Lung Cancer and the Debrisoquine Metabolic Phenotype

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In a case–control study, we tested the hypothesis that the genetically determined ability to metabolize debrisoquine is related to risk of lung cancer. Overall, individuals who were extensive metabolizers of debrisoquine were at significantly greater risk of lung cancer than those who were poor or intermediate metabolizers (odds ratio = 6.1; 95% confidence interval = 2.2–17.1). In this study, case patients had lung cancer, and control subjects had either chronic obstructive pulmonary disease or cancers other than lung cancer. Results were adjusted for age, race, asbestos exposure, and smoking. Both black and white individuals who were extensive metabolizers of debrisoquine were at significantly increased risk after similar adjustment (for blacks, odds ratio = 4.5, 95% confidence interval = 1.1–18.1; for whites, odds ratio = 10.2, 95% confidence interval = 2.0–51.4). Significantly increased risk of lung cancer was also present for individuals who were extensive metabolizers when subjects with chronic obstructive pulmonary disease or other cancers were considered separately. These data confirm that the ability to metabolize debrisoquine is a major determinant of susceptibility to lung cancer. Evaluation of the marker in other case–control settings, further exploration of racial differences, and the prospective evaluation of this marker in subgroups at high risk of lung cancer are areas worthy of further study. [J Natl Cancer Inst 82:1264–1272, 1990]

While exposure to tobacco smoke is widely accepted as the major etiologic factor in lung cancer, differences in individual susceptibility have been inferred from the observation that only a minority of cigarette smokers have diagnoses of lung cancer (*1,2*). Variation in the ability to metabolize xenobiotics has been considered as a possible explanation for this phenomenon (*3*), and this hypothesis is consistent with family and twin studies (*4–6*), as well as cytogenetic and molecular investigations (*7–12*) that have indicated a role for genetic predisposition in lung cancer etiology.

The metabolism of the antihypertensive drug debrisoquine is under autosomal genetic control (*13–15*), and inheritance of the trait conferring ability to "extensively" metabolize the drug has been suggested as a host susceptibility factor for lung cancer (*16,17*). In an earlier study comparing patients with lung cancer and patients with chronic obstructive pulmonary disease, white, British cigarette smokers with the extensive debrisoquine-metabolizer phenotype were at higher risk of developing bronchial carcinoma than were intermediate and poor metabolizers of the drug. One concern in interpreting these data was the use of subjects with chronic obstructive pulmonary disease as a sole comparison group. Other studies considering this association have produced conflicting results (*18,19*) or have attracted criticism of the epidemiologic methods (*20,21*).

To examine the hypothesis of an association of risk of lung cancer with the ability to metabolize debrisoquine, we conducted a formal epidemiologic case–control study. We used two separate comparison groups and adjusted results for recognized risk factors for lung cancer. This work focuses on the assessment of genetically determined differences in the ability to metabolize debrisoquine as an approach to elucidating a genetic component of lung cancer susceptibility.

Subjects and Methods

Subjects

Patients with histologically confirmed lung cancer who had not yet received radiation or chemotherapy were identified at the University of Maryland Hospital and the Baltimore Veterans

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