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Associations between XPC polymorphisms and risk of cancers: A meta-analysis

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ABSTRACT

Several polymorphisms (Lys[939]Gln, PAT+/– and Ala[499]Val) in the DNA nuclear excision repair gene xeroderma pigmentosum complementation group C (XPC) are thought to have significant effects on cancer risk. In this meta-analysis, we assessed reported studies of associations between three XPC polymorphisms and risk of cancers from 16 studies with 6797 cases and 9018 controls for Lys[939]Gln, from 11 studies with 5581 cases and 6351 controls for Ala[499]Val and from 16 studies with 4514 cases and 5538 controls for PAT+/–. We found an increased overall cancer risk for variant homozygotes of Lys[939]Gln (OR = 1.16, 95% CI, 1.05–1.28) and Ala[499]Val (OR = 1.24, 95% CI, 1.08–1.42) compared with their corresponding wild-type homozygotes. When stratified by cancer type, the variant [939]Gln homozygous genotype was a risk factor for lung cancer (OR = 1.28, 95% CI, 1.07–1.53), whereas the [499]Val variant homozygous genotype was a risk factor for bladder cancer (OR = 1.33, 95% CI, 1.06–1.68) compared with their corresponding wild-type homozygous genotypes. For the XPC-PAT polymorphism, we found a decreased cancer risk associated with the PAT+/– genotype only in Asians compared with the PAT–/– genotype. Five studies were pooled for stratification analysis to explore the gene–smoking interaction. There was a joint effect of PAT +/+ and smoking in cancer risk. These analyses suggest that XPC Lys[939]Gln, PAT+/– and Ala[499]Val likely contribute to susceptibility to cancers. However, single larger studies with subjects of the same ethnic background and tissue-specific biochemical and biological characterisation are warranted to validate these findings.

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1. Introduction

The xeroderma pigmentosum complementation group C (*XPC*) is one of the eight core genes (i.e. *ERCC1, XPA, XPB, XPC, XPD, XPE, XPF* and *XPG*) in the nuclear excision repair (NER) pathway. XPC binds to HR23B and forms the XPC-HR23B complex, which is involved in the DNA damage recognition and DNA repair initiation in the NER pathway,[1–3] and the binding of *XPC* to damaged DNA is the rate-limiting step for NER.[4,5]

Amongst all identified single nucleotide polymorphisms (SNPs) of *XPC*, three are commonly studied: PAT–/+, Lys[939]Gln (A33512C, rs2228001) and Ala[499]Val (C21151T, rs2228000). *XPC*-PAT, a novel variant in intron 9 first reported by Khan,[6] was found to be in linkage disequilibrium with an A to C substitution in exon 15 that gives rise to a Lys to Gln substitution at position 939,[6] and this variant was later investigated for its functional relevance.[7] It was demonstrated that homozygous carriers of the PAT+ allele had lower DNA repair capacity measured in lymphocytes than homozygous carriers of the

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PAT– allele in 102 healthy subjects.[7] The *XPC* Lys[939]Gln polymorphism was also found to be associated with DNA repair capacity as measured chromatid aberrations.[8] The *XPC* Ala[499]-Val is non-synonymous but its impact on the protein function was unknown, although it was in strong linkage disequilibrium with other two polymorphisms in the 3′-untranslated region (Exon 15–184 and Exon 15–177).[9] The PAT+ is also linked to the C allele of exon 15 and the A allele in intron 11 splice acceptor that is associated with a higher frequency of deletion of exon 12. The deletion of exon 12 results in the loss of function of the *XPC* cDNA in correcting the defective XP-C cells with the host-cell reactivation assay as well as in dominant negative inhibition of function in normal cells. Furthermore, the *XPC* mRNA isoform without exon 12 has reduced DNA repair activity, whilst there is evidence that the exon 12 region of XPC protein binds to HHR23B protein. This linkage analysis establishes a correlation between the genotype of *XPC* gene and cancer predisposition.[10]

The knowledge acquired from the mutated *XPC* gene suggested that a normal *XPC* gene is critical for the cells to complete excision repair of bulky DNA lesions,[11] including smoking-induced DNA adducts. Numerous epidemiological studies had been conducted to explore the association of *XPC* polymorphisms with cancer risk but the results were contradicting. For example, Vogel and colleagues found an increased risk for lung cancer associated with the [939]Gln allele in a Danish population;[12] Sanyal and colleagues reported that carriers with C-allele had an increased risk of bladder cancer in a Swedish population;[13] and Shen and colleagues found that the *XPC* variant [939]Gln genotype was associated with a borderline significant risk of lung cancer in a Chinese population.[14]

For the Ala[499]Val SNP, Sak and colleagues showed that individuals homozygous for the minor allele of Ala[499]Val had an increased risk of bladder cancer compared with those homozygous for the common allele.[9] A case–control study of 320 lung cancer patients and 322 controls in a Chinese population conducted by Hu and colleagues revealed that the *XPC* 499CT/TT genotype was associated with lung cancer risk compared with the 499CC.[15] An and colleagues also found that carriers of the *XPC* 499 Val/Val genotype had a significantly increased risk of head and neck cancer in non-Hispanic whites with adjustment for age, sex, smoking and alcohol use when assuming a recessive genetic model.[16]

A recent study carried out in an Asian population of 432 cases and 432 controls found that the PAT–/+ polymorphism was associated with a significantly decreased risk of small cell carcinoma of the lung in a Korean population under a dominant model.[17] Casson and colleagues found that patients with oesophageal adenocarcinoma demonstrated a significantly higher frequency of the *XPC* -PAT homozygous variant genotype compared with asymptomatic controls after adjusting for age, sex, smoking status and alcohol use.[18] Shen and colleagues concluded the *XPC* -PAT+ allele may contribute to the risk of developing SCCHN in non-Hispanic whites.[19]

Taken together, single studies may have been underpowered to detect modest effects of *XPC* variants on cancer risk. In this meta-analysis, we used accumulated data from published studies to enhance statistical power and to obtain summary risk estimates for the above-mentioned three SNPs of *XPC* associated with cancers, mostly tobacco-related, such as cancers of the lung, upper aerodigestive tract, bladder, stomach, liver and pancreas as well as myeloid leukaemia.[20]

2. Materials and methods

2.1. *Search strategy and identification of relevant studies*

We conducted searches on the PubMed database (http://www.ncbi.nlm.nih.gov/) and the EMBASE database (http://www.embase.com/), last search updated on March 2008, with the keywords 'XPC' and 'cancer'. At the beginning, a total of 244 and 249 articles were retrieved from PubMed and EMBASE, respectively. To expand the coverage of our searches, we further carried out searches on Chinese Biomedical (CBM) database (http://cbmwww.imicams.ae.cn/cbmbin) (1978–) on the combinations of 'XPC' and 'cancer' in Chinese, and 102 articles were obtained.

All retrieved articles were examined by reading the titles and abstracts, and the full texts of the potentially relevant publications were further checked for their suitability for this meta-analysis. Besides the database search, the reference lists of the retrieved articles or preceding reviews on this topic were also screened for other potential articles. We also did manual searches of conference abstracts in the past 2 years (American Association of Cancer Research Meeting Abstracts).

Articles included in the current meta-analysis were original case–control or cohort studies with human subjects and without any language restriction. Studies with obvious overlapping data were carefully examined, and the most complete report was finally included. In addition, all the studies to be included should have described the well-defined sources of cases and controls and also provided other essential information including smoking history, characteristics of cases and controls and family cancer history. Publications should also have presented data necessary for the calculation of crude odds ratios or data allowing such outcomes to be derived.

Studies either using *XPC* polymorphisms to predict survival in cancers or considering *XPC* variants as indicators for response to therapy were excluded. Studies concentrating on the phenotypic markers (e.g. sisters discordant, sister chromatid exchange and chromatid aberrations) of the *XPC* gene as well as the studies only investigating the levels of *XPC* mRNA or *XPC* protein expression were also excluded. We included only case–control or cohort design studies, rather than the studies merely confining to patients with interested cancers or healthy subjects in the general population. We did not include breast cancer, endometrial cancer, melanoma, skin cancers (including base cell carcinoma and squamous cell carcinoma), colorectal cancer and hepatocellular carcinoma that were less likely to be caused by tobacco smoking, nor premalignant lesions,[21,22] in this meta-analysis.

One study composed by Hu and colleagues[23] using the same study population, though published in a different language (either in Chinese or in English), was excluded. The another case–control study was excluded because it concentrated on *XPC* mutation in cancer cases rather than the association between its polymorphisms and cancer risk, without presenting relevant data for odds ratio calculation.[24]

Another two studies[12,25] were excluded because they obviously overlapped with the recently updated studies that had a larger number of subjects.[26,27] One additional study of Zhu and colleagues[28] reanalysed the data of the study by Wu and colleagues[29] and thus was excluded. Finally, all cancer case only studies were excluded.[30–32]

After careful screening, 27 published papers examining the association between *XPC* polymorphisms and risk of tobacco-related cancers were included in the final meta-analysis.[9,13–19,26,27,29,33–48] Publications using the same population but examining different gene polymorphisms were treated as one study.[9,39,44,48] Meanwhile, studies investigating more than one kind of cancer (e.g. oesophageal cancer and gastric cancer) were counted as individual data sets.[43,44] Thus, in fact there were totally 27 data sets from 25 studies in these 27 publications, of which 24 were case–control studies and only one[26] was nested case-cohort study; in addition, 16 data sets focused on the exon 15 polymorphism, 11 concentrated on the exon 8 polymorphism and 16 investigated the intron 9 polymorphism.

2.2. Data extraction and quality assessment

For each publication, the methodological quality assessment and data extraction were carried out by two investigators (Qiu and Wang) independently to ensure the accuracy of the data. In case of disagreement on any item of the data, the problem would be fully discussed to reach a consensus.

The following parameters from each study were recoded on a spreadsheet: first author, the year of publication, the country of origin, ethnicity, types of cancer, sources of cancer cases and controls, matching variables, exclusion of specific types of diseases amongst controls, response rates of cases and controls, histopathologic subgroup information if possible, genotyping information and the number of cases and controls with the variant allele and the wild type. For studies including subjects of different ethnic groups, data were extracted separately for each ethnic group whenever possible. The histopathological information of each cancer was recorded, if available, to determine the comparability amongst different studies.

2.3. Methods for quantitative synthesis

The meta-analysis was performed on crude odds ratios, since the adjusted odds ratios lacked comparability because different covariates were adjusted for in the multivariate regression models. As mentioned above, we referred tobacco-related cancers to cancers in the lung, bladder, upper aerodigestive tract, stomach and pancreas. Summary odds ratios were estimated for each cancer site separately (stratified by lung cancer, bladder cancer and other mixed cancers), if there were at least three studies available, and all combined. We also performed the stratified analysis by ethnicity whenever possible.

For all three polymorphisms, *XPC* Lys^{939}Gln, Ala^{499}Val and PAT+/–, we evaluated the risks of the variant homozygotes and heterozygotes individually, both compared with their wild-type homozygotes. To be more specific, for *XPC* Lys^{939}Gln, Gln/Gln and Lys/Gln were compared with Lys/Lys, so were Ala^{499}Val and PAT+/– polymorphisms. We also examined their associations with cancer risk in both recessive and dominant models. In addition, we performed stratified analyses by smoking status (smokers and non-smokers) when the data on smoking and genotypes were available, to explore the gene–environment interaction of *XPC* polymorphisms and smoking for risk of cancers.

For each analysis, we assessed the between-study heterogeneity across the eligible comparisons using the Chi-square-based Q test,[49] and the heterogeneity was considered significant if $P < 0.10$ to avoid underestimation of the presence of heterogeneity. We also used the statistic of I^2 to efficiently test for the heterogeneity,[50] with $I^2 < 25\%$, 25–75% and >75% to represent low, moderate and high degree of inconsistency, respectively.[51] Values from single studies were combined using models of both fixed effects (the Mantel–Haenszel method) and random effects (the DerSimonian and Laird method).[52] These two methods provided identical results in the absence of the between-study heterogeneity. Because random effect model incorporates an estimate of the between-study variance and tends to provide wider confidence intervals, it is more appropriate when the results of the constituent studies differ amongst themselves. When there was an evidence of heterogeneity and when the number of the studies included was large enough to perform the multivariable regression analysis, a meta-regression model was employed to explore the sources of heterogeneity, using the metareg module with the STATA software, version 8.0 (Stata Corporation, College Station, Texas). Important factors, including sample size, source of controls, ethnicity and types of cancer, were examined in the multivariable meta-regression model.

Inverted funnel plots were drawn to estimate publication biases and the Egger's and the Begg's test were both employed to provide diagnosis of the funnel-plot symmetry.[53,54] The Egger's test involves a linear regression model using the standardised estimate of the size effect as the dependant variable and the inverse of the standard error as independent variable. If the intercept was significantly different from zero, the estimate of the effect was considered biased.

All the statistical analyses were performed with the STATA software. All the *P* values were two-sided. Statistical significance was defined as *P*-value less than 0.05, if not specially stated otherwise.

3. Results

3.1. Literature search and meta-analysis databases

A total of 27 publications were retrieved through PubMed, EMBASE and CBM databases, including 25 independent studies, of which 14 studies genotyped the variant allele for exon 15, 10 examined exon 8 and 16 investigated intron 9. Amongst the 25 studies, four[16,19,29,33] were conducted in the United States, one[18] was in Canada, eight[9,13,26,27,35,36,39,43,47] were conducted in European countries and 12[14,15,17,34,37,38,40–42,44–46] were in Asian countries. Amongst the 27 publications, 23 were published in English and the other four[40,41,44,46] were in Chinese.

Study characteristics are summarised in Table 1. Amongst the 25 studies, 22 studies used frequency matching and three

Table 1 – Characteristics of the 25 case–control studies included in this meta-analysis

First author, year	Cancer	Racial descent	Study design	Respon-se rate%case/ control	Matching	Number genotyped, exon15 (exon8) [intron9]	Matching variables	Adjustment variables	Genotyping	%variant allele exon 15 (exon 8) [intron 9]	% Power OR > 1.5
Sanyal (2004)	Bladder	Caucasian	Population-based	NA	Not done	309/246	Age, region, ethnic	NA	RFLP	34	51
Broberg (2005)	Bladder	Caucasian	Population	64/52	Frequency	(61/155) [61/155]	Sex, age, year of enrolment in the study, county of living	Age, sex, smoking	MALDI-TOF	(23)[37]	22
Garcia-Closas (2006)	Bladder	Caucasian	Hospital	84/88	Individual	1137/1138(1108/1109)	Age(±5y),sex, ethnicity, region	Age, sex, region, smoking status	Taqman	40(26)	98
Wu (2006)	Bladder	Caucasian	Hospital	75/92	Frequency	606/596 (603/590) [617/604]	Age(±5y),sex, ethnicity	Age, sex, ethnicity, smoking status	Taqman	41(24*)[34*]	85
Sak (2005, 2006)	Bladder	Caucasian	Hospital-based and communit-y based	99/ 80	Frequency	532/561(538/565)[577/544]	Age, sex, region	Age, sex, smoking, occupation exposure, family history of bladder cancer	Taqman and PCR	40(25)[38]	82
Andrew (2006)	Bladder	Caucasian	Population-based	85/70	Not done	[348/435]	NA	Age, sex, pack-years of smoking	PCR-RFLP	[42]	67
Wang (2003)	Lung	Asian	Population-based	NA	Frequency	[597/509]	Age (±5y), sex	Age, sex, smoking status	PCR	[37]	81
Hu (2005)	Lung	Asian	Population-based	NA	Frequency	320/322 (320/322)	Age(±5y),sex, ethnicity	Age, sex, pack-years of smoking	PIRA-PCR(exon8); RFLP (exon15)	33(28)	58%
Lee (2005)	Lung	Asian	Hospital-based	NA	Frequency	431/431 (432/432) [432/432]	Age(±5y),sex	Age, sex, smoking status, pack-years	RFLP(exon8, exon15), PCR(intron9)	39(71) [37]	71
Shen (2005)	Lung	Asian	Population-based	98/100	Individual	114/105 (116/110)	Age(±2y),sex, type of fuel used for cooking and home heating	Age, sex, current fuel type, pack-years of smoking, smoky coal use	RT-PCR	35*(33)	25
Bai (2007)	Lung	Asian	Hospital-based	77.8/ 81.3	Frequency	991/992 (994/990)	Age(±5y),sex, residential area	Age, sex, residential area, family history of cancer, pack-years of smoking	Taqman	36(32)	97
De Ruyck (2007)	Lung	Caucasian	Hospital-based	NA	Frequency	[110/109]	Age, sex	Age, sex, pack-years of smoking	PCR	[44]	24

Lopez-Cima (2007)	Lung	Caucasian	Hospital-based	93.8/ 98.5	Individual	[516/533]	Age(±5y),sex, ethnicity	Age, sex, cumulative tobacco consumption	PCR-RFLP	[40]	79
Vogel (2008)	Lung	Caucasian	case-cohort	100	Frequency	427/789	Age(±5y), sex, year of birth, duration of smoking (±10 y)	Duration, average intensity and status of smoking	RT- PCR	37	82
Shen (2001)	SCCHN	Caucasian	Hospital-based	NA	Frequency	[287/311]	Age(±5y),sex, smoking status	Age, sex, smoking status, alcohol use	modified-PCR[a]	[33]	55
An (2007)	SCCHN	Caucasian	Hospital-based	93/85	Frequency	829/854 (829/854)	Age(±5y), sex	Age, sex, smoking and drinking status	PIRA-PCR(exon8); RFLP (exon15)	38(27)	94
Casson (2005)	EADC	Caucasian	Hospital-based	100	Frequency	[56/95]	NA	Age, sex, smoking, use of alcohol	PCR	[35]	18
Ye (2006)	oesophageal, Gastric	Caucasian	Population	EAC88;SCC73; GCA84/73	Frequency	96/472;81/472;126/ 472	Age(±10y),sex, ethnicity	Age, sex, socioeconomic status, symptomatic GOR, BMI, tobacco smoking, alcohol consumption, intake of fruits and vegetables	PCR-RFLP	38	51;43
Liu (2006)	oesophageal	Asian	Population-based	NA	Frequency	[182/375]	Age(±5 y), sex	Age, sex, smoking status	PCR	[64]	49
Wang (2006)	Pancreatic	Asian	Population-based	NA	Frequency	[101/337]	Age(±5y), sex	Age, sex, smoking and drinking status	PCR	[38]	35
Zhou (2006)	ESCC, GCA	Asian	Population-based	NA	Not done	327/612 (327/ 612);253/612 (253/ 612)	Age, sex	Age, sex	PCR-RFLP	35(33)	71;64
Guo (2008)	ESCC	Asian	Population-based	NA	Not done	[327/612]	Age, sex	Age, sex	PCR	[35]	71
Hirata (2006)	RCC	Asian	Hospital	NA	Frequency	112/180	Age, sex	Not done	PCR-RFLP	65	31
Kietthubth-ew (2005)	OSCC	Asian	Population-based	NA	Frequency	106/164 [106/164]	Age, sex, region	Betel chewing	RFLP	27[26]	28
Sugimura (2006)	OSCC	Asian	Hospital-based	NA	Not done	[122/241]	NA	Age, sex, smoking status, alcohol consumption	PCR	[41]	35
Yang (2005)	SCCHN	Asian	Hospital-based	NA	Not done	[75/82]	Age, sex	NA	Modified-PCR[a]	[34]	19

NA, not available; SCCHN, squamous cell carcinoma of the head and neck; EADC, oesophageal adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; GCA, gastric cardia adenocarcinoma; RCC, renal cell carcinoma; OSCC, oral squamous cell carcinoma.*Indicates a significant deviate from Hardy–Weinberg equilibrium (HWE) in controls ($P < 0.05$). [a]a modified PCR-based non-radioactive assay.

studies[14,27,36] implied individual matching. Age and sex were the common matching factors, and some studies were also matched by ethnicity, region of residence and smoking. For age, the difference between cases and controls was no more than 5 years, except for one study[43] in which the difference between cases and controls was >5 years. Twelve studies[16–19,27,29,34,36,37,42,45,47] recruited hospital controls (hospital-based studies referred to those conducted in hospital no matter if they were patients with no interested diseases or health examination volunteers or outpatient clinics or population registers), whereas[13,13–15,33,35,38,40,41,43,44,46,48] used healthy populations as controls. Besides, one study[9,39] recruited both hospital controls and community healthy controls, and another study[26] employed a nest case-cohort design. Eighteen studies had clear exclusion presentation of the cases and controls, and 20 studies had histological or pathological confirmation of the cases.

All the studies either reported mean or median age or presented the proportion of different age groups of cases and controls. Except for the study by Hirata and colleagues,[37] all other studies investigated smoking status including percentage of smokers and pack-year of smoking of the cases and the controls. Eighteen studies[9,14–19,27,29,34,35,37–42,44,47] had demographic comparisons to ascertain the comparability between cases and controls, of which three studies[18,35,42] had baseline differences between cases and controls, mainly on age, sex and smoking status. For smoking status, the prevalence of smokers was higher in cases than in the controls amongst[10,9,15,17,18,27,29,34,39,41,42,47] of the 18 studies. All but three[13,37,42] studies calculated ORs adjusted for age, sex and smoking status, of which 11 studies simultaneously adjusted for other potential confounders, such as alcohol use, family history of cancer and region of residence. Ten studies performed subgroups analysis stratified by smoking status or smoking intensity.[9,15,19,26,27,36,39,41,44–46,48]

All studies used PCR-based methods for genotyping. Only seven studies[9,15,17,27,33,39,42,43] mentioned blindness in the assessment of genotyping results. Nineteen studies[9,13–19,26,27,29,33–36,39,42–45,48] reported the quality control measures for genotyping with replicates, and 13 studies stated that the achieved concordance was >95%. The distribution of genotypes in control groups was consistent with Hardy–Weinberg equilibrium in all except two studies.[14,29] Thirteen studies tested the gene–gene interactions or gene–environment interactions or both.[9,14–17,26,27,29,33,36,39,41,43,46]

3.1.1. *XPC Lys^{939}Gln*

The pooled studies included 6797 cases of various cancers and 9018 controls. The prevalence rate of Gln allele was 38% (95% CI, 37–40) and 38% (95% CI, 30–46) in control subjects of Caucasian and Asian descent, respectively. There was no statistical significance between Caucasians and Asians in terms of the variant ^{939}Gln allele frequency.

3.1.2. *XPC Ala^{499}Val*

The pooled studies included 5581 cases of different cancers and 6351 cases of controls. The prevalence rate of Val allele was 25% (95% CI, 24–27) and 32% (95% CI, 30–33) control subjects of Caucasian and Asian descent, respectively. Asians had a higher frequency of ^{499}Val allele than Caucasians.

3.1.3. *XPC PAT+/–*

The pooled studies included 4514 cases of various cancers and 5538 cases of controls. The prevalence rate of PAT + allele was 38% (95% CI, 35–41) and 39% (95% CI, 31–47) in control subjects of Caucasian and Asian descent, respectively. There were no significant ethnic differences in the variant allele frequencies.

3.2. *Quantitative synthesis*

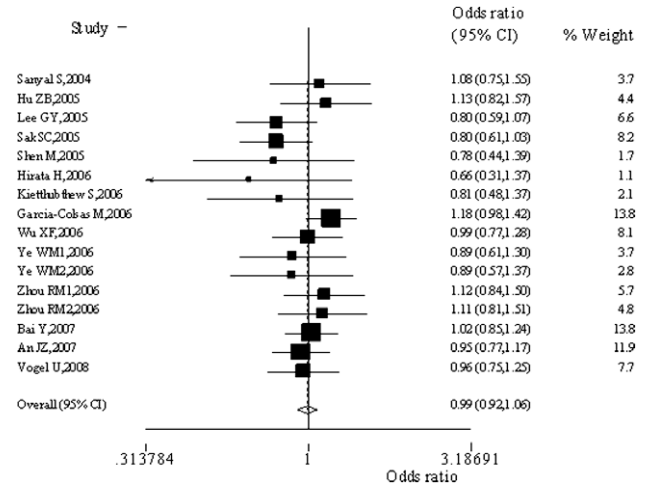
3.2.1. *XPC Lys^{939}Gln*

Sixteen data sets were extracted from 14 case–control studies for *XPC* Lys^{939}Gln. Overall there was no heterogeneity amongst these 16 data sets either for heterogenous genotype or for variant homogeneous genotype of the Lys^{939}Gln polymorphism ($\chi^2 = 13.6$ with df = 15, $P = 0.55$ for Lys/Gln versus Lys/Lys and $\chi^2 = 14.0$, $P = 0.53$ for Gln/Gln versus Lys/Lys). Using the fixed-effect model, the summary odds ratios were 0.99 (95% CI, 0.92–1.06) for heterozygote (Lys/Gln versus Lys/Lys) and 1.16 (95% CI, 1.05–1.28) for variant homozygote (Gln/Gln *versus* Lys/Lys) (Fig. 1a and b). As shown in Table 2, further stratification analyses by cancer type and ethnicity showed that carriers with ^{939}Gln homozygote had a significant increase in risk of lung cancer (OR = 1.28; 95% CI, 1.07–1.53; $P = 0.34$ for heterogeneity). There was a significant association between ^{939}Gln homozygous genotype and cancer risk in Asians (OR = 1.21; 95% CI, 1.03–1.43; $P = 0.70$ for heterogeneity). However, as shown in Table 2, under the recessive model of ^{939}Gln allele, significantly increased cancer risks were found in both overall and subgroup analyses except for the bladder cancer.

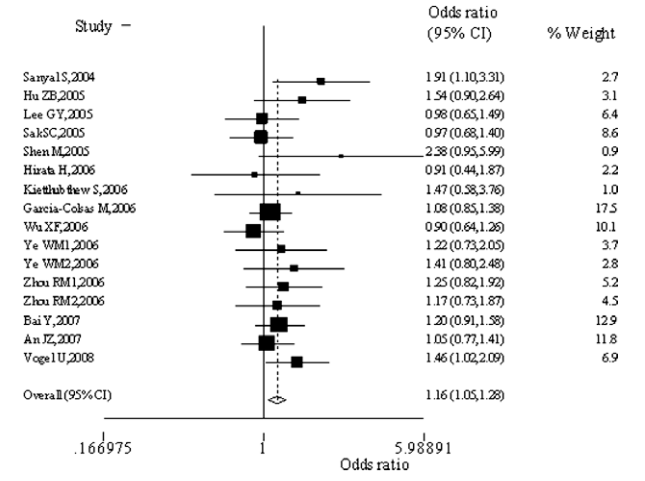
Bias diagnostic. For *XPC* Lys^{939}Gln, the Egger's test results were as follows: $t = -2.1$ with 15 df, $P = 0.06$ for the heterozygote; $t = 2.2$ with 15 df, $P = 0.05$ for the variant homozygotes, but there was a publication bias that could also be graphically judged from the shape of funnel plot (Figs. 2a and b).

3.2.2. *Meta-analysis of XPC Ala^{499}Val and cancer risk*

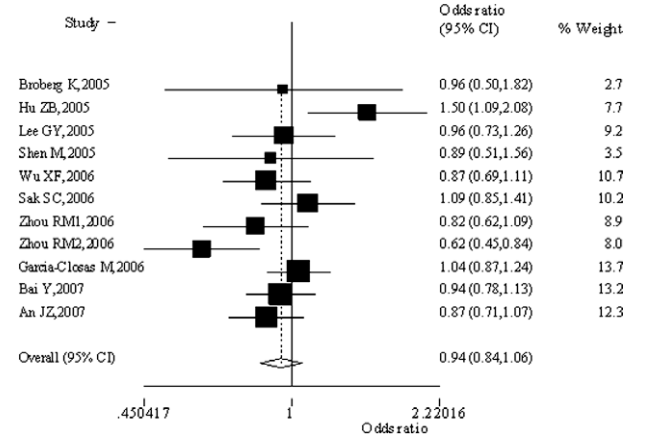
Eleven data sets from 10 studies were for *XPC* Ala^{499}Val. When examining ^{499}Val heterozygotes, there was heterogeneity amongst the 11 data sets ($\chi^2 = 19.5$, $P = 0.03$). However, for ^{499}Val homozygotes, heterogeneity was not found amongst the data sets ($\chi^2 = 11.7$, $P = 0.31$). The combined ORs for the two pairs of comparisons were 0.94 (95% CI, 0.84–1.06) for Ala/Val versus Ala/Ala in the random-effect model and 1.24 (95% CI, 1.08–1.42) for Val/Val versus Ala/Ala under the fixed-effect model (Fig. 1c and d). In the stratification analysis by cancer type, the ^{499}Val homozygous genotype was associated with increased risk of bladder cancer (OR = 1.33; 95% CI, 1.06–1.68; $P = 0.59$ for heterogeneity), whereas ^{499}Val heterozygotes had a decreased risk of other cancers as defined in this meta-analysis (OR = 0.88 using random model; 95% CI, 0.79–0.97; $P = 0.22$ for heterogeneity). When stratified by ethnicity, Caucasians with the homozygous variant genotype showed a 1.41-fold increased cancer risk (95% CI, 1.16–1.71; $P = 0.53$ for heterogeneity) compared with those with the homozygous wild-type genotype in the fixed-effect model.



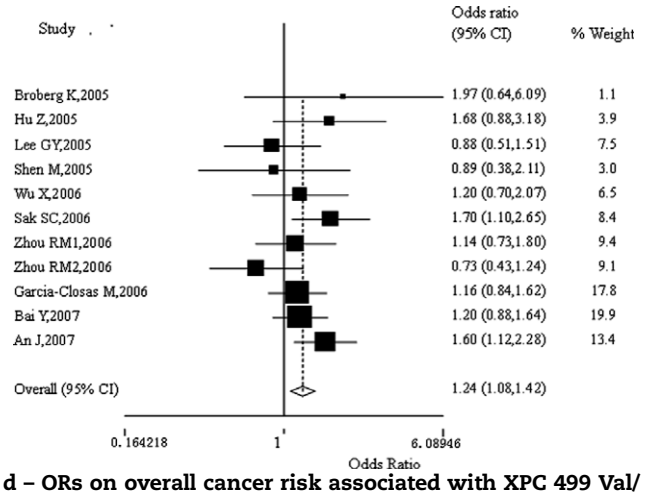
a – ORs of overall cancer risk associated with XPC 939 Lys/Gln compared with Lys/Lys.



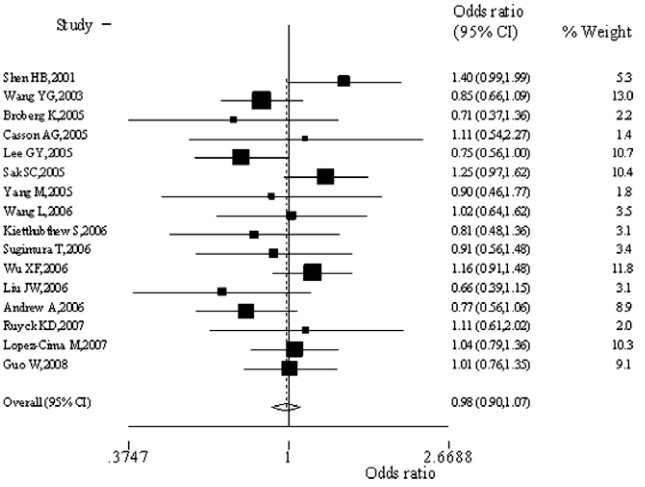
b – ORs of overall cancer risk associated with XPC 939 Gln/Gln compared with Lys/Lys.



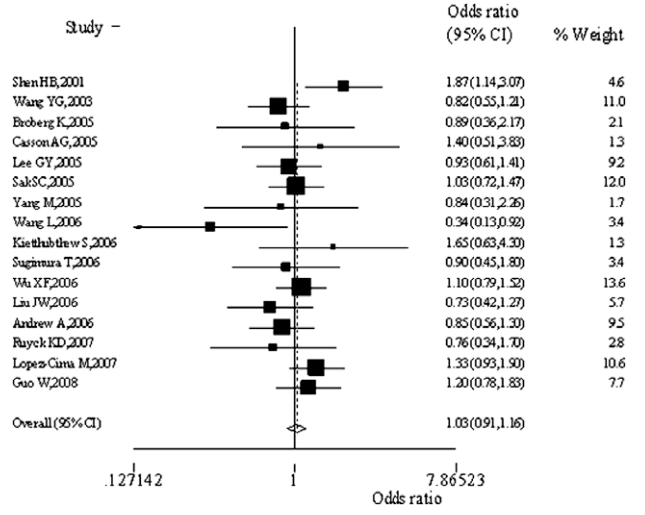
c – ORs on overall cancer risk associated with XPC 499 Ala/Val compared with Ala/Ala.



d – ORs on overall cancer risk associated with XPC 499 Val/Val compared with Ala/Ala.



e – ORs on overall cancer risk associated with XPC PAT+/– compared with PAT–/–.



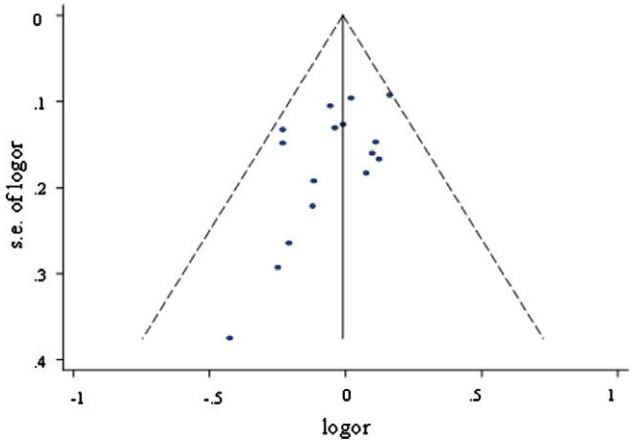
f – ORs on overall cancer risk associated with XPC PAT+/+ compared with PAT–/–.

Fig. 1 – ORs for the associations between overall cancer risk and genotypes. For each study, the OR estimate is plotted with a box; the area of each box is inversely proportional to the estimated square root of the standard deviation in the study. Diamond and dashed vertical lines represent pooled odds ratios; horizontal lines represent 95% confidence intervals.

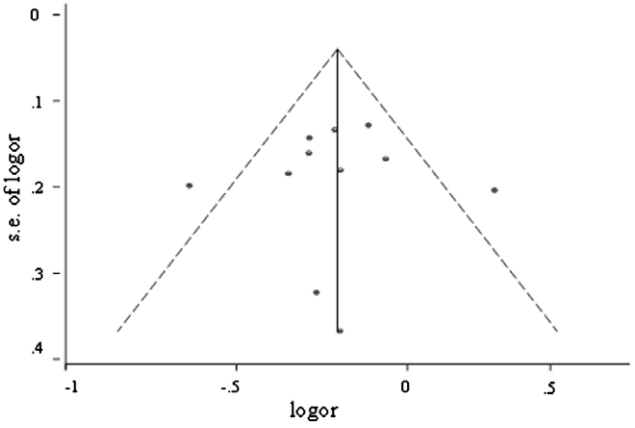
As shown in Table 2, there was a significant association between ^{499}Val allele genotypes and cancer risk under the recessive genetic model both in all subjects, in the subgroups of either bladder cancer or other cancers, and in Caucasians.

Test of heterogeneity. For heterozygous Ala/Val genotype, heterogeneity existed in the overall analysis ($\chi^2 = 19.5$, df = 10, $P = 0.03$), in the subgroups of lung cancer ($\chi^2 = 6.7$, df = 3, $P = 0.08$) and in Asians ($\chi^2 = 16.0$, df = 5, $P = 0.01$). We further employed meta-regression analysis to evaluate the source of heterogeneity, in which we coded population-based sampling as 0 and the type of cancer was used as dummy variable. The results showed that the types of cancer might be a source of heterogeneity (the P value of the dummy variable was 0.05 for bladder cancer and 0.03 for lung cancer, respectively). After careful examination of the individual studies included, we found that the study by Hu and colleagues[15] was the major cause of the heterogeneity. Therefore, we did sensitivity analysis to identify its impact. When it was excluded from the analysis, the estimations of between-study variance Tau-square had been reduced substantially, from 0.0048 to 0.0009 for overall analysis, from 0.0069 to 0.0000 for lung cancer and from 0.0126 to 0.0027 for Asians. Hu and colleagues' study was the first case–control study that investigated the association between the Ala^{499}Val polymorphism and cancer risk. However, the earlier finding appeared to be more prone to a false positive result.[55–57] We also graphed the L'Abbe plot to explore the source of heterogeneity and found that the study by Hu and colleagues was an outlier (data not shown).

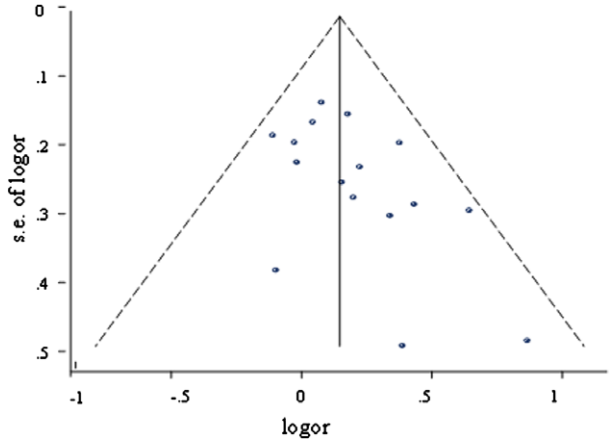
Then we tried to explore the source of heterogeneity by stratified analysis. When we stratified the studies by cancer type and ethnicity, we observed the lack of homogeneity amongst studies within the subgroups of lung cancer and Asians. Therefore, the heterogeneity amongst the studies included in the meta-analysis was due to different cancer types or ethnicity. Both the meta-regression and subgroup analyses revealed that ethnicity was a significant factor for heteroge-



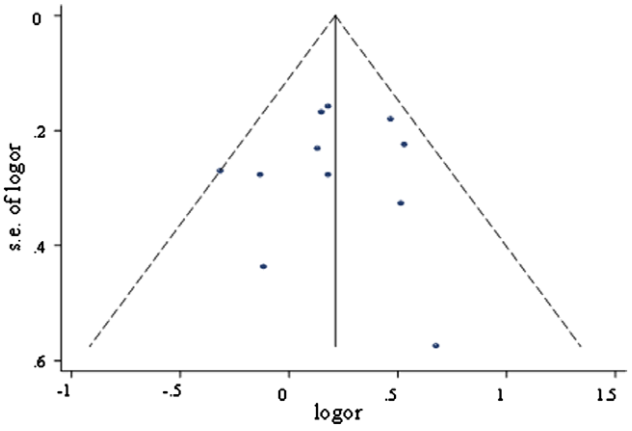
a – Funnel plot of the meta-analysis of overall cancer risk and the XPC 939 Lys/Gln genotype.



c – Funnel plot of the meta-analysis of overall cancer risk and the XPC 499 Ala/Val genotype.



b – Funnel plot of the meta-analysis of overall cancer risk and the XPC 939 Gln/Gln genotype.



d – Funnel plot of the meta-analysis of overall cancer risk and the XPC 499 Val/Val genotype.

Fig. 2 – Funnel plot analysis to detect publication bias. Each data point represents a separate study for the indicated association. For each study, the OR is plotted on a logarithmic scale against the precision (the reciprocal of the standard error).

Table 2 – Summary of odds ratios (OR) with confidence interval (CI) for various genetic comparisons of the association of XPC polymorphism and cancer risk

	Lys[939]Gln OR(95%CI)			Ala[499]Val OR(95%CI)			PAT+/- OR(95%CI)		
	n	Lys/Gln *versus* Lys/Lys	Gln/Gln *versus* Lys/Lys	*n*	Ala/Val *versus* Ala/Ala	Val/Val *versus* Ala/Ala	*n*	+/– *versus* –/–	+/+ *versus* –/–
Total	16	0.99 (0.92–1.06)	1.16 (1.05–1.28)	11	0.94(0.84–1.06)[a]	1.24 (1.08–1.42)	16	0.98 (0.90–1.07)	1.03 (0.91–1.16)
Bladder cancer	4	1.03 (0.91–1.16)	1.07 (0.90–1.26)	4	1.00 (0.89–1.13)	1.33 (1.06–1.68)	4	1.01 (0.89–1.14)[a]	1.00 (0.86–1.16)
Lung cancer	5	0.97 (0.86–1.09)	1.28 (1.07–1.53)	4	1.05 (0.84–1.32)[a]	1.16 (0.91–1.47)	4	0.89 (0.76–1.03)	1.01 (0.81–1.24)
Others	7	0.97 (0.86–1.10)	1.16 (0.97–1.38)	3	0.80 (0.69–0.92)	1.14 (0.74–1.77)	8	1.01 (0.86–1.18)	1.05 (0.74–1.48)[a]
Asians	8	0.99 (0.89–1.11)	1.21 (1.03–1.43)	6	0.92 (0.74–1.15)[a]	1.08 (0.89–1.31)	8	0.86 (0.76–0.98)	0.89 (0.73–1.08)
Caucasians	8	0.99 (0.90–1.09)	1.13 (0.99–1.28)	5	0.97 (0.87–1.07)	1.41 (1.16–1.71)	8	1.04 (0.99–1.10)	1.09 (0.97–1.22)
Smokers		–	–	3	0.87 (0.58–1.29) [a]	1.09 (0.57–2.08) [a]	5	1.00 (0.85–1.18)	0.99 (0.77–1.26)
Non-smokers		–	–	3	0.80 (0.63–1.02)	1.11 (0.72–1.69)	5	1.10 (0.77–1.56)[a]	1.44 (1.02–2.05)
	n	Gln/Gln *versus* Lys/ Gln + Lys/Lys	Lys/Gln + Gln/ Gln *versus* Lys/Lys	n	Val/Val *versus* Ala/ Val + Ala/Ala	Ala/Val + Val/ Val *versus* Ala/Ala	n	(+/+) *versus* (+/–) + (–/–)	(+/–) + (+/+) *versus* (–/–)
Total	16	1.17 (1.06–1.28)	1.03 (0.96–1.10)	11	1.27 (1.11–1.45)	0.99 (0.88–1.10)[a]	16	1.04 (0.93–1.16)	1.00 (0.92–1.08)
Bladder cancer	4	1.04 (0.90–1.21)	1.04 (0.93–1.17)	4	1.32 (1.05–1.66)	1.05 (0.93–1.17)	4	0.98 (0.81–1.18)	1.04 (0.91–1.20)
Lung cancer	5	1.31 (1.11–1.55)	1.03 (0.92–1.16)	4	1.15 (0.92–1.32)	1.06 (0.86–1.33)[a]	4	1.06(0.87–1.29)	0.91 (0.79–1.05)
Others	7	1.19 (1.01–1.40)	1.01 (0.90–1.14)	3	1.35 (1.07–1.71)	0.83 (0.65–1.06)[a]	8	1.09 (0.90–1.32)	1.04 (0.89–1.20)
Asians	8	1.23 (1.06–1.43)	1.04 (0.93–1.15)	6	1.13 (0.94–1.37)	0.94 (0.77–1.17)[a]	8	0.99 (0.83–1.17)	0.87 (0.77–0.99)
Caucasians	8	1.13 (1.00–1.27)	1.06 (0.97–1.16)	5	1.43 (1.18–1.72)	1.03 (0.93–1.13)	8	1.08 (0.94–1.26)	1.10 (0.99–1.23)
Smokers	3	–	1.08 (0.88–1.33)	3	1.26 (0.90–1.76)	0.90 (0.58–1.41)[a]	5	1.14 (0.92–1.40)	1.03 (0.88–1.21)
Non-smokers	3	–	1.22 (0.96–1.55)	3	1.24 (0.83–1.87)	0.85 (0.67–1.06)	5	0.81 (0.39–1.68)[a]	1.07 (0.85–1.35)

Boxes only with a short line in indicate there was no relevant data available for the odds ratio calculation for the specific comparisons.
a In random model.

neity. The results of subgroup analysis demonstrated that there was variability amongst studies within the same cancer type group. A possible explanation for this variability may be possibly related to unknown study differences that could not be explored in the current analysis, such as histological subtypes of cancer.

Bias diagnostic. As shown in Fig. 2c, there was no obvious publication bias in the analysis of the *XPC* Ala/Val polymorphism, and the Egger's test provided a further evidence for the lack of publication bias.

3.2.3. *Meta-analysis of XPC PAT+/– and cancer risk*

Overall there was no heterogeneity amongst the 16 studies when examining either PAT + heterozygotes ($I^2 = 26\%$, $P = 0.16$ for heterogeneity) or PAT + homozygotes ($I^2 = 21\%$, $P = 0.22$ for heterogeneity). Under either the fixed-effects model or the random-effect model, there was no substantial association between cancer risk and either one of the two genotypes of *XPC* PAT+/– polymorphism (OR = 0.98, 95% CI, 0.90–1.07 for PAT+/- and OR = 1.03, 95% CI, 0.91–1.16 for PAT–/– under the fixed-effect model) (Fig. 1e and f). Similarly no statistical association was observed in the subgroups stratified by cancer type. Amongst the eight studies investigating other cancers, heterogeneity existed with a P value of 0.06 and $I^2 = 48\%$ for the variant homozygotes and the OR was 1.05 (95% CI, 0.74–1.48, under the random-effect model). When stratified by ethnicity, studies including Asians showed that *XPC* PAT+/– heterozygotes had significantly decreased the risk of cancers using the fixed-effect model (OR = 0.86, 95% CI, 0.76–0.98; $P = 0.83$ for heterogeneity). However in Caucasians, no significant correlation was detected in either genotype. As shown in Table 2, there was a significantly decreased cancer risk in Asians under the dominant genetic model of PAT + allele (OR = 0.87, 95% CI 0.77–0.99; $P = 0.87$ for heterogeneity with df = 7).

Bias diagnostic. Under the level of $\alpha = 0.05$, Egger's test did not detect a publication bias in either the overall analysis or the subgroup analysis of the *XPC* PAT+/– polymorphisms.

3.3. *Gene–environment interaction*

The data on PAT–/+ genotypes of cases and controls stratified by smoking status were available in five studies.[19,27,39,45,48] In non-smokers, carriers with the PAT+/+ genotype had a significantly increased cancer risk (OR = 1.44, 95% CI 1.02–2.05; $P = 0.77$ for heterogeneity). However, this effect was not present in carriers with the PAT+/– heterozygous genotype (OR = 0.99, 95% CI 0.77–1.26), nor in smokers with either genotype (OR = 1.00, 95% CI 0.85–1.18 for PAT+/– heterozygotes; OR = 1.10, 95% CI 0.77–1.56 for PAT+/+ homozygotes). For Ala^{499}Val, three data sets from two studies[9,44] were pooled, and there was no association between Ala^{499}Val genotypes and cancer risk regardless of the smoking status, as presented in Table 2.

4. Discussion

This meta-analysis examined the associations between three commonly studied *XPC* polymorphisms (Lys^{939}Gln, Ala^{499}Val and PAT-/+) and selected tobacco-related cancer risk. A total of 9641 cases and 10,662 controls from 25 studies were included in the final analysis. We found an increased overall cancer risk for carriers of two variant alleles of Lys^{939}Gln and Ala^{499}Val compared with the wild homozygotes. When stratified by cancer type, the ^{939}Gln variant homozygous genotype was a significant risk factor for lung cancer, and the ^{499}Val variant homozygotes had increased risk of bladder cancer by 33% compared with the wild homozygotes. However, these results should be considered preliminary because for each cancer site the number of the studies included was relatively small. For the *XPC* -PAT polymorphism, we found a decreased cancer risk associated with the PAT–/+ genotype only in Asians, whereas in Caucasians there was no evidence of association between the PAT-polymorphism and risk of all cancers combined.

For those comparisons that did not exhibit a statistically significant association of *XPC* polymorphisms and cancer risk may be due to the characteristics of low-penetrance genes.[58–60] However, cancer aetiology is polygenic, and a single genetic variant is usually insufficient to predict risk of cancer that has a complex disease phenotype. It is likely that DNA repair may take place in a rather non-specific manner for different carcinogens and different cancers.[61] Although some researchers had the explanation for tissue-specific balance between apoptotic signals and repair effects in the different tissues, the result that some SNPs seem to present opposite risk trends at different cancer sites may be more likely due to chance.

However, caution should be exercised when considering these conclusions because of the presence of publication bias. The *P* value of the Egger's test was < 0.05 for the variant homozygote of Lys^{939}Gln, which is shown in Fig. 2b and there were some small sample size studies with negative results missing for ^{939}Gln homozygotes. Nevertheless, for the other genotypes not only with all cancers combined but also with subtype of cancers, the analyses were non-biased to some extent for the *P* values of the Egger's and Begg's test being all >0.05. Furthermore we did a search of AACR meeting abstracts online from 2004 to 2006 to assess the reliability of the results. There were 7 eligible case–control studies, amongst which 4 were fully or partially published and had been included in this meta-analysis. A large study with 1396 cases and 1423 controls examined the association of *XPC* (PAT–/+, Ala^{499}Val, Lys^{939}Gln) and lung cancer, and found no statistically significant differences in the distributions between cases and controls.[62] Another multicentric study in Central Europe investigated the association between upper aerodigestive tract cancer (i.e. the oral cavity, pharynx, larynx and oesophagus) and Lys^{939}Gln, with 775 cases and 1014 controls, showing no overall association either.[63] Both these two studies would be a challenge for the validity of our conclusion. Thus, a preferred alternative is to combine these large studies together, once these data become available, for additional analysis to achieve a more valid result.

In addition, there are other challenges that limit the generalisation of our conclusions to the general population when taking into account the quality of the studies included. First, four[13,33,44,45] studies did not clearly state the use of a matching design for cases during the selection process of controls; 28% of the studies did not ascertain the comparability of cases

and controls statistically;[13,26,33,36,43,45,46] and in another three studies the cases and controls did not match well.[18,35,42] Second, there were some outliers in light of the rare allele frequency in controls; for example, it is surprising that a much higher frequency (0.64) of the PAT + allele in a Chinese population was reported in a small case–control study.[46] It is rare to have such a great variation of one polymorphism within the same ethnic population, if any. Third, given the sample sizes of the included studies, only a limited power could be obtained to detect a moderate risk effect. As shown in Table 1, only seven studies had a power $\geqslant$ 80% to detect a 1.5-fold increase in the risk assuming a 20% prevalence of the rare allele in the control group. Fourth, histological types of cancer might vary amongst different studies especially for lung cancer. As different histological types of lung cancer may have altered susceptibility when the hosts had certain SNPs,[34] it is better to use the similar proportion of various histological types. We compared the proportion of histological subgroup of lung cancer if the data were available, and found that there was substantial difference amongst these studies (Chi-square test, $P < 0.01$). Finally, as revealed by the Begg's test and the funnel plot, a considerable number of unpublished negative studies could not be included in this meta-analysis, although they are likely to be small in terms of sample size. Publication bias has long been associated with funnel plot asymmetry including language bias. Difference in methodological quality is another source of asymmetry. Smaller studies are on average conducted and analysed with less methodological rigour than larger studies. Studies of lower quality also tend to show the larger effects.

For both Lys^{939}Gln and PAT+/– polymorphisms, there was no overall heterogeneity between studies, indicating that our current combined analyses may be unbiased, regardless of tumour types. However, for ^{499}Val heterozygotes, there was a moderate heterogeneity between studies, and in subgroups there was also evidence of homogeneity. Ideally, meta-analyses should use individual data of each study rather than the analysed results that are more likely to introduce heterogeneity because of the differences of constructed models (e.g. variable denotes and adjustments).

Besides smoking-related cancers included in this meta-analysis, the *XPC* polymorphisms have also been studied extensively in other cancers, such as those of the skin,[64–68] breast[69–71] and endometrium.[72] For most of these studies, the investigators did not find any statistically significant association, and only a very limited number of studies had shown significant association.[73] A previous meta-analysis on these three SNPs of *XPC* by Zhang and colleagues[74] had included breast, skin and endometrium cancers, and another meta-analysis by Francisco and colleagues[75] also examined the association between *XPC* polymorphisms and cancers, but only limited to Lys^{939}Gln and Ala^{499}Val. For the following comparisons, all these meta-analyses, including ours, conclude a significant association: the genotype of Val/Val with bladder cancer, the Lys^{939}Gln with lung cancer and Ala^{499}Val with bladder cancers in a recessive model. Though our findings are consistent with those of other meta-analyses, our meta-analysis was irreplaceable with regard to the following: first, for variant homozygotes of Lys^{939}Gln and Ala^{499}Val, there were overall cancer risks in our findings, which were not statistically significant in the other two meta-analyses; second, our meta-analysis explored the heterogeneity of studies in more details; third, we performed further analyses on the gene–smoking interaction; furthermore, in the combined studies, subgroup analysis included a moderate number of subjects, 1313 cases and 1351 controls in smokers and 482 cases and 923 controls in non-smokers for the PAT–/+ polymorphism.

The main limitation of this meta-analysis is insufficient number of studies on *XPC* polymorphisms when specifying one kind of cancer type or ethnicity. Second, because of lack of individual data, we could not reliably assess the impact of the genotypes in potentially relevant subgroups, such as those defined by cancer histology. Though we did a meta-analysis of *XPC* polymorphisms and cancer risk in subgroups stratified by smoking status, the results were subject to some degree of bias for at least two reasons: (1) the number of the cases and controls was not large enough yet and (2) the definition of smokers varied across studies. Third, literature search may be incomprehensive, resulting in inadequacy and potentially missing some pertinent studies.

It is possible that the relative contribution of each polymorphism to cancer risk might be due to linkage disequilibrium, for instance Lys^{939}Gln and PAT–/+, which indicates the need to further investigate the haplotypic effect of a gene. It is well known that multiple genes probably act independently, collectively or interact with each other, to influence the occurrence of complex diseases like cancer. Combinations of certain genotypes may be more efficient in discriminating risk factors than a single locus genotype. Therefore, large studies including multiple SNPs of different genes involved in the same NER pathway are necessary to further validate the associations between SNPs of DNA repair genes and risk of cancer.

Conflict of interest statement

None declared.

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