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Is Lung Cancer in the Nonsmoker a Different Disease?

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levels of VEGF-C were not significantly different between the group of patients with N1 nodal metastases (in whom surgery is still beneficial), and those with N2 nodal metastases (in whom surgery has not demonstrated significant benefit). The most valuable finding of Tamura and coworkers was that classifying patients into quartiles based on serum levels of VEGF-C increased the accuracy of CT criteria alone in determining the presence or absence of lymph node metastases. However, the authors did not examine the ability of this approach to distinguish N1 and N2 lymph node involvement. Additionally, since these results are based on a retrospectively determined cutoff of VEGF-C levels, this must be viewed as a hypothesis-generating study. Prospective validation of these findings is necessary in a broader range of patients. Finally, given the increasing use of fluorodeoxyglucose (FDG) positron emission tomography (PET) in the preoperative evaluation of patients with suspected lung cancer, it is disappointing that this study did not address whether serum measurements of VEGF-C could add to the accuracy of PET scanning. It is doubtful that VEGF-C levels could significantly improve on the sensitivity of PET scanning (97%). However, it would be intriguing to determine the ability of serum VEGF-C levels, or other biomarkers, to improve on the specificity of FDG-PET (approximately 78%).⁹

In pointing out these shortcomings, it is important to consider that any successful approach to this problem may eventually involve multiple markers that, like VEGF-C, reflect a known feature of the tumor biology (angiogenesis, apoptotic resistance, unrestricted growth, stroma formation). In addition to markers of activated lymphatic endothelium, other rational biomarkers may reflect "tumor-specific" antigens, angiogenic factors, growth factors, or markers of stromal activation. Such a multivariate approach may provide important information in the management of patients that is not possible with a single variable. Tamura and colleagues are to be congratulated for bringing some focus to the search for novel lung cancer biomarkers, but much work remains to be done.

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Is Lung Cancer in the Nonsmoker a Different Disease?

Cigarette smoking is without any doubt the leading cause of preventable death in the United States. The health-related economic loss associated with cigarette smoking is approximately \$157 billion, and 440,000 premature deaths occur annually only in this country.¹ Worldwide, 10 million people will die annually from tobacco-attributable diseases by 2030.² Eighty percent of the particle products of *Nicotiana tabacum* liberated through a lit cigarette deposit in the tracheobronchial tree. At least 55 of the > 2,000 chemical compounds identified in the tobacco leaf are proven carcinogens.³ The epidemiologic evidence accumulated over almost 6 decades since the reports of Doll and Hill^{4,5} prove an association between smoking and lung cancer. Tobacco smoke has a causal role as well in the tragic worldwide epidemic of lung cancer. Tobacco products not only cause harm to the users, but nonusers are affected as well (environmental tobacco exposure).

Tobacco smoking exposure is associated with all of the histologic subtypes of lung cancer.⁶ Patients who

acquire adenocarcinoma, the most common subtype of lung cancer,⁷ are at least as susceptible to the different carcinogens present in the tobacco smoke. Furthermore, patients with adenocarcinoma had less smoking exposure (fewer pack-years) and a prolonged excess risk after smoking was stopped (longer time since quitting smoking).⁶

Although TNM classification and morphologic status may be indicative of prognosis, it is difficult to predict which surgically managed patient is at risk for early relapse, or which rare patient with advanced stage disease may experience prolonged survival. Furthermore it is not possible, at this time, to predict likelihood of response to a particular treatment based on any morphologic or molecular variables. A systematic review⁸ investigating patients and tumor factors predictive of survival in non-small cell lung cancer identified 887 articles published between January 1990 and July 2001, examining 169 different prognostic factors. This highlights not only the importance, but also the complexity of reaching a uniformly applicable, clinically useful prognostic model for non-small cell lung cancer. With the evolution of targeted therapies for cancer, a better understanding of tumorigenesis and genetic changes leading to the cancer phenotype is essential.

There is also a clear need for a clinically available prognostic model for survival and response, by which patients can be stratified into different categories when enrolled into clinical trials. In this context, the study by Nordquist et al published in this issue of *CHEST* (see page 347) is important. The authors attempted to compare patient characteristics and survival between current smokers and never-smokers with adenocarcinoma of the lung. They postulated that differences found in the natural history of adenocarcinoma of the lung would serve as further evidence that the tumor biology is different in these groups. Their study showed that never-smokers with adenocarcinoma of the lung are older, more often female, have a higher proportion of bronchoalveolar cell histology, and have better overall and cancer-specific survival when compared to current smokers. Smoking was an independent negative prognostic factor.

This study was a well-performed evaluation of a pertinent question. However, interpretation of these results first requires the reader to determine the validity of the reported differences in the characteristics and natural history of the groups studied, and we must evaluate whether the differences are suggestive enough to be used as a surrogate marker of differences in tumor biology. When assessing the validity of the reported differences, a few things should be considered. Patient characteristics—age, sex—were clearly different between the groups stud-

ied. Internally, the self-reported nature of smoking status could affect validity. Externally, the population studied appears different than commonly encountered in practice, with more women than men reported in the current smoking group as well as the never smoking group. All factors that could influence the natural history were not considered, the most important of these being performance status and treatments received. It is well established that these factors are important determinants of survival.^{9,10} It is also reasonable to postulate that they may differ between active smokers and never-smokers. Other prognostic factors, including small differences in stage distribution as well as differences in the proportion of bronchoalveolar cell histology,¹¹ and sex, were well described in the study and controlled for in multivariate analyses. Including former smokers, although adding complexity, may have influenced the conclusions drawn about the meaning of apparent differences in natural history. Thus, this study is unable to stand alone to establish differences in tumor biology, but must be evaluated in the context of other work in this area. Assuming the above points do not influence the results, it is not unreasonable to suspect that differences in natural history are related to differences in tumor biology; in this regard, the current study is in keeping with others who have evaluated similar epidemiologic questions.¹² There is also a growing body of literature on differences in tumor biology between smokers and never-smokers.

Identifying smoking history as an independent prognostic factor in patients with adenocarcinoma of the lung could point out the difference in tumors arising in smokers compared to those in nonsmokers. A high susceptibility to smoking-related lung cancer has been associated with CYP1A1 polymorphism status. This gene is responsible for the metabolic activation of benzopyrene found in cigarette smoke. In addition, the susceptible genotype is associated with higher recurrence rates and lower survival rates.¹³

It is possible that lung carcinomas in smokers and never-smokers may arise via distinct pathogenetic mechanisms. Genetic analyses have revealed that widespread chromosomal abnormalities are frequent in lung adenocarcinoma in smokers but are infrequent in never-smokers.^{14–16} The differences in smokers are most likely due to direct repeated exposure to tobacco-related carcinogens such as benzopyrene and N-nitrosamines, which are known to induce widespread genetic damage. Such a genetic environment would lead to alteration of important oncogenes and tumor suppressor genes, thus allowing tumor progression and possibly leading to tumor resistance. In nonsmokers, the frequency of chromosomal instability per tumor is significantly

lower compared with tobacco-related tumors.¹⁴ Loss of heterozygosity on chromosomes 9p and 17p, likely targeting the p16 and p53 genes respectively, are observed far more frequently in tobacco-induced tumors. Also, a high frequency of alteration on chromosome 19 was observed in smokers, pointing to the existence of an important tumor suppressor gene on that chromosome.^{14,17} Loss of heterozygosity at chromosome 3p21.3 is one of the most common and one of the earliest events that occur in the pathogenesis of lung cancer.^{18–20} RASSF1A (Ras association domain family 1A) gene is a candidate tumor suppressor gene at 3p21.3. Kim et al²¹ found that early age smoking is associated with hypermethylation of the RASSF1A promoter, and is an independent poor prognostic factor in non-small cell lung cancer.

Studies^{22,23} of candidate genes, *eg*, p53 and *K-ras*, in malignant lung tumors from smokers and non-smokers have identified significant differences in their mutational spectra, suggesting that different molecular carcinogenic pathways are involved in their development. One of the most well-characterized cigarette oncogenes is *K-ras*, a downstream component of the epidermal growth factor receptor cascade.²⁴ However, activating *K-ras* mutations are found very rarely in never-smokers with primary adenocarcinomas.²⁵ In a study of patients with bronchoalveolar cell cancer (the least of lung cancer tumor types to be linked to smoking), only 2 of 20 tumors were found to have *K-ras* mutation; both tumors were derived from patients with significant smoking histories.²⁶ Thus, adenocarcinoma in smokers and nonsmokers represent a heterogeneous group of genetically different entities. This difference could result in the observed difference in survival observed by Nordquist et al.

More complicated, however, is the interaction of a specific treatment effect with a potential prognostic indicator. Do smokers and never-smokers respond to treatment differently? Clearly, that may be the case. For instance, amplification of PI3-K α , an antiapoptotic protein occurs in association with smoking in squamous cell carcinoma of the head and neck, is associated with resistance to the chemotherapeutic agent, cisplatin.²⁷ Miller et al²⁸ recently reported a response rate of 38% to the epidermal growth factor receptor inhibitor gefitinib, among lung cancer patients who never smoked, compared to 8% among smokers ($p < 0.001$). Because tumors in never-smokers seem to be less genetically complex than their counterparts in smokers, they may be more dependent on signaling through one or a few critical signaling pathways for tumor maintenance and survival.

Given the lack of a ready approach to identify a molecular fingerprint associated with prognosis and response to various therapies, a clinical profile or

characteristic that could predict response to a specific treatment is very useful. The report by Nordquist et al further highlights the importance of stratification of patients for smoking history in future clinical trials. Applying a validated instrument to record smoking history in patients participating in clinical trials of lung cancer is essential.

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Dutch Hypothesis

Revisited?

Bronchoreversibility in COPD has remained a matter of debate ever since the known association of tobacco smoking with its pathogenesis and

progression. What has remained enigmatic is the observation that not all smokers demonstrate a similar susceptibility to the decline in lung function and that bronchoreversibility in COPD patients is demonstrable only in a subgroup of patients. However, it is important to identify this subgroup of patients for making treatment decisions.

It has been proposed¹ that smokers with an allergic diathesis have a greater predisposition to develop severe and chronic airflow obstruction, what was popularly known as the “Dutch hypothesis.” Airway narrowing developed in hyperreactive individuals as the primary abnormality as a result of exposure to smoking or other environmental pollutants. This was contrary to the “British hypothesis,” which proposed chronic mucus hypersecretion as a marker of recurrent bronchial infections leading to chronic obstruction of the airways.² However, the infection hypothesis has been shown to be misconstrued by the findings of several subsequent reports.³ There was no demonstrable relationship shown between exacerbations of infections or their treatment and lung function decline.^{3,4}

The Dutch hypothesis supported an implied relationship of asthma with COPD. Despite the known differences between COPD and asthma, smokers who show accelerated decline in FEV₁ have marked similarities with asthma patients. There were earlier reports^{5,6} on demonstrable bronchial hyperreactivity, peripheral blood eosinophilia, and raised serum IgE levels in smokers compared to nonsmokers. Furthermore, the presence of eosinophils in peripheral blood was also shown to correlate with ventilatory impairment.⁵ Similar observations have been made in several studies.^{7,8} Eosinophilic inflammation of the airways in patients thus has been clearly defined in a subset of COPD patients. This is also the group of patients who are likely to show reversibility of airway obstruction with therapy with bronchodilators and/or antiinflammatory drugs, such as the corticosteroids.⁹

In this issue of *CHEST* (page 375), Perng et al have reported a significant relationship of bronchodilator reversibility in smoking-related COPD patients with sputum eosinophilia. Nonreversibility was associated with raised levels of neutrophils interleukin-8 and albumin in the sputum. It has been proposed that the assessment of inflammatory characteristics of induced sputum can be used to assess the bronchodilatory responsiveness in COPD patients.

Inflammation in COPD patients is complex and relatively more poorly understood than in asthma patients. The presence of inflammatory cells, proteolytic enzymes, and oxidative stress results in continued damage to the airways as well as to the alveolar

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