Lung cancer in never-smokers

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New studies suggest that passive smoking alone is insufficient to determine a somatic profile in lung cancer http://ow.ly/KJe99

The therapeutic landscape of lung cancer has evolved tremendously over the past 10 years with the discovery of oncogenic drivers constitutively activated by mutation, translocation or fusion. An activating EGFR mutation or ALK rearrangement is present in around 15% of Caucasian patients with non-small cell lung cancer (NSCLC), with targeted therapy constituting the basis of upfront treatment for these patients. Additional potential drivers in NSCLC patients have been found in adenocarcinomas, including mutations in KRAS, BRAF, HER2, and fusions involving the RET, and ROS oncogenes. Many of these molecular abnormalities are found more frequently in never-smokers, relaunching a clinical interest in this patient population. Approximately 25% of all lung cancers are not attributable to tobacco, and the proportion of never-smokers with lung cancer has been increasing over time [1]. Lung cancer in never-smokers is thus regarded as a distinct disease entity with a variable tumorigenic pattern, clinicopathology, and natural history. Two major issues are addressed in the head-to-head papers of the Biocast prospective study: the first describes data on risk factors for NSCLC in never-smokers, and the second concerns the molecular profile of NSCLC in never-smokers.

Currently, there is little information available regarding the descriptive epidemiology of lung cancer in never-smokers. One important analysis, derived from 35 databases around the world (13 cohorts and 22 cancer registries on lung cancer), indicates that death rates among never-smokers with lung cancer are greater in men, African Americans, and Asians living in Asia, compared with those of European ancestry [2]. Numerous risk factors have been suggested to explain the occurrence of lung cancer in never-smokers, including environmental smoke exposure, occupational exposure, indoor and outdoor pollution, prior diseases and genetic factors [3–5]. Evidence is now established for several of these factors, including environmental tobacco smoke, asbestos, chromium, arsenic, cadmium, silica, nickel and polycyclic aromatic hydrocarbons [6–9]. It has also been reported that workers exposed to tar and soot in concentrations exceeding those present in urban air, as is the case for diesel exhaust exposure (OR 1.3, 95% CI 1.2–1.4), are at increased risk of lung cancer [10, 11]. Diesel fumes are classified by the International Agency for Research on Cancer as carcinogenic to humans, leading to particular public health concerns in urban areas.

In the present issue of the *European Respiratory Journal*, Couraud *et al.* [12] reported the results of one of the largest prospective European trials conducted in lung cancer in never-smokers (defined as less than 100 cigarettes in a lifetime). The study recruited 384 French patients in 75 participating centres, each individually contacted to perform an interview on risk exposure. The authors showed that 13% of patients had been exposed to at least one occupational carcinogen (men 35%, women 8%), whereas domestic exposure (passive smoking and cooking oil) was higher in women (41% *versus* 18% for exposure to cooking oil fumes). Domestic exposure to passive smoking, 62% of which began during childhood, was significantly more frequent among women than men (64% *versus* 38%).

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Environmental tobacco smoke exposure is associated with an excess relative risk of lung cancer of around 20% [13, 14]. A frequent criticism of studies showing higher risk for women is that different baseline risks are likely in nonsmoking women compared to men who have never smoked (*e.g.* fewer work-related exposures to lung carcinogens). The present study further delineates that men are more exposed to occupational carcinogens and women more exposed to domestic carcinogens. In a large prospective study in 10 European countries (n=520 000), the proportion of lung cancers in never- and ex-smokers attributable to environmental tobacco smoke was estimated at 16–24%, mainly due to the contribution of work-related exposures [15]. Another case control study of lung cancer in 16 centres from seven European countries, including 223 never-smoking cases and 1039 controls, suggested an increased risk of lung cancer among women employed in suspected high-risk occupations, and in men and women combined, for exposure to nonferrous metal dust and fumes, silica and organic solvents [16]. These results are consistent with the present trial and reinforce the different exposures that might be observed between men and women, although most studies documenting such exposures have been largely based on data from male smokers.

The two major limitations of the current trial, as discussed by the authors, are the absence of a control group to enable any estimation of risk ratios, and the retrospective recording of risk factor exposure by patients themselves; this may lead to an under-reporting of exposure (recall bias). The use of face-to-face interviews by trained interviewers using a standardised questionnaire should have reduced recall bias to a minimum, although a possible bias due to differential inaccuracies cannot be excluded. Various definitions of never-smokers might also lead to a different population: in the current trial, a typical cut-off for never-smokers was employed (fewer than 100 cigarettes in the lifetime), with a double-check performed (physician data and during patient interview) to limit errors. The results also clarify that exposure to known occupational and domestic lung carcinogens cannot explain the vast majority of lung cancer cases observed in never-smokers.

The present trial identified a potential targetable molecular alteration in 73% of patients (without any significant sex difference): EGFR in 51% (Del 19 in 58% and exon 21 mutation in 32%), ALK in 8%, KRAS in 6%, HER2 in 3%, BRAF in 3%, PI3KCA in less than 1%, and multiple genetic modifications in 2%. Most cases were adenocarcinoma (85%), the most common type of lung cancer in never-smokers, with a higher than 50% estimated frequency of actionable oncogenic drivers [17, 18]. EGFR mutations, ALK rearrangements and KRAS mutations were the three most frequently identified and clinically relevant genetic alterations in NSCLC in never-smokers. These rates were similar to the largest ever cohort of East Asian NSCLC never-smokers, reported by Kim *et al.* [19], which observed 229 tumours; the frequency of EGFR mutations, ALK rearrangements, KRAS mutations and no mutations was 48%, 8.3%, 3.5%, and 40.2%, respectively. The gene modification frequencies reported by Couraud *et al.* [12] are slightly different from those seen in the Biomarker France study (preliminary results on 9911 NSCLC patients): EGFR (33%), KRAS (9.6%), BRAF (1.8%), PI3K (3.6%), HER2 (3.8%) mutations and ALK rearrangements (9.7%) in never-smokers (17.7% of the tested NSCLC patients) [20]. No mutations were reported in 35.2% of never-smokers in the Biomarker France study, compared to 27% in the present study. The Lung Cancer Mutation Consortium (LCMC, a 14-institution collaborative in the USA) published the first molecular profiling of 1007 patients with mutation frequencies detected in 33%, 4%, 15%, 5%, 1% and 1% concerning EGFR, KRAS, ALK, HER2, BRAF and PI3KCA, respectively, in never-smokers (n=341) [21]. These differences could be explained by a more rigorous selection of never-smokers in the Couraud *et al.* [12] study than in Biomarker France or the LCMC, since only the first study used a dedicated questionnaire and face-to-face meeting.

The presence of a driver mutation should be carefully evaluated in never-smokers, but 27% of NSCLC patients remain "wild-type" in this study. More recently identified biomarkers should therefore be investigated in never-smoking NSCLC patients, including ROS1 (2% of NSCLC), RET (2% of NSCLC) and NTRK 1/2/3 rearrangements; a method that might increase the number of patients with a potential targetable molecular abnormality [22–24]. Access to tumour samples is still an issue in lung cancer because biopsies are often too small to perform these additional analyses. The feasibility of testing these mutations on circulating free DNA is under assessment, with a sensitivity of 58% and a specificity of 87% reported [25]. This is a promising tool for accessing the tumour genome as a liquid biopsy, especially when it appears that individuals with drivers receiving a matched targeted agent might live longer (experience of the LCMC) [21]. It will be interesting to see any future survival data according to molecular alteration in the present study, and any molecular relation between oncogenic driver profile and occupational/domestic carcinogen exposure.

Not all KRAS mutations observed in men in the present trial were transversion mutations, and 40% were transition mutations in women. As these mutations are generally more commonly observed in lung cancers from smokers, this raises the possibility of an under-estimation of passive smoking in men [26]. In the present issue of the *European Respiratory Journal*, the same population is reported in a second article to have a nonsignificantly higher frequency of KRAS transversion in patients exposed to passive smoke

compared with those who were never exposed (82% *versus* 60%, respectively) [27]. This second paper is important as it reports no significant difference in terms of molecular profile of EGFR, KRAS, HER2, BRAF, PIK3CA and ALK between exposed to passive smoke and non-exposed never-smoking patients. The frequency of EGFR mutation decreased (46% in never-exposed patients to 39% in patients exposed >30 years) as the cumulative duration of passive smoke exposure increased, but this difference was not statistically significant. Previous data from Asian or US populations showed conflicting results regarding the association of passive smoke exposure with EGFR mutations in lung tumours [28–32]. One possible explanation is that the duration of exposure and intensity/concentration of passive smoke exposure is difficult to evaluate due to inaccuracy of memory, particularly as a child. Other reasons may include sample size limitation or tobacco type. Thus the major limitation of the second study may be intentional or unintentional recall bias of patients, with no biochemical test for validation. Different studies have reported genotoxic and epigenetic changes in smokers and in never-smokers exposed to environmental tobacco smoke, and it is possible that environmental tobacco smoke exposure is correlated with poor response to EGFR tyrosine kinase inhibitors [33, 34]. Other oncogenes (notably KRAS and ALK) have been poorly investigated and no clear differences have been found between never- and passive smokers [28, 31].

The current study contributes to existing literature regarding NSCLC in never-smokers by reinforcing our knowledge of the frequency of targetable molecular abnormalities in relation to environmental carcinogens and sex. Exposure to environmental tobacco smoke is a critical public health issue and may play a role as a negative predictive factor for EGFR mutations, a finding that may eventually allow clinicians to tailor therapies to never-smokers with lung cancer. However, at present, passive smoking alone appears to be insufficient to determine a somatic profile in lung cancer.

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