The association of XPD with lung cancer

Author: A. J. Thornton

Date: 18th August 2008

1. Objectives

XPD, also known as excision repair cross complementing group 2, is one of seven genetic complementation groups encoding for proteins involved in the nucleotide excision repair pathway and in basal transcription[1]. It functions as an evolutionary conserved ATP-dependent helicase within the transcription repair factor complex, TFIIH[1-4], and participates in the unwinding of DNA at the site of a lesion[3-5]. As TFIIH is required for all transcription by RNA polymerase II, XPD is considered as an essential gene, and inactivation leads to embryonic lethality in mice[1]. Mutations in the XPD gene also cause three severe syndromes in humans: Cockayne's syndrome, trichotiodystrophy, and xeroderma pigmentosum, in which the risk of sun-induced skin cancer is increased more than 1000-fold[3,6]. Several single nucleotide polymorphisms have also been described in the XPD gene[2-6], although it is unclear as to whether these have functional effects[2,3,6].

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

Twenty-eight 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 XPD in relation to lung cancer

4.1 Introduction

One relevant meta-analysis was available, and the results of this are summarized below. In addition, 12 papers that were not included in this meta-analysis were found relating to studies in which polymorphisms in the XPD 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 XPD gene between lung cancer patients and control subjects

4.2.1 *Meta-analysis*

A meta-analysis published in 2007[7] included results from 15 studies[1,2,6,8-19] that examined polymorphisms in the XPD 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 gave information on polymorphisms that were not included in the meta-analyses. Eleven studies provided data on the Asp312Asn polymorphism and risk estimates were based on 4110 cases and 5305 controls. Using Asp/Asp individuals as the reference

group, odds ratios of 0.95 (95% CI 0.84-1.07) and 1.14 (95% CI 0.95-1.37) were estimated for the risk of lung cancer for the genotypes Asp/Asn and Asn/Asn respectively based on a random effects model. There was no significant heterogeneity between the studies used to produce these estimates.

Information on the Lys751Gln polymorphism was available from 14 studies, and included 5004 cases and 6478 controls. For subjects who were Lys/Gln for this polymorphism, the risk of lung cancer was estimated at 1.06 (95% CI 0.97-1.16). The odds ratio for subjects who were Gln/Gln was estimated at 1.30 (95% CI 1.13-1.49). Again, these estimates were obtained using a random effects model, but there was no significant heterogeneity between the studies on which they were based.

4.2.2 *Additional individual studies*

In a study conducted in the USA[20], 150 lung cancer cases and 51 normal controls were screened for the Lys751Gln polymorphism using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. No further details of the study subjects were given. There was no significant difference in the frequency of the variant allele in the cases (0.34) and controls (0.35), but there was a significantly increased risk of lung cancer among smokers with the variant allele (OR2.1, 95% CI 1.1-4.1).

The case group in a study carried out in the USA[21] consisted of 32 Mexican Americans and 29 African Americans with lung cancer, while the control group was made up of 25 Mexican Americans and 20 African Americans, matched to the cases for age, sex, ethnicity and smoking. Information on Caucasian cases and controls was also collected, but these appear to have been included in a later study[1]. No further details of the age and sex distribution of the study subjects was given. The risk of lung cancer in subjects with the Gln allele was increased in African Americans (OR 3.0, 95% CI 1.7-12.5), but there was no observed association in Mexican Americans (OR 1.0, 95% CI 0.3-3.7).

A study carried out in the USA[22] examined polymorphisms in the XPD gene in 109 lung cancer patients and 269 controls without lung disease. The mean age of the entire case group, which also included 164 cases of head and neck squamous cell carcinoma, was 62.6 years compared to 59.9 years in the controls. The proportion of men varied significantly between the two groups, comprising 64.8% of the cases and 44.3% of the controls ($p< 0.001$). DNA was isolated from whole blood samples and the XPD gene screened for polymorphisms using TaqMan allele discrimination assays. For the Lys751Gln polymorphism, the frequency of the Lys/Lys, Lys/Gln and Gln/Gln genotypes was 56.88%, 31.23% and 11.89% respectively in the control group and 38.10%, 45.78% and 16.12% respectively in the entire case series. Subjects with at least one variant allele of this polymorphism had an increased risk of lung cancer compared to controls (OR 2.05, 95% CI 1.24-3.28).

The frequencies of the genotypes of the Asp312Asn polymorphism were 53.92%, 37.74% and 8.34% for the Asp/Asp, Asp/Asn and Asn/Asn respectively in the controls, and 43.14%, 45.59% and 11.27% in the entire case series. The unadjusted ORs for upper aerodigestive tract cancer were estimated at 1.5 (95% CI 0.9-2.2) for Asp/Asn subjects and 1.7 (95% CI 0.85-3.4) for Asn/Asn subjects, compared to Asp homozygotes. The OR for all subjects with the Asn allele was estimated at 1.3 (95% CI 1.0-1.8), adjusted for age and smoking status.

The cases in a study conducted in China[23] consisted of newly diagnosed primary lung cancer patients, while the control group was made up of non-cancer patients admitted to the bone wards in the same region. Cases and controls were matched for age, sex and ethnicity. Each subject gave a peripheral blood sample from which genomic DNA was extracted and polymorphisms in the XPD gene were detected using a modified PCR-RFLP method. Analysis of the Arg156Arg polymorphism was based on 149 cases and 137 controls, who had a mean age of 58 years and 57 years respectively. The proportion of men was 69.13% in the cases and 71.53% in the controls. The frequency of the C/C, A/C and A/A genotypes was 25.50%, 51.68% and

22.82% respectively in the cases, and 28.47%, 47.45% and 24.09% respectively in the controls. Compared to C/C individuals, the unadjusted ORs for lung cancer risk were estimated at 1.22 (95% CI 0.70-2.12) for A/C subjects, 1.06 (95% CI 0.55-2.04) for A/A homozygotes, and 1.16 (95% CI 0.69-1.96) for all subjects with the A allele. Adjustment for smoking duration reduced these estimates to 1.12 (95% CI 0.63-1.97), 1.04 (95% CI 0.75-1.44) and 1.06 (95% CI 0.82-1.38) respectively.

Analysis of the Lys751Gln polymorphism was based on 147 cases and 145 controls[24]. The mean age of the two groups was the same as for the previous polymorphism, while the proportion of men was approximately 70% in both groups. Lys/Lys homozygotes comprised 87.76% of the case group and 95.17% of the controls, with Lys/Gln individuals making up the rest of both groups. No Gln homozygotes were found. The risk of lung cancer in Lys/Gln subjects was estimated at 2.75(95% CI 1.11-6.80), which was increased to 2.78 (95% CI 1.12-6.93) after adjustment for duration of smoking.

Information relating to the Asp312Asn polymorphism in this study was based on 201 cases and 171 controls[25]. The mean ages of the two groups remained unchanged, but the proportion of men was 70.1% in the cases and 73.7% in the controls. Only one case had the Asp/Asn genotype while one control was an Asn homozygote. The remaining study subjects were all Asp/Asp. The risk of lung cancer for all subjects with the Asn allele was estimated at 0.85 (95% CI 0.53-13.7), which was reduced to 0.68 (95% CI 0.20-2.36) after adjustment for smoking duration.

The case group in a study conducted in China[3] consisted of 1299 subjects with histopathologically confirmed lung cancer, while the control group was made up of 1011 patients with diseases other than cancer recruited from other clinics of the study hospital. Controls were matched to the cases for age, sex and residential area. Details of the age and sex distribution of the study subjects were not given, but it was stated that no significant differences existed in this respect between the cases and the controls. A venous blood sample was collected from each participant and Taqman assay was used to

determine polymorphisms in the XPD gene. The frequency of the A/A, A/G and G/G genotypes of the +282A>G polymorphism was 18.2%, 50.5% and 31.4% respectively in the cases and 20.2%, 49.5% and 30.3% respectively in the controls. Compared to A/A individuals, the odds ratios for the risk of lung cancer, adjusted for age, sex, pack-years of smoking and family history of cancer, were estimated at 1.10 (95% CI 0.86-1.40) for A/G subjects, 1.15 (95% CI 0.89-1.51) for G homozygotes, and 1.12 (95% CI 0.89-1.41) for all subjects with the G allele.

When the +58C>T polymorphism was examined, the frequency of the C/C, C/T and T/T genotypes was 87.5%, 12.1% and 0.4% respectively in the case group and 89.0%, 11.0% and 0.1% respectively in the controls. Using C/C subjects as a reference, the risk of lung cancer was increased in individuals with the C/T genotype (OR 1.12, 95% CI 0.84-1.49), T/T homozygotes (OR 6.18, 95% CI 0.68-56.5), and all subjects with the T allele (OR 1.16, 95% CI 0.87-1.54).

For the Asp312Asn polymorphism, the Asp/Asp genotype was found in 87.6% of the cases and 88.6% of the controls, with Asp/Asn and Asn/Asn subjects making up 12.0% and 0.4% of the case group respectively, and 11.3% and 0.1% of the controls respectively. Adjusted odds ratios of 1.06 (95% CI 0.80-1.41), 6.13 (95% CI 0.67-56.1) and 1.10 (95% CI 0.83-1.46) were estimated for the risk of lung cancer in subjects with the Asp/Asn and Asn/Asn genotypes, and all subjects with the Asn allele respectively, compared to Asp homozygotes.

Subjects with the AAAA/AAAA genotype of the polymorphism at rs3916823 made up 75.5% of the case group and 76.0% of the controls. AAAA/- subjects comprised 22.8% of cases and 23.0% of controls, while 1.7% of the cases and 1.0% of the controls had the -/- genotype. Compared to AAAA homozygotes, there was no real increased risk of lung cancer in AAAA/- subjects (OR 1.01, 95% CI 0.81-1.25). However, the estimate for -/- individuals was somewhat higher, at 1.88 (95% CI 0.84-4.21). The odds ratio for all subjects with the - allele was estimated at 1.04 (95% CI 0.84-1.29).

Finally, the Lys751Gln polymorphism was examined, and the Lys/Lys, Lys/Gln and Gln/Gln genotypes were found in 84.8%, 14.5% and 0.7% of the cases respectively. The corresponding values for the control group were 86.8%, 12.7% and 0.5% respectively. Compared to Lys/Lys individuals, lung cancer risk was increased in all the other genotypes, with adjusted odds ratios of 1.16 (95% CI 0.89-1.51), 1.64 (95% CI 0.50-5.36) and 1.18 (95% CI 0.91-1.53) being estimated for the Lys/Gln and Gln/Gln genotypes, and for all subjects with the Gln allele respectively.

A study carried out in Belgium[26] examined polymorphisms in the XPD gene in 110 patients with newly diagnosed histologically confirmed primary lung cancer and 110 age and sex-matched controls, selected from hospital patients and attendees at senior clubs with no history of cancer. The mean age of the cases was 62 years compared to 61 years in the controls, while the proportion of men varied from 78.2% in the cases to 73.6% in the controls. A heparinized blood sample was taken from each study participant and lymphocytes were isolated and frozen for genotyping. Polymorphic sites in the XPD gene were then examined by PCR-RFLP analysis. For the Asp312Asn polymorphism, the frequency of the Asp/Asp, Asp/Asn and Asn/Asn genotypes was 40.0%, 48.2% and 11.8% respectively in the cases, and 45.0%, 42.4% and 12.8% respectively in the controls. Unadjusted ORs of 1.28 (995% CI 0.73-2.26) and 1.03 (95% CI 0.44-2.44) were estimated for the risk of lung cancer in subjects with the Asp/Asn and Asn/Asn genotypes respectively, compared to Asp homozygotes. Adjustment for age, sex and pack-years of smoking reduced these to 1.25 (95% CI 0.67-2.34) for Asp/Asn individuals, and 0.96 (95% CI 0.37-2.48) for Asn homozygotes.

When the Lys751Gln polymorphism was examined, subjects with the Lys/Lys genotype made up 38.2% of the case group and 41.3% of the controls. Lys/Gln individuals comprised 48.2% of the cases and 48.6% of the controls and Gln homozygotes made up the remaining 13.6% of cases and 10.1% of controls. Compared to Lys/Lys subjects, the risk of lung cancer was estimated at 1.07 (95% CI 0.61-1.89) in Lys/Gln individuals and 1.46 (95% CI 0.60-

3.54) in Gln homozygotes. Adjustment reduced the estimate for Lys/Gln subjects markedly, to 0.89 (95% CI 0.47-1.66), but increased that for Gln/Gln individuals, to 1.53 (95% CI 0.56-4.09).

In a study carried out in Spain[27], 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 XPD polymorphisms. The frequency of the Asp/Asp, Asp/Asn and Asn/Asn genotypes of the Asp312Asn polymorphism was 46.5%, 42.8% and 10.7% respectively in the case group and 48.8%, 43.1% and 8.1% respectively in the controls. Compared to Asp/Asp subjects, the odds ratio for the risk of lung cancer, adjusted for age, sex and pack-years of smoking, was estimated at 1.01 (95% CI 0.76-1.35) for subjects with the Asp/Asn genotype, and 1.52 (95% CI 0.91-2.51) for Asn homozygotes.

For the Lys751Gln polymorphism, the frequency of the Lys/Lys, Lys/Gln and Gln/Gln genotypes was 43.0%, 45.9% and 11.1% respectively in the cases and 45.6%, 45.0% and 9.4% respectively in the controls. Using the Lys/Lys group as a reference, the risk of lung cancer was estimated at 1.12 (95% CI 0.84-1.50) in Lys/Gln subjects and 1.38 (95% CI 0.85-2.25) in Gln homozygotes, after adjustment.

Participants in a study conducted in India[5] consisted of 211 lung cancer patients and 211 healthy controls. The mean age of the cases was 57.82 years, compared to 56.21 years in the controls, while the proportion of men varied from 86.3% in the case group to 87.2% in the controls. Each participant provided a blood sample, from which genomic DNA was isolated and PCR-RFLP used to identify XPD polymorphisms. The frequency of the Lys/Lys, Lys/Gln and Gln/Gln genotypes of the Lys751Gln polymorphism was 51.7%,

42.2% and 6.2% respectively in the cases, and 65.9%, 28.9% and 5.2% 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 1.8 (95% CI 1.233-2.807) after adjustment for age, sex and smoking status. The odds ratio for Gln homozygotes was estimated at 1.5 (95% CI 0.650-3.495).

4.3 Summary of study characteristics of the additional individual studies

Of the eight individual studies that investigated polymorphisms in the XPD gene in relation to lung cancer risk, three were conducted in the USA, two were carried out in China, and one each was conducted in Belgium, India and Spain.

The largest study[3] was based on 1299 cases. One of the remaining studies[27] gave information on around 500 cases, two studies[5,25] included approximately 200 cases each, and three studies[20,22,26] were based on around 100 cases each. The smallest study[21] included just 61 cases.

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

In six of the studies both the case and control groups were of mixed sex, and were matched accordingly in four of the studies[3,23,26,27]. In one of these studies[3], no further details of the sex distribution of the study subjects was given, but it was stated that no significant differences existed between the cases and controls in this respect. In one of the studies[22] in which matching had not taken place, the proportion of men was significantly higher in the case group. In one further study[5], no matching had been carried out but the case and control groups appeared to be comparable for sex distribution. Two studies[20,21] did not give any information on the sex of the participants, although one of these studies[21] did state that the cases and controls had been matched for sex.

Five of the studies[3,21,23,26,27] matched the cases and controls for age. One of these studies[21] did not give any further details of the age of the study subjects, while another study[3] 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[22], there was no significant difference in the mean age of the controls compared to the entire case series, which included patients with head and neck cancer, but a mean age for lung cancer patients was not given. There was no significant difference in the age of the cases and controls in the other study[5] where matching on age had not been carried out. One study[20] did not give any information regarding the age of the study participants.

All of the studies appear to have included both smokers and non-smokers, although only one of them[21] matched the cases and controls for this aspect. In three studies[5,22,27] there were significantly more smokers in the case group, although in one of these studies[22] the case group was not restricted to lung cancer patients but also contained subjects with head and neck cancer. In another study[3], there were also more smokers in the case group than among the controls, although this was based on a subset of the study population, and the significance of the difference was not apparent. In addition, two studies[26,27] reported that there were significantly more heavy smokers among the cases, and one study[23] found that cases had smoked for a significantly longer duration than the controls. One study[20] failed to give any detailed information on the proportion of smokers in the case and control groups.

Six of the studies adjusted their results for at least some potential confounding factors. Five studies[3,5,22,26,27] adjusted for age and four studies[3,5,26,27] included sex as a potential confounder. Variables relating to smoking history were included by five studies[3,5,23,26,27]. In addition, one study[3] adjusted for family history of cancer. Two studies[20,21] failed to state whether adjustment for potential confounders had taken place during analysis.

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 XPD polymorphisms are presented in Tables 2 and 3 respectively. The results are discussed below for each polymorphism separately.

Arg156Arg

One study[17] reported that, compared to subjects with the A/A genotype, there was no association between the risk of lung cancer and the A/C genotype. Lung cancer risk was non-significantly reduced in subjects with both the C/C genotype, and in all subjects with the C allele. Using C homozygotes as the reference group, another study[23] found that lung cancer risk was non-significantly raised for both the A/C and A/A genotypes, and for all subjects with the A allele. As both these studies used a different reference group, it was not possible to combine the results in a meta-analysis.

His201Tyr

Compared to His homozygotes, one study[18] reported that the risk of lung cancer was non-significantly increased in subjects with the His/Tyr genotype of this polymorphism.

Asp312Asn

Using subjects with the Asp/Asp genotype as the reference group, three studies[3,26,27] reported a non-significantly increased risk of lung cancer in subjects with the Asp/Asn genotype, while another study[22] found a non-significantly increased risk of upper aerodigestive cancer for this genotype. One study[7], based on a meta-analysis of 11 studies, found a decreased risk of lung cancer in this genotype, which failed to reach statistical significance. When these results were combined in a meta-analysis, the overall estimate of the risk of lung cancer was 1.00 (0.91-1.11) using a fixed effects model, and 1.03 (95% CI 0.90-1.16) using a random effects model, including the least adjusted odds ratios where both unadjusted and adjusted were given. Substituting the most adjusted odds ratios made very little difference to these findings (fixed effects: OR 1.00, 95% CI 0.91-1.10; random effects: OR 1.02, 95% CI 0.90-1.15). When the analysis was restricted to the four studies carried out in Caucasian populations, the overall estimate of risk was much higher, at 1.13 (95% CI 0.99-1.29) for both the fixed and random effects models, and based on both least adjusted and most adjusted odds ratios. Conversely, the

estimate for Asian populations was close to that for the overall dataset, at 1.00 (95% CI 0.83-1.21) for both the fixed and random effects models.

For Asn/Asn subjects, four studies[3,7,26,27] found a non-significantly raised odds ratio for the risk of lung cancer, and one study[22] reported a non-significant increase in the risk of upper aerodigestive tract cancer. No reduced odds ratios were reported. Meta-analysis of these results produced an overall estimate of the risk of lung cancer of 1.21 (95% CI 1.03-1.42) using the fixed effects model, and 1.03 (95% CI 0.83-1.27) from the random effects model, using the least adjusted odds ratios where applicable. Substituting the most adjusted odds ratios made little difference to the estimate from the fixed effects model (OR 1.21, 95% CI 1.02-1.42), but markedly increased that from the random effects model (OR 1.25, 95% CI 1.01-1.54). When the analysis was restricted to studies in Caucasian populations, the odds ratio was estimated at 1.17 (95% CI 1.01-1.36) for both the fixed and random effects models, and using the most adjusted odds ratios where available made no difference to this result.

Two studies reported on the risk of lung cancer in all subjects with the Asn allele, with one study[3] finding a non-significantly increased risk, and the other[25] reporting a decreased risk, which failed to reach statistical significance. In addition, one study[22] found a significantly increased risk of upper aerodigestive tract cancer for these individuals. Meta-analysis, based on the least adjusted odds ratios where applicable, produced an overall estimate of the risk of lung cancer of 1.19 (95% CI 0.97-1.45) for both the fixed and random effects models. Full adjustment reduced this slightly, to 1.17 (95% CI 0.96-1.44) for both models. The overall risk from the studies carried out in Asian populations was somewhat lower than that for the overall dataset, at 1.09 (95% CI 0.83-1.44) for both models using the least adjusted odds ratios, and 1.07 (95% CI 0.82-1.41) for both models when the most adjusted odds ratios were substituted.

The Asp allele of this polymorphism was present in about 40% of the total population, with Asp homozygotes making up just under 9% of both the

case and control groups. However, this allele was far more common in Caucasians than in Asians, occurring in nearly 60% of the former group compared to about 11% in the latter population. Asp/Asp subjects were particularly rare in Asians, making up just 0.7% of cases and 0.1% of controls.

Lys751Gln

Compared to Lys homozygotes, subjects with the Lys/Gln genotype were reported to have a higher risk of lung cancer by six studies[3,5,7,24,26,27], which reached statistical significance in two studies[5,24]. One of these estimates[7] was based on a meta-analysis of 14 studies. After adjustment for potential confounders, the odds ratio estimated from one of these studies[26] was below 1.00. Meta-analysis of the available odds ratios, using the least adjusted results where applicable, produced an overall estimate of lung cancer risk of 1.10 (95% CI 1.02-1.19) for the fixed effects model and 1.21 (95% CI 1.01-1.45) for the random effects model. Substitution of the most adjusted odds ratios available from the studies made no difference to the fixed effects result, but reduced the random effects model estimate slightly, and removed its significance (OR 1.20, 95% CI 0.996-1.45). The estimates from analyses restricted to Caucasian subjects were similar to those for the entire dataset, at 1.11 (95% CI 1.01-1.23) for both models using the least adjusted odds ratios, and 1.11 (95% CI 1.00-1.22) for both models when fully adjusted odds ratios were used. When analyses were restricted to Asian subjects, the odds ratio for the fixed effects model was 1.10 (95% CI 1.01-1.20), while that for the random effects model was 1.32 (95% CI 0.995-1.75), and there was significant heterogeneity between the studies on which these estimates were based (p=0.017). Full adjustment did not alter these results.

For Gln homozygotes, all five of the studies[3,5,7,26,27] that examined lung cancer risk in these subjects reported an increased risk of lung cancer, which reached statistical significance in one study[7]. No reduced odds ratios were reported. Meta-analysis of these odds ratios produced an overall risk estimate of 1.32 (95% CI 1.16-1.50) for both the fixed and random effects models, using least adjusted odds ratios where applicable. Substituting the most adjusted odds ratios did not make any difference to these results. Using the

least adjusted odds ratios where both unadjusted and adjusted were available, and restricting the analysis to studies undertaken in Caucasian populations produced an overall estimate of the risk of lung cancer of 1.54 (95% CI 1.05-2.26) for both the fixed and random effects models, which was increased to 1.56 (95% CI 1.06-2.29) when fully adjusted odds ratios were used. The overall risk from Asian studies was also higher than that for the full dataset, at 1.45 (95% CI 0.77-2.74) for both models.

Four studies examined the risk of lung cancer in all subjects with the Gln allele, and three of these[3,21,22] reported an increased incidence of the disease, which reached statistical significance in one study[22]. The fourth study[20] failed to find any association between the Gln allele and lung cancer risk. Meta-analysis produced an overall risk of lung cancer of 1.35 (95% CI 1.08-1.68) using the fixed effects model, and 1.50 (95% CI 0.99-2.26) for the random effects model.

Approximately 45% of the total population carried the Gln allele of this polymorphism, with Gln homozygotes comprising about 10% of subjects. However, there was a significant difference in the occurrence of this allele according to ethnicity. In Caucasian subjects, the Gln allele was found in about 60% of subjects, with Gln/Gln individuals making up approximately 15% of the case and control groups. The Gln allele was much rarer in Asians, being found in only about 20% of the population, with Gln homozygotes accounting for less than 2% of both the case and control groups.

-70C>T

One study[17] found that compared to subjects with the C/C genotype, the risk of lung cancer in individuals with the C/T genotype, and in all subjects with the T allele, was reduced, significantly so for this latter genotype. After more careful adjustment, the odds ratio estimated for the C/T genotype also became statistically significant.

+282A>G

Using A/A subjects as a reference group, one study[3] reported that the risk of lung cancer was non-significantly increased in individuals with the A/G and G/G genotypes, and in all subjects with the G allele.

+58C>T

The one study[3] that examined this polymorphism found that, compared to C homozygotes, the risk of lung cancer was non-significantly increased for both the C/T and T/T genotypes, and for all subjects with the T allele.

rs3916823

Compared to AAAA homozygotes, one study[3] reported that the risk of lung cancer in subjects with the -/- genotype, and in all subjects with the - allele, was non-significantly increased. There was no real association between lung cancer risk and the AAAA/- genotype.

4.5 <u>The effect of stratification by smoking status and intensity on risk of lung cancer according to XPD 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 Kiyohara et al[7] where applicable. Three studies[1,9,11] 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[23] presented results for all subjects with the A allele compared to C/C homozygotes. When the duration of smoking was examined, the odds ratios for smokers were lower than for never smokers, which was significantly raised, although there was no clear pattern of decreasing risk with increasing duration.

Asp312Asn

Compared to Asp/Asp never smokers, the risk of lung cancer was higher in smokers[6]. When intensity of smoking was examined, there was a clear pattern of increasing risk with amount smoked in two studies[6,12]. Another study[4] also reported an increase in risk with amount smoked per day, but this was less marked in those smoking >20g/day than in those smoking less than this amount per day. This study also found that the risk of lung cancer increased with duration of smoking. Using Asn/Asn subjects as a reference group, one study[8] reported higher odds ratios for smokers than for never smokers. Compared to all subjects with the Asn allele, the odds ratio for smokers of $\leq$34.5 pack-years in this study was higher than that for never smokers, while that for heavier smokers was lower than in those who had never smoked.

For Asp/Asn subjects, there was no clear pattern of increasing risk with smoking status, with the highest odds ratio being reported for ETS exposed never smokers[27]. When intensity of smoking was examined, one study[27] found that the risk of lung cancer decreased as the amount smoked per day increased, while another study[26] also reported lower odds ratios with higher pack-years of smoking. One study[4] found an increase in lung cancer risk per 5g tobacco smoked per day only in those smoking <20 g/day. Compared to Asp/Asp never smokers, one study[12] found a clear trend of increasing risk with increasing intensity of smoking. Another study[8] found that the risk of lung cancer increased in those smoking $\leq$ 34.5 pack-years compared to never smokers, although in this study Asn/Asn individuals were used as the reference group. Finally, one study[4] found a significant increase in risk per five years of smoking.

When the risk of lung cancer in Asn homozygotes was stratified by smoking status, it was found that the highest odds ratio was seen in ETS exposed never smokers, with those for ever, former and current smokers being comparable[27]. There was no clear pattern of increasing risk with increasing amount smoked in this study, although the highest odds ratio was seen for the heaviest smokers. Another study found that the heaviest smokers had a

decreased risk of lung cancer[26], while elsewhere the risk increased with every 5g tobacco smoked per day, but only in those smoking ≤20 g/day[4]. Using Asp/Asp never smokers as the reference group, one study reported a clear increase in risk with increasing intensity of smoking[12]. One study[4] found an increase in the risk of lung cancer with every five years duration of smoking.

For all subjects with the Asn allele, the risk of lung cancer was reduced in ever smokers compared to never smokers in one study[2], but markedly increased in another[6]. This study also reported an increase in risk as the intensity of smoking increased.

Lys751Gln

Compared to Lys/Lys never smokers, one study found an increased risk of lung cancer in smokers[6], while another[22] reported a decreased risk of cancers of the upper aerodigestive tract. When intensity of smoking was examined, two studies found a clear pattern of increasing risk with increasing amount smoked[6,12]. One study[4] found an increase in risk with every 5g tobacco smoked per day in those smoking ≤20g per day, but not in those smoking more than this. This study also found a significant increase in risk per five years duration of smoking.

For Lys/Gln subjects, in one study[12] the odds ratios reported increased with the intensity of smoking, while in another[26] they were comparable. One study[4] found a significant increase in the risk of lung cancer per 5g tobacco smoked per day, but only in the group with moderate daily tobacco consumption. This study also reported an increase in risk per five years of smoking. In another study[24], the risk in the group smoking for at least 21 years was markedly higher than for never smokers, while that for those who had smoked for fewer years was lower.

When the risk of lung cancer in Gln homozygotes was stratified by smoking intensity, one study[12] found a clear increase in risk with amount smoked, while another study[26] reported a much lower odds ratio for the group with the highest smoking exposure. Elsewhere[4], an increase in risk per 5g

tobacco smoked per day was reported for those with moderate consumption, but not for those who smoked more than 20g day. This study also found an increased odds ratio per five years duration of smoking.

In all subjects with the Gln allele, the odds ratio for smokers was lower than for never smokers in one study[2], but higher in another[6]. Another study[20] presented a significantly raised odds ratio for the risk of lung cancer in smokers, but did not report their findings for non-smokers, although no association had been found in the total study population. One study[22] reported that the risk of upper aerodigestive tract cancer was higher in smokers than in non-smokers. When intensity of smoking was considered, one study[6] found that the risk of lung cancer increased with the amount smoked, while another[14] found that it was decreased in those who smoked the most.

4.6 Conclusions

There was no really convincing evidence of a relationship between lung cancer risk and the Arg156Arg, His201Tyr, -70C>T, +282A>G, +58C>T and rs3916823 polymorphisms of the XPD gene, due mostly to the small number of studies reporting results for each of these polymorphisms. Findings for the Asp312Asn were suggestive of an increased risk of lung cancer in Asn homozygotes, with all of the odds ratios reported being raised, although none was significantly so. The fixed effects model of the meta-analysis also estimated an odds ratio that was significantly above 1.00. Similarly, results for the Lys751Gln polymorphism suggested there may be a positive relationship with lung cancer in subjects with the Lys/Gln genotype, Gln homozygotes, and in all subjects with the Gln allele, with virtually all of the odds ratios presented being raised, and meta-analysis estimating significantly increased overall estimates of risk. However, for both these polymorphisms, more studies will be needed before definitive conclusions can be drawn.

When the risk of lung cancer according to genotype of the various XPD polymorphisms was stratified by smoking status and/or intensity, no clear pattern emerged. Again, this was due in part to the small number of studies presenting results.

Some weaknesses in the studies were noted, particularly a failure by some studies to give full details of the study population. There was also a tendency in several of the studies for the proportion of smokers, and the intensity of smoking, to vary between the cases and the controls. Finally, most of the studies failed to consider more than a very few potentially confounding factors, and two did not even state whether any adjustment had taken place.

5. Overall conclusions

Eight individual studies and one meta-analysis, based on a maximum of 14 studies, examined polymorphisms in the XPD gene with regard to the risk of lung cancer. There was no clear evidence of an association between most of the polymorphisms examined by the studies and lung cancer risk. However, the data for the Asn/Asn genotype of the Asp312Asn polymorphism, and for all genotypes of the Lys751Gln polymorphism, was suggestive of an increased risk of lung cancer in subjects with the variant alleles of these polymorphisms, but 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. There was also an issue with the lack of information about study subjects given by some of the studies.

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

Ref.	Author (Country)	Year[a]	Cases/ controls	Genotype	Odds ratios[b]	Sig[c]	Adjustment factors[d]
Arg156Arg[e]							
17	Shen (China)	2005	117/111	A/C	1.01 (0.52-1.96	NS	A,FT,S
					1.02 (0.52-2.01)	NS	A,FT,PY,S,SC
				C/C	0.50 (0.23-1.05)	NS	A,FT,S
					0.47 (0.22-1.01)	NS	A,FT,PY,S,SC
				All C allele	0.79 (0.42-1.46)	NS	A,FT,S
					0.77 (0.41-1.46)	NS	A,FT,PY,S,SC
23	Yin[f] (China)	2005	149/137	A/C	1.22 (0.70-2.12)	NS	None
					1.12 (0.63-1.97)	NS	SD
				A/A	1.06 (0.55-2.04)	NS	None
					1.04 (0.75-1.44)	NS	SD
				All A allele	1.16 (0.69-1.96)	NS	None
					1.06 (0.82-1.38)	NS	SD
His201Tyr[g]							
18	Zienolddiny (Norway)	2006	339/405	His/Tyr	1.14 (0.77-1.60)	NS	A,PY,S
Asp312Asn[h]							
22	Buch[i] (USA)	2005	204[4]/204	Asp/Asn	1.50 (0.90-2.20)	NS	None
				Asn/Asn	1.70 (0.85-3.40)	NS	None
				All Asn allele	1.30 (1.00-1.80)	p=0.05	A,SS
23	Yin[j](China)	2005	201/171	All Asn allele	0.85 (0.53-13.7)	NS	None
					0.68 (0.20-2.36)	NS	SD
3	Hu (China)	2006	970/986	Asp/Asn	1.06 (0.80-1.41)	NS	A,FHC,PY,S
				Asn/Asn	6.13 (0.67-56.1)	NS	A,FHC,PY,S
				All Asn allele	1.10 (0.83-1.46)	NS	A,FHC,PY,S
26	De Ruyck (Belgium)	2007	110/109	Asp/Asn	1.28 (0.73-2.26)	NS	None
					1.25 (0.67-2.34)	NS	A,PY,S
				Asn/Asn	1.03 (0.44-2.44)	NS	None
					0.96 (0.37-2.48)	NS	A,PY,S
7	Kiyohara[k] (Various)	2007	4110/5305	Asp/Asn	0.95 (0.84-1.07)	NS	None
				Asn/Asn	1.14 (0.95-1.37)	NS	None
27	Lopez-Cima (Spain)	2007	516/533	Asp/Asn	1.01 (0.76-1.35)	NS	A,PY,S
				Asn/Asn	1.52 (0.91-2.51)	NS	A,PY,S
Lys751Gln[l]							
20	Escobar (USA)	1999	150/51	All Gln allele	No association	NS	Not stated
21	Wu (USA)	1999	32/25[m]	All Gln allele	1.00 (0.30-3.70)	NS	Not stated
			29/20[n]	All Gln allele	3.00 (0.70-12.5)	NS	Not stated
22	Buch (USA)	2005	109/269	All Gln allele	2.05 (1.24-3.28)	p<0.05	Not stated
23	Yin[o] (China)	2005	147/145	Lys/Gln	2.75 (1.11-6.80)	p=0.02	None
					2.78 (1.12-6.93)	p=0.03	SD
3	Hu (China)	2006	975/997	Lys/Gln	1.16 (0.89-1.51)	NS	A,FHC,PY,S
				Gln/Gln	1.64 (0.50-5.36)	NS	A,FHC,PY,S
				All Gln allele	1.18 (0.91-1.53)	NS	A,FHC,PY,S
26	De Ruyck (Belgium)	2007	110/109	Lys/Gln	1.07 (0.61-1.89)	NS	None
					0.89 (0.47-1.66)	NS	A,PY,S
				Gln/Gln	1.46 (0.60-3.54)	NS	None
					1.53 (0.56-4.09)	NS	A,PY,S
7	Kiyohara[k] (Various)	2007	5004/6478	Lys/Gln	1.06 (0.97-1.16)	NS	None
				Gln/Gln	1.30 (1.13-1.49)	p<0.05	None
27	Lopez-Cima (Spain)	2007	516/533	Lys/Gln	1.12 (0.84-1.50)	NS	A,PY,S
				Gln/Gln	1.38 (0.85-2.25)	NS	A,PY,S
5	Sreeja (India)	2008	211/211	Lys/Gln	1.80 (1.23-2.81)	p=0.003	A,S,SS
				Gln/Gln	1.50 (0.65-3.50)	NS	A,S,SS

-70C>T[f]							
17	Shen (China)	2005	117/111	C/T	0.46 (0.21-1.03)	NS	A,FT,S
					0.44 (0.19-0.99)	p=0.047	A,FT,PY,S,SC
				All T allele	0.42 (0.19-0.92)	p=0.03	A,FT,S
					0.40 (0.18-0.90)	p=0.03	A,FT,PY,S,SC
+282A>G[e]							
3	Hu (China)	2006	975/985	A/G	1.10 (0.86-1.40)	NS	A,FHC,PY,S
				G/G	1.15 (0.89-1.51)	NS	A,FHC,PY,S
				All G allele	1.12 (0.89-1.41)	NS	A,FHC,PY,S
+58C>T[f]							
3	Hu (China)	2006	965/986	C/T	1.12 (0.84-1.49)	NS	A,FHC,PY,S
				T/T	6.18 (0.68-56.5)	NS	A,FHC,PY,S
				All T allele	1.16 (0.87-1.54)	NS	A,FHC,PY,S
rs3916823[p]							
3	Hu (China)	2006	986/987	AAAA/-	1.01 (0.81-1.25)	NS	A,FHC,PY,S
				-/-	1.88 (0.84-4.21)	NS	A,FHC,PY,S
				All - allele	1.04 (0.84-1.29)	NS	A,FHC,PY,S

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, S = sex, SC = smoky coal use, SD = smoking duration, SS = smoking status
e Using A/A individuals as the reference group
f Using C/C individuals as the reference group
g Using His/His individuals as the reference group
h Using Asp/Asp individuals as the reference group
i Cancers of the upper aerodigestive tract
j Data came from reference[25]
k Meta-analysis
l Using Lys/Lys individuals as the reference group
m Mexican Americans
n African Americans
o Data came from reference[24]
p Using AAAA/AAAA individuals as the reference group

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

Genotype	No. of studies[a]	Heterogeneity Chisquared, p	Odds ratio (95% confidence interval) Fixed effects model	Random effects model	Notes
Asp312Asn					
Asp/Asn	5	4.75, NS	1.00 (0.91-1.11)	1.03 (0.90-1.16)	Least adjusted
	5	4.51, NS	1.00 (0.91-1.10)	1.02 (0.90-1.15)	Most adjusted
	4	2.33, NS	1.13 (0.99-1.29)	1.13 (0.99-1.29)	Caucasian studies, least adjusted
	4	2.24, NS	1.13 (0.99-1.29)	1.13 (0.99-1.29)	Caucasian studies, most adjusted
	2	0.31, NS	1.00 (0.83-1.21)	1.00 (0.83-1.21)	Asian studies
Asn/Asn	5	4.31, NS	1.21 (1.03-1.42)	1.03 (0.83-1.27)	Least adjusted
	5	4.40, NS	1.21 (1.02-1.42)	1.25 (1.01-1.54)	Most adjusted
	4	2.50, NS	1.17 (1.01-1.36)	1.17 (1.01-1.36)	Caucasian studies, least adjusted
	4	2.58, NS	1.17 (1.01-1.36)	1.17 (1.01-1.36)	Caucasian studies, most adjusted
All Asn allele	3	0.81, NS	1.19 (0.97-1.45)	1.19 (0.97-1.45)	Least adjusted
	3	1.42, NS	1.17 (0.96-1.44)	1.17 (0.96-1.44)	Most adjusted
	2	0.09, NS	1.09 (0.83-1.44)	1.09 (0.83-1.44)	Asian studies, least adjusted
	2	0.56, NS	1.07 (0.82-1.41)	1.07 (0.82-1.41)	Asian studies, Most adjusted
Lys751Gln					
Lys/Gln	6	10.22, NS	1.10 (1.02-1.19)	1.21 (1.01-1.45)	Least adjusted
	6	10.70, NS	1.10 (1.02-1.19)	1.20 (0.996-1.45)	Most adjusted
	3	0.02, NS	1.11 (1.01-1.23)	1.11 (1.01-1.23)	Caucasian studies, least adjusted
	3	0.47, NS	1.11 (1.00-1.22)	1.11 (1.00-1.22)	Caucasian studies, most adjusted
	4	10.20, p=0.017	1.10 (1.01-1.20)	1.32 (0.995-1.75)	Asian studies, least adjusted
	4	10.25, p=0.017	1.10 (1.01-1.20)	1.32 (0.995-1.75)	Asian studies, most adjusted
Gln/Gln	5	0.34, NS	1.32 (1.16-1.50)	1.32 (1.16-1.50)	Least adjusted
	5	0.38, NS	1.32 (1.16-1.50)	1.32 (1.16-1.50)	Most adjusted
	3	0.99, NS	1.54 (1.05-2.26)	1.54 (1.05-2.26)	Caucasian studies, least adjusted
	3	0.97, NS	1.56 (1.06-2.29)	1.56 (1.06-2.29)	Caucasian studies, most adjusted
	3	0.23, NS	1.45 (0.77-2.74)	1.45 (0.77-2.74)	Asian studies
All Gln allele[b]	4	5.26, NS	1.35 (1.08-1.68)	1.50 (0.99-2.26)	

a Number of studies does not always add up as the published meta-analysis[7] included data for both Caucasian and Asian populations and the study by Wu et al[21] included data for both Mexican American and African American populations

b Excludes one study[20] due to insufficient data

NS $p \geq 0.05$

Table 3: Prevalence of genotypes of XPD polymorphisms

Polymorphism/ population	No. of cases	Prevalence of genotypes[a]			No. of controls	Prevalence of genotypes[a]		
Arg156Arg		**A/A**	**A/C**	**C/C**		**A/A**	**A/C**	**C/C**
Total	266	64 (24.1)	141 (53.0)	61 (22.9)	248	57 (23.0)	115 (46.4)	76 (30.6)
His201Tyr		**His/His**	**His/Tyr**	**Tyr/Tyr**		**His/His**	**His/Tyr**	**Tyr/Tyr**
Total	339	272 (80.2)	66 (19.5)	1 (0.29)	405	328 (81.0)	77 (19.0)	0 (0.0)
Asp312Asn		**Asp/Asp**	**Asp/Asn**	**Asn/Asn**		**Asp/Asp**	**Asp/Asn**	**Asn/Asn**
Total	6111	3672 (60.1)	1896 (31.0)	543 (8.9)	7308	4198 (57.4)	2475 (33.9)	635 (8.7)
Caucasian[b]	3816	1643 (43.1)	1645 (43.1)	528 (13.8)	5018	2166 (43.2)	2220 (44.2)	632 (12.6)
Asian	2295	2029 (88.4)	251 (10.9)	15 (0.7)	2290	2032 (88.7)	255 (11.1)	3 (0.1)
Lys751Gln		**Lys/Lys**	**Lys/Gln**	**Gln/Gln**		**Lys/Lys**	**Lys/Gln**	**Gln/Gln**
Total[c]	7236	4017 (55.5)	2471 (34.1)	748 (10.3)	8742	4810 (55.0)	3060 (35.0)	872 (10.0)
Caucasian[b]	4267	1656 (38.8)	1920 (45.0)	691 (16.2)	5755	2418 (42.0)	2522 (43.8)	815 (14.2)
Asian	2969	2361 (79.5)	551 (18.6)	57 (1.9)	2987	2392 (80.1)	538 (18.0)	57 (1.9)
-70C>T		**C/C**	**C/T**	**T/T**		**C/C**	**C/T**	**T/T**
Total	117	106 (90.6)	11 (9.4)	0 (0.0)	111	89 (80.2)	20 (18.0)	2 (1.8)
+282A>G		**A/A**	**A/G**	**G/G**		**A/A**	**A/G**	**G/G**
Total	975	177 (18.2)	492 (50.5)	306 (31.4)	985	199 (20.2)	488 (49.5)	298 (30.3)
+58C>T		**C/C**	**C/T**	**T/T**		**C/C**	**C/T**	**T/T**
Total	965	844 (87.5)	117 (12.1)	4 (0.4)	986	877 (88.9)	108 (11.0)	1 (0.1)
rs3916823		**AAAA/ AAAA**	**AAAA/-**	**-/-**		**AAAA/A AAA**	**AAAA/-**	**-/-**
Total	986	744 (75.5)	225 (22.8)	17 (1.7)	987	750 (76.0)	227 (23.0)	10 (1.0)

a Number (percent)
b 6% of subjects in 1 study [22] were African-Americans, this study also includes cancers of upper aerodigestive tract
c Subjects in two studies[20,21] not included due to insufficient data

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

Ref.	Author (year[a])	Smoking variable	Genotype	Odds ratios[b]	Adjustment factors[c]
Arg156Arg[d]					
23	Yin (2005)	Never smokers	All A allele	2.49 (1.10-5.64)	None
		≤20 years duration	All A allele	0.44 (0.16-1.24)	None
		≥21 years duration	All A allele	0.71 (0.25-2.01)	None
Asp312Asn[e]					
8	Butkiewicz (2001)[f]	Never smokers	Asp/Asn[g]	0.74 (0.18-3.04)	A
			Asp/Asp[g]	1.24 (0.31-5.01)	A
			Asp/Asp[h]	1.52 (0.55-4.19)	A
		≤34.5 pack-years	Asp/Asn[g]	1.70 (0.43-6.74)	A
			Asp/Asp[g]	5.32 (1.35-21.02)	A
			Asp/Asp[h]	3.89 (1.32-11.5)	A
		>34.5 pack-years	Asp/Asp[h]	1.12 (0.37-3.37)	A
2	Hou (2002)	Never smokers	All Asn allele	1.80 (0.90-3.30)	A,ETS,S
		Ever smokers	All Asn allele	0.80 (0.40-1.50)	PY,S
12	Zhou[i] (2002)	Non-smokers	Asp/Asn	1.39 (0.80-2.50)	A,OG,S,SS,TC
			Asn/Asn	4.44 (2.20-9.20)	A,OG,S,SS,TC
		Mild smokers	Asp/Asp	7.99 (4.40-14.0)	A,OG,S,SS,TC
			Asp/Asn	7.94 (4.40-14.0)	A,OG,S,SS,TC
			Asn/Asn	13.0 (6.30-27.0)	A,OG,S,SS,TC
		Moderate smokers	Asp/Asp	15.8 (9.30-27.0)	A,OG,S,SS,TC
			Asp/Asn	19.0 (11.0-33.0)	A,OG,S,SS,TC
			Asn/Asn	20.3 (10.0-41.0)	A,OG,S,SS,TC
		Heavy smokers	Asp/Asp	53.7 (30.0-96.0)	A,OG,S,SS,TC
			Asp/Asn	34.5 (20.0-60.0)	A,OG,S,SS,TC
			Asn/Asn	36.0 (18.0-72.0)	A,OG,S,SS,TC
6	Liang[f,i,j] (2003)	Non-smokers	All Asn allele	1.04 (0.37-2.94)	A,S
		Smokers	Asp/Asp	4.01 (2.32-6.93)	A,S
			All Asn allele	8.57 (4.10-17.9)	A,S
		<29 pack-years	Asp/Asp	2.08 (1.10-3.95)	A,S
			All Asn allele	2.53 (0.87-7.35)	A,S
		≥29 pack-years	Asp/Asp	4.74 (2.88-9.49)	A,S
			All Asn allele	14.3 (5.80-35.2)	A,S
16	Vogel[f,k] (2004)	Duration (per 5 years)	Asp/Asp	1.43 (1.27-1.62)	IF,IV,SI,SS
			Asp/Asn	1.54 (1.36-1.75)	IF,IV,SI,SS
			Asn/Asn	1.41 (1.17-1.69)	IF,IV,SI,SS
		≤20g/day (per 5g/day)	Asp/Asp	2.01 (1.49-2.71)	IF,IV,SD,SS
			Asp/Asn	1.97 (1.46-2.64)	IF,IV,SD,SS
			Asn/Asn	1.71 (1.14-2.56)	IF,IV,SD,SS
		>20g/day (per 5g/day)	Asp/Asp	1.02 (0.76-1.37)	IF,IV,SD,SS
			Asp/Asn	0.95 (0.76-1.18)	IF,IV,SD,SS
			Asn/Asn	1.06 (0.79-1.42)	IF,IV,SD,SS
26	De Ruyck (2007)	<25 pack-years	Asp/Asn	1.44 (0.58-3.59)	A,PY,S
			Asn/Asn	2.33 (0.64-8.51)	A,PY,S
		≥25 pack-years	Asp/Asn	1.27 (0.46-3.51)	A,PY,S
			Asn/Asn	0.49 (0.13-1.84)	A,PY,S
27	Lopez-Cima (2007)	ETS exposed	Asp/Asn	1.75 (0.72-4.24)	A,PY,S
			Asn/Asn	2.58 (0.60-11.1)	A,PY,S
		Ever smokers	Asp/Asn	1.06 (0.80-1.40)	A,PY,S
			Asn/Asn	1.58 (0.96-2.60)	A,PY,S
		Former smokers	Asp/Asn	1.11 (0.75-1.65)	A,PY,S
			Asn/Asn	1.36 (0.69-2.68)	A,PY,S
		Current smokers	Asp/Asn	1.00 (0.65-1.54)	A,PY,S
			Asn/Asn	1.72 (0.78-3.75)	A,PY,S
		Light smokers	Asp/Asn	1.11 (0.40-3.05)	A,S
			Asn/Asn	1.75 (0.37-8.31)	A,S
		Moderate smokers	Asp/Asn	0.98 (0.64-1.51)	A,S
			Asn/Asn	1.24 (0.59-2.62)	A,S
		Heavy smokers	Asp/Asn	0.87 (0.53-1.45)	A,S
			Asn/Asn	2.07 (0.74-5.75)	A,S

Lys751Gln[l]					
20	Escobar (1999)	Smokers	All Gln allele	2.10 (1.10-4.10)	Not stated
10	Chen (2002)	Never smokers	All Lys allele[m]	4.66 (0.46-47.73)	OG
		≥30 pack-years	All Lys allele[m]	1.03 (0.06-16.76)	OG
2	Hou (2002)	Never smokers	All Gln allele	2.00 (1.10-3.80)	A,ETS,S
		Ever smokers	All Gln allele	0.80 (0.40-1.50)	PY,S
12	Zhou[n] (2002)	Non-smokers	Lys/Gln	1.23 (0.70-2.20)	A,OG,S,SS,TC
			Gln/Gln	2.05 (1.00-4.20)	A,OG,S,SS,TC
		Mild smokers	Lys/Lys	7.34 (4.10-13.0)	A,OG,S,SS,TC
			Lys/Gln	6.44 (3.60-12.0)	A,OG,S,SS,TC
			Gln/Gln	8.59 (4.20-18.0)	A,OG,S,SS,TC
		Moderate smokers	Lys/Lys	12.6 (7.40-21.0)	A,OG,S,SS,TC
			Lys/Gln	16.2 (9.50-27.0)	A,OG,S,SS,TC
			Gln/Gln	16.8 (8.70-32.0)	A,OG,S,SS,TC
		Heavy smokers	Lys/Lys	50.6 (28.0-92.0)	A,OG,S,SS,TC
			Lys/Gln	30.1 (17.0-52.0)	A,OG,S,SS,TC
			Gln/Gln	24.3 (13.0-47.0)	A,OG,S,SS,TC
6	Liang[f,j,n] (2003)	Non-smokers	All Gln allele	1.39 (0.78-2.48)	A,S
		Smokers	Lys/Lys	4.18 (2.40-7.26)	A,S
			All Gln allele	7.24 (3.53-14.8)	A,S
		<29 pack-years	Lys/Lys	2.23 (1.17-4.23)	A,S
			All Gln allele	1.86 (0.63-5.53)	A,S
		≥29 pack-years	Lys/Lys	4.89 (2.75-8.71)	A,S
			All Gln allele	11.8 (5.08-27.3)	A,S
14	Harms (2004)	≤40 pack-years	All Gln allele	3.30 (1.02-10.7)[o]	None
		>40 pack-years	All Gln allele	1.06 (0.46-2.44)[o]	None
16	Vogel[f,p] (2004)	Duration (per 5 years)	Lys/Lys	1.48 (1.30-1.69)	IF,IV,SI,SS
			Lys/Gln	1.51 (1.34-1.71)	IF,IV,SI,SS
			Gln/Gln	1.35 (1.14-1.61)	IF,IV,SI,SS
		≤20g/day (per 5g/day)	Lys/Lys	2.00 (1.46-2.74)	IF,IV,SD,SS
			Lys/Gln	2.02 (1.54-2.67)	IF,IV,SD,SS
			Gln/Gln	1.60 (1.04-2.46)	IF,IV,SD,SS
		>20g/day (per 5g/day)	Lys/Lys	0.94 (0.69-1.29)	IF,IV,SD,SS
			Lys/Gln	1.03 (0.84-1.26)	IF,IV,SD,SS
			Gln/Gln	1.06 (0.78-1.46)	IF,IV,SD,SS
22	Buch[n,q] (2005)	Non-smokers	All Gln allele	1.26 (0.73-2.18)	A,SS
		Smokers	Lys/Lys	0.79 (0.45-1.36)	A,SS
			All Gln allele	3.99 (2.30-6.92)	A,SS
23	Yin[r] (2005)	Never smokers	Lys/Gln	3.19 (0.80-12.7)	None
		≤20 years duration	Lys/Gln	1.17 (0.18-7.50)	None
		≥21 years duration	Lys/Gln	4.98 (0.60-41.7)	None
26	De Ruyck (2007)	<25 pack-years	Lys/Gln	0.96 (0.38-2.40)	A,PY,S
			Gln/Gln	3.62 (1.01-13.0)	A,PY,S
		≥25 pack-years	Lys/Gln	1.03 (0.37-2.83)	A,PY,S
			Gln/Gln	0.46 (0.11-1.96)	A,PY,S

a Year of publication
b 95% confidence interval shown in brackets where available
c Abbreviations used for confounders:
A = age, ETS = environmental tobacco smoke, FHC = family history of cancer, IF = intake of fruit, IV = intake of vegetables, OG = other genotype, PY = pack-years of smoking, RA = residential area, S = sex, SD = smoking duration, SS = smoking status, TC = time since smoking cessation
d Using C/C individuals as the reference group
e Using Asp/Asp individuals as the reference group
f Originally included in the published meta-analysis[7]
g Using Asn/Asn individuals as the reference group
h Using all individuals with Asn allele as the reference group
i Using Asp/Asp never smokers as the reference group
j Data came from reference[28] and was based on a subset of 167 cases and 338 controls
k Data came from reference[4] and was based on 424 cases and 787 controls
l Using Lys/Lys individuals as the reference group
m Using Gln/Gln individuals as the reference group
n Using Lys/Lys never smokers as the reference group
o Estimated from data given
p Data came from reference[4] and was based on 429 cases and 790 controls
q Cancers of the upper aerodigestive tract
r Data came from reference[24]

References

1. Spitz MR, Wu X, Wang Y, Wang LE, Shete S, Amos CI, *et al*. Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. *Cancer Res* 2001;**61**:1354-7.

2. Hou S-M, Fält S, Angelini S, Yang K, Nyberg F, Lambert B, *et al*. The *XPD* variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. *Carcinogenesis* 2002;**23**:599-603.

3. Hu Z, Xu L, Shao M, Yuan J, Wang Y, Wang F, *et al*. Polymorphisms in the two helicases *ERCC2/XPD* and *ERCC3/XPB* of the transcription factor IIH complex and risk of lung cancer: a case-control analysis in a Chinese population. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1336-40.

4. 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.

5. Sreeja L, Syamala VS, Syamala V, Hariharan S, Raveendran PB, Vijayalekshmi RV, *et al*. Prognostic importance of DNA repair gene polymorphisms of *XRCC1* Arg399Gln and *XPD* Lys751Gln in lung cancer patients from India. *J Cancer Res Clin Oncol* 2008;**134**:645-52.

6. Liang G, Xing D, Miao X, Tan W, Yu C, Lu W, *et al*. Sequence variations in the DNA repair gene *XPD* and risk of lung cancer in a Chinese population. *Int J Cancer* 2003;**105**:669-73.

7. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. *Int J Med Sci* 2007;**4**:59-71.

8. Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M, Harris CC. Genetic polymorphisms in DNA repair genes and risk of lung cancer. *Carcinogenesis* 2001;**22**:593-7.

9. David-Beabes GL, Lunn RM, London SJ. No association between the XPD (Lys751G1n) polymorphism or the XRCC3 (Thr241Met) polymorphism and lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:911-2.

10. Chen S, Tang D, Xue K, Xu L, Ma G, Hsu Y, *et al*. DNA repair gene *XRCC1* and *XPD* polymorphisms and risk of lung cancer in a Chinese population. *Carcinogenesis* 2002;**23**:1321-5.

11. Park JY, Lee SY, Jeon H-S, Park SH, Bae NC, Lee EB, *et al*. Lys751Gln polymorphism in the DNA repair gene XPD and risk of primary lung cancer [Letter]. *Lung Cancer* 2002;**36**:15-6.

12. Zhou W, Liu G, Miller DP, Thurston SW, Xu LL, Wain JC, *et al*. Gene-environment interaction for the *ERCC2* polymorphisms and cumulative cigarette smoking exposure in lung cancer. *Cancer Res* 2002;**62**:1377-81.

13. Misra RR, Ratnasinghe D, Tangrea JA, Virtamo J, Andersen MR, Barrett M, *et al*. Polymorphisms in the DNA repair genes *XPD, XRCC1, XRCC3*, and *APE/ref-1*, and the risk of lung cancer among male smokers in Finland. *Cancer Lett* 2003;**191**:171-8.

14. Harms C, Salama SA, Sierra-Torres CH, Cajas-Salazar N, Au WW. Polymorphisms in DNA repair genes, chromosome aberrations, and lung cancer. *Environ Mol Mutagen* 2004;**44**:74-82.

15. Popanda O, Schattenberg T, Phong CT, Butkiewicz D, Risch A, Edler L, *et al*. Specific combinations of DNA repair gene variants and increased risk for non-small cell lung cancer. *Carcinogenesis* 2004;**25**:2433-41.

16. Vogel U, Laros I, Jacobsen NR, Thomsen BL, Bak H, Olsen A, *et al*. Two regions in chromosome 19q13.2-3 are associated with risk of lung cancer. *Mutat Res* 2004;**546**:65-74.

17. 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.

18. Zienolddiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland L, *et al*. Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. *Carcinogenesis* 2006;**27**:560-7.

19. Matullo G, Dunning AM, Guarrera S, Baynes C, Polidoro S, Garte S, *et al*. DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. *Carcinogenesis* 2006;**27**:997-1007.

20. Escobar P, Modugno F, Kanbour-Shakir A, Naus G, Mohrenweiser H, Romkes M. Analysis of the DNA repair enzyme XPD exon 23 polymorphism and cancer risk [Abstract]. *Proc Am Assoc Cancer Res* 1999;**40**:213.

21. Wu X, Amos CI, Hong WK, Mohrenweiser HW, Spitz MR. Association of a polymorphism in exon 23 of the DNA repair gene, XPD, and lung cancer risk. *Proc Am Assoc Cancer Res* 1999;**40**:89.

22. Buch S, Zhu B, Davis AG, Odom D, Siegfried JM, Grandis JR, *et al*. Association of polymorphisms in the *Cyclin D1* and *XPD* genes and susceptibility to cancers of the upper aero-digestive tract. *Mol Carcinog* 2005;**42**:222-8.

23. Yin J, Li J, Ma Y, Guo L, Wang H, Vogel U. The DNA repair gene *ERCC2/XPD* polymorphism Arg 156Arg (A22541C) and risk of lung cancer in a Chinese population. *Cancer Lett* 2005;**223**:219-26.

24. Yin J, Vogel U, Ma Y, Guo L, Wang H, Qi R. Polymorphism of the DNA repair gene *ERCC2* Lys751Gln and risk of lung cancer in a northeastern Chinese population. *Cancer Genet Cytogenet* 2006;**169**:27-32.

25. Yin J, Vogel U, Ma Y, Qi R, Sun Z, Wang H. A haplotype encompassing the variant allele of DNA repair gene polymorphism *ERCC2/XPD* Lys751Gln but not the variant allele of Asp312Asn is associated with risk of lung cancer in a northeastern Chinese population. *Cancer Genet Cytogenet* 2007;**175**:47-51.

26. 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.

27. 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.

28. Xing D, Tan W, Wei Q, Lin D. Polymorphisms of the DNA repair gene *XPD* and risk of lung cancer in a Chinese population. *Lung Cancer* 2002;**38**:123-9.