

# APSR RESPIRATORY UPDATES



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The articles in this issue were selected and commented on by:

Prof. Chunxue Bai, Director, Shanghai Respiratory Research Institute, Shanghai, China

Director, Respiratory Research Institute, Fudan University, Shanghai, China

Editorial Board Member, American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Cell and Molecular Biology

and

Dr. Dawei Yang, MD

Shanghai Respiratory Research Institute, Shanghai, China

Annual number of lung cancer deaths potentially avertable by screening in the United States.

**Authors:** Ma J *et al.*

**Reference:** Cancer, 2013, Feb 25 Epub ahead of print; DOI: 10.1002/cncr.27813

**URL:** <http://onlinelibrary.wiley.com/doi/10.1002/cncr.27813/pdf>

**Comments:** In this article, the authors provided an estimate of the annual number of lung cancer deaths that could have been averted by screening, assuming the screening regimens adopted in the National Lung Screening Trial (NLST) were fully implemented in the United States. NLST conducted between 2002 and 2009, demonstrated that screening with low-dose computed tomography (LDCT) reduced lung cancer mortality by 20% among screening-eligible populations compared with chest x-ray. According to the authors approximately 8.6 million Americans met the NLST criteria for lung cancer screening in 2010. They estimated that 12,000 lung cancer deaths per year could have been averted by screening based on screening effect, the US population size, prevalence of screening eligibility, and the lung cancer mortality rates among screening-eligible populations

Several factors might have affected their estimate. The control group in the NLST received screening with chest radiography, whereas the general population of the United States was unlikely to undergo any screening, which could have resulted in under estimation of avertable deaths. The lung cancer mortality rates for screening-eligible populations were estimated based on deaths occurring between 2000 and 2006, possibly overestimating the current rates. The use of self-reported smoking data could have led to an underestimation of the true number of screening-eligible individuals because smokers tend to underreport their tobacco use. They also made an unrealistic assumption that 100% of the high risk population would be screened.

Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study

**Authors:** Veronesi, G. *et al*

**Reference:** Annals of internal medicine; 2012, 157: 776-784.

**URL:** <http://annals.org/article.aspx?articleid=1467428>

**Comments:** This article discussed the risk of over diagnosis due to lung cancer screening and calculated the percentage of cases that would never become symptomatic leading to overtreatment. The authors used changes in size on sequential low-dose computed tomography (LDCT) screening, expressed as volume-doubling time (VDT) to distinguish aggressive cancer from the ones that were unlikely to become symptomatic. VDT was measured on LDCT and classified as fast-growing (<400 days), slow-growing (between 400 and 599 days), or indolent (>600 days). A total of 5203 participants with a mean age of 57.7 years (SD, 5.6) were initially enrolled in the study and had baseline LDCT; 3439 (66.0%) were men, and 4164 (80.3%) were active smokers with a median of 44 (range, 20 to 255) pack-years. A total of 4122 participants presented for all 5 annual scans (adherence, 79.2%). One hundred and seventy-five cases of

primary lung cancer were diagnosed in the cohort over 5 years; 66% of these were stage I, and 89% were radically resected. Fifty-five cases of cancer were prevalent (1.1% of the screened population) and 120 were incident during subsequent screening rounds. Six percent (5 of 53) of the prevalent cases examined by CT-PET were negative compared with 43.9% (50 of 114) of incident cases. Median follow-up was 5.8 years for prevalent cancer, 3.2 years for incident cancer, 3.6 years for fast-growing cancer, and 3.7 years for slow-growing or indolent cancer. The authors reported significantly higher (9.2% per year) Lung cancer-specific mortality in patients with new cancers compared to those with slow-growing or indolent (0.9% per year) cancers. It was reported that slow-growing or indolent cancer comprised approximately 25% of incident cases, many of which may have been over diagnosed.

### Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer

**Authors:** Olaide Y. Raji, et al.

**Reference:** Ann Intern Med, 2012; 157:242-250

**URL:** <http://annals.org/article.aspx?articleid=1351360>

**Comments:** : In this Case-control and prospective cohort study, participants' data from 3 independent studies from Europe and North America: European Early Lung Cancer (EUELC), Harvard case-control studies and the Liverpool Lung Project (LLP) population-based prospective cohort (LLPC) study were applied into analysis, in order to determine the discrimination of the Liverpool Lung Project (LLP) risk model, developed from LLP case-control (LLCC) study, and the effect of the model on stratifying patients for CT screening. The study measured 5-year absolute risks for lung cancer predicted by the LLP model. The model applied well in both the Harvard (AUC, 0.76 [95% CI, 0.75 to 0.78]) and the LLPC (AUC, 0.82 [CI, 0.80 to 0.85]) studies, while with modest discrimination in the EUELC (AUC, 0.67 [CI, 0.64 to 0.69]) study. As a result, it is concluded that LLP model has good discrimination and provides benefits to stratifying patients for lung cancer CT screening. Further more, when taking both harm and benefit of using this risk model in clinical decision making into consideration, the performance of LLP model was better than smoking duration or family history alone in stratifying high-risk patients for lung cancer CT screening. However, the model failed to assess the improved accuracy by other risk factors, such as lung function or genetic markers. And the validation was also limited due to the lack of information in LLPC study. Further studies are needed to prospectively evaluate model performance and set up optimal population risk thresholds for initiating lung cancer screening.



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## Two microRNA panels to discriminate three subtypes of lung carcinoma in bronchial brushing specimens

**Authors:** Huang W et al.

**Reference:** Am J Resp Crit Care Med., 2012, 186: 1160-1167

**URL:** <http://ajrccm.atsjournals.org/content/186/11/1160.long>

**Comments:** This study is an example of recent efforts to demonstrate the utility of microRNA as tool for the early detection and diagnosis of lung cancer. In this study, microarrays with 723 different microRNAs were used to test laser-captured, microdissected cancer cells from 82 surgical lung specimens. The discovery study produced 7 candidate microRNA's. These microRNA's were further evaluated in a training set of 85 microdissected lung cancer samples by quantitative RT-PCR. Four microRNA's were used to generate two panels of 2 microRNAs each and these panels were validated on 68 samples. These 2 microRNA panels were then tested on 207 bronchial brushing specimens (85 adenocarcinomas, 69 squamous cell carcinomas and 53 small cell lung cancers). Panel A (miR-29a and miR-375) was able to separate NSCLC from SCLC and within NSCLC (AUC=0.947). Panel B (miR-34a and miR-205) was able to distinguish between adenocarcinoma and squamous cell carcinoma (AUC=0.962). These 2 microRNA panels demonstrated value in the differential diagnosis of lung cancer subtypes, which is critical for optimizing treatment strategies for each individual patient.

## Non-invasive breath analysis of pulmonary nodules.

**Authors:** Peled N et al.

**Reference:** J of Thoracic Oncol, 2012, 7:1528-1533.

**URL:** <http://journals.lww.com/jto/pages/articleviewer.aspx?year=2012&issue=10000&article=00008&type=abstract>

**Comments:** This prospective study evaluated the ability of the measurement of volatile organic compounds from exhaled-breath to distinguish between benign and malignant pulmonary nodules (PN) in a high-risk cohort. Fifty-three malignant PN and 19 benign BN were included in this pilot study. Thirty patients had early disease and 23 had advanced disease. The majority (n=47) were non-small cell lung cancer. Breath samples were analyzed for their profile of volatile organic compounds by 1) gas chromatography/mass spectrometry and 2) a chemical nanoarray. The concentration of 1-octene was significantly (p=0.49) in malignant vs. benign PN. Using a discriminant factor analysis, the nanoarray was able to distinguish between early and benign PN (p<0.0001) with a sensitivity of 86% and a specificity of 88% and an area under the ROC of 0.986. The nanoarray was also able to separate adenocarcinoma from squamous cell carcinoma and early disease from late disease. This study provides another indication of the potential for breath analysis to be used in the early diagnosis of lung cancer.

## Biomarkers to help guide management of patients with pulmonary nodules.

**Authors:** Patz EF et al.

**Reference:** Am J Respir Crit Care Med. 2013, Jan 10, doi: 10.1164/rccm.201210-1760OC

**URL:** <http://ajrccm.atsjournals.org/content/early/2013/01/04/rccm.201210-1760OC.full.pdf>

**Comments:** In this study, the authors examined a panel of serum biomarkers as an aid in distinguishing benign and malignant indeterminate pulmonary nodules (PN). The serum panel included carcinoembryonic antigen (CEA), alpha-1-antitrypsin (AAT), and squamous cell carcinoma antigen (SCC). The study consisted of a training set of 298 patients with lung cancer and 211 patients without lung cancer. The results were evaluated with classification and regression tree and logistic regression models, which used the 3 biomarkers and nodule size as parameter. Multiple models were then validated in a second set of patients with (n=203) and without (n=196) lung cancer. The classification and regression tree model had a sensitivity of 88% and a specificity of 86% on the validation samples. For the logistic regression model, the sensitivity was 80% and the specificity was 89%. The addition of the biomarkers in the logistic regression model improved the results of nodule size alone with CEA having the greatest effect ( $p < 0.001$ ). The addition of SCC and AAT to the model with CEA and nodule size added value ( $p = 0.04$ ). This study demonstrates the value of using serum biomarkers to aid in the identification of indeterminate PN that are malignant.

## Definition of a positive test result in computed tomography screening for lung cancer

**Authors:** Henschke CI, et al.

**Reference:** Ann Intern Med, 2013; 158:246-252

**URL:** <http://annals.org/article.aspx?articleid=1583810>

**Comments:** In this prospective cohort study, 21,136 participants with baseline computed tomography performed between 2006 and 2010 were enrolled. The researchers investigated the frequency of solid and part-solid pulmonary nodules and the rate of lung cancer diagnosis by using current (5 mm) and more restrictive thresholds of nodule diameter. In results, firstly they found the frequency of positive results in the baseline round by using the current definition of positive result (any parenchymal, solid or part-solid, noncalcified nodule 5.0 mm) was 16% (3396/21,136). While, alternative threshold values of 6.0, 7.0, 8.0 and 9.0mm were used, the frequencies of positive results were increased to 10.2% (95% CI, 9.8% to 10.6%), 7.1% (CI, 6.7% to 7.4%), 5.1% (CI, 4.8% to 5.4%), and 4.0% (CI, 3.7% to 4.2%), respectively. Secondly, using these alternative definitions would have reduced the work-up by 36%, 56%, 68%, and 75%, respectively. Vice versa, lung cancer diagnostics would have been increasingly delayed by at most 9 months for 0%, 5.0% (CI, 1.1% to 9.0%), 5.9% (CI, 1.7 to 10.1%), and 6.7% (CI, 2.2% to 11.2%) of the cases of cancer, respectively. In conclusion, they suggest that using a threshold of 7 or 8 mm to define positive results in the baseline round of computed tomography screening for lung cancer should be evaluated to determine if the beneficial effect of decreasing further work-up outweigh the consequent delay in diagnosis in some patients. Further larger scale studies are needed.

### Selection criteria for lung-cancer screening

**Authors:** Tammemagi MC, *et al.*

**Reference:** New Engl J Med, 2013, 368: 728-736

**URL:**

**Comments:** This publication discussed the selection criteria for lung cancer screening. PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial was compared with the NLST (National Lung Screening Trial), the former of which was a model (M2012) developed and validated with data from the 80,375 persons in the PLCO control and intervention groups who had ever smoked, and the latter used risk factors for lung cancer, e.g.,  $\geq 30$  pack-years of smoking and  $< 15$  years since quitting as the selection criteria. Discrimination (area under the receiver-operating-characteristic curve (AUC)) and calibration were assessed in this study. The accuracy of PLCO (M2012) to detect lung cancer was compared with NLST criteria: 14,144 of 37,332 persons (37.9%) fulfilled NLST criteria and 14,144 persons with the highest risk were considered positive according to the PLCO criteria; PLCO criteria were shown to have 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% vs. 62.7%,  $P = 0.54$ ); less than 41.3% of lung cancers were missed. The NLST screening effect did not vary according to PLCO risk. This study provides an accurate model that may be helpful in identifying more persons who have or will develop lung cancer.

### Using socio-demographic and early clinical features in general practice to identify people with lung cancer earlier

**Authors:** Iyen-Omofoman B, *et al.*

**Reference:** Thorax. 2013 Jan 15. doi: 10.1136/thoraxjnl-2012-202348

**URL:**

**Comments:** This study explores the predictive value of a risk prediction model in identifying people with lung cancer earlier using socio-demographic and clinical features. 12,074 cases of lung cancer and 120,731 controls in a large general practice database were studied. This model was developed using variables that were independently associated with lung cancer up to 4 months before diagnosis, and the model performance was assessed in an independent data set of 1,826,293 patients from the same database. A receiver-operating-characteristic (ROC) curve was adopted to assess the discrimination. This study showed that patient's age, sex, socioeconomic status and smoking history were the clinical and socio-demographic features that were independently associated with lung cancer. The study also showed that from 4 to 12 months before diagnosis, the frequency of consultations and symptom records of cough, haemoptysis, dyspnoea, weight loss, lower respiratory tract infections, non-specific chest infections, chest pain, hoarseness, upper respiratory tract infections and chronic obstructive pulmonary disease were also independently predictive of lung cancer. This new model performed much better than the current NIH and Clinical Excellence Referral Guidelines and all comparable models. It is predictive of lung cancer, making detection at a curable stage more likely by allowing the clinicians to better stratify their patients according to the risks. However, the absolute benefits to the patients and the cost effectiveness of this model in practice still need to be quantified by a clinical trial.

## Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial.

**Authors:** Horeweg N, *et al.*

**Reference:** Am J Respir Crit Care Med. 2013;1

**URL:** <http://ajrccm.atsjournals.org/content/early/2013/01/23/rccm.201209-1651OC.abstract>

**Comments:** : In this lung cancer computer tomography screening trial, 15,822 participants in European were followed by a volumetry-based screening strategy, stringent criteria for a positive screening and an increasing length of the screening .

All NELSON participants with screen-detected lung cancer in the first three rounds were included. Lung cancer stage at diagnosis, histological subtype, and tumor localization were compared between the screening rounds, the genders and with other screening trials. In the first three screening rounds, 200 participants were diagnosed with 209 lung cancers. 70.8% of the lung cancers were diagnosed at stage I, 8.1% at stage IIIB-IV and 51.2% were adenocarcinomas. They found there was no significant difference in cancer stage, histology or tumor localization across the screening rounds. Besides, in this study women were diagnosed at a significantly more favorable cancer stage than men. In further, to compare with other trials, the screen-detected lung cancers of the NELSON trial were relatively more often diagnosed at stage I and less often at stage IIIB-IV. As a result, they concluded that, the screening strategy they applied in the NELSON trial could improved early cancer stage distribution at diagnosis.

*APSR Respiratory Updates is an initiative of the APSR Education Committee*

*Articles selected and commented on by Prof. Chunxue Bai, Director, Shanghai Respiratory Research Institute, Shanghai, China*

*Director, Respiratory Research Institute, Fudan University, Shanghai, China*

*Editorial Board Member, American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Cell and Molecular Biology*

*and*

*Dr. Dawei Yang, MD*

*Shanghai Respiratory Research Institute, Shanghai, China*

*Coordinator: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China*

*Compiled by Dr Christel Norman, Respirology Editorial Office, Perth, Australia*

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**Asian Pacific Society of Respiriology**

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