Specificities of Lung Adenocarcinoma in Women Who Have Never Smoked

Julien Mazières, MD, PhD, Isabelle Rouquette, MD,† Benoit Lepage, MD,‡ Julie Milia, PhD,* Laurent Brouchet, MD, PhD,§ Nicolas Guibert, MD,* Michèle Beau-Faller, MD, PhD,‖ Pierre Validire, MD, PhD,¶ Paul Hofman, MD, PhD,# and Pierre Fouret, MD, PhD***

Introduction: No clear data are available on the high rate of tobacco-independent lung cancer in women. We hypothesize that genetic events or hormonal factors may be partly involved.

Methods: We aimed to compare clinical, pathological, and biological characteristics of lung cancer in two cohorts of women: smokers and never-smokers. A total of 140 women (63 never-smokers and 77 former/current smokers) with adenocarcinoma, were included in this study.

Results: The never-smokers were characterized by a higher age (67 versus 58.7 years; $p < 0.0001$) and a higher frequency of lepidic features (60.3% versus 37.7%; $p = 0.008$) compared with smokers. We observed differential genetic alteration repartition in women according to their tobacco status: 50.8% of never-smokers displayed an epidermal growth factor receptor (*EGFR*) mutation versus 10.4% of smokers ($p < 0.001$). In contrast, *K-Ras* was more frequently mutated in smokers (33.8%) than in never-smokers (9.5%; $p = 0.001$). We also observed a higher percentage of estrogen receptors (ER) α expression ($p = 0.03$; and $p = 0.008$ with two different antibodies) in patients who never smoked when compared with smokers. There was no significant difference in ERβ and progesterone receptors between the groups. Finally, ERα expression was correlated with the presence of an *EGFR* mutation.

Conclusions: This study suggests that when lung cancer occurs in women who have never smoked, it is more frequently associated with an *EGFR* mutation and ERα expression, with a correlation between both markers. These findings underline the possibility of treating women who have never smoked by targeting both hormonal factors and genetic abnormalities.

*Service de Pneumologie, Hôpital Larrey—CHU de Toulouse, Université de Toulouse III (Paul Sabatier), Cedex 9, France; †Service d'anatomopathologie, CHU Rangueil, Faculté de Médecine, Toulouse, France; ‡Service d'épidémiologie; §Service de chirurgie thoracique, Hôpital Larrey, CHU Toulouse, France; ‖Laboratoire de Biologie Moléculaire, Hôpital de Hautepierre, EA 3430, Université de Strasbourg, Faculté de Médecine, Strasbourg, France; ¶Service d'anatomopathologie, Institut Mutualiste Montsouris; #Laboratoire de Pathologie Clinique et Experimentale et Biobanque CRB, CHU de Nice, France; and **Université Pierre et Marie Curie, Paris, France et INSERM 985 Génétique des tumeurs, Villejuif, France.

Disclosure:The authors declare no conflict of interest.

Address for correspondence: Julien Mazières, MD, PhD, Unité d'Oncologie Thoracique, Service de Pneumologie, Hôpital Larrey, CHU Toulouse, Chemin de Pouvourville, 31059 Toulouse Cedex, France. E-mail: mazieres.j@chu-toulouse.fr

Copyright © 2013 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/13/0807-0923

Key Words: Epidermal growth factor receptor, Estrogen receptor, K-Ras, Non–small-cell-lung-cancer, Tobacco.

(*J Thorac Oncol.* 2013;8: 923-929)

The incidence of lung cancer in women affects an estimated 516,000 women worldwide, of which 100,000 are in the United States and 70,000 in Europe.[1] Lung cancer is now the fourth most frequent cause of death from cancer worldwide, and the first cause in the United States and some European countries. These epidemiological data underline that cancer in women deserves specific attention.

Until now, lung cancers occurring in women have been treated similarly to lung cancers in men. However, numerous studies have highlighted different characteristics of lung cancer in women. We along with others have described the specificities of clinical and radiological presentations, pathology types, the response-to-cancer treatments, and patient outcomes in women.[2,3] Besides these clinical observations, other research has added new data that reinforce the specificities of lung cancer in women.

Two main mechanisms have emerged from recent findings on lung carcinogenesis in women: the high prevalence of genetic alterations, such as epidermal growth factor receptor (*EGFR*) mutations,[4,5] and the potential involvement of hormonal factors.[6] *EGFR* seems to be more frequently mutated in women than in men, leading to a better response rate to EGFR-tyrosine kinase inhibitor (TKI) therapy.[7] Recent epidemiological and clinical studies have provided evidence of a role for estrogens in the genesis and progression of lung cancer, especially non–small-cell lung tumors.[6,8]

Preclinical studies have shown a solid rationale for the crucial involvement of hormones in lung carcinogenesis. Many hormonal receptors, such as ERα, ERβ (estrogen receptors α and β), and PR (progesterone receptors) have been isolated from lung cancer tissues. We have recently reported a higher expression of ERs in women operated on for lung cancer compared with men.[9] Moreover, ERs have been shown to be involved in the onset of lung cancer in cells and animal models.[10] Last, the interaction of ERs with growth factor receptor signaling, including EGFR, has been demonstrated.[11] A direct correlation between both pathways has been also suggested by two recent studies,[12,13] indicating that lung cancer

treatment could include both EGFR- and hormone-targeting drugs.[14]

Tobacco smoking is the main cause of lung cancer. However, lung cancer also occurs in people who have never smoked, and it ranks as the seventh most common cause of cancer death worldwide.[15,16] Lung cancer in never-smokers is more frequently observed in women, representing 20% to 70% of these cases, according to geographical origin and patient selection.[17] Lung cancer in never-smokers is also characterized by a higher rate of gene mutations, involving *EGFR*, *HER2,* or *PI3K*, and of *EML4–ALK* translocations. We have recently identified, in a national collaborative study, other genetic abnormalities in this population.[18] Nevertheless, no clear data are available to improve our understanding of the higher rate of tobacco-independent lung cancer in women.

We hypothesize that genetic events or hormonal factors may be part of this observation. Herein, we have aimed to compare clinical and pathological characteristics of lung cancer in two cohorts of women smokers and women never-smokers, with a specific focus on driver oncogenes and hormonal receptors.

PATIENTS AND METHODS

Patients and Tissues

Tumor specimens were collected from 50 women who underwent surgery at the Thoracic Oncology Department (Toulouse University Hospital, France; this comprised the Ligue collection). A second collection of 90 tumor samples was collected from the Lung Genes (LG-collection) study, which involved 13 centers in France.[18] Only women were included in this study, and all patients had been treated with surgery.

We collected specific tobacco-exposure status from all women by checking each patient's file and subsequently performing a telephone- or mail-based survey. The 63 patients who had never smoked were defined according to current guidelines[19] as persons with lifetime exposure of less than 100 cigarettes.

A lung cancer pathologist assessed the diagnoses by applying the latest World Health Organization classification,[20] and the clinicopathological stage was assigned according to the tumor, node, metastasis (TNM) classification.[21] Patients who were included before the last classification were reclassified, especially for lepidic components. All patients signed an informed consent permitting analysis of tissues. Patients were treated and follow-up was done at our institutions, to ensure collection of clinical data.

Immunohistochemistry

We selected the most relevant antibodies[8,10,13,22,23] from the literature (Fig. 1 and Table 1). We chose the N-terminal ERα (1D5 clone DAKO) and the PR (PgR 636 clone DAKO) used in breast carcinoma because of their therapeutic implications. A C-terminal α-ER monoclonal antibody (clone sc-8002 F10; Santa-Cruz Biotechnology, Dallas, TX) and an ERβ polyclonal rabbit antibody (Biogenex, Fremont, CA) were also chosen because of their supposed prognostic implications.[9]

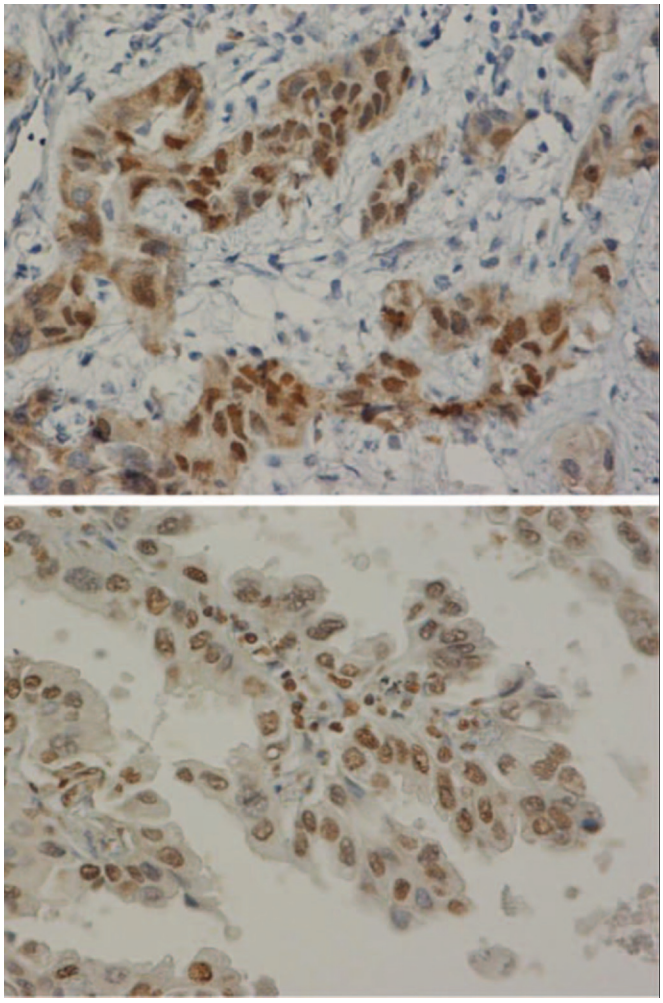

FIGURE 1. Immunohistochemistry of hormonal tumor staining (scale magnitude ×400). *A*, ERα staining of lung tumor tissue (× 400) (F10). Nucleus score is +++, cytoplasm score is ++; (*B*), ERβ staining of lung tumor tissue (× 400). ERβ score is 6 (*A*). ER, estrogen receptor.

Samples (5-µm sections) of lung tumor tissue were mounted on positively charged slides and dried for 1 hour at 60°C before they underwent immunohistochemical assays for ERα, ERβ, and PR expression. We used the PT link pretreatment module (DAKO, Carpentaria, CA), which allows the entire pretreatment process of deparaffinization, rehydration, and epitope retrieval to be combined in a three-in-one specimen-preparation procedure.

The slides were treated with 3% hydrogen peroxide to block endogenous peroxidase activity. Nonimmune serum was used to block nonspecific staining. Antigen retrieval was achieved by proteinase K digestion for 10 minutes, and the primary antibody was applied at a dilution of 1:50, and then incubated for 2 hours at room temperature. Biotinylated secondary antimouse antibodies (1:100) were applied to the sections for 20 minutes. Visualization was obtained, using the labeled streptavidin–biotin staining method (LSAB kit; DAKO). We then evaluated staining intensity, its nuclear or

Copyright © 2013 by the International Association for the Study of Lung Cancer

Download English Version:

https://daneshyari.com/en/article/6193542

Download Persian Version:

https://daneshyari.com/article/6193542

Daneshyari.com