Published in final edited form as:

Clin Lung Cancer. 2008 May ; 9(3): 140. doi:10.3816/CLC.2008.n.020.

Molecular Epidemiology to Better Predict Lung Cancer Risk

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Lung cancer is the most preventable of all of the major forms of cancer, with 85%–90% of lung cancer–related deaths resulting from active cigarette smoking.¹ An enormous effort has been undertaken attempting to better understand the underlying mechanistic factors involved in lung cancer susceptibility. In their review, Reid et al provide an overview of some of the potentially important markers for lung cancer susceptibility.² As described in their review, an abundance of studies have been performed examining the role of single-nucleotide polymorphisms (SNPs) in pertinent carcinogen-metabolizing and DNA repair enzyme genes and lung cancer susceptibility, with modest main effects observed for most SNPs examined. The authors correctly conclude that the ability to evaluate the combined effects of numerous pertinent SNPs in complex statistical models will be required. Reid et al also describe the importance of providing biomarker data, including DNA adduct levels, to better validate high-risk SNP modeling. Additional functional studies should also be incorporated into this validation, including an in vitro analysis of their effect on protein activity or expression and comparative genotype-phenotype modeling such as target tissue expression, activity analysis, or urinary metabolite analysis. A full assessment of the involvement of the enzymes to be targeted for susceptibility studies should be conducted. Is the enzyme in question expressed in target tissues such as the lung, and how active and well-expressed is that enzyme relative to other enzymes that perform the same function are some of the questions that should be posed when a molecular epidemiologic approach is undertaken. Not addressed in the review is the necessity of incorporating targeted haplotype analysis into future molecular epidemiologic studies and the incorporation of newly discovered SNPs demonstrated to be associated with lung cancer risk using genome-wide association analysis.

Perhaps the most timely issue addressed by Reid et al is the identification of the factors involved in the higher lung cancer risk observed in women compared with men, a risk that is particularly high for lung adenocarcinoma. As discussed in their review, women with lung cancer tend to be younger and have smoked less than men, and there is some evidence that women are more susceptible to tobacco smoke carcinogens. The authors point to a number of plausible mechanisms for this increased susceptibility, including potential induction of activating enzymes like CYP1A1 via crosstalk between the estrogen and aryl hydroxylase receptors,³ data which are supported by higher observed levels of *CYP1A1* gene expression in female versus male smokers.^{3,4} Not cited in this review are recent studies examining the role of the UGT2B17 deletion polymorphism in lung cancer risk. This enzyme was shown to be the most active hepatic enzyme against the major metabolite (4-[methylnitrosamino]-1-(3-pyridyl)-1-butanol; NNAL) of the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a carcinogen strongly associated with the induction of adenocarcinoma in rodent models.^{5–7} In case-control studies, lung cancer risk was linked

with increased risk specifically for lung adenocarcinoma in women but not in men.⁸ Like many other UGTs, UGT2B17 is active against a variety of steroids, including C19 steroids, and we have hypothesized that several UGTs may be steroidally regulated. Consistent with a role for estrogen in UGT regulation are recent studies demonstrating that another UGT involved in NNAL glucuronidation, UGT1A10 (Chen et al, unpublished results), was strongly induced by estrogen.⁹ As indicated in the review by Reid et al, much work needs to be performed to validate this estrogen link with UGT regulation and to better explore potential sex hormone–linked associations with lung cancer risk.²

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