Lung Cancer in Asian Women

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Abstract

The incidence of lung cancer has been observed to be two to three times higher among Asian women. The mortality rate of lung cancer in Asian women has also significantly increased in the past few decades. The etiology for such increase remains elusive although studies have implicated and attributed it to both environmental factors and genetic predisposition. Among which, the most consistent findings have shown an association with exposure to oil vapor from high temperature cooking, the use of unrefined oil and indoor air pollution caused by open coal burning wok with inadequate ventilation. In addition, diet has been considered to be a contributing factor. Diets rich in anti-oxidants, such as fruits, leafy green vegetables, and vitamin A, may be protective, while cured meat, including Chinese sausage, and deep-fried cooking increased the risk. Human papillomavirus infection has also been linked to lung cancer among non-smoking females in a study in Taiwan. On the other hand, both active and passive smoking, may not be major risk factors for development of lung cancer in the Asian female population, according to the publications. The interplay between environmental and genetic factors seems to have a more fundamental role in lung cancer among Asian women. [NAJ Med Sci. 2009;2(2):69-73.]

Introduction

Lung cancer is one of the most common malignancies in the world, with a poor prognosis of approximately 15% overall survival in a 5-year period. Smoking is the most important risk factor for lung cancer. Smoking increases the risk of all histological sub-types of lung cancer, with the relative greater risk for squamous cell and small cell carcinoma than for adenocarcinoma. It was estimated that about 85 to 90% of lung cancer cases were attributed to smoking. Among women non-smokers, adenocarcinoma was most frequently observed. Interestingly, there is an increasing rate of adenocarcinoma and decreasing incidence of squamous cell carcinoma reported in men in United States and Europe. Most of these studies were done in Western countries that included male patients with lung cancer worldwide. When the researchers are taking a closer look, it's becoming clear that lung cancer is a different disease in women than it is in men. Early research indicates that susceptibility to tobacco smoke, estrogen and even differences in DNA may all play a role in the way lung cancer behaves in women.

However, recent data from Asian population, especially among female patients with lung cancer, suggest that other risk factors are as important, as smoking alone cannot explain the epidemiologic characteristics of lung cancer seen in some Asian countries. In these countries, the incidence of smoking is low among women. However, there is a relatively high incidence of lung cancer among them. Lung cancer incidence was observed to be two to three times higher among Asian women living in East Asia (Philippines, Hong Kong, Japan, and Singapore) as compared with women living in Western countries with similarly low female smoking rates. The researchers found a fourfold increase in the incidence of lung cancer for Chinese-American women and a twofold increase for Filipino-American women versus non-Hispanic whites of the same age living in the same areas, after taking into account smoking prevalence for each population. The contribution of other biological, environmental, occupational, and socioeconomic factors may be more important in a population with high lung cancer incidence but low attributable risk from smoking.

Active Smoking

In Singapore, the prevalence rate of smoking in the male population is 26.9% but only 3.1% for female subjects. This rate among the female population is much lower compared to that in the United States. However, the standardized adjusted rate for lung cancer in Singapore female subjects is among the highest in the Southeast Asian countries, whereas the smoking rate is among the lowest. Among them, the percentage of patients with lung cancer who were non-smokers was 36.3%, which is much higher than that seen in Western countries. In addition, among the non-smokers, 73.9% were women and 75% of them had adenocarcinoma. The high incidence of female non-smokers with adenocarcinoma is often seen only in the Asian population. The possible etiologic factors and risk factors are still largely unknown, and this is a relatively unexplored area of research.
Passive Smoking
Passive smoking has long been postulated as a contributory factor. However, the mean age at diagnosis for non-smokers was almost a decade earlier compared to smokers, which may argue against passive smoking as a significant factor. In addition, exposure to environmental tobacco smoke is difficult to quantify objectively, and therefore is subject to self-reported estimates, which are not accurate.\textsuperscript{16} It is known that there is a clear dose-response relationship between smoking and lung cancer, in which the risk increases with the number of cigarettes smoked, years of smoking, and earlier age at onset of smoking.\textsuperscript{17} Patients exposed to passive smoke would have a lower amount of carcinogen compared to the active smokers and should, by inference, acquire lung cancer later. But one epidemiologic study showed that the mean age at which non-smokers succumb to lung cancer was lower than that of smokers in Asian countries like Japan and Hong Kong.\textsuperscript{3}

Cooking Fumes
Several studies in the Chinese population have suggested exposure to oil fumes during cooking may be a significant risk factor among nonsmokers for lung cancer.\textsuperscript{14,15} Factors such as the type of cooking (deep frying or stir-frying), presence or absence of fume extractors, and duration of total cooking years may play a very important role in the etiology of lung cancer among Chinese.\textsuperscript{18,21} A case-control study of 672 women with lung cancer (65% never smoked) and 735 controls identified rapeseed oil fumes to be associated with increased risk for lung cancer.\textsuperscript{22} Another study indicates increased lung-cancer risk among Asian-American women is linked with the exposure to unrefined cooking oils.\textsuperscript{23}

Stir-frying more than 30 dishes per week was associated with a higher risk. Exposure experiments using cell lines have suggested emissions from heated rapeseed and soybean oil to be mutagenic.\textsuperscript{24} Several other case-control studies have further identified cooking oil fumes as a risk factor for lung cancer in Chinese women.\textsuperscript{18-26}

Coal fume exposure has also been reported to be associated with increased risk for lung cancer in Chinese women.\textsuperscript{21,27-28} A case-control study (965 patients and 959 controls) on Chinese women reported an increased risk for lung cancer with the use of heating Kang, a form of indoor heating that uses coal in Northern China.\textsuperscript{23} However, the same study did not detect a significant risk in persons exposed to fumes from coal stoves or coal burners. A more recent study detected increased risk for lung cancer in both men and women when exposed to burning coal as indoor heating fuel over a period of 30 years.\textsuperscript{28} The odds ratio was significant after adjusting for smoking and socioeconomic status. However, there have been other studies reporting no increased risk for lung cancer from coal fumes.\textsuperscript{19,22,26} A few other studies that reported higher risk neither achieved significance based on sample size.

Diet
Daily diet may be a factor for the development of lung cancer in Asian women. A hospital-based, case-control study demonstrated that fruit intake and the use of soy in Chinese women provided a protective effect against lung cancer.\textsuperscript{29} The same protective effect was observed with the consumption of green tea in a population-based, case-control study.\textsuperscript{30} Another study\textsuperscript{31} examined the relationship between smoking, dietary anti-oxidants, and lung cancer risk, indicating women who consumed five or more carrots per week had a relatively low risk to develop lung cancer compared with women who had not consumed carrots.\textsuperscript{32} Two prospective US cohorts also support this observation. The risk of lung cancer was significantly reduced in those who had consumed a variety of carotenoids for a maximum protective period of 4 to 8 years even after adjusting for residual confounding from smoking. Of note, the association was stronger in women than in men. Among female who never smoked, a significant 63% lower risk was noted.

Virus Infection
A study in Taiwan revealed the presence of human papillomavirus virus (HPV) DNA (types 16 and 18) in the cancer cells of non-smoking women with lung cancer.\textsuperscript{33} HPV infection is a well-recognized causative factor of cervical cancer. Among them are types 6 and 11 HPV viruses, which are associated with intraepithelial neoplasia, and types 16 and 18 HPV viruses, which are associated with invasive cervical carcinoma. Using polymerase chain reaction (PCR) and \textit{in situ} hybridization HPV DNA was detected in the tumors of 49% of women with lung cancer who also had a history of high-grade cervical intraepithelial neoplasia (grade III).\textsuperscript{34} Interestingly, HPV infection seems to be most associated with squamous cell lung cancer. Studies in Japan have detected HPV DNA (serotypes 6, 11, 16, and 18) in well-differentiated squamous cell carcinoma and in adenocarcinoma cells that were adjacent to squamous cell carcinoma.\textsuperscript{35,36} It is also quite possible that an association of HPV in lung cancer reflects the coexistence of increased and earlier smoking behavior with a peculiar sexual behavior.

Genetic Abnormalities
The development of lung cancer is the end result of a complex interplay of multiple factors\textsuperscript{7} including carcinogen exposure, metabolism, and genetics. Tobacco contains more than a hundred diverse mutagens and carcinogens, including polycyclic aromatic hydrocarbons, N-nitro amines, and aromatic amines. Inhalation of these chemicals has been attributed to the foremost causative risk in lung cancer development. Even after smoking cessation, the initial damaging effects remain for an extended period.

Enzymes including the phase I activating and phase II detoxifying enzymes play a crucial role in the metabolism of tobacco-related carcinogens. While phase I enzymes (i.e., cytochrome P450, monoxygenases) activate carcinogens to reactive intermediates, phase II enzymes serve to convert these same reactive intermediates (i.e., reactive oxygen species) to inactive conjugates that are more water soluble and hence excreted more readily. If undetoxified, those active metabolites bind to DNA forming DNA adducts. Polymorphisms have been found to alter the metabolic activity of both those phase I and phase II enzymes. It shows that women have higher levels of these DNA adducts when compared to men.\textsuperscript{38-39} The higher DNA adduct levels were
also found to be associated with the expression of the cytochrome P4501A1 (CYP1A1) gene, an aryl hydrocarbon hydroxylase enzyme. This enhanced enzyme inducibility causes bioactivation of benzoarene, a polycyclic aromatic hydrocarbon found in cigarette smoke. Increased adduct levels correlated with CYP1A1 levels, which were substantially higher in female than male subjects. It remains unclear whether the levels of CYP1A1 in Chinese women can be further induced by their unique environmental factors, such as oil vapors.

A receptor for the autocrine growth factor, gastrin releasing peptide receptor (GRPR), has been also identified in lung cancer. The GRPR gene is on the X chromosome and escapes X-inactivation. It is expressed more frequently in female non-smokers (than male) and is activated earlier in response to tobacco exposure.

There is a study suggested that the polymorphisms of the HER-2 gene are associated with an increased susceptibility to lung cancer in females, non-smokers and non-drinkers subgroups in the Korean population.

Many genetic and epigenetic alterations of tumor suppressor gene and oncogenes have been demonstrated in lung cancer. Among them, smoking causes the most frequent alterations in p53 and K-ras genes. In response to DNA damage the p53 arrest the cell cycle in both the G1 and G2 phases to allow for DNA repair or apoptosis. Mutations abrogate p53 such key arrest and perpetuation of DNA damage, which consequently inhibit the normal apoptotic mechanism. Smoking increases p53 mutation and the formation of DNA adducts. Women have been found to have higher levels of pulmonary DNA adducts per pack-year than men. Of the Ras family of proto-oncogenes, K-ras is the most frequently affected gene. As in the p53 gene mutation, the formation of DNA adducts secondary to the effects of smoking appears to play a pivotal role. Women are three times more likely to carry the K-ras mutation than men. In most studies Ras mutations are predominantly associated with adenocarcinoma.

Differences in DNA repair capacity have been implicated in the pathogenesis of lung cancer. A complex family of proteins function to remove damaged DNA segments and/or to repair mismatched nucleotides. Deficiencies in this process are unequivocally mutagenic and carcinogenic, thus clearly lead to cancer. Case-control studies have been used to evaluate the repair of tobacco carcinogen-induced DNA adducts and lung cancer risk using lymphocytes isolated from newly diagnosed lung cancer patients or from age, sex, and smoking status-matched control subjects. Lymphocytes were cultured and transfected with a plasmid containing a reporter gene, followed by exposure to a known tobacco-derived carcinogen, benzo(a)pyrene diolepoxide. If the plasmid DNA was damaged, the reporter gene would not be expressed. The results showed that lymphocytes from younger patients with a family history of lung cancer, and female patients had a lower DNA repair capacity and a higher lung cancer risk.

Hormonal Influences
With observation of increasing rates of lung cancer in women and their increased susceptibility to the detrimental effects of environmental factors such as tobacco smoke compared to men, female steroid sex hormones should be considered as another layer of complexity in lung carcinogenesis. Indeed, estrogen has been found as an important factor in the pathogenesis of breast, endometrial, and ovarian cancers. Estrogen receptors are abundantly expressed in both normal lung tissue and lung tumor cell lines. β-Estradiol has a proliferative effect on normal lung fibroblasts and lung cancer cell lines in vitro. However, β-estradiol caused a 17-fold increase in cellular proliferation in lung cancer-derived cell line as opposed to only a 3.8-fold increase in normal lung, suggesting an increased responsiveness of malignant clones to estrogen.

It appears that estrogen may promote cancer growth by working in concert with EGFR (epidermal growth factor receptor), a gene involved in cancer development. However, a study suggests that the selected polymorphic variants in the estrogen biosynthesis and metabolism pathways are unlikely to be major genetic modifiers of the prevalence of EGFR-mutant NSCLC. On the other hand, women with lung cancer always live longer. So estrogen actually may play a role in survival, but we don't yet understand its protective effect.

A Boston Study
A case-control study of lung cancer in the metropolitan Boston area found that Asian immigrants with lung cancer have more advanced stage of disease, more prolonged symptomatology, and reduced survival rate, compared with non-Asians. A similar predominance of advanced stage lung cancer was also reported in China. These observations raise the possibility that Asian patients with lung cancer delay seeking medical attention despite having serious symptoms.

Language may be an important potential barrier, causing delay in seeking medical care as more than 80% of Asian patients in this study required an interpreter. This delay may have been caused by the cultural reluctance to accept western-style medical care. Also, reliance on traditional Asian methods of treatment may explain this finding. It has been also reported that a higher incidence of large cell carcinoma was found in the Asian group. The ethnic differences and outcome in lung cancer found in these studies may reflect an important interaction between genetic make-up and environmental exposure. For example, polymorphisms in the NAD(P)H:quinone oxidoreductase (NQO1) enzyme and in the microsomal peroxide hydrolase gene may be risk factors for smoking-associated lung cancer in Asia.

Occupational or environmental carcinogen exposures also differ between Asians and non-Asians. These studies did not specifically examine lung cancer and its risk factors in Asian women.

Summary
Cooking fumes, particularly from frying, contain proven carcinogens, and the resulting indoor pollution from these fumes, seems to play a very important role for the increased incidence of lung cancer in Asian women, compared with other contributing factors. Simple public health measures, such as wearing a mask while cooking, improving ventilation
of smoke and avoidance of certain cooking methods, may prove to be effective in preventing lung cancer. However, the evidence for indoor coal fumes is more controversial and requires additional studies to be considered as a major risk factor for lung cancer in this ethnic group. Future cohort and case control studies are required in this population. More laboratory and animal models are needed to identify the causative effect of possible carcinogens dispersed through fumes from high temperature cooking oil and coal burning on lung cancer development. The genetic basis of susceptibility and the effects of hormones also need to be explored further.

References


