COMMENTARY

Women who smoke: are women more susceptible to tobacco-induced lung cancer?

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More women are smoking

The WHO estimates that lung cancer is the most frequent cancer in the world today and the global incidence of lung cancer is increasing at 0.5% per year due to the fact that the smoking epidemic continues to spread to developing countries. Lung cancer is strongly related to smoking. We know that ~85–90% of lung cancer patients are smokers. The cigarette epidemic is also becoming a serious issue in women's health. Presently, ~47% of men and 12% of women worldwide aged 15 years and over are smokers. In many developed countries the smoking prevalence is about the same among women and men and may in several countries surpass the rate in men in the near future (1–3). In several countries, lung cancer has surpassed breast cancer and is now the leading cause of cancer deaths among women.

For men in developed countries, the full effect of cigarette smoking can already be seen. For women in these countries, the peak of the tobacco epidemic has not yet arrived mainly due to a more recent spread of the habit to females. It is probable that the rate of lung cancer among females is increasing mainly because younger women smoke more. A question of great interest is in the younger generation of women that smoke as much as men, will their rates of lung cancer eventually become different from males? Is sex a possible factor in determining lung cancer risk? Recent results from both epidemiological and molecular studies may indicate a sex difference in the risk of developing lung cancer.

Epidemiological studies

Several recent epidemiological studies in the last 20 years have indicated that female smokers may be more susceptible to lung cancer than male smokers. In a population-based study McDuffie et al. observed that the age at diagnosis of lung cancer in women was younger even though the average male smoker had a higher tobacco use and started to smoke earlier (4). In western countries several groups have reported, in case-control studies, a higher risk of lung cancer among women. In a large study in Europe, Lubin and Blot observed an increased relative risk of lung cancer for women (5). Brownson et al. reported higher odds ratios in women compared with men for all histological types except adenocarcinoma (6). Risch et al. found a higher odds ratio for females compared with males for all major histologic types of lung cancer (7). A study by Harris et al. reported similar findings (8). The data sets from the studies of Brownson, Risch and Harris and their collaborators (6–8) show that women were from 1.3 to 2.9 times more likely to develop lung cancer than men. Osann et al. and Schoenberg et al. found that the odds ratio for small cell carcinoma was much higher in females but the odds ratios were similar for squamous cell carcinoma (9–11). In the US, Zang and Wynder in a hospital-based case-control study found that given the same level of lifelong exposure to cigarettes, women had ~1.5 higher relative risk of developing lung cancer than men (12). The sex difference was statistically significant for the three major histological types of lung cancer. In this study the incidence of lung cancer among men and women non-smokers was more than twice as high in women than in men. In a Norwegian cohort study a tendency for a higher risk of lung cancer in females than in males was found (13).

The epidemiological studies so far have not led to a uniform conclusion. A recent multicentre case-control study in Germany and Italy indicated that the relative risk estimates of lung cancer due to smoking did not differ substantially between men and women with similar levels of tobacco smoking (14). 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 lower baseline absolute risk of lung cancer for non-smoking women. However, in some of the studies the differences in the odds ratios were so large that it cannot be explained by differences in baseline exposure and smoking history. Another possible source of bias is the underreporting of smoking habits and confounding effects of passive smoking, which are probably higher in women than in men.

Laboratory studies

Epidemiological studies are useful to determine whether sex plays a role in lung carcinogenesis. Molecular epidemiological and laboratory studies may be used to identify factors involved and provide mechanistic information.

Lung carcinogenesis is mediated through an interaction between several putative carcinogens. Available evidence suggests that PAHs and tobacco-specific nitrosamines are major risk factors exerting their genotoxic effects through the formation of DNA adducts and mutations in transforming genes (15,16). There are several findings suggesting that levels of DNA adducts are important in the cause of lung cancer. In the light of the high complexity of carcinogenic compounds in tobacco smoke and their metabolism in the body, the DNA adduct level in the lung may be a good dosimetric exposure marker and also a useful parameter in the study of susceptibility to lung cancer. The extent of DNA-adduct formation depends on the balance between the rates of oxidation of the compounds, the rates of detoxification of the reactive products via conjugation and DNA repair capacity. In our laboratory, we investigated the relationship between exposure, lung DNA adduct level, mutations and genetic factors in lung cancer patients. By utilizing the post-labelling method for detection and quantita-
tation of hydrophobic DNA adducts we could show that lung cancer patients with high PAH–DNA adduct levels in their lung developed lung cancer after lower smoking dose and/or shorter duration than patients with low adduct levels. Interestingly, PAH-adduct levels were significantly higher in women suggesting that the susceptibility to DNA damage caused by PAH-like compounds may be higher in women compared with men despite smoking significantly less (17,18). PAHs are oxidized by phase I enzymes into reactive metabolites that are detoxified by phase II enzymes. The gene product of CYP1A1 catalyses the first step in the metabolism of PAH and CYP1A1 inducibility is considered important in determining individual susceptibility to lung cancer. By quantitative reverse transcription–PCR it was found that female smokers exhibited a significant higher expression 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 the CYP1A1 expression may be an important factor in influencing sex difference in aromatic/hydrophobic DNA adduct levels in the lung (18). 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. In vitro studies suggest a cross talk between estrogen receptor (ER) and aryl hydrocarbon receptor signalling pathways that may modulate the expression of PAH metabolizing enzymes (19). ERs (subtypes ER-alpha and ER-beta) have been identified in human lung cells (20–23). Studies also indicate that women smokers on estrogen therapy were at increased risk for lung cancer (24). To date, there have been few studies on differences in phase II enzymes between men and women. A study by Tang et al. indicates that the GSTM1 null genotype have the greater effect in female smokers than in male smokers (25). The GSTM1 gene is suggested to be particularly important in detoxifying BP diol epoxide.

Findings from studies on p53 mutations in lung cancer are supporting the adduct data. There are many studies showing an association between p53 gene mutations and smoking in lung cancer cases, and it has been demonstrated that the dominating mutational type in p53 is G to T transversions (26). Approximately 30–40% of the p53 mutations in lung cancer are G to T transversions. In vitro studies have shown that PAH adducts form preferentially at the mutational hotspots in the p53 gene (27,28). PAH forms quanine adducts and G to T transversions are induced preferentially. Interestingly, the frequency of G to T transversions in p53 has been found to be elevated in lung tumors from female smokers compared with male smokers (29,30).

Variation in susceptibility may also in part be due to a genetically determined variability in DNA repair. There is little information on sex differences in DNA repair. However, Wei et al. (31) have shown that women have a significantly lower DNA repair capacity (DRC) than men. DRC was measured in the host-cell reactivation assay utilizing lymphocytes transfected with a reporter damaged by B[a]P. Other lines of evidence for sex differences in lung cancer risk comes from studies on the gastrin-releasing peptide (GRP). Studies have shown that bombesin-like peptides such as GRP induce cell proliferation in various cell types, also human bronchial epithelial cells (32,33). The effect of these peptides is mediated mainly through and interaction with the gastrin releasing peptide 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 the non-smoking women and ~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 similar smoking history (25 or fewer pack years) (34). The authors hypothesized the observed sex difference in lung cancer risk may be explained by the expression of GRPR mRNA at a significantly lower exposure to tobacco smoke in female than males. Nicotine appears to induce GRPR expression in human lungs, thereby stimulating proliferation and the promotion step in lung carcinogenesis.

### Conclusion

The importance of sex difference in lung cancer risk is a current topic of debate. Recent epidemiological and laboratory studies may indicate a sex difference. However, the mechanisms are still unknown and so far little research has been done at the experimental level. Appropriate studies include identifying factors related to sex that influence the initiation, promotion and progression steps in lung carcinogenesis (Figure 1). Lungs in males and females experience a different hormonal environment. Levels of many hormones are different in males and females and many of them are powerful regulators of gene expression. Important elements in lung carcinogenesis may be hormonal regulation of genes involved in the metabolism of tobacco carcinogens and DNA repair, interactions of smoking and hormone status, hormones and the activation of growth promoting pathways, cross talk between various signalling pathways and the interaction between stroma and epithelial cells during tumor development.

### References

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