# Preface: lung cancer in never smokers

This focused edition of the journal highlights lung cancer in never smokers. While tobacco exposure is the major cause of lung cancer worldwide (about 80% of cases), an important subset of cases occurs in lifetime never smokers (LCNS), ranking LCNS as one of the top 7 or 8 causes of cancers worldwide. For several reasons, LCNS can be regarded as a distinct form of lung cancer from that arising in ever smokers (LCES), based on etiology, demographics, molecular pathogenesis, clinical presentation and management (1-4). While the major cause of LCES is self-evident, the major cause of LCNS has not been convincingly identified. While many contributory factors have been identified, none of them, including passive smoking, can be regarded as the major cause of most cases. Until the major cause or causes have been identified, our understanding of the pathogenesis, prevention and rational therapy options will be limited.

The focused issue contains five articles covering a range of interesting topics. While a large, more comprehensive series of articles was originally planned, the failure of some putative authors to fulfil their commitments has resulted in a more modest scope.

Zhou and Zhou summarize the molecular and clinical pathogenesis of LCNS arising in East Asians. This is of especial importance as a high and rising incidence occurs in this population due to a combination of genetic susceptibility, exposure to carcinogens and possibly to geographic location. Of special interest, a remarkably high percent of cases arises in women. As many as 90% of these tumors have an identifiable driver mutation, rendering them to be more likely to receive targeted therapies than tumors arising in ever smokers. While LCNS arising in East Asians is well studied, there are large gaps in our knowledge of many of the subpopulations and our knowledge of this disease is lacking entirely for some ethnic or geographic groups. Hopefully these gaps will be filled soon.

Yamamoto *et al.* describe inherited syndromes associated with lung cancers, focusing on two relatively rare but highly interesting and informative syndromes involving inherited mutations in *EGFR* and *HER2* genes. Surprisingly, both syndromes target relatively young women who are never or light smokers. An interesting question is whether smoking delays or prevents the onset of lung cancers in this small group of patients. While these inherited mutations are rare, they have a high penetrance and high frequency of lung cancer development. By contrast, several single nucleotide polymorphisms (SNPs) (i.e., those occurring at frequencies greater than 1%) associated with lung cancers are relatively common, but the incidence of lung cancer associated with any single SNP is modest. Combinations of various susceptibility associated SNPs are more likely to be associated with lung cancer. Of interest, while some susceptibility associated SNPs are common to cancers arising in smokers and never smokers, others target Asians, especially Asian women. These findings may help identify never smokers at increased risk of developing lung cancer and result in them being enrolled in screening programs.

With the widespread use of computed tomography (CT) scanning for the early detection of lung cancers, one of the major problems encountered is the large number of nodules detected. Many of these are ground-glass nodules (GGNs), which are hazy radiological findings on CT. Most persistent or growing GGNs are lung adenocarcinomas or their preinvasive lesions. Some of the potentially preneoplastic lesions have *EGFR* or *KRAS* or other mutations in driver oncogenes. Surprisingly, *EGFR*-mutant GGNs may predispose to cancer progression while *KRAS*-mutant lesions often regress. Kobayashi and Mitsudomi, who have done much of the pioneering work in this field, offer insights into how to predict the natural course of GGNs.

Akbay and Kim describe autochthonous tumors of the lung arising in mouse models, both carcinogen induced and genetically engineered mouse models (GEMMs). Fortunately, good models exist for both LCNS and LCES. In this exciting era of immunotherapy, GEMMs are particularly useful as they have intact immune systems, unlike the other commonly used *in vitro* models, cell lines and xenografts (5). The wide variety of animal models for lung cancer has greatly aided the study and understanding of this disease.

One of the limitations of studying LCNS (and LCES) is the lack of a quantitative assay for determining the presence and degree of molecular damage in individual tumors. We have known for some years that the LCES tumors have a frequency of a specific type of mutation, C>A, G>T transversions, while never smoker lung cancers are characterized by a much lower mutation burden and C>T, G>A transitions (6). Using these two mutational changes, Song and Gazdar explored several approaches to developing quantitative methods for assessing smoke related damage in lung cancers. They demonstrated that the smoking history is incorrect in up to 10% of cases. As most squamous cell and small cell lung cancers had relatively low

 

percentages of never smokers, quantitation appears most useful for lung adenocarcinomas which include most of the lung cancers arising in never smokers.

The five articles in this focused issue summarize the relevant information on five important issues about lung cancers arising in never smokers and demonstrate approaches for assessing the extent of smoke related damage in lung cancers.

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