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The Forum for Early Diagnosis and Treatment of Lung Cancer

John D. Mitchell, MD

Limited Resection for Non-Small Cell Lung Cancer

By John D. Mitchell, MD

The optimal treatment for early stage non-small cell lung carcinoma (NSCLC) in the medically fit patient is surgical resection, preferably anatomic lobectomy.[1] This recommendation is based on a landmark study conducted by the Lung Cancer Study Group (LCSG) that randomized 247 clinical stage IA patients to either lobectomy or sublobar (segment or wedge) resection. Published in 1995,[2] this report suggested the superiority of lobectomy with a three-fold improvement in loco-regional recurrence rates, and a trend (though not statistically significant) towards improved overall and disease-free survival. Although the findings were impressive, several criticisms of the LCSG trial emerged: the sample size was relatively small, tumors up to 3 cm were included, thus compromising sublobar resection techniques in some patients, and clinical staging was inexact, compared to modern standards. Despite these concerns, the LCSG study remains the only randomized trial comparing lobar with sublobar resection in patients with early stage NSCLC, and it firmly established lobectomy as the surgical standard of care.

However, do *all* patients with stage IA lung cancer require lobectomy? Since the publication of the LCSG report, a number of retrospective series comparing lobectomy and sublobar resection have demonstrated equivalent outcomes in *selected* patient populations.[3-7] Vast improvements in imaging technology have occurred, allowing for detection of very small (< 1 cm) lung cancers. In addition, improved diagnostic and staging techniques, along with a better understanding of the impact of pathologic factors on prognosis, have created a subset of patients with early stage disease for whom lobectomy may be excessive. The benefits of limited resection include the preservation of pulmonary function, enhanced quality of life, and ability to tolerate further resection in the event of a second primary lung cancer.

Certainly, some patients lack the cardiopulmonary reserve to undergo lobar resection, but when is *intentional* sublobar resection for early stage disease appropriate? In this brief review, I examine several factors that may impact outcomes in light of the extent of resection: tumor size, histology, patient age, and sublobar resection techniques.

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.

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Tumor Size

Tumor size within the stage IA subset has consistently been found to be an important prognostic variable and may allow for limited resection. Using data from the Surveillance, Epidemiology and End Results (SEER) registry, Wisnivesky and colleagues[8] found tumor size correlated directly with prognosis in patients who underwent curative resection for stage I disease. Using similar methods, Mery[9] reported significant improvement in survival in patients with tumors < 2 cm in size. Port and coworkers[10] found survival in patients with stage IA tumors < 2 cm significantly better than those with tumors > 2 cm and suggested subclassification of stage IA based on tumor size. In a separate report, Birim[11] demonstrated similar findings, also using a 2 cm size cutoff.

The improved survival in very small (< 2 cm) tumors suggests a lack of occult metastatic disease, and thus tumors < 2 cm may be more amenable to limited resection techniques. Okada and colleagues[12] examined the records of 1,272 consecutive patients with stage I disease and found tumor size, particularly if < 2 cm, to be an independent predictor of survival, with no difference in disease-free survival between those undergoing lobectomy or segmentectomy. In a separate study, Okada[13] found equivalent overall and disease-free survival between lobectomy and limited resection in 567 patients with tumors < 2 cm. A recent report from Kates and coworkers[14] using SEER data from over 2,000 patients demonstrated equivalent survival between lobectomy and segmentectomy in patients with NSCLC tumors < 1 cm in size. These and other studies support the role of limited resection in patients with small (< 2 cm) tumors.

Histology

A number of reports[15-21] have linked improved survival and lack of metastatic potential with certain pathologic factors, most notably adenocarcinoma in situ (previously known as bronchioloalveolar cell carcinoma), making these tumors potentially amenable to limited resection. "Pure" ground glass opacities seen on computed tomography imaging, corresponding to Noguchi type A or B tumors,[22] are associated with a 100% survival rate. A significant solid component within the tumor is suggestive of an invasive component and increasing metastatic potential. Strategies have focused on imaging features[15, 23-27] or intraoperative pathologic evaluation[28, 29] to identify tumors amenable to limited resection.

Patient Age

Several studies have suggested equivalent outcomes with either lobectomy or limited resection for elderly patients with NSCLC. Okami[30] reported no differences in overall or disease-free survival for patients > 75 years of age undergoing either lobectomy or segmentectomy for early stage disease (***Figure 1***). Kilic and colleagues[4] reported similar findings for patients > 75 years and found significantly reduced morbidity and mortality in the limited resection group. Using SEER data from more than 14,500 patients, Mery and coworkers[31] examined the effect of patient age on outcomes comparing lobectomy with sublobar resection for patients with early stage lung cancer. They found the survival benefit of lobectomy was lost at age > 71 years. Wisnivesky[32] reported outcomes of patients with tumors < 2 cm using the SEER registry for patients > 65 years of age, and found no differences in survival related to type of resection. These studies and others suggest the impact of other comorbid factors on patient survival in the elderly population that likely outweigh the influence of the extent of surgery on outcome.

Segmentectomy vs. Wedge Resection

Anatomic segmentectomy is clearly superior to wedge resection as an oncologic approach to early stage lung cancer. Segmentectomy allows for a wider margin around the primary tumor, and it resects the proximal lymphatic bed of the original tumor site in a fashion similar to that of lobectomy. Several studies[12, 33, 34] have demonstrated improved loco-regional recurrence rates with segmentectomy compared with non-anatomic wedge resection. Sienel and colleagues,[35] described significantly better survival and local recurrence rates with segmentectomy compared to wedge resection in 87 patients receiving sublobar resection because of severe cardiopulmonary impairment. Segmentectomy should be performed whenever possible if sublobar resection is planned in the stage IA patient.

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Figure 1. Postoperative Survival Curves According to Type of Surgery and Age

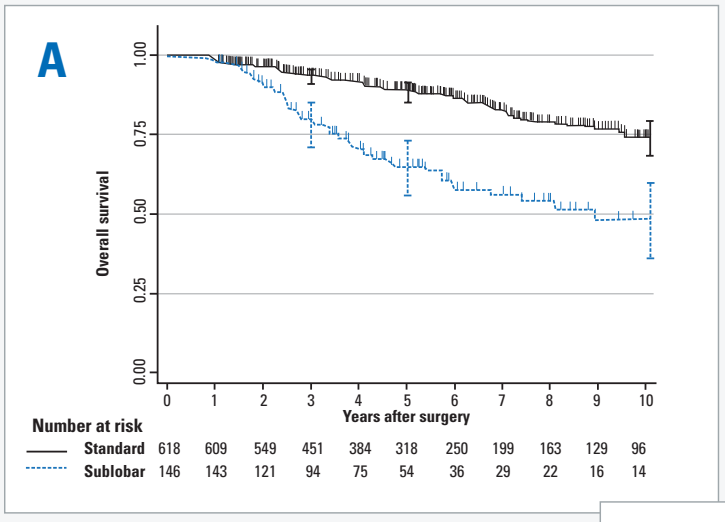
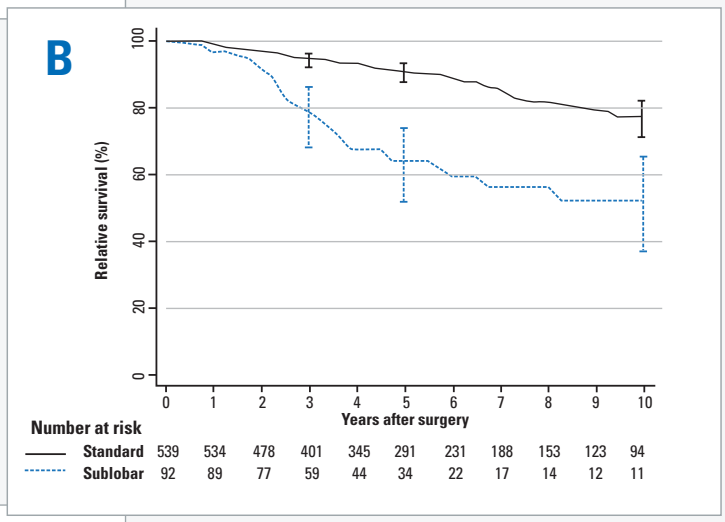
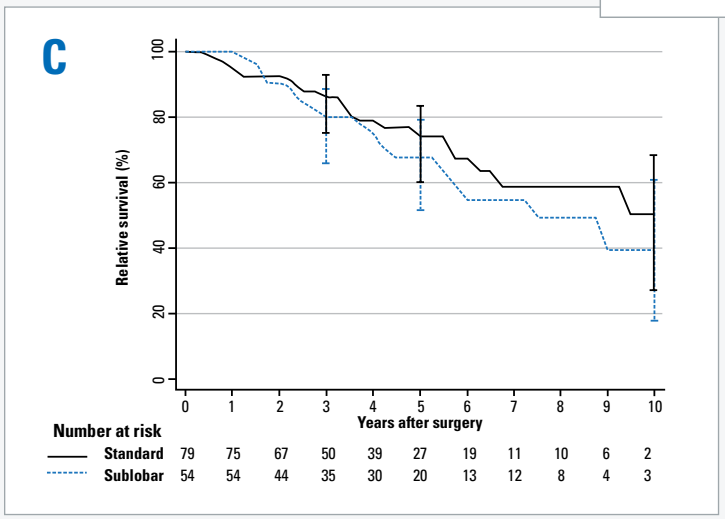


Figure 1. Postoperative survival curves according to the types of surgery (standard surgery or sublobar resection) with 95% confidence intervals at 3, 5, and 10 years after surgery. (A) The overall survival of the overall cohort (all ages); (B) the relative survival of the younger patients (< 75 years); and (C) the relative survival of the elderly patients (≥ 75 years). Reprinted with permission from reference 30.





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Summary and Future Directions

The use of anatomic lobectomy as a "one size fits all" treatment for stage IA lung cancer, based on the results of a single randomized clinical trial, may be excessive. The influence of tumor size, histology, and other patient factors including age may identify a subset of patients with early stage NSCLC whose tumors are suitable for intentional limited resection. To test this hypothesis, two new phase III studies are underway in the US (CALGB 140503)[36] and Japan (JCOG 0802)[37] that randomize patients with tumors < 2 cm in size to either lobectomy or sublobar resection. The results of these new trials will have a pivotal effect on the use of sublobar resection in patients with early stage lung cancer.

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Disclosures

Dr. Mitchell has served as a board member for Spiration, as a consultant for Maquet and Covidien, and he has developed educational presentations for Covidien.

Selections from the Peer-Reviewed Literature

By Jeffrey A. Kern, MD, Editor in Chief

***Jeffrey A. Kern, MD**, is Professor of Medicine, Chief of the Division of Oncology, and Vice Chair of the Department of Medicine at National Jewish Health. He established the Division of Oncology and the Thoracic Oncology program at National Jewish Health. He was named Editor in Chief of **Lung Cancer Frontiers** in January, 2010. He recently served on the Editorial Boards of the **Journal of Laboratory and Clinical Medicine** and the **Journal of Investigative Medicine**. His research interests include the role of the epidermal growth factor receptor family and other receptor tyrosine kinases in pulmonary tumorigenesis.*

MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer

Boeri M, Verri C, Conte D, Roz L, Modena P, Facchinetti F, Calabrò E, Croce CM, Pastorino U, Sozzi G; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy. *Proc Natl Acad Sci* USA 2011; 108:3713-8.

ABSTRACT: The efficacy of computed tomography (CT) screening for early lung cancer detection in heavy smokers is currently being tested by a number of randomized trials. Critical issues remain the frequency of unnecessary treatments and impact on mortality, indicating the need for biomarkers of aggressive disease. We explored microRNA (miRNA) expression profiles of lung tumors, normal lung tissues and plasma samples from cases with variable prognosis identified in a completed spiral-CT screening trial with extensive follow-up. miRNA expression patterns significantly distinguished: (i) tumors from normal lung tissues, (ii) tumor histology and growth rate, (iii) clinical outcome, and (iv) year of lung cancer CT detection. Interestingly, miRNA profiles in normal lung tissues also displayed remarkable associations with clinical features, suggesting the influence of a permissive microenvironment for tumor development. miRNA expression analyses in plasma samples collected 1-2 years before the onset of disease, at the time of CT detection and in disease-free smokers enrolled in the screening trial, resulted in the generation of miRNA signatures with strong predictive, diagnostic, and prognostic potential (area under the ROC curve ≥ 0.85). These signatures were validated in an independent cohort from a second randomized spiral-CT trial. These results indicate a role for miRNAs in lung tissues and plasma as molecular predictors of lung cancer development and aggressiveness and have theoretical and clinical implication for lung cancer management.

EDITORIAL COMMENT: This report describes the use of miRNAs as biomarkers to predict the development of lung cancer and guide therapy. miRNAs are small RNA molecules that regulate gene expression, and miRNA expression is remarkably tissue specific. As biomarkers, they could be useful because of their specificity, their deregulation in cancer, their remarkable stability even with tissue fixation, their presence in blood, and ease of measurement with simple assays, such as the quantitative real time polymerase chain reaction. Using two completed lung cancer screening trials as training and validation sets, subjects diagnosed with lung cancer in the training set had their miRNA expression profiled in tumor and adjacent normal lung tissue. Normal tissue and lung cancer differed significantly in their expression of 56 miRNAs. These differences could discriminate histology, growth rate, and disease-free survival.

Plasma samples from the same patients were then used to develop miRNA markers prior to and at the time of lung cancer diagnosis. One hundred miRNAs were found to be consistently expressed and were used to develop a panel of miRNAs to predict risk, diagnosis and prognosis. The markers developed in the training set were then applied to the validation set. miRNA signatures were found to identify a population at risk to develop lung cancer 1-2 years before the diagnosis of lung cancer (80% sensitivity, 90% specificity), and a signature was found to be diagnostic at the time of surgery (75% sensitivity, 100% specificity). Other associations were found between miRNA expression and

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disease aggressiveness and prognosis, but interpretation was limited by small sample size.

This study is remarkable for its comparison of normal and diseased lung tissue, its evaluation of plasma samples collected prior to and at the time of disease diagnosis, the use of training and validation sets for its class prediction studies, and extended follow-up. The identification of biomarkers as diagnostic and prognostic tools is an area of intensive study at the moment. We need to be able to identify patients at risk for lung cancer who may require CT screening, those who will not benefit from CT screening, and patients who might benefit from specific therapy, which was not addressed in this article. The miRNAs identified as important in this analysis belong to major pathways, lending biological plausibility to the findings. The identification of a different set of predictive miRNAs in tissue vs. plasma points out the high tissue specificity of miRNAs and suggests that the two pools of miRNA may carry different clinical information.

Considering the ease of plasma sampling and detection of miRNAs, and their remarkable stability, I anticipate that we will see many more studies exploring the concept of miRNAs as biomarkers.

International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma

Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, Garg K, Austin JH, Asamura H, Rusch VW, Hirsch FR, Scagliotti G, Mitsudomi T, Huber RM, Ishikawa Y, Jett J, Sanchez-Cespedes M, Sculier JP, Takahashi T, Tsuboi M, Vansteenkiste J, Wistuba I, Yang PC, Aberle D, Brambilla C, Flieder D, Franklin W, Gazdar A, Gould M, Hasleton P, Henderson D, Johnson B, Johnson D, Kerr K, Kuriyama K, Lee JS, Miller VA, Petersen I, Roggli V, Rosell R, Saijo N, Thunnissen E, Tsao M, Yankelewitz D; Memorial Sloan Kettering Cancer Center, New York, NY. *J Thorac Oncol* 2011; 6:244-85.

INTRODUCTION: Adenocarcinoma is the most common histologic type of lung cancer. To address advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma, an international multidisciplinary classification was sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. This new adenocarcinoma classification is needed to provide uniform terminology and diagnostic criteria, especially for bronchioloalveolar carcinoma (BAC), the overall approach to small nonresection cancer specimens, and for multidisciplinary strategic management of tissue for molecular and immunohistochemical studies.

METHODS: An international core panel of experts representing all three societies was formed with oncologists/pulmonologists, pathologists, radiologists, molecular biologists, and thoracic surgeons. A systematic review was performed under the guidance of the American Thoracic Society Documents Development and Implementation Committee. The search strategy identified 11,368 citations of which 312 articles met specified eligibility criteria and were retrieved for full text review. A series of meetings were held to discuss the development of the new classification, to develop the recommendations, and to write the current document. Recommendations for key questions were graded by strength and quality of the evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation approach.

RESULTS: The classification addresses both resection specimens, and small biopsies and cytology. The terms BAC and mixed subtype adenocarcinoma are no longer used. For resection specimens, new concepts are introduced such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas with either pure lepidic growth (AIS) or predominant lepidic growth with ≤ 5 mm invasion (MIA) to define patients who, if they undergo complete resection, will have 100% or near 100% disease-specific survival, respectively. AIS and MIA are usually nonmucinous but rarely may be mucinous. Invasive adenocarcinomas are classified by predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumors with nonmucinous BAC), acinar, papillary, and solid patterns; micropapillary is added as a new histologic subtype. Variants include invasive mucinous adenocarcinoma (formerly mucinous BAC), colloid, fetal, and enteric adenocarcinoma. This classification provides guidance for small biopsies and cytology specimens, as approximately 70% of lung cancers are diagnosed in such samples. Non-small cell lung carcinomas (NSCLCs), in patients with advanced-stage disease, are to be classified into

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more specific types such as adenocarcinoma or squamous cell carcinoma, whenever possible for several reasons: (1) adenocarcinoma or NSCLC not otherwise specified should be tested for epidermal growth factor receptor (EGFR) mutations as the presence of these mutations is predictive of responsiveness to EGFR tyrosine kinase inhibitors, (2) adenocarcinoma histology is a strong predictor for improved outcome with pemetrexed therapy compared with squamous cell carcinoma, and (3) potential life-threatening hemorrhage may occur in patients with squamous cell carcinoma who receive bevacizumab. If the tumor cannot be classified based on light microscopy alone, special studies such as immunohistochemistry and/or mucin stains should be applied to classify the tumor further. Use of the term NSCLC not otherwise specified should be minimized.

CONCLUSIONS: This new classification strategy is based on a multidisciplinary approach to diagnosis of lung adenocarcinoma that incorporates clinical, molecular, radiologic, and surgical issues, but it is primarily based on histology. This classification is intended to support clinical practice, and research investigation and clinical trials. As EGFR mutation is a validated predictive marker for response and progression-free survival with EGFR tyrosine kinase inhibitors in advanced lung adenocarcinoma, we recommend that patients with advanced adenocarcinomas be tested for EGFR mutation. This has implications for strategic management of tissue, particularly for small biopsies and cytology samples, to maximize high-quality tissue available for molecular studies. Potential impact for tumor, node, and metastasis staging include adjustment of the size T factor according to only the invasive component (1) pathologically in invasive tumors with lepidic areas or (2) radiologically by measuring the solid component of part-solid nodules.

EDITORIAL COMMENT: This landmark publication addresses the confusion that exists within the pathologic spectrum of lung adenocarcinoma subtype classification. This is a critical area, because improved understanding of the molecular pathogenesis of lung cancer, clinical trials and therapy now require exact molecular and pathologic classification. Agreement in tumor classification is essential to appropriately interpret results of trials, predict outcomes, and adequately inform patients. This reclassification proposal is unique in that it is a joint effort of pathologists, radiologists, molecular biologists, oncologists, pulmonologists, and surgeons. It defines criteria for pathologic diagnosis, yet conveys information important in patient management and specimen handling to obtain optimal information for immunohistochemical or molecular studies. It also defines an approach to small biopsies (transbronchial biopsies, fine needle aspirates, cytologic specimens).

The expert panel made a number of specific recommendations, the most significant of which I have summarized below, but many I don't discuss. For those I refer you to the entire document.

1. The term bronchioloalveolar cell (BAC) carcinoma should be discontinued.
2. The term adenocarcinoma in situ (AIS) should be used for small (< 3 cm) solitary adenocarcinomas with purely lepidic growth.
3. The term minimally invasive adenocarcinoma (MIA) should be used to describe small (< 3 cm) solitary adenocarcinomas with predominantly lepidic growth and an area of invasion < 0.5 cm.
4. Comprehensive histologic subtyping with assessment of histologic patterns semiquantitatively in 5% increments is recommended. Tumors should be classified according to the single predominant histologic pattern and the percentages of subtypes.
5. For small biopsies and cytology, NSCLC should be further classified into a more specific histologic type, such as adenocarcinoma or squamous cell carcinoma, whenever possible.
6. To guide therapy for patients with advanced lung adenocarcinoma, each institution should develop a multidisciplinary team that coordinates the optimal approach to obtain and process biopsy/cytology specimens in order to provide expeditious diagnostic and molecular results.
7. In patients with advanced lung adenocarcinoma, testing for *EGFR* mutations is strongly recommended.

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8. When an opacity in the lung adenocarcinoma spectrum is either a pure ground glass nodule or a part-solid nodule with a predominant ground-glass component by CT imaging, the term BAC should no longer be used, and the opacity should be classified using one of the new terms: adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), or lepidic predominant adenocarcinoma (LPA).

If widely accepted, these recommendations will have far-reaching effects on staging related to the proposed new concepts of AIS, MIA and LPA. One potential benefit of the recommended classification system is that therapy can be better tailored to the pathologic tumor type. For example, patients with correctly identified AIS may only require observation, whereas those with true adenocarcinoma will be considered for surgical resection, radiation, and/or chemotherapy.

Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries

Öberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A; Karolinska Institute, Stockholm, Sweden. *Lancet* 2011; 377:139-46.

BACKGROUND: Exposure to second-hand smoke is common in many countries but the magnitude of the problem worldwide is poorly described. We aimed to estimate the worldwide exposure to second-hand smoke and its burden of disease in children and adult non-smokers in 2004.

METHODS: The burden of disease from second-hand smoke was estimated as deaths and disability-adjusted life-years (DALYs) for children and adult non-smokers. The calculations were based on disease-specific relative risk estimates and area-specific estimates of the proportion of people exposed to second-hand smoke, by comparative risk assessment methods, with data from 192 countries during 2004.

FINDINGS: Worldwide, 40% of children, 33% of male non-smokers, and 35% of female non-smokers were exposed to second-hand smoke in 2004. This exposure was estimated to have caused 379,000 deaths from ischaemic heart disease, 165,000 from lower respiratory infections, 36,900 from asthma, and 21,400 from lung cancer. 603,000 deaths were attributable to second-hand smoke in 2004, which was about 1.0% of worldwide mortality. 47% of deaths from second-hand smoke occurred in women, 28% in children, and 26% in men. DALYs lost because of exposure to second-hand smoke amounted to 10·9 million, which was about 0.7% of total worldwide burden of diseases in DALYs in 2004. 61% of DALYs were in children. The largest disease burdens were from lower respiratory infections in children younger than 5 years (5,939,000), ischaemic heart disease in adults (2,836,000), and asthma in adults (1,246,000) and children (651,000).

INTERPRETATION: These estimates of worldwide burden of disease attributable to second-hand smoke suggest that substantial health gains could be made by extending effective public health and clinical interventions to reduce passive smoking worldwide.

FUNDING: Swedish National Board of Health and Welfare and Bloomberg Philanthropies.

EDITORIAL COMMENT: Though not solely dealing with lung cancer, this article for the first time assesses the worldwide burden of second-hand smoke measured as deaths and disability-adjusted life-years (DALYs). The World Health Organization gathered data from Africa, the Americas, and Europe. The exact amount of smoke exposure is difficult to determine in these retrospective studies and in studies where second-hand smoke is not directly measured. In this study, exposure was operationally defined as having parents who smoked, being exposed to a person who smokes indoors, having a spouse who smokes, or exposure to tobacco smoke at work, with further characterization by the number of cigarettes smoked by the smoker, the duration of exposure (years) and frequency of exposure (days/week). School-based surveys of children (Global Youth Tobacco Survey) as well as other national and multinational surveys were included for childhood exposure. For countries that did not have second-hand smoke exposure data, the data were modeled.

Overall, this study found that 40% of children, 33% of male non-smokers, and 35% of female non-smokers were exposed to second-hand smoke. The highest exposures were estimated in Europe, the western Pacific and part of Southeast Asia, with more than 50% of some populations exposed. The Americas and eastern Mediterranean regions were intermediate, while the lowest exposure rates were in Africa.

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Worldwide, 21,400 lung cancer deaths were attributed to second-hand smoke (3.5% of total deaths due to second-hand smoke), ranking below deaths from ischemic heart disease (63%), lower respiratory infections in children (27.4%), and adult asthma (5.9%). The disease burden from second-hand smoke was, surprisingly, not distributed equally across the studied populations, with women having the highest death rate attributable to second-hand smoke (47%), men the lowest (26%), and children intermediate (28%). The opposite proportions were seen in DALYs, with children having the largest disease burden (61%), men the lowest burden (16%), and women intermediate (24%).

Exposure to second-hand smoke remains extremely common. Geographic variations are most likely due to differences in the development of the tobacco industry and a lack of standard exposure policies. The information provided by this analysis is critical for policy makers and public health programs for their respective countries. Though the data can be criticized for its self-reporting nature, inexact attribution of smoke exposure, modeling of disease where necessary, and lack of underlying health data, it is ground breaking in its attempt to amass and integrate the existing available data to describe this significant problem. Less than 10% of the world population lives in areas with smoke-free laws. It is clear that smoke-free laws effectively reduce second-hand smoke exposure. Smoke-free legislation covering the workplace and public sites can reduce exposure to second-hand smoke in high risk areas (bars, restaurants) up to 90% and has reduced adult exposure to second-hand smoke as much as 60%. Considering the burden that second-hand smoke will add to the human and financial health care costs in developed and developing countries, this can be effectively addressed now through easily implemented policy decisions. Most importantly, the impact comes at no cost.

Disclosures

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

Lung Cancer Meetings and Symposia

Thomas L. Petty Aspen Lung Conference
54th Annual Meeting
COPD and Lung Cancer: Common Pathogenesis, Shared Clinical Challenges

June 8-11, 2011
Aspen, Colorado
With an emphasis on integration between basic, translational and clinical sciences, the meeting will focus on the underlying shared and unique mechanisms and clinical impact of the two diseases.
Abstract deadline is February 14, 2011.
Contact: Jeanne.Cleary@ucdenver.edu, or visit www.aspen-lungconference.org

IASLC 14th World Conference on Lung Cancer

July 3-7, 2011
Amsterdam, The Netherlands
Information: 2011worldlungcancer.org

12th International Lung Cancer Congress

August 11-14, 2011
Carlsbad, CA
Information: cancerlearning.com

AACR-IASLC Joint Conference: Lung Cancer

January 8-12, 2012
San Diego, CA
Information: aacr.org

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Learn how to recognize the history of NTM disease, differentiate the various types of NTM, and how to diagnose and treat NTM infections.

Featuring: Michael Iseman, MD, Charles Daley, MD and Shannon Kasperbauer, MD

September 15-17, 2011, Denver, CO

Sarcoidosis: A Review and Update*

This conference will address the latest genetic and environmental associations with sarcoidosis, and the diagnosis and management of pulmonary and extra-pulmonary sarcoidosis.

Featuring: Nabeel Hamzeh, MD, Lisa Maier, MD, MSPH, Cecile Rose, MD, MPH and Bibi Gottschall, MD

September 21, 2011, Denver, CO

*This activity has been approved for AMA PRA Category 1 Credit.

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