The association of XRCC1 with lung cancer

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1. Objectives

The X-ray repair cross complementing group 1 (XRCC1) protein plays a central role in two DNA repair pathways, base excision repair (BER) and single-strand break repair (SSBR)[1-5]. In these pathways, XRCC1 interacts directly with at least seven other proteins, including 8-oxoguanine glycosylase, apurinic/apyrimidinic endonuclease, polymeraseβ, DNA ligaseIIIα, proliferating cell nuclear antigen, poly(ADP-ribose) polymerase and polynucleotide kinase/phosphatase[1-5]. The human XRCC1 gene has 17 exons and is located on chromosome 19q13.2[4]. More than 60 single nucleotide polymorphisms have been found in XRCC1, among which about 30 variants are located in exons or promoter regions[5], although the functional consequences of many of these polymorphisms remain unclear[4,6-8]. Some of the polymorphisms occur in evolutionarily conserved regions, suggesting potential functional relevance[9], and some studies have demonstrated embryonic lethality in XRCC1 knockout mice[3,8]. The Arg194Trp variant on exon 6 has been shown to be associated with lower bleomycin and benzo(α)pyrene diolepoxide sensitivity *in vitro*[5,6]. The Arg280His variant, located in the proliferating cell nuclear antigen binding region, shows less efficient localization of a damaged site in the chromosome, thereby reducing the cellular BER/SSBR efficiency[5]. The Arg399Gln polymorphism is situated within the BRCT-1 region and is associated with an altered DNA repair activity[1,2,5], possibly due to an effect on the functional interaction between XRCC1 and ADPRT[5,7]. A novel polymorphism, -77T>C, located in the 5' untranslated region appears to decrease transcriptional activity of C-allele containing promoter with higher affinity to Sp1 binding[5].

The objective of this report is to determine, based on the available literature, whether genetic polymorphisms in XRCC1 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

Thirty-one 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 XRCC1 in relation to lung cancer

4.1 Introduction

One relevant meta-analysis was available, and the results of this are summarized below. In addition, 13 papers that were not included in this meta-analysis were found relating to studies in which polymorphisms in the XRCC1 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 XRCC1 gene between lung cancer patients and control subjects

4.2.1 *Meta-analysis*

A meta-analysis published in 2006[4] combined results from 17 studies[1-3,6,7,9-20] that examined polymorphisms in the XRCC1 gene in relation to lung cancer risk, although not all of these studies provided data for each of the identified polymorphisms. For the Arg399Gln polymorphism, information was available for a total of 7385 cases and 9380 controls from all 17 of the studies. Using a random effects model, the unadjusted risk for lung cancer in subjects

with the Arg/Gln genotype was estimated at 0.99 95% CI 0.93-1.06), while Gln homozygotes had a risk estimate of 1.02 (0.88-1.19). There was significant heterogeneity between the studies used to produce this latter estimate (p=0.026). Eight studies provided data on the Arg194Trp polymorphism and risk estimates were based on 3714 cases and 5385 controls. Odds ratios of 0.89 (95% CI 0.78-1.03) and 1.19 (95% CI 0.76-1.86) were estimated for the risk of lung cancer for the genotypes Arg/Trp and Trp/Trp respectively. There was no significant heterogeneity between the studies. Information on the Arg280His polymorphism was available from seven studies, and included 3640 cases and 3981 controls. For subjects who had the Arg/His genotype, the risk of lung cancer was estimated at 1.03 (95% CI 0.88-1.20), while the odds ratio for all subjects with the His allele was estimated at 1.06 (95% CI 0.91-1.23). Again, there was no significant heterogeneity between the studies on which these estimates were based.

4.2.2 *Additional individual studies*

The case group in a study carried out in Poland[21] consisted of 96 men with primary non-small cell lung cancer, diagnosed according to the WHO classification. The control group was made up of 96 unrelated healthy men some of whom were selected from a population previously recruited for occupational studies, matched to the cases by age, smoking habit and occupational exposure. The mean age of the cases was 56.8 years, compared to 56.3 years in the controls. DNA was isolated from frozen non-tumourous lung tissue samples from the cases and blood samples from the controls, and the frequency of the Arg194Trp, Arg280His and Arg399Gln polymorphisms in the XRCC1 gene were identified. The frequency of the minor allele was 0.04 in cases and 0.05 in controls for the Arg194Trp polymorphism, 0.02 in cases and 0.05 in controls for the Arg280His polymorphism and 0.35 in both cases and controls for the Arg399Gln polymorphism. No odds ratios were presented, and there was not enough data given for these to be estimated.

A study conducted in the USA[22] was based on 524 lung cancer cases and an equal number of controls, but no further details of the subjects were given. For the Arg194Trp polymorphism, the combined prevalence of the

Arg/Arg and Arg/Trp genotypes was 13.7% in the cases and 13.9% in the controls. An odds ratio of 1.02 (95% CI 0.72-1.44) was estimated for the risk of lung cancer in subjects with the Trp/Trp genotype compared to all subjects with the Arg allele. The frequency of the Arg/Arg/, Arg/Gln and Gln/Gln genotypes of the Arg399Gln polymorphism were 41.6%, 45.8% and 12.6% respectively in the cases and 39.7%, 45.2% and 15.1% respectively in the controls. Odds ratios of 0.97 (95% CI 0.74-1.26), 0.80 (95% CI 0.55-1.16) and 0.92 (95% CI 0.72-1.18) were estimated for the Arg/Gln and Gln/Gln genotypes and for all subjects with the Gln allele respectively, using Arg homozygotes as a reference group.

In a study carried out in the USA[23], the case group consisted of 935 histologically confirmed, newly diagnosed lung cancer patients. The control group was made up of 1233 healthy, unrelated friends and spouses of cancer and cardiothoracic disease patients, and was not matched to the cases. The median age of the cases was 67 years, compared to 60 years in the controls, and the proportion of men in each group varied from 53% in the cases to 46% in the controls. Both of these differences reached statistical significance ($p < 0.01$ for age and sex). DNA was extracted from a peripheral blood sample obtained from each subject, and polymorphisms in the XRCC1 gene detected using polymerase chain reaction (PCR) -pyrosequencing. The proportion of subjects with the Arg/Arg, Arg/Gln and Gln/Gln genotypes of the Arg399Gln polymorphism was 43%, 42% and 15% respectively in the case group and 45%, 44% and 11% respectively in the controls. Compared to Arg homozygotes, unadjusted odds ratios of 1.02 (95% CI 0.85-1.22) and 1.33 (95% CI 1.02-1.74) were estimated for the risk of lung cancer in subjects with the Arg/Gln and Gln/Gln genotypes respectively. Adjustment barely altered the estimate for Arg/Gln individuals (OR 1.04, 95% CI 0.84-1.29), but reduced the estimate for Gln homozygotes, and removed its significance (OR 1.27, 95% CI 0.92-1.75).

Cases in a study carried out in China[24] consisted of 75 patients (82.7% men) with non-small cell lung cancer, while the control group was made up of 162 patients (85.8% men) with no history of pulmonary disease, matched to

the cases for age and sex. The mean age of the men in the study was 63.2 years for the cases and 62.5 years for the controls, while for the women the median age was 62.8 years for the cases and 60.3 years for the controls. DNA was extracted from uninvolved lung tissue samples in the case group and from blood samples in the controls, and polymorphisms in the XRCC1 gene identified using PCR-restriction fragment length polymorphism (RFLP). For the Arg194Trp polymorphism, the Arg/Arg, Arg/Trp and Trp/Trp genotypes occurred in 66.7%, 29.3% and 4.0% of the cases respectively, compared to 48.8%, 41.4% and 9.9% of the controls respectively. Compared to Arg homozygotes, odds ratios for lung cancer risk were estimated at 0.519 (0.285-0.943) for Arg/Trp subjects, 0.296 (95% CI 0.082-1.069) for Trp homozygotes, and 0.476 (0.269-0.842) for all subjects with the Trp allele. The Arg/Arg, Arg/Gln and Gln/Gln genotypes of the Arg399Gln polymorphism occurred in 53.3%, 41.3% and 5.3% of the cases respectively and 55.6%, 37.7% and 6.8% of the controls respectively. When Arg/Arg subjects were used as a comparison group, the risk of lung cancer was estimated at 1.143 (95% CI 0.646-2.023) in Arg/Gln individuals, 0.818 (95% CI 0.246-2.726) in Gln homozygotes, and 1.094 (95% CI 0.631-1.895) in all subjects with the Gln allele.

The case group in a study conducted in China[25] consisted of 710 newly histopathologically diagnosed lung cancer patients (73.2% men). The control group was made up of 710 cancer-free individuals (72.3% men), randomly selected from 10,500 subjects participating in a community-based screening program for non-infectious diseases. Controls were matched to cases for age, sex and residential area. The mean age of the cases was 59.6 years, compared to 59.3 years for the controls. A venous blood sample was obtained from each study subject, from which genomic DNA was extracted, and polymorphisms in the XRCC1 gene identified using PCR-RFLP. The frequency of the TT, CT, and CC genotypes of the -77T>C polymorphism were 70.4%, 27.9% and 1.7% respectively in the cases and 78.6%, 20.9% and 0.6% in the controls. Compared to TT individuals, the risk of lung cancer was estimated at 1.49 (95% CI 1.17-1.91) in CT subjects, 3.35 (95% CI 1.07-10.45) in CC subjects and 1.54 (95% CI 1.21-1.96) in all individuals with the C allele. Adjustment

did not substantially alter the results for the CT genotype (OR 1.51, 95% CI 1.17-1.94) or for all those with the C allele (OR 1.55, 95% CI 1.21-1.98), but the risk estimate for C allele homozygotes was reduced and the significance was removed (OR 2.98, 95% CI 0.93-9.59).

For the Arg194Trp polymorphism, 47.2% of the cases were wild-type homozygotes, compared to 47.8% of the controls. The Arg/Trp genotype was observed in 43.8% of cases and 43.4% of controls, while Trp homozygotes made up 9.0% of the case group and 8.9% of the controls. Unadjusted odds ratios for lung cancer were estimated at 1.02 (95% CI 0.82-1.27) for the Arg/Trp genotype, 1.03 (95% CI 0.70-1.50) for the Trp/Trp genotype, and 1.02 (95% CI 0.83-1.26) for all subjects with the Trp allele. Adjustment did not alter these conclusions (Arg/Trp: OR 1.01, 95% CI 0.81-1.26; Trp/Trp: OR 1.11, 95% CI 0.75-1.63; all Trp allele: OR 1.03, 95% CI 0.83-1.27).

When the Arg399Gln polymorphism was examined, the frequency of the Arg/Arg, Arg/Gln and Gln/Gln genotypes was 53.2%, 40.0% and 6.8% respectively in the cases, and 52.1%, 39.7% and 8.2% respectively in the controls. Odds ratios for lung cancer were reduced compared to Arg homozygotes, and were estimated at 0.99 (95% CI 0.79-1.23) for Arg/Gln subjects, 0.81 (95% CI 0.54-1.22) for Gln homozygotes, and 0.96 (95% CI 0.78-1.18) for all subjects with the Gln allele. Adjustment made little difference to these findings (Arg/Gln: OR 0.98, 95% CI 0.78-1.23; Gln/Gln: OR 0.83, 95% CI 0.54-1.25; All Gln allele: OR 0.95, 95% CI 0.77-1.18).

A study conducted in China[26] used PCR-RFLP to compare XRCC1 polymorphisms in 50 patients with lung cancer and 50 controls, all of whom were non-smoking women. No details of the age distribution of the study subjects was given. The Arg399Gln polymorphism was examined, and the frequency of the Arg/Arg, Arg/Gln and Gln/Gln genotypes was 54%, 42% and 4% in the controls respectively and 44%, 40% and 16% in the cases respectively. Compared to Arg homozygotes, odds ratios for lung cancer, adjusted for age and cooking oil smoke, were estimated at 0.99 (95% CI 0.4-2.46) for Arg/Gln subjects, 5.43 (95% CI 0.99-29.7) for Gln homozygotes, and

0.73 (95% CI 0.31-1.72) for all carriers of the Gln allele. It is not clear whether these subjects were later included in the study by[5].

The cases in a study carried out in China[8] consisted of 1024 patients with histopathologically confirmed primary lung cancer. The 1118 controls were selected from a group of cancer-free individuals recruited from a nutritional survey, and were frequency matched to the cases for age, sex and ethnicity. The proportion of men in the case group was 70.6%, compared to 67.5% in the controls, and although a mean age was not given, there was no significant difference in the age distribution of the two groups. Genomic DNA was extracted from the controls and most of the cases from blood leukocytes, although in about 30% of the cases DNA samples came from surgically resected normal lung tissue. XRCC1 genotypes were analysed by PCR-RFLP. The frequency of the T/T, T/C and C/C genotypes of the -77T>C polymorphism was 76.5%, 21.8% and 1.7% respectively in the cases and 82.6%, 16.3% and 1.1% respectively in the controls. Compared to T/T individuals, the risk of lung cancer was significantly raised in subjects with the T/C genotype (OR 1.44, 95% CI 1.16-1.80) and all carriers of the C allele (OR 1.46, 95% CI 1.18-1.82), and was non-significantly raised for C homozygotes (OR 1.87, 95% CI 0.87-4.01).

The Arg/Arg, Arg/Trp and Trp/Trp genotypes of the Arg194Trp polymorphism occurred in 51.2%, 39.9% and 8.9% of the cases respectively and 51.2%, 41.1% and 7.7% of the controls. Adjusted odds ratios were estimated at 0.98 (95% CI 0.82-1.18), 1.11 (95% CI 0.90-1.54) and 1.00 (95% CI 0.84-1.20) for Arg/Trp subjects, Trp homozygotes and all carriers of the Trp allele respectively, compared to Arg/Arg individuals.

When the Arg280His polymorphism was examined, Arg homozygotes comprised 82.8% of the case group and 80.9% of the controls. The Arg/His genotype occurred in 16.5% of the cases and 18.2% of the controls, and His homozygotes made up just 0.7% of the cases and 0.9% of the controls. Compared to Arg/Arg subjects, the risk of lung cancer was estimated at 0.90 (95% CI 0.71-1.13) in individuals with the Arg/His genotype, 0.72 (95% CI

0.27-1.93) for His homozygotes, and 0.89 (95% CI 0.71-1.12) for all carriers of the His allele.

The distribution of the Arg/Arg, Arg/Gln and Gln/Gln genotypes of the Arg399Gln polymorphism was 55.3%, 36.7% and 8.0% respectively in the cases and 52.3%, 38.6% and 9.1% respectively in the controls. Odds ratios for lung cancer were all reduced, compared to Arg homozygotes, at 0.89 (95% CI 0.74-1.07), 0.86 (95% CI 0.62-1.18) and 0.88 (95% CI 0.74-1.05) for the genotypes Arg/Gln and Gln/Gln, and all carriers of the Gln allele respectively.

A study conducted in Sweden[27] used a case group made up of 177 newly diagnosed lung cancer patients. The control group consisted of 153 individuals selected from a population register covering the study area, frequency matched to the cases by hospital catchment area, sex, age and smoking category. The median age in the case group was 69 years, compared to 68 years in the controls. The proportion of men varied from 25.4% in the cases to 28.8% in the controls. A blood sample was obtained from each subject, from which DNA was extracted and polymorphisms in the XRCC1 gene identified using PCR. The Gln allele of the Arg399Gln polymorphism was present in 56.5% of the cases and 61.44% of the controls, giving an odds ratio for the risk of lung cancer of 0.81 (95% CI 0.52-1.25) for all subjects with this allele compared to those with the Arg/Arg genotype.

In a study conducted in Belgium[28], the case group consisted of 110 patients with newly diagnosed, previously untreated, histologically confirmed primary lung cancer from the respiratory medicine department of one hospital. The 110 age and sex-matched controls, all of whom had no history of cancer, were selected from a group of 350 individuals identified from the occupational medicine and geriatric departments of the same hospital and from local senior clubs. There were 81 men and 29 women, with a mean age of 61 years, in the case group and 86 men and 24 women, with a mean age of 62 years, in the control group. A heparinized blood sample was obtained from each study subject, from which lymphocytes were isolated and frozen for genotyping. This was carried out using PCR-RFLP analysis. For the -77T>C

polymorphism, the frequencies of the T/T, T/C and C/C genotypes were 36.4%, 47.3% and 16.4% respectively in the control group and 33.9%, 48.6% and 17.4% respectively in the cases. Compared to T homozygous individuals, the risk of lung cancer was increased in subjects with both the T/C (OR 1.10, 95% CI 0.61-1.98) and C/C (OR 1.14, 95% CI 0.52-2.50) genotypes. Adjustment for age, sex and pack-years of smoking had little effect on these estimates (T/C: OR 1.12, 95% CI 0.59-2.12; C/C: OR 1.12, 95% CI 0.48-2.58).

When the Arg194Trp polymorphism was examined, the control group was made up of 84.5% of subjects with the Arg/Arg genotype and 15.5% with the Arg/Trp genotype. There were no Trp homozygotes in the control group. The cases consisted of 91.8% Arg homozygotes, 7.3% Arg/Trp individuals and 0.9% Trp homozygotes. An unadjusted OR was estimated at 0.43 (0.18-1.05) for the risk of lung cancer in subjects with the Arg/Trp genotype compared to Arg homozygotes. Adjustment reduced this estimate and it became statistically significant (OR 0.32, 95% CI 0.12-0.86). No ORs were calculated for Trp homozygotes.

Subjects with the Arg/Arg genotype of the Arg280His polymorphism made up 87.3% of the control group and 96.3% of the cases, with Arg/His individuals comprising the remaining 12.7% and 3.7% of each group respectively. There were no study subjects with the His/His genotype. Compared to the Arg/Arg genotype, the risk of lung cancer in Arg/His subjects was significantly reduced (OR 0.26, 95% CI 0.08-0.82). Adjustment barely altered this estimate (OR 0.25, 95% CI 0.07-0.86).

The frequency of the Arg/Arg, Arg/Gln and Gln/Gln genotypes of the Arg399Gln polymorphism was 42.2%, 45.9% and 11.9% respectively in the controls, and 34.9%, 48.6% and 16.5% respectively in the cases. The unadjusted ORs for the risk of lung cancer were estimated at 1.28 (95% CI 0.72-2.29) for Arg/Gln subjects and 1.68 (95% CI 0.73-3.86) for Gln/Gln subjects, compared to Arg homozygotes. Although adjustment altered these

ORs, the overall conclusions remained unchanged (Arg/Gln: OR 1.44, 95% CI 0.76-2.69; Gln/Gln: OR 1.62, 95% CI 0.66-3.98).

The case group in a study carried out in Spain[29] consisted of 516 incident cases of histologically confirmed lung cancer while the control group was made up of 533 patients admitted to participating hospitals for diagnoses believed to be unrelated to the exposures of interest. Controls were matched to cases for age, sex and ethnicity. The proportion of men was 88.4% in the cases and 86.3% in the controls, while the mean age was 64.79 years in the cases compared to 63.54 in the controls. Genomic DNA was extracted from peripheral blood samples or exfoliated buccal cells and polymorphisms in the XRCC1 gene were examined using PCR-RFLP. The Arg/Arg genotype of the Arg399Gln polymorphism occurred in 43.0% of the cases and 40.7% of the controls, while the Arg/Gln and Gln/Gln genotypes were present in 42.5% and 14.5% of the cases respectively and 43.9% and 15.4% of the controls respectively. Compared to Arg/Arg homozygotes, the risk of lung cancer was non-significantly reduced in both Arg/Gln subjects (OR 0.86, 95% CI 0.63-1.16) and Gln homozygotes (OR 0.87, 95% CI 0.57-1.31).

Cases in a study conducted in India[30] consisted of 103 newly diagnosed histologically confirmed lung cancer patients, while the control group was made up of 122 healthy subjects from the local population. The proportion of men varied from 87.3% in the cases to 85.2% in the controls. No details of the age distribution of the study subjects were given. A peripheral blood sample was collected from each participant, from which DNA was extracted and polymorphisms in the XRCC1 gene identified using PCR-RFLP. When the Arg399Gln polymorphism was examined, the frequency of the Arg/Arg, Arg/Gln and Gln/Gln genotypes was 51.5%, 36.9% and 11.7% respectively in the cases and 28.7%, 57.4% and 13.9% in the controls. Adjusted ORs of 0.3 (95% CI 0.19-0.67), 0.4 (95% CI 0.18-1.18) and 0.6 (95% CI 0.46-0.80) were estimated for the Arg/Gln and Gln/Gln genotypes and for all subjects with the Gln allele respectively, compared to Arg homozygotes.

The Arg/Arg, Arg/Trp and Trp/Trp genotypes of the Arg194Trp polymorphism occurred in 38.8%, 37.9% and 23.3% of the cases respectively, and 42.6%, 38.5% and 18.9% of the controls respectively. There was no association between the Arg/Trp genotype and lung cancer, with an OR of 1.0 (95% CI 0.75-1.45) being estimated. The risk in Trp homozygotes and in all subjects with the Trp allele was non-significantly raised (Trp/Trp: OR 1.3, 95% CI 0.63-2.92; all Trp allele: OR 1.1, 95% CI 0.66-2.07).

A study conducted in China[31] compared polymorphisms in the XRCC1 gene in 247 lung cancer cases and 253 cancer-free controls. The controls were randomly selected from non-cancer patients admitted to bone wards in the same region as the cases, and were matched for age and sex. The proportion of men was 70% in both the case and control groups, and the mean age in both groups was 58 years. Genomic DNA was extracted from a peripheral blood sample obtained from each subject and XRCC1 polymorphisms detected using modified PCR-RFLP. For the Arg194Trp polymorphism, the frequency of the Arg/Arg, Arg/Trp and Trp/Trp genotypes was 49.8%, 40.7% and 9.5% respectively in the cases and 47.8%, 43.8% and 8.4% in the controls. The odds ratio for lung cancer, adjusted for duration of smoking, was estimated at 0.97 (95% CI 0.67-1.40) for all carriers of the Trp allele.

The frequency of A/A, A/G and G/G genotypes of the Pro206Pro polymorphism was 70.7%, 28.5% and 0.8% in the cases, compared to 82.5%, 17.5% and 0% in the controls. The risk of lung cancer was significantly raised in subjects with the G allele (OR 1.96, 95% CI 1.26-3.06) compared to those with the A/A genotype.

When the Arg280His polymorphism was investigated, the frequency of the Arg/Arg, Arg/His and His/His genotypes was 79.8%, 19.3% and 0.8% respectively among the cases and 74.0%, 24.4% and 1.7% in the controls. The risk of lung cancer in carriers of the His allele was reduced, although not significantly so (OR 0.86, 95% CI 0.69-1.07).

The Arg/Arg genotype of the Arg399Gln polymorphism occurred in 67.3% of the cases, compared to 68.4% of the controls. Arg/Gln subjects made up 31.7% and 26.9% of the two groups respectively, while Gln homozygotes accounted for 1.0% of the cases and 4.7% of the controls. An odds ratio of 0.97 (95% CI 0.78-1.20) was estimated for the risk of lung cancer in carriers of the Gln allele.

Finally, the G/G, G/A and A/A genotypes of the Gln632Gln polymorphism occurred in 80.6%, 18.9% and 0.4% of the cases and 78.9%, 20.2% and 0.8% of the controls. There was no association between lung cancer risk and carriers of the A allele of this polymorphism (OR 0.96, 95% CI 0.76-1.21).

The case group in a study carried out in China[5] consisted of 350 non-smoking women newly diagnosed with histopathologically confirmed lung cancer, while the control group was made up of 350 non-smoking female cancer-free controls, selected from the same hospital during the same time period as the cases. Controls were frequency matched to cases by age, and the mean age in the cases was 55.5 years, compared to 57.5 years in the controls. Genomic DNA was extracted from surgically resected normal tissue in the cases and from a venous blood sample in the controls. XRCC1 polymorphisms were analysed by PCR-RFLP. The T/T, T/C and C/C genotypes of the -77T>C polymorphism were found in 75.4%, 21.4% and 3.1% of the cases respectively, compared to 83.1%, 15.7% and 1.1% of the controls respectively. Compared to T/T individuals, the odds ratios for lung cancer were estimated at 1.51 (95% CI 1.01-2.24) for T/C subjects, 3.14 (95% CI0.96-10.30) for C homozygotes, and 1.61 (95% CI 1.12-2.39) for all carriers of the C allele.

When the Arg194Trp polymorphism was examined, Arg homozygotes made up 52.6% of the case group and 56.0% of the controls. Subjects with the Arg/Trp genotype comprised 38.9% of the cases and 38.0% of the controls, while the Trp/Trp genotype was found in 8.6% of the cases and 6.0% of the controls. An odds ratio for the risk of lung cancer of 0.94 (95% CI 0.68-1.30)

was estimated for the Arg/Trp genotype compared to Arg homozygotes, while that for Trp homozygotes was estimated at 1.53 (95% CI 0.84-2.81).

For the Arg280His polymorphism, the Arg/Arg, Arg/His and His/His genotypes were seen in 76.0%, 22.6% and 1.4% of the cases and 78.3%, 20.6% and 1.1% of the controls. Compared to Arg homozygotes, odds ratios for the risk of lung cancer in Arg/His and His/His individuals were both raised, although neither reached statistical significance (Arg/His: OR 1.15, 95% CI 0.80-1.67; His/His: OR 1.78, 95% CI 0.47-6.75).

The Arg/Arg genotype of the Arg399Gln polymorphism occurred in 48.0% of the cases and 57.4% of the controls, while the Arg/Gln genotype was seen in 39.7% of the cases and 35.1% of the controls. Gln homozygotes made up 12.3% of the cases and 7.4% of the control group. The risk of lung cancer was raised in both Arg/Gln and Gln/Gln subjects, compared to Arg homozygotes, but only reached statistical significance for Gln homozygotes (Arg/Gln: OR 1.26, 95% CI 0.91-1.75; Gln/Gln: OR 1.73, 95% CI 1.01-2.97).

4.3 Summary of study characteristics of the additional individual studies

Of the 13 individual studies that investigated polymorphisms in the XRCC1 gene in relation to lung cancer risk, six took place in China, and two were conducted in the USA. One each was carried out in Belgium, India, Poland, Spain and Sweden.

The largest study[8] was based on 1024 cases, and none of the other studies included more than 1000 cases. Four studies[22,23,25,29] were based on between 500 and 1000 cases, and all but three of the remaining studies were based on case groups of between 100 and 500 subjects, with the exception of the studies by Butkiewicz et al[21],Chan et al[24] and Li and Hemminki[26] which included only 96, 75 and 50 cases respectively.

All 13 of the studies were of a conventional case-control design.

One of the studies[21] included only male participants, two studies[5,26] were based on women only, and one study[22] failed to give any information on the sex of the subjects. In the remaining studies both the case and control groups were of mixed sex, and were matched accordingly in seven of the studies[8,24,25,27-29,31]. In one of the studies in which matching had not taken place[23], the proportion of men in the case group was significantly higher than in the control group.

Nine of the studies [5,8,21,24,25,27-29,31] matched the cases and controls for age. One of these studies[8] stated that cases and controls were comparable for age but failed to give any further details. Three other studies[22,26,30] gave no details of the age distribution of the study subjects at all. In the remaining study[23], in which matching for age had not taken place, cases were significantly older than controls.

Nine of the studies[8,21-23,25,27,29-31] included both smokers and non-smokers. In two of these studies[21,27], cases and controls were matched for smoking status. In six studies[8,23,25,29-31] where matching had not taken place there were more smokers in the case group, and in four of these studies[8,23,25,29] the difference reached statistical significance. In addition, five studies[8,23,25,29,31] reported that there were significantly more heavy smokers among the cases, and one study[23] found that cases had smoked for a longer duration than the controls. Two studies[5,26] were based on non-smokers only, while another two studies[24,28] did not give any details of the smoking status of participants, but one[28] did report that there were significantly more heavy smokers in the case group than among the controls.

All but three of the studies[21,22,24] adjusted their results for at least some potential confounding factors. Only the study by Yin et al[31] failed to adjust for age, while sex was included as an adjustment factor by seven studies[8,23,25,27-30]. Variables relating to smoking history were included by eight studies[8,23,25,27-31]. Two studies[5,26] adjusted for exposure to cooking oil smoke, while two others[8,27] included other genotypes as a potential confounder.

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 XRCC1 polymorphisms are presented in Tables 2 and 3 respectively. The results are discussed below for each polymorphism separately.

-77T>C

Three studies[5,8,25] reported that, compared to subjects with the T/T genotype, the risk of lung cancer was significantly raised in the T/C genotype, while in the remaining study the risk was non-significantly raised. Meta-analysis of these results, using the least adjusted risk estimates where both unadjusted and adjusted estimates were presented, produced an overall estimate of lung cancer risk of 1.44 (95% CI 1.25-1.67) for both the fixed and random effects models. Substituting the most adjusted odds ratios where applicable made little difference to these findings (OR 1.45, 95% CI 1.25-1.69 for both fixed and random effects models). This result was heavily influenced by the three studies in Asian populations, for when meta-analysis was restricted to these studies only the results were very similar to those for the entire data set (least adjusted: OR 1.47, 95% CI 1.26-1.71 for both fixed and random effects models; most adjusted: OR 1.48, 95% CI 1.27-1.72 for both fixed and random effects models).

When C/C homozygotes were examined, all four of the studies found that the risk of lung cancer was increased. This reached statistical significance in only one of the studies[25], but this was removed after adjustment for potentially confounding variables. Meta-analysis based on the least adjusted odds ratios produced an overall risk estimate of 1.88 (95% CI 1.19-2.96) for the fixed effects model and 1.90 (95% CI 1.17-3.06) for the random effects model. Substitution of the most adjusted odds ratios where available reduced this estimate slightly, to 1.86 (95% CI 1.17-2.98) for both models. When meta-analysis was restricted to the three Asian studies, the overall risk estimate was somewhat higher, at 2.42 (95% CI 1.38-4.23) for both models

using least adjusted odds ratios, and 2.34 (95% CI 1.33-4.11) for both models when the most adjusted odds ratios were used.

Only the studies conducted in Asian populations presented estimates of the risk of lung cancer in relation to the overall prevalence of the C allele of this polymorphism, and all three reported that the risk was significantly raised. Using the least adjusted odds ratios, meta-analysis produced an overall estimate of lung cancer risk of 1.51 (95% CI 1.30-1.75) for both the fixed and random effects models, which was marginally increased to 1.52 (95% CI 1.31-1.76) when the most adjusted odds ratios were used.

From Table 3 it can be seen that the prevalence of the C allele of this polymorphism is far more common in Caucasians than in Asian populations, although this is based on only one study in Caucasians. The C allele occurred in about two-thirds of the population of this study, compared to approximately 20% of Asians.

Arg194Trp

Compared to Arg homozygotes, five studies[4,5,8,24,28] reported that the risk of lung cancer was reduced in subjects with the Arg/Trp genotype of this polymorphism, with one of these results being based on a meta-analysis of eight studies[4]. The difference reached statistical significance in only one study[24], although in another study[28] the risk estimate became significant following adjustment for potential confounders. One study[30] failed to find any association between this genotype and the incidence of lung cancer, while in another[25], the odds ratio was non-significantly raised. Meta-analysis of the available results, using the least adjusted odds ratios where applicable, produced an overall risk estimate of 0.93 (95% CI 0.85-1.01) for the fixed effects model, and 0.92 (95% CI 0.82-1.04) for the random effects model. Substitution of the most adjusted odds ratio did not significantly alter these findings (fixed effects model: OR 0.92, 95% CI 0.84-1.01; random effects model: OR 0.91, 95% CI 0.80-1.04). When results from the two studies based on Caucasian populations were analysed separately, the overall risk was lower, but still failed to reach statistical significance for either the fixed effects model

(OR 0.88, 95% CI 0.77-1.01) or the random effects model (OR 0.71, 95% CI 0.36-1.40). Using the most adjusted odds ratios made no difference to the result for the fixed effects model, but reduced the risk estimate produced by the random effects model, although it remained non-significant (OR 0.61, 95% CI 0.23-1.62). Meta-analysis of the results from the six Asian populations produced an overall risk estimate of 0.96 (95% CI 0.86-1.08) which remained unaltered regardless of the model used, or when adjusted odds ratios were substituted.

Five studies[4,5,8,25,30] reported that the risk of lung cancer in Trp homozygotes was increased compared to Arg homozygotes, although in none of these did the difference reach statistical significance. Again, one of these studies[4] was reporting the results of a meta-analysis of eight individual studies. One other study[22] found a non-significantly increased risk, using a reference group of all subjects with the Arg allele. In one study[24], the risk of lung cancer was non-significantly reduced. When these results were combined in a meta-analysis, the overall risk was estimated at 1.12 for both the fixed and random effects models, although the confidence intervals varied slightly (fixed effects model: 95% CI 0.92-1.36; random effects model: 95% CI 0.91-1.38). Substitution of adjusted odds ratios where applicable increased the risk estimate to 1.14 for both models (fixed effects model: 95% CI 0.94-1.39; random effects model: 95% CI 0.93-1.40). When the meta-analysis was restricted to results solely from Asian populations, the results remained virtually unchanged (least adjusted: fixed effects model OR 1.12, 95% CI 0.91-1.37; random effects model OR 1.12, 95% CI 0.89-1.40; most adjusted: fixed effects model OR 1.14, 95% CI 0.93-1.41; random effects model OR 1.14, 95% CI 0.92-1.42).

When the risk of lung cancer was examined in all subjects with the Trp allele, two studies[25,30] reported a non-significantly raised incidence of lung cancer, two studies[24,31] found that the risk was reduced, significantly so in one of the studies[24], and two studies[8,21] failed to find any association between the Trp allele and lung cancer risk. Meta-analysis of the available odds ratios, using the least adjusted where applicable, produced an overall estimate of risk

of 0.97 (95% CI 0.86-1.10) for the fixed effects model, and 0.95 (95% CI 0.80-1.13) for the random effects model. Using the most adjusted odds ratios had little effect on these results (fixed effects model: OR 0.98, 95% CI 0.87-1.10; random effects model: 0.95, 95% CI 0.80-1.14).

Overall, the Trp allele occurred in about 30% of subjects, but there was great variation according to ethnicity. In Caucasians, the prevalence of this allele was a little over 10%, while in Asians it was five times higher, at about 50%. In particular, Trp homozygotes made up nearly 10% of the Asian population, but less than 1% of Caucasian subjects.

Pro206Pro

Compared to subjects with the A/A genotype, one study[19] reported a non-significantly increased risk of lung cancer in subjects with the A/G genotype but a decreased risk in G homozygotes, which also failed to reach statistical significance. Another study[31] reported that the risk of lung cancer in all subjects with the G allele was significantly raised.

Table 3 shows that the G allele was far commoner in Caucasians than in Asians, occurring in approximately 70% of the former population, compared to around 30% of cases and 20% of controls in the latter. It was notable that the G/G genotype was found in only two Asian individuals, but subjects with this genotype made up about 20% of the Caucasian population.

Arg280His

Subjects with the Arg/His genotype were reported to have a lower risk of lung cancer by two studies[8,28], significantly so in one study[28], and a higher risk by two studies[4,5], using Arg/Arg individuals as a reference group. One of these risk estimates was based on a meta-analysis of seven studies[4]. Meta-analysis of the available odds ratios, using the least adjusted where both unadjusted and adjusted were presented, produced an overall estimate of lung cancer risk of 0.99 (95% CI 0.88-1.12) using a fixed effects model and 0.96 (0.77-1.20) using a random effects model. Substitution of adjusted odds ratios made no difference to the fixed effects estimate, but increased the one for the

random effects model slightly (OR 0.97, 95% CI 0.78-1.20). When the meta-analysis was restricted to Caucasian populations, the estimate for the fixed effects model was similar to that for the entire dataset (OR 0.97, 95% CI 0.83-1.15), while the risk estimate for the random effects model was much lower, at 0.58 (95% CI 0.16-2.12). Using adjusted odds ratios where available made little difference to these findings (fixed effects model: OR 0.98, 95% CI 0.83-1.15; random effects model: OR 0.58, 95% CI 0.15-2.18). When studies based on Asian populations were examined separately, a slightly raised overall risk was estimated, at 1.01 (95% CI 0.84-1.21) for the fixed effects model and 1.02 (95% CI 0.83-1.25) for the random effects model.

For His/His subjects, one study[8] reported a reduced risk of lung cancer, while another study[5] found an increased risk. Neither finding reached statistical significance. Meta-analysis of these odds ratios produced an overall risk estimate of 0.99 (95% CI 0.45-2.19) using a fixed effects model and 1.01 (95% CI 0.43-2.38) using a random effects model.

When the risk of lung cancer was examined in all subjects with the His allele of this polymorphism, two studies[8,31] reported a non-significant decrease in risk, one study[4] found a non-significant increase in risk, based on the meta-analysis of seven studies, and one study[21] failed to find any association. The overall risk obtained from a meta-analysis of these results was estimated at 0.97 (95% CI 0.87-1.08) using a fixed effects model and 0.95 (95% CI 0.83-1.10) with a random effects model. When the analysis was restricted to studies in Asian populations, the fixed effects model produced a risk estimate of 0.93 (0.80-1.08) while the random effects model estimate was 0.97 (0.76-1.24).

From Table 3, it can be seen that the His allele was not particularly common, occurring in just over 10% of the total population. However, subjects with the Arg/His genotype were twice as common in the Asian population, making up nearly 20% of subjects, as in Caucasians, where this genotype accounted for less than 10% of study subjects. His homozygotes were rare in both populations, accounting for about 1% of Asians, and less than 0.5% of Caucasians.

Arg399Gln

Compared to Arg homozygotes, when the risk of lung cancer in individuals with the Arg/Gln genotype of this polymorphism was examined, seven studies[4,8,22,25,26,29,30] found a decreased incidence of lung cancer, which reached statistical significance in one study[30]. One of these estimates[4] was based on a meta-analysis of 17 individual studies. A further four studies[5,23,24,28] reported a non-significantly increased risk of lung cancer. A meta-analysis of all the available data, using the least adjusted odds ratios where applicable, produced an overall risk estimate of 0.98 (95% CI 0.93-1.03) for the fixed effects model and 0.97 (0.87-1.07) for the random effects model. Substituting the most adjusted odds ratios made no difference for the fixed effects estimate, and only slightly altered the confidence interval for the random effects model (95% CI 0.86-1.08). Results for studies based in Caucasian populations were very similar to the entire dataset, with an odds ratio of 0.99 (95 % CI 0.92-1.07) being estimated for both models, which was not altered when based on adjusted data. The overall risk for Asian studies was slightly lower, at 0.95 (95% CI 0.87-1.05) 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 either model, but did slightly change the confidence intervals (fixed effects model: 95% CI 0.87-1.04; random effects model: 95% CI 0.77-1.12).

With regard to Gln homozygotes, six studies[8,22,24,25,29,30] reported that the risk of lung cancer was lower in these subjects than in Arg homozygotes, although the difference did not reach statistical significance in any of them. Five studies[4,5,23,26,28], one of which was based on a meta-analysis of 17 other studies[4], found an increased risk, which was statistically significant in two studies[5,23], and just failed to reach significance in another[26]. Meta-analysis of the available data produced an overall risk estimate of 1.02 (95% CI 0.92-1.13) using the fixed effects model and 1.01 (95% CI 0.84-1.22) with the random effects model. Substituting adjusted odds ratios where applicable reduced the risk estimate to 1.00 for both models, with a 95% confidence

interval of 0.90-1.11 for the fixed effects model and 0.83-1.20 for the random effects model. Ethnicity made little difference to these findings, with the odds ratios estimated for both Caucasian and Asian populations being similar to those for the entire dataset (Caucasians, least adjusted: fixed effects OR 1.00, 95% CI 0.88-1.13, random effects OR 1.02, 95% CI 0.82-1.26; most adjusted: fixed effects OR 0.97, 95% CI 0.85-1.10, random effects OR 0.98, 95% CI 0.83-1.17; Asians, least adjusted: fixed effects OR 0.99, 95% CI 0.88-1.12, random effects OR 0.98, 95% CI 0.75-1.29; most adjusted: fixed effects OR 1.00, 95% CI 0.88-1.13, random effects OR 0.99, 95% CI 0.75-1.29).

The risk of lung cancer was also examined in all subjects with the Gln allele. Seven studies [8,22,25-27,30,31] reported that the risk was reduced in these individuals compared to Arg homozygotes, with the difference reaching statistical significance in one of the studies[30]. One study[21] failed to find any association, and only one study[24] found an increase in lung cancer risk, which failed to reach statistical significance. When these results were combined in a meta-analysis, the overall risk estimate, using the least adjusted odds ratios where both unadjusted and adjusted were presented, was significantly reduced, at 0.88 (95% CI 0.80-0.96) for the fixed effects model and 0.87 (95% CI 0.78-0.98) for the random effects model. These findings were unaltered by substitution of adjusted odds ratios. Results were similar when the analysis was restricted to Caucasians, although the significance of the association was lost (fixed effects: OR 0.89, 95% CI 0.72-1.11; random effects: OR 0.89, 95% CI 0.72-1.11). Analysis of the Asian populations separately produced risk estimates of 0.88 (95% CI 0.79-0.97) and 0.87 (95% CI 0.74-1.01) for the fixed effects and random effects models respectively, using unadjusted odds ratios where applicable. Substitution of adjusted odds ratios barely altered these findings (fixed effects: OR 0.87, 95% CI 0.79-0.97; random effects: OR 0.86, 95% CI 0.74-1.01).

The Gln allele of this polymorphism occurred in just over 50% of the total study population, and there was less variation due to ethnicity than for some of the other polymorphisms. This allele was seen less frequently in

Asians than in Caucasians, occurring in approximately 45% and 55% of subjects respectively.

Gln632Gln

The one study[31] that presented data for this polymorphism reported a non-significantly decreased risk of lung cancer in all subjects with the A allele, compared to those with the G/G genotype. No meta-analysis was conducted. Table 3 shows that the A allele occurred in about 20% of study subjects.

4.5 The effect of stratification by smoking status and intensity on risk of lung cancer according to XRCC1 genotype

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[4] where applicable.

-77T>C

Both of the studies[8,25] that presented results for all subjects with the C allele compared to T/T homozygotes found that odds ratios for smokers were higher than those for non-smokers. However, when the intensity of smoking was examined, the odds ratio for heavier smokers was lower than for those with less exposure[8].

Arg194Trp

Only one study[30] presented results for Arg/Trp individuals compared to Arg homozygotes stratified by smoking status, and the results were comparable in non-smokers and smokers.

When Trp homozygotes were examined, odds ratios in smokers were higher than in non-smokers in two studies[3,17], although in one of these studies[3] this was based on a comparison of never smokers and those with at least 30 pack-years of exposure as no odds ratio was available for smokers with less exposure, and were comparable in another study[30].

For all subjects with the Trp allele, odds ratios were lower in smokers than in non-smokers in one study[6], and comparable in another study[30]. One further study[17] reported a higher odds ratio for ever smokers than for never smokers, although for both groups this was in comparison to never smoking Arg homozygotes. When intensity of smoking was examined, one study[9] found a lower odds ratio with a higher number of cigarettes smoked per day, while another study[6] did not find a consistent pattern of association with amount smoked. One further study[17] found that odds ratios generally increased with increasing number of pack-years of exposure, but this was in comparison to never smoking Arg homozygotes.

Arg280His

When the risk of lung cancer was stratified by intensity of smoking for all subjects with the His allele, one study[31] found a consistent increase in risk with longer duration of smoking. One study[6] reported lower risks in light and heavy smokers compared to never smokers, but a higher risk in moderate smokers. A third study[17] found that, compared to never smoking Arg homozygotes, risks in smokers were higher, but showed no consistent association with pack-years of exposure.

Arg399Gln

One study[14] reported that for subjects with the Arg/Gln genotype, odds ratios were higher in former and current smokers than in never smokers, although this study used never smoking Arg homozygotes as the reference group. One study[29] found that the risk in former smokers was lower while that in current smokers was higher than in subjects who did not smoke, and one study[30] reported a slightly lower odds ratio for smokers than for non-smokers. When intensity of smoking was examined, one study[9] found a lower odds ratio in subjects who smoked a higher number of cigarettes per day. Two studies[2,29] found that the risk of lung cancer was not affected by the level of smoking exposure, while another study[12] reported odds ratios that were comparable for non, mild and moderate smokers. However, the risk for heavy smokers in this study was markedly reduced. Similarly, the odds ratio in the study by De Ruyck et al[28] was much lower for smokers with the highest exposure than for

those with lower exposure. One study[14] reported an increase in risk with increasing exposure to smoking, although this was in comparison to never smoking Arg homozygotes. In one study[6], the risks for all smoking categories were slightly higher than that for never smokers, but did not follow a general pattern of increasing risk with increasing smoking intensity.

When Gln homozygotes were examined, one study[29] found that odds ratios were generally higher in subjects who were ever, ex or current smokers than in never smokers. One study[14] found that the risk of lung cancer was reduced in ex-smokers but increased in current smokers, compared to never smokers, but this was using Arg/Arg never smokers as a reference group. One study[30] found no effect of stratification for smoking status on the risk of lung cancer. When the intensity of smoking was considered, one study[9] found that the odds ratio was lower for those who smoked more per day, while another three studies[2,12,28] reported a similar finding when pack-years of exposure were examined. In one of these studies[12], the odds ratio for smokers with the heaviest exposure was markedly reduced. One study[14] found that the odds ratio for heavy smokers was much higher than that for never smokers, although both odds ratios used never smoking Arg homozygotes as a reference group. Two studies[6,29] found that the risk of lung cancer was not particularly affected by stratification for smoking intensity.

For all subjects with the Gln allele, one study[27] reported a higher odds ratio for ever smokers than for never smokers, while another study[30] found that the risk in smokers was lower. When results were stratified by intensity of smoking exposure, one study[11] reported that odds ratios were higher for subjects with intermediate daily tobacco consumption, but lower for those in the highest category, compared to subjects who smoked the least per day, and two studies[13,17] found that the risk increased as smoking exposure went up, although in one of these studies[17], the reference group used was Arg/Arg never smokers. Finally, one study[2] found that there was no real association between smoking intensity and the risk of lung cancer.

4.6 Conclusions

These findings are suggestive of a positive relationship between the -77T>C polymorphism and lung cancer risk, particularly with the T/C genotype. All of the odds ratios reported for this polymorphism were raised, and all of the overall risks estimated by meta-analysis were significantly increased. However, more studies will be needed before definitive conclusions can be drawn. There was also some evidence for a decrease in lung cancer risk for all subjects with the Gln allele of the Arg399Gln polymorphism, with seven of the nine studies that included relevant data presenting an odds ratio below 1.00, and meta-analysis estimating a significantly reduced overall risk. However, when specific genotypes were considered, no such association was seen, even though these were examined by a larger number of studies. No clear association with lung cancer risk was seen for any of the other XRCC1 polymorphisms.

Due partly to the small number of studies presenting results, no clear pattern emerges when the risk of lung cancer according to genotype of the various XRCC1 polymorphisms is stratified by smoking status and/or intensity.

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

Thirteen individual studies and one meta-analysis, based on a maximum of 17 studies, examined polymorphisms in the XRCC1 gene with regard to the risk of lung cancer. All of the studies that examined lung cancer risk in relation to the -77T>C polymorphism found that it was raised, and overall meta-analyses consistently estimated significantly increased odds ratios for each of the genotypes examined. There was also evidence of a reduction in lung cancer risk in association with the Arg399Gln polymorphism, although this was mostly restricted to all subjects with the Gln allele, for whom a significantly reduced odds ratio was estimated by meta-analysis. The picture was less clear when specific genotypes were examined. There was no obvious evidence of any association between the other polymorphisms and lung cancer risk. 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 XRCC1 genotype

Ref.	Author (Country)	Year[a]	Cases/ controls	Genotype	Odds ratios[b]	Sig[c]	Adjustment factors[d]
-77T>C[e]							
25	Hu (China)	2005	710/710	C/T	1.49 (1.17-1.91)	p<0.05	None
					1.51 (1.17-1.94)	p<0.05	A,PY,S
				C/C	3.35 (1.07-10.45)	p<0.05	None
					2.98 (0.93-9.59)	NS	A,PY,S
				All C allele	1.54 (1.21-1.96)	p<0.05	None
					1.55 (1.21-1.98)	p<0.05	A,PY,S
8	Hao (China)	2006	1024/1118	T/C	1.44 (1.16-1.80)	p<0.05	A,OG,S,SS
				C/C	1.87 (0.87-4.01)	NS	A,OG,S,SS
				All C allele	1.46 (1.18-1.82)	p<0.05	A,OG,S,SS
28	De Ruyck (Belgium)	2007	110/110	T/C	1.10 (0.61-1.98)	NS	None
					1.12 (0.59-2.12)	NS	A,PY,S
				C/C	1.14 (0.52-2.50)	NS	None
					1.12 (0.48-2.58)	NS	A,PY,S
5	Li (China)	2008	350/350	T/C	1.51 (1.01-2.24)	p<0.05	A,CS
				C/C	3.14 (0.96-10.30)	NS	A,CS
				All C allele	1.61 (1.12-2.39)	p<0.05	A,CS
Arg194Trp[f]							
21	Butkiewicz (Poland)	2001	96/96	All Trp allele	No association reported	NS	-
22	Spitz (USA)	2003	524/524	Trp/Trp[g]	1.02 (0.72-1.44)	NS	None
24	Chan (China)	2005	75/162	Arg/Trp	0.52 (0.29-0.94)	p=0.03	None
				Trp/Trp	0.30 (0.08-1.07)	NS	None
				All Trp allele	0.48 (0.27-0.84)	p=0.01	None
25	Hu (China)	2005	710/710	Arg/Trp	1.02 (0.82-1.27)	NS	None
					1.01 (0.81-1.26)	NS	A,PY,S
				Trp/Trp	1.03 (0.70-1.50)	NS	None
					1.11 (0.75-1.63)	NS	A,PY,S
				All Trp allele	1.02 (0.83-1.26)	NS	None
					1.03 (0.83-1.27)	NS	A,PY,S
8	Hao (China)	2006	1024/1118	Arg/Trp	0.98 (0.82-1.18)	NS	A,OG,S,SS
				Trp/Trp	1.11 (0.80-1.54)	NS	A,OG,S,SS
				All Trp allele	1.00 (0.84-1.20)	NS	A,OG,S,SS
4	Kiyohara[h] (Various)	2006	3714/5385	Arg/Trp	0.89 (0.78-1.03)	NS	None
				Trp/Trp	1.19 (0.76-1.86)	NS	None
28	De Ruyck (Belgium)	2007	110/110	Arg/Trp	0.43 (0.18-1.05)	NS	None
					0.32 (0.12-0.86)	p<0.05	A,PY,S
				Trp/Trp	1 subject found	-	-
30	Pachouri (India)	2007	103/122	Arg/Trp	1.00 (0.75-1.45)	NS	A,S,SS
				Trp/Trp	1.30 (0.63-2.92)	NS	A,S,SS
				All Trp allele	1.10 (0.66-2.07)	NS	A,S,SS
31	Yin (China)	2007	241/249	All Trp allele	0.97 (0.67-1.40)	NS	SD
5	Li (China)	2008	350/350	Arg/Trp	0.94 (0.68-1.30)	NS	A,CS
				Trp/Trp	1.53 (0.84-2.81)	NS	A,CS
Pro206Pro[i]							
19	Matullo (10 European countries)	2006	116/1093	A/G	1.53 (0.90-2.60)	NS	BMI,D,E, EL,ETS, PS,S
				G/G	0.81 (0.41-1.60)	NS	BMI,D,E, EL,ETS, PS,S
31	Yin (China)	2007	239/246	All G allele	1.96 (1.26-3.06)	p=0.003	SD
Arg280His[f]							
21	Butkiewicz (Poland)	2001	96/96	All His allele	No association reported	NS	-
8	Hao (China)	2006	1024/1118	Arg/His	0.90 (0.71-1.13)	NS	A,OG,S,SS
				His/His	0.72 (0.27-1.93)	NS	A,OG,S,SS
				All His allele	0.89 (0.71-1.12)	NS	A,OG,S,SS
4	Kiyohara[h] (Various)	2006	3640/3981	Arg/His	1.03 (0.88-1.20)	NS	None
				All His allele	1.06 (0.91-1.23)	NS	None

28	De Ruyck (Belgium)	2007	109/110	Arg/His	0.26 (0.08-0.82)	p<0.05	None
					0.25 (0.07-0.86)	p<0.05	A,PY,S
				His/His	No subjects found	-	-
31	Yin (China)	2007	238/242	All His allele	0.86 (0.69-1.07)	NS	SD
5	Li (China)	2008	350/350	Arg/His	1.15 (0.80-1.67)	NS	A,CS
				His/His	1.78 (0.47-6.75)	NS	A,CS
Arg399Gln[f]							
21	Butkiewicz (Poland)	2001	96/96	All Gln allele	No association reported	NS	-
22	Spitz (USA)	2003	524/524	Arg/Gln	0.97 (0.74-1.26)[j]	NS	None
				Gln/Gln	0.80 (0.55-1.16)[j]	NS	None
				All Gln allele	0.92 (0.72-1.18)[j]	NS	None
23	Liu (USA)	2004	935/1233	Arg/Gln	1.02 (0.85-1.22)	NS	None
					1.04 (0.84-1.29)	NS	A,PY,S,SS, YSC
				Gln/Gln	1.33 (1.02-1.74)	p<0.05	None
					1.27 (0.92-1.75)	NS	A,PY,S,SS, YSC
24	Chan (China)	2005	75/162	Arg/Gln	1.14 (0.65-2.02)	NS	None
				Gln/Gln	0.82 (0.25-2.73)	NS	None
				All Gln allele	1.09 (0.63-1.90)	NS	None
25	Hu (China)	2005	710/710	Arg/Gln	0.99 (0.79-1.23)	NS	None
					0.98 (0.78-1.23)	NS	A,PY,S
				Gln/Gln	0.81 (0.54-1.22)	NS	None
					0.83 (0.54-1.25)	NS	A,PY,S
				All Gln allele	0.96 (0.78-1.18)	NS	None
					0.95 (0.77-1.18)	NS	A,PY,S
26	Li (China)	2005	50/50	Arg/Gln	0.99 (0.4-2.46)	NS	A,CS
				Gln/Gln	5.43 (0.99-29.7)	NS	A,CS
				All Gln allele	0.73 (0.31-1.72)	NS	A,CS
8	Hao (China)	2006	1024/1118	Arg/Gln	0.89 (0.74-1.07)	NS	A,OG,S,SS
				Gln/Gln	0.86 (0.62-1.18)	NS	A,OG,S,SS
				All Gln allele	0.88 (0.74-1.05)	NS	A,OG,S,SS
4	Kiyohara[h] (Various)	2006	7385/9380	Arg/Gln	0.99 (0.93-1.06)	NS	None
				Gln/Gln	1.02 (0.88-1.19)	NS	None
27	Ryk (Sweden)	2006	177/153	All Gln allele	0.81 (0.52-1.25)	NS	A,OG,PY, S
28	De Ruyck (Belgium)	2007	109/109	Arg/Gln	1.28 (0.72-2.29)	NS	None
					1.44 (0.76-2.69)	NS	A,PY,S
				Gln/Gln	1.68 (0.73-3.86)	NS	None
					1.62 (0.66-3.98)	NS	A,PY,S
29	Lopez-Cima (Spain)	2007	516/533	Arg/Gln	0.86 (0.63-1.16)	NS	A,PY,S
				Gln/Gln	0.87 (0.57-1.31)	NS	A,PY,S
30	Pachouri (India)	2007	103/122	Arg/Gln	0.30 (0.19-0.67)	p<0.05	A,S,SS
				Gln/Gln	0.40 (0.18-1.18)	NS	A,S,SS
				All Gln allele	0.60 (0.46-0.80)	p=0.0008	A,S,SS
31	Yin (China)	2007	205/193	All Gln allele	0.97 (0.78-1.20)	NS	SD
5	Li (China)	2008	350/350	Arg/Gln	1.26 (0.91-1.75)	NS	A,CS
				Gln/Gln	1.73 (1.01-2.97)	p<0.05	A,CS
Gln632Gln[k]							
31	Yin (China)	2007	227/242	All A allele	0.96 (0.76-1.21)	NS	SD

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, BMI = body mass index, CS = cooking oil smoke, D = dietary factors, E = exercise, EL = educational level, ETS = environmental tobacco smoke, OG = other genotype, PS = previous smoking, PY = pack-years of smoking, S = sex, SD = smoking duration, SS = smoking status, YSC = years since smoking cessation
e Using T/T individuals as the reference group
f Using Arg/Arg individuals as the reference group
g Using Arg/Arg and Arg/Trp individuals as the reference group
h Meta-analysis
i Using A/A individuals as the reference group
j Estimated from data given
k Using G/G individuals as the reference group

Table 2: Results of meta-analysis for the risk of lung cancer in relation to XRCC1 polymorphisms

Genotype	No. of studies[a]	Heterogeneity Chisquared, p	Odds ratio (95% confidence interval) Fixed effects model	Random effects model	Notes
-77T>C					
T/C	4	0.93, NS	1.44 (1.25-1.67)	1.44 (1.25-1.67)	Least adjusted
	4	0.77, NS	1.45 (1.25-1.69)	1.45 (1.25-1.69)	Most adjusted
	3	0.06, NS	1.47 (1.26-1.71)	1.47 (1.26-1.71)	Asian studies, least adjusted
	3	0.09, NS	1.48 (1.27-1.72)	1.48 (1.27-1.72)	Asian studies, most adjusted
C/C	4	3.27, NS	1.88 (1.19-2.96)	1.90 (1.17-3.06)	Least adjusted
	4	2.77, NS	1.86 (1.17-2.98)	1.86 (1.17-2.98)	Most adjusted
	3	0.94, NS	2.42 (1.38-4.23)	2.42 (1.38-4.23)	Asian studies, least adjusted
	3	0.73, NS	2.34 (1.33-4.11)	2.34 (1.33-4.11)	Asian studies, most adjusted
All C allele	3	0.23, NS	1.51 (1.30-1.75)	1.51 (1.30-1.75)	Least adjusted
	3	0.24, NS	1.52 (1.31-1.76)	1.52 (1.31-1.76)	Most adjusted
Arg194Trp					
Arg/Trp	7	8.26, NS	0.93 (0.85-1.01)	0.92 (0.82-1.04)	Least adjusted
	7	9.66, NS	0.92 (0.84-1.01)	0.91 (0.80-1.04)	Most adjusted
	2	2.63, NS	0.88 (0.77-1.01)	0.71 (0.36-1.40)	Caucasian studies, least adjusted
	2	4.15, p=0.042	0.88 (0.77-1.01)	0.61 (0.23-1.62)	Caucasian studies, most adjusted
	6	4.59, NS	0.96 (0.86-1.08)	0.96 (0.86-1.08)	Asian studies, least adjusted
	6	4.50, NS	0.96 (0.86-1.08)	0.96 (0.86-1.08)	Asian studies, most adjusted
Trp/Trp[b]	6	5.39, NS	1.12 (0.92-1.36)	1.12 (0.91-1.38)	Least adjusted
	6	5.18, NS	1.14 (0.94-1.39)	1.14 (0.93-1.40)	Most adjusted
	6	5.45, NS	1.12 (0.91-1.37)	1.12 (0.89-1.40)	Asian studies, least adjusted
	6	5.24, NS	1.14 (0.93-1.41)	1.14 (0.92-1.42)	Asian studies, most adjusted
All Trp allele[c]	5	6.42, NS	0.97 (0.86-1.10)	0.95 (0.80-1.13)	Least adjusted
	5	6.49, NS	0.98 (0.87-1.10)	0.95 (0.80-1.14)	Most adjusted
Arg280His					
Arg/His	4	6.61, NS	0.99 (0.88-1.12)	0.96 (0.77-1.20)	Least adjusted
	4	6.16, NS	0.99 (0.88-1.12)	0.97 (0.78-1.20)	Most adjusted
	2	5.05, p=0.025	0.97 (0.83-1.15)	0.58 (0.16-2.12)	Caucasian studies, least adjusted
	2	4.61, p=0.032	0.98 (0.83-1.15)	0.58 (0.15-2.18)	Caucasian studies, most adjusted
	3	2.32, NS	1.01 (0.84-1.21)	1.02 (0.83-1.25)	Asian studies
His/His	2	1.15, NS	0.99 (0.45-2.19)	1.01 (0.43-2.38)	
All His allele[c]	3	3.03, NS	0.97 (0.87-1.08)	0.95 (0.83-1.10)	
	3	4.74, NS	0.93 (0.80-1.08)	0.97 (0.76-1.24)	Asian studies

Arg399Gln					
Arg/Gln	11	18.97,p=0.041	0.98 (0.93-1.03)	0.97 (0.87-1.07)	Least adjusted
	11	19.67,p=0.033	0.98 (0.93-1.03)	0.97 (0.86-1.08)	Most adjusted
	5	1.70, NS	0.99 (0.92-1.07)	0.99 (0.92-1.07)	Caucasian studies, least adjusted
	5	2.39, NS	0.99 (0.92-1.07)	0.99 (0.92-1.07)	Caucasian studies, most adjusted
	7	16.82, p=0.01	0.95 (0.87-1.05)	0.93 (0.77-1.13)	Asian studies, least adjusted
	7	16.76, p=0.01	0.95 (0.87-1.04)	0.93 (0.77-1.12)	Asian studies, most adjusted
Gln/Gln	11	21.01, p=0.021	1.02 (0.92-1.13)	1.01 (0.84-1.22)	Least adjusted
	11	18.23, NS	1.00 (0.90-1.11)	1.00 (0.83-1.20)	Most adjusted
	5	8.23, NS	1.00 (0.88-1.13)	1.02 (0.82-1.26)	Caucasian studies, least adjusted
	5	5.38, NS	0.97 (0.85-1.10)	0.98 (0.83-1.17)	Caucasian studies, most adjusted
	7	13.44,p=0.037	0.99 (0.88-1.12)	0.98 (0.75-1.29)	Asian studies, least adjusted
	7	13.19,p=0.04	1.00 (0.88-1.13)	0.99 (0.75-1.29)	Asian studies, most adjusted
All Gln allele[c]	8	9.85, NS	0.88 (0.80-0.96)	0.87 (0.78-0.98)	Least adjusted
	8	9.65, NS	0.88 (0.80-0.96)	0.87 (0.78-0.98)	Most adjusted
	2	0.25, NS	0.89 (0.72-1.11)	0.89 (0.72-1.11)	Caucasian studies
	6	9.58, NS	0.88 (0.79-0.97)	0.87 (0.74-1.01)	Asian studies, least adjusted
	6	9.38, NS	0.87 (0.79-0.97)	0.86 (0.74-1.01)	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 Excludes one study[22] as the reference group was all subjects with Arg allele rather than Arg homozygotes

c Excludes one study[21] due to insufficient data

NS $p \geq 0.05$

Table 3: Prevalence of genotypes of XRCC1 polymorphisms

Polymorphism/ population	No. of cases	Prevalence of genotypes[a]			No. of controls	Prevalence of genotypes[a]		
-77T>C		**T/T**	**T/C**	**C/C**		**T/T**	**T/C**	**C/C**
Total	2194	1611	529	53	2288	1786	457	45
		(73.4)	(24.1)	(2.4)		(78.1)	(20.0)	(2.0)
Caucasian	110	37	53	19	110	40	52	18
		(33.9)	(48.6)	(17.4)		(36.4)	(47.3)	(16.4)
Asian	2084	1574	476	34	2178	1746	405	27
		(75.5)	(22.8)	(0.02)		(80.2)	(18.6)	(1.2)
Arg194Trp		**Arg/Arg**	**Arg/Trp**	**Trp/Trp**		**Arg/Arg**	**Arg/Trp**	**Trp/Trp**
Total[b]	6321	4505	1538	278	8202	5947	1960	295
		(71.3)	(24.3)	(4.4)		(72.5)	(23.9)	(3.6)
Caucasian	3335[c]	2933	384	18	4824	4191	614	19
		(87.9)	(11.5)	(0.5)		(86.9)	(12.7)	(0.4)
Asian	2832[c]	1430	1144	258	3135	1551	1310	274
		(50.5)	(40.4)	(9.1)		(49.5)	(41.8)	(8.7)
Pro206Pro		**A/A**	**A/G**	**G/G**		**A/A**	**A/G**	**G/G**
Total	355	205	126	24	1339	545	551	243
		(57.7)	(35.5)	(6.8)		(40.7)	(41.2)	(18.1)
Caucasian	116	36	58	22	1093	342	508	243
		(31.0)	(50.0)	(19.0)		(31.3)	(46.5)	(22.2)
Asian	239	169	68	2	246	203	43	0
		(70.7)	(28.5)	(0.8)		(82.5)	(17.5)	(0.0)
Arg280His		**Arg/Arg**	**Arg/His**	**His/His**		**Arg/Arg**	**Arg/His**	**His/His**
Total[d]	5366	4666	666	34	5801	5012	760	29
		(87.0)	(12.4)	(0.6)		(86.4)	(13.1)	(0.5)
Caucasian	3537	3195	329	13	3772	3405	358	9
		(90.3)	(9.3)	(0.4)		(90.3)	(9.5)	(0.2)
Asian	1829	1471	337	21	2029	1607	402	20
		(80.4)	(18.4)	(1.1)		(79.2)	(19.8)	(1.0)
Arg399Gln		**Arg/Arg**	**Arg/Gln**	**Gln/Gln**		**Arg/Arg**	**Arg/Gln**	**Gln/Gln**
Total[e]	11456	5450	4779	1227	13949	6541	5885	1523
		(47.6)	(41.7)	(10.7)		(46.9)	(42.2)	(10.9)
Caucasian	7089[c]	3032	3152	905	9002	3878	4007	1117
		(42.8)	(44.5)	(12.8)		(43.1)	(44.5)	(12.4)
Asian	4213[c]	2313	1581	319	4704	2499	1808	397
		(54.9)	(37.5)	(7.6)		(53.1)	(38.4)	(8.4)
Gln632Gln		**G/G**	**G/A**	**A/A**		**G/G**	**G/A**	**A/A**
Total	227	183	43	1	242	191	49	2
		(80.6)	(18.9)	(0.4)		(78.9)	(20.2)	(0.8)

a Number (percent)
b Excluding two studies[21,22] as no details of genotypes given
c Do not add up to total as the African-Americans in one study[9] not included
d Excluding one study[21] as no details of genotypes given
e Excluding three studies[21,22,27] as no details of genotypes given

Table 4: Effect of stratification by smoking variables on lung cancer risk according to XRCC1 genotype

Ref.	Author (year[a])	Smoking variable	Genotype	Odds ratios[b]	Adjustment factors[c]
-77T>C[d]					
25	Hu (2005)	Non-smokers	All C allele	1.57 (1.08-2.27)	A,S
		Ever smokers	All C allele	1.67 (1.19-2.35)	A,PY,S
8	Hao (2006)	Non-smokers	All C allele	1.28 (0.94-1.76)	A,S,SS
		Smokers	All C allele	1.63 (1.20-2.21)	A,PY,S,SS
		≤27 pack-years	All C allele	1.90 (1.22-2.95)	A,S,SS
		>27 pack-years	All C allele	1.44 (0.94-2.19)	A,S,SS
Arg194Trp[e]					
9	David-Beabes (2001)[f]	<20 cigarettes per day	All Trp allele	1.14 (0.22-5.94)	A,CPD,R,S,SD,YSC
		20+ cigarettes per day	All Trp allele	0.34 (0.14-0.82)	A,CPD,R,S,SD,YSC
3	Chen (2002)[f]	Never smokers	Trp/Trp	0.81 (0.12-5.34)	OG
		<30 pack-years	Trp/Trp	Not available	OG
		≥30 pack-years	Trp/Trp	3.32 (0.30-36.71)	OG
6	Hung (2005)[f]	Never smokers	All Trp allele	1.47 (0.88-2.45)	AD,C,S
		Light smokers	All Trp allele	0.88 (0.49-1.56)	AD,C,S
		Moderate smokers	All Trp allele	1.01 (0.75-1.37)	AD,C,S
		Heavy smokers	All Trp allele	0.65 (0.46-0.93)	AD,C,S
17	Schneider (2005)[f]	Never smokers	All Trp allele	0.35 (0.65-1.86)	A,S
		Ever smokers	Arg/Arg	8.61 (4.77-15.6)[g]	A,S
			All Trp allele	8.50 (4.31-16.8)[g]	A,S
		1-20 pack-years	Arg/Arg	2.86 (1.51-5.38)[g]	A,S
			All Trp allele	4.64 (1.77-12.2)[g]	A,S
		21-40 pack-years	Arg/Arg	11.8 (5.66-24.5)[g]	A,S
			All Trp allele	17.7 (6.57-47.7)[g]	A,S
		41-60 pack-years	Arg/Arg	40.4 (17.4-93.9)[g]	A,S
			All Trp allele	15.6 (4.26-57.1)[g]	A,S
		>60 pack-years	Arg/Arg	56.3 (21.4-147)[g]	A,S
			All Trp allele	79.3 (8.53-737)[g]	A,S
30	Pachouri (2007)	Non-smokers	Arg/Trp	0.50 (0.16-1.47)	A,S
			Trp/Trp	0.70 (0.24-2.32)	A,S
			All Trp allele	0.50 (0.19-1.48)	A,S
		Smokers	Arg/Trp	0.60 (0.21-217)	A,S
			Trp/Trp	0.60 (0.20-2.20)	A,S
			All Trp allele	0.60 (0.25-1.82)	A,S
Arg280His[e]					
6	Hung (2005)[f]	Never smokers	All His allele	1.15 (0.60-2.18)	AD,C,S
		Light smokers	All His allele	0.88 (0.44-1.76)	AD,C,S
		Moderate smokers	All His allele	1.17 (0.84-1.65)	AD,C,S
		Heavy smokers	All His allele	0.56 (0.36-0.86)	AD,C,S
17	Schneider (2005)[f]	Never smokers	All His allele	1.04 (0.94-5.62)	A,S
		Ever smokers	Arg/Arg	10.3 (5.65-18.8)[g]	A,S
			All His allele	7.10 (3.69-13.7)[g]	A,S
		1-20 pack-years	Arg/Arg	3.49 (1.83-6.63)[g]	A,S
			All His allele	4.82 (1.81-12.8)[g]	A,S
		21-40 pack-years	Arg/Arg	13.7 (6.66-28.3)[g]	A,S
			All His allele	9.63 (3.29-28.2)[g]	A,S
		41-60 pack-years	Arg/Arg	44.8 (19.2-104)[g]	A,S
			All His allele	16.0 (4.06-63.1)[g]	A,S
		>60 pack-years	Arg/Arg	56.3 (21.9-145)[g]	A,S
			All His allele	Not available	A,S
31	Yin (2007)	Never smokers	All His allele	0.38 (0.19-0.75)	None
		≤20 years	All His allele	1.11 (0.41-2.97)	None
		>20 years	All His allele	1.44 (0.62-3.37)	None

Arg399Gln[e]					
9	David-Beabes (2001)[f]	<20 cigarettes per day	Arg/Gln	1.23 (0.71-2.12)[h]	A,CPD,R,S,SD,YSC
			Gln/Gln	1.61 (0.55-4.73)[h]	A,CPD,R,S,SD,YSC
		20+ cigarettes per day	Arg/Gln	0.68 (0.44-1.06)[h]	A,CPD,R,S,SD,YSC
			Gln/Gln	0.39 (0.18-0.85)[h]	A,CPD,R,S,SD,YSC
2	Park (2002)[f,i]	≤40 pack-years	Arg/Gln	1.48 (0.78-2.80)	A
			Gln/Gln	5.75 (1.46-22.69)	A
			All Gln allele	1.79 (0.98-3.28)	A
		>40 pack-years	Arg/Gln	1.44 (0.50-4.17)	A
			Gln/Gln	1.38 (0.28-6.83)	A
			All Gln allele	1.43 (0.53-3.85)	A
11	Misra (2003)[f]	<15 cigarettes per day	All Gln allele	0.96 (0.43-2.14)	A,SD,VI
		15-19 cigarettes per day	All Gln allele	1.16 (0.49-2.75)	A,SD,VI
		20-24 cigarettes per day	All Gln allele	1.64 (0.91-2.95)	A,SD,VI
		≥25 cigarettes per day	All Gln allele	0.59 (0.34-1.04)	A,SD,VI
12	Zhou (2003)[f]	Non-smokers	Arg/Gln	1.20 (0.70-2.10)	None
				1.20 (0.70-2.10)	A,OG,PY,S,SS,YSC
			Gln/Gln	2.40 (1.20-4.90)	None
				2.40 (1.20-5.00)	A,OG,PY,S,SS,YSC
		Mild smokers	Arg/Gln	1.30 (0.80-1.90)	None
				1.30 (0.80-1.90)	A,OG,PY,S,SS,YSC
			Gln/Gln	1.30 (0.70-2.40)	None
				1.30 (0.70-2.40)	A,OG,PY,S,SS,YSC
		Moderate smokers	Arg/Gln	1.20 (0.90-1.70)	None
				1.10 (0.80-1.60)	A,OG,PY,S,SS,YSC
			Gln/Gln	1.90 (1.10-3.10)	None
				1.70 (1.00-3.00)	A,OG,PY,S,SS,YSC
		Heavy smokers	Arg/Gln	0.70 (0.50-1.10)	None
				0.60 (0.30-1.10)	A,OG,PY,S,SS,YSC
			Gln/Gln	0.70 (0.40-1.10)	None
				0.50 (0.30-1.00)	A,OG,PY,S,SS,YSC
13	Harms (2004)[f]	≤40 pack-years	All Gln allele	0.78 (0.25-2.41)[h]	None
		>40 pack-years	All Gln allele	1.52 (0.66-3.53)[h]	None
14	Ito (2004)[f]	Never smokers	Arg/Gln	0.83 (0.43-1.61)	A,S
			Gln/Gln	2.80 (0.90-8.77)	A,S
		Former smokers	Arg/Arg	1.08 (0.52-2.27)[g]	A,S
			Arg/Gln	1.51 (0.67-3.39)[g]	A,S
			Gln/Gln	0.66 (0.07-5.79)[g]	A,S
		Current smokers	Arg/Arg	3.39 (1.76-6.50)[g]	A,S
			Arg/Gln	3.67 (1.80-7.46)[g]	A,S
			Gln/Gln	3.15 (1.04-5.79)[g]	A,S
		Never smokers	Arg/Gln	0.86 (0.44-1.67)	A,S
			Gln/Gln	2.72 (0.86-8.57)	A,S
		Light smokers	Arg/Arg	0.92 (0.45-1.90)[g]	A,S
			Arg/Gln	1.69 (0.77-3.06)[g]	A,S
			Gln/Gln	Not available	-
		Heavy smokers	Arg/Arg	8.07 (3.82-17.0)[g]	A,S
			Arg/Gln	5.41 (2.46-11.9)[g]	A,S
			Gln/Gln	7.55 (2.28-24.9)[g]	A,S
6	Hung (2005)[f]	Never smokers	Arg/Gln	0.98 (0.66-1.46)	AD,C,S
			Gln/Gln	0.83 (0.46-1.48)	AD,C,S
		Light smokers	Arg/Gln	1.15 (0.75-1.78)	AD,C,S
			Gln/Gln	0.90 (0.44-1.83)	AD,C,S
		Moderate smokers	Arg/Gln	1.08 (0.87-1.35)	AD,C,S
			Gln/Gln	1.02 (0.74-1.40)	AD,C,S
		Heavy smokers	Arg/Gln	1.05 (0.80-1.39)	AD,C,S
			Gln/Gln	0.91 (0.60-1.38)	AD,C,S

17	Schneider (2005)[f]	Never smokers	All Gln allele	1.53 (0.52-4.50)	A,S
		Ever smokers	Arg/Arg	13.4 (5.44-33.2)[g]	A,S
			All Gln allele	3.98 (2.53-6.27)[g]	A,S
		1-20 pack-years	Arg/Arg	4.42 (1.69-11.6)[g]	A,S
			All Gln allele	4.30 (1.62-11.4)[g]	A,S
		21-40 pack-years	Arg/Arg	15.6 (5.23-46.8)[g]	A,S
			All Gln allele	17.2 (5.87-50.2)[g]	A,S
		41-60 pack-years	Arg/Arg	62.1 (17.7-218)[g]	A,S
			All Gln allele	36.6 (11.3-119)[g]	A,S
		>60 pack-years	Arg/Arg	80.3 (20.0-322)[g]	A,S
			All Gln allele	61.9 (15.7-245)[g]	A,S
27	Ryk (2006)	Never smokers	All Gln allele	0.52 (0.27-0.99)	A,OG,S
		Ever smokers	All Gln allele	1.22 (0.66-2.27)	A,OG,PY,S
28	De Ruyck (2007)	<25 pack-years	Arg/Gln	3.87 (1.36-11.03)	A,PY,S
			Gln/Gln	4.92 (1.27-19.04)	A,PY,S
		≥25 pack-years	Arg/Gln	0.65 (0.24-1.72)	A,PY,S
			Gln/Gln	0.68 (0.18-2.54)	A,PY,S
29	Lopez-Cima (2007)	ETS exposed	Arg/Gln	0.68 (0.28-1.64)	A,PY,S
			Gln/Gln	0.53 (0.14-1.92)	A,PY,S
		Ever smokers	Arg/Gln	1.01 (0.75-1.35)	A,PY,S
			Gln/Gln	0.94 (0.63-1.40)	A,PY,S
		Former smokers	Arg/Gln	0.79 (0.52-1.18)	A,PY,S
			Gln/Gln	0.78 (0.44-1.39)	A,PY,S
		Current smokers	Arg/Gln	1.32 (0.84-2.06)	A,PY,S
			Gln/Gln	1.04 (0.58-1.87)	A,PY,S
		Light smokers	Arg/Gln	0.66 (0.22-1.98)	A,S
			Gln/Gln	1.62 (0.47-5.56)	A,S
		Moderate smokers	Arg/Gln	1.13 (0.73-1.76)	A,S
			Gln/Gln	0.67 (0.36-1.24)	A,S
		Heavy smokers	Arg/Gln	0.70 (0.41-1.18)	A,S
			Gln/Gln	1.11 (0.52-2.36)	A,S
30	Pachouri (2007)	Non-smokers	Arg/Gln	0.50 (0.16-1.47)	A,S
			Gln/Gln	0.70 (0.24-2.32)	A,S
			All Gln allele	0.50 (0.19-1.48)	A,S
		Smokers	Arg/Gln	0.30 (0.12-1.02)	A,S
			Gln/Gln	0.70 (0.51-1.15)	A,S
			All Gln allele	0.30 (0.12-0.95)	A,S

a Year of publication
b 95% confidence interval shown in brackets where available
c Abbreviations used for confounders:
A = age, AD = age at diagnosis, C = country, CPD = cigarettes per day, OG = other genotype, PY = pack-years of smoking, R = race, S = sex, SD = smoking duration, SS = smoking status, VI = vitamin intervention, YSC = years since cessation of smoking
d Using T/T individuals as the reference group
e Using Arg/Arg individuals as the reference group
f Originally included in the published meta-analysis[4]
g Using Arg/Arg never smokers as the reference group
h Estimated from data given
i Squamous cell carcinoma cases only

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