Lung cancer

Lung cancer in never-smokers

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The mystery behind never-smokers being more prone to lung cancer is unlocked with regard to smoking status and sex

Never-smokers with lung cancer constitute an understudied and under-represented subset of patients. Although there have been hints that never-smokers can be afflicted with lung cancer,[1] especially among Asian Chinese women,[2] it is only recently that attention has turned towards this much ignored group of patients. Sparking the attention was the finding that somatic mutations of the epidermal growth factor receptor (EGFR) were consistently more common among lung tumours of never-smokers,[3] and that these mutations could possibly explain the higher response rates to single agent gefitinib.[4 5] The attention was further intensified by media reports of a non-smoking wife of a celebrity who developed lung cancer.

Most studies on never-smokers with lung cancer have emerged from Asia, as the smoking prevalence rates in Asia are lower compared with the West. In Singapore, where the population is predominantly Chinese, the smoking prevalence in the general population is 24.3% in men and 3.6% in women.[6] About 10–15% of lung cancers occur in a lifetime among never-smokers in the West,[7] whereas about 30–40% of patients with lung cancer are never-smokers among the Asian countries.[8] Whether this represents a higher risk of lung cancer among never-smokers in Asia or is a mere reflection of the higher numbers of never-smokers at risk is unclear at present. A recent large prospective study by Thun *et al*[9] may help to put things in perspective. The study among African Americans and Whites provides estimates of mortality due to lung cancer among never-smokers, with rates of 17.1 and 14.7 per 100 000 person-years among men and women, respectively. These figures highlight that the burden of lung cancer among never-smokers is fairly significant among the western population. In fact, they are comparable to the death rates due to lung cancer among Chinese women in Singapore,[10] where only 3.6% of women smoke in the general population.[6] Confounding these studies assessing mortality due to lung cancer is the fact that the death rates could be affected by incorrect documentation of cause of death, duration of survival and treatment, and a lack of a uniform definition of current, former and never-smokers. A Japanese study found that lung cancer death rates were higher among Japanese never-smokers compared with the Americans; however, there were differences in definition of smoking, which could have resulted in inclusion of more former smokers among the Japanese never-smokers.[11] These issues are best resolved with prospective studies evaluating incidence rates, which would be a better reflection of risk.

It is likely that never-smokers across the world have similar susceptibility to lung cancer. The subsequent discussion will address (1) whether there is a biological basis for differences between never-smokers and smokers; (2) the possible aetiological factors for the development of lung cancer; and (3) future research directions for this group of patients.

IS LUNG CANCER AMONG NEVER-SMOKERS A DIFFERENT DISEASE ENTITY FROM THAT IN SMOKERS?

Many epidemiological studies have found that the characteristics of lung cancer among never-smokers are significantly different from those among smokers.[1 8 12] Consistent findings include a higher proportion of women, presence of adenocarcinoma, as well as an earlier age at diagnosis among the never-smokers. We recently reported that the never-smokers with lung cancer also have better survival compared with the smokers, after adjusting for sex, performance status, stage, comorbidities, significant weight loss and treatment.[8] This was also seen in several other studies.[13] The improved survival suggests that lung cancer in the never-smokers may be biologically different and inherently more indolent. In the molecular analysis of tumours from patients in a trial of erlotinib versus placebo,[14] there is a suggestion that tumours with EGFR mutations, when untreated, may have a more indolent behaviour. As EGFR mutations are more commonly found in never-smokers, this further supports the hypothesis in question. The converse is also true, as histological subtypes exclusively associated with smoking, such as small-cell lung cancer and the pleomorphic variant of non-small-cell lung cancer, have an extremely aggressive behaviour.

Prior to the reporting of EGFR mutations, other genetic alterations have been described to be different between smokers and never-smokers. These include deletions of the short arm of chromosome 3,[15] mutations of the p53[16] and K-ras genes.[17] Although Gealy *et al*[18] found that the frequency of mutations in the p53 gene was similar in lifetime never-smokers compared with long-term smokers, the types and spectra of mutations were significantly different between the two groups, again suggesting that different pathways may be involved leading to p53 mutation. Gene expression profiles using microarray analysis have been obtained for lung adenocarcinomas of smokers and never-smokers.[19] Four times as many genes changed in the transition between non-malignant lung and tumour in smokers compared with never-smokers, suggesting that the non-malignant lung of smokers already had many alterations in gene expression. This is consistent with the fact that smoking causes widespread genetic changes in the lungs of smokers. The corollary is that tumours in never-smokers arise within a field of relatively normal cells.

Additional studies[20] have examined histologically normal bronchial and bronchiolar epithelium from patients with lung adenocarcinoma containing EGFR mutations among never-smokers. In all, 43% of patients with EGFR mutant adenocarcinoma had mutations in the normal respiratory epithelium, whereas none was found in those without mutations in their tumours. In addition, these mutations were found more frequently in the normal epithelium within tumour than in adjacent sites. This suggests that EGFR mutations, more common among never-smokers, may be important in the pathogenesis of lung cancer. Recent mechanistic studies have shown that transfection of normal type II pneumocytes with mutant EGFR can lead to the development of adenocarcinoma.[21] Further evidence for independent pathways for lung adenocarcinomas between smokers and never-smokers was also found in the epigenetic alteration of tumour suppressor genes.[22]

As illustrated above, there are possible divergent pathways of lung cancer development between smokers and never-smokers. Preliminary work in our centre, which is prospectively performing gene expression profiling of newly diagnosed

patients with lung cancer, shows a clear delineation between smokers and non-smokers that is independent of histology.[23] Hopefully, we may be able to provide more information about the molecular differences between the two groups of patients and its relation to prognosis, response to current therapeutic modalities, and development of therapeutics directed along a new pathway.

POSSIBLE AETIOLOGICAL FACTORS FOR LUNG CANCER IN NEVER-SMOKERS

Genetic

Never-smokers with non-small cell lung cancer have a median age of diagnosis of lung cancer that is 7 years earlier than that of smokers.[8] Koo and Ho[1] also described that, among Asians, younger patients with lung cancer tend to be never-smokers. Most early-onset cancers have some genetic predisposition, and a genetic component be involved in the carcinogenesis of lung cancer. Due to a similar shared environment, whether the aggregation of cancer within a family is the result of exposure to tobacco smoke in the same household or is truly a higher predisposition of the individuals may be difficult to determine. Despite this, a series of studies has shown an increased susceptibility among the relatives of patients with lung cancer, after adjusting for smoking exposure. Tokuhata and Lilienfeld[24] first reported an increase in lung cancer mortality in relatives of lung cancer probands, especially among female never-smoking relatives. Further studies, including case–control[25 26] and registry-based investigations,[27 28] have shown about a twofold increase in risk of lung cancer among relatives of patients after adjusting for smoking and age. Among these studies, some have found that the familial risk was higher among relatives of never-smoking lung cancer probands, whereas others have reported that the increased risk was limited to early-onset cases. Schwartz *et al*[26] reported a sixfold increase in lung cancer among family members of never-smokers with lung cancer, but this was limited to probands $<$60 years of age. Kreuzer *et al*[29] found that lung cancer in a first-degree relative was associated with a 2.6-fold increase in risk of lung cancer in younger people ($\leqslant$45 years old) compared with older people (55–69 years old), while Bromen *et al*[30] reported a 4.75-fold increase in lung cancer risk among young subjects ($\leqslant$50 years old). These studies are limited by small numbers of patients with early-onset disease and varying definitions of young, which is often arbitrarily defined. Despite these limitations, most of these epidemiological studies suggest a trend of a mild to moderate increase in risk of lung cancer among relatives of patients with lung cancer, especially among those with early onset of disease.

This increase in risk of cancers among the relatives of probands does not seem to be limited to lung cancer as Schwartz *et al*[31] reported in another study that family members of never-smoking patients with lung cancer had increased risk for cancers other than lung cancer. Gorlova *et al*[32] also found that a history of early-onset ($<$50 years old) cancer (including breast, lung, skin and colon cancer) among first-degree relatives was associated with significantly increased risk in lung cancer in their study subjects.

Although most studies have described positive associations, there are also studies showing negative associations. Etzel *et al*[33] evaluated the risk for smoking-related cancers (defined as lung, bladder, head and neck, kidney and pancreatic cancers) among relatives of patients with lung cancer. They did not find evidence of familial aggregation of smoking-related cancers among young people with lung cancer ($\leqslant$55 years old). They also found no increased risk of lung cancer among relatives of never-smoking people. However, the number of never-smoking patients in their study was quite small ($<$10%).

Interethnic differences in the incidence of lung cancer attest further to a possible genetic component in the risk of lung cancer. A large US study on early-onset lung cancer (in patients $<$50 years old) found that the first-degree relatives of African American individuals have greater risk of lung cancer than Caucasian Americans.[34] Other supporting evidence for a genetic link in lung cancer carcinogenesis includes the recent finding of a major susceptibility locus that can influence lung cancer risk at the short arm of chromosome 6.[35]

The genetic inheritance of lung cancer possibly involves low-penetrance oncogenes or tumour suppressor genes. In addition, genetic differences in cancer susceptibility that may involve metabolism of carcinogens, DNA repair, apoptosis, angiogenesis and other hallmarks of cancer remain to be elucidated.

Environment

Passive smoking is a known cause of lung cancer among never-smokers. More than 50 studies have found an association between passive smoking and lung cancer.[36] The pooled excess risk of lung cancer from exposure to spousal smoking was about 20% for women and 30% for men, whereas exposure to environmental tobacco smoke at the workplace increases the risk to about 12–19%. However, passive smoking cannot explain all the lung cancer cases among never-smokers, as only an estimated 3000 deaths due to lung cancer in the US were attributable to second-hand smoke,[37] which leaves the majority of cases unaccounted for. Furthermore, molecular differences in tumours between smokers and never-smokers suggest that the causative factor(s) is unlikely to be tobacco smoke, as the same aetiological agent should usually result in similar genomic profiles.

Other well-described causes include indoor exposure to asbestos, radon, arsenic, chromium, nickel, tar and soot. However, only a few have been studied specifically in never-smokers. A review of literature on occupational lung cancer in never-smokers found that asbestos, radon decay products and possibly arsenic are occupational carcinogens.[38] Abbey *et al*,[39] in a study on never-smoking individuals, found that inhalable particles $<$10 μm in diameter showed a strong association with lung cancer deaths for males, while Gorlova *et al*[32] showed that exposure to dust in never-smokers was associated with an increased risk of lung cancer. There are many other causes that have been postulated and suggested by studies, but results of many are not duplicated, so the purported causative factors remain as postulations.

Many risk-evaluation studies focusing on never-smoking individuals have been performed in Asia. Several interesting postulations are discussed here. In Taiwan, investigators found a high prevalence of human papillomavirus (HPV) 16/18 among never-smoking female lung cancer patients compared with the males and suggested an association between HPV and lung cancer.[40] They further tested blood HPV DNA and found that the prevalence rate of HPV 16/18 in lung cancer cases was significantly higher than that among controls without cancer.[41] However, Shigematsu *et al*[42] did not find any relationship between the presence of high-risk HPV DNA sequences (HPV 16 and 18) and EGFR TK domain mutations in their tumour specimens from Taiwan.

A case–control study in Taiwan found a higher risk of lung cancer among women who waited until the cooking oil has been heated and did not use a fume extractor, suggesting that a proportion of lung cancer cases may be attributable to cooking oil fumes.[43] However, this was not duplicated in a study among Singapore Chinese women,[44] which could be related to different cooking practices. Other case–control studies have found that diet can affect the risk of lung cancer, including a protective effect from tomatoes and lettuce, and a detrimental effect from meat consumption.[45] Dietary

phyto-oestrogens have also been shown to be associated with a reduction in the risk of lung cancer.[46] Further analysis of a European study found that the combination of two common risk factors, low dietary consumption of lettuce and high exposure to environmental tobacco smoke, can increase the odds ratio of lung cancer among never-smokers by twofold.[47]

How do we interpret the abundance of studies, mainly case–control designs, which suggest the protective or detrimental effect of a particular environmental or genetic factor? The important thing to bear in mind is that the factors studied do not occur in isolation. Every individual is genetically heterogeneous and exposed to multiple factors within the environment. No doubt the environment plays a dominant role in most common cancers,[48] but the contribution of genetic factors cannot be simply dismissed. The myriad of ongoing gene-association studies attests to the importance of studying gene–environment interactions in lung cancer causation, and never-smokers represent the ideal subjects to examine unknown, yet important, environmental and genetic factors.

FUTURE DIRECTIONS

It is imperative that investigators adopt a consistent definition of a never-smoker in order to allow comparisons across all studies. Most studies define a never-smoker as one who either has never smoked at all or has smoked <100 cigarettes (or the equivalent amount of tobacco) in his or her lifetime, which is in line with that proposed by the World Health Organization.[49]

It has been consistently observed that most never-smokers are women, and that most women with lung cancer are never-smokers. Due to this intricate relationship between non-smoking status and women, it is important to unravel the associations between lung cancer, smoking status and sex. Whether never-smoking women are at an increased risk of lung cancer compared with men is still controversial, although Thun *et al*[9] found that the lung cancer death rates are higher in men than in women. Preliminary analysis of our cohort of patients with lung cancer seems to show that there are no differences between never-smoking men and women.

Another priority area would be gene–environment association studies that are needed to unravel important aetiological factors in the causation of lung cancer among the never-smokers. Due to the complexity of the interaction, these studies have to be of optimal design, quality and size in order to have clinically relevant outcomes. This will require international collaboration as well as close cooperation between clinicians, scientists and epidemiologists to achieve the goal in a realistic time. Detailed studies into the family history, environmental factors and polymorphisms in genes related to DNA repair and carcinogen metabolism would be of importance.

CONCLUSION

Understanding the biology of lung cancer in never-smokers will be important in the present era of targeted therapy and personalised medicine. Developing a robust genotype–phenotype correlation and selecting the right population[50] is going to be increasingly important. The days of non-selective killing of cancer cells with chemotherapeutic agents are numbered, as drugs that target a selected group of patients are now being developed. Never-smokers with lung cancer represent a select group of patients who may possibly be treated differently from smokers in the foreseeable future. The ongoing large randomised phase III study in Asia[51] focusing on never-smokers and light smokers is an example of studies that should continue to take place in the future. Henceforth, never-smokers with lung cancer should no longer feel ignored.

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