

ARTICLE

XPC polymorphisms play a role in tissue-specific carcinogenesis: a meta-analysis

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XPC participates in the initial recognition of DNA damage during the DNA nucleotide excision repair process in global genomic repair. Polymorphisms in XPC gene have been analyzed in case–control studies to assess the cancer risk attributed to these variants, but results are conflicting. To clarify the impact of XPC polymorphisms in cancer risk, we performed a meta-analysis that included 33 published case–control studies. Polymorphisms analyzed were Lys939Gln and Ala499Val. The overall summary odds ratio (OR) for the associations of the 939Gln/Gln genotype with risk of cancer was 1.01 (95% confidence interval (95% CI): 0.94–1.09), but there were statistically significant associations for lung cancer, observed for the recessive genetic model (Lys/Lys + Lys/Gln vs Gln/Gln), (OR 1.30; 95% CI: 1.113–1.53), whereas for breast cancer a reduced but nonsignificant risk was observed for the same model (OR 0.87; 95% CI: 0.74–1.01). The results for Ala499Val showed a significant overall increase in cancer risk (OR 1.15; 95% CI: 1.02–1.31), and for bladder cancer in both the simple genetic model (Ala/Ala vs Val/Val) (OR 1.30; 95% CI: 1.04–1.61) and the recessive genetic model (Ala/Ala + Ala/Val vs Val/Val) (OR 1.32; 95% CI: 1.06–1.63). Our meta-analysis supports that polymorphisms in XPC may represent low-penetrance susceptibility gene variants for breast, bladder, head and neck, and lung cancer. XPC is a good candidate for large-scale epidemiological case–control studies that may lead to improvement in the management of highly prevalent cancers.

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Introduction

The development and progression of cancer has been attributed to the acquisition of capabilities that would allow for tumor growth, encompassing self-sufficiency for growth signals, tissue invasion and metastasis. The acquisition of these hallmarks are due to mutations in the genome of the cell,¹ arising from unrepaired DNA lesions caused by

UV exposure, ionizing radiation, environmental chemical agents and some substances produced by cell metabolism. Accumulation of such mutations drives the carcinogenic process. To safeguard the integrity of the genome, eukaryotic cells developed complex DNA repair systems that can recognize the lesions, excise them and restore the DNA, allowing for cell survival and thus preventing cancer.² At least six distinct repair systems have been identified so far, including the *nucleotide excision repair* (NER), which has an important function as a versatile system that can eliminate a wide variety of lesions, such as UV-induced lesions, intrastrand cross-links and bulky adducts induced by chemical carcinogens.³

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Nucleotide excision repair operates through two subpathways, namely the transcription-coupled repair (TCR) and the global genomic repair (GGR), which differ, among other aspects, in the step of recognition of damaged DNA. While in TCR it is the stalled RNA polIII that initiates the repair process, in GGR the recognition of damage and initiation of repair is triggered by the XPC protein. The gene *XPC* is localized at 3p25 and encodes a protein of 940 amino acids that *in vivo* form a supramolecular complex including HR23B, homolog to Rad23 in yeast, and centrin 2.⁴ Regarding its function in DNA repair, the XPC complex binds to various types of lesions by recognizing alterations in the DNA structures rather than the lesions themselves.⁵ Following recognition, the XPC complex interacts with XPA, which constitutes with RPA the preincision complex. XPC also interacts with TFIIH, recruiting it to the lesion site, where this factor acts as a helicase opening the double helix allowing for the following steps of NER, excision and restoring of DNA.⁶

The relationship of XPC and cancer is based on the observation of high incidence of skin cancers (about 1000-fold) in patients with mutations in the *XPC* gene, which characterize the inherited disease xeroderma pigmentosum (XP). In XP patients, defects in NER are caused by mutations in one of the seven genes (*XPA–G*),⁷ increasing cancer susceptibility. Moreover, it has been suggested that XPC may play an important role in lung carcinogenesis⁸ and lymphomagenesis.⁹ Thus, based on its functions in recognition and initiation of NER, XPC is a key player in the repair of potential carcinogenic lesions.

A growing body of evidence has indicated that several low-penetrance gene variants (polymorphisms) have been considered to be involved in the pathogenesis of cancer, each contributing with small effects to the total genetic component.¹⁰ On the basis of that, a large number of molecular epidemiologic studies have been performed to evaluate the role of polymorphisms in DNA repair genes, including *XPC*, on various types of cancer. In *XPC* gene, three common polymorphisms are the most studied and include (1) a substitution of alanine for valine in codon 499 (Ala499Val), in the interaction domain of XPC with hHRAD23; (2) a substitution of lysine for glutamine in codon 939 (Lys939Gln), located in the interaction domain with TFIIH; and (3) a poly AT region on intron 9.¹¹ Even with a considerable number of reports analyzing XPC polymorphisms, the results remain conflicting rather than conclusive. Studies with relative small sample sizes may have been underpowered to detect the effect of low-penetrance genes and their estimates may lack precision.

Thus, a quantitative synthesis may help to provide clearer evidence on the association of such genetic polymorphisms with cancer, as previously reported,^{12,13} and find, even small but, relevant associations. The aim of the present study was to obtain summary risk estimates for the association of specific polymorphisms in XPC and risk

of cancer, by conducting a meta-analysis from the available studies.

Materials and methods

Identification and eligibility of relevant studies

To identify all studies that examined the association of XPC polymorphisms with cancer, a search in the PubMed database (last search update in May 2007) was conducted using the keywords 'XPC,' 'polymorphism,' 'polymorphisms' and 'cancer.' Additional studies were identified by search of references from original papers and review articles. The inclusion criteria adopted included published studies that used an unrelated case–control design and had genotype frequency available.

Data extraction

Data were collected on the authors, journal, year of publication, country of origin, selection and characteristics of cancer cases and controls, sociodemographic information, ethnicity, genotyping information, genotyping method and interaction between environmental factors. Ethnicity was categorized as Caucasian, African and Asian. If a study did not state the ethnic descent or if it was not possible to separate participants according to such phenotype, the group reported was termed 'mixed ethnicity.'

Meta-analysis

Polymorphisms analyzed were the substitution Lys/Gln in codon 939 and Ala/Val in codon 499 of XPC. Another XPC polymorphism reported in the studies identified was an insertion of a 83-bp PAT (poly AT) in intron 9.¹¹ However, this polymorphism is in strong linkage disequilibrium (LD) with Lys939Gln (Lewontin's LD = 1.0).^{14–16} Thus, studies that just analyzed XPC PAT were considered as the same genotype frequency that XPC 939 due to this LD.

The association between XPC polymorphisms and cancer was estimated by calculating summary odds ratios (ORs). For Lys939Gln, we estimated the OR of cancer associated with Gln/Gln genotype compared with the wild-type Lys/Lys, and then the OR of Gln/Gln with (Lys/Lys + Lys/Gln) in a recessive genetic model and the OR of (Gln/Gln + Lys/Gln) with Lys/Lys in a dominant genetic model. Similar models were analyzed for the Ala499Val polymorphism. In addition to estimates of OR for all subjects in each study, studies were categorized into subgroups according to their sample's ethnicity and tumor type. Tumors sites that were studied in only one article were categorized into the 'other cancers' group.

Summary OR were obtained using fixed-effects models using the Mantel–Haenszel method.¹⁷ For each meta-analysis performed, a χ^2 -based Q-statistic test and an I^2 was performed to assess the between-study heterogeneity,¹⁷ and heterogeneity was considered significant

for $P < 0.05$. In the case of heterogeneity, random-effects models with DerSimonian and Laird method were then used to pool the results.¹⁸ The significance of the pooled OR was determined by the Z-test. Publication bias was investigated by funnel plots and by the Egger's test.¹⁹ Hardy–Weinberg equilibrium (HWE) was tested by the χ^2 test for goodness of fit. A sensitivity analysis was performed by calculating summary OR without studies not in HWE, and comparing results with those obtained with all available studies. All analyses were done in GraphPad Prism version 4 (GraphPad, San Diego, CA, USA), Stata version 9 and Review Manager 4.2 (Stata, Oxford, England). All the P -values were for two-sided analysis.

Bioinformatics analysis

Two *in silico* algorithms, the PolyPhen algorithm (<http://tux.embl-heidelberg.de/ramensky/>) and the SIFT algorithm (<http://blocks.fhcr.org/sift/SIFT.html>), were used to predict the putative impact of the two polymorphisms in XPC on protein function. PolyPhen predicts the functional impact of amino-acid changes by considering evolutionary conservation, the physicochemical differences and the proximity of the substitution to predicted functional domains or structural features. PolyPhen scores (PISC) were designated as probably damaging (2.00), possibly damaging (1.50–1.99), potentially damaging (1.25–1.49), borderline (1.00–1.24) or benign (0.00–0.99) according to the classification proposed.²⁰ SIFT predicts the functional importance of amino-acid substitutions on the basis of the alignment of ortholog or paralog protein sequences. SIFT scores were classified as intolerant (0.00–0.05), potentially intolerant (0.051–0.10), borderline (0.101–0.20) or tolerant (0.201–1.00) according to the classification proposed.^{20,21} PolyPhen has been shown to have more than 80% accuracy of predicting deleterious amino-acid changes and the accuracy of SIFT is over 70%.²⁰ The sensitivity of PolyPhen and SIFT for identifying deleterious mutations in XP genes is 85 and 83%, respectively.^{20,21}

Results

Meta-analysis data

The literature search yielded 37 studies that examined the relationship between XPC polymorphisms and different types of cancer. Four studies were excluded because they had case-only designs^{22–25} and another because it investigated a sample already reported.²⁶ Thus, the meta-analyses were based on 33 studies (Table 1). Thirty-one studies analyzed the relationship between XPC Lys939Gln and/or XPC PAT and risk of cancer, and two analyzed only XPC Ala499Val. Eleven studies analyzed both polymorphisms in the same article. Two studies reported results on different racial descent population^{35,58} and each population was treated as a separate comparison in meta-analysis.

In general, tumors samples were confirmed by histological analysis. Regarding the choice of genotyping assays, a classic PCR-RFLP was done in 21 studies (64%), whereas the other 12 studies (36%) used a fluorogenic-based real-time PCR method. When the efficiency of both genotyping assays was compared, the PCR-RFLP method showed a mean rate of sample loss $< 1\%$ (range: from 0 to 7%), whereas in real-time PCR-based method the mean rate of sample loss was 4% (range: from 1 to 14.5%). Table 1 shows the 33 studies included in this analysis and lists the cancer type of the study, country, ethnicity, number of cases and controls genotyped, and the frequency of minor allele in cases and controls.

The distribution of genotype frequencies among the control groups indicated that the gene variants were in HWE in all studies, but one³⁸ ($P = 0.03$). The interaction between XPC polymorphisms and environmental risk factors was investigated in 23 out of 33 studies (70%), 9 of which found some type of positive gene–environment association. In all, 2 of the 10 studies (30%) that did not analyze risk factors found association between XPC variants and the tumor studied.

Quantitative synthesis

XPC Lys939Gln The studies that examined the relation between XPC Lys939Gln polymorphism and cancer risk analyzed a total of 14080 cases and 14011 controls. The Gln allele frequency in the three major ethnicities was 37.5% (95% CI: 35.4–39.6) for Caucasians, 36.1% (95% CI: 29.6–42.6) for Asians and 28% for African (Figure 1a), indicating a significant difference among Africans, as compared with the two other groups ($P < 0.001$).

Overall, individuals with XPC Gln/Gln genotype did not have elevated cancer risk compared with individuals with Lys/Lys genotype, as shown by a summary OR of 1.01 (95% CI: 0.94–1.09; Figure 2). There was a trend for heterogeneity between studies, as suggested by a P -value of 0.05 for the χ^2 test for heterogeneity, but the amount of variance between studies attributed to heterogeneity was only 30%. When the analyses were performed by cancer type (Figure 2), the homozygous variant of XPC Gln/Gln was associated with a significant increase in risk of lung cancer (OR 1.21; 95% CI: 1.02–1.44), and a borderline risk effect for head and neck (OR 1.37; 95% CI: 0.97–1.93) was observed. On the other hand, a nonsignificant ($P = 0.07$) borderline protective effect was observed for breast cancer (OR 0.86; 95% CI: 0.73–1.01). To assess the importance of the heterozygous genotype, dominant and recessive genetic models were applied (Table 2). The recessive model confirmed the increased risk for lung cancer (OR 1.30; 95% CI: 1.11–1.53) and the nonsignificant borderline protective effect for breast cancer ($P = 0.05$; OR 0.87; 95% CI: 0.74–1.01). No association with cancer risk was found in either tumor site using the dominant model (Table 2). Exclusion of the one study that was not HWE did not

Table 1 Characteristics of studies included in the meta-analysis

First author and year	Country	Cancer	Racial descent	Cases/controls genotyped to codons 939 ^{Gln} and [499 ^{Val}]	Allele frequency among cases/controls to 939 ^{Gln} and [499 ^{Val}]
Sak (2005) ¹⁶	England	Bladder	Mixed ethnicity	532/561	0.39/0.40
Sanyal (2004) ²⁷	Sweden	Bladder	Caucasian	275/246	0.44/0.33
Garcia-Closas (2006) ²⁸	Spain	Bladder	Caucasian	1137/1137; [1108/1109]	0.58/0.40; [0.27/0.26]
Sak (2006) ²⁹	England	Bladder	Mixed ethnicity	[538/565]	[0.29/0.25]
Zhu (2007) ³⁰	USA	Bladder	Caucasian	550/554; [546/549]	0.39/0.40; [0.23/0.24]
Wu (2006) ³¹	USA	Bladder	Mixed ethnicity	606/596; [603/590]	0.38/0.41; [0.23/0.24]
Forsti (2004) ³²	Finland	Breast	Caucasian	233/296	0.32/0.30
	Polish	Breast	Caucasian	166/203	0.36/0.42
Shen (2006) ³³	USA	Breast	Mixed ethnicity	155/150; [155/150]	0.38/0.41; [0.22/0.22]
Jorgensen (2007) ³⁴	Canadian	Breast	Mixed ethnicity	281/287; [281/287]	0.41/0.39; [0.41/0.39]
Mechanic (2006) ³⁵	USA	Breast	African Americans ^{35a}	761/679	0.27/0.28
	USA	Breast	Mixed ethnicity ^{35b}	1267/1123	0.38/0.40
Zhang (2005) ³⁶	China	Breast	Asian	220/310	0.325/0.30
Hu (2005) ³⁷	China	Lung	Asian	320/322; [320/322]	0.36/0.32; [0.34/0.28]
Shen (2005) ³⁸	USA	Lung	Asian	114/105; [116/110]	0.40/0.35; [0.31/0.33]
Lee (2005) ³⁹	South Korea	Lung	Asian	431/431; [432/432]	0.38/0.39; [0.28/0.29]
Marin (2004) ⁴⁰	Spain	Lung	Caucasian	359/375	0.45/0.39
Vogel (2005) ⁴¹	Danish	Lung	Caucasian	256/269	0.39/0.35
Bai (2007) ⁴²	China	Lung	Asian	991/992; [994/990]	0.37/0.36; [0.33/0.32]
Yang (2005) ⁴³	South Korea	Head and neck	Asian	73/82	0.32/0.34
Sugimura (2006) ⁴⁴	Japan	Oral SCC	Asian	122/241	0.40/0.41
Shen (2001) ⁴⁵	USA	Head and neck	Mixed ethnicity	287/311	0.40/0.33
Kietthubthew (2006) ⁴⁶	Thailand	Oral SCC	Asian	106/164	0.27/0.26
Li (2006) ⁴⁷	USA	Melanoma	Caucasian	602/603; [602/603]	0.40/0.42; [0.26/0.27]
Blankenburg (2005) ¹⁵	Germany	Melanoma	Caucasian	294/373	0.41/0.37
Blankenburg (2005) ⁴⁸	Germany	Melanoma	Caucasian	[294/373]	[0.21/0.22]
Casson (2005) ⁴⁹	Canadian	Esophageal	Mixed ethnicity	56/95	0.38/0.35
Zhou (2006) ⁵⁰	China	Gastroesophageal	Asian	580/612; [580/612]	0.37/0.35; [0.29/0.32]
Ye (2006) ⁵¹	Sweden	Esophageal	Caucasian	303/472	0.39/0.38
Festa (2005) ⁵²	Sweden	Basal cell	Caucasian	197/545	0.325/0.31
Nelson (2005) ⁵³	USA	Basal cell	Caucasian	732/613	0.39/0.40
	USA	Squamous cell	Caucasian	572/613	0.38/0.40
Weiss (2005) ⁵⁴	USA	Endometrial	Mixed ethnicity	371/420; [371/420]	0.38/0.37; [0.25/0.29]
Huang (2006) ⁵⁵	USA	Colorectal	Mixed ethnicity	665/667; [689/703]	0.39/0.40; [0.23/0.24]
Hirata (2006) ⁵⁶	Japan	Renal	Asian	112/180	0.67/0.65
Hirata (2007) ⁵⁷	Japan	Prostate	Asian	165/165	0.30/0.35

SCC, squamous cell carcinoma.

Note: Mixed ethnicity: Sak (2005), Caucasian population and others; Sak (2006), Caucasian population and others; Shen (2006), unknown; Wu (2006) Caucasian, Mexican Americans, Africans and others; Jorgensen (2007), unknown; Mechanic (2006), Caucasian population; Shen (2001), Caucasian non-hispanic population; Casson (2005), unknown; Weiss (2005), Caucasian and African-American population; Huang (2006), Caucasian, African American and others. (a) and (b) refer to distinct ethnical groups, as referred also in Figure 2.

change the observed results. The next step was to analyze the studies according to racial descent (Caucasians, Asians and mixed ethnicity), and to ethnicity and tumor site (Table 3). We did not find any association between XPC Lys939Gln for any genetic model stratified by ethnicity. However, lung cancer in the Asian samples showed a borderline risk associated with the Gln/Gln genotype (OR 1.23; 95% CI: 1.00–1.51) and an increased risk when the recessive genetic model was applied (OR 1.26; 95% CI: 1.04–1.52).

XPC Ala499Val The studies included genotyped a total of 7603 cases and 7772 controls. There were significant differences in Val allele frequency between Caucasians and Asians (Caucasians: 24.75%, 95% CI: 21.2–28.27; Asian:

30.5%, 95% CI: 26.7–34.2; $P < 0.001$; Figure 1b). No study analyzed cancer risk attributed to Ala499Val genotype in Africans.

Overall, individuals with Val/Val had an increased risk of cancer, compared with individuals with the Ala/Ala genotype, as shown by the summary OR of 1.15 (95% CI: 1.02–1.31; $P = 0.03$), with no evidence of heterogeneity between studies (Figure 3). This increased cancer risk was also observed using the recessive genetic model (Table 2). When the analysis were performed by tumor site, an increased risk of bladder cancer was found in Val/Val genotype individuals, as compared with Ala/Ala ones (OR 1.30; 95% CI: 1.04–1.61) (Figure 3). This increased risk for bladder cancer was also observed when data were analyzed using the recessive model (Table 2). When summary OR

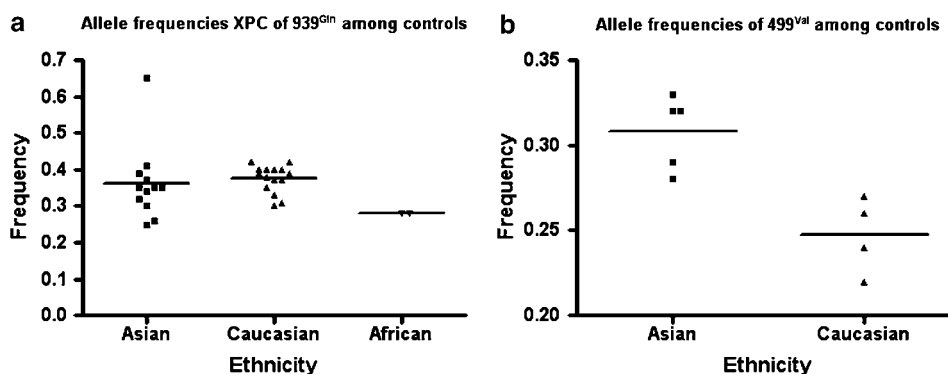


Figure 1 Allele frequencies (%) in the three major ethnical groups in controls to (a) XPC codon 939^{Gln} and (b) XPC codon 499^{Val}. Each data point represents a separate study for the indicated association. Horizontal line represents the mean value.

values were examined by racial descendent, no significant association was verified, but Caucasians showed a borderline effect in Val/Val genotype and in the recessive model (Table 3).

Test of heterogeneity

There was marginal statistical heterogeneity between the 33 studies that examined the Lys939Gln polymorphism ($P=0.05$). When analyzing all cancer sites together, only the recessive model showed significant heterogeneity ($\chi^2=49.21$, d.f. = 32, $P=0.03$). Significant heterogeneity was also observed in the 'other cancers' subgroup using the recessive model ($\chi^2=8.10$, d.f. = 3, $P=0.04$), in the melanoma group using the dominant model ($\chi^2=4.18$, d.f. = 1, $P=0.04$), and between studies with Caucasian samples (Lys/Lys vs Gln/Gln; $\chi^2=22.18$, d.f. = 11, $P=0.02$; recessive model, $\chi^2=21.40$, d.f. = 11, $P=0.03$). No significant heterogeneity was observed between the 15 studies that analyzed XPC Ala499Val, in any genetic model, apart from when the data were stratified by tumor site, the 'other cancers' subgroup showing heterogeneity using the dominant model ($\chi^2=8.23$, d.f. = 2, $P=0.02$).

Publication bias

The funnel plot and Egger's test for the OR of studies comparing Gln/Gln with Lys/Lys for XPC Lys939Gln provided no evidence of publication bias ($t=0.37$, $P=0.37$). Similarly, there was no evidence of publication bias for the comparison Val/Val vs Ala/Ala for XPC Ala499Val ($t=0.45$, $P=0.66$).

'In silico' analysis of polymorphisms in XPC

With the aim of understanding the possible impact of these two amino-acid substitutions on XPC protein structure, we performed *in silico* analysis using PolyPhen and SIFT algorithms. Predictions utilizing PolyPhen indicated that the substitution of Lys939Gln could be possibly damaging to the protein, with a PSIC score of 1.618, whereas for the

Ala499Val polymorphic variant, this exchange was predicted as benign, based on the score previously established, since the observed PSIC score was 0.346. When the predictions were carried out using the SIFT program, the Lys939Gln variant was classified as intolerant (score 0.00), whereas Ala499Val had a score of 0.20, classifying it as a 'borderline' substitution. However, predictions to Lys939Gln using SIFT had a low confidence result due to less than six aligned representative sequences.

Discussion

This meta-analysis of 33 case-control studies examined the association of two well-characterized polymorphisms of the DNA repair gene XPC (Lys939Gln and Ala499Val) with cancer risk. There was no overall effect on cancer risk for the Lys939Gln polymorphism in any genetic model, while a small increase in cancer risk was found for the Ala499Val polymorphism. When the XPC variants were analyzed by tumor site, for dominant or recessive genetic models, and by ethnic group, a few summary OR values were statistically significant. Different scenarios concerning the role of these polymorphisms can be interpreted from these results.

The overall no increase in risk of cancer for Lys939Gln represents the weighted average of the OR obtained from each study. While this suggests that this polymorphism may not play a major role in the risk of any cancer, it is a potential candidate for interaction studies. When examining the role of polymorphisms in DNA repair genes on cancer susceptibility, it is important to consider the importance of 'gene-environment' interactions, which are crucial to characterize low-penetrance genes.⁵⁸ For example, for lung cancer and head and neck cancer, the main risk factor seems to be the exposure to tobacco carcinogens, such as benzo(a)pyrene, which form DNA adducts⁵⁹ preferentially repaired by the NER pathway,

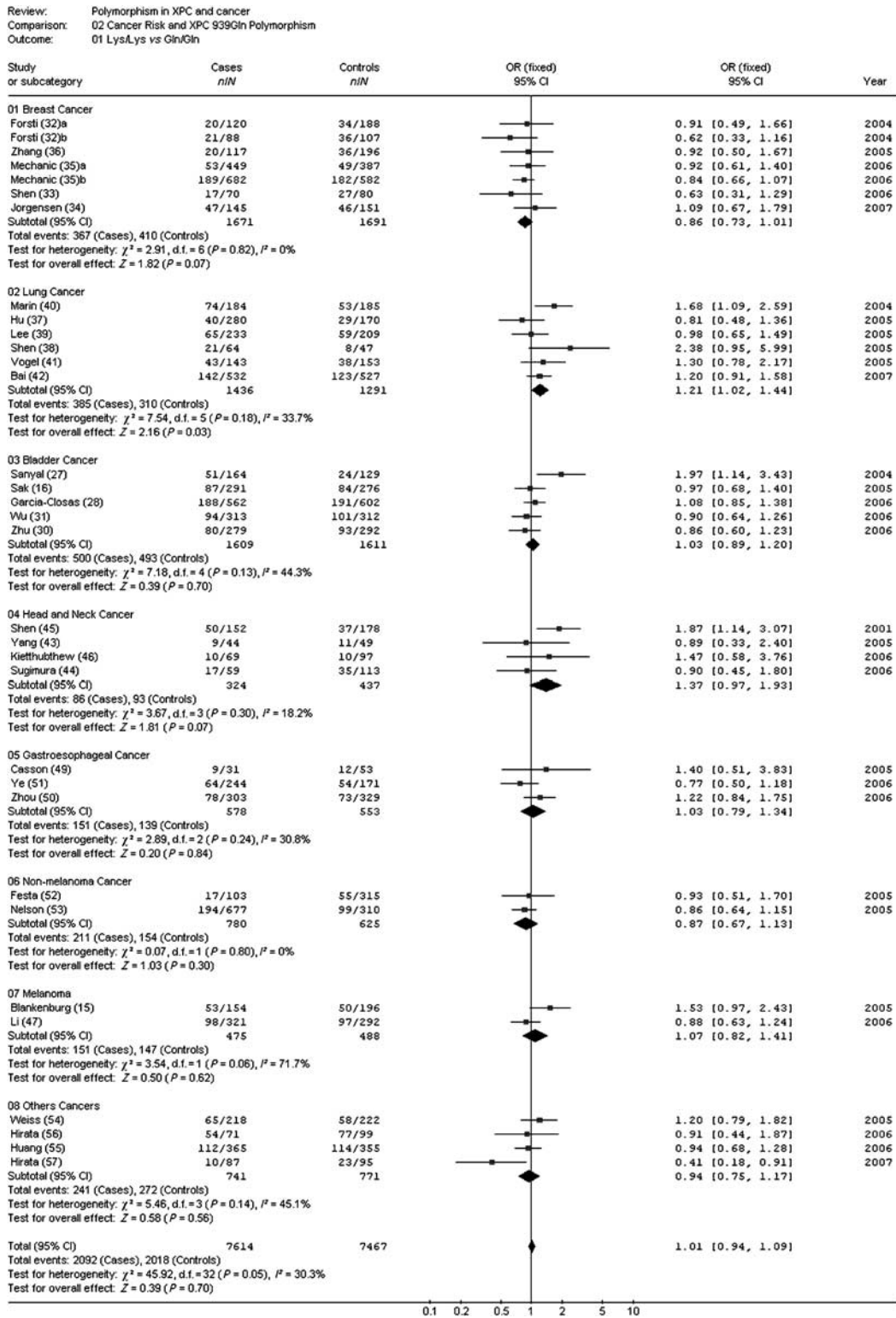


Figure 2 Forest plot showing ORs (log scale) (box) and 95% CI (horizontal line) for each study of cancer associated with XPC codon 939 for Lys/Lys genotype compared with Gln/Gln genotype. Studies are categorized by tumor site. *n/N*, *n* = number of Gln/Gln genotype, *N* = number of Lys/Lys plus Gln/Gln genotype. ♦, pooled OR and its 95% CI.

Table 2 Summary ORs (95% CI) for XPC variants under different genetic models and tumor site^a

XPC Lys939Gln Tumor site	No. of studies	Cases n/N	Controls n/N	Genetic model recessive	Cases n/N	Controls n/N	Genetic model dominant
Breast	7	367/3073	410/3048	0.87 (0.74–1.01) [‡]	1769/3073	1770/3048	0.97 (0.87–1.07)
Lung	6	401/2580	331/2604	1.30 (1.11–1.53) [§]	1608/2580	1598/2604	1.05 (0.93–1.17)
Bladder	5	500/3130	493/3095	1.01 (0.88–1.15)	2021/3130	2037/3095	0.95 (0.86–1.05)
Head and neck	4	204/1417	207/1652	1.29 (0.94–1.77)	867/1417	993/1652	1.14 (0.92–1.42)
Gastroesophageal Nonmelanoma	3	196/1435	212/1622	0.97 (0.75–1.24)	882/1435	952/1622	1.10 (0.92–1.31)
Melanoma	2	211/1501	154/1158	0.89 (0.70–1.14)	932/1501	685/1158	0.97 (0.81–1.15)
Other sites	2	151/896	147/976	1.14 (0.89–1.46)	572/896	635/976	0.99 (0.66–1.48) ^b
Total	4	241/1313	272/1432	1.04 (0.85–1.27) ^b	813/1313	933/1432	0.91 (0.77–1.06)
Total	33	2271/15345	2226/15587	1.03 (0.97–1.11) ^b	9649/15345	9603/15587	0.99 (0.94–1.04)

XPC Ala499Val Tumor site	Recessive			Dominant			
Lung	4	188/1862	161/1854	1.18 (0.95–1.47)	10088/1862	1003/1854	1.00 (0.88–1.14)
Bladder	4	204/2765	162/2813	1.32 (1.06–1.63) [§]	1255/2765	1254/2813	1.04 (0.93–1.15)
Breast	2	22/408	19/426	1.23 (0.65–2.30)	159/408	178/426	0.89 (0.68–1.18)
Melanoma	2	64/896	45/8221	1.37 (0.92–2.04)	373/896	439/8221	0.86 (0.72–1.03)
Other sites	3	120/1672	142/1703	0.85 (0.66–1.09)	792/1672	790/1703	1.03 (0.90–1.18) ^b
Total	15	598/7603	529/7618	1.15 (1.02–1.30) [§]	3587/7603	3664/7618	1.00 (0.93–1.06)

^aAll summary ORs were calculated using fixed-effects models, unless stated otherwise.

^bRandom-effect estimate.

[§] $P < 0.01$; [‡] $P = 0.05$. The column labeled as *No. of studies* indicates the number of reports compiled for the overall analysis. *n* = individuals with genotype tested; *N* = total of individuals.

Table 3 Summary ORs (95% CI) for XPC variants categorized by ethnicity and ethnicity/tumor site under different genetic models^a

XPC Lys939Gln Ethnicity	No. of studies	Homozygous analysis Lys/Lys vs Gln/Gln	Genetic models	
			Recessive	Dominant
Asian	11	1.11 (0.95–1.30)	1.13 (0.98–1.30)	1.01 (0.92–1.12)
Caucasian	12	1.04 (0.88–1.24) ^b	1.02 (0.87–1.19) ^b	1.05 (0.97–1.14)
Mixed ethnicity	10	0.98 (0.86–1.11)	1.01 (0.90–1.14)	0.95 (0.87–1.04)
<i>Asian</i>				
Lung cancer	4	1.23 (1.00–1.51) [‡]	1.26 (1.04–1.52) [§]	1.02 (0.89–1.16)
Head and neck	3	1.02 (0.63–1.66)	1.07 (0.68–1.68)	0.91 (0.68–1.23)
<i>Caucasian</i>				
Bladder	3	1.09 (0.90–1.32)	1.08 (0.76–1.54) ^b	1.12 (0.98–1.28)
<i>XPC Ala499Val</i>				
		Ala/Ala vs Val/Val	Recessive	Dominant
<i>Ethnicity</i>				
Asian	5	1.09 (0.84–1.42)	1.02 (0.79–1.31)	1.10 (0.95–1.28)
Caucasian	4	1.25 (0.99–1.57)	1.24 (0.99–1.55)	0.95 (0.85–1.06)
Mixed ethnicity	6	1.05 (0.83–1.31)	1.13 (0.91–1.41)	0.98 (0.88–1.09)
<i>Asian</i>				
Lung cancer	4	1.16 (0.92–1.47)	1.18 (0.95–1.47)	1.02 (0.88–1.14)

^aAll summary ORs were calculated using fixed-effects models, unless stated otherwise.

^bRandom-effect estimate.

[‡] $P = 0.05$. [§] $P = 0.02$. The column labeled as *No. of studies* indicates the number of reports compiled for the overall analysis.

where XPC acts in the initial recognition process of the DNA lesion. Therefore, interactions of the Gln/Gln genotype and tobacco exposure may lead to an increased risk of lung cancer, as previously reported,⁴⁰ and head and neck

cancer⁴⁵ as well. Intriguingly, although smoking status also seems to be a risk factor for breast carcinogenesis.⁶⁰ The XPC Gln/Gln variant seems to play a borderline protective role for breast cancer, such protective role

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Comparison: 01 Cancer Risk and XPC 499Val Polymorphism
Outcome: 01 Ala/Ala vs Val/Val

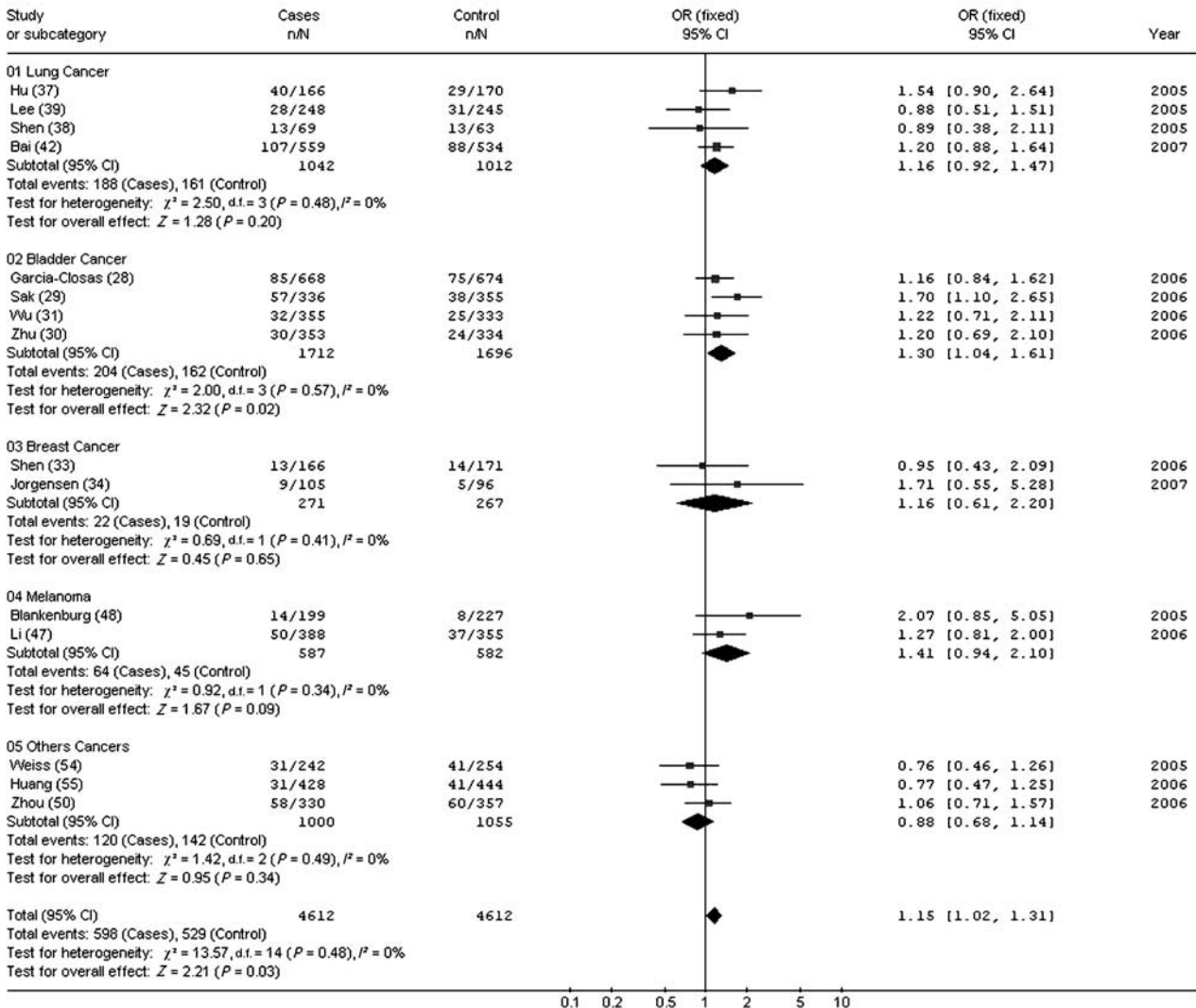


Figure 3 Forest plot showing ORs and 95% CI for each study of cancer associated with XPC codon 499 for Ala/Ala genotype compared with Val/Val genotype. Studies are categorized by tumor site. n/N, n = number of Gln/Gln genotype, N = number of Ala/Ala plus Gln/Gln genotype. ♦, pooled OR and its 95% CI.

was not statistically significant in any genetic model applied. It is still not possible to compare the exposure of airway epithelial cells and breast epithelial cells with the tobacco-derived carcinogens. Future studies using surrogate markers of carcinogen exposure will be useful to clarify this issue. However, as it is widely accepted, tobacco is quite a complex mixture of carcinogens, which may act in distinct phases of the carcinogenesis process. For example, toxicological studies point to the presence of organic solvents and distinct polycyclic aromatic hydrocarbons, which are not only mutagenic but may also be breast cancer promoters, acting as hormone disruptors.⁶¹

When applying the recessive genetic model to the different tumor sites, a significant increase in risk for lung cancer was also observed, strengthening the possibility of a role of XPC Gln/Gln genotype in these tissues. For head and neck cancer, however, no association could be seen in the recessive genetic model. Head and neck cancer may be a too general classification including a variety of cancer types in this anatomic region, whereas the role of XPC may be tissue specific.

The polymorphism in the XPC codon 939 replaces the positively charged amino acid lysine by the polar uncharged amino acid glutamine. The substitution does not change radically the hydrophathy index of these amino

acids (−3.9 to −3.5).⁶² However, *in silico*, the results indicated that Lys939Gln could be possibly damaging to the protein. It is important to consider that even though the computational analysis suggests a possible damage, this prediction may be not always correct, since protein–protein interactions may minimize amino-acid substitution-dependent conformation changes. Again, if this is correct, the effects observed will be either cell or tissue specific. Both biological and biochemical evidence also indicate the importance of XPC Lys939Gln polymorphism associated with a differential repair capacity.^{63–66} Low repair capacity of benzo(a)pyrene DNA adducts was also observed in lymphocytes of individuals with this XPC variant,⁶⁷ although the protein levels of XPC were not measured in that study. Moreover, XPC has two other polymorphisms in linkage with the Gln allele – an insertion of an 83-bp ATs (PAT) in intron 9 and an exchange of C to A in splicing site of intron 11 – that might contribute to a decreased expression of XPC, due to abnormalities in RNA stability and splicing process.^{11,21} In a very elegant study, Wei *et al*⁶⁸ showed that lymphocytes from head and neck cancer patients had an attenuated induction of XPC protein expression when transfected with damaged DNA, as compared with controls. For lung cancers, there is evidence for XPC promoter hypermethylation, leading to decreased transcription levels of the gene in the early events of carcinogenesis.⁶⁹ Depletion of the XPC gene also led to lung tumors in mice, pointing to the importance of this gene for lung carcinogenesis.⁸ More recently, the involvement of XPC in photocarcinogenesis was suggested by experiments using XPC/CDKN2a double knockout mice.⁷⁰

The *in silico* results for conformational changes in the substitution Ala499Val indicated an effect ranging between benign and borderline. However, in the Val/Val vs Ala/Ala and in the recessive genetic model, the variant genotype showed increased risk for bladder cancer, where the Val allele might contribute to the low efficiency for DNA repair in bladder tissue, contributing then to carcinogenesis. There are no biochemical reports showing the contribution of Val allele in repair or genetic stability assays, but a study analyzing the telomere length in bladder cancer patients demonstrated that individuals with Val/Val genotype had a nonsignificant ($P=0.06$) telomere shortening.⁷¹ For bladder cancer, established risk factors also include smoking habits as well as exposure to industrially related aromatic amines.⁷² The only two studies that analyzed the influence of risk factors adjusted to XPC Val/Val genotype also found an interaction between genetic and environmental factors for bladder cancer.^{29,30}

The present study has some limitations. First, the effect of XPC might be best represented by its haplotype. Among the nine studies that analyzed XPC haplotype,^{30,33,34,37,39,42,47,50,54} six found some type of association with cancer risk for the haplotypes analyzed. However,

in the present meta-analysis, it was not possible to use XPC haplotypes, due to the small number of studies that had information about haplotype frequencies. Second, multiple testing may explain some or even all statistically significant associations observed in the present study. Given the multiplicity of comparisons for different cancer types, different genetic models and ethnic groups, and the unavoidable flexibility of choosing and defining the correlates, associations might have been detected by chance alone. Third, for some subgroup analyses there were only a very limited number of studies available, and therefore not having enough statistical power to detect association may explain some negative results. Even the total number of studies that analyzed Ala499Val polymorphism (15) was relatively small, in comparison to the number of studies that looked at the Lys939Gln polymorphism. Heterogeneity of ethnic ancestry may have also limited the ability of the meta-analyses in finding estimates of the true associations, since pooling samples with different ethnic backgrounds might produce a population average toward the null. However, summary estimates were obtained using the Mantel–Haenszel method, which calculates first an OR for each study and then an average estimate weighted for the precision of each study, and it is likely that within each study cases and controls had similar ethnic ancestry, thus reducing the likelihood of a summary estimate biased by differential ethnic ancestry between studies. On the other hand, the current meta-analysis has some key advantages, compared with individual studies. First, a substantial number of cases and controls were pooled from several studies, which significantly increased the statistical power of the analysis. Second, the subgroups that showed significant or borderline results did not have heterogeneity, which strengthens the analysis. Third, publication bias was not observed in both polymorphisms, which indicates that the pooled results should be unbiased.

In conclusion, this meta-analysis supports that polymorphisms in XPC gene may represent a low-penetrance gene for cancer risk, especially for breast, lung, head and neck, and bladder cancer. The current meta-analysis also illustrates the need to design epidemiologic case–control studies that include samples sizes with adequate statistical power to provide more conclusive evidence for associations between genotypes and diseases. These larger studies should also include analysis of risk factors, clarifying the interaction of haplotypes, gene–gene and gene–environment to tissue-specific cancer and to ethnicity specific populations. XPC plays a central role as a sensor of DNA distortions, such as those caused by both mutagenic and chemotherapeutic agents, such as cisplatin.⁷³ Therefore, it will be important to complete the analysis of the involvement of specific XPC variants in tumorigenesis, with studies of its role on tumor progression and response to chemotherapy. Moreover, based on what we have addressed in the present study, XPC is a good candidate

for the new generation of large-scale epidemiological case-control studies that will ultimately lead to a better diagnosis, treatment and prevention of prevalent cancers.

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