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Molecular Epidemiology to Better Predict Lung Cancer Risk

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Abstract

Although it is clear that smoking causes lung cancer, it is not known why some smokers develop the disease while others do not. Little is also known regarding risk factors for lung cancer among never-smokers, particularly women, or why women with lung cancer are more likely to have a family history of cancer, to be diagnosed at a young age, or to have adenocarcinoma. The application of molecular epidemiology to the study of lung cancer risk might facilitate elucidation of these questions. In this review, the molecular epidemiology of lung cancer is discussed, with an emphasis on studies of genetic variability in metabolic pathways as a means for determining susceptibility. Work that has assessed intermediate markers of risk, such as DNA adducts, is also presented, as are studies of tumor tissue alterations, such as mutations and DNA methylation, in relation to risk of lung cancer. Finally, approaches to evaluating factors that might explain the differing epidemiology of lung cancer between men and women are also presented. It is likely that, by incorporating biomarkers of susceptibility, exposure, and effect, molecular epidemiologic approaches might better define factors that explain some of the variability in lung cancer risk.

Keywords

Biomarkers; DNA adducts; DNA methylation; DNA repair genes; XRCC1

Introduction

Since the early epidemiologic investigations of potential relationships between smoking and lung cancer in the 1950s, it has become clear that cigarette smoking causes lung cancer. However, despite the overwhelming evidence that tobacco smoke exposure is in the causative pathway of lung cancer, it is estimated that only 1 in 10 smokers develops the disease.[1,2] Further elucidation of the role of other exposures, such as asbestos, radon, particulate air matter, cooking fuel exhaust, special foods, and nutritional components, in lung cancer etiology does not explain this interindividual variability in risk associated with smoking. In the past 2 decades, there has been growing interest in the role of genetic differences in metabolism of tobacco smoke carcinogens, sensitivity to DNA damage and DNA repair capabilities, and other factors impacting carcinogenesis as explanatory factors

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for the development of lung cancer in some smokers but not all. Furthermore, the study of determinants of intermediate markers, such as DNA adducts, has also furthered our understanding of lung cancer susceptibility. Evaluation of tumor tissue characteristics, particularly in relation to genetic and nongenetic risk factors, might also inform our understanding of lung cancer etiology. The incorporation of these biomarkers of susceptibility, exposure, and effect into epidemiologic studies form the basis of molecular epidemiology and will be reviewed in this report.

Genetic Susceptibility to Lung Cancer

Although it is clear that smoking causes lung cancer, since the 1950s, there have been suggestions that a genetic component exists. Early work by Tokuhata and Lilienfeld[3] demonstrated that, even after controlling for smoking among relatives, the risk of lung cancer was increased among those with a family history of the disease. In 1990, Sellers and colleagues[4] used segregation analysis to determin that a major autosomal gene was associated with earlier age of onset of the cancer, and a locus on chromosome 6 has been identified through linkage analysis as associated with familial lung cancer.[5] The role of this susceptibility allele in sporadic lung cancer is unclear, and it is likely that some of the variability in lung cancer incidence results from more common differences between individuals. Other authors have explored the role of host factors.[6,7]

Early studies of genetic susceptibility focused on variability in metabolism of chemical carcinogens, with polycyclic aromatic hydrocarbons (PAH) as a primary focus, and much work has been conducted to determine the role of genetic variability in phase I/II enzymes in smoking-related lung cancer risk.[8] A number of polymorphisms in cytochrome P4501A1 (*CYP1A1*) have been extensively studied in epidemiologic studies, and meta- and pooled analyses have shown that some of the single nucleotide polymorphisms (SNPs) are associated with increased risk of lung cancer, particularly among specific subgroups, such as light or never-smokers.[9,10] The glutathione S-transferases (GSTs), which catalyze detoxification of a number of carcinogen metabolites as well as oxidative products, have been extensively studied in relation to lung cancer. A majority of studies have found that the null allele for *GSTM1* was associated with increased risk of lung cancer, but the increase in risk was slight.[11,12]

Genetic polymorphisms in genes that metabolize PAHs and N-nitrosamines have also been evaluated. Additionally, there has been focused research on pathways related to DNA repair, cell cycle control, and mediation of inflammation, but no clear strong relationships have been observed for any single genes.[13] It is possible that notable increases in risk will only be observed among those with a number of gene variants that together result in greater activation and lesser detoxification of chemical carcinogens found in tobacco smoke, deficiencies in DNA repair, and alleles in genes that regulate cell cycle, reduce inflammation, and control immune function (Figure 1). There has been extensive work on the role of DNA repair genes as a determinant of inherited susceptibility to lung cancer.[7,13] Several DNA repair genes have been evaluated with respect to lung cancer risk particularly XRCC1 (X-ray cross-complementing group 1),[14,15] XRCC3, ERCC1 (excision repair cross-complementing group 1), XPD,[16] and XPA,[17] and showed a link with tobacco exposure.

XRCC1 and ERCC2 were evaluated alone and in combination.[14] Overall, the XRCC1 polymorphism was found to be a significant high-risk allele. When stratified by smoking status, this risk estimate increased among nonsmokers whereas heavy smokers showed an inverse risk, consistent with a large case-control study completed in Europe.[15] Other smaller studies[18] did not find associations between lung cancer and XPD or XRCC3 polymorphisms. An SNP of XPA was found to be associated with lung cancer primarily among heavy smokers with occupational exposures to a variety of carcinogens, suggesting a gene-environmental interaction for this particular gene.[17]

Studies of genes related to cell cycle control and lung cancer have been less numerous. Zhang et al reported on a large Chinese case control study of > 1000 subjects in each group exploring the relationship of mouse double minute 2 and TP53 to lung cancer. While both genes were independently associated with lung cancer, an association strengthened when both SNPs were combined and in smokers.[19]

Genes related to inflammation through pro- and anti-inflammatory pathways have been associated with lung cancer. Campa et al reported on several genes related to inflammation and prostaglandin synthesis, cyclooxygenase-2 (COX2), interleukin (IL)–6, IL-8, and peroxisome proliferators-activated receptor γ.[20] Only 1 allele of COX2 was associated with a significant risk of lung cancer. Three polymorphisms of IL-10 were found to be related to lung cancer,[21] as were 2 SNPs of the pro-inflammatory IL-1β.[22] Recent studies have also suggested ethnic differences in several cytokines, including IL-1, IL-6, and IL-10.[23]

Clearly, the ability to evaluate the combined effects of numerous polymorphisms in complex statistical models requires extremely large sample sizes and the establishment of consortia that pooled data, such as the Genetic Susceptibility to Environmental Carcinogenesis Consortium[24] and the International Lung Cancer Consortium,[25] which will greatly facilitate future efforts to construct profiles of genetic susceptibility to lung cancer.

Intermediate Markers of Lung Cancer Risk

Tobacco smoke carcinogens are activated to reactive metabolites, and these metabolites have the capabilities to bind to DNA and form DNA adducts, which if not repaired, can result in mutations or in errors in replication. Thus, DNA adducts serve as a marker of exposure, which also incorporates capabilities in metabolism, DNA repair, and cell cycle control.

Most, but not all, studies have found that DNA adducts are higher in populations exposed to chemical carcinogens than in controls.[26,27] Adducts in lung tissue and in mononuclear cells have been associated with risk of lung cancer, and data from a prospective cohort show that DNA adducts can predict later risk of lung cancer, particularly among smokers.[28] There has also been extensive data on the relationships between DNA adducts and genetic differences in carcinogen metabolism. Because of similar levels of exposure (eg, number of cigarettes smoked), there are enormous interindividual differences in DNA damage levels, indicating that SNPs in genes involved in the activation and detoxification of these carcinogens might impact adduct formation and cancer risk. In fact, a review of 10 studies looking at the

relationship between *CYP1A1*2* and adducts in lung tissue found significant associations between BPDE-DNA adducts and genotype.[29]

Recently, a group of investigators in the Netherlands used discriminant analyses to investigate the association of genetic polymorphisms with DNA adduct formation among healthy smokers.[30] Investigating 19 polymorphisms in 12 genes involved in carcinogen metabolism, DNA repair, and oxidant metabolism, the authors found that *GSTM1* null genotype, *mEH*2*, and *GPX1*1* were strong predictors of adduct levels. Those with higher levels of combined alleles had higher risk of adducts than those not carrying risk alleles.

Lung Tumor Characteristics

Base changes resulting in amino acid substitutions that disrupt the p53 tumor suppressor gene are thought to be important in the development of lung cancer and might additionally indicate etiologic pathways. In patients with lung cancer, p53 mutations are most common in exon 5 and are G → T transversions. The relationship between smoking and the occurrence of G → T transversions in p53 is well documented, and a mechanistic link was established between BP (benzo[a]pyrene) and the G → T transversion.[31] These studies demonstrated that BP preferentially forms adducts at codons that are hot spots for mutations in lung cancer. The International Agency for Research on Cancer database of approximatey 2000 mutations in lung cancer demonstrates differences with smoking status; p53 mutations are more common in squamous cell carcinoma (SCC; 65%) than in adenocarcinoma (33%), and more G → T transversions are observed in SCC (45%) than in adenocarcinoma (23%).[32,33] Gealy et al evaluated p53 and K-*ras* mutations in lung carcinoma of smoking and nonsmoking women.[34] In nonsmoking women, 83% of the p53 mutations were transitions, whereas only 20% of the tumors of smoking women had transitions in p53. Among smokers, mutations were mainly transversions (60%) and deletions (20%). Interestingly, transition mutations predominate in breast and ovarian cancer, similar to that in lung cancer in nonsmoking women. For the K-*ras* oncogene in lung cancer, mutations appear to be more common in smokers than in nonsmokers,[35] with most mutations found in K-*ras* codon 12. It is likely that additional evaluation of relationships between gene mutations in lung tumors and lung cancer risk factors will provide more information on who, among smokers and nonsmokers, is likely to get lung cancer.

An additional tumor characteristic that is getting more attention recently is hypermethylation of promoters in key genes in growth control, including genes involved in cell cycle control, apoptosis, cell differentiation and proliferation, and DNA repair, likely leading to gene silencing. A fairly large body of work has been conducted in this area, showing relationships between methylation and lung cancer risk. Recently, in a prospective cohort at high risk for lung cancer, Belinsky et al showed that the prevalence of methylation of gene promoters increased as the time to lung cancer diagnosis decreased.[36] Six of 14 genes were associated with a > 50% increased lung cancer risk, and methylation of ≥ 3 of those 6 genes was associated with a 6.5-fold increase in risk. The study of gene methylation in the molecular epidemiology of lung cancer is still young, but shows much promise for the future not only for a better understanding of lung cancer etiology, but also for identifying people at high risk for lung cancer.

Lung Cancer in Women

Within the past 3 decades there has been a shocking rise in the number of deaths from lung cancer in women. Although it is well established that cigarette smoking is the major risk factor for lung cancer in men and women, the proportion of never-smoking patients with lung cancer is higher in women than in men, with age-adjusted incidence rates ranging from 14.4–20.8 per 100,000 person-years in women, and 4.8–13.7 per 100,000 person-years in men.[37] Whether or not lung cancer risk is higher in women than in men could still be debated, but it is clear that the epidemiology of lung cancer varies remarkably by sex.[38] Women with lung cancer are more likely than men to have adenocarcinoma, to be younger at diagnosis, to have smoked less, and to have a first-degree relative with lung cancer.[39,40] There is evidence that, at a similar smoking dose, women might be more susceptible to the carcinogens in cigarette smoke than men,[41] although some investigators have not found such an association.[42] Molecular epidemiology might be useful for addressing these disparities between men and women. Higher lung cancer risk for women than men is supported by biomarker studies. In studies using the [^{32}P] postlabeling and/or immunologic assay, DNA adducts were higher in normal adjacent nontumor tissue of women than men after adjustment for level of smoking.[43] Among nonsmoking subjects, DNA adducts were higher in cases compared with controls and in women compared with men.[44] In a study of antibodies to 5-hydroxy-methyl-2'-deoxyuridine, a DNA base that is oxidized by tobacco smoke, female smokers had higher levels than male smokers,[45] reaching peak levels at a lower cumulative smoking exposure than men. Interestingly, levels were highest in women aged < 50 years, indicating that hormones could play a role in greater susceptibility to damage among women. Together, these results suggest a potential mechanism (increased DNA damage in women compared with men) for the hypothesized increased risk for lung cancer in women. This mechanism is also supported by studies of bladder cancer in which the slope of the linear regression lines of the 3- and 4-ABP-hemoglobin adducts by cigarettes per day were significantly steeper in women compared with in men.[46]

A number of biologic mechanisms have been proposed to explain higher lung cancer susceptibility among women, mainly related to sex differences in nicotine and carcinogen metabolism by cytochrome P450 and other phase I/II enzymes. For example, 2 studies have found that, in squamous and small-cell carcinomas, the prevalence of the null *GSTM1* genotype was higher among female compared with male patients with lung cancer[47,48] and compared with all controls, and in a study at Fox Chase Cancer Center,[49] the effects of *CYP1A1* high inducibility alleles were greater among women than men (odds ratio [OR], 4.98 vs. 1.37), as were the combined effects of *CYP1A1* and *GSTM1* null genotypes (OR, 6.54 vs. 2.36). *CYP1A1* messenger RNA (mRNA) levels have been shown to be higher in the lung tissue of female smokers compared with male smokers, and in vitro studies suggest a crosstalk between estrogen receptor and aryl hydrocarbon receptor signaling pathways that might influence levels of metabolism enzymes.[50] Recently, in a study of metabolic enzymes in normal lung tissue, it was shown that the median level of expression of *CYP1A1* in women was almost 4 times that found in men, with lung adducts significantly related to *CYP1A1*.[51] There are also clinical and epidemiologic data to support a role for endogenous and exogenous hormones in relation to lung cancer risk,[38,52,53] although results from other

studies have not supported this inverse association.[54,55] Moreover, there are molecular characteristics of tumors that indicate that steroid hormones might be involved in neoplasia.[38,56] These factors, coupled with the fact that more nonsmoking women than men are diagnosed with lung cancer, support a possible role of steroid hormones in lung cancer susceptibility among women and reasons for the sex differences in lung cancer related to histologic type, smoking habits, and age at onset.

Conclusion

Over the past 2 decades, enormous strides have been made in better understanding lung carcinogenesis, with the implementation of molecular epidemiologic biomarker studies in identifying who is most susceptible and how lung cancer occurs and progresses. With the rapid advances in technology to interrogate the human genome, there will be more opportunities to determine genetic profiles (combinations of numerous gene variants) to identify those most at risk of lung cancer. Through the establishment of consortia to greatly expand sample sizes, it is likely that many of the unanswered questions in lung cancer epidemiology will be answered.

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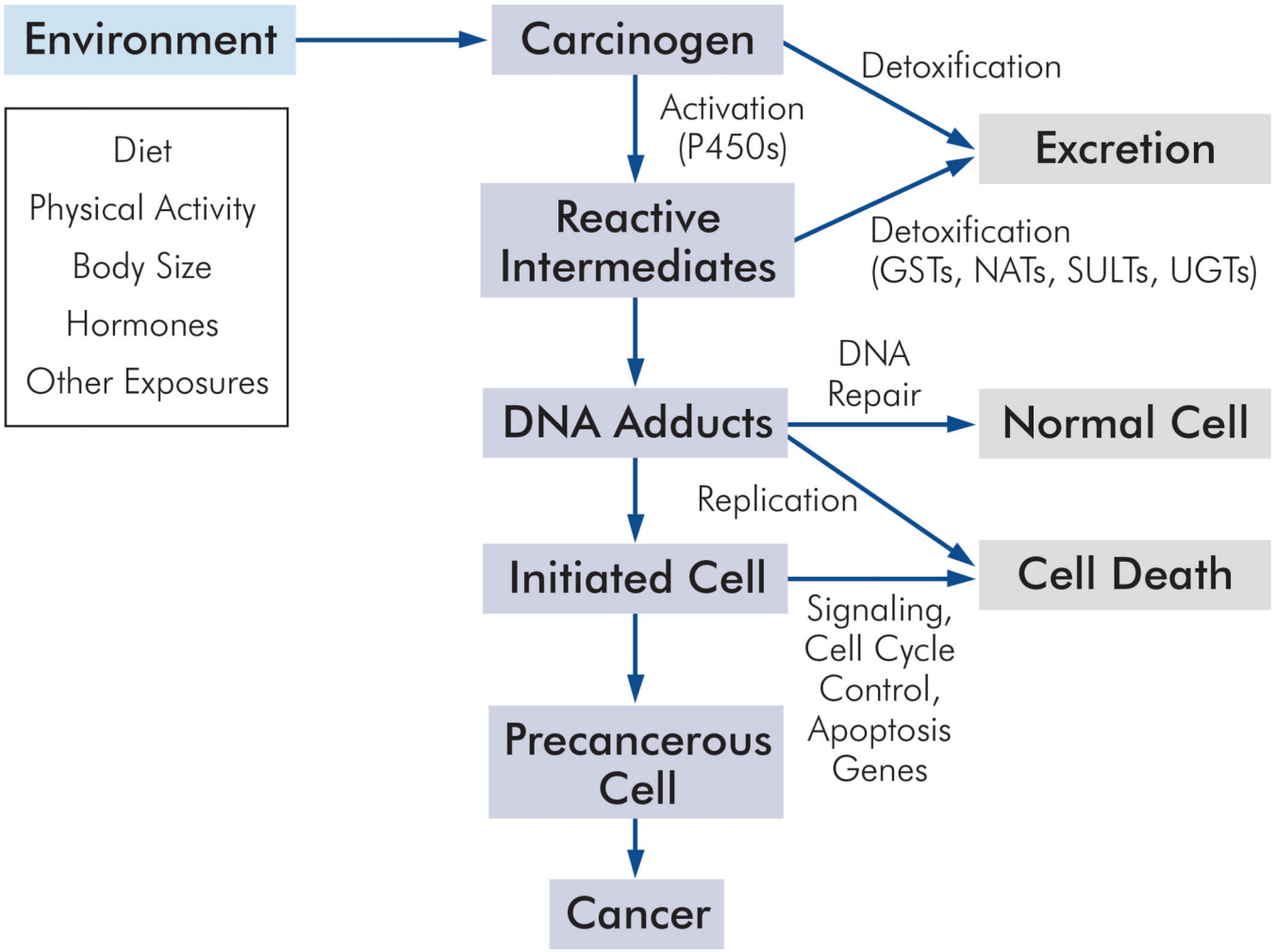

Figure 1.

Environmental and Metabolic Factors Affecting Susceptibility to Cancer Development

Abbreviations: GSTs = glutathione-*S*-transferases; NATs = *N*-acetyltransferases; SULTs = sulfotransferases; UGTs = UDP-glucuronosyl transferases