Characteristics of lung cancers arising in germline EGFR T790M mutation carriers

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Two studies are providing new insight into germline epidermal growth factor receptor (EGFR) T790M mutation in familial non-small cell lung cancer (NSCLC). The findings suggest the need for tailored approaches for early detection and treatment, as well as for genetic testing to identify carriers.

"These studies now solidify the fact that routine clinical management of lung cancer now has to include the awareness of this inherited cancer syndrome," wrote David P. Carbone, MD, PhD, President-Elect of the International Association for the Study of Lung Cancer (IASLC), in an editorial. The editorial accompanies the two articles in the April issue of the *Journal of Thoracic Oncology*, the official journal of the IASLC.

In one of the two studies, researchers found that germline EGFR T790M mutation results in a rare and unique lung cancer hereditary syndrome associated with an estimated 31% risk for the disease in never-smokers. Lead author Adi Gazdar, MD, of the Department of Pathology, UT Southwestern Medical Center, Dallas, TX, and colleagues studied a family with germline EGFR T790M mutations over five generations (14 individuals) and combined their observations with data obtained from a literature search (15 individuals). They found that the mutation occurred in approximately 1% of NSCLCs and in less than one in 7,500 subjects without lung cancer.

Female never-smokers were overrepresented in the family cohort. Among 13 patients for whom gender and smoking status were known, nine were female never-smokers, two were male never-smokers, and two were ever-smokers (one male and one female).

"The risk of lung cancer development in never-smoking carriers is greater than the risk of heavy smokers with or without the mutation," says Dr. Gazdar, who is an IASLC member. "Unaffected carriers with this mutation are at increased risk for the development of lung cancer irrespective of their smoking status and should be followed by increased surveillance, including low-dose computed tomography," he adds.

The cancers associated with germline EGFR T790M mutations share several similar features with lung cancers containing sporadic EGFR mutations, such as a predominance for adenocarcinoma histology, female gender, and never-smoking status. However, a difference with lung cancers having sporadic EGFR mutations is a predominance for white ethnicity (compared with East Asian).

In the second study, Helena A. Yu, MD, of Memorial Sloan-Kettering Cancer Center, New York, NY, and colleagues identified the germline EGFR T790M mutation in a 44-year-old female never-smoker. The researchers subsequently tested eight family members and detected the mutation in two additional members (mother and daughter), also never-smokers. Metastatic lung cancer developed in the proband's mother, and the radiographic appearance of the lung cancer was the same for both women, with bilateral ground-glass opacities and pulmonary nodules.

"Germline EGFR T790M mutations are present in approximately 50% of all patients with baseline EGFR T790M identified in their tumor specimens before treatment," says Dr. Yu, also an IASLC member. "In our practice, we recommend that all patients with baseline EGFR T790M identified in their lung tumor tissue be referred to clinical genetics to discuss EGFR T790M germline testing. Carriers of this mutation need to be prospectively studied to better understand the clinical implications of this germline mutation.

The presence of a germline EGFR T790M mutation also predicts for resistance to standard tyrosine kinase inhibitors (TKIs), which adds complexity to

treatment. Until newer third- and fourth-generation TKIs designed to overcome T790M-mediated resistance become available, standard chemotherapy may be the preferred first-line therapy option in the absence of another known or suspected molecular target.

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