Pulmonary Perspective

Familial Lung Cancer

Genetic Susceptibility and Relationship to Chronic Obstructive Pulmonary Disease

Ann G. Schwartz and John C. Ruckdeschel

Population Studies and Prevention Program, Karmanos Cancer Institute; and Department of Internal Medicine, Wayne State University, Detroit, Michigan

Lung cancer continues to be the leading cause of cancer death, and although most lung cancer is attributable to cigarette smoking, underlying genetic susceptibility is suggested by studies demonstrating familial aggregation. The first family linkage study of lung cancer has identified linkage of lung, laryngeal, and pharyngeal cancer in families to a region on chromosome 6q23–25. Because lung cancer and chronic obstructive pulmonary disease (COPD) are known to aggregate in families beyond shared risk associated with smoking, the linkage results are compared and contrasted with results from genomewide linkage and association studies and candidate gene studies searching for genes for lung cancer, lung function, and COPD. Linkage on chromosome 6q to both lung cancer and lung function, and on 12 to lung cancer, COPD, and lung function, together with overlap in candidate genes for these outcomes, suggests that future research into underlying genetic mechanisms of lung disease would benefit from broadening the collection of family history data and better defining the “high risk” population. As familial risk of lung disease is better defined, referral to screening programs and prevention trials can be better targeted to reach families with both a history of lung cancer and COPD.

Keywords: chronic obstructive pulmonary disease; genetics; linkage; lung cancer

Lung cancer remains at epidemic proportions and continues to be the leading cause of cancer death in both men and women (1). It is well accepted that 85 to 90% of all lung cancers are attributable to cigarette smoking (2), so that our major focus has been on prevention of initiation of smoking through youth-oriented programs and smoking cessation efforts. Through extraordinary personal and public health measures, the rate of smoking among adults has dropped substantially in the past two decades and there is now a concomitant drop in lung cancer rates (1). There remain, however, an estimated 46 million former smokers who continue to be at risk, in addition to the 45.8 million who continue to smoke (3).

Because cigarette smoking is such an overwhelming risk factor, and preventable, the importance of family history and genetic susceptibility to lung cancer risk has often been overlooked. The first reports of familial aggregation of lung cancer were

published over 40 years ago (4). Most observers have believed that the similar smoking environment within the family setting or workplace accounted for findings of familial aggregation, but even after adjusting for smoking patterns, individuals with a family history of lung cancer are at approximately two- to threefold increased risk of developing this disease (reviewed in References 5–7).

This article attempts to place in context for the practicing pulmonary specialist and internist the role of familial risk in lung cancer and to suggest an important linkage to familial risk for chronic obstructive pulmonary disease (COPD) and the potential for shared genetic susceptibility.

THE GENETIC EPIDEMIOLOGY OF LUNG CANCER

Recently published work by Bailey-Wilson and coworkers (8) describes results of the first family linkage study searching for genes for lung cancer. This work was developed and conducted by the Genetic Epidemiology of Lung Cancer Consortium (GELCC), which includes a multidisciplinary team of investigators studying the genetics underlying lung cancer susceptibility. Linkage studies require the construction of large extended families, with multiple affected relatives from whom DNA can be obtained or genotypes inferred by genotyping spouses and offspring. Hundreds of genomewide markers are typed in family members to identify chromosomal regions that are inherited with disease. Although the evidence pointing to a gene for lung cancer is substantial, problems associated with the conduct of a linkage study in lung cancer are even greater. The average age of lung cancer diagnosis is 70 years and 5-year survival after a diagnosis continues to be poor, at 15%, so affected family members are typically deceased, as are their parents, siblings, and spouses. Lung tissue is often not available because not all lung cancer is detected at a resectable stage. The confounding risks due to variations in patterns of cigarette smoking also need to be considered. It took the multiinstitutional, multidisciplinary efforts of GELCC to conduct this study.

Bailey-Wilson and colleagues (8) report that 13.7% of the over 26,000 patients screened with lung cancer had at least one first-degree relative with lung cancer. Fifty-two families were informative for linkage analysis, having at least three relatives with lung cancer, and were therefore included in the study. To allow for a more comprehensive look at the phenotype, family members with laryngeal and pharyngeal cancers were also considered to be affected. The mean age of onset for lung, laryngeal, and pharyngeal cancer in these families was 60 years. The median age of onset for the youngest family member affected in each family was 50.5 years, demonstrating a skewing toward an earlier age at onset within these high-risk families compared with the general population. More than 90% of those affected smoked cigarettes.

(Received in original form February 14, 2005; accepted in final form August 31, 2005)

Supported by National Institutes of Health grants R01 CA60691, U01 CA76293, and P30 CA22453-24, and contract N01-PC-25005.

Correspondence and requests for reprints should be addressed to Ann G. Schwartz, Ph.D., Karmanos Cancer Institute, 110 East Warren Avenue, Detroit, MI 48201. E-mail: schwarta@med.wayne.edu

Am J Respir Crit Care Med Vol 173, pp 16–22, 2006

Originally Published in Press as DOI: 10.1164/rccm.200502-235PP on September 1, 2005

Internet address: www.atsjournals.org

Multipoint parametric linkage analysis was conducted using an autosomal-dominant, low-penetrance model assuming a susceptibility allele frequency of 0.01, 10% penetrance in gene carriers and 1% penetrance in noncarriers. The model used was based on segregation studies suggesting evidence for a dominant or codominant rare gene for lung cancer (reviewed in Reference 5). Under this simple model, a maximum HLOD (logarithm of the odds favoring genetic linkage given heterogeneity) of 2.79 on chromosome 6q (155 cM) was achieved. An LOD (logarithm of the odds favoring genetic linkage) score of 3.0 corresponds to a p value of 0.0001 and has traditionally been used as a significance threshold. In this study, HLOD scores were calculated (instead of LOD scores) because of the inclusion of African American and white families in whom underlying gene frequencies might vary; the HLOD analysis considers potential heterogeneity. Recent work suggests that using an HLOD of 4.0 as the critical threshold for declaring significance is conservative when multipoint HLODs are calculated and multiple penetrance models are used (9). In a subset of 38 families with four or more affected family members, the HLOD was 3.47. In the most highly affected families, with five or more affected relatives in multiple generations ($n = 23$), the HLOD was 4.26, with 94% of these families estimated to be linked to this region. The 1-HLOD support interval in these 23 families extended from 146 to 164 cM. The reported HLOD in these most highly affected families exceeds the conservative critical significance threshold. Nonparametric tests, which do not require specification of an underlying inheritance model, supported the parametric linkage findings. This work demonstrates the existence of a chromosomal region linked to lung cancer inheritance in families.

This work also provides some initial insight into the relationship between smoking and lung cancer occurrence in high-risk families. In a set of 21 of the 23 families most tightly linked to this region, carrier status was assigned. In both carriers and noncarriers of a putative lung cancer susceptibility region, smoking was associated with a threefold increase in lung cancer risk. However, it was only among the noncarriers that the typical dose-response relationship was observed, with a 2% increase in lung cancer risk with each pack-year of exposure ($p = 0.0023$). Among the carriers, this dose-response relationship was not apparent, indicating that any amount of smoking increases risk in this group.

These results provide the first evidence supporting linkage between a region on 6q23–25 (146–164 cM) and lung, laryngeal, and pharyngeal cancer. Additional analyses are being conducted that are limited to lung cancer. Allelic loss in this region has been reported in a number of tumor types, suggesting the existence of a tumor suppressor gene. The region identified is large, encompassing 74 known genes and 41 unknown genes, including four putative tumor suppressor genes (*SASH1*, *LATS1*, *IGF2R*, and *PARK2*), as well as genes involved in regulating cellular proliferation and preventing DNA damage. In addition to linkage on 6q, some evidence for linkage on 12q was also reported. Expanding the number of families studied and restricting analyses to lung cancer-affected members only are necessary next steps. The work to identify the specific gene(s) associated with familial lung cancer is just beginning.

An alternative approach to lung cancer gene identification was taken by Yanagitani and colleagues (10, 11). Adenocarcinoma of the lung in mice has been mapped to mouse chromosome 6q near the *Kras2* locus. This region also contains the pulmonary adenoma susceptibility 1 (*Pas1*) locus linked to inherited predisposition to lung adenocarcinoma in mice. *Kras2* and *Krag* (*K*-ras oncogene-associated gene) loci are within the *Pas1* region. In the human, *Kras2* and *Krag* have been mapped to 12p12.1 and 12p11.2, respectively. Using 13 microsatellite mark-

ers in the 12p12–12q12 region and comparing cases with adenocarcinoma of the lung with control samples, Yanagitani and coworkers (10) reported increased risk of lung cancer associated with marker D12S0134, suggesting a putative lung adenocarcinoma locus in this region. This marker falls between *Kras2* and *Krag*. Yanagitani and colleagues (11) also performed a genomewide association study using 322 microsatellite markers in a series of cases with adenocarcinoma of the lung and hospital-based control subjects. Cases and control subjects differed in allele and genotype frequencies at D6S474 at 6q22 ($p = 0.06$), close to the family linkage region. A significant association was also seen with marker D19S246, at 19q13.3 ($p = 0.03$). In particular, the distribution of A1, A8, and A9 alleles was significantly different between cases and control subjects after adjusting for age, sex, and smoking. *ERCC1* and *XPB*, DNA repair genes, are located in this region at 19q13.2–3. Because control subjects in this study included individuals with chronic lung diseases, risk estimates from this study are likely to be underestimated if similar pathways underlie risk of lung cancer and chronic lung diseases.

Although a specific lung cancer gene has not been identified, understanding risks associated with family history of lung cancer is essential in the clinical setting. One recent study estimated lung cancer risk given family history and smoking history (7). Estimates such as these can be used in counseling patients and targeting groups for inclusion in screening and prevention trials. In addition to smoking and family history of cancer, the link between an obstructive lung disease diagnosis and risk of lung cancer needs to be reevaluated. Airway obstruction has been shown prospectively to increase risk of developing lung cancer (12), as has COPD (13), and has the same underlying risk profile: about 10 to 20% of smokers develop COPD and there is familial aggregation of COPD and lung function.

THE LUNG FUNCTION, COPD, AND LUNG CANCER CONNECTION

Given the similarities and association between COPD and lung cancer, an obvious question is whether there is a common underlying genetic susceptibility acting in addition to the known shared risk associated with cigarette smoking. As far back as the mid-1970s, Cohen and colleagues (14, 15) demonstrated a common familial component to lung function, COPD, and lung cancer not completely explained by smoking or α_1 -antitrypsin genotype. First-degree relatives of patients with lung cancer and patients with COPD showed significantly greater impaired lung function ($FEV_1 < 68\%$ of FVC) than relatives of neighborhood control subjects, after adjustment for age, race, sex, and smoking. The connection between family history of lung cancer and COPD was also reported in a segregation analysis, with susceptibility to lung cancer in families of nonsmoking lung cancer cases younger than 60 years modified by family history of lung cancer, smoking, and a personal history of COPD (16). These studies provide indirect evidence for a common underlying genetic determinant of susceptibility to lung disease.

LINKAGE STUDIES

Although the familial lung cancer linkage study was the first of its kind, a number of linkage studies have been done to identify genes for lung function and COPD. In a linkage study undertaken using 330 families in the Framingham study, Joost and coworkers (17) identified chromosomal regions influencing FEV_1 and FVC. This study, like the GELCC linkage study, used 399 markers spaced at an average 10 cM across the genome. A region on 6q was most strongly linked to FEV_1 , with an LOD score of

2.4. The region of tightest linkage was at the 6q terminus, with increasing LOD scores beginning at approximately 165 cM, just beyond the newly described lung cancer linkage region, and extending to the end of the chromosome. In an effort to narrow the region, additional markers were typed, resulting in an LOD score of 5.0 at 184.5 cM (18). This study was conducted in a population unselected for lung disease and the authors suggest that a gene in this region is most likely to influence FEV₁ and airflow obstruction. A candidate gene in this region is *SMOC2* (secreted modular calcium-binding protein 2). The encoded protein contains a serine protease inhibitor domain.

A similar linkage study in 72 families ascertained through severe early-onset COPD probands without severe α_1 -antitrypsin deficiency has been conducted. Evidence for linkage of lung function to mild obstructive lung disease in smokers was reported on chromosome 12p (LOD = 3.14) (19). 12p (35 cM) linkage was also reported for post-bronchodilator forced expiratory flow, midexpiratory phase, in smokers in these families (LOD = 5.03) (20). One potential candidate gene for lung function is microsomal *GSTM1*, located on 12p, which is involved in detoxification of oxygen radicals and matrix Gla protein, a lung extracellular matrix component. Using quantitative measures of FEV₁ and FVC, an LOD score of 4.42 for linkage of FEV₁/FVC on 2q36 (222 cM) was reported (21). Interleukin-8 receptor- α gene (*IL8RA*) is located on 2q. IL-8 is a cytokine involved in neutrophil recruitment to the lung, leading to increased delivery of neutrophil proteases and increased risk of lung elastin destruction and decline in lung function. The phenotype of post-bronchodilator FEV₁ in these families was linked to a region on 8p23 (LOD = 3.30). In this region, candidate genes include the defensin genes, which are cytotoxic proteins produced by neutrophils. These proteins may modulate lung inflammation in COPD.

The linkage studies conducted to date have been relatively small, regions identified are large and include a number of genes, and regions do not exactly overlap between studies. Kruglyak and Lander (22), however, suggest that, because of underlying linkage disequilibrium, susceptibility genes will often lie outside regions of maximum allele sharing, particularly when genes confer risk on the order of two- to threefold. The criteria used to define statistical significance of linkage studies (23) are also debatable, as is the best approach (i.e., parametric vs. nonparametric). Even with these limitations, there is some potential overlap in regions linked to lung function, COPD, and lung cancer on chromosomes 6q and 12p. These linkage studies can serve as initial screens for more focused mapping and experimental approaches to prove causality.

CANDIDATE SUSCEPTIBILITY GENES FOR COPD AND LUNG CANCER

Alternative approaches to gene identification include candidate gene association studies, and work in this area also suggests possible overlap between genes predicting lung function, COPD, and lung cancer. Candidate genes in several groups are discussed below and presented in Table 1.

α_1 -Antitrypsin is an antiprotease that binds and inhibits neutrophil serine proteases such as elastase in the lung, protecting against lung tissue destruction. An imbalance between neutrophil elastase and α_1 -antitrypsin (or, more generally, a proteinase/antiproteinase imbalance) has been hypothesized to contribute to the development of COPD, as well as lung cancer (24). The gene for α_1 -antitrypsin is located on chromosome 14q32.1 and over 75 alleles have been identified. Two common alleles (S and Z) are associated with α_1 -antitrypsin deficiency. It is well known that individuals homozygous for the Z allele are at high risk of COPD. The deficiency results in unneutralized neutrophil elastase and

an associated breakdown of elastin in lung tissue, leading to early-onset and severe emphysema. Cigarette smoking contributes to faster tissue destruction through stimulation of neutrophils and increased secretion of elastase and further inactivation of α_1 -antitrypsin. Recent studies have shown that the MZ genotype is also associated with decline in lung function (25, 26) and airway obstruction (27), whereas one study reported no association (Table 1) (28). A recent meta-analysis concludes that the MZ-COPD association is stronger in case-control studies (odds ratio (OR), 2.97; 95% confidence interval (CI), 2.08–4.26) than in cross-sectional studies (OR, 1.50; 95% CI, 0.97–2.31) (29). Both Z and S allele carriers have been reported to be more common among patients with lung cancer than in the general population (30), but only one study has been completed.

Neutrophil elastase itself has been evaluated as a candidate in lung cancer etiology. The gene encoding this enzyme (*ELA2*) is located on chromosome 19p13.3. Taniguchi and colleagues (31) identified two polymorphisms in the promoter (T-903G [REP-a] and G-741A [REP-b]) and evaluated the contribution to lung cancer risk from these polymorphisms in a case-control setting. The TT genotype at REP-a was associated with 2.3-fold increased risk of lung cancer (95% CI, 1.2–4.7), whereas the GG genotype at REP-b was associated with a 1.4-fold increased risk (95% CI, 1.0–2.0). Higher promoter activity was associated with the risk genotypes. Similar findings for the TT genotype at REP-a were reported by Park and coworkers (OR, 3.2; 95% CI, 1.03–10.4) (32). The role of neutrophil elastase in COPD development has not been evaluated.

In addition to breaking down lung tissue, neutrophil elastase activates matrix metalloproteinases (MMPs), a family of more than 20 proteolytic enzymes that degrade extracellular membranes. MMP1 (interstitial collagenase), MMP12 (human macrophage elastase), and MMP9 (gelatinase B) have been associated with lung disease in animal models. Haplotypes at *MMP1*/*MMP12* and an *MMP1* promoter single nucleotide polymorphism (SNP), G-1607GG, have been associated with lung function decline in smokers (Table 1) (33). The same *MMP1* promoter SNP alters risk of lung cancer (34), as does an *MMP3* promoter SNP (35). In addition, lung cancer risk associated with the *MMP1* 2G/2G genotype has been shown to be higher in those with emphysema than in those without this condition (36). An *MMP2* promoter SNP is associated with a twofold increase (95% CI, 1.7–2.8) in lung cancer risk (Table 1) (37). The MMP genotype–lung cancer risk association was stronger as cigarette smoke exposure increased (34, 37).

COPD is characterized by inflammation of the airway induced by cigarette smoke. Animal models implicate IL-13 overexpression in MMP- and cathepsin-dependent emphysema, elevated mucus production, and COPD-like inflammation. SNPs occur in *IL-13* (5q31) and the *IL-13* receptor, made up of an *IL-4* receptor α (*IL4RA*, 5q31) subunit and either an *IL13RA1* or *IL13RA2* subunit (both on Xq13). In addition to IL-13 and its associated receptors, investigators have evaluated decline in lung function and COPD and lung cancer risk associated with *IL-1*, *IL1 β* (on 2q14), *IL1RN*, and *IL8RA* polymorphisms (Table 1) (38–42). Both *IL4RA* Q551R genotype (38) and *IL1 β /IL1RN* haplotype (39) predict lung function decline in smokers. *IL1 β* promoter SNPs also are associated with development of non-small cell lung cancer (43).

Microsomal epoxide hydrolase is found in bronchial epithelial cells and hydrolyses arenes, alkenes, and aliphatic epoxides, making them less reactive. However, in some instances, polycyclic aromatic hydrocarbons found in tobacco smoke become more reactive when metabolized by microsomal epoxide hydrolase. The gene for microsomal epoxide hydrolase, *EPHX1*, has been mapped to 1q42.1 and includes two polymorphisms:

TABLE 1. SELECTED RECENT ASSOCIATION STUDIES OF CANDIDATE SUSCEPTIBILITY LOCI FOR LUNG FUNCTION DECLINE, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AND LUNG CANCER

Author	Study Population	Results
α_1-AD		
Lung function		
Silva and colleagues (28)	Cohort of 2,016 individuals > 18 yr and monitored for at least 5 yr; outcome measure of FEV ₁ rapid decline compared with nondecliners	While rate of decline was associated with COPD diagnoses, it was not associated with MS or MZ genotype. Genotype was not associated with COPD diagnosis.
Dahl and colleagues (25)	9,187 randomly selected cohort members; whites	Average annual decrease in FEV ₁ was 19% greater in MZ individuals and 169% greater in SZ individuals than in MM individuals; MZ genotype was associated with airway obstruction (OR, 1.3; 95% CI, 1.0–1.7), as was the ZZ genotype (OR, 2.2; 95% CI, 3.5–134) compared with the MM genotype.
Sandford and colleagues (26)	283 FEV ₁ rapid decliners and 308 FEV ₁ nondecliners	MZ individuals were 2–8 times more likely to be rapid decliners (95% CI, 1.2–7.3) than nondecliners. MZ individuals with a family history of COPD were 9.7 times more likely to be rapid decliners (95% CI, 1.7–185).
COPD		
Sandford and colleagues (27)	193 COPD cases and 73 control subjects, heavy smokers, selected from patients with resected lung cancer	MZ genotype was associated with airway obstruction ($p = 0.04$). There was no association with MS genotype.
Lung cancer		
Yang and colleagues (30)	260 lung cancer cases compared with published data; whites	α_1 -AD carrier rate in lung cancer patients (12.3%) was higher than the 7% rate expected ($p = 0.002$).
MMPs		
Lung function		
Joos and colleagues (33)	284 smokers with rapid decline in lung function, 306 smokers with no decline in lung function	<i>MMP-1</i> promoter SNP G-1607GG, 1G/2G, and 2G/2G genotypes negatively associated with fast decline in lung function (OR, 0.6; 95% CI, 0.4–0.9); <i>MMP-1</i> (G-1607GG) and <i>MMP-12</i> (Asn357Ser) haplotypes associated with rate of decline in lung function.
Lung cancer		
Zhu and colleagues (34)	456 lung cancer cases and 451 control subjects	<i>MMP-1</i> promoter SNP G-1607GG, 2G/2G genotype associated with lung cancer risk (OR, 1.8; 95% CI, 1.3–2.4), with risk in current smokers even higher (OR, 3.2; 95% CI, 1.9–5.4).
Yu and colleagues (37)	781 lung cancer cases and 852 control subjects	<i>MMP-2</i> promoter SNP C-1306T, CC genotype associated with lung cancer risk (OR, 2.2; 95% CI, 1.7–2.8); risk increased with increasing amount smoked.
Fang and colleagues (35)	243 NSCLC cases and 350 control subjects; Chinese	<i>MMP-3</i> promoter SNP 6A-1171–5A, 5A genotypes associated with increased risk of lung cancer in smokers (OR, 1.7; 95% CI, 1.0–2.7); no increased risk associated with <i>MMP-1</i> promoter SNP G-1607GG.
Cytokines and receptor antagonists		
Lung function		
He and colleagues (38)	282 smokers with rapid decline in lung function, 306 smokers with no decline in lung function	<i>IL4RA</i> Q551R genotype associated with rapid decline (OR, 2.2; $p = 0.04$); no association with <i>IL-13</i> R130Q, <i>IL-13</i> C-1112T, <i>IL13RA1</i> A1398G, <i>IL4RA</i> 150V.
Joos and colleagues (39)	284 smokers with rapid decline in lung function, 306 smokers with no decline in lung function	<i>IL1β/IL1RN</i> haplotypes associated with rapid decline in lung function ($p = 0.0005$).
COPD		
Ishii and colleagues (40)	53 COPD cases and 65 control subjects	No differences in allele or genotype frequencies for <i>IL-1β</i> C-511T and 105 or <i>IL-1RN</i> intron 2 SNPs between cases and control subjects.
van der Pouw Kraan and colleagues (41)	151 COPD cases, 99 control subjects, 78 smoking control subjects	<i>IL-13</i> C-1055T SNP, T allele more frequent in cases; No association with <i>IL-13</i> G2044A, <i>IL-4</i> C-590T or C33T.
Stemmler and colleagues (42)	182 adult COPD cases and 454 control subjects; Germans	<i>IL8RA</i> M31R ($p = 0.007$) and R335C ($p = 0.23$) alleles associated with increased risk of COPD.
Lung cancer		
Zienolddiny and colleagues (43)	251 NSCLC and 272 smoking control subjects	<i>IL-1β</i> T-31C SNP, T allele associated with lung cancer (T/T vs. C/C; OR, 2.4; 95% CI, 1.3–4.4); <i>IL-1β</i> C-511T SNP, C allele associated with risk (C/C vs. T/T; OR, 2.5; 95% CI, 1.5–4.6); both risk genotypes associated with higher frequency of p53 mutations.
mEH		
Lung function		
Sandford and colleagues (26)	283 FEV ₁ rapid decliners and 308 FEV ₁ nondecliners	His113–His139 (lower activity haplotype) was associated with rapid decline in lung function (OR, 2.4; 95% CI, 1.1–5.4). This haplotype in combination with a family history of COPD was associated with a sixfold increased risk of rapid decline in lung function (OR, 6.2; 95% CI, 1.4–28).
COPD		
Yoshikawa and colleagues (44)	40 COPD cases, 71 lung cancer cases, 247 controls; Japanese	Predicted low-activity allele in exon 3 SNP found more often in those with severe COPD (OR, 2.9; 95% CI, 1.1–7.4).
Takeyabu and colleagues (57)	79 smokers with emphysema, 58 smokers without emphysema, 114 control subjects; Japanese	No association between the exon 3 or exon 4 variant allele frequencies or genotypes and emphysema.

(continued)

TABLE 1. (continued)

Author	Study Population	Results
Cheng and colleagues (45)	184 COPD cases and 212 control subjects; all smokers or ex-smokers; Taiwanese	Homozygous exon 3 variant genotype associated with severe COPD.
Xiao and colleagues (46)	100 COPD cases and 100 control subjects; Chinese	Heterozygosity for the exon 3 variant was associated with increased risk of COPD (OR, 3.0; 95% CI, 1.2–7.1).
Park and colleagues (47)	131 COPD cases and 261 control subjects; whites	Homozygosity for the exon 3 variant was associated with increased risk of COPD (OR, 2.4; 95% CI, 1.1–5.1).
Lung cancer		
Benhamou and colleagues (48)	150 lung cancer cases and 172 control subjects; whites	Predicted high mEH activity based on genotype at two SNPs in the <i>EPHX</i> gene was associated with lung cancer risk ($p < 0.02$).
London and colleagues (49)	337 lung cancer cases and 700 control subjects; whites and African Americans	Exon 3 variant allele conferring low activity was associated with reduced risk in African Americans (OR, 0.08; 95% CI, 0.01–0.6); combined exon 3 and exon 4 low-activity variants also reduced risk in African Americans (OR, 0.1; 95% CI, 0.01–0.8); no associations seen in whites.
Zhou and colleagues (56)	974 lung cancer cases and 1,142 control subjects; whites	Overall, no association between combined exon 3 and exon 4 predicted very-low-activity genotypes and risk of lung cancer (OR, 1.0; 95% CI, 0.7–1.3); almost twofold increased risk among nonsmokers with the very-low-activity genotypes (OR, 1.9; 95% CI, 1.1–3.3); steady decrease in risk with pack-years (p -trend < 0.01), with 80 smokers with the very-low-activity genotype at reduced risk (OR, 0.7; 95% CI, 0.4–1.0).
Wu and colleagues (50)	138 lung cancer cases and 148 control subjects; Mexican American and African American	Increased risk associated with carrying one or more exon 4 “fast activity” alleles in Mexican Americans (OR, 3.6; 95% CI, 1.3–10.4); no associations seen with exon 3 in Mexican Americans nor with exon 3 or 4 in African Americans.
Lee and colleagues (51)	Meta-analysis of 2,078 lung cancer cases and 3,081 control subjects; pooled analysis of 986 cases with lung cancer and 1,633 control subjects	Meta-analysis showed no association between either exon 3 (OR, 1.0; 95% CI, 0.7–1.4) or exon 4 genotype (OR, 1.0; 95% CI, 0.7–1.4) and lung cancer; decreased lung cancer risk was associated with the low-activity variant (OR, 0.7; 95% CI, 0.5–1.0) in the pooled analysis.
Zhao and colleagues (52)	181 lung cancer cases and 163 control subjects; non-Hispanic whites	Borderline increased risk associated with carrying one or more exon 4 “fast activity” alleles (OR, 1.6; 95% CI, 1.0–2.5); no associations seen with exon 3 variant.
Cajas-Salazar and colleagues (53)	110 lung cancer cases and 119 control subjects; whites	High enzyme activity genotype (exons 3 and 4 variants combined) was associated with increased risk (OR, 2.5; 95% CI, 1.1–5.7); among cases, chromosomal aberrations increased with genotype-predicted activity.
Gsur and colleagues (54)	277 lung cancer cases and 496 control subjects; whites	Decreased risk was associated with the homozygous exon 3 variant genotype (OR, 0.4; 95% CI, 0.2–0.8); no association with the exon 4 SNP.
Park and colleagues (55)	182 lung cancer cases and 365 control subjects; whites	Decreased risk was associated with the homozygous exon 3 variant genotype (OR, 0.6; 95% CI, 0.3–1.0). Combined genotypes predicting high EH activity were associated with increased risk (OR, 2.3; 95% CI, 1.2–4.3).

Definition of abbreviations: AD = antitrypsin deficiency; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EH = epoxide hydrolase; IL = interleukin; mEH = microsomal epoxide hydrolase; MMP = matrix metalloproteinase; NSCLC = non-small cell lung cancer; OR = odds ratio; SNP = single nucleotide polymorphism.

Try113His, which is associated with decreased activity, and His139Arg, which is associated with increased activity. The low-activity haplotype (His113–His139) has been associated with rapid decline in lung function (26), whereas the His113 genotype has been associated with COPD (44–47). Studies in lung cancer have generally reported that the predicted high-activity genotype is associated with increased risk (Table 1) (48–55). In one of the largest studies, lung cancer risk associated with *EPHX1* varied with pack-years of smoking, with a twofold increased risk among nonsmokers with the low-activity genotype and 30% decreased risk in smokers of 80 pack-years with the low-activity genotype (56). This decrease in lung cancer risk in individuals with the low-activity genotype (or equivalently, increased risk in those with the high-activity alleles) was similar to that seen in a pooled analysis (51). Given microsomal epoxide hydrolase's role in detoxification and activation, it is not surprising to see variation in results based on cigarette smoke exposure and by disease outcome.

CONCLUSIONS

The prevention of lung cancer through the elimination of smoking continues to be the best way to decrease mortality from this disease in the long term. However, even if everyone stopped

smoking today, lung cancer incidence and mortality would continue to be high for several decades. While debate continues about the efficacy of spiral computed tomography screening for lung cancer in broad populations of smokers, the ability to focus screening efforts in a truly high-risk subpopulation would clearly be of benefit now. Pack-years of exposure and lung function have been used as criteria for entry into screening trials and chemoprevention studies. Consistent epidemiologic data and the recent lung cancer linkage results suggest that family history should be included in a “high risk” definition as well. We are of the opinion that studies of spiral computed tomography screening and lung function testing is warranted in current or former smokers with a strong family history of lung cancer, particularly when age at diagnosis of the family member is young (7).

Associations between markers on chromosome 6q to both lung cancer and lung function, and on 12 to lung cancer, COPD, and lung function, together with overlap in candidate genes for these outcomes, suggest that future research into underlying genetic mechanisms of lung disease would benefit from broadening the collection of family history and lung function data. We suggest that the collection of family history of lung cancer in patients with COPD and family history of COPD in patients with lung cancer become routine. Age at diagnosis of family

members with lung cancer or COPD should be collected, if possible. As familial risk of lung disease is better defined, referral into screening programs and prevention trials can be better targeted to reach families with both a history of lung cancer and COPD. The identification of genes for lung cancer and COPD will require larger linkage and association studies that would benefit from the collection of lung function and lung disease history and a more extensive family history.

Conflict of Interest Statement: Neither of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

- Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK, editors. SEER cancer statistics review, 1975–2001. Bethesda, MD: National Cancer Institute; 2004. Available from: http://seer.cancer.gov/csr/1975_2001/ (accessed November 15, 2004).
- Mattson ME, Pollack ES, Cullen JW. What are the odds that smoking will kill you? *Am J Public Health* 1987;77:425–431.
- CDC. Cigarette smoking among adults: United States, 2002. *MMWR Morb Mortal Wkly Rep* 2004;53:428–431.
- Tokuha GK, Lilienfeld AM. Familial aggregation of lung cancer in humans. *J Natl Cancer Inst* 1963;30:289–312.
- Schwartz AG. Genetic susceptibility to lung cancer. In: Pass HI, Carbone DP, Johnson DH, Minna JD, Turrissi AT, editors. Lung cancer principles and practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 50–60.
- Jonsson S, Thorsteinsdottir U, Gudbjartsson DF, Jonsson HH, Kristjansson K, Arnason S, Gudnason V, Isaksson HJ, Hallgrímsson J, Gulcher JR, et al. Familial risk of lung carcinoma in the Icelandic population. *JAMA* 2004;292:2977–2983.
- Cote ML, Kardia SLR, Wenzlaff AS, Ruckdeschel JC, Schwartz AG. Risk of lung cancer among white and black relatives of individuals with early-onset lung cancer. *JAMA* 2005;293:3036–3042.
- Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, et al. A major lung cancer susceptibility locus maps to chromosome 6q23–25. *Am J Hum Genet* 2004;75:460–474.
- Greenberg DA, Abreu PC. Determining trait locus position from multipoint analysis: accuracy and power of three different statistics. *Genet Epidemiol* 2001;21:299–314.
- Yanagitani N, Kohno T, Sunaga N, Kunitoh H, Tamura T, Tsuchiya S, Saito R, Yokota J. Localization of a human lung adenocarcinoma susceptibility locus, possibly syntenic to the mouse *Pas1* locus, in the vicinity of the D12S1034 locus on chromosome 12p11.2–p12.1. *Carcinogenesis* 2002;23:1177–1183.
- Yanagitani N, Kohno T, Kim J-G, Kunitoh H, Tamura T, Takei Y, Tsuchiya S, Saito R, Yokota J. Identification of *D19S246* as a novel lung adenocarcinoma susceptibility locus by genome survey with 10-cM resolution microsatellite markers. *Cancer Epidemiol Biomarkers Prev* 2003;12:366–371.
- Tockman MS, Anthonisen NR, Wright EC, Donithan MG, for the Intermittent Positive Pressure Breathing Trial Group, the Johns Hopkins Lung Project for the Early Detection of Lung Cancer. Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987;106:512–518.
- Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. *Ann Intern Med* 1986;105:503–507.
- Cohen BH, Ball WC, Bias WB, Brashears S, Chase GA, Diamond EL, Hsu SH, Kreiss P, Levy DA, Menkes HA, et al. A genetic-epidemiologic study of chronic obstructive pulmonary disease. *Johns Hopkins Med J* 1975;137:95–104.
- Cohen BH, Diamond EL, Graves CG, Kreiss P, Levy DA, Menkes HA, Permutt S, Quaskey S, Tockman MS. A common familial component in lung cancer and chronic obstructive pulmonary disease. *Lancet* 1977;2:523–526.
- Yang P, Schwartz AG, McAllister AE, Swanson GM, Aston CE. Lung cancer risk in families of nonsmoking probands: heterogeneity by age at diagnosis. *Genet Epidemiol* 1999;17:253–273.
- Joost O, Wilk JB, Cupples A, Harmon M, Shearman AM, Baldwin CT, O'Conner GT, Myers RH, Gottlieb DJ. Genetic loci influencing lung function: a genome-wide scan in the Framingham study. *Am J Respir Crit Care Med* 2002;165:795–799.
- Wilk JB, DeStefano AL, Joost O, Myers RH, Cupples LA, Slater K, Atwood LD, Heard-Costa NL, Herbert A, O'Conner GT, et al. Linkage and association with pulmonary function measures on chromosome 6q27 in the Framingham Heart Study. *Hum Mol Genet* 2003;12:2745–2751.
- Silverman EK, Mosley JD, Palmer LJ, Barth M, Senter JM, Brown A, Darzen JM, Kwiatkowski DJ, Chapman HA, Campbell EJ, et al. Genome-wide linkage analysis of severe, early-onset chronic obstructive pulmonary disease: airflow obstruction and chronic bronchitis phenotypes. *Hum Mol Genet* 2002;11:623–632.
- DeMeo DL, Celedon JC, Lange C, Reilly JJ, Chapman HA, Sylvia JS, Speizer FE, Weiss ST, Silverman EK. Genomewide linkage of forced mid-expiratory flow in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:1294–1301.
- Palmer LJ, Celedon JC, Chapman HA, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage analysis of bronchodilator responsiveness and post-bronchodilator spirometric phenotypes in chronic obstructive pulmonary disease. *Hum Mol Genet* 2003;12:1199–1210.
- Kruglyak L, Lander ES. Limits on fine mapping of complex traits. *Am J Hum Genet* 1996;58:1092–1093.
- Lander ES, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 1995;11:241–247.
- Sun Z, Yang P. Role of imbalance between neutrophil elastase and α_1 -antitrypsin in cancer development and progression. *Lancet Oncol* 2004;5:182–190.
- Dahl M, Tybjaerg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in α_1 -antitrypsin MZ heterozygotes: a longitudinal study of the general population. *Ann Intern Med* 2002;136:270–279.
- Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the Lung Health Study. *Am J Respir Crit Care Med* 2001;163:469–473.
- Sandford AJ, Weir TD, Spinelli JJ, Pare PD. Z and S mutations of the α_1 -antitrypsin gene and the risk of chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 1999;20:287–291.
- Silva GE, Sherrill DL, Guerra S, Barbee RA. A longitudinal study of α_1 -antitrypsin phenotypes and decline in FEV₁ in a community population. *Chest* 2003;123:1435–1440.
- Hersh CP, Dahl M, Ly NP, Berkey CS, Nordestgaard BG, Silverman EK. Chronic obstructive pulmonary disease in alpha1-antitrypsin P1 MZ heterozygotes: a meta-analysis. *Thorax* 2004;59:843–849.
- Yang P, Wenzlaff KA, Katzmann JA, Marks RS, Allen MS, Lesnick TG, Lindor NM, Myers JL, Wiegert E, Midthun DE, et al. Alpha₁-antitrypsin deficiency allele carriers among lung cancer patients. *Cancer Epidemiol Biomarkers Prev* 1999;8:461–465.
- Taniguchi K, Yang P, Jett J, Bass E, Meyer R, Wang Y, Deschanmps C, Liu W. Polymorphisms in the promoter region of the neutrophil elastase gene are associated with lung cancer development. *Clin Cancer Res* 2002;8:1115–1120.
- Park JY, Chen L, Lee J, Sellers T, Tockman MS. Polymorphisms in the promoter region of neutrophil elastase gene and lung cancer risk. *Lung Cancer* 2005;48:315–321.
- Joos L, He J-Q, Shepherdson MB, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. The role of matrix metalloproteinase polymorphisms in the rate of decline in lung function. *Hum Mol Genet* 2002;11:569–576.
- Zhu Y, Spitz MR, Lei L, Mills GB, Wu X. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter enhances lung cancer susceptibility. *Cancer Res* 2001;61:7825–7829.
- Fang S, Jin X, Wang R, Li Y, Guo W, Wang N, Wang Y, Wen D, Wei L, Zhang J. Polymorphisms in the *MMP1* and *MMP3* promoter and non-small cell lung carcinoma in north China. *Carcinogenesis* 2005;26:481–486.
- Schabath MB, Delclos GL, Martynowicz MM, Greisinger AJ, Lu C, Wu X, Spitz MR. Opposing effects of emphysema, hay fever, and select genetic variants on lung cancer risk. *Am J Epidemiol* 2005;161:412–422.
- Yu C, Pan K, Xing D, Liang L, Lin D. Correlation between a single polymorphism in the matrix metalloproteinase-2 promoter and risk of lung cancer. *Cancer Res* 2002;62:6430–6433.
- He J-Q, Connett JE, Anthonisen NR, Sandford AJ. Polymorphisms in the *IL13*, *IL13RA1*, and *IL4RA* genes and the rate of decline in lung function in smokers. *Am J Respir Cell Mol Biol* 2003;28:379–385.
- Joos L, McIntyre L, Ruan J, Connett JE, Anthonisen NR, Weir TD, Pare PD, Sandford AJ. Association of IL-1beta and IL1 receptor antagonist haplotypes with rate of decline in lung function in smokers. *Thorax* 2002;57:863–866.
- Ishii T, Matsuse T, Teramoto S, Matsui H, Miyao M, Hosoi T, Takahashi H, Fukuchi Y, Ouchi Y. Neither IL-1beta, IL-1 receptor antagonist,

- nor TNF- α polymorphisms are associated with susceptibility to COPD. *Respir Med* 2000;94:847–851.
41. van der Pouw Kraan TCTM, Kucukaycan M, Bakker AM, Baggen JMC, van der Zee JS, Dentener MA, Wouters EFM, Verweij CL. Chronic obstructive pulmonary disease is associated with the -1055 *IL-13* promoter polymorphism. *Genes Immun* 2002;3:436–439.
 42. Stemmler S, Arinir U, Klein W, Rohde G, Hoffjan S, Wirkus N, Reinitz-Rademacher K, Bufer A, Schultze-Werninghaus G, Eppel JT. Association of interleukin-8 receptor α polymorphisms with chronic obstructive pulmonary disease and asthma. *Genes Immun* 2005;6:225–230.
 43. Zienolddiny S, Ryberg D, Maggini V, Skaug V, Canzian F, Haugen A. Polymorphisms of the interleukin-1 β gene are associated with increased risk of non-small cell lung cancer. *Int J Cancer* 2004;109:353–356.
 44. Yoshikawa M, Hiyama K, Ishioka S, Maeda H, Maeda A, Yamakido M. Microsomal epoxide hydrolase genotypes and chronic obstructive pulmonary disease in Japanese. *Int J Mol Med* 2000;5:49–53.
 45. Cheng SL, Yu CJ, Chen CJ, Yang PC. Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. *Eur Respir J* 2004;23:818–824.
 46. Xiao D, Wang C, Du M, Pand B, Zhang H, Xiao B, Liu J, Weng X, Su I, Christiani DC. Relationship between polymorphisms of genes encoding microsomal epoxide hydrolase and glutathione S-transferase P1 and chronic obstructive pulmonary disease. *Chin Med J (Engl)* 2004;117:661–667.
 47. Park JY, Chen L, Wadhwa N, Tockman MS. Polymorphisms for microsomal epoxide hydrolase and genetic susceptibility to COPD. *Int J Mol Med* 2005;15:443–448.
 48. Benhamou S, Reinikainen M, Bouchardy C, Dayer P, Hirvonen A. Association between lung cancer and microsomal epoxide hydrolase genotypes. *Cancer Res* 1998;58:5291–5293.
 49. London SJ, Smart J, Daly AK. Lung cancer risk in relation to genetic polymorphisms of microsomal epoxide hydrolase among African-Americans and Caucasians in Los Angeles County. *Lung Cancer* 2000;28:147–155.
 50. Wu X, Gwyn K, Amos CI, Makin N, Hong WK, Spitz MR. The association of microsomal epoxide hydrolase polymorphisms and lung cancer risk in African-Americans and Mexican-Americans. *Carcinogenesis* 2001;22:923–928.
 51. Lee WJ, Brennan P, Boffetta P, London SJ, Benhamou S, Rannug A, To-Figueras J, Ingelman-Sundberg M, Shields P, Gaspari L, et al. Microsomal epoxide hydrolase polymorphisms and lung cancer risk: a quantitative review. *Biomarkers* 2002;7:230–241.
 52. Zhao H, Spitz MR, Gwyn KM, Wu X. Microsomal epoxide hydrolase polymorphisms and lung cancer risk in non-Hispanic whites. *Mol Carcinog* 2002;33:99–104.
 53. Cajas-Salazar N, Au WW, Zwischenberger JB, Sierra-Torres CH, Salama SA, Alparid SK, Tying SK. Effect of epoxide hydrolase polymorphisms on chromosome aberrations and risk of lung cancer. *Cancer Genet Cytogenet* 2003;145:97–102.
 54. Gsur A, Zidek T, Schnattinger K, Feik E, Haidinger G, Hallaus P, Mohn-Staudner A, Armbruster C, Madersbacher S, Schatzl G, et al. Association of microsomal epoxide hydrolase polymorphisms and lung cancer risk. *Br J Cancer* 2003;89:702–706.
 55. Park JY, Chen L, Elahi A, Lazarus P, Tockman MS. Genetic analysis of microsomal epoxide hydrolase gene and its association with lung cancer risk. *Eur J Cancer Prev* 2005;14:223–230.
 56. Zhou W, Thurston SW, Liu G, Xu LL, Miller DP, Wain JC, Lynch TJ, Su K, Christiani DC. The interaction between microsomal epoxide hydrolase polymorphisms and cumulative cigarette smoking in different histologic subtypes of lung cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:461–466.
 57. Takeyabu K, Yamaguchi E, Suzuki I, Nishimura M, Hizawa N, Kamakami Y. Gene polymorphism for microsomal epoxide hydrolase and susceptibility to emphysema in a Japanese population. *Eur Respir J* 2000;15:891–894.