have shown that as more years of screening are accumulated in a population at risk, the reduction in mortality becomes larger. These and other details of the recommended protocols will need to be addressed in further studies, particularly cost-effectiveness studies that might shed light onto who will benefit most from lung cancer screening.

These guidelines are welcomed and will certainly change the negative perception of lung cancer screening which has been predominant up to now, but more importantly, they will provide physicians and patients with tools to help change the grim statistics of this dreaded disease. Positive guidelines from other major organizations are expected soon.

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Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer

Jacobs PC, Gondrie MJ, van der Graaf Y, de Koning HJ, Isgum I, van Ginneken B, Mali WP. *Am J Roentgenol* 2012; 198:505-11.

OBJECTIVE: Performing coronary artery calcium (CAC) screening as part of low-dose CT lung cancer screening has been proposed as an efficient strategy to detect people with high cardiovascular risk and improve outcomes of primary prevention. This study aims to investigate whether CAC measured on low-dose CT in a population of former and current heavy smokers is an independent predictor of all-cause mortality and cardiac events.

SUBJECTS AND METHODS: We used a case-cohort study and included 958 subjects 50 years old or older within the screen group of a randomized controlled lung cancer screening trial. We used Cox proportional-hazard models to compute hazard ratios (HRs) adjusted for traditional cardiovascular risk factors to predict all-cause mortality and cardiovascular events.

RESULTS: During a median follow-up of 21.5 months, 56 deaths and 127 cardiovascular events occurred. Compared with a CAC score of 0, multivariate-adjusted HRs for all-cause mortality for CAC scores of 1-100, 101-1000, and more than 1000 were 3.00 (95% CI, 0.61-14.93), 6.13 (95% CI, 1.35-27.77), and 10.93 (95% CI, 2.36-50.60), respectively. Multivariate-adjusted HRs for coronary events were 1.38 (95% CI, 0.39-4.90), 3.04 (95% CI, 0.95-9.73), and 7.77 (95% CI, 2.44-24.75), respectively.

CONCLUSION: This study shows that CAC scoring as part of low-dose CT lung cancer screening can be used as an independent predictor of all-cause mortality and cardiovascular events.

EDITORIAL COMMENT: As positive results from lung cancer screening trials are published, the use of LDCT for the diagnosis of other prevalent thoracic diseases is progressively gaining more attention. Our group and others have shown that the detection of emphysema on LDCT in the context of a screening program is associated with a greater risk of lung cancer (*Chest* 2007; 132:1932-8). We also recently reported that the presence of emphysema is associated with an increase in mortality from lung cancer and from COPD (*Chest* 2012; 141:1216-23).

Coronary calcifications observed on computed tomography are known to be associated with underlying coronary artery disease. Large studies in the past used ECG-gated electron beam tomography of the chest to quantify CAC and clearly showed a directly proportional relationship between the magnitude of CAC scores and the risk for cardiovascular events and death. Currently, multidetector gated CT is widely used in clinical practice, with radiation doses ranging between 1.5 and 6.2 mSv.

The study by Jacobs et al. demonstrated that the use of non-ECG gated LDCT in the context of a lung cancer screening trial is reliable in determining CAC scores, and that these show a directly proportional relationship with cardiovascular and all-cause mortality. The results confirm those of a previous study using a very similar population participating in a lung cancer screening trial (*Radiology* 2010; 257:541-8). The advances confirmed by this study are two-fold. Firstly, CAC scores can be obtained reliably with significantly lower doses of radiation than is commonly used. Secondly, ECG-gating does not appear to be necessary to assess cardiovascular risk in evaluating the extent of CAC.

In summary, the usefulness of LDCT appears to go beyond lung cancer screening, allowing for the detection and quantification of CAC and emphysema. The concept of a "one stop" screening test for three of the most common causes of death (coronary artery disease, lung cancer, and COPD) is becoming progressively more attractive as data from different studies are published.

Disclosures

Dr. Zulueta submitted a ICMJE Disclosure Form to ***Lung Cancer Frontiers***. Dr. Zulueta stated that he is a shareholder and serves on the medical advisory board of VisionGate, Inc., a company that specializes in three-dimensional cell imaging.

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