The association of XPC with lung cancer

Author: A. J. Thornton

Date: 16th July 2008

1. Objectives

The nucleotide excision repair (NER) pathway is the primary mechanism for removal of DNA adducts[1-4], and individuals with suboptimal NER capacity have been reported to be at increased risk of cancers[2,4]. XPC binds to HR23B, forming the XPC-HR23B complex[1,2,4], which is involved in the damage recognition step of NER[1-5]. Some 145 polymorphisms in the XPC gene have been reported[6], although the functional effects of some of these remain unclear[2]. Homozygous carriers of the PAT+ allele have been shown to have a lower DNA repair capacity than -/- homozygotes[1,3,5], while elsewhere it has been reported that the XPC 939C variant influences irradiation-specific DNA repair rates in peripheral lymphocytes[1]. Mice defective in the XPC gene are very prone to skin cancer following exposure to UV radiation and are also vulnerable to cancers of the internal organs, including liver and lung, when exposed to chemical carcinogens, suggesting that XPC is important for preventing carcinogenesis[2,4].

The objective of this report is to determine, based on the available literature, whether genetic polymorphisms in XPC 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

Eleven 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 XPC in relation to lung cancer

4.1 Introduction

One relevant meta-analysis was available, and the results of this are summarized below. In addition, four papers that were not included in this meta-analysis were found relating to studies in which polymorphisms in the XPC gene were compared in lung cancer patients and healthy subjects. The results of these studies are detailed below in chronological order.

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

4.2.1 *Meta-analysis*

A meta-analysis published in 2008[4] included results from 6 studies[1,2,5-8] that examined polymorphisms in the XPC gene in relation to lung cancer risk, although not all of these studies provided data for each of the identified polymorphisms, and some of the studies also provided information on polymorphisms that were not included in meta-analyses. Three studies provided data on the Ala499Val polymorphism and risk estimates were based on 1746 cases and an equal number of controls. Odds ratios of 1.05 (95% CI

0.84-1.32) and 1.16 (95% CI 0.91-1.47) were estimated for the risk of lung cancer for the genotypes Ala/Val and Val/Val respectively. The former estimate was based on a random effects model, as the p value for heterogeneity exceeded the authors' criteria for significance (p = 0.08). For all subjects with the Val allele, an odds ratio of 1.07 (0.86-1.33) was estimated from a random effects model (p for heterogeneity = 0.08).

Information on the PAT +/- polymorphism was available from three studies, and included 901 cases and 896 controls. For subjects who were +/- for this polymorphism, the risk of lung cancer was estimated at 0.99 (95% CI 0.69-1.41). Again, this estimate was obtained using a random effects model (p for heterogeneity = 0.07). The odds ratio for subjects who were +/+ was estimated at 1.24 (95% CI 0.94-1.65), while that for all subjects with the + allele was 1.09 (95% CI 0.71-1.66), using a random effects model (p for heterogeneity = 0.03).

Although a meta-analysis was carried out on the results from the four studies that examined the Lys939Gln polymorphism, one of these studies has been superceded by a more recent publication that included a higher number of subjects[3]. Information was thus taken from this more up-to-date paper and the results from the other studies included were examined separately.

4.2.2 *Additional individual studies*

A study carried out in China[9] used polymerase chain reaction (PCR) to examine polymorphisms in the XPC gene in 597 lung cancer patients and 509 healthy controls. The mean age of the cases was 58.2 years compared to 58.1 years in the controls, and the two groups appear to have been comparable for sex distribution. The -/-, +/- and +/+ genotypes of the PAT+/- polymorphism accounted for 42.1%, 46.7% and 11.2% of the cases respectively, and 37.9%, 49.7% and 12.4% of the control group respectively. Adjusted odds ratios of 0.85 (0.66-1.09) and 0.82 (0.55-1.21) were estimated for subjects with the +/- and +/+ genotypes respectively, compared to -/- individuals. No details of the adjustment factors were given.

The cases in a study conducted in China[10] consisted of 122 newly diagnosed lung cancer patients. For each patient a control, matched on sex, age and type of fuel used for cooking and heating, was randomly selected from the same study area. There were 79 men and 43 women in each group, and although a mean age was not given, the age distribution of the cases and controls was comparable.

For the +315C→G polymorphism, subjects with the C/C, C/G and G/G genotypes made up 48%, 48% and 5% of the case group respectively and 44%, 49% and 7% of the control group respectively. Compared to C/C individuals, odds ratios for the risk of lung cancer, adjusted for age, sex and current fuel type, were estimated at 0.91 (95% CI 0.52-1.58) for C/G subjects and 0.58 (95% CI 0.18-1.93) for G allele homozygotes. Further adjustment for pack-years of smoking and smoky coal use did not substantially alter these findings (C/G: OR 0.90, 95% CI 0.51-1.58; G/G: OR 0.56, 95% CI 0.16-1.91).

When the Lys939Gln polymorphism was examined, Lys homozygotes comprised 38% of the case group and 37% of the controls, Lys/Gln subjects accounted for 44% and 55% of the cases and controls respectively, and Gln homozygotes made up 18% of the case group and just 8% of the controls. Compared to Lys/Lys individuals, the partially adjusted odds ratio for the risk of lung cancer was estimated at 0.78 (95% CI 0.44-1.38) for Lys/Gln subjects and 2.45 (95% CI 0.96-6.21) for Gln homozygotes. Further adjustment reduced these estimates, to 0.67 (95% CI 0.37-1.23) and 2.22 (95% CI 0.86-5.74) respectively.

The Ala/Ala, Ala/Val and Val/Val genotypes of the Ala499Val polymorphism were found in 48%, 41% and 11% of the cases respectively and 45%, 43% and 12% of the controls respectively. Using Ala homozygotes as a reference group, the risk of lung cancer in Ala/Val and Val/Val subjects was estimated at 0.89 (95% CI 0.51-1.56) and 0.89 (95% CI 0.38-2.11) respectively, adjusted for age, sex and fuel type. Further adjustment increased

these risk estimates, to 0.91 (95% CI 0.52-1.62) for Ala/Val subjects and 0.98 (95% CI 0.41-2.38) for Val homozygotes.

In a study carried out in Spain[11], the case group consisted of 516 patients with histologically confirmed lung cancer, while the control group was comprised of 533 subjects, matched for race, sex and age, who were patients at participating hospitals with diagnoses believed to be unrelated to the exposures of interest. The mean age of the cases was 64.79 years, compared to 63.54 years in the controls, and the proportion of men was 88.4% in the cases and 86.3% in the controls. Genomic DNA was extracted from peripheral blood samples or exfoliated buccal cells and PCR used to identify XPC polymorphisms. The frequency of the -/-, +/- and +/+ genotypes of the PAT+/- polymorphism was 33.3%, 47.1% and 19.6% respectively in the case group and 35.6%, 48.6% and 15.8% respectively in the controls. Compared to -/- subjects, the odds ratio for the risk of lung cancer, adjusted for age, sex and pack-years of smoking, was estimated at 1.08 (95% CI 0.79-1.47) for subjects with the +/- genotype, and 1.28 (95% CI 0.85-1.92) for + homozygotes.

Participants in a study conducted in Denmark[3] were drawn from the Diet, Cancer and Health (DCH) prospective study. The case group consisted of 430 subjects with lung cancer, while the control group was made up of 790 subjects randomly selected from the study cohort. The proportion of men varied from 53% in the case group to 54% in the controls. No mean age was given, but the age distribution of the groups did not appear to be comparable, with the proportion of cases age 61-70 years far exceeding that of the controls (66% vs. 23%). Each participant provided a blood sample at enrolment to the study, from which DNA was isolated, and real-time PCR used to identify XPC polymorphisms. The frequency of the Lys/Lys, Lys/Gln and Gln/Gln genotypes of the Lys939Gln polymorphism was 37.2%, 45.7% and 17.1% respectively in the cases, and 38.7%, 49.2% and 12.2% in the controls. Using Lys homozygotes as a comparison group, an odds ratio for the risk of lung cancer in Lys/Gln individuals was estimated at 0.91 (95% CI 0.65-1.28) after adjustment for smoking duration, average smoking intensity and smoking

status. The odds ratio for Gln homozygotes was estimated at 1.41 (95% CI 0.87-2.30).

4.3 Summary of study characteristics of the additional individual studies

Of the four individual studies that investigated polymorphisms in the XPC gene in relation to lung cancer risk, two took place in China, and one each was conducted in Denmark and Spain.

The largest study[9] was based on 597 cases. Two of the remaining studies[3,11] were each based on around 500 cases, while the third study[10] included only 122 cases.

All four of the studies were of a conventional case-control design, although in one study[3] participants were drawn from a prospective study.

In all four of the studies both the case and control groups were of mixed sex, and were matched accordingly in two of the studies[10,11]. In both of the studies in which matching had not taken place, the case and control groups appeared to be comparable for sex distribution.

Two of the studies[10,11] matched the cases and controls for age. One of these studies[10] did not give a mean age, but the age distribution of the cases and controls was comparable. In one of the studies where matching had not taken place[3], the proportion of older subjects was much higher in the case group than in the controls. The significance of this difference was not given.

Three of the studies[3,10,11] included both smokers and non-smokers, although none of them matched the cases and controls for this aspect. In two studies[3,11] there were more smokers in the case group, and in one of these studies[11] the difference reached statistical significance. In addition, three studies[3,10,11] reported that there were more heavy smokers among the cases, significantly so in one study[11], and one study[3] found that cases had smoked for a longer duration than the controls. One study [9] did not give any details of the smoking status of participants.

All of the studies adjusted their results for at least some potential confounding factors, although in one study[9] no details of the factors adjusted for were given. Two studies[10,11] adjusted for age and sex. Variables relating to smoking history were included by three studies[3,10,11]. One study[10] adjusted for the type of fuel used.

4.4 Summary of main results and meta-analyses

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

-449G→C

One study[2] reported that, compared to subjects with the G/G genotype, the risk of lung cancer was non-significantly reduced in subjects with both the G/C and C/C genotypes.

-371G→A

Compared to G homozygotes, one study[6] reported that the risk of lung cancer was reduced in subjects with the G/A genotype of this polymorphism, while in another study[2], the odds ratio was non-significantly raised. Meta-analysis of the available results produced an overall risk estimate of 0.89 (95% CI 0.76-1.04) for the fixed effects model, and 0.90 (95% CI 0.73-1.10) for the random effects model.

When A homozygotes were examined, again one study[6] reported a reduced risk of lung cancer while the other[2] found an increased risk. Both these results failed to reach statistical significance. When these results were combined in a meta-analysis, the overall risk was estimated at 0.93 (95% CI 0.68-1.27) for the fixed effects model and 1.02 (95% CI 0.54-1.94) for the random effects model.

One study[6] reported a significantly reduced risk of lung cancer in all subjects with the A allele.

-27G→C

Compared to subjects with the G/G genotype, one study[6] reported a non-significantly increased risk of lung cancer in subjects with the G/C genotype but a decreased risk in C homozygotes, which also failed to reach statistical significance.

Two studies[2,6] reported on the risk of lung cancer in all subjects with the C allele, and both found an increased risk, which reached statistical significance in one study[2]. Meta-analysis of these results produced risk estimates of 1.39 (95% CI 1.05-1.83) for the fixed effects model and 1.47 (95% CI 0.87-2.48) for the random effects model.

Ala499Val

Compared to Ala/Ala homozygotes, subjects with the Ala/Val genotype were reported to have a lower risk of lung cancer by one study [10] and a higher risk by one study [4]. This latter result was based on a meta-analysis of three studies. Meta-analysis of the available odds ratios, using the least adjusted results where applicable, produced an overall estimate of lung cancer risk of 1.03 (95% CI 0.83-1.27) for both the fixed and random effects models. Substitution of the most adjusted odds ratios available from the studies made virtually no difference to these findings (OR 1.03, 95% CI 0.84-1.27 for both fixed and random effects models).

For Val/Val subjects, again one study[10] reported a reduced risk of lung cancer, while another study[4] found an increased risk. Neither finding reached statistical significance. Meta-analysis of these odds ratios produced an overall risk estimate of 1.14 (95% CI 0.90-1.43) for both the fixed and random effects models, using least adjusted odds ratios where applicable. Using the most adjusted results increased this estimate only slightly, to 1.15 (95% CI 0.91-1.45) for both models.

Only one study[4] examined the risk of lung cancer in all subjects with the Val allele, and reported a non-significantly increased incidence of the disease.

Lys939Gln

Compared to Lys homozygotes, when the risk of lung cancer in individuals with the Lys/Gln genotype of this polymorphism was examined, two studies[1,6] found an increased incidence of lung cancer, although the difference did not reach statistical significance in either study. Three studies[2,3,10] reported a decreased risk of lung cancer, which was of borderline significance in one of the studies[2]. A meta-analysis of all the available data, using the least adjusted odds ratios where applicable, produced an overall risk estimate of 0.94 (95% CI 0.83-1.07) for the fixed effects model and 0.94 (0.81-1.08) for the random effects model. Substituting the most adjusted odds ratios made no difference for the fixed effects estimate, and only slightly altered the result for the random effects model (OR 0.93, 95% CI 0.78-1.10). The overall risk for Asian studies was very similar to that for the whole dataset, at 0.95 (95% CI 0.82-1.09) for the fixed effects model and 0.93 (95% CI 0.77-1.13) for the random effects model, using the least adjusted odds ratios where both unadjusted and adjusted were presented. Full adjustment did not alter the overall risk estimates for the fixed effects model, but did slightly reduce the risk estimate for the random effects model (OR 0.92, 95% CI 0.73-1.16).

With regard to Gln homozygotes, four studies[1,3,6,10] reported that the risk of lung cancer was higher in these subjects than in Lys homozygotes, although the difference did not reach statistical significance in any of them. One study[2] found a non-significantly reduced risk. Meta-analysis of the available data produced an overall risk estimate of 1.24 (95% CI 1.02-1.51) using the fixed effects model and 1.25 (95% CI 1.02-1.54) with the random effects model. Substituting adjusted odds ratios where applicable reduced the risk estimate to 1.20 (95% CI 0.99-1.46) for both models. Ethnicity made little difference to these findings, with the odds ratios estimated for Asian populations being similar to those for the entire dataset when the least adjusted

results were used (fixed effects: OR 1.21, 95% CI 0.98-1.50; random effects: OR 1.24, 95% CI 0.95-1.62). Overall risk estimates were slightly lower when the most adjusted findings were used where appropriate (OR 1.17, 95% CI 0.94-1.45 for both models).

The risk of lung cancer was also examined in all subjects with the Gln allele by two of the studies[1,6], both of which reported a non-significantly increased risk. Meta-analysis of these findings produced an overall odds ratio of 1.08 (95% CI 0.92-1.26) for both models, which remained unaltered when adjusted results were substituted.

The Gln allele of this polymorphism occurred in over 50% of the total study population, and there was not much variation due to ethnicity. In the cases, the Lys allele was slightly more common in Asians than in Caucasians, and conversely Gln homozygotes occurred slightly less frequently in Asian populations. In the controls, the proportions were more or less equal in the two populations.

PAT+/-

Two studies[4,9] that presented data for this polymorphism reported a non-significantly decreased risk of lung cancer in subjects with the +/- genotype, compared to those with the -/- genotype. A third study[11] found a raised odds ratio, which was also non-significant. Meta-analysis, using the least adjusted odds ratios where applicable, gave an overall risk estimate of 0.95 (95% CI 0.80-1.12) for both the fixed and random effects models. Substitution of the most adjusted odds ratios made virtually no difference to this result (OR 0.95, 95% CI 0.80-1.13). Results from the three studies carried out in Caucasian populations were much higher than for the total dataset, with meta-analysis producing an odds ratio estimate of 1.15 (95% CI 0.93-1.42) for both the fixed and random effects models. Conversely, findings in Asian populations were lower, with the overall risk being significantly reduced when both the least adjusted (OR 0.81, 95% CI 0.67-0.97 for both models) and most adjusted (OR 0.80, 95% CI 0.66-0.98 for both models) results were used.

When + homozygotes were examined, one study[9] reported a reduced risk of lung cancer, while two studies[4,11] found an increased risk. None of these results reached statistical significance. Meta-analysis, using the least adjusted odds ratios where appropriate, produced overall risk estimates of 1.12 (95% CI 0.92-1.37) for the fixed effects model and 1.11 (95% CI 0.85-1.45) for the random effects model. Substitution of the most adjusted results reduced these to 1.10 (95% CI 0.90-1.35) and 1.07 (95% CI 0.77-1.49) for the fixed and random effects models respectively. Again, results from the studies in Caucasian populations were much higher than for the entire dataset, at 1.35 (95% CI 1.02-1.78) for the fixed effects model and 1.31 (95% CI 0.92-1.88) for the random effects model. When the studies conducted in Asian populations were considered separately, the risk estimate, using least adjusted odds ratios where applicable, was 0.87 (95% CI 0.65-1.16) for both the fixed and random effects models. Using the most adjusted odds ratios reduced this to 0.82 (95% CI 0.61-1.10).

The one study[4] that examined the risk of lung cancer in all subjects with the + allele reported a non-significantly raised odds ratio compared to -/- subjects.

Table 3 shows that there was some variation in the prevalence of the + allele according to ethnicity, although this was mostly restricted to lung cancer patients. In Caucasians, less than one-third of the cases were of the -/- genotype, compared to over 40% of Asian cases. Nearly 20% of Caucasian cases were + homozygotes, while only 12% of Asians lung cancer patients were. The proportions of the various genotypes in the controls were much more equal.

IVS11-5C→A

The one study[2] that examined this polymorphism reported that, compared to C homozygotes, both C/A and A/A subjects had a non-significantly reduced risk of lung cancer.

12413C→G

One study[6] examined the risk of lung cancer in subjects with this polymorphism. Compared to C homozygotes, lung cancer incidence was increased in C/G subjects but decreased in G/G homozygotes. When all subjects with the G allele were considered, the risk of cancer was increased. None of these differences reached statistical significance.

+315C→G

The risk of lung cancer in relation to the occurrence of this polymorphism was investigated by one study[10]. Both C/G and G/G subjects had a reduced risk of lung cancer compared to C/C individuals, but the differences failed to reach statistical significance.

4.5 <u>The effect of stratification by smoking status and intensity on risk of lung cancer according to XPC genotype</u>

Results for the risk of lung cancer stratified for smoking status and/or intensity are presented for each of the polymorphisms in Table 4. Information is given individually for each of the studies originally included in the meta-analysis by Zhang et al[4] where applicable. Two studies[2,9] stated that stratification for smoking had no effect on the risk of lung cancer according to genotype, but did not give any further details of their findings and thus are not included in the table.

-371G→A

One study[6] presented results for all subjects with the A allele compared to G/G homozygotes. When smoking status was examined, the odds ratio for smokers was higher than for non-smokers, although both were below 1.00, with that for non-smokers being significantly so. However, there was little difference in the risks estimated when intensity of smoking was investigated.

Ala499Val

Compared to never smoking Ala homozygotes, the risk of lung cancer in ever smokers was significantly increased both for Ala homozygotes and for all subjects with the Val allele[1].

Lys939Gln

When the risk of lung cancer was stratified by smoking status, ever smokers had a significantly higher risk of lung cancer for both Lys/Lys subjects and all individuals with the Gln allele, compared to never smoking Lys homozygotes[1]. Another study[3] reported significantly increased odds ratios for all genotypes per five years of smoking and per five grams of tobacco smoked per day, although this latter finding only applied to those smoking less than 20 grams per day. In heavier smokers, the risk was reduced for Lys homozygotes, but non-significantly increased for Lys/Gln and Gln/Gln subjects.

PAT+/-

For subjects with the +/- genotype, one study[5] reported that compared to never smokers, odds ratios in ever and current smokers were higher, while that in ex-smokers was similar. Another study[11] found that odds ratios for ETS exposed subjects and ever smokers were comparable, while the risk in current smokers was higher. Ex-smokers showed a reduced risk of lung cancer. When intensity of smoking was examined, the risk in light smokers was below 1.00, but it was increased in moderate and heavy smokers, although the difference in risk estimate between these two groups was not great[11].

When +/+ individuals were examined, one study[5] found that the odds ratio for ever smokers was similar to that for never smokers. However, the odds ratio for ex-smokers was somewhat higher, while that for current smokers was lower than for subjects who had never smoked. Another study[11] found that ever smokers had a higher risk of lung cancer than subjects who had never smoked but were exposed to ETS. The risk in ex-smokers was also higher, but there was no real difference between current smokers and the unexposed group. However, within the group of current smokers, the risk of lung cancer increased with the intensity of smoking.

4.6 Conclusions

There was no really convincing evidence of a relationship between lung cancer risk and any of the polymorphisms of the XPC gene examined by the studies. This was partly due to the small number of studies reporting results for each of the polymorphisms. Findings for the Lys939Gln polymorphism suggested there may be a positive relationship with lung cancer in Gln homozygotes, but more studies will be needed before definitive conclusions can be drawn.

No clear pattern emerges when the risk of lung cancer according to genotype of the various XPC polymorphisms is stratified by smoking status and/or intensity, again due in part to the small number of studies presenting results.

Some weaknesses in the studies were noted, particularly a tendency in some studies for the proportion of smokers, and the intensity of smoking, to vary between the cases and the controls, and a failure by most of the studies to consider more than a very few potentially confounding factors.

5. Overall conclusions

Four individual studies and one meta-analysis, based on a maximum of three studies, examined polymorphisms in the XPC gene with regard to the risk of lung cancer. There was no clear evidence of an association between any of the polymorphisms examined by the studies and lung cancer risk. More studies are needed before any firm conclusions can be drawn. Some of the studies reported results separately for subjects with differing smoking habits, but this did not help to clarify the situation, mostly due to the small number of studies from which relevant data was available. Most of the studies only adjusted for a very few potential confounders, and there were also problems regarding differences between cases and controls with regard to smoking status and/or intensity of exposure in several of the studies.

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

Ref.	Author (Country)	Year[a]	Cases/ controls	Genotype	Odds ratios[b]	Sig[c]	Adjustment factors[d]
-449G→Ce							
2	Lee (South Korea)	2005	432/431	G/C	0.90 (0.68-1.20)	NS	A,PY,S
				C/C	0.76 (0.42-1.38)	NS	A,PY,S
-371G→Ae							
2	Lee (South Korea)	2005	432/431	G/A	1.03 (0.77-1.37)	NS	A,PY,S
				A/A	1.47 (0.83-2.62)	NS	A,PY,S
6	Bai (China)	2007	967/985	G/A	0.83 (0.69-1.01)	NS	A,FHC,PY,RA,S
				A/A	0.76 (0.52-1.11)	NS	A,FHC,PY,RA,S
				All A allele	0.82 (0.68-0.99)	p<0.05	A,FHC,PY,RA,S
-27G→Ce							
2	Lee (South Korea)	2005	430/429	All C allele	1.97 (1.22-3.17)	P=0.005	A,PY,S
6	Bai (China)	2007	992/994	G/C	1.16 (0.82-1.66)	NS	A,FHC,PY,RA,S
				C/C	0.78 (0.14-4.34)	NS	A,FHC,PY,RA,S
				All C allele	1.15 (0.81-1.62)	NS	A,FHC,PY,RA,S
Ala499Valf							
10	Shen (China)	2005	116/110	Ala/Val	0.89 (0.51-1.56)	NS	A,FT,S
					0.91 (0.52-1.62)	NS	A,FT,PY,S,SC
				Val/Val	0.89 (0.38-2.11)	NS	A,FT,S
					0.98 (0.41-2.38)	NS	A,FT,PY,S,SC
4	Zhang[g] (Various)	2008	1746/1746	Ala/Val	1.05 (0.84-1.32)	NS	None
				Val/Val	1.16 (0.91-1.47)	NS	None
				All Val allele	1.07 (0.86-1.33)	NS	None
Lys939Glnh							
1	Hu (China)	2005	320/322	Lys/Gln	1.13 (0.82-1.58)	NS	None
					1.20 (0.85-1.70)	NS	A,PY,S
				Gln/Gln	1.54 (0.90-2.64)	NS	None
					1.28 (0.72-2.28)	NS	A,PY,S
				All Gln allele	1.20 (0.88-1.64)	NS	None
					1.21 (0.87-1.69)	NS	A,PY,S
2	Lee (South Korea)	2005	431/431	Lys/Gln	0.74 (0.55-1.00)	p=0.05	A,PY,S
				Gln/Gln	0.97 (0.63-1.48)	NS	A,PY,S
10	Shen (China)	2005	114/105	Lys/Gln	0.78 (0.44-1.38)	NS	A,FT,S
					0.67 (0.37-1.23)	NS	A,FT,PY,S,SC
				Gln/Gln	2.45 (0.96-6.21)	NS	A,FT,S
					2.22 (0.86-5.74)	NS	A,FT,PY,S,SC
6	Bai (China)	2007	992/991	Lys/Gln	1.01 (0.83-1.22)	NS	A,FHC,PY,RA,S
				Gln/Gln	1.17 (0.88-1.56)	NS	A,FHC,PY,RA,S
				All Gln allele	1.04 (0.87-1.25)	NS	A,FHC,PY,RA,S
3	Raasch (Denmark)	2008	427/789	Lys/Gln	0.91 (0.65-1.28)	NS	SD,SI,SS
				Gln/Gln	1.41 (0.87-2.30)	NS	SD,SI,SS
PAT+/-i							
9	Wang (China)	2003	597/509	+/-	0.85 (0.66-1.09)	NS	None
					0.85 (0.65-1.10)	NS	No details given
				+/+	0.82 (0.55-1.21)	NS	None
					0.73 (0.48-1.09)	NS	No details given
11	Lopez-Cima (Spain)	2007	516/533	+/-	1.08 (0.79-1.47)	NS	A,PY,S
				+/+	1.28 (0.85-1.92)	NS	A,PY,S
4	Zhang[g] (Various)	2008	901/896	+/-	0.99 (0.69-1.41)	NS	None
				+/+	1.24 (0.94-1.65)	NS	None
				All + allele	1.09 (0.71-1.66)	NS	None
IVS11-5C→Aj							
2	Lee (South Korea)	2005	432/431	C/A	0.78 (0.58-1.05)	NS	A,PY,S
				A/A	0.90 (0.52-1.58)	NS	A,PY,S

12413C→Gj							
6	Bai (China)	2007	936/933	C/G	1.14 (0.88-1.48)	NS	A,FHC,PY,RA,S
				G/G	0.90 (0.54-1.50)	NS	A,FHC,PY,RA,S
				All G allele	1.09 (0.86-1.39)	NS	A,FHC,PY,RA,S
+315C→Gj							
10	Shen (China)	2005	109/107	C/G	0.91 (0.52-1.58)	NS	A,FT,S
					0.90 (0.51-1.58)	NS	A,FT,PY,S,SC
				G/G	0.58 (0.18-1.93)	NS	A,FT,S
					0.56 (0.16-1.91)	NS	A,FT,PY,S,SC

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, FHC = family history of cancer, FT = fuel type, PY = pack-years of smoking, RA = residential area, S = sex, SC = smoky coal use, SD = smoking duration, SI = smoking intensity, SS = smoking status
e Using G/G individuals as the reference group
f Using Ala/Ala individuals as the reference group
g Meta-analysis
h Using Lys/Lys individuals as the reference group
i Using -/- individuals as the reference group
j Using C/C individuals as the reference group

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

Genotype	No. of studies[a]	Heterogeneity Chisquared, p	Odds ratio (95% confidence interval) Fixed effects model	Random effects model	Notes
-371G→A					
G/A	2	1.50, NS	0.89 (0.76-1.04)	0.90 (0.73-1.10)	
A/A	2	3.53, NS	0.93 (0.68-1.27)	1.02 (0.54-1.94)	
-271G→C					
All C allele	2	3.20, NS	1.39 (1.05-1.83)	1.47 (0.87-2.48)	
Ala499Val					
Ala/Val	2	0.29, NS	1.03 (0.83-1.27)	1.03 (0.83-1.27)	Least adjusted
	2	0.21, NS	1.03 (0.84-1.27)	1.03 (0.84-1.27)	Most adjusted
Val/Val	2	0.34, NS	1.14 (0.90-1.43)	1.14 (0.90-1.43)	Least adjusted
	2	0.13, NS	1.15 (0.91-1.45)	1.15 (0.91-1.45)	Most adjusted
Lys939Gln					
Lys/Gln	5	4.65, NS	0.94 (0.83-1.07)	0.94 (0.81-1.08)	Least adjusted
	5	6.16, NS	0.94 (0.83-1.07)	0.93 (0.78-1.10)	Most adjusted
	4	4.60, NS	0.95 (0.82-1.09)	0.93 (0.77-1.13)	Asian studies, least adjusted
	4	6.11, NS	0.95 (0.82-1.09)	0.92 (0.73-1.16)	Asian studies, most adjusted
Gln/Gln	5	4.36, NS	1.24 (1.02-1.51)	1.25 (1.02-1.54)	Least adjusted
	5	3.07, NS	1.20 (0.99-1.46)	1.20 (0.99-1.46)	Most adjusted
	4	4.05, NS	1.21 (0.98-1.50)	1.24 (0.95-1.62)	Asian studies, least adjusted
	4	2.58, NS	1.17 (0.94-1.45)	1.17 (0.94-1.45)	Asian studies, most adjusted
All Gln allele	2	0.61, NS	1.08 (0.92-1.26)	1.08 (0.92-1.26)	Least adjusted
	2	0.62, NS	1.08 (0.92-1.26)	1.08 (0.92-1.26)	Most adjusted
PAT+/-					
+/-	3	1.46, NS	0.95 (0.80-1.12)	0.95 (0.80-1.12)	Least adjusted
	3	1.39, NS	0.95 (0.80-1.13)	0.95 (0.80-1.13)	Most adjusted
	3[b]	0.37, NS	1.15 (0.93-1.42)	1.15 (0.93-1.42)	Caucasian studies
	2[b]	0.41, NS	0.81 (0.67-0.97)	0.81 (0.67-0.97)	Asian studies, least adjusted
	2[b]	0.39, NS	0.80 (0.66-0.98)	0.80 (0.66-0.98)	Asian studies, most adjusted
+/+	3	3.32, NS	1.12 (0.92-1.37)	1.11 (0.85-1.45)	Least adjusted
	3	5.07, NS	1.10 (0.90-1.35)	1.07 (0.77-1.49)	Most adjusted
	3[b]	3.00, NS	1.35 (1.02-1.78)	1.31 (0.92-1.88)	Caucasian studies
	2[b]	0.18, NS	0.87 (0.65-1.16)	0.87 (0.65-1.16)	Asian studies, least adjusted
	2[b]	0.66, NS	0.82 (0.61-1.10)	0.82 (0.61-1.10)	Asian studies, most adjusted

a Number of studies does not always add up as the published meta-analysis[4] included data for both Caucasian and Asian populations

b ORs for individual studies originally included in meta-analysis by Zhang et al[4] calculated from data given and then meta-analysed

NS $p \geq 0.05$

Table 3: Prevalence of genotypes of XPC polymorphisms

Polymorphism/ population	No. of cases	Prevalence of genotypes[a]			No. of controls	Prevalence of genotypes[a]		
-449G→C		**G/G**	**G/C**	**C/C**		**G/G**	**G/C**	**C/C**
Total	432	238	171	23	431	223	179	29
		(55.1)	(39.6)	(5.3)		(51.7)	(41.5)	(6.7)
-371G→A		**G/G**	**G/A**	**A/A**		**G/G**	**G/A**	**A/A**
Total	1399	777	529	92	1416	755	570	92
		(55.5)	(37.8)	(6.6)		(53.3)	(40.3)	(6.5)
-27G→C		**G/G**	**G/C**	**C/C**		**G/G**	**G/C**	**C/C**
Total	1421	1288	131	2	1424	1325	93	6
		(90.6)	(9.2)	(0.1)		(93.0)	(6.5)	(0.4)
Ala499Val		**Ala/Ala**	**Ala/Val**	**Val/Val**		**Ala/Ala**	**Ala/Val**	**Val/Val**
Total	1862	852	837	173	1856	868	835	151
		(45.8)	(45.0)	(9.3)		(46.8)	(45.0)	(8.1)
Lys939Gln		**Lys/Lys**	**Lys/Gln**	**Gln/Gln**		**Lys/Lys**	**Lys/Gln**	**Gln/Gln**
Total	2289	900	1062	322	2646	1025	1279	334
		(39.3)	(46.4)	(14.1)		(38.7)	(48.3)	(12.6)
Caucasian	427	159	195	73	789	305	388	96
		(37.2)	(45.7)	(17.1)		(38.7)	(49.2)	(12.2)
Asian	1862	741	867	249	1857	720	891	238
		(39.8)	(46.6)	(13.4)		(38.8)	(48.0)	(12.8)
PAT+/-		**-/-**	**+/-**	**+/+**		**-/-**	**+/-**	**+/+**
Total	2014	760	935	319	1938	717	943	278
		(37.7)	(46.4)	(15.8)		(37.0)	(48.7)	(14.3)
Caucasian	985	317	477	191	997	357	482	158
		(32.2)	(48.4)	(19.4)		(35.8)	(48.3)	(15.8)
Asian	1029	443	458	128	941	360	461	120
		(43.1)	(44.5)	(12.4)		(38.3)	(49.0)	(12.8)
IVSS11-5C→A		**C/C**	**C/A**	**A/A**		**C/C**	**C/A**	**A/A**
Total	431	167	202	62	432	152	222	58
		(38.7)	(46.9)	(14.4)		(35.2)	(51.4)	(13.4)
12413C→G		**C/C**	**C/G**	**G/G**		**C/C**	**C/G**	**G/G**
Total	936	756	149	31	933	768	130	35
		(80.8)	(15.9)	(3.3)		(82.3)	(14.0)	(3.7)
+315C→G		**C/C**	**C/G**	**G/G**		**C/C**	**C/G**	**G/G**
Total	109	52	52	5	107	47	52	8
		(47.7)	(47.7)	(4.6)		(43.9)	(48.6)	(7.5)

a Number (percent)

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

Ref.	Author (year[a])	Smoking variable	Genotype	Odds ratios[b]	Adjustment factors[c]
-371G→Ad					
6	Bai (2007)[e]	Non-smokers	All A allele	0.74 (0.55-0.99)	A,FHC,RA,S
		Smokers	All A allele	0.90 (0.71-1.13)	A,FHC,PY,RA,S
		<30 pack-years	All A allele	0.88 (0.61-1.25)	A,FHC,RA,S
		≥30 pack-years	All A allele	0.91 (0.66-1.24)	A,FHC,RA,S
Ala499Valf					
1	Hu (2005)[e,g]	Never smokers	All Val allele	1.52 (0.99-2.35)	A,S
		Ever smokers	Ala/Ala	3.22 (1.89-5.50)	A,S
			All Val allele	5.06 (3.06-8.37)	A,S
Lys939Glnh					
1	Hu (2005)[g]	Never smokers	All Gln allele	1.37 (0.89-2.13)	A,S
		Ever smokers	Lys/Lys	3.68 (2.16-6.27)[i]	A,S
			All Gln allele	4.16 (2.51-6.89)[i]	A,S
					A,S
3	Raasch (2008)	Duration (per 5 years)	Lys/Lys	1.59 (1.37-1.84)	IF,IV,SI,SS
			Lys/Gln	1.46 (1.30-1.63)	IF,IV,SI,SS
			Gln/Gln	1.53 (1.26-1.85)	IF,IV,SI,SS
		≤20g/day (per 5g/day)	Lys/Lys	2.21 (1.59-3.07)	IF,IV,SD,SS
			Lys/Gln	1.73 (1.31-2.29)	IF,IV,SD,SS
			Gln/Gln	1.88 (1.26-2.81)	IF,IV,SD,SS
		>20g/day (per 5g/day)	Lys/Lys	0.87 (0.70-1.08)	IF,IV,SD,SS
			Lys/Gln	1.12 (0.83-1.50)	IF,IV,SD,SS
			Gln/Gln	1.22 (0.87-1.72)	IF,IV,SD,SS
PAT+/-j					
5	Marin (2004)[e]	Never smokers	+/-	0.81 (0.28-2.31)	A,FHC,HT,S
			+/+	1.59 (0.37-6.81)	A,FHC,HT,S
		Ever smokers	+/-	1.12 (0.77-1.62)	A,FHC,HT,S
			+/+	1.69 (1.04-2.75)	A,FHC,HT,S
		Former smokers	+/-	0.85 (0.51-1.42)	A,FHC,HT,S
			+/+	2.15 (1.07-4.31)	A,FHC,HT,S
		Current smokers	+/-	1.40 (0.80-2.46)	A,FHC,HT,S
			+/+	1.26 (0.62-2.54)	A,FHC,HT,S
11	Lopez-Cima (2007)	ETS exposed	+/-	1.03 (0.41-2.55)	A,S
			+/+	1.05 (0.31-3.51)	A,S
		Ever smokers	+/-	1.02 (0.75-1.37)	A,S
			+/+	1.40 (0.94-2.08)	A,S
		Former smokers	+/-	0.86 (0.57-1.30)	A,S
			+/+	1.59 (0.90-2.82)	A,S
		Current smokers	+/-	1.14 (0.71-1.81)	A,S
			+/+	1.06 (0.59-1.92)	A,S
		Light smokers	+/-	0.59 (0.21-1.69)	A,S
			+/+	1.24 (0.31-5.05)	A,S
		Moderate smokers	+/-	1.12 (0.71-1.77)	A,S
			+/+	1.29 (0.73-2.28)	A,S
		Heavy smokers	+/-	1.19 (0.70-2.03)	A,S
			+/+	1.40 (0.66-3.00)	A,S

a Year of publication
b 95% confidence interval shown in brackets where available
c Abbreviations used for confounders:
A = age, FHC = family history of cancer, HT = histological type of cancer, IF = intake of fruit, IV = intake of vegetables, PY = pack-years of smoking, RA = residential area, S = sex, SD = smoking duration, SS = smoking status
d Using G/G individuals as the reference group
e Originally included in the published meta-analysis[4]
f Using Ala/Ala never smokers as the reference group
g Data came from reference[12]
h Using Lys/Lys individuals as the reference group
i Using Lys/Lys never smokers as the reference group
j Using -/- individuals as the reference group

References

1. Hu Z, Wang Y, Wang X, Liang G, Miao X, Xu Y, *et al*. DNA repair gene *XPC* genotypes/haplotypes and risk of lung cancer in a Chinese population. *Int J Cancer* 2005;**115**:478-83.

2. Lee GY, Jang J-S, Lee SY, Jeon H-S, Kim KM, Choi JE, *et al*. *XPC* polymorphisms and lung cancer risk. *Int J Cancer* 2005;**115**:807-13.

3. Raaschou-Nielsen O, Sørensen M, Overvad K, Tjønneland A, Vogel U. Polymorphisms in nucleotide excision repair genes, smoking and intake of fruit and vegetables in relation to lung cancer. *Lung Cancer* 2008;**59**:171-9.

4. Zhang D, Chen C, Fu X, Gu S, Mao Y, Xie Y, *et al*. A meta-analysis of DNA repair gene XPC polymorphisms and cancer risk. *J Hum Genet* 2008;**53**:18-33.

5. Marín MS, López-Cima MF, García-Castro L, Pascual T, Marrón MG, Tardón A. Poly (AT) polymorphism in intron 11 of the *XPC* DNA repair gene enhances the risk of lung cancer. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1788-93.

6. Bai Y, Xu L, Yang X, Hu Z, Yuan J, Wang F, *et al*. Sequence variations in DNA repair gene *XPC* is associated with lung cancer risk in a Chinese population: a case-control study. *BMC Cancer* 2007;**7**:81.

7. Vogel U, Overvad K, Wallin H, Tjønneland A, Nexø BA, Raaschou-Nielsen O. Combinations of polymorphisms in *XPD, XPC* and *XPA* in relation to risk of lung cancer. *Cancer Lett* 2005;**222**:67-74.

8. De Ruyck K, Szaumkessel M, De R, I, Dehoorne A, Vral A, Claes K, *et al*. Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. *Mutat Res* 2007;**631**:101-10.

9. Wang YG, Xing DY, Tan W, Wang LJ, Tang PZ, Lin DX. (Poly(AT) polymorphism in DNA repair gene XPC and lung cancer risk). *Zhonghua Zhong Liu Za Zhi* 2003;**25**:555-7.

10. Shen M, Berndt SI, Rothman N, Demarini DM, Mumford JL, He X, *et al*. Polymorphisms in the DNA nucleotide excision repair genes and lung cancer risk in Xuan Wei, China. *Int J Cancer* 2005;**116**:768-73.

11. López-Cima MF, González-Arriaga P, García-Castro L, Pascual T, Marrón MG, Puente XS, *et al*. Polymorphisms in *XPC*, *XPD*, *XRCC1*, and *XRCC3* DNA repair genes and lung cancer risk in a population of northern Spain. *BMC Cancer* 2007;**7**:162.

12. Hu Z, Wang Y, Ma H, Tan W, Niu J, Lin D, *et al*. (Association of two exonic genetic polymorphisms in the DNA repair gene *XPC* with risk of lung cancer in Chinese population). *Chin J Med Genet* 2005;**22**:415-8.