Nonsmall cell lung cancer in never smokers

Giorgio V. Scagliotti, Marina Longo and Silvia Novello

Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

Correspondence to Giorgio V. Scagliotti, MD, University of Turin, Department of Clinical and Biological Sciences, S. Luigi Hospital, Regione Gonzole, 10, Orbassano, Turin 10043, Italy
Tel: +39 011 9026414; fax: +39 011 9038616; e-mail: giorgio.scagliotti@unito.it

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Purpose of review

To summarize the available knowledge about nonsmall cell lung cancer (NSCLC) in never smokers in terms of biological and clinical–pathological findings.

Recent findings

Overall in newly diagnosed NSCLC, 10% of men and 20% of women, with a much higher proportion among Asiatic women, are never smokers and among them an overwhelming proportion have adenocarcinoma. Several environmental, genetic, hormonal and viral factors have been associated with an increased risk of NSCLC in never smokers, but for none of them there is definitive evidence. The incidence of epidermal growth factor receptor mutations is higher in never smokers, whereas K-*ras* mutations are rarely detected in this group of never smoking patients. The role of never smoking status in NSCLC as a positive prognostic factor or predictive of a better chemosensitivity to systemic treatments is still undefined.

Summary

Epidemiological, molecular and clinical–pathological features indicate NSCLC in never smokers as a distinct entity. Future preclinical studies should address more deeply the biological differences between NSCLC in smokers and never smokers and, to avoid biased results due to differences in survival outcomes, smoking status should be considered among stratification factors in future clinical studies.

Keywords

adenocarcinoma, epidermal growth factor tyrosine kinase mutations, never smoker, nonsmall cell lung cancer, smoking

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Introduction

In lung cancer, due to the overwhelming etiological role of tobacco smoking, only recently has attention turned toward the minority of never smoker patients with this disease. Although definitions vary in the literature, the one commonly used refers to an individual who has had a lifetime exposure of less than 100 cigarettes; however, reliability of smoking information from population-based registries and old clinical trials has been limited.

It has been estimated that 10% of men and 20% of women in whom lung cancer develops are never smokers and, among these cases, an overwhelming proportion of adenocarcinomas as well as an earlier age at diagnosis have been reported.

Sparking the attention on never smoker patients was the clinical observation that patients with nonsmall cell lung cancer (NSCLC) who have never smoked have a better response and survival to inhibitors of the epidermal growth factor receptor (EGFR)-associated tyrosine kinase, such as gefitinib and erlotinib, than do those with a history of tobacco smoking.

Epidemiological features

It is currently unclear whether the recently reported increase in never smokers with advanced NSCLC represents an increase in the lung cancer incidence in never smokers or the increasing prevalence of never smokers in the general population [1,2], but no temporal trends have been detected in a large series of cohort and registry studies [3].

Data from six different cohorts reported the truncated age-adjusted incidence rates of lung cancer in never smokers ranging from 14.4 to 20.8 per 100 000 person-years in women and 4.8 to 13.7 per 100 000 person-years in men, supporting earlier observations that women are more likely than men to have nonsmoking-associated lung cancer [4•].

Relevant geographic differences in the proportion of lung cancer cases in never smoker women have been

documented, ranging from 83% in Asiatic countries to 15% in the United States, whereas less geographic variations have been observed in men.

Pathological features

Clinical–pathological features associated with a higher probability of response to EGFR-associated tyrosine kinase inhibitors in addition to never smoker status include female sex, histological subtype of adenocarcinoma, especially bronchioloalveolar carcinoma and Asiatic ethnicity. Most of these features overlap with the characteristics of terminal-respiratory-unit (TRU) type adenocarcinoma, which has been recently described [5]. TRU is composed of alveolar cells and nonciliated bronchiolar epithelium, and its characteristics are highlighted by morphology and expression of thyroid transcription factor-1 (TTF-1) and surfactant proteins. TRU-type adenocarcinoma, which is putatively derived from the TRU, demonstrates a different pattern of alteration of cancer-associated genes, suggesting a distinct molecular pathway of its carcinogenesis. In a retrospective study, EGFR mutation was detected in 97 of 195 adenocarcinomas, 91 of 149 TRU-type adenocarcinomas and six of 46 tumors of other types. Conversely, 91 of 97 EGFR-mutated adenocarcinomas were categorized as TRU-type adenocarcinomas [6].

Gene expression profiling

Two studies investigated potential differences in the gene expression profiling between smokers and never smokers with lung adenocarcinoma but both, even if they found genes differentially expressed, failed to observe a separation in hierarchical clustering analysis. Gene expression in the noninvolved lungs of smokers differed from that of never smokers, and multidimensional scaling showed that noninvolved lungs of smokers segregate with tumors rather than noninvolved lungs of never smokers [7].

An expression profiling study analyzed gene transcripts in 90 cases of adenocarcinoma and two subgroups were identified [8]. One of these subgroups had morphological features resembling TRU-type adenocarcinoma. TRU-type adenocarcinomas were seen significantly more frequently than non-TRU types in women ($P = 0.005$) and in never smokers ($P < 0.001$).

Risk factors

Identifying risk factors for lung cancer in never smokers has been an intense area of epidemiological research.

Environmental tobacco smoke

In two meta-analyses [9,10], never smokers had a statistically significant greater risk of lung cancer if their spouses were smokers than if their spouses were nonsmokers [9]. The risk is approximately 25% greater than expected for women, 35% greater than expected for men and 20% greater than expected for involuntary smoking at the workplace [10].

In a population-based prospective study on 28 414 Japanese lifelong never smoking women, the hazard ratio for lung cancer incidence in women who lived with a smoking husband was 1.34. An association was clearly identified for adenocarcinoma (hazard ratio 2.03) for which dose–response relationships were seen for both the intensity and the amount of the husband's smoking [11••].

Exposure to cooking fumes

The higher proportion of never smokers among Chinese women led to investigate the potential role of exposure to cooking oil vapours and indoor coal burning, especially in the absence of fume extractors.

A meta-analysis of studies conducted in China consistently reported an increased risk of lung cancer as a consequence of the exposure to domestic coal used for heating and cooking, indoor exposure to coal dust and chronic exposure to cooking oil vapour, but the results for the last two kinds of exposure might be affected by publication bias [12].

More recently, a study linked cooking fumes exposure and lung cancer among Chinese women using a quantitative indicator for cumulative exposure, the cooking dish-year. Compared with nonsmoking Chinese women who never cooked or cooked 50 dish-years or less, the odds ratio of lung cancer was approximately 3–4 for those with more than 100 total cooking dish-years and increased to more than 8 among those with more than 200 total cooking dish-years. Different methods of frying were associated with different levels of risks, with deep-frying having the highest risk and stir-frying the lowest [13].

Occupational and environmental factors

Residential radon exposure is associated with a small but detectable increase in the risk of cancer in smokers and never smokers, although the risk is much greater in smokers [14], whereas nonoccupational exposure to asbestos does not have a significant role in increasing the mortality from lung cancer in never smokers.

Hormonal status

The higher proportion of never smoking women with lung cancer compared to men, the predominant adenocarcinoma histology among never smokers and the preclinical evidence that estrogens induce NSCLC cell

proliferation and can modulate gene expression suggest a potential role for sex-related hormones in lung cancer.

Estrogen receptors (estrogen receptor-α and estrogen receptor-β) are encoded by separate genes and display a different tissue distribution, but they have been detected in lung normal tissue and cancer both in women and in men [15]. Estrogen receptor-β is more frequently expressed than estrogen receptor-α in lung tissue [16], and it has been detected more commonly in never smokers than in smokers and, among never smokers, more in women than in men [17]. Recent data support the intratumoral production of estradiol by NSCLC, mainly mediated by local aromatase activity, which could play an important role in the growth of estrogen receptor-α-positive or estrogen receptor-β-positive NSCLC [18•].

The role of hormone replacement therapy (HRT) yielded conflicting results. In nearly 500 female lung cancer patients, a significant association has been reported between both a lower median age at lung cancer diagnosis and a shorter median survival time in women who used HRT around the time of diagnosis [19]. This effect was more evident in smoking versus nonsmoking women, suggesting an interaction between estrogens and tobacco carcinogens. However, other reports suggest that HRT use prior to diagnosis could actually protect women from developing lung cancer, especially if they smoked. An inverse relationship was also observed between HRT use and NSCLC risk in postmenopausal women with estrogen receptor-positive, but not estrogen receptor-negative lung tumors [20]. This may suggest that there are different effects on the balance between induction of cell differentiation and cell proliferation by estrogen in normal lung compared with malignant tissues. As lung tumors are also known to produce aromatase [18•], HRT may reduce local estrogen production by inhibiting aromatase expression.

Genetic susceptibility

A large linkage analysis of 52 families has identified a major susceptibility locus for inherited lung cancer on chromosome 6q23–25, and the search for a lung cancer susceptibility gene in this region is ongoing [21].

Familial aggregation may provide indirect evidence for a genetic role in lung cancer susceptibility. Most studies did not identify a statistically significant increased susceptibility among the relatives of patients with never smoking lung cancer, after adjusting for smoking exposure. In a meta-analysis [22], 11 studies considered familial lung cancer aggregation specifically in never smokers and a 1.51-fold significant risk was reported. Gorlova *et al.* [23] analyzed 2465 first-degree relatives of 316 never smoker lung cancer patients and 2441 first-degree relatives of 318 never smoker controls. Whereas smoking relatives of patients had a not statistically significant 68% excess risk of lung cancer (it was only statistically significant by the age 85) compared with smoking control relatives, no risk excess was noted in nonsmoking case relatives.

Candidate genes for lung cancer have been extensively studied with most of the reports focusing on mechanistically plausible single nucleotide polymorphisms (SNPs) of genes coding for enzymes involved in the activation (phase I enzymes responsible for the oxidation, reduction and hydrolysis of polycyclic aromatic hydrocarbons), detoxification (phase II enzymes responsible for the conjugation with glutathione) and repair of damage caused by tobacco smoke. Nonsmokers have lower exposures to carcinogens in the tobacco smoke through environmental tobacco smoke, so contribution from genetic polymorphisms may be stronger [24••].

A pooled analysis of 14 studies indicated that white never smokers with cytochrome P450 1A1 polymorphism *Ile463-Val* showed a three-fold increased risk but no effect of *CYP1A1Msp*I polymorphism (*T3801C*). This effect was particularly strong for adenocarcinoma and for patients with glutathione-S-transferase M1 (*GSTM1)* null genotype. The *GSTM1* null genotype is associated with the loss of GSTM1 enzyme activity, but it does not seem to generate major changes in the carcinogenic effect of either environmental tobacco smoke or urban residence among never smokers [25]. In a study performed in never smoking Korean women, *CYP1A1-Ile463Val* polymorphism was associated with a significant reduction in the risk of adenocarcinoma, whereas the combination of *CYP1A1-I462V* and *CYP1B1 Leu432Val* with an increased risk of lung cancer irrespective of the histotype [26]. A protective effect on lung cancer in never smokers was observed with the combination of *CYP1A1* wild-type, *GSTM1* null and *GSTT1* nonnull genotypes exclusively in white but not in Asian nonsmokers [27]. However, these interactions have been detected in a limited number of patients.

Lung cancer risk associated with suboptimal DNA repair capacity (DRC) was measured by the host-cell reactivation assay in lifetime never smokers in a case–control study. Suboptimal DRC level conferred a 1.92 increase of risk of lung cancer in never smokers ($P = 0.0024$). There was a 3.38-fold risk for individuals with DRC below the first quartile compared with individuals with DRC above the third quartile. Second-hand smoke exposure in individuals with DRC below the control median was associated with a 3.8-fold risk of lung cancer. A 2.5-fold risk was noted for the joint effects of lung cancer family history in first-degree relatives and suboptimal DRC [28•].

DNA repair mechanisms are important for maintaining DNA integrity and preventing carcinogenesis, and polymorphisms in genes coding for DNA repair enzymes have been investigated.

In a case–control study, the association between lung cancer and genetic polymorphisms in two base excision repair genes, *XRCC1* and *APEX1*, and two genes involved in double-strand break, *XRCC3* and *NBS1*, was analyzed. The presence of the *XRCC1 399Gln* allele was associated with a significantly decreased risk for lung cancer among nonsmoking women (odds ratio = 0.4). The *NBS1 185Gln* allele was significantly associated with an increased risk for lung cancer among nonsmoking women (odds ratio 2.2) and low-dose smoking women (odds ratio 4.8) [29]. Another large case–control study [30] detected an interaction between tobacco use and the *XRCC1 Arg299Gln Gln/Gln* genotype with an increased risk of lung cancer in nonsmokers with the variant genotype. Advances in identification of new polymorphisms and in high-throughput genotyping techniques will facilitate analysis of multiple genes in multiple DNA repair pathways.

Epigenetic changes

The most widely studied epigenetic event in relation to cancer is gene promoter hypermethylation. Several genes have been investigated in multiple pathways, including those regulating cell cycle (*p16*), apoptosis (*DAPK* and *RASSF1A*), cell differentiation and proliferation (retinoid acid receptor-β) and DNA repair [O6-methylguanine-DNA methyltransferase, mutL homolog-1 (MLH1), mutS homolog-2 (MSH2)].

The loss of protein expression in protein mismatch repair genes MLH1 and MSH2 was more frequently seen in never smokers than in tobacco-associated cancers [31].

Viral factors

One study reported that female lung cancer patients who were never smokers and older than 60 years of age had a higher prevalence of infection with human papilloma virus (HPV) 16 and 18 [32], but a further study did not demonstrate the same results in a similar population [33].

Although the mechanism associated with a potential risk increase is unclear, further studies are necessary to explore the relation between HPV infection and lung adenocarcinoma risk, also considering effect modifications due to genetic variations.

Molecular features

Tumor sensitivity and response to treatment with EGFR-tyrosine kinase inhibitors is associated with the presence of EGFR mutation detected in the tyrosine kinase domain. The incidence of EGFR mutations is higher in never smokers, independent of any geographical difference, and is inversely correlated with the cumulative amount of tobacco-smoke exposure [34]. Similar to EGFR mutation, K-*ras* mutations are more frequently reported in adenocarcinoma of the lung but more frequently detected in smokers and less commonly in Asiatic patients [35]. In addition, when the type of K-*ras* mutation in adenocarcinoma of the lung is examined, never smokers are significantly more likely than current or former smokers to have a transition mutation (G>A) rather than the trasversion mutations known to be smoking related (G>T or G>C) [36]. In NSCLC, EGFR and K-*ras* mutations are mutually exclusive leading some investigators to speculate that lung cancer in smokers and never smokers is arising through alterations along different molecular pathways [37].

p53 mutations occur in 40–60% of NSCLC and have been more frequently reported in smokers than in never smokers and also the type of mutation (same pattern as reported above for p53) differs between the two groups [38].

Clinical features

No conclusive data are available about a different stage distribution in never smokers with a higher proportion of patients presenting with advanced disease stage reported in an epidemiological study on Chinese patients [38], but not among whites [39,40]. The higher disease stage at diagnosis may be the consequence of a lower physicians' awareness about the diagnostic possibility of lung cancer among never smokers.

Although striking differences in response rate and survival have been seen according to the smoking status following EGFR-tyrosine kinase inhibitors, it is still a matter of controversy whether the clinical condition of NSCLC in never smokers is a pure prognostic factor or predictive of a better chemosensitivity to systemic treatments.

In some studies, an improvement in 5-year survival rate has been reported [39–43], particularly in early stage NSCLC, whereas no difference was observed in others [44,45]. In a recently published study in which the combination of cisplatin/pemetrexed was compared with cisplatin/gemcitabine in stage IIIB/IV NSCLC [46], never smoking status was a favorable prognostic factor, independent of the treatment received.

In few studies [45,47], the impact of smoking status on the efficacy of cytotoxic chemotherapy in terms of response rate and survival has been investigated and again controversial results have been reported.

Conclusion

The better understanding of the molecular biology of lung cancer in never smokers represents a research priority because of the growing epidemiological relevance and potential differential therapeutic approach.

As long as the prognostic and/or the predictive role of never smoking status in NSCLC is not properly addressed, the improvements in lung cancer survival over time could be a result of an increasing proportion of never smokers among lung cancer patients rather than improved therapies [4•], and in future clinical trials, smoking status should be included among the stratification factors.

References and recommended reading

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