SEX-RELATED DIFFERENCES IN LUNG CANCER

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Abstract: Although controversial, one of the puzzles in lung carcinogenesis is that women may be at a higher risk of lung cancer than men. The mechanisms underlying the sex differences in lung cancer susceptibility is likely to be multifactorial. Molecular studies have pointed to sex differences in the metabolism of polycyclic aromatic hydrocarbons (PAH). We have reported higher levels of PAH-DNA adducts in the lungs of females compared to males although the females had smoked less. When expressing PAH-DNA adduct level in relation to smoking dose we found that adducts/pack year and adducts/cigarette/day were significantly higher among females. The expression of genes in the PAH bioactivation pathway was investigated and CYP1A1 was significantly increased in smokers compared to ex-smokers and never smokers. CYP1B1 was also increased in smokers although to a lesser extent than CYP1A1. When analyzed in relation to sex, current smoking females had a 3.9 fold higher median level of CYP1A1 mRNA compared to current smoking males. Median levels of CYP1A1 were similar among female and male ex-smokers and never-smokers, indicating similar un-induced CYP1A1 transcript levels in females and males. Lung DNA adducts were highly significantly related to CYP1A1 irrespective of smoking-status. Estrogen-regulated events affecting the lung, lung cancer prognosis, or handling of lung carcinogens could exert a selective effect on women. Estrogen receptors are expressed in the lung and increased intratumoral estradiol concentrations have been reported. Down regulating ERα/β by siRNA resulted in altered constitutive and induced expression of CYP1A1 indicating a role of these receptors in lung carcinogenesis. To get further insight into CYP1A1 regulation, we investigated the role of DNA methylation of the 5’-regulatory region of CYPIA1 in human lung, and evaluated its importance in lung adenocarcinoma.

Key words: DNA adducts, CYP450, estrogen receptor, DNA methylation.