The association of XPG with lung cancer

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1. Objectives

Xeroderma pigmentosum group G (XPG) is one of seven genetic complementation groups encoding for the proteins involved in the nucleotide excision repair (NER) pathway of DNA repair[1,2]. It functions as a structure-specific endonuclease that cleaves the damaged DNA strand on the 3' side, and is also required non-enzymatically for a subsequent 5' incision by the XPF/excision repair cross-complementing group 1 heterodimer during NER in human cells[1-3]. Furthermore, it is involved in the stabilization of a pre-incision complex on the damaged DNA[2]. Several polymorphisms in the coding sequence of the XPG gene have been identified[1-3], and while the functional effects of these polymorphisms are still unknown, it has been suggested that they may have an effect on host capacity for removing bulky adducts caused by cigarette smoke, and thus modulate the susceptibility to lung cancer[1].

The objective of this report is to determine, based on the available literature, whether genetic polymorphisms in XPG predict risk of mortality from, or incidence of, lung cancer.

2. Literature searches

Papers that appeared likely from their titles and abstracts to supply relevant information were sought from:

(i) our in-house database, and

(ii) Medline searches

Six papers were identified.

3. Plan

If apparently valid meta-analyses or comprehensive reviews have been published recently that are relevant to the objective of this review, the conclusions reached would be summarized without any attempt to analyse all the individual papers in detail (other than perhaps to look for more recent relevant publications based on larger samples). If no such meta-analysis or reviews are available, the literature would be studied and a formal meta-analysis attempted.

4. Genetic polymorphisms in XPG in relation to lung cancer

4.1 Introduction

No relevant meta-analyses were available, but six papers were found relating to studies in which polymorphisms in the XPG gene were compared in lung cancer patients and healthy subjects. The results of these studies are summarized below.

4.2 Differences in the XPG gene between lung cancer patients and control subjects

Cases in a study carried out in Korea[1] consisted of 310 newly diagnosed patients with primary lung cancer, while the control group was made up of 311 healthy subjects, drawn from a pool of randomly selected volunteers who visited the general health check-up centre at the study hospital during the relevant time period. Controls were matched to the cases for age

and sex. The mean age of the case group was 61.5 years, compared to 60.5 years in the controls, and the proportion of men varied from 80% in the cases to 79.1% in the controls. Genomic DNA was extracted from peripheral blood lymphocytes, and XPG polymorphisms determined by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The frequency of the His/His, His/Asp and Asp/Asp genotypes of the His1104Asp polymorphism was 28.4%, 52.9% and 18.7% respectively in the cases and 28.6%, 42.4% and 28.9% respectively among the controls. Compared to His homozygotes, the risk of lung cancer was increased in those with the His/Asp genotype, although the difference was not significant (OR 1.26, 95% CI 0.87-1.83). Adjustment for age, sex and pack-years of smoking reduced this estimate to 1.20 (95% CI 0.82-1.75). However, when Asp homozygotes were examined, the risk of lung cancer was reduced (OR 0.65, 95% CI 0.42-1.01), and after adjustment, this became statistically significant (OR 0.60, 95% CI 0.38-0.95).

In a study carried out in Japan[4], polymorphisms in the XPG gene were examined in 752 adenocarcinoma cases, 250 squamous cell carcinoma cases and 685 controls. All the cases were either cytologically and/or histologically confirmed and were all primary lung cancer cases. The controls consisted of 383 inpatients/outpatients at the study hospitals and 302 healthy volunteers and had no history of cancer. The mean age of the adenocarcinoma cases was 61.7 years, while that of the squamous cell carcinoma cases was 65.6 years, compared to 55.4 years in the control group. Men made up 61.3% of the adenocarcinoma group, 89.6% of the squamous cell carcinoma cases and 70.5% of the controls. From each individual, a 10 or 20 ml whole blood sample was obtained from which genomic DNA was isolated. Genotyping was carried out using a PCR process. The frequency of the His/His, His/Asp and Asp/Asp genotypes of the His1104Asp polymorphism of the XPG gene was 31%, 49% and 20% respectively in the adenocarcinoma cases, 26%, 52% and 22% respectively in the squamous cell carcinoma cases and 33%, 49% and 18% respectively in the controls. Compared to His homozygotes, the risk of adenocarcinoma in His/Asp subjects was estimated at 1.1 (95% CI 0.9-1.4), while that for Asp homozygotes was estimated at 1.2 (95% CI 0.9-1.6).

Adjustment for sex, age and pack-years of smoking reduced the estimate for His/Asp individuals slightly (OR 1.0, 95% CI 0.9-1.4), while that for Asp homozygotes remained virtually unchanged (OR 1.2, 95% CI 0.9-1.7). The odds ratio for the risk of squamous cell carcinoma in subjects with the His/Asp genotype was estimated at 1.4 (95% CI 1.0-1.9), and the risk for Asp homozygotes was even higher, at 1.6 (95% CI 1.0-2.4). However, adjustment reduced both these estimates, to 1.1 (95% CI 0.7-1.6) for His/Asp subjects and 1.4 (95% CI 0.8-2.5) for Asp/Asp individuals.

A study conducted in China[5] compared polymorphisms in the XPG gene in 122 newly diagnosed lung cancer cases and 122 population controls, randomly selected from households in the same villages. Controls were matched to the cases for age, sex and type of fuel currently used for cooking and home heating. A mean age for the cases and controls was not given, but the age distribution of the two groups appeared to be comparable. The proportion of men was 65% in both groups. A sputum sample was collected from each study participant, from which DNA was extracted and genotyped using real-time PCR. Genotyping was carried out in 119 cases and 113 controls, but results for each of the polymorphisms considered were not always available for every subject. For the His46His polymorphism, the frequency of the T/T, T/C and C/C genotypes was 47%, 42% and 12% respectively in the cases and 56%, 32% and 12% respectively in the controls. Compared to T/T individuals, the risk of lung cancer, adjusted for age, sex and current fuel type, was estimated at 1.56 (95% CI 0.89-2.75) for subjects with the T/C genotype and 1.23 (95% CI 0.53-2.85) for C homozygotes. Adding pack-years of smoking and smoky coal use to the adjustment factors reduced the odds ratio for T/C subjects slightly, to 1.54 (95% CI 0.87-2.74), and increased the estimate for C homozygotes, to 1.31 (95% CI 0.55-3.07).

When the Cys529Ser polymorphism was examined, it was found that Cys homozygotes made up 87% of the case group and 90% of the control group. Twelve percent of the cases had the Cys/Ser genotype, compared to 10% of the controls, and only one Ser/Ser individual was found, in the case group. Using Cys/Cys subjects as the reference group, the odds ratio for the

risk of lung cancer in Cys/Ser individuals was estimated at 1.25 (95% CI 0.54-2.91), which was increased to 1.34 (95% CI 0.57-3.19) after more careful adjustment.

The C/C and C/A genotypes of the Leu700Leu polymorphism were found in 92% and 8% of the cases respectively and 89% and 11% of the controls respectively. No A homozygotes were reported. Compared to C/C individuals, the risk of lung cancer was reduced in subjects with the C/A genotype (OR 0.75, 95% CI 0.29-1.91), and this remained after further adjustment (OR 0.79, 95% CI 0.30-2.06).

Finally, the His1104Asp polymorphism was examined. His homozygotes comprised 33% of the cases and 35% of the controls, while His/Asp subjects made up 45% of the cases and 42% of the controls. The proportion of Asp/Asp individuals was comparable, at 22% for the cases and 23% for the controls. Using His homozygotes as the reference group, the risk of lung cancer in His/Asp subjects was estimated at 1.16 (95% CI 0.63-2.12), while that for Asp homozygotes was estimated at 1.05 (95% CI 0.52-2.14). More careful adjustment reduced both of these estimates slightly, to 1.08 (95% CI 0.58-2.01) for His/Asp subjects and 1.03 (95% CI 0.49-2.13) for Asp homozygotes.

In a study carried out in the USA[2], the case group consisted of 611 newly diagnosed, histologically confirmed, lung cancer patients, while the control group was made up of 1040 cancer-free subjects selected from the same neighbours as the cases, and matched for age and sex. A mean age for the cases and controls was not given, and there did appear to be a higher proportion of older subjects in the case group. The proportion of men varied from 49.6% in the cases and 59.9% in the controls. Buccal cells were obtained from each study participant, from which genomic DNA was extracted and polymorphisms in the XPG gene determined using a PCR-RFLP assay. Genotyping data was available for only 497 cases and 902 controls. The frequency of the His/His, His/Asp and Asp/Asp genotypes of the His1104Asp polymorphism was 49.1%, 42.7% and 8.2% respectively in the cases, and

51.9%, 39.5% and 8.6% respectively in the controls. Using His homozygotes as the reference group, the odds ratios for the risk of lung cancer were estimated at 1.1 (95% CI 0.91-1.4) for His/Asp subjects and 1.0 (95% CI 0.67-1.5) for Asp/Asp individuals. Adjustment for age, sex, ethnicity, educational level and pack-years of smoking did not really change the estimate for the His/Asp genotype (OR 1.1, 95% CI 0.80-1.4), but the odds ratio for Asp homozygotes was reduced (OR 0.65, 95% CI 0.39-1.1).

The case group in a study conducted in Norway[6] consisted of 343 patients with newly diagnosed histologically confirmed lung cancer, while the control group was made up of 413 randomly selected healthy individuals, with no known history of cancer, who had taken part in a general health survey. Controls were matched to the cases for age, sex and smoking. The median age of the case group was 65 years, compared to 60 years in the controls, and the proportion of men varied from 75.8% in the cases to 76.5% in the controls. DNA was extracted from whole blood samples or normal lung tissue, and genotyping was performed by Arrayed Primer Extension (APEX). Information on the His46His polymorphism was available for 316 cases and 373 controls. The C/C, C/T and T/T genotypes were found to occur in 43.4%, 37.7% and 19.0% of the cases respectively, and 37.0%, 33.8% and 29.2% of the controls respectively. The risk of lung cancer in subjects with the C/T genotype was estimated at 0.87 (95% CI 0.68-1.37), while that for T/T individuals was estimated at 0.56 (95% CI 0.38-0.84). These estimates were adjusted for age, sex and pack-years of smoking.

In a study carried out in France[3], the case group consisted of 151 patients with lung cancer, while the control group was made up of 172 consecutive patients with no malignant disease. The controls were matched to the cases for age, sex and hospital, and all study subjects were regular smokers. The mean age of the cases was 58.4 years, while that of the controls was 54.9 years, and this difference was statistically significant ($p = 0.003$). The proportion of men was similar in the two groups, at 93% in the cases and 95% in the controls. DNA was extracted from peripheral blood samples and genotyping was carried out using the Illumina Bead Array genotyping

platform method, Taqman assay, or direct sequencing. For the rs732321 polymorphism, the frequency of the A/A, A/C and C/C genotypes was 87.1%, 12.2% and 0.7% respectively in the cases. A/A and A/C subjects made up 94% and 6% of the controls respectively, with no C homozygotes being found in this group. The odds ratio for the risk of lung cancer in A/C individuals compared to A/A subjects was estimated at 2.39 (95% CI 1.05-5.46), adjusted for age and pack-years of smoking.

The C/C, C/T and T/T genotypes of the rs2018836 polymorphism made up 56.8%, 37.0% and 6.2% of the case group respectively and 44.2%, 46.5% and 9.3% of the controls respectively. Compared to C homozygotes, the risk of lung cancer was reduced in both C/T subjects (OR 0.60, 95% CI 0.37-0.97) and individuals with the T/T genotype (OR 0.55, 95% CI 0.22-1.41).

When the rs3759500 polymorphism was analysed, the C/C genotype accounted for 69.2% of the case group and 56.4% of the controls. C/T individuals made up 26.6% of the cases and 36.6% of the controls, while T homozygotes comprised 4.2% and 7.0% of the cases and controls respectively. Using C/C subjects as a reference group, the risk of lung cancer was estimated at 0.62 (95% CI 0.37-1.03) for the C/T genotype, and 0.59 (95% CI 0.21-1.66) for the T/T genotype.

The G/G, G/A and A/A genotypes of the rs3818356 polymorphism were found in 69.2%, 26.6% and 4.2% of the cases respectively, compared to 56.1%, 36.8% and 7.0% of the control group respectively. The odds ratios for the risk of lung cancer were reduced for both subjects with the G/A genotype (OR 0.61, 95% CI 0.37-1.02) and for A homozygotes (OR 0.58, 95% CI 0.21-1.64), compared to G/G individuals.

Finally, the frequency of the A/A, A/C and C/C genotypes of the rs4771436 polymorphism was 69.2%, 26.7% and 4.1% respectively in the case group, and 57.0%, 36.0% and 7.0% respectively in the controls. Compared to A homozygotes, the odds ratio for the risk of lung cancer in A/C subjects was

estimated at 0.65 (95% CI 0.39-1.08). The odds ratio for C/C individuals was also non-significantly reduced (OR 0.60, 95% CI 0.21-1.69).

4.3 Summary of study characteristics

Of the six studies that investigated polymorphisms in the XPG gene in relation to lung cancer risk, one each was carried out in China, France, Japan, Korea, Norway and the USA.

The largest study[4] was based on 1002 cases, although the results in this study were given separately for each lung cancer type and were not available for the entire case series combined. One other study[2] included more than 500 cases. All of the remaining studies were based on case groups of between 100 and 500 subjects.

All of the studies were of a conventional case-control design.

In all of the studies both the case and control groups were of mixed sex and were matched accordingly in five of the studies[1-3,5,6]. Despite this, in one of these studies[2] the proportion of men was lower in the case group than in the controls, although it was not clear whether the difference reached statistical significance. In one other study[4], there was a marked difference in the proportion of men in the case and control groups, although the significance of this difference was not given.

Five of the studies[1-3,5,6] matched the cases and controls for age. Despite this, the cases were older than the controls in two of these studies[3,6], and in one other study[4] where matching had not taken place. Whilst the difference in the study by Michiels et al[3] was statistically significant, it was not clear whether the differences in the other two studies reached significance. No details of the age distribution of the study subjects were available in two studies[2,5]. In one of these studies[2], there did appear to be a higher proportion of older subjects in the case group, although the significance of this difference

was not clear, while in the other study[5], cases and controls appeared to be comparable for age.

Five of the studies[1,2,4-6] included both smokers and non-smokers, but in three of the studies[1,2,4] there were more smokers in the case group, and the difference was statistically significant in one study[1]. The difference in another two studies[2,4] was so marked that although no estimate was made, statistical significance must have been reached. One study[6] found that the proportion of smokers was higher in the control group, although this related to the number of current vs. ex-smokers, as all study subjects had smoked at one time. All measures relating to the intensity or duration of smoking in this study were comparable between the cases and controls. In addition, five studies[1-5] reported that there were more heavy smokers among the cases, a difference that reached statistical significance in three studies[1-3]. Again, the difference in an additional study[4] would almost certainly have reached significance had an estimate been made. One study[3] reported a significantly longer duration of smoking in the case group compared to the controls.

All of the studies adjusted their results for at least some potential confounding factors. All of the studies adjusted for age, while sex was included as an adjustment factor by five studies[1,2,4-6]. Pack-years of smoking was included by all of the studies. One study[5] also adjusted for fuel type and smoky coal use, while another[2] included race and education as potential confounders.

4.4 Summary of main results and meta-analyses

The results of the individual studies are summarized in Table 1, with meta-analyses and overall prevalences of the various genotypes of the XPG polymorphism being presented in Tables 2 and 3 respectively. The results are discussed below for each polymorphism separately.

His46His

Using T homozygotes as the reference group, one study[5] reported that the risk of lung cancer was non-significantly raised in both the T/C and C/C genotypes. In another study[6], compared to C/C subjects, T/C individuals had a non-significantly reduced risk of lung cancer. T homozygotes also had a reduced risk, but this time the difference was statistically significant. As the two studies used different reference groups, it was not possible to combine their results in a meta-analysis.

From Table 3, it can be seen that the proportion of T homozygotes in the total population is somewhat higher in the control group than in the cases, although the numbers of C homozygotes are similar. When Caucasian and Asian subjects were examined separately, a similar pattern was observed, although the occurrence of the C allele was much higher in Caucasians than in Asians. The frequency of T homozygotes in the Caucasian subjects was about half that of the Asian population, while there were nearly four times as many C homozygotes in Caucasians as there were in Asians.

Cys529Ser

One study[5] found a non-significantly increased risk of lung cancer in subjects with the Cys/Ser genotype compared to Cys homozygotes.

Leu700Leu

Compared to C/C individuals, the one study[5] that examined this polymorphism found that the risk of lung cancer was non-significantly reduced in subjects with the C/A genotype.

His1104Asp

All four of the studies[1,2,4,5] that presented information for this polymorphism reported that the risk of lung cancer in His/Asp individuals was non-significantly raised compared to His homozygotes, although in one study[4] the estimate for subjects with squamous cell carcinoma was of borderline significance. As the separate odds ratios for each lung cancer type from the study by Sakiyama et al [4] both used the same control group, these were combined to produce one odds ratio for this study which could then be

included in a meta-analysis. Using the least adjusted odds ratios from each study, this meta-analysis produced an overall estimate of risk of 1.15 (95% CI 1.01-1.32) for both the fixed and random effects models. Substitution of the most adjusted odds ratios reduced this to 1.08, and removed the significance (95% CI 0.92-1.26). The estimate from the three studies based on Asian populations was slightly higher than for the entire dataset, at 1.19, and was of borderline significance (95% CI 1.00-1.41). However, when the most adjusted odds ratios were used, the estimate was reduced to 1.07 and became non-significant (95% CI 0.89-1.29).

When Asp homozygotes were considered, the odds ratio estimated in one study[1] was non-significantly reduced. Two studies[4,5] reported raised risks of lung cancer. In one of these studies[4], the estimate for subjects with squamous cell carcinoma was statistically significant, although this was removed after adjustment for potential confounders. A fourth study[2] failed to find any association between lung cancer risk and this genotype. Again, the results from the study by Sakiyama et al[4] were combined before being included in a meta-analysis. Using the least adjusted odds ratios, this produced an overall estimate of lung cancer risk of 1.04 (95% CI 0.86-1.26) for the fixed effects model, and 0.99 (95% CI 0.72-1.34) for the random effects model. When the most adjusted odds ratios were substituted, these estimates were markedly reduced, to 0.92 (95% CI 0.74-1.14) for the fixed effects model, and 0.85 (95% CI 0.57-1.27) for the random effects model. There was also significant heterogeneity between the studies (p=0.036) between the studies on which these estimates were based. When the analysis was restricted to the three studies based on Asian populations, the risk estimate for the fixed effects model was 1.05 (95% CI 0.85-1.31) and for the random effects model it was 0.97 (95% CI 0.61-1.53), using the least adjusted odds ratios. There was significant heterogeneity between the studies included in this analysis (p = 0.039). When the most adjusted odds ratios were used, the estimate for the fixed effects model was reduced to 0.99 (95% CI 0.78-1.26), while that for the random effects model was reduced to 0.92 (95% CI 0.56-1.51). Again, the estimate of heterogeneity between the studies reached statistical significance (p=0.039).

Table 3 shows that the Asp allele occurred in about 60% of the total population, although the proportion was slightly higher in the cases than in the controls. In Caucasians, the Asp allele was less common than in the total population, with His homozygotes comprising about half of all study subjects. The proportion of Asp homozygotes was reduced by about 50% compared to all subjects. In Asians, there was a lower incidence of His homozygotes and a higher proportion of Asp homozygotes than in Caucasians, with the frequency of the His/Asp genotype also being slightly higher in Asians.

rs732321

One study[3] reported that, compared to A/A subjects, the risk of lung cancer in individuals with the A/C genotype was significantly increased.

rs2018836

Using C homozygotes as the reference group, one study[3] estimated odds ratios for the risk of lung cancer that were below 1.00 for both the C/T and T/T genotypes, with the difference for C/T subjects reaching statistical significance.

rs3759500

One study[3] found that, compared to C/C subjects, the risk of lung cancer in both C/T individuals and T homozygotes was non-significantly reduced.

rs3818356

It was reported by the one study[3] that examined this polymorphism that the risk of lung cancer in the G/A and A/A genotypes was non-significantly reduced compared to G homozygotes.

rs4771436

Using A homozygotes as a reference group, the risk of lung cancer was reported to be non-significantly reduced in both A/C and C/C subjects in one study[3].

4.5 The effect of stratification by smoking status and intensity on risk of lung cancer according to XPG genotype

Results from the three studies[1,2,6] that considered the risk of lung cancer stratified for smoking status and/or intensity are given for each polymorphism in Table 4.

His46His

One study[6] reported that the odds ratio for the heaviest smokers was significantly reduced, but did not present results for non-smokers or lighter smokers for comparison. However, the results given for the entire population in this study were also reduced, although the decrease in risk was not as marked.

His1104Asp

One study[1] found that all Asp homozygotes had a reduced risk of lung cancer, but there was no clear pattern of decreasing risk with increasing intensity of smoking, and it was unclear what the reference group was for these comparisons. Another study[2] used Asp/Asp never smokers as the reference group, and found an obvious trend of increasing risk of lung cancer with increasing pack-years of smoking both for Asp homozygotes and for all subjects with the His allele.

4.6 Conclusions

For the majority of polymorphisms considered here, there are simply too few studies reporting for any conclusions to be drawn. The evidence for the His/Asp genotype of the His1104Asp polymorphism could be suggestive of a possible positive relationship with lung cancer risk, with all five of the odds ratios reported being raised, although none was significantly so. Meta-analysis produced an overall estimate of risk that reached statistical significance, although this was removed in an analysis based on more adjusted odds ratios.

Due to the small number of studies presenting results, no conclusions can be drawn when the risk of lung cancer according to genotype in various XPG polymorphisms is stratified by smoking status and/or intensity.

Some weaknesses in the studies were noted, particularly a tendency in several studies for the age and sex distribution to vary between the cases and the controls. The proportion of smokers varied between the cases and controls in the majority of the studies, and there were also differences in the intensity and duration of smoking in some studies. Finally, none of the studies considered more than a very few potentially confounding factors.

5. Overall conclusions

Six studies examined polymorphisms in the XPG gene with regard to the risk of lung cancer. For most of the polymorphisms considered, there were too few studies reporting results for any conclusions to be drawn. The evidence for the His/Asp genotype of the His1104Asp polymorphism was possibly suggestive of a positive relationship with lung cancer risk, with all of the five odds ratios presented being raised, although none was significantly so. Meta-analysis of the results for this genotype also suggested a significantly raised risk of lung cancer, although this was removed after adjustment. Although a few of the studies reported results separately for subjects with differing smoking habits, this did not help to clarify the picture. There were problems with age and sex differences between cases and controls in several of the studies, and in the majority the case and control groups varied with regard to the proportion of smokers, and in the intensity and duration of smoking. None of the studies adjusted for more than a very few potential confounders.

Table 1: Risk of lung cancer incidence in relation to XPG genotype

Ref.	Author (Country)	Year[a]	Cases/ controls	Genotype	Odds ratios[b]	Sig[c]	Adjustment factors[d]
His46His							
5	Shen[e] (China)	2005	118/112	T/C	1.56 (0.89-2.75)	NS	A,FT,S
					1.54 (0.87-2.74)	NS	A,FT,PY,S,SC
				C/C	1.23 (0.53-2.85)	NS	A,FT,S
					1.31 (0.55-3.07)	NS	A,FT,PY,S,SC
6	Zienolddiny[f]	2006	316/373	T/C	0.87 (0.68-1.37)	NS	A,PY,S
	(Norway)			T/T	0.56 (0.38-0.84)	p<0.05	A,PY,S
Cys529Ser[g]							
5	Shen (China)	2005	118/111	Cys/Ser	1.25 (0.54-2.91)	NS	A,FT,S
					1.34 (0.57-3.19)	NS	A,FT,PY,S,SC
Leu700Leu[f]							
5	Shen (China)	2005	106/99	C/A	0.75 (0.29-1.91)	NS	A,FT,S
					0.79 (0.30-2.06)	NS	A,FT,PY,S,SC
His1104Asp[h]							
1	Jeon (Korea)	2003	310/311	His/Asp	1.26 (0.87-1.83)	NS	None
					1.20 (0.82-1.75)	NS	A,PY,S
				Asp/Asp	0.65 (0.42-1.01)	NS	None
					0.60 (0.38-0.95)	p=0.03	A,PY,S
4	Sakiyama (Japan)	2005	752[i]/685	His/Asp	1.10 (0.90-1.40)	NS	None
					1.00 (0.80-1.30)	NS	A,PY,S
				Asp/Asp	1.20 (0.90-1.60)	NS	None
					1.20 (0.90-1.70)	NS	A,PY,S
			250[j]/685	His/Asp	1.40 (1.00-1.90)	NS	None
					1.10 (0.70-1.60)	NS	A,PY,S
				Asp/Asp	1.60 (1.00-2.40)	p=0.04	None
					1.40 (0.80-2.50)	NS	A,PY,S
5	Shen (China)	2005	116/109	His/Asp	1.16 (0.63-2.12)	NS	A,FT,S
					1.08 (0.58-2.01)	NS	A,FT,PY,S,SC
				Asp/Asp	1.05 (0.52-2.14)	NS	A,FT,S
					1.03 (0.49-2.13)	NS	A,FT,PY,S,SC
2	Cui (USA)	2006	497/902	His/Asp	1.10 (0.91-1.40)	NS	None
					1.10 (0.80-1.40)	NS	A,E,EL,PY,S
				Asp/Asp	1.00 (0.67-1.50)	NS	None
					0.65 (0.39-1.10)	NS	A,E,EL,PY,S
Rs732321[k]							
3	Michiels (France)	2007	147/166	A/C	2.39 (1.05-5.46)	p<0.05	A,PY
Rs2018836[f]							
3	Michiels	2007	146/172	C/T	0.60 (0.37-0.97)	p<0.05	A,PY
	(France)			T/T	0.55 (0.22-1.41)	NS	A,PY
Rs3759500[f]							
3	Michiels	2007	143/172	C/T	0.62 (0.37-1.03)	NS	A,PY
	(France)			T/T	0.59 (0.21-1.66)	NS	A,PY
Rs3818356[l]							
3	Michiels	2007	143/171	G/A	0.61 (0.37-1.02)	NS	A,PY
	(France)			A/A	0.58 (0.21-1.64)	NS	A,PY
Rs4771436[k]							
3	Michiels	2007	146/172	A/C	0.65 (0.39-1.08)	NS	A,PY
	(France)			C/C	0.60 (0.21-1.69)	NS	A,PY

a Year of publication
b 95% confidence interval shown in brackets where available
c NS = not significant ($p \geq 0.05$)
d Abbreviations used for confounders:
A = age, E = ethnicity, EL = educational level, FT = fuel type, PY = pack-years of smoking, S = sex, SC = smoky coal use
e Using T/T individuals as the reference group
f Using C/C individuals as the reference group
g Using Cys/Cys individuals as the reference group
h Using His/His individuals as the reference group
i Adenocarcinoma cases
j Squamous cell carcinoma cases
k Using A/A individuals as the reference group
l Using G/G individuals as the reference group

Table 2: Results of meta-analysis for the risk of lung cancer in relation to XPG polymorphisms

Genotype	No. of studies	Heterogeneity Chisquared, p	Odds ratio (95% confidence interval) Fixed effects model	Random effects model	Notes
His1104Asp					
His/Asp	4	0.42, NS	1.15 (1.01-1.32)	1.15 (1.01-1.32)	Least adjusted
	4	0.55, NS	1.08 (0.92-1.26)	1.08 (0.92-1.26)	Most adjusted
	3	0.12, NS	1.19 (1.00-1.41)	1.19 (1.00-1.41)	Asians, least adjusted
	3	0.52, NS	1.07 (0.89-1.29)	1.07 (0.89-1.29)	Asians, most adjusted
Asp/Asp	4	6.52, NS	1.04 (0.86-1.26)	0.99 (0.72-1.34)	Least adjusted
	4	8.55, p=0.036	0.92 (0.74-1.14)	0.85 (0.57-1.27)	Most adjusted
	3	6.47, p=0.039	1.05 (0.85-1.31)	0.97 (0.61-1.53)	Asians, least adjusted
	3	6.50, p=0.039	0.99 (0.78-1.26)	0.92 (0.56-1.51)	Asians, most adjusted

NS $p \geq 0.05$

Table 3: Prevalence of genotypes of XPG polymorphisms

Polymorphism/ population	No. of cases	Prevalence of genotypes[a]			No. of controls	Prevalence of genotypes[a]		
His46His		**T/T**	**T/C**	**C/C**		**T/T**	**T/C**	**C/C**
Total	434	115 (26.5)	168 (38.7)	151 (34.8)	485	172 (35.5)	162 (33.4)	151 (31.1)
Caucasian	316	60 (19.0)	119 (37.7)	137 (43.4)	373	109 (29.2)	126 (33.8)	138 (37.0)
Asian	118	55 (46.6)	49 (41.5)	14 (11.9)	112	63 (56.3)	36 (32.1)	13 (11.6)
Cys529Ser		**Cys/Cys**	**Cys/Ser**	**Ser/Ser**		**Cys/Cys**	**Cys/Ser**	**Ser/Ser**
Total	118	103 (87.3)	14 (11.9)	1 (0.8)	111	100 (90.1)	11 (9.9)	0 (0.0)
Leu700Leu		**C/C**	**C/A**	**A/A**		**C/C**	**C/A**	**A/A**
Total	106	97 (91.5)	9 (8.5)	0 (0.0)	99	88 (88.9)	11 (11.1)	0 (0.0)
His1104Asp		**His/His**	**His/Asp**	**Asp/Asp**		**His/His**	**His/Asp**	**Asp/Asp**
Total	1925	670 (34.8)	928 (48.2)	327 (17.0)	2007	823 (41.0)	867 (43.2)	317 (15.8)
Caucasian	497	244 (49.1)	212 (42.7)	41 (8.2)	902	468 (51.9)	356 (39.5)	78 (8.6)
Asian	1428	426 (29.8)	716 (50.1)	286 (20.0)	1105	355 (32.1)	511 (46.2)	239 (21.6)
Rs732321		**A/A**	**A/C**	**C/C**		**A/A**	**A/C**	**C/C**
Total	147	128 (87.1)	18 (12.2)	1 (0.7)	166	156 (94.0)	10 (6.0)	0 (0.0)
Rs2018836		**C/C**	**C/T**	**T/T**		**C/C**	**C/T**	**T/T**
Total	146	83 (56.8)	54 (37.0)	9 (6.2)	172	76 (44.2)	80 (46.5)	16 (9.3)
Rs3759500		**C/C**	**C/T**	**T/T**		**C/C**	**C/T**	**T/T**
Total	143	99 (69.2)	38 (26.6)	6 (4.2)	172	97 (56.4)	63 (36.6)	12 (7.0)
Rs3818356		**G/G**	**G/A**	**A/A**		**G/G**	**G/A**	**A/A**
Total	143	99 (69.2)	38 (26.6)	6 (4.2)	171	96 (56.1)	63 (36.8)	12 (7.0)
Rs4771436		**A/A**	**A/C**	**C/C**		**A/A**	**A/C**	**C/C**
Total	146	101 (69.2)	39 (26.7)	6 (4.1)	172	98 (57.0)	62 (36.0)	12 (7.0)

a Number (percent)

Table 4: Effect of stratification by smoking variables on lung cancer risk according to XPG genotype

Ref.	Author (year[a])	Smoking variable	Genotype	Odds ratios[b]	Adjustment factors[c]
His46His[d]					
6	Zienolddiny (2006)	≤29 pack-years	All T allele	0.46 (0.26-0.80)	Not stated
His1104Asp					
1	Jeon (2003)[e]	Never smokers	Asp/Asp	0.59	None
				0.59 (0.25-1.43)	A, S
		≤39 pack-years	Asp/Asp	0.41	None
				0.48 (0.25-0.94)	A, S
		>39 pack-years	Asp/Asp	0.63	None
				0.63 (0.35-1.13)	A, S
2	Cui (2006)[f]	Never smokers	All His allele	1.90 (0.78-4.50)	A,E,EL,S
		1-20 pack-years	Asp/Asp	2.40 (0.70-8.10)	A,E,EL,S
			All His allele	2.20 (0.91-5.30)	A,E,EL,S
		>20 pack-years	Asp/Asp	13.0 (4.40-37.0)	A,E,EL,S
			All His allele	23.0 (9.5-56.0)	A,E,EL,S

a Year of publication
b 95% confidence interval shown in brackets where available
c Abbreviations used for confounders:
A = age, E = ethnicity, EL = educational level, S = sex
d Using C/C individuals as the reference group
e Reference group unclear
f Using Asp/Asp never smokers as the reference group

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