

## Editorial

# Histologic Evaluation of Bronchial Squamous Lesions: Any Role in Lung Cancer Risk Assessment?

Ignacio I. Wistuba

Departments of Pathology and Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Texas

Lung cancer is the leading cause of cancer deaths in the United States and worldwide, and the high mortality of this disease is primarily due to the fact that the majority of the lung cancers are diagnosed at advanced stages (1) when the options for treatment are mostly palliative. Experience with other epithelial tumors, such as uterine cervical, esophageal, and colon carcinomas, has shown that if neoplastic lesions can be detected and treated at their intraepithelial stage the cure rate can be improved significantly. Thus, to reduce the mortality of lung cancer, new techniques and approaches must be developed to diagnose and treat preinvasive lesions.

However, lung cancer represents an enormous challenge. From histopathologic and biological perspectives, lung cancer is a highly complex neoplasm (2), probably having multiple preneoplastic pathways (3). Lung cancer consists of several types, including small cell carcinoma (20%) and the non-small cell carcinoma types squamous cell carcinoma (30%), adenocarcinoma (including the noninvasive type of bronchioloalveolar carcinoma; 40%), and large cell carcinoma (10%; ref. 4). Lung cancer may arise from the major bronchi (central tumors) or from the distant airway bronchioles and alveoli (peripheral tumors) of the lung. Squamous cell carcinoma and small cell carcinoma usually arise centrally, whereas adenocarcinoma and large cell carcinoma usually arise peripherally. Because examination of the sputum and bronchoscopy specimens examines the central airways, whereas spiral computed tomography mainly detected peripheral tumors, different approaches are required for the detection of tumors in different compartments of the lung.

As with other epithelial malignancies, lung cancers are believed to arise after a series of progressive pathologic changes (preneoplastic lesions; ref. 5). Many of these preneoplastic changes are frequently accompanying lung cancers and may be present in the respiratory mucosa of smokers. Although the sequential preneoplastic changes have been defined for centrally arising squamous carcinomas of the lung, they

have been poorly documented for large cell carcinomas, adenocarcinomas, and small cell carcinomas. Mucosal changes in the large airways that may precede or accompany invasive squamous cell carcinoma include hyperplasia (basal cell hyperplasia and goblet cell hyperplasia), squamous metaplasia, different grades (mild, moderate, and severe) of squamous dysplasia, and carcinoma *in situ* (4). Whereas hyperplasia and squamous metaplasia are considered reactive and reversible changes, dysplasias and carcinoma *in situ* are the changes most frequently associated with the development of squamous cell lung carcinomas. To improve bronchoscopic detection of the squamous preneoplastic lesions of the bronchial tree, laser-induced fluorescence bronchoscopy has been developed to detect high-grade carcinoma (moderate to severe) and carcinoma *in situ* by tissue autofluorescence (6, 7). Several studies have shown that the use of fluorescent bronchoscopy improves the detection rate of high-grade squamous preneoplastic changes compared with standard white light bronchoscopy (6, 8).

In the last decade, several studies have provided some information regarding the molecular characterization of the premalignant changes involved in the squamous carcinoma pathway (reviewed in ref. 3). The current working model of the sequential molecular abnormalities in the pathogenesis of squamous cell lung carcinoma indicates that (a) genetic abnormalities commence in histologically normal epithelium and increase with increasing severity of histologic changes (9); (b) mutations follow a sequence, with allelic losses at multiple 3p chromosome sites as the earliest detected change (10, 11); (c) molecular changes in the respiratory epithelium are extensive and multifocal throughout the bronchial tree of smokers and lung cancer patients, indicating a field effect (“field cancerization”) by which much of the respiratory epithelium has been mutagenized, presumably from exposure to tobacco-related carcinogens (12, 13); and (d) multiple clonal and subclonal patches of molecular abnormalities (not much larger in size than the average bronchial biopsy obtained by fluorescent bronchoscopy) can be detected in the normal and slightly abnormal bronchial epithelium of patients with lung cancer (14). Despite all this knowledge, histopathologic evaluation remains as the “gold standard” end point for lung cancer risk assessment, chemoprevention monitoring, and early detection strategies.

In the January 15<sup>th</sup> issue of *Clinical Cancer Research*, Breuer et al. (15) report a longitudinal study addressing the natural histopathologic course of squamous preneoplastic lesions in bronchial epithelium obtained using white light and fluorescent bronchoscopy examinations. Although similar studies on the natural history of lung squamous preneoplastic lesions have been done in the past using sputum and tissue specimens, the relatively lack of information on this important issue makes

Received 10/21/04; accepted 10/27/04.

**Grant support:** NIH Grant 1PO1 CA91844-03.

**Requests for reprints:** Ignacio I. Wistuba, Departments of Pathology and Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Box 85, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-563-1659; Fax: 713-745-5493; E-mail: iiwistuba@mdanderson.org.

©2005 American Association for Cancer Research.

this report significant. Breuer et al. have taken the enormous task of performing repeated longitudinal bronchoscopy examinations ( $n = 237$ ) and histologic sampling ( $n = 483$ ) on 52 individuals at risk of harboring lung preneoplastic lesions during several years. Using the latest WHO histologic classification for squamous preneoplastic lesions of the bronchus, they examined the progression, regression, and stabilization rate of squamous metaplasia; mild, moderate, and severe dysplasias to carcinoma *in situ*; and invasive squamous carcinoma. The four major findings of their study are as follows: (a) progression rate to carcinoma *in situ* and invasive carcinoma was significantly higher in severe dysplasia (32%) lesions compared with metaplasias (4%) and low-grade dysplasias (9%); (b) however, when analyzed by subjects, the rates of progression to carcinoma *in situ* and invasive carcinoma rate were not significantly higher (39%) in individuals harboring at least one severe dysplastic lesion compared with individuals having only lower-grade lesions (26%); (c) progression to carcinoma *in situ* and invasive carcinoma (9% of lesions) from squamous metaplasia and low-grade dysplasias (mild and moderate) was detected, suggesting that a stepwise histopathologic multistage development of lung carcinoma does not always occur or it is not always detected because rapid progression; and (d) surprisingly, current smoking status did not influence the incidence of higher-category dysplastic lesions and the progression to *in situ* and invasive carcinoma. Based on these findings, the authors concluded that the histologic classification of preneoplastic squamous lesions of the bronchial epithelia cannot be reliably used for accurate risk assessment of field carcinogenesis, because histologic grading cannot differentiate the true potential malignant of preneoplastic squamous lesions. Thus, based on the findings of this study and in the results obtained in several chemoprevention studies on lung, it is clear that other types of biomarkers, including molecular and genetic markers, are needed (16).

This study also poses very important questions in the field of biomarkers for lung cancer risk assessment. First, what is the best type(s) of biomarker(s) to address the risk of developing lung squamous cell carcinoma? Second, if those biomarkers are not histologic or cytologic evaluations, do we really have alternative biomarkers of use for predicting any histologic type of lung cancer? Unfortunately, the answers to both questions are not very encouraging. The definition of a predictive biomarker includes cost-effectiveness as well as good reproducibility, acceptable sensitivity, and specificity. Although histologic grading of squamous dysplastic changes is still be used as a “gold standard” to address the malignant potential of those lesions, experienced pathologists know that the reproducibility of such a grading system is not high. As it has been shown by Breuer et al. (15), histologic evaluation (with acceptable reproducibility data) is good enough to predict progression to *in situ* and invasive squamous carcinoma at foci level but not at the subject level. On the other hand, the molecular counterpart has not made enough progress to postulate any reliable marker. During the last decade, encouraged by the recent development of methodologies for isolation of cells from small histologic lesions, such as laser microdissection, combined with techniques to perform genomic studies from minute amount of DNA and

RNA, several groups have made substantial progress on unveiling the molecular and genetic abnormalities of lung cancer precursor lesions, including those evolving to squamous cell carcinoma (reviewed in 3). However, it seems that the enthusiasm has vanished. In the last few years, little progress has been added in the field even for the more accessible and better-characterized bronchial squamous lesions. The recent development of new high-throughput genomic (17) and proteomic (18, 19) profiling techniques that can be applied to small amount of microdissected tissues may stimulate the scientific community to perform innovative investigations in the fields of molecular and pathology research to understand the molecular malignant potential of respiratory epithelium even before histologic changes occur. Currently, two major National Cancer Institute programs, Specialized Programs of Research Excellence and Early Detection Research Network, are concentrating on a search for new biomarkers in lung (and other) cancers. All those new efforts may help to better characterize the malignant potential of lung cancer preneoplastic lesions and understand the field cancerization compartmental (central versus periphery) phenomenon in lung cancer pathogenesis. Studies, such as those by Breuer et al. (15) reported in this issue of *Clinical Cancer Research*, provide invaluable samples from well-characterized cohort of individuals that can be used to test future promising molecular markers.

## ACKNOWLEDGMENTS

I thank Adi F. Gazdar for helpful suggestions.

## REFERENCES

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15–36.
- Minna JD, Gazdar A. Focus on lung cancer. *Cancer Cell* 2002;1:49–52.
- Wistuba II, Mao L, Gazdar AF. Smoking molecular damage in bronchial epithelium. *Oncogene* 2002;21:7298–306.
- Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new WHO classification of lung tumours. *Eur Respir J* 2001;18:1059–68.
- Colby TV, Wistuba II, Gazdar A. Precursors to pulmonary neoplasia. *Adv Anat Pathol* 1998;5:205–15.
- Lam S, leRiche JC, Zheng Y, et al. Sex-related differences in bronchial epithelial changes associated with tobacco smoking. *J Natl Cancer Inst* 1999;91:691–6.
- Kennedy TC, Lam S, Hirsch FR. Review of recent advances in fluorescence bronchoscopy in early localization of central airway lung cancer. *Oncologist* 2001;6:257–62.
- Hirsch FR, Prindiville SA, Miller YE, et al. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study. *J Natl Cancer Inst* 2001;93:1385–91.
- Wistuba II, Behrens C, Milchgrub S, et al. Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. *Oncogene* 1999;18:643–50.
- Wistuba II, Behrens C, Virmani AK, et al. Allelic losses at chromosome 8p21-23 are early and frequent events in the pathogenesis of lung cancer. *Cancer Res* 1999;59:1973–9.
- Wistuba II, Behrens C, Virmani AK, et al. High resolution chromosome 3p allelotyping of human lung cancer and preneoplastic/preinvasive bronchial epithelium reveals multiple, discontinuous sites of 3p allele loss and three regions of frequent breakpoints. *Cancer Res* 2000;60:1949–60.

12. Mao L, Lee JS, Kurie JM, et al. Clonal genetic alterations in the lungs of current and former smokers. *J Natl Cancer Inst* 1997;89:857–62.
13. Wistuba II, Lam S, Behrens C, et al. Molecular damage in the bronchial epithelium of current and former smokers. *J Natl Cancer Inst* 1997;89:1366–73.
14. Park IW, Wistuba II, Maitra A, et al. Multiple clonal abnormalities in the bronchial epithelium of patients with lung cancer. *J Natl Cancer Inst* 1999;91:1863–8.
15. Breuer RH, Pasic A, Smit EF, et al. The natural course of preneoplastic lesions in bronchial epithelium. A longitudinal study. *Clin Cancer Res* 2005;11:537–43.
16. Hirsch FR, Franklin WA, Gazdar AF, Bunn PA Jr. Early detection of lung cancer: clinical perspectives of recent advances in biology and radiology. *Clin Cancer Res* 2001;7:5–22.
17. Kobayashi K, Nishioka M, Kohno T, et al. Identification of genes whose expression is upregulated in lung adenocarcinoma cells in comparison with type II alveolar cells and bronchiolar epithelial cells *in vivo*. *Oncogene* 2004;23:3089–96.
18. Melle C, Ernst G, Schimmel B, et al. A technical triad for proteomic identification and characterization of cancer biomarkers. *Cancer Res* 2004;64:4099–104.
19. Yanagisawa K, Shyr Y, Xu BJ, et al. Proteomic patterns of tumour subsets in non-small-cell lung cancer. *Lancet* 2003;362:433–9.