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review

NQO1, *MPO*, and the risk of lung cancer: A HuGE review

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The aim of this study is to summarize the available molecular epidemiologic studies of lung cancer and metabolic genes, such as NAD(P)H quinone reductase 1 (*NQO1*) and myeloperoxidase (*MPO*). NQO1 plays a dual role in the detoxification and activation of procarcinogens whereas MPO has Phase I activity by converting lipophilic carcinogens into hydrophilic forms. Variant genotypes of both *NQO1* Pro187 Ser and *MPO* G-463A polymorphisms may be related to low enzyme activity. The Pro/Ser and Ser/Ser genotypes combined of *NQO1* was significantly associated with decreased risk of lung cancer in Japanese [random effects odds ratio (OR) = 0.70, 95% confidence interval (CI) = 0.56–0.88] among whom the variant allele is common. The variant genotype of *MPO* was associated with decreased risk of lung cancer among Caucasians (random effects OR = 0.70, 95% CI = 0.47–1.04). Gene-environment interactions in both polymorphisms may be hampered by inaccurate categorization of tobacco exposure. Evidence on gene-gene interactions is extremely limited. As lung cancer is a multifactorial disease, an improved understanding of such interactions may help identify individuals at risk for developing lung cancer. Such a study should include larger sample size and other polymorphisms in the metabolism of tobacco-derived carcinogens and address interactions with smoking status. The effects of polymorphisms are best represented by their haplotypes. In future studies on lung cancer, the development of haplotype-based approaches will facilitate the evaluation of haplotypic effects, either for selected polymorphisms physically close to each other or for multiple genes within the same drug-metabolism pathway. ***Genet Med* 2005:7(7):463–478.**

Key Words: *lung cancer, NAD(P)H quinone oxidoreductase 1 polymorphism, myeloperoxidase polymorphism, molecular epidemiology, meta-analysis*

GENES

NAD(P)H quinone reductase 1

NAD(P)H quinone oxidoreductase 1 (NQO1, EC 1.6.99.2), formerly referred to as DT-diaphorase, is an important flavoprotein that catalyzes the two-electron reduction of carcinogenic quinoid compounds into their reduced form, such as hydroquinones.[1] Benzo(a)pyrene (BP) is one of the most important carcinogens, and the formation of BP quinone-DNA adduct is prevented by NQO1.[2] In contrast, carcinogenic heterocyclic amines present in smoke are metabolically activated by NQO1.[3] Therefore, this enzyme is thought to be involved in both metabolic activation and detoxification of carcinogens. Higher levels of tissue (cytoplasm) expression of the NQO1 have been detected in the lung, kidney, liver, and skeletal muscle, with lower levels in the heart, brain, and placenta.[4]

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Myeloperoxidase

Myeloperoxidase (MPO, EC 1.11.1.7) is a lysosomal hemoprotein located in the azurophilic granules of polymorphonuclear leukocytes and monocytes. MPO is the most abundant protein in neutrophils, constituting approximately 5% of their dry weight.[5] MPO has Phase I metabolizing activity by converting lipophilic carcinogens into hydrophilic forms.[6] Exposure to a variety of pulmonary insults, including cigarette smoke, stimulates recruitment of neutrophils into lung tissue[7] with local release of MPO.[8,9] MPO has been shown to activate an intermediate metabolite of BP, the 7,8-diol BP, to the highly reactive and carcinogenic benzo(a)pyrene 7,8-diol-9,10 epoxide (BPDE)[10] and to enhance the binding to BPDE to lung DNA in vitro.[11] MPO also activates carcinogens in tobacco smoke including polycyclic aromatic hydrocarbons (PAHs),[10–12] aromatic amines,[13–15] and heterocyclic amines[16] and catalyzed the endogenous formation of carcinogenic free radicals.[17] MPO may also function as an antimicrobial agent in neutrophils by catalyzing the production of genotoxic hypochlorous

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acid and other reactive oxygen species.[18] Upon activation of the neutrophils, MPO is released into phagocytic vacuoles and the extracellular milieu.[19,20]

VARIANTS

NQO1 variants

The *NQO1* gene, which is also known as *DTD, QR1, DHQU, DIA4,* or *NMORI*, consists of 6 exons and 5 introns and is located on chromosome 16q22.1. It covers 35.35 kb, from 69536903 to 69501551, on the reverse strand. A common polymorphic variant is a C-to-T point mutation at position 609 of exon 6 of the *NQO1* cDNA that encodes for a proline to serine substitution at position 187 in the amino acid sequence of the protein. The three genotypes of this gene are the Pro/Pro (normal activity), the Pro/Ser (mild activity), and the Ser/Ser (2–4% of normal activity).[21–25] The genotype frequencies in different populations are shown in Table 1.[26–65] The summary frequency of the Ser allele among Caucasians was 18.9% (95% CI = 15.6–22.1%), and the summary frequency of the Ser/Ser and Pro/Ser genotypes combined was 31.8% (95% CI = 30.0–33.7%).[26–42] The Ser allele (summary frequency = 43.0%, 95% CI = 39.8–46.2%) was predominant among Asians; 68% (95% CI = 64–72%) of the individuals had the Ser/Ser and Pro/Ser genotypes combined.[51–63] The frequency of Ser allele in Asians was approximately 2.3-times more than in Caucasians. The only other mutation in the exon 2 is a G-to-A transition (G8015A) leading to a synonymous mutation.[66] Other single nucleotide polymorphisms of this gene are in the 5′-flanking region and intron 1.[66]

MPO variants

The *MPO* gene is located on chromosome 17q23.1, consists of 11 introns and 12 exons. It covers 11.10 kb, from 56832934 to 56821840, on the reverse strand. A common G to A transition at position –463 in the promoter region of the *MPO* gene, which leads to the loss of a SP1 transcription binding site in an Alu hormone-responsive element,[67,68] has been shown to reduce *MPO* mRNA expression.[68,69] Because transcriptional activity is decreased in individuals with the variant A allele, less enzyme would ultimately be available for conversion of the BP intermediate to the highly carcinogenic BPDE. As shown in Table 2, the summary frequency of the A allele has been found to be 23.4% (95% CI = 21.8–25.0%) in Caucasians and 14.4% (95% CI = 11.3–17.6%) in Asians.[36,46,50,62,70–101] The A allele was more frequently (1.6 times) observed in Caucasians than in Asians. Three missense mutations associated with MPO deficiency have been described, namely Tyr173Cys (exon 4),[102] Met251Thr (exon 6, T4311C),[103] and Arg569Trp (exon 10).[104] Recently, another G-to-A transition at position –129 in the promoter region of the *MPO* gene was described.[105] There are no reports of these polymorphisms in relation to lung cancer risk.

Disease

Although the incidence has peaked in the United States and most of Europe, lung cancer is showing increasing incidence and mortality in many countries around the world. An estimated 1,239,000 (902,000 males and 337,000 females) new cases of lung cancer were diagnosed worldwide in 2000, accounting for 12.3% of all new cases of cancer, and 1,103,000 (810,000 males and 293,000 females) died from the disease, accounting for 17.8% of all deaths from cancer.[106] This disease ranks as the foremost cancer killer in men and the second largest in women. The case fatality (ratio of mortality to incidence), which is an indicator of prognosis, is 0.89 for lung cancer (the third-worst). Other cancers with bad prognosis are pancreas (0.99, the worst) and liver (0.97, the second-worst) cancers.[107]

Worldwide, the incidence rate in men exceeds that in women by a factor of 2.7. Lung cancer mortality among men is now abating in several countries, whereas the mortality in women continues to climb in most countries, as predicted by later onset tobacco abuse.[108] Principal histological types of lung cancer are squamous cell carcinoma, large cell carcinoma, small cell carcinoma, and adenocarcinoma, and the former three are strongly associated with smoking. In recent decades, the frequency of adenocarcinoma has risen and that of squamous cell carcinoma has declined in a number of developed couries.[109-115] The increase in incidence of adenocarcinoma could be partly explained by an increase in filtered cigarette smoking. Filter cigarettes with low-tar and low-nicotine have replaced nonfilter cigarettes. One key characteristic of such changes over time has been the increased nitrate content of the tobacco blend from about 0.5% to 1.3%.[116] Tobacco-specific *N*-nitrosamines (TSNAs) are formed by *N*-nitrosation of nicotine and other minor alkaloids during tobacco processing and smoking.[117] Because nitrate is the major precursor for nitrogen oxides, increased nitrate content leads to higher yields of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in the smoke.[118] To satisfy the craving for nicotine, a smoker of low-yield nicotine filtered cigarettes may tend to compensate by increasing the number and depth of puffs. Therefore, the peripheral lung, where adenocarcinoma generally arises, is exposed to a higher amount of smaller particles such as NNK. NNK is a systemic carcinogen that induced lung carcinoma in laboratory animals, whereas intratracheal instillation of PAHs preferentially induced squamous cell carcinoma.[119] It is biologically plausible that TSNAs such as NNK cause adenocarcinoma in humans.

Smoking

Most of the lung cancer debate has been focused on tobacco smoking. Given the many risk factors that have been identified for lung cancer, a practical question is the relative contribution of these factors to the summary burden of lung cancer. The population attributable fraction (PAF) takes into account the magnitude of relative risk that is associated with an exposure along with the likelihood of exposure in the general population. The WHO Global Burden of Disease 2000 study reported that the PAF of lung cancer mortality due to smoking was 79% in men and 48% in women.[120] The risk among smokers relative to the risk among never-smokers is 8 to 15 times in men and 2

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Table 1

NQO1 Pro187Ser polymorphism frequencies in different populations

Geographic areas of study population	Ethnicity	Total (no.)	Source of population	Genotype (no.) Pro/Pro	Pro/Ser	Se/Ser	Frequency (%) of Ser allele	Frequency (%) of Ser/Ser genotype	Frequency (%) of Pro/ser and Ser/ser genotypes combined	Hardy-Weinberg equilibrium (P for Pearson $\chi 2$)(P_{HWE})	Researcher, published year, study location(ref. no.)
North America and Europe											
	Caucasian[a]	145	Hospital patients	111	32	2	12.4	1.4	23.4	0.86	Lewis et al.,[26] 2001, UK
	Caucasian	231	Hospital patients/population/ hospital nurses/office workers	175	53	3	12.8	1.3	24.2	0.65	Menzel et al.,[27] 2004, Austria & Czech Republic
	Caucasian	252	Blood donors	185	63	4	14.1	1.6	26.6	0.60	Zhang et al., [28] 2003, Germany
	Caucasian[a]	530	laboratory workers, welders/ chimney sweepers	368	153	9	16.1	1.7	30.6	0.12	Alexandrie et al.,[29] 2004, Sweden
	Caucasian	169	Police officers	111	53	3	17.5	1.8	33.1	0.24	Verdina et al.,[30] 2001, Italy
	Caucasian	100	Blood donors	67	31	2	17.5	2.0	33.0	0.46	Steiner et al.,[31] 1999, Germany
	Caucasian	323	Population	221	89	13	17.8	4.0	31.6	0.29	Krajinovic et al.,[32] 2002, Canada
	Caucasian	836	Population	562	274		Approx. 18	–	32.8	Not calculable	Smith et al.,[33] 2001, UK
	Caucasian	345	Screening examinees	232	102	11	18.0	3.1	32.8	0.96	Mitrou et al.,[34] 2002, UK
	Caucasian	239	Population	163	66	10	18.0	4.2	32.8	0.32	Park et al.,[35] 2003, USA
	Caucasian	258	Neonatal blood spots	174	74	10	18.2	3.9	32.6	0.55	Kiffmeyer et al., [36] 2004, USA
	Caucasian	205	Population	135	62	8	19.0	3.9	34.1	0.79	Harth et al.,[37] 2000, Germany
	Caucasian	124	Hospital patients	83	34	7	19.4	5.6	33.1	0.18	Sanyal et al.,[38] 2004, Sweden
	Caucasian	210	Population	136	66	8	19.5	3.8	35.2	1.00	Longuemaux et al.,[39] 1999, France
	Caucasian[a]	171	Population	105	62	4	20.5	2.3	38.6	0.14	Chen et al.,[40] 1999, USA
	Caucasian	175	Blood donors	110	53	12	22.0	6.8	37.1	0.12	Seedhouse et al.,[41] 2002, UK
	Caucasian	76	Hospital patients/blood donors	46	24	6	23.7	7.9	39.5	0.27	Bartsch et al.,[42] 1998, USA
Summary[b]							18.9 (15.6 - 22.1)	2.8 (2.1 - 3.5)	31.8 (30.0 - 33.7)		
	Caucasian[a] (over 94%)	159	Population/office workers/ volunteers	109	48	2	16.4	1.3	31.4	0.19	Rosvold et al.,[43] 1995, USA
	Caucasian (over 90%)	100	Population	67	32	1	17.0	1.0	33.0	0.18	Wiemels et al.,[44] 1999, UK
	Caucasian (over 90%)	182	Volunteers/friends of cases/ population	120	55	7	19.0	3.8	34.1	0.82	Olson et al.,[45] 2004, USA
	Caucasian[a] (over 96%)	1123	Friends/non-blood related family member	733	348	42	19.2	3.7	34.7	0.93	Xu et al.,[46] 2001,USA
	Caucasian (over 87%)	259	Volunteers	161	83	15	21.8	5.8	37.8	0.33	Morin et al.,[47] 2004, France
	Not specified	260	Volunteers	195	61	4	13.3	1.5	25.0	0.80	Schulz et al.,[48] 1997, Germany
	Not specified	85	Hospital	56	22	7	21.2	8.2	34.1	0.04	Fern et al.,[49] 2004, UK
	Not specified	214	Hospital	135	66	13	21.5	6.1	36.9	0.21	Hung et al.,[50] 2004, Italy
Asia											
	Korean	170	Hospital patients	64	90	16	35.9	9.4	62.4	0.0497	Choi et al.,[51] 2003, Korea
	Japanese[a]	167	Population	64	78	25	38.3	15.0	31.7	0.88	Chen et al.,[40] 1999, USA
	Japanese	204	Volunteers	76	93	35	40.0	17.2	62.7	0.48	Hori et al.,[52] 2003, Japan
	Japanese[a]	640	Hospital patients	240	286	114	40.1	17.8	62.5	0.17	Hamajima et al.,[53] 2002, Japan
	Japanese[a]	152	Hospital patients	52	77	23	40.5	15.1	65.8	0.53	Sunaga et al.,[54] 2002, Japan

Continued.

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Table 1
Continued

Geographic areas of study population	Ethnicity	Total (no.)	Source of population	Genotype (no.)			Frequency (%) of Ser allele	Frequency (%) of Ser/Ser genotype	Frequency (%) of Pro/ser and Ser/ser genotypes combined	Hardy-Weinberg equilibrium (P for Pearson $\chi2$)(P_{HWE})	Researcher, published year, study location(ref. no.)
				Pro/Pro	Pro/Ser	Se/Ser					
	Chinese	296	Population	97	157	42	40.7	14.2	67.2	0.09	Fowke et al.,[55] 2003, China
	Chinese	141	Blood donors	48	70	23	41.1	16.3	66.0	0.77	Zhang et al.,[28] 2003, Germany
	Korean	106	Volunteers	35	54	17	41.5	16.0	67.0	0.61	Winski et al.,[56] 2004, Korea
	Japanese	100	Population	33	50	17	42.0	17.0	67.0	0.80	Harada et al.,[57] 2001, Japan
	Japanese	241	Hospital patients	86	107	48	42.1	19.9	64.3	0.17	Kawase et al.,[58] 2003, Japan
	Chinese	165	Blood donors/volunteers	52	86	27	42.4	16.4	68.5	0.39	Zhang et al.,[59] 2003, China
	Chinese[a]	84	Hospital patients	26	41	17	44.6	20.2	69.0	0.91	Yin et al.,[60] 2001, China
	Chinese	50	Factory workers	19	17	14	45.0	28.0	62.0	0.03	Zheng et al.,[61] 2002, China
	Chinese	283	Factory workers	66	153	64	49.6	22.6	76.7	0.17	Wan et al.,[62] 2002, China
	Chinese (Hmong)	198	Neonatal blood spots	24	106	68	61.1	34.3	87.9	0.08	Kiffmeyer et al.,[36] 2004, USA
	Taiwanese[a]	332	Hospital patients	95	237		Not calculable	–	71.4	>0.05	Lin et al.,[63] 2003, China
Summary[b]							43.0 (39.8 - 46.2)	18.1 (15.4 - 20.8)	68.1 (63.8 - 72.3)		
Others											
	Hawaiian[a]	102	Population	60	39	3	22.1	2.9	41.2	0.26	Chen et al.,[40] 1999, USA
	Mexican-American[a]	161	Population	52	109		Not calculable	–	67.7	0.41	Wiencke et al.,[64] 1997, USA
	African-American[a]	139	Population	86	53		Not calculable	–	38.1	0.85	Wiencke et al.,[64] 1997, USA
	Not specified	108	Population	61	40	7	25.0	6.5	43.5	0.90	Moore et al.,[65] 2004, Argentina

Only studies with more than 50 participants are included in this table.
[a]Molecular epidemiologic studies on lung cancer.
[b]Based on random effects model.

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Table 2
MPO G-463A polymorphism frequencies in different populations

Geographic areas of study population	Ethnicity	Total (no.)	Source of population	Genotype (no.)			Frequency (%) of A allele	Frequency (%) of A/A genotype	Hardy-Weinberg equilibrium (P for Pearson $\chi 2$)(P_{HWE})	Researcher, published year, study location (ref. no.)
				G/G	G/A	A/A				
North America and Europe										
	Caucasian	174	Hospital patients	117	54	3	17.2	1.7	0.25	Reynolds et al.,[70] 2000, Finland
	Caucasian	241	Hospital patients	159	75	7	18.5	2.9	0.60	Kantarci et al.,[71] 2000, USA
	Caucasian	369	Neonatal blood spots	235	126	8	19.2	2.2	0.06	Kiffmeyer et al.,[36] 2004, USA
	Caucasian[a]	311	Population	206	84	21	20.3	6.8	0.04	Misra et al.,[72] 2001, USA
	Caucasian[a]	340	Hospital patients	218	105	17	20.4	5.0	0.35	Dally et al.,[73] 2002, Germany
	Caucasian[a]	196	Hospital patients	117	75	4	21.2	2.0	0.04	Cascorbi et al.,[74] 2000, Germany
	Caucasian	270	Volunteers	165	94	11	21.5	4.1	0.60	Cascorbi et al.,[74] 2000, Germany
	Caucasian	145	Population	86	55	4	21.7	2.8	0.17	Nelissen et al.,[75] 2000, Sweden
	Caucasian	449	Hospital patients	274	152	23	22.0	5.1	0.75	Hoy et al.,[76] 2003, France
	Caucasian	243	Population	143	88	12	23.0	4.9	0.74	Rutgers et al.,[77] 2003, The Netherlands
	Caucasian	191	Population	113	68	10	23.0	5.2	0.96	Rothkrantz-Kos et al.,[78] 2003, The Netherlands
	Caucasian[a]	459	Samples from driver's license (<65 years)/ Medicare beneficiaries (≥65 years)	280	143	36	23.4	7.8	0.005	London et al.,[79] 1997, USA
	Caucasian[a]	245	Hospital patients	140	93	12	23.9	4.9	0.49	Chevrier et al.,[80] 2003, France
	Caucasian	180	Population	102	65	13	25.3	7.2	0.55	Pakakasama et al.,[81] 2003, USA
	Caucasian[a]	171	Population	98	58	15	25.7	8.8	0.14	LeMarchand et al.,[82] 2000, USA
	Caucasian[a]	172	Hospital patients	96	63	13	25.9	7.6	0.55	Feyler et al.,[83] 2002, France
	Caucasian	217	Hospital patients	120	78	19	26.7	8.8	0.23	Nikpoor et al.,[84] 2001, Canada
	Caucasian[a]	119	Population	59	56	4	26.9	3.4	0.03	Cajar-Salazar et al.,[85] 2003, USA
	Caucasian	196	Population	100	84	12	27.6	6.1	0.30	Borgmann et al.,[86] 2003, Germany
	Caucasian	166	Population	83	62	21	31.3	12.7	0.09	Crawford et al.,[87] 2001, USA
	Caucasian	95	Hospital patients	47	35	13	32.1	13.7	0.13	Van Schooten et al.,[88] 2004, The Netherlands
	Caucasian	158	Population	67	74	17	34.2	10.8	0.61	Zappia et al.,[89] 2004, Canada
Summary[b]							23.4 (21.8 - 25.0)	5.4 (4.3 - 6.6)		
	Caucasian[a] (over 96%)	1128	Spouses and friends of patients	697	390	41	20.9	3.6	0.13	Xu et al.,[90] 2002, USA
	Caucasian[a] (95%)	307	Hospital patients	181	111	15	23.0	4.9	0.70	Kantarci et al.,[91] 2002, USA
	Caucasian[a] (83%)	378	Office workers	202	157	19	25.8	5.0	0.10	Schabath et al.,[92] 2002, USA
	Caucasian (over 90%)	179	Volunteers/friends of cases/population	77	80	22	34.6	12.3	0.86	Olson et al.,[46] 2004, USA
	Not specified	1083	Population	714	340	29	18.4	2.7	0.13	Meisel et al.,[93] 2002, Germany
	Not specified	246	Hospital patients	157	84	5	19.1	2.0	0.10	Leininger-Muller et al.,[94] 2003, France, Spain, Northern Ireland & Croatia
	Not specified	115	Blood donors/hospital employees	74	37	4	19.6	3.5	0.81	Buraczynska et al.,[95] 2003, Poland
	Not specified	99	Volunteers	70	18	11	20.2	11.1	0.00000	Zakrzewska-Pniewska et al.,[96] 2004, Poland
	Not specified	214	Hospital patients	129	63	22	25.0	10.3	0.002	Hung et al.,[50] 2004, Italy
Asia										
	Chinese	290	Factory workers	245	55	0	9.5	Not calculable	0.08	Wan et al.,[62] 2002, China
	Japanese	437	Health check examinees	354	77	6	10.2	1.4	0.44	Katsuda et al.,[97] 2003, Japan
	Japanese	241	Hospital patients	192	47	2	10.6	0.8	0.63	Hamajima et al.,[98] 2001, Japan
	Chinesea	320	Population	227	87	6	12.1	1.9	0.48	Lu et al.,[99] 2002, China
	Chinese (Hmong)	199	Neonatal blood spots	141	50	8	16.6	4.0	0.20	Kiffmeyer et al.,[36] 2004, USA
	Japanesea	163	Population	115	41	7	16.9	4.3	0.19	LeMarchand et al.,[82] 2000, USA
Summary[b]							14.4 (11.3 - 17.6)	1.9 (0.8 - 2.9)		
	Not specified	67	Population	153	12	2	11.9	3.0	0.22	Choi et al.,[100] 2001, India
	Not specified	104	Population	74	27	3	15.9	2.9	0.78	Ahsan et al.,[101] 2003, Bangladesh
Others										
	Hispanic	75	Population	42	29	4	24.7	5.3	0.73	Crawford et al.,[87] 2001, USA
	African-American[a]	244	Samples from driver's license (<65 years)/Medicare beneficiaries (≥65 years)	121	100	23	29.9	9.4	0.72	London et al.,[77] 1997, USA
	Hawaiiana	103	Population	81	17	5	26.2	4.9	0.005	LeMarchand et al.,[82] 2000, USA

Only studies with more than 50 participants are included in this table.
[a]Molecular epidemiologic studies on lung cancer.
[b]Based on random effects model.

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to 10 times in women.[121] Smoking cessation significantly reduces lung cancer risk, and after many years the risk of ex-smokers approaches that of never-smokers. It took more than 20 years for the risk in ex-smokers to approach the level in never-smokers.[122] A recent meta-analysis showed that environmental tobacco smoke exposure from husbands conferred a 1.20 times increase in lung cancer risk among nonsmoking women.[123]

Other risk factors

The PAF for lung cancer deaths due to environmental tobacco exposure accounts for 0.7%, 0.2% in men and 2.5% in women.[124] Doll and Peto estimated that approximately 20% of lung cancer deaths in the United States were potentially avoidable by the modification of diet.[125] Willett also estimated that 20% (range, 10–30%) was avoidable by dietary factors.[126] The PAF for lung cancer deaths due to outdoor air pollution accounts for 1% to 3.6%.[127] Radon may be responsible for only 1% of lung cancers.[128] In the USA, occupational exposure to carcinogens accounts for approximately 9% to 15% of lung cancer cases.[129]

Genetic epidemiology

Cigarette smoke contains several thousand chemicals. Most of these compounds are procarcinogens that must be activated by Phase I enzymes, such as cytochrome P450s (*CYPs*). All reactive carcinogens can bind to DNA and form DNA adducts that are capable of inducing mutations and initiating carcinogenesis. *CYP1-CYP4* are primarily involved in the drug metabolism.[130] Other Phase I enzymes are MPO, NQO1, microsomal epoxide hydrolase 1 (EPHX1), and alcohol dehydrogenase. A significant increased risk (2.4 to 3 times) of lung cancer for the *CYP1A1* T3801C or A2455G (Ile462Val) polymorphisms was observed among Japanese[131] and Caucasians.[132] Although a molecular epidemiological association is possible between the prevalence of the high activity genotype of *CYP2D6* and lung cancer, such an association, if it exists, could be weak.[131] As for *CYP2E1*, no clear evidence has been found that the reported polymorphisms are related to lung cancer risk.[131] Studies on other *CYP2* subfamily have indicated a relation between lung cancer and the occurrence of a rare allele, although future research is needed to establish a significant association.[131]

After the Phase I reaction, Phase II enzymes like glutathione S-transferases (GSTs) are responsible for detoxifying the activated forms of PAH epoxides. The GSTs also form a superfamily.[133,134] The major isoforms, which involve the metabolic activation of carcinogens derived from tobacco smoke or the detoxification of the respective activated carcinogens, are GSTM1, GSTM3, GSTT1, and GSTP1. Other Phase II enzymes are EPHX1, NQO1, N-acetyltransferases (NATs), UDP-glucuronosyltransferase, aldehyde dehydrogenase, sulfotransferase, and superoxide dismutase. The *GSTM1* null genotype and the concurrent lack of *GSTM1* and *GSTT1* may be modestly associated (approximately 2 times) with susceptibility to lung cancer.[135] It may be of great importance to study both *NAT1* and *NAT2* together as putative contributing factors for lung cancer susceptibility.[136] Among metabolic polymorphisms, *MPO*, *NQO1,* and *EPHX1* have been less reviewed than *CYPs*, *GSTs,* and *NATs*. The rest of the candidate genes remain little investigated.

The capacity to repair DNA damage induced by chemical carcinogens appears to be another host factor that may influence lung cancer risk. Potentially important DNA repair genes are 8-oxoguanine-DNA glycosylase 1, x-ray cross-complementing Group 1 (*XRCC1*), xeroderma pigmentosum C (*XPC*), excision repair cross-complementing Group 1 (*ERCC1*), *ERCC2* (*XPD*), *ERCC3* (XPB), *ERCC4* (*XPF*), *ERCC5* (*XPG*), xeroderma pigmentosum C (*XPC*), and *XRCC3*. Although each DNA repair gene may not be a major determinant of lung cancer susceptibility, *ERCC2* seems to be the most promising among DNA repair genes.[137] Furthermore, cell-cycle control genes (p53, cyclins, etc.), genes that influence smoking behavior [dopamine receptor (*DR) D2*, *DRD4*, *DRD5*, neuronal nicotine acetylcholine receptor, dopamine transporter and serotonin transporter] and genes involved in development of the immune system (interleukins and tumor necrosis factor) may have the potential to substantially affect lung cancer risk.

META-ANALYSIS METHODS

Identification and eligibility of relevant studies

We conducted a MEDLINE search using "NAD(P)H quinone reductase 1," "myeloperoxidase," "lung cancer," and "polymorphism" for articles published before August 2004. Additional articles were identified through the references cited in the first series of articles selected. Articles included in meta-analysis were English and non-English, human, published in the primary literature and had no obvious overlap of subjects with other studies. Case-control studies were eligible, if they had determined the distribution of the relevant genotypes in lung cancer cases and in concurrent controls using a molecular method for genotyping. We excluded studies with the same data or overlapping data by the same authors.

Data extraction and assessment of study quality

Two investigators (C.K. and K.Y.) independently extracted data and reached consensus on all items except for the Hardy-Weinberg equilibrium. The following items were sought from each report: authors, year of publication, place of study, ethnic group of the study population, characteristics of lung cancer cases (age distribution, sex ratio, histological type, smoking and occupational exposure), characteristics of controls (age distribution, sex ratio, source of population, smoking and occupational exposure), number of genotyped cases and controls, frequency of the genotypes, ORs, adjusted factors for OR, and the method for quality control of genotyping. For studies including subjects of different ethnic groups, data were extracted separately for each ethnic group, whenever possible.

Methods for defining study quality in genetic studies are more clearly defined than those for observational studies. We

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assessed the Hardy-Weinberg equilibrium via a goodness-of-fit χ^2 test (Pearson) to compare the observed and expected genotype frequencies among controls. We also assessed the homogeneity of the study population (Caucasian only or mostly Caucasian).

Meta-analysis

Data were combined using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird method) models.[139] Fixed effects and random effects analyses address fundamentally different research questions. The former asks what the best estimate of the true effect size is in the population studied, whereas the latter asks what the range and distribution of effect sizes in the sample of populations studied. Therefore, the calculation of the mean of the distribution of population effect sizes (random effects model) provides different information from the calculation of the mean of the distribution of sample effect sizes (fixed effects model). Random effects incorporate an estimate of the between-study variance and tend to provide wider confidence intervals, when the results of the constituent studies differ among themselves. The random effects model, compared to the fixed effects model, reduces the weight for each individual study proportion to the difference in effect size of an individual study from the pooled estimate of the effect for all other studies. Random effects model are more appropriate when heterogeneity is present.[138] Thus, estimates values were basically based on random effects model. Heterogeneity, evaluated by the Cochrane Q test[139,140] among the studies, was considered significant for $P < 0.10$. Both Begg's[141] and Egger's[142] tests were used to test for publication bias, which was considered significant for $P < 0.10$. Both the tests could also assess whether larger studies give different results from small studies. In a sensitivity analysis (subgroup analysis), we combined only studies with allelic frequencies being in Hardy-Weinberg equilibrium (Pearson χ^2 test, $P \geq 0.05$) because departure from Hardy-Weinberg equilibrium can imply the presence of genotyping error, possible ethnic admixture in the population or selection bias (short of representativeness of the general population). As the ethnic differences were observed in Tables 1 and 2, subgroup analyses by ethnic were also performed. Subgroup analyses by histologic type were performed if available. All the calculations were performed with computer program STATA Version 8.2 (Stata Corporation, College Station, TX).

ASSOCIATIONS

NQO1 Pro187Ser polymorphism and lung cancer risk

As the variant allele is related to low enzyme activity, subjects with at least one variant allele may be associated with decreased risk of lung cancer if NQO1 enzyme acts as a mechanism for metabolic activation of several carcinogens present in tobacco smoke. The Pro/Ser and Ser/Ser genotypes combined was significantly associated with decreased risk of lung cancer in Mexican-Americans.[64] All three Japanese[40,53,54] studies have also shown that the combined genotype was associated with decreased risk of lung cancer. In Chinese,[60] Hawaiians,[40] Caucasians,[40] and African-Americans,[64] the combined genotype was weakly associated with decreased risk of lung cancer. No evidence for an influence of genetic polymorphism in *NQO1* on lung cancer risk was found in two Caucasian populations[29,46] and one Taiwanese population.[63] In contrast, the combined genotype[26,43] was nonsignificantly associated with increased risk of lung cancer in Caucasians.

The 10 case-control studies in 13 different ethnic populations of lung cancer and the combined genotype included 2746 lung cancer cases and 3902 controls. As a clear gene-dose effect was suggested by the genotype-phenotype association studies,[21-25] a genetic model (codominant or decreasing model), in which lung cancer risks of the genotypes Pro/Pro, Pro/Ser, and Ser/Ser decrease in that order, was applied. As the Ser/Ser genotype has not been separated due to a low prevalence of the rare Ser allele in several studies, we combined the Pro/Ser genotype with Ser/Ser genotype. In our meta-analysis, summary frequencies of the combined genotype among Caucasians and Japanese based on random effects model were 30.8% (95% CI = 23.6–38.0%) and 62.9% (95% CI = 59.8–66.0%), respectively (Table 3). The summary ORs for the combined genotype in Caucasians and Japanese were 1.12 (95% CI = 0.96–1.47) and 0.70 (95% CI = 0.56–0.88), respectively. Statistically significant heterogeneity ($P = 0.032$) was seen in case of all studies combined. This result was not reproduced in any sensitivity analysis. Possible sources of heterogeneity are ethnicity (the prevalence of the "at risk" allele, ethnic differences in roles of the polymorphism), study design, and so on. The Begg's test was statistically significant ($P = 0.09$) for publication bias but not the Egger's test ($P = 0.11$) in a sensitivity analysis among mostly Caucasian and Caucasian only populations, because the largest study of Xu et al. showed null association.[46] The presence of heterogeneity and/or publication bias may compromise the interpretation of meta-analyses and result in an erroneous and potentially misleading conclusion.[143,144] The presence of publication bias indicates that nonsignificant or negative findings remain unpublished. Although publication bias is always a possible limitation of combining data from various sources as in a meta-analysis, Sutton et al. concluded that publication or related biases did not affect the conclusions in most meta-analyses.[145] The results of our meta-analysis indicate that the Ser allele, which is linked to low enzyme activity, was significantly associated with decreased risk of lung cancer in Asians among whom the variant allele is common. But such an association was not observed in Caucasians. The impact of *NQO1* was different among different populations. Reasons for this apparent difference in risk with different ethnic populations are as yet unknown but, if real, may be related to other genetic or environmental factors.

Histologic data were available for six studies and four studies have indicated a significant association between *NQO1* polymorphism and risk of certain histologic types of lung cancer. Small cell carcinomas were more likely to occur with a significant difference among those who had the Pro/Ser and Ser/Ser genotypes combined, compared to those who had two copies

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Table 3
Studies of *NQO1* Pro187Ser polymorphism and risk of lung cancer

Researcher, published year, study location (ref. no.)	Race/ethnicity	Cases: Description (age, % male, histologic type, smoking rate, etc.)	Cases: No.[a]	Controls: Description (age, % male, source of population, smoking rate, etc.)	Controls: No.[a]	Frequency (%) of Pro/Ser and Ser/Ser genotypes combined (frequency (%) of Ser/Ser genotype, if available): Cases	Frequency: Controls	OR (95% CI) for Pro/Ser and Ser/Ser genotypes combined (compared to Pro/Pro genotype)	Adjustment	Quality control of genotyping
Rosvold et al.,[43] 1995, USA	Caucasian(over 94%)	Mean age, 63.8 (aged 35 - 90 years); 53.3% male; histologic type, NS; 90% ever-smokers	150	Age, NS; sex ratio, NS; population/office workers/ volunteers; 51.9% ever-smokers	159	38.7 (4.7)	31.4 (1.3)	1.4 (0.9 - 2.1)	None	Sequencing
Wiencke et al.,[64] 1997, USA		Mean age, 62.1 (SD = 11); 76.3% male; histological type, NS; 58.2% current smokers, 37.9% ex-smokers	177	Mean age, 62.2 (SD = 11); 69.7% male; population; 30.0% current smokers, 26.9% ex-smokers	297	40.1	54.5	0.56 (0.38 - 0.81)	None	NS
	Mexican-American	31.1% Ad, 18.0% Sq, 13.1% SCC, 8.2% LCC, 29.5% others; 45.9% current smokers, 47.5% ex-smokers	61	28.0% current smokers, 26.0% ex-smokers	161	52.5	67.7	0.53 (0.29 - 0.96)	None	
	African-American	36.2% Ad, 37.9% Sq, 11.2% SCC, 6.0% LCC, 8.6% others; 64.7% current smokers, 32.8% ex-smokers	116	32.4% current smokers, 27.9% ex-smokers	139	33.6	38.1	0.79 (0.47 - 1.33)	None	
Chen et al.,[40] 1999, USA		Mean age, 64.5 (aged 26 - 79 years); sex ratio, NS; histologic type, NS; smoking status, NS	327	Mean age, 65.1 (aged 26 - 79 years); sex ratio, NS; population; smoking status, NS	440	40.1 (4.9)	48.0 (7.3)	0.73 (0.54 - 0.98)	None	
	Japanese	NS	109	NS	167	50.4 (6.4)	61.7 (15.0)	0.63 (0.38 - 1.06)	None	NS
	Caucasian	NS	135	NS	171	40.0 (3.7)	38.6 (2.3)	0.8 (0.4 - 1.5)	Age, sex, smoking, vegetable intake	
	Hawaiian	NS	83	NS	102	26.5 (4.8)	41.2 (2.9)	0.6 (0.2 - 1.3)	Age, sex, smoking, vegetable intake	
Xu et al.,[46] 2001, USA	Caucasian (over 96 %)	17.1% <age 55; 54.7% male; 47.9% Ad, 26.7% Sq, 25.4% others; 40.8% current smokers, 53.% ex-smokers	814	37.7% <age 55; 45.1% male; friends/non-blood related family member; 18.9% current smokers, 45.9% ex-smokers	1,123	34.7 (2.8)	34.7 (3.7)	1.00 (0.82 - 1.22)	None	NS
Yin et al.,[60] 2001, China	Chinese	Mean age, 60.3 (SD = 12); 72.6% male; 58.3% Ad, 41.7% Sq, 53.6% current smokers, never smokers 46.4%	84	Mean age, 60.9 (SD = 12); 72.6% male; hospital patients; 53.6% current smokers, 46.4% never smokers	84	66.7 (20.2)	69.0 (20.2)	0.74 (0.36 - 1.50)	None	NS
Lewis et al.,[26] 2001, UK	Caucasian	Mean age, 64.7 (SD = 10); 63.8% male; NSCLC 56.4% (11.7% Ad, 34.0% Sq), 20.0% SCC, 27.7% unknown; 29.8% current smokers, 68.1% ex-smokers	82	Mean age, 59.5 (SD = 14); 53.9% male; hospital patients; 25.5% current smokers, 48.5% ex-smokers	145	31.7 (2.4)	23.4 (1.4)	1.31 (0.66 - 2.58)	Age, sex, smoking	NS
Sunaga et al.,[54] 2002, Japan	Japanese	Mean age, 63 (SD = 10); 62.6% male; 100% Ad; 32.8% ever-smokers	198	Mean age, 65 (SD = 13); 71.1% male; hospital patients; 32.9% ever-smokers	152	58.1 (11.1)	65.8 (15.1)	0.72 (0.45 - 1.14)	None	NS
Hamajima et al.,[53] 2002, Japan	Japanese	Aged 26 - 81 years; 59.9% male; histological type, NS; smoking status, NS	192	Aged 18 - 81 years; 47.3% male; hospital patients; 38.0% current smokers, 20.1% ex-smokers	640	54.7 (17.7)	62.5 (17.8)	0.71 (0.50 - 1.00)[b]	Age, sex	PCR confronting two-pair primers
Lin et al.,[63] 2003, Taiwan	Taiwanese	Mean age, 64 (SD = 9); 72.2% male, 53.0% Ad, 42.0% Sq, 5.0% others; 48.0% current smokers, 39.2% ex-smokers	198	Mean age, 58 (SD = 12); 68.4% male, hospital patients; 39.2% current smokers, 7.8% ex-smokers	332	71.2	71.4	0.93 (0.63 - 1.41)	Age, sex, smoking	NS
Alexandrie et al.,[29] 2004, Sweden	Caucasian	Median age, 66 (aged 35 - 88); 77.9% male; 27.5% Ad, 31.6%, Sq 19.5% SCC, 3.1% LSCC, 8.8 % others, unknown 9.5%; 59.5% ever smokers	524	Median age, 44 (aged 19 - 79); 65.6% male; laboratory workers, welders/chimney sweepers; 51.5% ever smokers	530	34.3 (2.1)	30.6(1.7)	1.16 (0.72 - 1.88)	Age, sex	NS

Continued

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Table 3
Continued

Summary	Ethnicity	No.of cases	No. of populations	No. of controls	Frequency (%) of			OR (95% CI) for Pro/Ser and Ser/Ser genotypes combined (compared to Pro/Pro genotype)		Cochrane Q test for hetero-geneity
					Ser allele	Ser/Ser genotype	Pro/Ser and Ser/Ser genotypes combined	Random effects model	Fixed effects model	
	All	2,746	13	3,902	-	-	-	0.90 (0.77-1.06)	0.94 (0.84-1.04)	P=0.032
	Caucasian studies, mostly composed of Caucasians	1,705	5	2,128	2.2 (1.1 -3.2)	17.2 (14.7-19.7)	31.9 (27.9-36.0)	1.10 (0.96-1.26)	1.10 (0.96-1.26)	P=0.53
	Caucasian only	741	3	846	1.7 (0.8 -2.6)	16.1 (12.4-19.9)	30.8 (23.6-38.0)	1.12 (0.96-1.47)	1.12 (0.96-1.47)	P=0.65
	Asian	781	5	1375	17.0 (14.8-19.3)	40.3 (37.3-43.2)	66.5 (61.2-71.7)	0.78 (0.64-0.94)	0.78 (0.64-0.94)	P=0.62
	Japanese only	499	3	959	16.8 (14.4-19.2)	39.9 (36.8-43.0)	62.9 (59.8-66.0)	0.70 (0.56-0.88)	0.70 (0.56-0.88)	P=0.90

Ever-smokers include current and ex-smokers.
PHWE ≥ 0.05 in all studies.
NS, not specified. NC, not calculable.
Ad, adenocarcinoma; Sq, squamous cell carcinoma; SCC, small cell carcinoma; LCC, large cell carcinoma
[a]Number of subjects genotyped.
[b]$P < 0.05$

of the Pro allele (OR = 0.26, 95% CI = 0.08–0.84).[26] In Chinese, the combined genotype relative to the Pro/Pro genotype increased the OR for squamous cell carcinoma (3.23, 95% CI = 1.00–10.38).[60] In Caucasians, the Pro/Ser and Ser/Ser genotypes combined was significantly associated with increased risk of squamous cell carcinoma (OR = 2.21, 95% CI = 1.03–4.84).[29] The Ser/Ser genotype was significantly associated with decreased risk for adenocarcinoma among Japanese (OR = 0.47, 95% CI = 0.22–0.97).[54] There was no association between *NQO1* genotype and lung cancer risk, regardless of histologic type.[46,63] In subgroup analyses by histologic type among Caucasians and Asians, the Pro/Ser and Ser/Ser genotypes combined was marginally associated with increased risk of squamous cell carcinoma (OR = 1.29, 95% CI = 0.97–1.72), whereas the combined genotype was not associated with increased risk of adenocarcinoma (OR = 0.89, 95% CI = 0.71–1.13) (data not shown). The decreased risk (OR = 0.79, 95% CI = 0.59–1.07) was observed for adenocarcinoma patients with the combined genotype among Asians, however (data not shown). There was no clear evidence of the different role of *NQO1* among different histologic types, however.

MPO G-463A polymorphism and lung cancer risk

As the variant allele is related to low metabolic activation activity, subjects with at least one variant allele may be associated with decreased risk of lung cancer. London et al.79 first reported that subjects with the A/A genotype were significantly associated with decreased risk of lung cancer in Caucasians and a nonsignificant reduction in African Americans compared with those with the G/G genotype.A second study[82] of populations with Caucasian, Japanese, or Hawaiian ethnicity reported a significant reduction in risk for those with the A/A genotype compared with those with the G/G genotype in only a Japanese population. Also, the A/A genotype was associated with decreased risk of lung cancer among an American population.[91] In subsequent Caucasian (or mostly Caucasians) studies,[72,73,83,92] the A/A genotype was suggested as being a protective factor for lung cancer. However, the G/A and A/A genotypes combined was associated with increased risk of lung cancer among a subset of Caucasian men of > 64 years old (OR = 2.92, 95% CI = 1.33–6.43).[72] A statistically significant reduced risk of lung cancer was observed for the G/A and A/A genotypes combined among Caucasian men (OR = 0.55, 95% CI = 0.36–0.84), but not among women (OR = 0.81, 95% CI = 0.55–1.26).[92] The A/A genotype was nonsignificantly associated with increased risk of lung cancer among Caucasians.[85] No evidence for an influence of genetic polymorphism in *MPO* on lung cancer risk was found in three Caucasian populations[74,80,90] and one Chinese population.[99]

The 12 case-control studies of lung cancer among 15 ethnic groups and *MPO* genotype included 4285 lung cancer cases and 4656 controls. Although biological effects of each genotype have not been clarified, the previous meta-analysis suggested that the MPO activity was different among the three genotypes.[83] We used the genetic model (lung cancer risks of the genotypes G/G, G/A, and A/A decrease in that order),

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Table 4

Studies of *MPO* G-463A polymorphism and risk of lung cancer

Researcher, published year, study location (ref. no.)	Race/ethnicity	Cases: Description (age, % male, histologic type, smoking rate, etc.)	Cases: No.[a]	Controls: Description (age, % male, source of population, smoking rate, etc.	Controls: No.[a]	Frequency (%) of A/A genotype: Cases	Frequency (%) of A/A genotype: Controls	OR (95% CI) for A/A genotype (compared to G/G genotype)	Adjustment	Quality control of genotyping
London et al.,[79] 1997, USA		Mean age, 63.6 (SD = 9); 57.6% male; histological type, NS; 64.3% current smokers, 31.3% ex-smokers	339	Mean age, 62.5 (SD = 8); 66.7% male; samples from driver's license (<65 years)/ Medicare beneficiaries (≥65 years); 22.5% current smokers, 45.7% ex-smokers	683			NS		
	Caucasian	96.2% ever-smokers	182	64.7% ever-smokers	459	2.2	7.8	0.30 (0.10 - 0.93)	Age, sex, smoking	NS
	African-American	94.9% ever-smokers	157	69.3% ever-smokers	224	7.6	9.4	0.61 (0.26 - 1.41)	Age, sex, smoking	NS
LeMarchand et al.,[82] 2000, USA		Age, NS; sex ratio, NS; histological type, NS, smoking status, NS	323	Age, NS; sex ratio, NS; community-based; smoking status, NS;	437					
	Caucasian		135		171	5.2	8.8	0.6 (0.3 - 2.0)	Age, sex, smoking	NS
	Japanese		108		163	0.9	4.3	0.1 (0.0 - 0.5)	Age, sex, smoking	NS
	Hawaiian		80		103	5.0	4.9	1.5 (0.2 - 1.6)	Age, sex, smoking	NS
Cascorbi et al.,[74] 2000, German	Caucasian	Median age 63 (aged 35-87); 76.5% male; histological type, NS; smoking status, NS	196	Median age, 65 (aged 37-85); 76.5% male; hospital patients;smoking status, NS	196	3.1	2.0	1.25 (0.34 - 4.52)	None	Sequencing
Misra et al.,[72] 2001, USA	Caucasian	Median age, 60; 100% male; histological type, NS; all current smokers		Median age, 59; 100% male; population; all current smokers	311	5.1	6.8	0.72 (0.32 - 1.65)	Smoking	Replication
Feyler et al.,[83] 2002, France	Caucasian	Mean age, 58.4; 93.3% male; 65.3% Sq, 34.7% SCC; all current smokers; 19% occupational exposure to asbestos	150	Mean age, 55.0; 94.8% male; hospital patients; all current smokers; 7% occupational exposure to asbestos	172	6.7	7.6	0.84 (0.31 - 2.32)	Age, sex, hospital, smoking, occupational exposure	Replication
Xu et al.,[90] 2002, USA	Caucasians (over 96%)	31.1% <59 years; 54.5% male; 47.8% Ad, 22.8% Sq, 8.9% SCC, 7.8% LCC, 8.5% others and unknown; 41.0% current smokers, 52.5% ex-smokers	988	51.0% <59 years; 46.5% male, spouses and friends of patients; 19.4% current smokers, 44.9% ex-smokers	1,128	4.8	3.6	1.15 (0.7 - 1.9)	Age, sex, race, smoking	Replication
Kantarci et al.,[91] 2002, USA	Caucasian (95%)	Median age, 67 (aged 28-85); 58.3% male; 46.2% Ad, 24.8% Sq, 6.8% SCC, others 22.2%; 22.1% current smokers, 63.1% ex-smokers	307	Difference in mean age, 0.04 years; 58.3% male; hospital patients; 11.0% current smokers, 44.8% ex-smokers	307	2.9	4.9	0.39 (0.15 - 1.00)[b]	NS	NS
Lu et al.,[99] 2002, China	Chinese	Mean age, 58.6 (SD = 10); 69.7% male; 100% Ad +Sq; 64.6% ever-smokers	314	Mean age, 58.4 (SD = 6); 65.0% male; population; 52.2% ever-smokers	320	1.9	1.9	0.92 (0.24 - 3.48)	None	Sequencing
Schabath et al.,[92] 2002, USA	Caucasian (83%), Hispanic (10%), African-American (7%)	Mean age, 62.1 (SD = 9); 52.0% male; 39.2% Ad, 14.4% Sq, 6.9% SCC, 5.6% LCC, 10.9% others; 22.9% unknown; 91.8% ever-smokers	375	Mean age, 60.6 (SD = 10); 54.8% male; office workers; 89.8% ever-smokers	378	3.7	5.0	0.59 (0.27 - 1.30)	Age, sex, smoking	Replication
Dally et al.,[73] 2002, Germany	Caucasian	Mean age, 60.0 (aged 32 - 88); 77.3% male; 36.5% Ad, 35.8% Sq, 21.6% SCC; all ever-smokers; occupational exposure (dust, metals, welding fumes and tar)	625	Mean age, 57.0 (aged 19 - 84); hospital patients; 74.4% male; all ever-smokers; occupational exposure (dust, metals, welding fumes and tar)	340	3.7	5.0	0.57 (0.28 - 1.17)	Age, sex, smoking, occupational exposure	Replication
Cajar-Salazar et al.,[85] 2003, USA	Caucasian	Mean age, 59.9 (SD = 10); 57.3% male; 47.3% Ad, 37.3% Sq, 15.5% others; all current smokers	110	Mean age, 57.3 (SD = 11); population; 47.9% male; all current smokers	119	6.4	3.4	1.86 (0.50 - 7.00)	Age, sex, smoking	NS
Chevrier et al.,[80] 2003, France	Caucasian	Mean age, 59.4 (SD = 10); 100 % male; 45.7% Aq, 24.1% Ad, 18.8% SCC, 11.4% others; all ever-smokers	243	Mean age, 59.2 (SD = 10); 100% male; hospital patients; mean pack-years; 79.9% ever-smokers		4.1	4.9	0.97 (0.4 - 2.6)	Age, hospital, smoking	Sequencing

Continued

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Table 4
Studies of *MPO* G-463A polymorphism and risk of lung cancer

Summary	Ethnicity	Hardy-Weinberg equilibrium	No. of cases	No. of populations	No. of controls	Frequency (%) of		OR (95% CI) for Pro/Ser and Ser/Ser genotypes combined (compared to Pro/Pro genotype)		Cochrane Q test for heterogeneity
						Ser/Ser genotype	Pro/Ser and Ser/Ser genotypes combined	Random effects model	Fixed effects model	
						A/A genotype	A allele			
						(Random effects model)		Random effects model	Fixed effects model	
	All		4,285	15	4,656	-	-	0.81 (0.64 - 1.02)	0.83 (0.68 - 1.03)	P=0.32
	All	(PHWE ≥ 0.05)	3,402	10	3,468	-	-	0.84 (0.66 - 1.07)	0.84 (0.66 - 1.07)	P=0.42
	Caucasian studies, mostly composed of Caucasians	1,705	11	3,826	5.1 (3.9 - 6.2)	22.5 (20.7 - 24.2)	0.79 (0.59 - 1.05)	0.83 (0.66 - 1.05)	P = 0.18	
	Caucasian only	(PHWE ≥ 0.05)	1,153	4	928	5.9 (4.2 - 7.6)	23.2 (20.5 - 25.9)	0.70 (0.47 - 1.04)	0.70 (0.47 - 1.04)	P=0.87

Ever-smokers include current and ex-smokers.
NS, not specified. NC, not calculable.
Ad, adenocarcinoma; Sq, squamous cell carcinoma; SCC, small cell carcinoma; LCC, large cell carcinoma
[a]Number of subjects genotyped.
[b]$P < 0.05$

which was applied to our meta-analysis of the studies on *NQO1* polymorphism and lung cancer. The summary OR for the A/A genotype was 0.81 (95% CI = 0.64 - 1.02) (Table 4). The summary OR for the A/A genotype among Caucasian only studies with $P_{HWE} \geq 0.05$ was 0.70 (95% CI = 0.47 - 1.04). The Egger's test was statistically significant (P = 0.007) for publication bias but not the Begg's test (P = 0.21) in a sensitivity analysis among all studies with $P_{HWE} \geq 0.05$, because the largest study of Xu et al. showed null association.[91] Although the results concerning the association between lung cancer and the *MPO* polymorphism are still a matter of debate, the OR of 0.7 suggests an important role for *MPO* in lung cancer etiology among Caucasians, possibly through activation of carcinogens and/or production of free radicals in or near the target cells.

Of the 12 reports on the *MPO* genotype and lung cancer risk, eight provide information on the *MPO* genotype and lung cancer risk in histologic types. A significant protection of the A/A and G/A genotypes combined was seen among adenocarcinoma (OR = 0.24, 95% CI = 0.10–0.58) and squamous cell carcinoma (OR = 0.39, 95% CI = 0.18–0.82) cases.[74] In another study, a protective effect of the combined genotype was noted for adenocarcinoma (OR = 0.64, 95% CI = 0.42–0.96) cases and small cell carcinoma cases (OR = 0.43, 95% CI = 0.17–1.05), but not for squamous cell carcinoma cases (OR = 0.99, 95% CI = 0.54–1.82).[92] The decreased risk was significant for squamous cell carcinoma patients with the combined genotype (OR = 0.42, 95%CI = 0.25–0.71) but not for those with adenocarcinoma (OR = 0.75, 95% CI = 0.47–1.20).[99] The OR for the A/A genotype for squamous cell carcinoma was 0.49 (95% CI = 0.27–0.88).[83] A reduction in risk, although not statistically significant (OR = 0.66, 95% CI = 0.28–1.52), was also observed for small cell carcinoma patients with the A/A genotype.[83] Furthermore, a protective effect of the A/A and G/A genotypes combined was seen among patients with small cell carcinoma (OR = 0.58, 95% CI = 0.36 - 0.95) but not patients with squamous cell carcinoma (OR = 0.82, 95% CI = 0.56–1.21) and adenocarcinoma (OR = 0.81, 95% CI = 0.55–1.19).[73] In contrast, the A/A genotype was associated with increased risk of squamous cell carcinoma (OR = 1.82, 95% CI = 0.8–4.1) and adenocarcinoma (OR = 1.36, 95% CI = 0.8–2.5).[89] No significant association for the *MPO* genotype and patients with squamous cell carcinoma or adenocarcinoma was observed.[82] There was also no clear evidence of lung cancer risk by histologic types.[80] Stratification by histologic type yielded an OR of 0.91 (95% CI = 0.45–1.84) for adenocarcinoma and 1.33 (95% CI = 0.73–2.42) for squamous cell carcinoma (data not shown). These results may largely be affected by the study of Xu et al.[90] (more than one third of cases and nearly two thirds of controls were included). Taken together, results on the *MPO* genotype and risk for different histologic types of lung cancer are conflicting and suggest that confounders that have not been controlled for may have interfered with the analysis.

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GENE-ENVIRONMENT INTERACTIONS

NQO1 Pro187Ser polymorphism

The excess small cell lung cancer risk associated with the presence of the Ser allele was apparent in heavy smokers where the OR for the Ser/Ser and Pro/Ser genotypes combined was 12.5 (95% CI = 2.10–75.5); in light smokers the OR was 0.90 (95% CI = 0.08–9.60).[26] In contrast, the frequency of *NQO1* genotypes did not differ significantly between smokers and nonsmokers.[60] Current smokers with the Ser/Ser genotype had a smaller lung cancer risk than current smokers with the Pro/Pro and Pro/Ser genotypes combined; the OR for the Ser/Ser genotype versus the Pro/Pro genotype was 0.38 (95% CI = 0.19–1.00).[46] However, there was no statistically significant interaction between *NQO1* genotypes and smoking.[46] The ORs for the Ser/Ser genotype were 0.42 (95% CI = 0.18–1.10) in smokers and 0.34 (95% CI = 0.08–1.33) in nonsmokers.[54] Therefore, the result showed that the association of the *NQO1* polymorphism with lung adenocarcinoma risk appeared to be equal both in smokers and nonsmokers.[54] The *NQO1* genotype distribution in cases was similar to that found among controls in never, light and heavy smokers with ORs close to unity within each smoking group.[29] Only one[26] of five studies[26,29,46,54,60] suggested a possible interaction between *NQO1* genotypes and smoking upon investigation. Significant interaction can be seen when accurate categorization of tobacco exposure is used instead of a ternary variable, such as never, ex- and current smokers.

MPO G-463A polymorphism

Four studies suggested the existence of an interaction between *MPO* genotype and cigarette smoking.[72,73,92,99] The association between *MPO* genotype and lung cancer risk was modified by duration of smoking (P for interactio*n* = 0.014).[72] Among heavy smokers (≥ 26 pack-years) with the G/A and A/A genotypes combined, the OR for squamous cell carcinoma was 6.22 (95% CI = 1.72–22.47), against 1.39 (95% CI = 0.29–6.57) among light smokers with the combined genotype.[99] No such gene-smoking interaction was observed for adenocarcinoma, however.[99] There was a protective effect for the G/A and A/A genotypes combined in ever smokers (OR = 0.63, 95% CI = 0.45–0.87), but no effect in never smokers (OR = 1.14, 95% CI = 0.42–3.11).[92] A significant protective effect for individuals with the G/A and A/A genotypes combined with the lowest tertile of < 30 pack-years (OR = 0.39, 95% CI = 0.19–0.82). The cross-product interaction term between *MPO* genotype and pack-years was significant (P for interactio*n* = 0.025).[92] A protective effect for the A/A genotype was also found only in groups with lower tobacco consumption (OR = 0.43, 95% CI = 0.25–0.74), and heavy smoking abolished the *MPO*-related effect (OR = 1.03, 95% CI = 0.69–1.55).[73] Three studies[79,83,90] found no evidence of interaction between *MPO* genotypes and smoking. Two of these three studies measured tobacco smoking as a binary variable, such as nonsmokers and smokers. Assessment of gene-environment interaction should begin with appropriate measurement of tobacco smoking and large sample size.

GENE-GENE INTERACTIONS

NQO1 Pro187Ser polymorphism

Interactions between *NQO1* and other genes have been investigated in three studies.[29,53,54] The combined *NQO1* Pro/Pro and *GSTT1* null genotypes showed a significant association with lung adenocarcinoma risk. When using the *NQO1* Ser/Ser and *GSTT1* non-null genotypes combined as a reference, the OR for the *NQO1* Pro/Pro and *GSTT1* null genotypes combined was 4.61 (95% CI = 1.59–13.34).[54] A gene-gene interaction was suggested between *NQO1* and T3801C/A2455G (Ile462Val) polymorphisms combined of *CYP1A1*.[29] The OR for squamous cell carcinoma was higher in the group with the combined variant genotypes of *NQO1* and *CYP1A1* (OR = 3.54, 95% CI = 0.88–14.3) compared with the ORs in the groups with only one of the *NQO1* variant genotype (OR = 1.69, 95% CI = 0.85–3.39) and only one of the *CYP1A1* variant genotype (OR = 1.36, 95% CI = 0.46–3.90). However, no evidence was seen for effects of gene-gene interactions (all possible combinations of two genotypes for *NQO1*, *CYP1A1*, *GSTM1,* and *GSTT1*) on lung cancer risk.[53] In addition to adequate sample size, assessment of gene-gene interaction also depends upon the proper statistical evaluation of interaction on the multiplicative and additive models. Again, if such gene-gene interaction indeed exists, it may be hampered by the small sample size.

MPO G-463A polymorphism

Only two studies examined whether the association between *MPO* genotype and lung cancer risk was modified by other genes.[83,85] The *MPO* G/A genotype interacted with the presence of *GSTT1* (OR = 0.12, 95% CI = 0.02–0.71) and of both *GSTM1* and *GSTT1* genotypes (OR = 0.02, 95% CI = 0.01–0.50) to significantly decrease lung cancer among males but not in females.[85] On the other hand, no differences in risks associated with *MPO* genotypes were found according to *GSTM1*, *CYP1A1* T3801C, or *CYP1A1* A2455G (Ile462Val) genotype.[83] Nointeraction would either suggest that these proteins do not participate in the same pathway or, more likely, that there are backup or redundant mechanisms that compensate for the diminished or altered function of different enzymes.

Among smokers who smoked ≤ 25 pack-years, a significant reduction in risk for lung cancer was observed among individuals who had the *MPO* G/A genotype combined and the presence of *GSTT1*, compared with who had the *MPO* G/G genotype and *GSTT1* null genotype (OR = 0.03, 95% CI = 0.01–0.79).[85] Gene-gene-environment interaction was suggested despite the limited power for assessing three-way interaction. This finding must be interpreted with caution and needs to be validated in larger studies.

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Laboratory testing

Methods of genotyping for *NQO1* [146] and *MPO* [79] by means of the polymerase chain reaction and restriction fragment length polymorphism techniques have been described previously.

POPULATION TESTING

To date, there is insufficient evidence implicating *NQO*1 or *MPO* in the etiology of lung cancer to make population testing an issue.

OTHER POTENTIAL PUBLIC HEALTH APPLICATONS

At this writing, the available data are insufficient to support any public health recommendations.

DISCUSSION AND RECOMMENDATIONS FOR RESEARCH

The variant allele of *NQO1* Pro187Ser was associated with a 22% to 30% decrease in lung cancer risk among Asians. However, there are several conflicting reports on the association between this polymorphism and lung cancer risk among various populations. Although the reasons for the inconsistencies in the studies are not clear, possible explanations are as follows: (1) low frequency of the ″at risk″ genotype, which reduces the statistical power and (2) small size of the studies. Ethnic differences in roles of the polymorphism may be caused by gene-gene interactions, different linkages to the polymorphisms determining lung cancer risk and different lifestyles. On the other hand, the variant allele of *MPO* G-463A polymorphism was associated with decreased risk (30%) of lung cancer among Caucasians because most studies have been done on them. Thus, both polymorphisms appear to be candidates for lung cancer susceptibility genes. Although the summary risk for developing lung cancer in individuals with at each ″at risk″ genotype may be small, lung cancer is such a common malignancy that even a small increase in risk translates to a large number of excess lung cancer cases in the population. Therefore, polymorphisms, even those not significantly associated with lung cancer, should be considered an important public health issue.

Research into the role of *NQO1* and *MPO* polymorphisms in lung cancer is not in the last stages. The etiology of lung cancer cannot be explained by allelic variability at a single locus. Advances in identification of new variants and in high-throughput genotyping techniques will facilitate analysis of multiple polymorphisms within the genes with the same pathway.[147] Therefore, it is likely that the defining feature of future epidemiologic studies will be the simultaneous analysis of large samples of cases and controls.[148,149] The major burden of lung cancer in the population probably results from complex interaction between many genetic and environmental factors over time. The effects of polymorphisms are best represented by their haplotypes. Recently developed haplotype-based methods were not used in the studies we reviewed; however, it can be anticipated that in future association studies on lung cancer, the development of new approaches will facilitate the evaluation of haplotypic effects, either for selected polymorphisms physically close to each other or for multiple genes within the same drug-metabolism pathway.

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