SOUTHWESTERN NEWS

EMBARGOED FOR RELEASE 4 P.M. EDT SEPTEMBER 16

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RESEARCHERS FIND THAT GENETIC CHANGES PERSIST IN FORMER SMOKERS

Dallas — September 17, 1997 — Current and former smokers are not so different after all. Although the appearance of lung tissue in smokers fairly rapidly returns to normal once they cease smoking, molecular changes in their DNA do not.

Dr. Adi Gazdar, professor of pathology at UT Southwestern Medical Center at Dallas, and his colleagues detected genetic changes commonly found in lung-cancer tumors in noncancerous lung tissue from both current and former smokers. In fact, they could not distinguish between the two groups. Lung tissue from nonsmokers showed no genetic changes. Results of the study, conducted by investigators at UT Southwestern and the British Columbia Cancer Agency in Vancouver, are published in today's *Journal of the National Cancer Institute*.

The researchers believe that lung cancer is the culmination of a multistep process in which genetic lesions progressively accumulate in lung cells. They want to identify the early molecular changes, or markers, that may indicate risk of lung-cancer development.

In the present study the investigators examined lung epithelial tissue from 63 current smokers, former smokers and nonsmokers. After microscopically separating out multiple normal and suspicious areas from each patient, they examined the samples for the loss of genetic material at eight chromosomal regions frequently deleted in lung-cancer tumors. They also looked for signs of genetic instability by checking for microsatellite alterations, which are changes in the number of simple DNA (deoxyribonucleic acid) repeats.

Lung specimens were assigned to one of five pathologic categories from normal to precancerous. Smokers had the entire range of pathological changes seen prior to the development of a lung-cancer tumor. Only 4 percent of specimens from current smokers

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were normal, and 25 percent of former smoker specimens were normal. Of the specimens from nonsmokers, 97 percent were normal or only slightly abnormal.

Eighty-six percent of smokers had genetic loss at one or more chromosomal regions. Even in specimens with a normal appearance, about half showed loss of genetic material. The most common losses were found on the short arms of chromosome 3 and chromosome 9, thereby indicating that genetic loss in these regions may be relatively early events in the development of lung cancer. At least one microsatellite change was detected in 64 percent of smokers. Not a single specimen from nonsmokers showed any genetic change.

The authors found genetic changes present throughout the lungs of the vast majority of smokers. These results indicate that such changes, which are not present in lifetime nonsmokers, persist for many years after smoking cessation.

"It is apparent from these studies that the vast majority of heavy smokers, both current and former, have sustained extensive molecular damage to their lungs, and that these changes persist for many years, perhaps for life. We are currently exploring whether these changes can be reversed by various chemoprevention agents such as retinoids. These changes may also be useful for risk assessment, so as to determine which smokers are at highest risk for developing lung cancer," said Gazdar, holder of the W. Ray Wallace Distinguished Chair in Molecular Oncology Research.

Other UT Southwestern investigators participating in the study were Drs. Ignacio Wistuba, Carmen Behrens and Kwun Fong, all in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research; Dr. Arvind Virmani, instructor of pathology; and Dr. John Minna, director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics and the Hamon Center. He holds the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology, the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research and the Lisa K. Simmons Distinguished Chair in Comprehensive Oncology. Drs. Stephen Lam, Jean LeRiche, Jonathan Samet and Sudhir Srivastava were the researchers at the British Columbia Cancer Agency.

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