**Editorial**

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

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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 carcinomas 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 15th 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...
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 \textit{in situ}; and invasive squamous carcinoma. The four major findings of their study are as follows: (a) progression rate to carcinoma \textit{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 \textit{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 \textit{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 \textit{in situ} and invasive carcinoma. Based on these findings, the authors concluded that the histologic classification of preneoplastic squamous lesions of the bronchial epithelium 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 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 is has been shown by Breuer et al. \((15)\), histologic evaluation \((with acceptable reproducibility data)\) is good enough to predict progression to \textit{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 \textit{Clinical Cancer Research}, provide invaluable samples from well-characterized cohort of individuals that can be used to test future promising molecular markers.

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