Gender Difference in Lung Cancer Susceptibility

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ABSTRACT

Several epidemiological studies indicate that for a given number of cigarette smoked, females may be at higher risk of lung cancer compared with males. Females who smoke appear to be at higher risk of developing small cell lung cancer than squamous cell lung cancer, whereas men who smoke have a similar risk for the two histologic conditions.

Molecular epidemiological studies have also indicated gender differences in the genetic and biochemical alterations in lung cancer. Higher levels of polycyclic aromatic hydrocarbon-DNA adducts were observed in female lung cancer patients compared with males, even though the level of tobacco carcinogens was lower among the females than among the males. A higher frequency of G to T transversion mutations in the p53 gene has been observed in females compared with males. Gender differences have been identified in the expression of cytochrome P4501 A1 gene or gastrin-releasing peptide receptor gene, with females exhibiting higher gene expression.

Thus, the risk for lung cancer is consistently higher in females than in males at every level of exposure to cigarette smoking; odds ratios for an association of lung cancer with smoking are 1.4-fold to 1.9-fold higher for females than for males, depending on the histologic type of lung cancer.

Whether lung cancer represents a different disease in women than in men is unclear. If the hypothesis regarding gender differences in genetic susceptibility to lung cancer proves to be true, education for reducing passive and active exposure to cigarette smoke must have a high priority for female's health.

Key words : Lung cancer, Gender difference, Polymorphism, Epidemiology

1. Introduction

Lung cancer mortality among females has been increasing in recent years in Japan as well as in other developed countries. In Japan, lung cancer is now the third leading cause of death from cancer for females [1)]. Although lung tumors are classified into many different histopathologic subtypes, the predominant risk factor for all tumor types is cigarette smoking. Differing distributions of histologic types of lung cancer between males and females may be associated with differences in smoking patterns, but this does not fully explain the observed gender differences. Endogenous factors related to gender have been suggested to be determinants of gender differences in the distribution [2, 3)].

Epidemiological studies are useful to determine whether gender plays a role in lung carcinogenesis. Those studies so far have not led to a uniform conclusion. Molecular epidemiology of cancer involves the use of biomarkers of exposure and response in studies of exogenous or endogenous agents and/or host factors that play a role in human cancer etiology. This approach has the potential to identify susceptible individuals.

In this paper, we discuss the gender difference in lung cancer, with special emphasis on the genes of drug metabolizing enzymes, DNA adduct levels and the p53 tumor suppressor gene.

2. Epidemiological studies

In a large case-control study conducted in Western Europe, Lubin and Blot[4] found that the increase in relative risk (RR) with increasing years of smoking and number of cigarette smoked per day tended to be greater for females than males, and this finding held up across histologic types of lung cancer[5]. In a population-based study McDuffie et al.[6] observed that females were diagnosed with lung cancer at a younger age than males despite the fact that they consume fewer cigarettes. Brownson et al.[7] reported higher odds ratio (OR) in women compared with men for all histologic types except adenocarcinoma. Risch et al.[8] and Harris et al.[9] found a higher OR for females compared with males for all major histologic types of lung cancer. Osann et al.[10] and Shoenberg et al.[11] found that the OR for small cell carcinoma was more than 2-fold higher in females but the ORs were similar for squamous cell carcinoma. The data from the studies of Schoenberg[11], Brownson[7], Osann[10] and Risch[8] and their collaboration show that women were from 2.3-fold to 7.6-fold more likely to develop small cell lung cancer than men (Table 1). Zang and Wynder[12] in a hospital-based case-control study found dose-response ORs over cumulative exposure to cigarette smoking were 1.2-fold to 1.7-fold higher in women than in men for the three major histologic types of lung cancer. These differences were more pronounced for small cell carcinoma. They concluded that the observed gender-difference cannot be explained by differences in baseline exposure, smoking history, or body size, but that it is likely due to

Table 1 Odds ratios and 95% confidence intervals for cigarette smoking and lung cancer histologic types

Researcher	Squamous cell carcinoma		Small cell carcinoma		Adenocarcinoma	
Study place (ref.)	Males	Females	Males	Females	Males	Females
Schoenberg et al. USA (11)	18.9* (7.0-51.3)	10.6 (6.8-16.6)	22.9 (3.2-166)	59.0 (21.6-161)	4.8 (1.9-12.0)	3.6 (2.6-5.0)
Brownson et al. USA (7)	11.1** (9.5-12.9)	20.1 (16.4-24.8)	11.4 (9.1-14.2)	37.6 (28.5-49.3)	8.2 (6.9-9.7)	6.9 (6.1-7.9)
Osann et al. USA (10)	36.1 † (17.8-73.3)	26.4 (14.5-48.1)	37.5 (13.9-102)	86.0 (31.6-234)	17.9 (10.4-31.0)	9.5 (6.8-13.8)
Risch et al. Canada (8)	18.0 ‡ (5.5-111)	25.5 (7.93-156)	6.33 (2.2-27.0)	48.0 (10.5-849)	8.0 (2.3-50.6)	3.5 (1.8-7.1)
Kreuzer et al. Dutch & Italy(16)	42.3 ¶ (25.3-70.7)	7.5 (5.4-10.5)	40.1 (19.0-84.89)	9.5 (6.2-14.5)	5.1 (3.7-7.1)	2.2 (1.6-2.8)

*Adjusted for age, ethnicity, respondent type (self, spouse, other).
**Adjusted for age and carcinogenic job assignment (US Caucasian males).
† Adjusted for age and ethnicity. Controls were subjects diagnosed with cancers not associated with smoking.
‡ The same sex, residential area and matched for age (within 4 years).
¶ Adjusted for age and center.

a higher susceptibility to tobacco carcinogens in women. In a cohort study a tendency for a higher risk of lung cancer in females than males was found [13]. Only one case-control study did not find any gender difference [14]. In a large prospective population-based study, Prescott et al. [15] did not confirm previous reports from case-control studies of higher relative risk in women than in men for lung cancer associated with smoking. As shown in Table 1, a recent multicentre case-control study concluded that for comparable exposure to cigarette smoking, risk of lung cancer was comparable in women and men [16].

Various biases may affect comparisons of the differences and similarities between females and males. The higher risk for women than for men could be due in part to the lower baseline of absolute risk of lung cancer for nonsmoking women. Prescott et al. [15] found that baseline risks between males and females did not differ much. Several studies using baseline risk data demonstrated that the difference in baseline risk between male and female nonsmokers was small and therefore could not explain the 2- to 3-fold higher RR seen in females [17]. Another possible explanation for the gender difference is gender-related response bias. If women tend to underreport the amount they smoke more than men, this difference would result in overestimated risks associated with smoking among women. In the US, Brownson et al [18] reported that differential misclassification for smoking status did not vary significantly by gender. Smoking among Japanese women is not completely acceptable socially and it is therefore important to avoid differential reporting using appropriate method. Suitable biomarkers which can address these gaps in knowledge by providing direct measures of the internal and biologically effective dose of cigarette smoking as well as the biological effects and susceptibility factors should be applied in future studies.

3. Molecular epidemiological studies

Cigarette smoke contains several thousand chemicals, of which about 50 compounds are known carcinogens, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines and N-nitroso compounds. Some of these compounds are reactive carcinogens, but most are procarcinogens, which need to be activated by phase I enzymes such as those encoded by the cytochrome P450 (*CYP*) supergene family, and converted into reactive carcinogens. All these reactive carcinogens can bind to DNA and form DNA adducts capable of inducing mutations and initiating carcinogenesis. *CYP1*, *CYP2*, *CYP3* and *CYP4* are primarily involved in drug metabolism. Following phase I reaction, phase II enzymes such as glutathione S-transferases (GSTs) are responsible for detoxification of activated forms of PAH epoxides.

Since advances in molecular biology have allowed many allelic variants of several drug-metabolizing enzymes to be characterized at the molecular level, specific nucleotide changes have been identified as the basis for altered protein structure and/or function. Therefore, the existence of the high risk genotype in an individual can now be determined easily. The existence of multiple alleles at loci of those enzymes may result in individual differences in susceptibilities [19]. Since genetic polymorphisms have been found for both phase I and phase II enzymes, risk assessment sensitivity could be increased if polymorphisms in both phases of enzymes are taken into consideration as biomarkers for susceptibility to cancer. It is likely that an individual with the high risk genotype (either a genotype coding for a more active phase I enzyme or a less efficient phase II enzyme, or both of those) might be at higher risk of cancer than an individual with the opposite genotype (combination).

The gene product of CYP1A1 catalyses the first step in the metabolism of PAHs and CYP1A1 inducibility is considered important in determining individual susceptibility to lung cancer [20]. Women had a larger cancer risk than men if they possessed the mutant *CYP1A1* (exon 7) genotype [21]. Mollerup et al. [22] found that female smokers exhibited a significantly higher expres-

sion level of lung *CYP1A1* than men. In addition, the level of PAH-DNA adducts were related to expression of *CYP1A1* mRNA in target tissue, indicating that *CYP1A1* expression may be an important factor in influencing gender difference in PAH-DNA adduct levels in the lung. It is still unclear why female smokers have a higher expression of lung *CYP1A1*, but it is possible that hormones may be involved. Hormones are powerful regulators of gene expression and the levels of many of them differ between women and men. Brandenberger et al.[23] indicated that a cross talk between estrogen receptor (ER) and aromatic hydrocarbon receptor signaling pathways may modulate the expression of PAH metabolizing enzymes. ERs (subtypes ER-alpha and ER-beta) have been identified in human lung cells[24]. Taioli and Wynder[3] also indicated that women smokers on estrogen therapy were at increased risk for lung cancer. The *GSTM1* gene is suggested to be important in detoxifying BP diol epoxide. To date, three studies have examined gender differences in *GSTM1* enzyme. The first study by Alexandrie et al.[25] indicated that the *GSTM1* null genotype has a greater effect in female smokers than in male smokers. In the second study[26], female smokers with the *GSTM1* null genotype had the greatest lung cancer risk compared with other groups of females and males with different *GSTM1* genotypes. No significant gender difference was observed, although the combined *CYP1A1* and *GSTM1* genotypes conferred a higher OR for lung cancer in women than in men[21].

A good correlation between carcinogenic potency and DNA adducts formation ability has been observed experimentally for several carcinogens, including PAHs[27]. PAH-adduct levels were significantly higher in women[28,29]. These findings suggest that the susceptibility to DNA damage caused by PAH-type compounds may be higher in women compared with men despite smoking significantly less. The individual variation in DNA adduct levels may be large even at similar exposure doses, since this level is affected by not only the metabolism of carcinogens but also by DNA repair ability. There is little information on gender differences in DNA repair. Wei et al.[30] found that women have significantly lower DNA repair capacity than men. A significant gender-difference in autoantibodies to oxidative DNA damage from cigarette smoking was observed[31]. 4-aminobiphneyl (4-ABP) is another well-known human carcinogen found in cigarette smoke. 4-ABP-hemoglobin (4-ABP-Hb) adducts have been significantly correlated with recent past smoking[32]. Women had higher levels of 4-ABP-Hb adducts than men after adjustment for the amount of smoking[33].

p53 protein is a nuclear transcription factor with multiple functions, including cell cycle control, DNA repair and apoptosis. Alterations in the *p53* gene are the most common genetic alterations found in human malignancies. Many studies on the association between p53 gene mutations and smoking in lung cancer cases showed that the predominant mutation is G to T transversion. Approximately 30-40 % of the p 53 mutations in lung cancer are G to T transversions. Denissenko et al.[34] showed that PAH adducts form preferentially at the mutational hotspots in the p53 gene. PAH forms guanine adducts and G to T transversions in p53 has been found to be elevated in lung tumors from female smokers compared with male smokers[26, 29, 35].

A number of studies have shown that gastrin-releasing peptide (GRP), a member of the bombesin-like peptide family, plays an important role in carcinogenesis by stimulating cell proliferation. Growth stimulation by bombesin-like peptide has been shown to play an important role in human carcinogenesis. The effect of these peptides is mediated by interaction with the GRP receptor (GRPR). The GRPR gene is located on chromosome X in a region that contains several genes known to escape X inactivation. Thus, women may have two actively transcribed alleles of the *GRPR* gene, compared with one in men. A recent study

shows that the gene was expressed in 55% of non-smoking women and up to 75% of the smoking women with 25 or fewer pack-years. Among male non-smokers, the gene was not expressed at all, but was expressed in only 20% of male smokers with a similar smoking history [36]. They hypothesized that the observed gender difference in lung cancer risk may be explained by the expression of *GRPR* mRNA at a significantly lower exposure to tobacco smoke in females than males. Nicotine appears to induce *GRPR* expression in human lungs, thereby stimulating proliferation and the promotion step in lung carcinogenesis.

Besides the lung, the bladder is another site recognized to be susceptible to tobacco carcinogenesis in humans. There have been six case-control studies examining the gender-specific risk of bladder cancer in cigarette smokers. Five of six studies showed that the ORs for bladder cancer risk in female smokers were significantly higher (2 or more times) than those in male smokers.

4. Conclusion

The topic of gender difference in lung cancer risk is of importance to debate because lung cancer incidence is leveling off among men but continue to rise among women. In addition the percentage of women without occupation in the working population (people aged 18-60 years) is higher than that of men without occupation and those unemployed woman have less opportunity to undergo medical examination. There are epidemiological reports indicating than women smokers are 1.7-fold to 3.0-fold more likely to develop lung cancer than male smokers. The recent progress in the field of molecular biology will facilitate molecular epidemiological studies aimed at clarifying these important issues. While molecular epidemiological studies have suggested that there are important molecular differences between men and women that may be related to lung cancer risk, no mechanisms have yet been shown to have a direct role in the etiology of lung cancer. The hypothesis of a possible role of hormones has been put forward. Complex interactions between the ER and the aromatic hydrocarbon receptor pathways have been suggested. It is possible that circulating estrogen may interact with receptors present in the lung and modulate the expression of PAH metabolizing enzymes. It has been suggested that GRPR play a role in the promotion of lung carcinogenesis. Women may have two copies of the GRPR gene since it is located on the X chromosome, adjacent to the pseudoautosomal region, which escapes X inactivation. If blood can be demonstrated to be a good surrogate for airway cells, large-scale screening of GRPR expression in at-risk populations would be possible. These results could lead to new approaches in prevention through the early identification of populations and individuals at greater risk of lung cancer, especially women.

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