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REVIEW

Genetic susceptibility to lung cancer—light at the end of the tunnel?

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Lung cancer is one of the most common and deadliest cancers in the world. The major socio-environmental risk factor involved in the development of lung cancer is cigarette smoking. Additionally, there are multiple genetic factors, which may also play a role in lung cancer risk. Early work focused on the presence of relatively prevalent but low-penetrance alterations in candidate genes leading to increased risk of lung cancer. Development of new technologies such as genomic profiling and genome-wide association studies has been helpful in the detection of new genetic variants likely involved in lung cancer risk. In this review, we discuss the role of multiple genetic variants and review their putative role in the risk of lung cancer. Identifying genetic biomarkers and patterns of genetic risk may be useful in the earlier detection and treatment of lung cancer patients.

Introduction

Lung cancer is one of the most prevalent and deadliest cancers in the world. It is the most common cancer in men and the main cause of male cancer deaths worldwide, and it is the second leading cause of cancer deaths in women worldwide. About 1.6 million cases of lung cancer are diagnosed worldwide each year, with a resulting 1.4 million deaths yearly (1). In the USA, the lifetime chance of developing lung cancer is 1 in 13 (men) and 1 in 16 (women) (2). There are two main histological types of lung cancer: non-small cell lung cancer (NSCLC), which originates from bronchial epithelial-cell precursors and is divided into three types—squamous cell carcinoma, adenocarcinoma and large cell carcinoma—and small cell lung cancer, which originates from neuroendocrine-cell precursors. Squamous cell carcinomas are decreasing in incidence and adenocarcinomas are increasing in incidence (3).

Lung cancer is often diagnosed at a late age (47% of cases diagnosed in people aged 70 or older) and at a late stage (about 50% have advanced disease at the time of diagnosis) (4,5). Because of these and other factors, even with modern therapies survival remains poor. The 5 year estimated survival rates are <14% in males and <18% in females. The major socio-environmental risk factor involved in the development of lung cancer is cigarette smoking. In the USA, smoking is related to about 80% of lung cancers, and geographic and temporal variations in lung cancer incidence and prevalence reflect differences in tobacco consumption. In high-income countries, the incidence and mortality of lung cancers are generally declining in males and starting to plateau in females as over time male consumption of tobacco has declined considerably and female consumption has declined as well (albeit later than male consumption), and there is a higher incidence of lung cancer in countries where cigarette use is still endemic (6).

Though cigarette smoking is a major risk factor for most lung cancers, there are multiple genetic factors that may also play a role in lung cancer risk. Initial work in the field of lung cancer genetics focused on the use of candidate genes to identify mutations (often single nucleotide polymorphisms [SNPs]) that conferred an increased risk of lung cancer. The development of new technologies such as genomic profiling and genome-wide association studies (GWAS) allows the sequencing of up to 1 million (or more) genetic variants at a time without requiring prior knowledge of the functional significance of these variants. Identifying biomarkers and polymorphisms that are genetic risk factors may be useful in the earlier detection and treatment of lung cancer patients (7).

In this review, we will provide an overview of studies of those particular genetic variants, which have shown some role in the genetic risk for lung cancer (Table 1). We will first review those studies identified by the candidate-gene approach and then discuss more recent GWAS. We will then discuss the strengths and limitations of the studies, which have already been performed, and propose further lines of investigation (pathway and microarray analyses), which may be helpful in the future.

Studies were initially selected on the basis of a PubMed search using the terms ‘lung cancer’ and ‘risk’ and were further chosen on the basis of English-language studies, which describe the role of genetic factors on primary risk of lung cancer development (as opposed to risk of progression once a diagnosis has been made, risk of metastasis and so on). Over 600 studies meeting these criteria were screened, and only those which demonstrated a clear role (either positive or negative) for a specific genetic variant in the risk of lung cancer (either positive association, negative association or no association) were fully reviewed. In a second-tier search, meta-analyses were identified in a similar PubMed search using a combination of the terms ‘lung cancer’, ‘risk’, ‘meta-analysis’ and each gene of interest.

Discoveries based primarily on the candidate-gene approach

Carcinogen metabolism genes

CYP1A1. Various metabolic enzymes are involved in the bioactivation and detoxification of carcinogens. *CYP1A1* activates polycyclic aromatic hydrocarbons (PAH) in cigarette smoke into carcinogens. *CYP1A1* is highly expressed in normal lung tissue from smokers but not from non-smokers, and expression decreases over time in former smokers. *CYP1A1* messenger RNA (mRNA) expression is seen in lung cancer tissue but not in normal tissue (8). Several polymorphisms may modulate enzymatic activity and influence lung cancer risk.

The T3801C polymorphism located at an *MspI* restriction fragment length polymorphism site leads to increased enzymatic activity in the variant (9). The homozygous variant is more common in cancer patients and its presence has been linked with increased risk of lung cancer, particularly of squamous cell histology, and especially in Asian populations (10–12). Additionally, the presence of the variant allele has been associated with increased risk of lung cancer specifically in patients of younger age and in never smokers (13,14). A pooled analysis of Caucasian non-smokers by Hung *et al.* (15) demonstrated no significant association with lung cancer risk, further suggesting risk modification based on ethnicity. In a pooled analysis of Asian populations by Lee *et al*., (16) there was no association with overall risk, but an increased risk of squamous cell cancer with the variant genotype (P_{trend} = 0.003 for increasing numbers of C alleles). In a global meta-analysis by Chen *et al*., the variant was associated with increased risk (odds ratio [OR] 1.19, confidence interval [CI]

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; GWAS, genome-wide association studies; IL, interleukin; ILCCO, International Lung and Cancer Consortium; MEH, microsomal epoxide hydrolase; MMP, matrix metalloproteinase; MPO, myeloperoxidase; mRNA, messenger RNA; NER, nucleotide excision repair; NSCLC, non-small cell lung cancer; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; SNP, single nucleotide polymorphism.

Table 1. Commonly evaluated genetic variants which may influence lung cancer susceptibility.

	Author	OR	95% CI	Genotype analyzed	Other associations
Carcinogen metabolism					
CYP1A1					
T3801C	Hung *et al.*	1.49	(0.67–3.30)	T/C+C/C versus T/T	
	Lee *et al.*	1.1	(0.86–1.39)	T/C+C/C versus T/T	Significant in squamous histology
	Chen *et al.*	1.19*	(1.11–1.28)	C versus T	Significant in East Asian > Caucasians; squamous
A2455G (Ile>Val)	Hung *et al.*	2.21*	(1.12–4.37)	Ile/Val+Val/Val versus Ile/Ile	
	Chen *et al.*	1.2*	(1.08–1.33)	G versus A	Only significant in East Asian ethnicity
	Shi *et al.*	1.61*	(1.24–2.08)	Ile/Val+Val/Val versus Ile/Ile	
CYP2E1					
RsaI/Pst1	Zhan *et al.*	0.73*	(0.63–0.85)	c2/c2 versus c1/c1	Only significant in Asians and squamous histology
	Wang *et al.*	0.80*	(0.72–0.89)	c1/c2 versus c1/c1	Not significant for c2/c2 versus c1/c1; significant in Asians
DraI	Wang *et al.*	0.58*	(0.41–0.81)	CC versus DD	
GSTM1					
Null	Hung *et al.*	1.2	(0.89–1.63)	Null versus present	
	Lee *et al.*	1.11	(0.95–1.29)	Null versus present	Significant in squamous histology
	McWilliams *et al.*	1.41*	(1.23–1.61)	Null versus present	
	Houlston *et al.*	1.13*	(1.04–1.25)	Null versus present	
	Benhamou *et al.*	1.08	(0.98–1.18)	Null versus present	
	Ye *et al.*	1.18*	(1.14–1.23)	Null versus present	
	Carlsten *et al.*	1.22*	(1.14–1.30)	Null versus present	Significant only in East Asian ethnicity
	Langevin *et al.*	1.17*	(1.10–1.25)	Null versus present	
GSTP1					
A323G	Ye *et al.*	1.04	(0.99–1.09)	G versus A	
	Langevin *et al.*	1.03	(0.97–1.09)	AG+GG versus AA	Significant in East Asian ethnicity
	Cote *et al.*	1.04	(0.97–1.10)	AG+GG versus AA	Asians, non-smokers, adenocarcinoma in pooled analysis
GSTT1					
Null	Langevin *et al.*	1.07	(0.97–1.17)	Null versus present	
	Raimondi *et al.*	1.07	(0.96–1.19)	Null versus present	Significance in Asians in meta- but not pooled analysis
	Wang *et al.*	1.36*	(1.09–1.69)	Null versus present	
	Lee *et al.*	1.02	(0.84–1.24)	Null versus present	
NAT1					
Fast acetylator	Zienolddiny *et al.*	3.75*	(2.58–5.51)	Fast versus slow	
NAT2					
Slow acetylator	Borlak *et al.*	1.04	(0.96–1.14)	Slow versus fast	
	Cui *et al.*	1.02	(0.90–1.16)	Slow versus fast	
MEH					
T113C Tyr>His (exon 3)	Kiyohara *et al.*	0.83	(0.61–1.12)	His/His versus Tyr/Tyr	Significantly decreased risk in white population
A139G His>Arg (exon 4)	Kiyohara *et al.*	1.35	(0.94–1.92)	Arg/Arg versus His/His	
NQO1					
Exon 6 C>T (Pro187Ser)	Kiyohara *et al.*	0.9	(0.77–1.06)	Pro/Ser+Ser/Ser versus Pro/Pro	Significantly decreased risk in Japanese population
	Chao *et al.*	0.97	(0.86–1.10)	CT+TT versus TT	
MPO					
G463A	Kiyohara *et al.*	0.81	(0.64–1.02)	A/A+A/G versus GG	Significant decreased risk in Caucasians
	Taioli *et al.*	0.71*	(0.57–0.88)	A/A versus G/G	Significant only in Caucasians and ever smokers
Nucleotide excision repair					
ERCC2/XPD					
Asp312Asn (G>A)	Zhan *et al.*	1.24*	(1.09–1.42)	AA versus GG	Significant only in Asians and smokers
	Feng *et al.*	1.20*	(1.05–1.36)	Asn/Asn versus Asp/Asp	Significant in Asians>Caucasians and never smokers
	Qian *et al.*	1.04	(0.97–1.12)	AA versus GG	Significant in non-smokers
	Benhamou *et al.*	1.18	(0.84–1.67)	Asn/Asn versus Asp/Asp	
	Hung *et al.*	1.09	(0.97–1.23)	AA versus GG	
	Kiyohara *et al.*	1.19*	(1.03–1.38)	Asn/Asn versus Asp/Asp	Significant only in Asians

Table 1. *Continued*

	Author	OR	95% CI	Genotype analyzed	Other associations
Lys751Gln (A>C)	Zhan *et al.*	1.26*	(1.12–1.42)	CC versus AA	Significant only in Caucasians and smokers
	Feng *et al.*	1.31*	(1.17–1.46)	Gln/Gln versus Lys/Lys	Significant in Caucasians, Latinos, and never smokers
	Benhamou *et al.*	1.18	(0.95–1.47)	Gln/Gln versus Lys/Lys	
	Hung *et al.*	1.19*	(1.02–1.39)	CC versus AA	
	Kiyohara *et al.*	1.09*	(1.04–1.18)	Gln/Gln versus Lys/Lys	Significant only in Caucasians
ERCC1/XPF					
C8092A	Cao *et al.*	1.03	(0.95–1.11)	A versus C	
	Hung *et al.*	1.06	(0.88–1.29)	AA versus CC	
T19007C	Cao *et al.*	0.91	(0.80–1.04)	C versus T	
	Li *et al.*	0.94	(0.69–1.29)	C versus T	
XPA					
A23G	Kiyohara *et al.*	0.76*	(0.61–0.94)	GG versus AA	Not significant in Caucasian studies
	Qian *et al.*	1.28*	(1.12–1.47)	AA versus GG	Most significant in Asians
	Hung *et al.*	1.06	(0.82–1.37)	AA versus GG	
XPC					
PAT +/−	Qiu *et al.*	1.01	(0.81–1.24)	Homozygote variant	
C499T (Ala499Val)	Qiu *et al.*	1.16	(0.91–1.47)	Val/Val versus Ala/Ala	
A939C (Lys939Gln)	Qiu *et al.*	1.28*	(1.07–1.53)	Gln/Gln versus Lys/Lys	
ERCC5/XPG					
His1104Asp	Hung *et al.*	1	(0.81–1.25)	Asp/Asp versus His/His	
Base excision repair					
XRCC1					
Arg194Trp	Wang *et al.*	1.07	(0.85–1.33)	Significant in Arg/Trp and combined Trp/Trp + Arg/Trp	
	Zheng *et al.*	1.06	(0.89–1.27)	Trp/Trp+Arg/Trp versus Arg/Arg	
	Huang *et al.*	1.27*	(1.07–1.50)	Trp/Trp versus Arg/Arg	
	Hung *et al.* (HuGE)	1.05	(0.58–1.91)	Trp/Trp versus Arg/Arg	
	Kiyohara *et al.*	1.19	(0.76–1.86)		
	Hung *et al.* (ILCCO)	1.57	(0.76–3.26)	Trp/Trp versus Arg/Arg	
Arg280His	Zheng *et al.*	0.63	(0.28–1.41)	His/His+Arg/His versus Arg/Arg	
	Hung *et al.* (HuGE)	1.1	(0.84–1.43)	For combined Arg/His+His/His	
	Kiyohara *et al.*	1.06	(0.91–1.23)		
	Hung *et al.* (ILCCO)	2.06	(0.83–5.09)	His/His vs Arg/Arg	
Arg399Gln	Wang *et al.*	1.06	(0.89–1.25)		
	Zheng *et al.*	1.16*	(1.00–1.36)	Gln/Gln+Arg/Gln versus Arg/Arg	
	Hung *et al.* (HuGE)	1.07	(0.93–1.23)	Gln/Gln versus Arg/Arg	
	Kiyohara *et al.*	1.02	(0.88–1.19)		Significant in Asians
	Hung *et al.* (ILCCO)	0.93	(0.75–1.14)	Gln/Gln versus Arg/Arg	
OGG1					
Ser326Cys	Hung *et al.* (HuGE)	1.24*	(1.01–1.53)	Cys/Cys versus Ser/Ser	
	Kiyohara *et al.*	1.17	(0.88–1.56)		
	Hung *et al.* (ILCCO)	1.34*	(1.01–1.79)	Cys/Cys vs Ser/Ser	Significant in Caucasians but not in Asians
APE					

Table 1. *Continued*

	Author	OR	95% CI	Genotype analyzed	Other associations
Asp148Glu (T1349G)	Hung *et al.* (HuGE)	0.94	(0.77–1.14)	Glu/Glu versus Asp/Asp	
	Ji *et al.*	1	(0.86–1.15)	GG versus TT	Significant in smokers
	Kiyohara *et al.*	0.97	(0.83–1.14)		
	Hung *et al.* (ILCCO)	0.91	(0.78–1.06)	Glu/Glu versus Asp/Asp	
Double-strand break repair					
XRCC3					
Thr241Met	Hung *et al.* (ILCCO)	0.84*	(0.71–1.00)	Met/Met versus Thr/Thr	Significant in Caucasians but not in Asians
	Sun *et al.*	0.89	(0.65–1.22)	C/C versus T/T	
Cell cycle control					
TP53					
Arg72Pro	Matakidou *et al.*	1.18	(0.99–1.41)	Pro/Pro versus Arg/Arg	
	Hung *et al.* (ILCCO)	1.20*	(1.02–1.42)	Pro/Pro versus Arg/Arg	
	Yan *et al.*	1.08*	(1.00–1.17)	Pro versus Arg	Significant in Asians but not Caucasians
	Li *et al.*	1.15*	(1.04–1.23)	Pro/Pro+Pro/Arg versus Arg/Arg	Significant only in Asians, Caucasians, adeno, smokers
	Dai *et al.*	1.14*	(1.03–1.25)	Pro/Pro+Pro/Arg versus Arg/Arg	
MDM2					
T309G	Wilkening *et al.*	1.27*	(1.12–1.44)	GG versus TT	
	Gui *et al.*	1.17*	(1.02–1.34)	GG versus TT	Significant in Asians but not Caucasians
	Bai *et al.*	1.16*	(1.01–1.34)	GG versus TT	Significant in never smokers
p21					
Ser31Arg	Lin *et al.*	1.11	(0.85–1.45)	Ser/Ser versus Arg/Arg	
CCND1					
G870A	Li *et al.*	1.24*	(1.08–1.44)	A versus G	Significant in Asians not Caucasians
	Liu *et al.*	1.13*	(1.03–1.24)	A versus G	Significant in Asians not Caucasians
Inflammation					
IL-10					
C819T	Peng *et al.*	1.27*	(1.01–1.58)	C versus T	
G1082A	Peng *et al.*	2.35*	(1.16–4.76)	G versus A	
C592A	Peng *et al.*	1.17	(0.99–1.39)	C versus A	
IL-6					
G174C	Peng *et al.*	0.97	(0.90–1.05)	G versus C	
L-1B					
C-511T	Peng *et al.*	1.23	(0.93–1.62)	C versus T	
T-31C	Peng *et al.*	1.1	(0.93–1.30)	T versus C	
Tumor necrosis factor α					
A308G	Peng *et al.*	1.33	(0.62–2.85)	G versus A	
COX–2					
T8473C	Peng *et al.*	1	(0.83–1.21)	T versus C	
Telomere length					
Short telomeres	Ma *et al.*	2.39*	(1.18–4.88)	Short versus long	
Tumor microenvironment					
MMP1					
−16071G>2G	Xiao *et al.*	1.21*	(1.06–1.37)	2G versus 1G	Significant only in Asians not in Caucasians
MMP2					
−1306C>T	Peng *et al.*	0.55*	(0.48–0.63)	T versus C	
−735C>T	Peng *et al.*	0.72*	(0.61–0.85)	T versus C	
MMP9					
−1562C>T	Peng *et al.*	0.93	(0.55–1.57)	T versus C	

1.11–1.28 for the C versus T allele); this was modified by ethnicity with significantly increased risk in East Asian subgroups and marginal significance in Caucasians (17).

The *A2455G Ile>Val* polymorphism is associated with increased enzymatic activity and inducibility of aryl hydrocarbon hydrolase, which activates PAHs in smoke. Multiple small studies have demonstrated a relationship between the variant allele and increased risk in individual ethnic populations (Chinese, Brazilian, Spanish and northern Indian) (18–21). Again, these studies demonstrated risk modification based not only on polymorphism status but also on smoking status and quantity, and histology (increased risk of squamous histology). Several meta-analyses have found the variant allele (homozygous or heterozygous) to be associated with increased risk of lung cancer. The global meta-analysis by Chen *et al.* (17) showed the variant to be associated with increased risk (OR 1.20, CI 1.08–1.33), but with a significantly increased risk in East Asian subgroups only. A Chinese meta-analysis by Shi *et al.* (22) demonstrated increased risk with the combined *Ile/Val* and *Val/Val* genotypes (OR 1.61, CI 1.24–2.08) compared with the *Ile/Ile* genotype. Hung's pooled analysis also found increased risk with variant *Ile/Val* or *Val/Val* genotypes (OR 2.21, CI 1.12–4.37) (15).

Some studies have addressed the combined effect of having both the T3801C and the A2455G polymorphisms. Small studies described the increased risk for double homozygotes, again largely for squamous cell and modified by smoking status (23,24). However, there was no significant effect of either polymorphism on risk in a large meta-analysis (25).

CYP2E1. CYP2E1 is involved in the metabolic activation of carcinogenic *N*-nitrosamines, benzene and urethane. The *PstI/RsaI* polymorphism encompasses a 5'-flanking region with putative binding motif for hepatic transcription factor HNF-1. The variant *c2* allele of this polymorphism is associated with enhanced transcription and an increased level of CYP2E1 activity (26). The *c2* homozygous variant has been associated with decreased risk of lung cancer in some smaller studies, especially in Taiwanese, Mexican American and Swedish populations (27–29). A meta-analysis by Zhan *et al.* (30) demonstrated decreased risk of lung cancer in homozygous *c2/c2* (OR 0.73, CI 0.63–0.85) when compared with homozygous wild-type *c1/c1* carriers. A meta-analysis by Wang *et al.* (31) found decreased risk for the heterozygote *c1/c2* versus the homozygote *c1/c1* (OR 0.80, CI 0.72–0.89), but there was no significant association with risk for the homozygote *c2/c2* variant.

The *DraI* polymorphism in *CYP2E1* has a statistically different distribution of *CC* (wild-type) and *DD* (variants) among lung cancer cases versus controls. Wang's meta-analysis described a protective effect of the C allele (OR *CC* versus *DD* 0.58, CI 0.41–0.81) (31).

Glutathione-S-transferases

GSTM1. Glutathione S-transferases are involved in the detoxification of electrophilic metabolites of potential carcinogens in tobacco smoke, including benzo[α]pyrene and other PAH (32). The null (homozygote deleted) mutation in *GSTM1* leads to lack of expression of GSTM1 protein and has been associated with increased DNA adduct levels in lung tissue (33,34). The null mutation has been associated with an increased risk of lung cancer in multiple populations, with specific histologies and smoking status seen as modifiers of risk.

Extensive smaller studies have demonstrated the increased risk conferred by the null mutation largely in Asian populations, including studies conducted in Japan, China and Korea (35–37). The null mutation has also demonstrated risk in African Americans, Turkish and Slovakian populations (38–40). Many of these smaller studies observed more significant risk with squamous cell histology and risk modification by smoking status. Other smaller studies have conversely found either decreased lung cancer risk or no significant risk modification *via* the null genotype (41–43). In Lee's pooled analysis, there was no significant overall association with lung cancer risk, but the null mutation was associated with an increased risk of squamous cell cancer (OR 1.36, CI 1.05–1.77) (16). In Hung's pooled analysis, there was no significantly increased risk with the null genotype alone, but risk increased when the *GSTM1* 'null' genotype was combined with *CYP1A1 Ile/Val* and *Val/Val* genotypes (15).

Multiple meta-analyses have also demonstrated an association between *GSTM1* null genotype and lung cancer risk. A 1995 meta-analysis of 12 case-control studies by McWilliams *et al.* (44) concluded that *GSTM1* null genotype is a moderate risk factor for lung cancer (OR 1.41, CI 1.23–1.61), with increased risk evident for all major histological types of lung cancer. The authors felt that the high prevalence of *GSTM1* null means that though the increased risk is small, deficiency accounts for about 17% of all lung cancer cases. A 1999 UK meta-analysis by Houlston *et al.* (45) also found an increased risk with the null mutation (OR 1.13, CI 1.04–1.25) based on genotyping methods; this risk was lower than seen in pooled analysis based on phenotyping methods (OR 2.12, CI 1.43–3.13) suggesting early phenotyping studies were overinflated. A French meta-analysis from 2002 concluded that there was a slight excess risk with the null genotype, but a pooled analysis demonstrated no significant increased risk of lung cancer in nulls and no significant interaction between *GSTM1* genotype and smoking status (46). A 2006 meta-analysis by Ye *et al.* (47) found a positive association between null genotype and risk of lung cancer (OR 1.18, CI 1.14–1.23), which was no longer significant when analysis was restricted to larger studies. The HuGE meta-analysis in 2008 by Carlsten *et al*. (48) concluded that the *GSTM1* null genotype was associated with increased risk in lung cancer (OR 1.22, CI 1.14–1.30), seen most significantly in East Asians (OR 1.38, CI 1.24–1.55) but not in Caucasians. Finally, a meta-analysis in 2010 by Langevin *et al.* (49) based on the Venice interim guidelines found a significant association between *GSTM1* null and lung cancer (OR 1.17, CI 1.10–1.25), also seen in pooled analysis (adjusted OR 1.10, CI 1.04–1.16).

GSTP1. The pulmonary content of the GSTP1-1 isozyme has been found to be higher in cancer versus non-cancer patients (50). The *G* allele of the *Ile105Val (323A>G)* polymorphism results in lower conjugation activity and has been associated with increased levels of hydrophobic adducts in the lung. Lung cancer patients have significantly higher frequency of *GG* genotype versus *AA* genotype than controls, and in those patients with lung cancer, the *GG* genotype is associated with a significantly higher DNA adduct level than the *AA* genotype (51). Various small population-based studies have demonstrated mixed results in terms of lung cancer risk, with almost all studies showing interactions between *GSTP1* polymorphism status and age, smoking status and cancer histology. Significant associations have most often been found between the increased risk of lung cancer with the *GG* genotype in younger age (52) and in heavy smokers (53), as well as in combination with the *GSTM1* null genotype (54–56). However, three of the largest meta-analyses (by Ye *et al.* (47), Langevin *et al.* (49) and a 2009 HuGE review by Cote *et al.* (57)) found no significant overall association with lung cancer risk. The HuGE meta-analysis by Cote *et al*. (57) did find a slight increased risk for the combined *GG* and *AG* genotypes versus the *AA* genotype, seen only in Asian subjects and strongest in non-smokers and those with adenocarcinoma.

GSTT1. The GSTT1 glutathione transferase metabolizes potential carcinogens in cigarette smoke (alkyl halides ad halomethanes) and the null allele leads to lack of expression of GSTT1 protein (58). Smaller studies have in some cases demonstrated increased risk with the null genotype (59), but this association has not been consistently seen and in some cases has also been associated with decreased risk (60,61). Pooled and meta-analyses have generally not found significant risk associations. Lee's pooled analysis found no significant association with GSTT1 genotype and risk (16). Although one Chinese meta-analysis by Wang *et al.* (62) showed that the null allele conferred increased risk of lung cancer (OR 1.36, CI 1.09–1.69), the Venice interim-based analysis demonstrated no association between the null allele and lung cancer risk (49).

NAT1 and NAT2. NAT enzymes catalyze the biotransformation of aromatic amines by solubilizing chemical groups to products of phase I cytochrome P450 metabolism, thus producing readily excretable

compounds (63). Variations in NAT lead to both slow and fast acetylation capability. *NAT* slow acetylator genotypes are associated with increased lung levels of DNA adducts and have been associated in small studies with increased risk of lung cancer (64–66). Multiple other studies have demonstrated differential effects of NAT on lung cancer risk modified by smoking status, but results have been very inconsistent. Some studies show increased risk for slow acetylators in never smokers and for fast acetylators in smokers (67,68), and others demonstrating increased risk for fast acetylators in never smokers (69). Meta-analyses have been inconsistent as well. Most have found no overall association between *NAT* genotype and lung cancer risk (70,71), but a meta-analysis by Zienolddiny *et al.* (72) did find the *NAT1* fast acetylator genotype to be associated with higher risk (OR 3.75, CI 2.58–5.51).

MEH (EPHX) exons 3 and 4. Microsomal epoxide hydrolase (MEH, EPHX) catalyzes the hydrolysis of arene, alkene and aliphatic epoxides from PAH and aromatic amines. This is generally a detoxification reaction, but hydrolysis of some hydrocarbons such as benzo(a)pyrine in cigarette smoke generates more highly reactive and mutagenic compounds (73). The *T113C Tyr>His* polymorphism in exon 3 leads to a decrease in enzyme activity (the 'slow allele'), whereas the *A139G His>Arg* polymorphism in exon 4 leads to an increase in enzyme activity (the 'fast allele'). The majority of lung cancer tissues contain exon 3 *Tyr* (wild-type fast) and exon 4 *His* (wild-type slow) (74). The variant slow allele in exon 3 has been associated with decreased risk of lung cancer (75,76) and the variant fast allele of exon 4 with increased risk of lung cancer in smaller studies (77,78). However, these studies are difficult to interpret as *MEH/EPHX* genotype and lung cancer risk are often modified by ethnicity, age, histology and smoking status. There are few meta-analyses of *MEH/EPHX* and lung cancer risk; in a HuGE meta-analysis by Kiyohara *et al*., (79) there was no overall association between either variant allele and risk, but the exon 3 low-activity variant was associated with significantly decreased risk of lung cancer in a white-only population (OR 0.65, CI 0.44–0.96).

NQO1 (exon 6, chromosome 16q). NAD(P)H quinine oxidoreductase catalyses bioreduction and activation of quinone substrates. This activates and detoxifies carcinogens in smoke. The variant *T* allele in exon 6 *(C>T)* leads to decreased activity and may be associated with a lower risk of lung cancer (80–82). This has not been consistent across the literature, and the variant has also been associated with decreased risk (83,84) or no significant modifying effect on lung cancer risk (85–87). Again, these studies have all been in relatively small single-ethnicity populations, and additionally, many studies have seen significant effect modification based on smoking status, histology, sex and age (88–90). The HuGE meta-analysis by Kiyohara *et al.* (91) found no significant overall association, but did find that showed the variant homozygote + heterozygote genotypes to be associated with significantly decreased risk of lung cancer in a Japanese-only population, where the variant allele is common. A meta-analysis by Chao *et al.*, (92) which included multiple ethnicities including Caucasians, Asians and blacks found no significant increased risk in any specific ethnic population.

MPO. Myeloperoxidase (MPO) transforms pre-carcinogens such as benzo(α)pyrene and aromatic amines to highly reactive amines. The promoter region *G463A* polymorphism may reduce MPO mRNA expression through removal of a binding region for transcription factor Sp1 leading to decreased metabolic activation of carcinogenic compounds in smoke (93). The *A* allele has been associated with decreased lung cancer risk in multiple small studies in Caucasian (94), Japanese and Native Hawaiian (95), and Turkish (96) populations. However, studies in Finnish (97), French (98) and Korean (99) populations showed no significant associations. Again, when effects are seen, they are often modified by age, smoking status and histology (100–102). Kiyohara's meta-analysis found the *AA* and *AG* genotypes were not significantly associated with risk except in Caucasians, where risk was decreased (91). A meta-analysis by Taioli *et al.* (103) using data collected from the Genetic Susceptibility to Environmental Carcinogens database found significantly decreased risk associated with the *AA* genotype (OR 0.71, CI 0.57–0.88), particularly in Caucasian populations and ever smokers, though most studies included in this analysis were based on Caucasian populations.

Nucleotide excision repair

ERCC2/XPD. ERCC2/XPD is an adenosine triphosphate-dependent helicase in the TFIIH transcription repair factor complex; it is involved in nucleotide excision repair (NER) and basal transcription. Several variants may affect its functionality, most notably, the Asp312Asn and Lys751Gln variants, which are associated with decreased NER/DNA repair capacity (104). The *Asn/Asn* variant genotype of *Asp312Asn* has been associated with increased risk of lung cancer in non-smokers and decreased risk in heavy smokers (105), whereas the *Asp/Asp* wild-type was associated with increased risk of NSCLC in light smokers but not in never or heavy smokers (106). The *Asn* allele is also associated with increased risk of squamous cell cancer (107,108). Several large meta-analyses have found that the *Asn* allele may lead to increased risk of lung cancer. Zhan *et al.* (109) found a significant association between the *AA* versus *GG* genotype and risk (OR 1.24, CI 1.09–1.42), significant only in Asians and smokers in subgroup analysis. Feng *et al.* (110) also found a significant association between the homozygous genotype and risk (OR 1.20, CI 1.05–1.36), significant in both Asians and Caucasians but only in never smokers. The effect was also heavily modified by smoking status in a Chinese population-based meta-analysis performed by Qian *et al.*, (111) where no overall association was observed but the AA genotype was associated with risk in never smokers. A HuGE review by Benhamou *et al*. (112), an International Lung and Cancer Consortium (ILCCO) analysis by Hung *et al.* (113) and a meta-analysis by Kiyohara *et al.* (114) found no clear association with this polymorphism and lung cancer risk.

The variant *Gln* allele of the exon 23 *Lys751Gln* is associated with reduced DNA repair capacity (115). Smaller studies have described differential results regarding the impact of this polymorphism on lung cancer risk. Some have suggested that the variant *Gln* allele is associated with increased risk (116–118), whereas others have found it to be associated with decreased risk (119,120). These studies were for the most part performed in isolated ethnic populations and also demonstrated effect modification based on histology, smoking status and age. Most meta-analyses have found the *Gln* allele to have some association with increased risk. Zhan's study had an OR of 1.26 (CI 1.12–1.42) significant in Caucasians and smokers in subgroup analysis (109), and Feng's study found an OR of 1.31 (CI 1.17–1.46), significant in Caucasians, Latinos and never smokers in subgroup analysis (110). Hung's pooled ILCCO analysis found the *Gln/Gln* variant to be associated with increased risk (OR 1.19, CI 1.02–1.39 (113)), as did Kiyohara's study (OR 1.09, CI 1.04–1.18), significant in Caucasians (114), but there was no clear risk association in the HuGE meta-analysis by Benhamou (112).

ERCC1/XPF. ERCC1/XPF is the lead enzyme involved in NER and is required for the excision of damaged DNA strands (121). An *8092C>A* polymorphism in the 3'-untranslated region may affect mRNA stability (122) and the *AA* genotype was associated with increased lung cancer risk in never smokers (adjusted OR 2.11, CI 1.03–4.31) and decreased risk in heavy smokers (adjusted OR 0.50, CI 0.25–1.01) (123). The *TT* homozygote of the *Asn118Asn (T19007C)* polymorphism may be associated with increased lung cancer risk in primarily Caucasian populations but not in Chinese (124). A meta-analysis by Cao *et al.* (125) demonstrated no association between the C8092A or the T19007C polymorphisms and lung cancer risk, and Hung′s ILCCO analysis did not find a significant association between C8092A status and lung cancer risk (113). There was also no association between T19007C status and risk in a meta-analysis by Li *et al.* (126).

XPA. XPA interacts with replication protein A, transcription factor IIH and ERCC1/XPF (127). The *GG* genotype of an *A23G* polymorphism

at position –4 has been associated with reduced risk of lung cancer in Koreans (128), Caucasians and African Americans, perhaps related to more efficient DNA repair capacity (129). Similarly, the *AA* genotype has been associated with increased risk, but only in heavy smokers (130). Kiyohara's DNA repair pathway meta-analysis demonstrated a protective effect based on the *GG* genotype (OR 0.76, CI 0.61–0.94), which was not significant in Caucasians (114), and Qian's Chinese meta-analysis demonstrated that the *AA* versus *GG* genotype was associated with increased risk (OR 1.28, CI 1.12–1.47) most significant in Asians (111). Hung's ILCCO analysis found no significant association with risk (113).

XPC. XPC is a DNA damage sensor and repair recruitment factor; a poly-AT insertion in intron 9 has demonstrated decreased DNA repair capacity (131). The *PAT* +/+ genotype has been associated with increased risk of lung cancer in some studies, modified again by smoking status, age and histology (132,133). The *T* variant of the *Ala499Val (C499T)* and the *C* variant of the *Lys939Gln (A939C)* polymorphisms have been associated separately and in combination with the increased risk of lung cancer in China (134). A primarily Chinese and Caucasian meta-analysis by Qiu *et al.* (135) found no significant risk association for *PAT* +/– or *C499T,* but did find the *C* variant of *A939C* to be associated with increased risk of lung cancer (OR 1.28, CI 1.07–1.53 for the *CC* versus *AA* genotype).

ERCC5/XPG. ERCC5/XPG is an endonuclease, which functions to make a 3' nick prior to excision repair (136). The *Asp* variant of the *His1104Asp* polymorphism has been associated with decreased risk of lung cancer in small populations (137–139), with effect modification based on age, sex, smoking status and histology. The ILCCO study found no significant association between this polymorphism and risk of lung cancer (113).

Base excision repair

XRCC1. This enzyme interacts with nicked DNA and participates with poly-adenosine diphosphate-ribose polymerase, DNA ligase III and DNA polymerase B to repair single-strand DNA breaks (140). Multiple polymorphisms have been identified, which may affect both function and lung cancer risk.

The variant *Trp* allele of the *Arg194Trp* polymorphism has been associated with reduced risk in some small studies, but results are often modified by smoking status, and not always in a congruous manner. The presence of the *Trp* allele may lead to decreased risk in heavy smokers (141,142) but increased risk in non-smokers (143). Several meta-analyses have been performed demonstrating association with the heterozygote genotype only in a study by Wang *et al.* (144), and no association in analyses by Zheng *et al.* (145), Kiyohara's base excision repair meta-analysis (146), or the HuGE (147) and ILCCO reviews (113). One meta-analysis by Huang *et al.* did demonstrate to increased risk (OR 1.27, CI 1.07–1.50) (148). Though some risk association has been described between the *Arg280His* polymorphism and lung cancer risk in single small studies (149,150), results have generally been inconsistent and there was no significant risk association found in Zheng's (145) or Kiyohara's (146) meta-analyses and the HuGE (147) or the ILCCO reviews (113).

The *Arg399Gln* polymorphism results in a substitution in the poly-adenosine diphosphate-ribose polymerase binding domain and has been associated with higher levels of aflatoxin B1-adducts and glycophorin A somatic mutations (151). The *Gln/Gln* homozygous variant genotype has been associated with increased risk of lung cancer in mostly studies of small single-ethnicity populations or with strong risk modifications based on smoking amount and duration (152–154). Conversely, the *Gln* allele has also been associated with decreased risk of lung cancer, again in the same context of single ethnic groups and modified by smoking status (155–157). In Zheng's Chinese meta-analysis, the *Arg/Gln* and *Gln/Gln* genotypes were associated with a trend toward increased risk (OR 1.16, CI 1.00–1.36) (145), but the meta-analyses by Wang (144), Kiyohara (146) and the HuGE (147) and ILCCO analyses (113) by Hung showed no significant association with risk. In the HuGE meta-analysis, the *Gln/Gln* genotype was associated with increased risk in light smokers (OR 1.38, CI 0.11–1.94) but decreased risk in heavy smokers (OR 0.71, CI 0.51–0.99) (147). Finally, in Kiyohara's meta-analysis, the *Gln/Gln* genotype was associated with significantly increased risk of lung cancer in Asians (OR 1.34, CI 1.16–1.54) but not in Caucasians (146).

OGG1. This enzyme functions to repair 8-hydroxyguanine, a mutagen that causes oxidative DNA damage induced by reactive oxygen species (158). 8-Hydroxyguanine levels have been found to be higher in tissue from lung cancer patients compared with controls (in non-tumor tissue) (159). The *Cys* allele of the *Ser326Cys* polymorphism in *OGG1* has been associated with decreased activity in 8-hydroxyguanine repair (160). Case-control and observational studies have demonstrated some increased risk of lung cancer with the *Cys/Cys* genotype (161–163). This has been borne out to some extent in the HuGE analysis by Hung *et al.*, (113) with an OR of 1.24 (CI 1.01–1.53) for the *Cys/Cys* versus *Ser/Ser* genotypes (147) and in the ILCCO analysis (OR 1.34, CI 1.01–1.79). Results from the ILCCO analysis were significant only in Caucasians but not in Asians. Kiyohara's analysis did not demonstrate any significant association with risk (146).

APE. The apurinic/apyrimidinic endonuclease 1, APE, is a major repair enzyme for abasic sites. It incises the DNA phosphodiester backbone 5' to a lesion to initiate a cascade of events, which leads to the removal of abasic moieties and maintenance of genetic integrity (164). The variant *Glu/Glu* genotype of the *Asp148Glu (T>G)* polymorphism in exon 5 has a significantly longer cell cycle mitotic delay and may contribute to increased sensitivity to ionizing radiation (165). The *Asp/Glu* and *Glu/Glu* genotypes have been associated with both increased risk of lung cancer (166–168) (modified by smoking status) and lower risk of lung cancer (169,170). In general, large studies have not shown a significant impact on risk. There was no association with risk in Hung's HuGE review (147), the ILCCO analysis (113) or Kiyohara's analysis (146). A meta-analysis by Ji *et al.* (171) demonstrated no association with lung cancer risk in Caucasians or Asians in general but that the variant genotype led to an increased risk in smokers only.

Double-strand break repair

XRCC3. XRCC3 is involved in homologous recombination repair and chromosomal double-strand break repair. Cells defective in XRCC3 have a 25-fold decrease in homology-detected repair of DNA double-strand breaks (172). The *Met* variant of a *Thr241Met* polymorphism has been associated with higher DNA adduct levels and may affect DNA repair capacity (173). Small studies have been inconsistent in reporting associations between polymorphism status and lung cancer risk, as have been meta-analyses. In the ILCCO pooled analysis, the *Met/Met* variant was associated with decreased risk (OR 0.84, CI 0.71–1.00), significant in Caucasians and not in Asians (113). Similarly, there was no significant association in a Chinese meta-analysis by Sun *et al.* (174).

Cell cycle checkpoint control

p53. p53 is a central tumor suppressor gene. Mutations often lead to inactivation of transcriptional activity, and p53 is frequently lost in lung cancer (175). The *Arg72Pro (G12139C)* polymorphism leads to a *Pro* variant, which may be less efficient in suppressing cell transformation and inducing apoptosis (176). Multiple studies have demonstrated that the *Pro* allele is likely associated with increased risk of lung cancer, modified by age, smoking status and histology (177–185). A 2003 meta-analysis by Matakidou *et al.* (186) showed that *Pro/Pro* homozygotes had a borderline increased risk of lung cancer (OR 1.18, CI 0.99–1.41), and the ILCCO analysis also demonstrated increased risk (OR 1.20, CI 1.02–1.42) for *Pro/Pro* homozygotes (113). A meta-analysis by Yan *et al.* (187) showed that the *Pro* allele had increased risk for the population as a whole compared with the *Ser* allele (OR 1.08, CI 1.00–1.17), a finding that was significant only in Asians and not in Caucasians. A meta-analysis by Yi *et al.* (188) similarly found

increased risk for carriers of the *Pro* allele (*Pro/Pro* and *Pro/Arg* [OR 1.15, CI 1.04–1.23]), which was significant in both Caucasians and Asians and most significant for adenocarcinoma histology and in smokers. Finally, a 2009 pooled analysis by Dai *et al.* (189) of 32 case-control studies also demonstrated increased risk with the *Pro/Pro* and *Pro/Arg* combined genotypes (OR 1.14, CI 1.03–1.25) and concluded that the *Pro* allele is a low-penetrance susceptibility allele for lung cancer.

MDM2. This negative regulator of p53 binds to p53 and inhibits p53-mediated cell cycle arrest (190). A *T309G* polymorphism has been associated with increased levels of MDM2 RNA and protein. The *GG* genotype has been associated with increased risk of lung cancer in some studies (191), but it has also been associated with decreased risk of lung cancer (192,193) or not associated with risk of cancer in other studies (194,195). Three meta-analyses have demonstrated an increased risk for those with the *GG* genotype. The meta-analysis by Wilkening *et al.* (196) had an OR of 1.27 (CI 1.12–1.44) and was not modified by ethnicity or smoking status. The meta-analysis by Gui *et al.* (197) with an overall OR of 1.17 (CI 1.02–1.34) was significant in Asians but not in Caucasians, whereas the meta-analysis by Bai *et al.* (198) found an OR of 1.16 (CI 1.01–1.34) and was most significant in never smokers.

p21 is a downstream target of p53, and its expression is stimulated by p53 binding. p21 subsequently binds to cyclin complexes and inhibits the function of cyclin-dependent kinases in the DNA of damaged cells (199,200). A codon 31 polymorphism (*Ser31Arg*) has been associated with increased variant *Arg* frequency in lung cancer tissue (201), but variable and usually non-significant results in terms of lung cancer risk (202,203). A meta-analysis by Lin *et al.* (204) did not find a significant association between p21 genotype and lung cancer risk (OR 1.11, CI 0.85–1.45).

CCND1 (cyclin D1) regulates G_1/S phase and is frequently amplified in lung cancer (205). An *A870G* variant in exon 4 increases the frequency of a C-terminal domain with no splicing (206), allowing expression of an alternative D1b transcript that lacks the phosphorylation site needed for nuclear export (207). The *AA* homozygous wild-type genotype has been associated with increased risk of lung cancer in small studies of Chinese (208), North Indian (209) and Caucasian (210) populations modified by smoking status, age, sex and histology. A meta-analysis by Li *et al.* (211) found increased risk with the A versus G allele (OR 1.24, CI 1.08–1.44), which was significant only in Asians and not in Caucasians. Similarly, a meta-analysis by Liu *et al.* (212) demonstrated increased risk for A versus G alleles (OR 1.13, CI 1.03–1.24), which was significant only in Asians and not in Caucasians.

TP53BP1. TP53BP1 is involved in DNA damage signaling, checkpoint signaling and DNA repair; it interacts with the DNA-binding domain of TP53 to enhance TP53-mediated transcriptional activity (213). Reduced or absent expression of TP53BP1 in lung cancer tissue has been reported (214). Polymorphisms in *TP53BP1* have been associated with G_2/M arrest, less efficient checkpoint control and therefore increased risk of lung cancer (215). The *rs560191* variant is associated with decreased lung cancer risk, especially of squamous cell, in an ILCCO analysis (OR 0.91, CI 0.86–0.97 for all histologies and OR 0.86, CI 0.79–0.94 for squamous cell histology) (216). Additionally, a GWAS revealed that the *T* allele of a sequence variant at 15q15.2 (*rs748404*), located 140 kb centromeric of TP53BP1, was associated with increased risk; in this same study, non-synonymous coding variants in TP53BP1 (*Q1136K, rs2602141* and *E35D, rs560191*) were associated with lung cancer risk but not significant after adjustment for *rs748404* (217).

Inflammatory genes

Interleukins and related genes. Alveolar macrophages from patients with lung cancer secrete significantly more IL-1B than those from non-cancer patients (218). Small studies have shown roles for several polymorphisms in risk prediction. The variant *TT* (and heterozygote *CT*) of a *+3954C>T* polymorphism has been associated with increased risk, modified by smoking status, sex and alcohol intake (219,220). Two promoter variants (*C-511T* and *T-31C*) have been identified; the *−511C* and *−31T* may both lead to increased risk perhaps due to higher promoter expression (221–224), but this has not been consistent across all studies (225,226). A meta-analysis by Peng *et al.* (227) demonstrated no significant risk of lung cancer associated with either of these variants. Additionally, small studies of polymorphisms in the interleukin (IL)-1 receptor (228), IL-8 (229) and IL-10 (230) have been performed, but there was no association with three polymorphisms in IL-10 and lung cancer risk in Peng's meta-analysis as well as no association with a polymorphism in IL-6 (227).

Tumor necrosis factor is a pro-inflammatory cytokine, which acts as a central mediator of the immune response and modulates airway inflammation. Studies of the *−308A>G* and *−238AG* promoter polymorphisms, which may lead to altered protein levels and transcription rates (231), have yielded mixed results (232,233), and there was no significant association with lung cancer risk in Peng's meta-analysis (227).

Cyclooxygenase 2 mediates the production of prostaglandins from arachidonic acid. Cyclooxygenase 2 is induced by cigarette smoke and lung cancer tumor cells, and may function to promote tumor growth, angiogenesis and metastasis (234). A promotion in the 3'-untranslated region (*C8473T*) has been described (235), but was not associated with risk in Peng's meta-analysis (227).

Telomere length. The telomerase enzyme adds hexameric TTAGGG nucleotide repeats to ends of telomeres to compensate for losses during each round of DNA replication. Somatic cells typically lack telomerase activity and stop dividing when telomeric ends reach a critical length (236). Smoking is associated with increased telomerase activity in normal bronchial epithelial cells and may lead to an extended lifespan in cells at risk for malignant transformation (237). Telomerase has been detected in a high proportion of lung cancer tissues, potentially leading to cancer cell immortalization (238). Downregulation of DNA repair genes (*MLH* and *PARP3*) has been detected in tumors with reactivated telomerase (239). SNPs in telomere maintenance genes *POT1, TERT, TERF2* and *TNKS1* have been associated with lung cancer risk in individual studies (240,241). A meta-analysis by Ma *et al.* (242) found that short telomere length was associated with a significantly increased risk of lung cancer (OR 2.39, CI 1.18–4.88), but this was not in the context of individual polymorphisms but rather a general measure of telomere length.

Cell microenvironment

MMP1. Matrix metalloproteinase 1 (MMP1) is the most highly expressed interstitial collagenase and is involved in the degradation of fibrillar collagens, which are major components of the extracellular matrix. Higher expression of MMP1 has been described in tumor tissues compared with normal tissues (243). The *−1607 1G>2G* polymorphism may create an ETS-binding site and the *2G* has significantly higher transcription and binds more nuclear extract and recombinant ETS (E-twenty six)-1 compared with the *1G* (244). The *2G/2G* variant genotype has been associated with higher risk of lung cancer, modified by smoking status and sex (245,246). A meta-analysis by Xiao *et al.* (247) described an increased risk with the *2G* versus *1G* allele (OR 1.21, CI 1.06–1.37), which was significant only in Asians and not in Caucasians.

MMP2. MMP2 is a gelatinase, which cleaves type IV collagen, a major structural component of the basement membrane (248). A *C-1306T* polymorphism disrupts the Sp1-type promoter site (CCACC box) and loss of Sp1 binding linked with the *T* allele is correlated with lower promoter activity. The *TT* genotype has been associated with decreased risk of lung cancer, modified by smoking status (249). The *−735C>T* polymorphism also destroys an Sp1-binding element and the *T* allele is similarly associated with decreased promoter activity; the *TT* haplotype of these two polymorphisms has even lower promoter activity (250). The *TT* haplotype has been associated with much decreased risk, likely synergistic based on magnitude (251).

The *T* alleles of both polymorphisms were associated with decreased risk of lung cancer in a single meta-analysis by Peng *et al.* (252) (OR 0.55, CI 0.48–0.63 for the −1306C>T and OR 0.72, CI 0.61–0.85 for the −735C>T, respectively, though the synergistic interaction was not highlighted in this study.

MMP9. MMP9 functions as a gelatinase that digests denatured collagens and gelatins; there is a higher expression of MMP9 in lung cancer versus normal tissue (253). Several polymorphisms in *MMP9* have been associated with lung cancer risk. The *−1562CT* polymorphism leads to increased promoter activity *via* a putative transcription repressor, which binds preferentially to the *C* allelic promoter (254), and small studies have shown both increased frequency of the *CC* genotype in tumor tissue (255) and decreased risk of lung cancer with the *TT* genotype (256). Two other polymorphisms—the *R279Q*, which lies in a gelatinase-specific fibronectin type II domain, and the *P574R*, which is located in a homeopexin domain (257)—have been associated with risk in one study (258). Significant risk modification was not seen in Peng's meta-analysis (252).

Other notable polymorphisms

EGFR. The epidermal growth factor receptor (EGFR) family plays an important role in the regulation of multiple physiologic processes mediated by epidermal growth factor, transforming growth factor-α and several other ligands. EGFR overexpression is seen in many lung cancers, and a population of patients who are predominantly nonsmoking, Asian females have been found to harbor *somatic* activating mutations in *EGFR* that confer response to EGFR tyrosine kinase inhibitors (259). Specific mutations have been described, which lead tumors in such patients to develop acquired drug resistance. The *T790M* mutation is one such mutation and has been described not only in this context but more recently in the context of potential germline cancer predisposition. A family with multiple cases of NSCLC was determined to have germline transmission of the *T790M* mutation, and four of the six tumors studied were found to have a secondary activating EGFR mutation (260). Other mutations in exons 19 and 21 have also been implicated in adenomatous hyperplasia and other types of adenocarcinomas (261), and further work should be done to identify EGFR mutations, which are not only predictive in the clinical setting of already diagnosed lung cancer but also prognostic in terms of risk development. The germline determinants of the observed *EGFR* somatic mutations remain unknown and should be an area of active investigation.

Discoveries based primarily on GWAS

Nicotinic acid/acetylcholine receptor (15q25)

The nicotine-derived carcinogenic nitrosamine 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a high-affinity agonist for the α7 nicotinic acetylcholine receptor (nAChR). Initial studies demonstrated that α7 mRNA levels are higher in small cell lung cancer cells than normal cells (262). Tobacco-specific 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosonornicotine bind to some nAChRs with affinities higher than nicotine itself; it is thought that nAChRs may enhance the targeting of bronchial cells by tobacco carcinogens and that smoking may increase the function of specific nAChRs, which stimulate cancer cells and reduce the function of receptors that inhibit cancer cells (263).

The genes for nAChR subunits *CHRNA5/A3/B4* are located on the 15q25 chromosomal region; they are expressed in alveolar epithelial cells and bind to N-nitrosonornicotines and potential other lung carcinogens. *CHRNA3* is a target of DNA hypermethylation and silencing in lung cancer; *CHRNB4* is also moderately methylated, whereas *CHRNA5* is not methylated (264). A 30-fold upregulation of *CHRNA5* and a 2-fold downregulation of *CHRNA1* have been demonstrated in tissue from lung adenocarcinoma versus normal lung. Carriers of the *N* allele of the *D398N* polymorphism of *CHRNA5* may be at an increased risk of adenocarcinoma (265), which may be secondary to altered receptor function and variability in CHRNA5 mRNA expression (266).

In small single-ethnicity studies, individual SNPs and SNP haplotypes in the 15q25 region (primarily in *CHRNA3* and *CHRNA5*) have been associated with lung cancer risk (267–270). Several large studies have also demonstrated risk associations. A 2008 GWAS performed by Hung *et al.* (271) analyzing over 300 000 SNPs in lung cancer cases and controls from central European countries identified the 15q25 locus as strongly associated with lung cancer ($P = 5 \times 10^{-20}$ overall) and reported to account for 14% of the attributable risk of lung cancer cases regardless of smoking status. A 2009 GWAS performed by Amos *et al.* (272) analyzing lung cancer cases and controls in the USA and UK described two SNPs (rs1051730 and rs8034191) in the 15q25.1 region containing the genes for CHRNA3 and CHRNA5, to be significantly associated with risk (combined $P < 1 \times 10^{-17}$). Finally, an ILCCO pooled analysis demonstrated that both rs8034191 and another SNP in *CHRNA5*, rs16969968, were associated with risk of lung cancer, though modified by age, ethnicity and smoking status (273). A recent mediation analysis by Van de Weele *et al.* (274) and ILCCO GWAS consortium found that there was an association of the *CHRNA5* variant and lung cancer risk independent of smoking status.

TERT-CLPTM1L (5p15.33)

TERT is a reverse transcriptase component of telomerase and is essential for enzymatic activity and maintenance of telomeres (275). CLPTM1L is thought to potentially induce apoptosis of lung cells under genotoxic exposures such as tobacco carcinogen-related stress. The *TERT* and *CLPTM1L* genes are closely located on chromosome 5 at 5p15.33 and several GWAS have demonstrated associations with lung cancer risk. Wang's GWAS found that rs401681 in *CLPTM1L* was highly correlated with risk ($P = 7.9 \times 10^{-9}$). rs401861 was again associated with risk ($P = 7.2 \times 10^{-8}$) in a European-based GWAS by Rafnar *et al.* (276). rs402701 (in *TERT*) and rs2736100 (in *CLPTM1L*) were associated with lung cancer risk, at $P = 2 \times 10^{-7}$ and $P = 4 \times 10^{-6}$, respectively, in a European-based GWAS by McKay *et al.* (277). Several other studies have shown multiple separate *TERT* and *CLPTM1L* polymorphisms, which may modify risk based on histology, ethnicity and smoking status (278–280).

BAT3 (6p21.33) modulates p53 in response to genotoxic stress by affecting gene stability; it also interacts with Heat-shock protein 70 and apoptosis-inducing factor. SNPs in *BAT3* may be involved with lung cancer risk, such as rs1052486 ($P = 0.006$ in a Caucasian-based UK GWAS performed by Rudd *et al.* (281)). However, the ILCCO pooled analysis and several smaller analyses have not confirmed the role of *BAT3* polymorphisms in lung cancer risk (282).

Discussion

The study of genetic risk factors predisposing to lung cancer has evolved from a candidate-gene approach toward a larger scale GWAS approach, and we believe there are other approaches that could be taken in the future to further elucidate the genetic basis of lung cancer. The candidate-gene approach has identified multiple genes, primarily in carcinogen metabolism, nucleotide and base excision repair, and cell cycle control, which appear to have a role in lung cancer risk. However, the candidate-gene approach is limited by prior knowledge (or at least putative knowledge) of the presence and functional significance of genes involved in carcinogenesis. Most of the initial candidate-gene studies have been performed in small, single ethnic populations and the meta-analyses that we have reviewed reflect their component studies placing limits on the generalizability of these results. The great majority of the meta-analyses we reviewed have been either in Caucasian or in Asian populations and often show differential results based on ethnicity, gender, smoking status and tumor histology. Although this is informative in the sense of risk factors for certain populations, knowledge gained from candidate-gene studies and even meta-analyses limits our understanding of 'risk' and leads to other questions such as whether there are interactions between genes underlying the biology of ethnicity, gender, predilection to a

particular tumor histology and even behavioral components of nicotine dependence and addiction.

For instance, estrogen has been associated with benzo[α]pyrene-induced lung carcinogenesis through oxidative stress damage (283), and polymorphisms in the estrogen receptor have been demonstrated to have some impact on the risk of lung cancer (284,285). It is possible that polymorphisms in the glutathione-S-transferase genes impact risk of lung cancer in part based on exposure to estrogens or androgens. Telomeres and cell division are central to the aging process and it is plausible that polymorphisms in telomere-associated genes modify lung cancer risk in an age-dependent manner, and through interactions with other genes involved in the aging process. Some of the identified polymorphisms in *CHRNA5* lie in a locus also thought to be responsible for smoking behavior. These are just examples of questions that could be asked about the multiple interactions seen between genes, which putatively impact the risk of lung cancer, and the epidemiologic factors, which appear to modify the degree of risk conferred.

Although GWAS allows for examination of a much wider variety of genetic alterations than do candidate-gene studies, they also have limitations. Many GWAS have been performed in the context of single-ethnicity populations or populations of a single smoking status, which are not necessarily generalizable to the majority of the population at risk for lung cancer worldwide. For instance, novel lung cancer susceptibility loci have been described in the Chinese population (286), in non-smokers only (287), and even specifically in a population of never-smoking Asian women (288). Although very valuable in further understanding the role of specific genetic alterations involved in lung cancer risk in these individual populations, we believe that further efforts should be made based on multiethnic populations with the variety of smoking statuses and histologic types, which reflect the worldwide population.

Furthermore, GWAS is not based on a functional hypothesis, and SNPs identified by this method may not be driver mutations but instead represent common low-penetrance variants (some not even in identified genes) without clearly defined functional significance. These alterations may not reflect the highly mutated environment of lung tumors and thus may not reflect biologic alterations with significant impact on lung cancer development. In fact, there has been little concordance between these SNPs and the SNPs studied using the candidate-gene method. Although the possibility of false-positive findings based on the candidate-gene approach must be considered, there is often a clearly defined functional significance of SNPs identified with this approach, which cannot be ignored. It is possible that these results have not been replicated in GWAS due to loss through multiple comparison testing, but given the biologic plausibility of many of the candidate-gene findings, we do not believe they should be discarded in favor of the findings of GWAS. Instead, ways must be found to couple the toxicological- and pathophysiological-based methods of the candidate-gene approach with the expanded field of large sequence and whole-genome analysis and to search for interactions between many potential genes involved in risk simultaneously. Interactions between multiple genes may be investigated through pathway analysis using either genotyping data (SNP) or expression data (RNA/transcriptome). Using microarray data, multiple genes in a pathway or area of interest can be studied simultaneously. This way, variations in single genes are examined not in an isolated manner, but in the larger context of a network of genes involved in a specific biologic context (transcription, cell cycle regulation and so on), which could interact to modify risk. This could lead to a higher level understanding of the ways multiple genes interact with one another to modify cancer risk. For instance, multiple genes (*PPARG, CEBPB, ETV4, FLI1, TAL1* and *NFKB1*) involved in the regulation of transcription were demonstrated in a single study as 'hub nodes' and the authors not only described the impact of each gene individually but also described in the context of a 'transcriptome network' (289). We hope that further studies of pathways (for instance, cell cycle control, base excision repair, NER and so on) will be performed and that authors will address the role of multiple genes, which interact with one another in the context of a particular biological pathway to modify the risk of lung cancer. For instance, the technique of kernel machine SNP-set analysis has been used to group SNPs into sets based on genomic features and assess the impact of each SNP-set on survival outcomes. This technique has proven very useful in using genetic information from multiple SNPs in combination, and in accounting for linkage disequilibrium, SNP–SNP interactions and joint effects of multiple causal variants (290). This may not only provide further knowledge as to the role of multiple genes already implicated in cancer risk but also provide information regarding genes that have not thus far been evaluated in the context of predisposition to lung cancer.

A further complication in understanding the genetics of lung cancer is missing heritability; the possible contribution of variants of low minor allele frequency, defined as roughly 0.5 < minor allele frequency <5%, or of rare variants (minor allele frequency < 0.5) (291). Such variants are not sufficiently frequent to be captured by current GWA genotyping arrays, nor do they carry sufficiently large effect sizes to be detected by classical linkage analysis in family studies. For modest effect sizes, association testing may require composite tests of overall 'mutational load', comparing frequencies of mutations of potentially similar functional effect in cases and controls. Such low-frequency variants could have substantial effect sizes without demonstrating clear Mendelian patterns of inheritance.

Individual genes and pathways provide some insight into mechanisms of risk, but more comprehensive analyses such as microarrays should be developed to stratify risk based on overall genetic makeup. Spitz's expanded lung cancer prediction model, which uses two DNA repair markers, provides increased sensitivity above a model using clinical factors alone (292). A comprehensive risk prediction model that incorporates genetic variation may provide improved information about risk, especially in the setting of patients with already demonstrated high risk due to other sociological factors, predominantly smoking. Multiple gene signature profiles have been developed, which predict clinical outcome and response to treatment in largely early-stage lung cancers (293–297), but such models have not yet been developed in the pre-diagnosis, risk-assessment setting. It has been demonstrated that low-dose chest computed tomography performed in patients at high risk for lung cancer led to decreased mortality rates (298), but of course, the cost of screening all high-risk patients may be prohibitive. Genetic risk-assessment models could be helpful in the identification of those 'high-risk' patients who are at the highest risk for cancer and could potentially be used to guide further screening in the future. Isolating the genetic component of lung cancer might provide limited predictive value given the strong environmental component in the majority of lung cancers. However, the real translational value of genetic association studies lies not so much in the development of diagnostic tests, but with the identification of relevant genes and pathways implicated in disease. Effective chemoprevention and improved therapies may well be directed against gene products that exhibit no naturally occurring variation (299).

Conclusion

The association between smoking, other inhaled carcinogens and the development of lung cancer is well established, but the role of genetic variation as a risk factor for lung cancer has been more difficult to define, underscoring the complexity and heterogeneity of the disease complex that we call NSCLC. We have summarized primarily based on the results of meta-analyses the role of multiple alterations in a variety of genes that may play a part in the genetic predisposition to lung cancer. Many of these variations have been described in the context of a candidate-gene approach, often limited by small study size and individual ethnicity populations, even in meta-analyses of multiple studies. Other genes have more recently been identified by large-scale GWAS, but even these genes that appear to be highly associated with risk were often studied in single- or limited-ethnicity populations and do not all have a biologically defined role or a pathophysiologic basis for involvement in lung cancer risk. The use of pathway and kernel-based analysis, gene-based analysis and multiplatform (gene expression, epigenomic and proteomic) analyses could potentially be used as tools for early risk assessment. We advocate for further work to be performed using international collaborative databases,

which include patients from multiple geographic regions, multiple ethnicities, with a variety of lung cancer histologies and reflecting the current patterns of cigarette smoking worldwide. There is a significant amount of work that remains in identifying heritable risk factors for lung cancer, and identification of pathways and signatures involved in lung cancer risk may be of assistance in better understanding the pathophysiologic basis of cancer development, the early identification of individuals at high risk for lung cancer and ultimately in the development of more effective preventive interventions for this prevalent and deadly disease.

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