J Hum Genet (2008) 53:18–33
DOI 10.1007/s10038-007-0215-5

ORIGINAL ARTICLE

A meta-analysis of DNA repair gene *XPC* polymorphisms and cancer risk

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Received: 25 July 2007 / Accepted: 13 October 2007 / Published online: 17 November 2007

Abstract Polymorphisms (A33512C, C21151T and PAT −/+) of the xeroderma pigmentosum group C (*XPC*) were shown to contribute to genetic susceptibility to cancer. However, association studies on these polymorphisms in cancer have shown conflicting results. Thus, we performed a meta-analysis. Overall, there was no significant association between 33512C (9,091 patients and 11,553 controls) and cancer risk. No significant association was found in stratification analysis by tumor sites and ethnicities except an elevated lung cancer risk under the recessive genetic model in all subjects [$P = 0.04$, odds ratio (OR) = 1.20, 95% confidence interval (CI) 1.00–1.45, $P_{\text{heterogeneity}} = 0.88$]. There was no significant association between 21151T (5,227 patients and 5,959 controls) and cancer risk in all subjects but an increased cancer risk in Caucasians under the recessive genetic model ($P = 0.006$, OR = 1.45, 95% CI 1.11–1.90, $P_{\text{heterogeneity}} = 0.75$) and homozygote comparison ($P = 0.02$, OR = 1.41, 95% CI 1.07–1.81, $P_{\text{heterogeneity}} = 0.41$). It might be that 21151T increases bladder cancer risk under the recessive genetic model ($P = 0.02$, OR = 1.49, 95% CI 1.06–2.09, $P_{\text{heterogeneity}} = 0.47$) and homozygote comparison ($P = 0.02$, OR = 1.49, 95% CI 1.05–2.11, $P_{\text{heterogeneity}} = 0.23$). There was no significant association between PAT + (4,600 patients and 4,866 controls) and cancer risk in all subjects. An increased cancer risk in Caucasians was found under the recessive genetic model ($P = 0.02$, OR = 1.20, 95% CI 1.03–1.40, $P_{\text{heterogeneity}} = 0.37$) and homozygote comparison ($P = 0.008$, OR = 1.26, 95% CI 1.06–1.50, $P_{\text{heterogeneity}} = 0.13$). The *XPC* PAT + allele might increase head and neck cancer risk ($P = 0.02$, OR = 1.29, 95% CI 1.04–1.59, $P_{\text{heterogeneity}} = 0.15$). More studies based on larger, stratified, case–control population, especially studies investigate the combined effect of *XPC* A33512C, C21151T, and PAT, are required to further evaluate the role of these polymorphisms in different cancers.

Keywords *XPC* · Cancer · Polymorphisms · Meta-analysis

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Introduction

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. DNA repair systems play a critical role in protecting the genome from the insults of cancer-causing agents. Unrepaired damage can result in apoptosis or may lead to unregulated cell growth and then cancer. In humans, more than 70 genes are involved in the four major DNA repair pathways: nucleotide excision repair (NER), base excision repair, mismatch repair, and double-strand-break repair (Hoeijmakers 2001). NER is a versatile repair pathway that can eliminate a wide variety of DNA lesions, including UV-induced photolesions and chemical carcinogen-induced bulky DNA adducts. It is composed of at least two subpathways, global genome repair (GGR) and transcription-coupled repair (TCR) (de Laat et al. 1999). Individuals with decreased NER capacity are at increased risk of cancers. As with many other phenotypic traits, variation in NER capacity may be the result of functional polymorphisms in NER genes. Therefore, it

has been hypothesized that inherited polymorphisms in NER genes may modulate susceptibility to cancer.

The xeroderma pigmentosum complementation group C (*XPC*) protein had been reported to be involved in the early damage recognition and initiation of NER. The *XPC* protein binds tightly with HR23B (one of two human homologs of Saccharomyces cerevisiae NER factor RAD23), forming the *XPC*–HR23B complex (Masutani et al. 1997; Sugasawa et al. 1998). Sequence variants of the *XPC* gene may alter NER capacity and modulate cancer risk. Hollander et al. found deletion of *XPC* led to lung tumors in mice, and *XPC* was associated with early events in human lung carcinogenesis (Hollander et al. 2005). Khan et al. discovered an intronic biallelic poly (AT) insertion/deletion polymorphism (PAT) in intron 9 of *XPC* (Khan et al. 2000). Two nonsynonymous single nucleotide polymorphisms (SNPs), Lys939Gln (an A → C transversion) in exon 15 and Ala499Val (a C → T transition) in exon 8, have also been identified (Hu et al. 2005; Khan et al. 2002).

A large number of molecular epidemiologic studies have been preformed to evaluate the role of *XPC* polymorphisms in various neoplasms. The Val499Arg (*XPC* C21151T, rs2228000) and Lys939Gln (*XPC* A33512C, rs2228001) substitution and a poly (AT) insertion/deletion polymorphism (*XPC* PAT −/+) in intron 9 are the most thoroughly investigated polymorphism in *XPC*. However, studies on the *XPC* A33512C, C21151T and PAT −/+ polymorphisms have shown conflicting results. These polymorphisms might play different roles in different cancers and ethnicities. Even at the same tumor site, considering the possible small effect size of these genetic polymorphisms to cancer and the relatively small sample size in some studies, a small but real association maybe underpowered, which will lead to apparent discrepancy between studies. To assess the association of *XPC* polymorphisms with the risk of cancer, we conducted a meta-analysis from all eligible case–control studies published to date.

Methods

Identification and eligibility of relevant studies

To identify all studies that examined the association of *XPC* polymorphisms with cancer, we conducted a computerized literature search of PubMed database (prior to May 2007) using the following keywords and subject terms: "*XPC*", "polymorphism" and "cancer". References of retrieved articles were also screened. Abstracts, case reports, editorials, and review articles were excluded. If an article reported results on different ethnicity subpopulations or tumor sites, each subpopulation or tumor was treated as a separate study in our meta-analysis. Studies included in the meta-analysis had to meet all the following criteria: (1) use an unrelated case–control design, (2) have available genotype frequency, and (3) genotype distribution of control population must be in Hardy–Weinberg equilibrium (HWE).

Data extraction

Data were collected on the genotype of A33512C, C21151T, and PAT −/+ according to different kinds of cancers. First author, year of publication, ethnicity of study population, number of cases and controls, and allele frequency were described (Table 1).

Statistical analysis

The strength of the association between *XPC* polymorphisms and cancer was measured by odds ratio (OR) corresponding to 95% confidence interval (CI), which was calculated according to the method of Woolf (1955). We examined the association between allele C of *XPC* A33512C and cancer risk, as well as the dominant genetic model (CC + CA vs. AA), the recessive genetic model (CC vs. CA + AA), homozygote comparison (CC vs. AA), CC vs. CA contrast, and CA vs. AA contrast. The same method was applied to analysis of the C21151T and PAT −/+ polymorphisms. We conducted two models of meta-analysis for dichotomous outcomes in Review-Manager 4.2 software: the fixed-effects model and the random-effects model. A fixed-effects model using the Mantel–Haenszel method assumes that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance. A random-effects model assumes that studies are taken from populations with varying effect sizes and calculates study weights both from in-study and between-study variances, with consideration of the extent of variation, or heterogeneity. A chi-square-based Q statistic test was performed to assess the between-study heterogeneity (Lau et al. 1997). Heterogeneity was considered significant for $P < 0.10$. A random-effects model (if $P < 0.10$) or a fixed-effects model (if $P > 0.10$) was used to pool the results (Petitti 1994). The significance of the pooled OR was determined by the Z test. A P value of <0.05 was considered significant.

Subgroup analysis was stratified by the study characteristics of ethnicity and tumor site, respectively. Tumor sites only investigated once in all the studies were grouped as "other cancers".

Table 1 Characteristics of studies that investigated the association between xeroderma pigmentosum group C (*XPC*) polymorphisms and cancer risk

First author (year)	Ethnicity	Cancer type	Single nucleotide polymorphism studied	Case no.	Control no.	Allele frequency (%) A33512/C21151/PAT−
Hu et al. (2005)	Asian (Chinese)	Lung cancer	A33512C, C21151T	320	322	63.4/65.5
Lee et al. (2005)	Asian (Korean)	Lung cancer	A33512C, C21151T, PAT	432	432	61.9/72.2/65.2
Vogel et al. (2005)	Caucasian	Lung cancer	A33512C	256	269	61.1
Bai et al. (2007)	Asian (Chinese)	Lung cancer	A33512C, C21151T	994	992	62.5/67.4
Marin et al. (2004)	Caucasian	Lung cancer	PAT	359	355	55
De Ruyck et al. (2007)	Caucasian	Lung cancer	PAT	110	109	58.6
Mechanic et al. (2006) African American	African American	Breast cancer	A33512C	761	679	72.5
Mechanic et al. (2006) whites	Caucasian	Breast cancer	A33512C	1,267	1,123	62
Zhu et al. (2007)	Caucasian	Bladder cancer	A33512C, C21151T, PAT	561	562	60.8/76.8/61.5
Sanyal et al. (2004)	Caucasian	Bladder cancer	A33512C	305	246	60.2
Sak et al. (2005)	Caucasian	Bladder cancer	A33512C, PAT	544	577	61.0/61.8
Sak et al. (2006)	Caucasian	Bladder cancer	C21151T, PAT	544	577	70.6/61.8
Huang et al. (2006)	Mixed (USA)	Colorectal adenoma	A33512C, C21151T	689	703	60.6/76.6
Hansen et al. (2007)	Caucasian	Colorectal adenoma	A33512C	395	797	61.5
Li et al. (2006)	Caucasian	Cutaneous melanoma	A33512C, C21151T	602	603	60.4/73.9
Blankenburg et al. (2005)	Caucasian	Cutaneous melanoma	A33512C, PAT	294	375	58.7/58.3
Shen et al. (2001)	Caucasian	Head and neck cancer	PAT	287	311	59.1
Yang et al. (2005)	Asian (Korean)	Head and neck cancer	PAT	73	82	67.8
Ye et al. (2006) GcAde	Caucasian	Gastric cardia adenocarcinoma	A33512C	126	472	59.5
Zhou et al. (2006) GcAde	Asian (Chinese)	Gastric cardia adenocarcinoma	A33512C, C21151T	253	612	63.0/73.5
Casson et al. (2005)	Caucasian	Esophageal adenocarcinoma	PAT	307	95	61.6
Ye et al. (2006) EsAde	Caucasian	Esophageal adenocarcinoma	A33512C	96	472	61.5
Ye et al. (2006) ESCC	Caucasian	Esophageal squamous cell carcinoma	A33512C	81	472	60.5
Zhou et al. (2006) ESCC	Asian (Chinese)	Esophageal squamous cell carcinoma	A33512C, C21151T	327	612	62.4/68.0
Kietthubthew et al. (2006)	Asian Thailand)	Oral squamous cell carcinoma	A33512C, PAT	106	164	73.1/73.6
Sugimura et al. (2006)	Japanese	Oral carcinogenesis	PAT	122	241	60.2
Nelson et al. (2005) SCC	Mixed (New Hampshire)	Squamous cell carcinoma of nonmelanoma skin cancer	PAT	572	613	61.5
Nelson et al. (2005) BCC	Mixed (New Hampshire)	Basal cell carcinoma of nonmelanoma skin cancer	PAT	732	613	60.7
Festa et al. (2005)	Caucasian	Basal cell carcinoma	A33512C	197	545	67.5
Hirata et al. (2007)	Asian(Japanese)	Prostate cancer	A33512C	165	165	70.3
Weiss et al. (2005)	Mixed (Washington)	Endometrial cancer	A33512C, C21151T	371	420	61.8/74.3
Wang et al. (2006)	Asian (Chinese)	Pancreatic cancer risk	PAT	101	337	68.3

GcAde gastric cardia adenocarcinoma, *EsAde* esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma, *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma

Publication bias was investigated with the funnel plot, in which the standard error of ln(OR) of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test (Egger et al. 1997). The significance of the intercept was determined by the t test, and a P value of <0.05 was considered significant. Hardy–Weinberg equilibrium was tested by the chi-square test for goodness of fit with a Web program (http://www.ihg.gsf.de/cgi-bin/hw/hwa1.pl). Analyses were performed using the software Stata version 7, ReviewManager 4.2 (Oxford, England). All P values were two-sided.

Results

Study inclusion

Through literature search and selection based on the inclusion criteria, 32 articles (37 studies) were found, and 28 articles (Bai et al. 2007; Blankenburg et al. 2005; Casson et al. 2005; De Ruyck et al. 2007; Festa et al. 2005; Hansen et al. 2007; Hirata et al. 2007; Hu et al. 2005; Huang et al. 2006; Kietthubthew et al. 2006; Lee et al. 2005; Li et al. 2006; Marin et al. 2004; Mechanic et al. 2006; Nelson et al. 2005; Sak et al. 2005, 2006; Sanyal et al. 2004; Shen et al. 2001, 2005; Sugimura et al. 2006; Vogel et al. 2005; Wang et al. 2006; Weiss et al. 2005; Yang et al. 2005; Ye et al. 2006; Zhou et al. 2006; Zhu et al. 2007) (32 studies) met our inclusion criteria, as listed in Table 1. One study of A33512C (Hirata et al. 2006) reported an extremely high variant allele frequency, which may result from wrong allele counting or poor genotyping quality, and was finally excluded from our meta-analysis.

Among the 28 eligible articles, 18 articles (Bai et al. 2007; Blankenburg et al. 2005; Festa et al. 2005; Hansen et al. 2007; Hirata et al. 2007; Hu et al. 2005; Huang et al. 2006; Kietthubthew et al. 2006; Lee et al. 2005; Li et al. 2006; Mechanic et al. 2006; Sak et al. 2005; Sanyal et al. 2004; Vogel et al. 2005; Weiss et al. 2005; Ye et al. 2006; Zhou et al. 2006; Zhu et al. 2007) (23 studies) described A33512C, ten articles (Bai et al. 2007; Hu et al. 2005; Huang et al. 2006; Lee et al. 2005; Li et al. 2006; Sak et al. 2006; Shen et al. 2005; Weiss et al. 2005; Zhou et al. 2006; Zhu et al. 2007) (11 studies) described C21151T, and 13 articles (Blankenburg et al. 2005; Casson et al. 2005; De Ruyck et al. 2007; Kietthubthew et al. 2006; Li et al. 2006; Marin et al. 2004; Nelson et al. 2005; Sak et al. 2005; Shen et al. 2001; Sugimura et al. 2006; Wang et al. 2006; Yang et al. 2005; Zhu et al. 2007) (14 studies) described PAT −/+; 82.1% (23/28) stated that the age and gender status were matched between case and control population. All studies used blood sample for genotyping.

In all the eligible articles, Zhou et al. (2006) provided data on two kinds of cancers: esophageal squamous cell carcinoma (ESCC) and gastric cardiac adenocarcinoma (GcAde). Nelson et al. (2005) provided data on two kinds of cancers: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Thus, each type of cancer in these two articles was treated as a separate study in our meta-analysis (Table 2). Mechanic et al. (2006) provided data on subjects of two ethnicities: Africa American and white. Similarly, these two ethnicities were treated as separate studies. Studies providing genotyping data of the population of America were indicated as "mixed" ethnic (Huang et al. 2006; Nelson et al. 2005; Weiss et al. 2005).

Summary statistics

The allele frequencies were calculated for controls from the corresponding genotype distributions (Table 2). The A33512 allele had a higher representation among controls of Asian descent (65.2%, 95% CI 61.1–69.4) than in controls of European descent (61.3%, 95% CI 59.7–62.8). The C21151 allele had a lower representation among controls of Asian descent (69.2%, 95% CI 66.0–72.4) than in controls of European descent (74.5%, 95% CI 69.9–79.1). The PAT− allele had a higher representation among controls of Asian descent (67.0%, 95% CI 61.0–73.1) than in controls of European descent (59.4%, 95% CI 57.4–61.7). The allele frequencies of these three polymorphisms did not show big differences between Asians and Caucasians. Overall, the prevalence of A33512, C21151, and PAT− allele was 63.0%, 72.1%, and 62.4% in controls, respectively (Table 2).

Quantitative synthesis

XPC *A33512C*

The fixed-effects model was used to pool the result, as the between-study heterogeneity was insignificant. There was no significant association between the 33512C allele and cancer risk in all subjects ($P = 0.60$, OR = 1.01, 95% CI 0.97–1.05, $P_{\text{heterogeneity}} = 0.34$), as well as in Asians or Caucasians. However, under the recessive genetic model, an elevated but not significant association between CC genotype and cancer risk was found in all subjects ($P = 0.05$, OR = 1.08, 95% CI 1.00–1.18, $P_{\text{heterogeneity}} = 0.25$); CC genotype showed a significant association with cancer risk in all subjects in analysis of CC vs. CA contrast ($P = 0.03$, OR = 1.11, 95% CI 1.01–1.20, $P_{\text{heterogeneity}} = 0.26$) (Table 3).

Table 2 Distribution of xeroderma pigmentosum group C (*XPC*) A33512C, C21151T, and poly (AT) insertion/deletion polymorphism (PAT) −/+ genotype and allele among cancers of cases and controls in the meta-analysis

A33512C		Genotype						Allele			
		AA		AC		CC		A		C	
Author (year)	Ethnicity	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)
Hu et al. (2005)	Asian	126 (39.4)	141 (43.8)	154 (48.1)	152 (47.2)	40 (12.5)	29 (9.0)	406 (63.4)	434 (67.4)	234 (36.6)	210 (32.6)
Lee et al. (2005)	Asian	168 (39.0)	150 (34.8)	198 (45.9)	222 (51.5)	65 (15.1)	59 (13.7)	534 (61.9)	522 (60.6)	328 (38.1)	340 (39.4)
Vogel et al. (2005)	Caucasian	100 (39.1)	115 (42.8)	113 (44.1)	116 (43.1)	43 (16.8)	38 (14.1)	313 (61.1)	346 (64.3)	199 (38.9)	192 (35.7)
Bai et al. (2007)	Asian	390 (39.4)	404 (40.7)	459 (46.3)	465 (46.9)	142 (14.3)	123 (12.4)	1239 (62.5)	1273 (64.2)	743 (37.5)	711 (35.8)
Li et al. (2006)	Caucasian	223 (37.0)	195 (32.3)	281 (46.7)	311 (51.6)	98 (16.3)	97 (16.1)	727 (60.4)	701 (58.1)	477 (39.6)	505 (41.9)
Festa et al. (2005)	Caucasian	86 (43.7)	260 (47.7)	94 (47.7)	230 (42.2)	17 (8.6)	55 (10.1)	266 (67.5)	750 (68.8)	128 (32.5)	340 (31.2)
Zhu et al. (2007)	Caucasian	199 (36.2)	199 (35.9)	271 (49.3)	262 (47.3)	80 (14.5)	93 (16.8)	669 (60.8)	660 (59.6)	431 (39.2)	448 (40.4)
Huang et al. (2006)	Mix	253 (38.0)	241 (36.1)	300 (45.1)	312 (46.8)	112 (16.8)	114 (17.1)	806 (60.6)	794 (59.5)	524 (39.4)	540 (40.5)
Sanyal et al. (2004)	Caucasian	113 (37.0)	105 (42.7)	141 (46.2)	117 (47.6)	51 (16.7)	24 (9.8)	367 (60.2)	327 (66.5)	243 (39.8)	165 (33.5)
Mechanic et al. (2006) African	African American	396 (52.0)	338 (49.8)	312 (41.0)	292 (43.0)	53 (7.0)	49 (7.2)	1104 (72.5)	968 (71.3)	418 (27.5)	390 (28.7)
Mechanic et al. (2006) whites	Caucasian	493 (38.9)	400 (35.6)	585 (46.2)	541 (48.2)	189 (14.9)	182 (16.2)	1571 (62.0)	1341 (59.7)	963 (38.0)	905 (40.3)
Hirata et al. (2007)	Asian	77 (46.7)	72 (43.6)	78 (47.3)	70 (42.4)	10 (6.1)	23 (13.9)	232 (70.3)	214 (64.8)	98 (29.7)	116 (35.2)
Sak et al. (2005)	Caucasian	204 (38.3)	192 (34.2)	241 (45.3)	285 (50.8)	87 (16.4)	84 (15.0)	649 (61.0)	669 (59.6)	415 (39.0)	453 (40.4)
Ye et al. (2006) EsAde	Caucasian	38 (39.6)	180 (38.1)	42 (43.8)	228 (48.3)	16 (16.7)	64 (13.6)	118 (61.5)	588 (62.3)	74 (38.5)	356 (37.7)
Ye et al. (2006) ESCC	Caucasian	31 (38.3)	180 (38.1)	36 (44.4)	228 (48.3)	14 (17.3)	64 (13.6)	98 (60.5)	588 (62.3)	64 (39.5)	356 (37.7)
Ye et al. (2006) GcAde	Caucasian	48 (38.1)	180 (38.1)	54 (42.9)	228 (48.3)	24 (19.0)	64 (13.6)	150 (59.5)	588 (62.3)	102 (40.5)	356 (37.7)
Zhou et al. (2006) ESCC	Asian	126 (38.5)	256 (41.8)	156 (47.7)	283 (46.2)	45 (13.8)	73 (11.9)	408 (62.4)	795 (65.0)	246 (37.6)	429 (35.0)
Zhou et al. (2006) GcAde	Asian	99 (39.1)	256 (41.8)	121 (47.8)	283 (46.2)	33 (13.0)	73 (11.9)	319 (63.0)	795 (65.0)	187 (37.0)	429 (35.0)
Hansen et al. (2007)	Caucasian	141 (35.7)	307 (38.5)	204 (51.6)	392 (49.2)	50 (12.7)	98 (12.3)	486 (61.5)	1006 (63.1)	304 (38.5)	588 (36.9)
Weiss et al. (2005)	Mix	153 (41.2)	164 (39.0)	153 (41.2)	198 (47.1)	65 (17.5)	58 (13.8)	459 (61.9)	526 (62.6)	283 (38.1)	314 (37.4)
Kietthubthew et al. (2006)	Asian	59 (55.7)	87 (53.0)	37 (34.9)	67 (40.9)	10 (9.4)	10 (6.1)	155 (73.1)	241 (73.5)	57 (26.9)	87 (26.5)
Blankenburg et al. (2005)	Caucasian	104 (35.4)	147 (39.2)	137 (46.6)	178 (47.5)	53 (18.0)	50 (13.3)	345 (58.7)	472 (62.9)	243 (41.3)	278 (37.1)

Table 2 continued

C21151T		CC		CT		TT		C		T	
Author (year)	Ethnicity	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)
Hu et al. (2005)	Asian	124 (38.8)	158 (49.1)	171 (53.4)	145 (45.0)	25 (7.8)	19 (5.9)	419 (65.5)	461 (71.6)	221 (34.5)	183 (28.4)
Lee et al. (2005)	Asian	220 (50.9)	214 (49.5)	184 (42.6)	187 (43.3)	28 (6.5)	31 (7.2)	624 (72.2)	615 (71.2)	240 (27.8)	249 (28.8)
Bai et al. (2007)	Asian	452 (45.5)	446 (45.1)	435 (43.8)	456 (46.1)	107 (10.8)	88 (8.9)	1339 (67.4)	1348 (68.1)	649 (32.6)	632 (31.9)
Li et al. (2006)	Caucasian	338 (56.1)	318 (52.7)	214 (35.5)	248 (41.1)	50 (8.3)	37 (6.1)	890 (73.9)	884 (73.3)	314 (26.1)	322 (26.7)
Zhu et al. (2007)	Caucasian	323 (59.2)	310 (56.5)	193 (35.3)	215 (39.2)	30 (5.5)	24 (4.4)	839 (76.8)	835 (76.0)	253 (23.2)	263 (24.0)
Huang et al. (2006)	Mix	397 (57.6)	403 (57.3)	261 (37.9)	259 (36.8)	31 (4.5)	41 (5.8)	1055 (76.6)	1065 (75.7)	323 (23.4)	341 (24.3)
Zhou et al. (2006) ESCC	Asian	156 (47.7)	272 (44.4)	133 (40.7)	282 (46.1)	38 (11.6)	58 (9.5)	445 (68.0)	826 (67.5)	209 (32.0)	398 (32.5)
Zhou et al. (2006) GcAde	Asian	141 (55.7)	272 (44.4)	90 (35.6)	282 (46.1)	22 (8.7)	58 (9.5)	372 (73.5)	826 (67.5)	134 (26.5)	398 (32.5)
Sak et al. (2006)	Caucasian	279 (51.9)	317 (56.1)	202 (37.5)	210 (37.2)	57 (10.6)	38 (6.7)	760 (70.6)	844 (74.7)	316 (29.4)	286 (25.3)
Weiss et al. (2005)	Mix	211 (56.9)	213 (56.1)	129 (34.8)	166 (39.5)	31 (8.4)	41 (9.8)	551 (74.3)	592 (70.5)	191 (25.7)	248 (29.5)
Shen et al. (2005)	Asian	56 (48.3)	50 (45.5)	47 (40.5)	47 (42.7)	13 (11.2)	13 (11.8)	159 (68.5)	147 (66.8)	73 (31.5)	73 (33.2)
PAT −/+		− −		−+		++		−		+	
Author(year)	Ethnicity	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)	Case *n* (%)	Control *n* (%)
Lee et al. (2005)	Asian	192 (44.4)	167 (38.7)	179 (41.4)	208 (48.1)	61 (14.1)	57 (13.2)	563 (65.2)	542 (62.7)	301 (34.8)	322 (37.3)
Zhu et al. (2007)	Caucasian	213 (38.0)	214 (38.1)	264 (47.1)	258 (45.9)	84 (15.0)	90 (16.0)	690 (61.5)	686 (61.0)	432 (38.5)	438 (39.0)
Kietthubthew et al. (2006)	Asian	60 (56.6)	89 (54.3)	36 (34.0)	66 (40.2)	10 (9.4)	9 (5.5)	156 (73.6)	244 (74.4)	56 (26.4)	84 (25.6)
Sak et al. (2006)	Caucasian	215 (39.5)	204 (35.4)	242 (44.5)	288 (49.9)	87 (16.0)	85 (14.7)	672 (61.8)	696 (60.3)	416 (38.2)	458 (39.7)
Shen et al. (2001)	Caucasian	102 (35.5)	141 (45.3)	135 (47.0)	133 (42.8)	50 (17.4)	37 (11.9)	339 (59.1)	415 (66.7)	235 (40.9)	207 (33.3)
Yang et al. (2005)	Asian	35 (47.9)	38 (46.3)	29 (39.7)	33 (40.2)	9 (12.3)	11 (13.4)	99 (67.8)	109 (66.5)	47 (32.2)	55 (33.5)
Wang et al. (2006)	Asian	42 (41.6)	129 (38.3)	54 (53.5)	163 (48.4)	5 (5.0)	45 (13.4)	138 (68.3)	421 (62.5)	64 (31.7)	253 (37.5)
Sugimura et al. (2006)	Asian	42 (34.4)	78 (32.4)	63 (51.6)	128 (53.1)	17 (13.9)	35 (14.5)	147 (60.2)	284 (58.9)	97 (39.8)	198 (41.1)
Casson et al. (2005)	Caucasian	120 (39.1)	41 (43.2)	138 (45.0)	42 (44.2)	49 (16.0)	12 (12.6)	378 (61.6)	124 (65.3)	236 (38.4)	66 (34.7)
Nelson et al. (2005) BCC	Mix	278 (38.0)	211 (34.4)	333 (45.5)	303 (49.4)	121 (16.5)	99 (16.2)	889 (60.7)	725 (59.1)	575 (39.3)	501 (40.9)
Nelson et al. (2005) SCC	Mix	205 (35.8)	211 (34.4)	294 (51.4)	303 (49.4)	73 (12.8)	99 (16.2)	704 (61.5)	725 (59.1)	440 (38.5)	501 (40.9)
Blankenburg et al. (2005)	Caucasian	101 (34.4)	148 (39.5)	141 (48.0)	179 (47.7)	52 (17.7)	48 (12.8)	343 (58.3)	475 (63.3)	245 (41.7)	275 (36.7)
Marin et al. (2004)	Caucasian	110 (30.6)	132 (37.2)	175 (48.7)	170 (47.9)	74 (20.6)	53 (14.9)	395 (55.0)	434 (61.1)	323 (45.0)	276 (38.9)
De Ruyck et al. (2007)	Caucasian	35 (31.8)	35 (32.1)	59 (53.6)	53 (48.6)	16 (14.5)	21 (19.3)	129 (58.6)	123 (56.4)	91 (41.4)	95 (43.6)

EsAde esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma, *GcAde* gastric cardia adenocarcinoma, *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma

Table 3 Summary of odds ratios (OR) with confidence intervals (CI) for various genetic contrasts of the association of the xeroderma pigmentosum group C (*XPC*) polymorphism and cancer risk

Subgroup	Studies	Contrast								
A33512C		C vs. A			CC vs. (CA + AA)			(CC + CA) vs. AA		
Ethnicity		P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)
Asian	7	0.41	0.20	1.05(0.97–1.14)	0.20	0.11	1.14(0.97–1.33)	0.57	0.50	1.04(0.93–1.15)
Caucasian	12	0.20	0.87	1.00(0.95–1.06)	0.23	0.25	1.07(0.96–1.19)	0.34	0.49	0.97(0.90–1.05)
Other	3	0.76	0.51	0.97(0.88–1.07)	0.41	0.57	1.06(0.87–1.29)	1.00	0.20	0.92(0.80–1.05)
Tumor site										
Lung cancer	4	0.43	0.15	1.07(0.98–1.17)	0.88	0.04	1.20(1.00–1.45)	0.30	0.53	1.04(0.92–1.18)
Breast cancer	2	0.74	0.08	0.92(0.84–1.01)	0.80	0.39	0.92(0.76–1.12)	0.71	0.07	0.89(0.78–1.01)
Bladder cancer	3	0.07	0.72[a]	1.03(0.86–1.24)[a]	0.04	0.48[a]	1.15(0.78–1.71)[a]	0.16	0.73	0.97(0.83–1.14)
Gastric cardia adenocarcinoma	2	0.85	0.28	1.10(0.93–1.31)	0.38	0.19	1.25(0.90–1.75)	0.67	0.55	1.08(0.85–1.37)
Esophageal	3	0.92	0.26	1.09(0.94–1.27)	0.94	0.17	1.23(0.92–1.65)	0.72	0.54	1.07(0.87–1.32)
Colorectal cancer	2	0.35	0.94	1.00(0.89–1.13)	0.83	0.99	1.00(0.80–1.25)	0.32	0.94	0.99(0.84–1.17)
Cutaneous melanoma	2	0.05	0.81[a]	1.03(0.79–1.35)[a]	0.20	0.29	1.14(0.89–1.46)	0.07	0.84[a]	0.96(0.67–1.38)[a]
Other cancers	4	0.47	0.90	0.99(0.87–1.13)	0.03	0.81[a]	0.94(0.55–1.60)[a]	0.62	0.81	0.98(0.82–1.17)
Overall	22	0.34	0.60	1.01(0.97–1.05)	0.25	0.05	1.08(1.00–1.18)	0.57	0.50	0.98(0.93–1.04)
Subgroup	Studies	Contrast								
A33512C		CC vs. AA			CA vs. AA			CC vs. CA		
Ethnicity		P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)
Asian	7	0.20	0.13	1.14(0.96–1.35)	0.61	0.84	0.92(0.74–1.15)	0.21	0.15	1.13(0.96–1.33)
Caucasian	12	0.18	0.59	1.03(0.92–1.16)	0.41	0.30	0.96(0.88–1.04)	0.33	0.14	1.09(0.97–1.22)
Other	3	0.59	0.97	1.00(0.80–1.24)	0.85	0.12	0.89(0.78–1.03)	0.35	0.30	1.12(0.90–1.38)
Tumor site										
Lung cancer	4	0.61	0.07	1.20(0.99–1.46)	0.35	0.98	1.00(0.87–1.14)	0.96	0.05	1.21(1.00–1.46)
Breast cancer	2	0.71	0.17	0.86(0.70–1.06)	0.79	0.10	0.89(0.78–1.02)	0.83	0.79	0.97(0.79–1.19)
Bladder cancer	3	0.04	0.58[a]	1.13(0.74–1.72)[a]	0.23	0.52	0.95(0.80–1.12)	0.03	0.56[a]	1.14(0.73–1.78)[a]
Gastric cardia adenocarcinoma	2	0.62	0.21	1.26(0.88–1.81)	0.42	0.85	1.03(0.79–1.32)	0.27	0.23	1.24(0.87–1.77)
Esophageal	3	0.99	0.19	1.24(0.90–1.70)	0.62	0.85	1.02(0.82–1.28)	0.82	0.21	1.22(0.89–1.67)
Colorectal cancer	2	0.51	1.00	1.00(0.78–1.28)	0.14	0.002	1.32(1.11–1.56)	0.87	0.97	1.01(0.79–1.28)
Cutaneous melanoma	2	0.07	0.66[a]	1.06(0.81–1.40)[a]	0.13	0.24	0.89(0.73–1.08)	0.46	0.17	1.20(0.92–1.56)
Other cancers	4	0.10	0.91	0.98(0.73–1.32)	0.32	0.77	0.97(0.80–1.17)	0.01	0.86[a]	0.95(0.51–1.75)[a]
Overall	22	0.21	0.24	1.06(0.97–1.15)	0.64	0.19	0.96(0.90–1.02)	0.26	0.03	1.11(1.01–1.20)

Table 3 continued

Subgroup	Studies	Contrast								
C21151T		T vs. C			TT vs. (TC + CC)			(TT + TC) vs. CC		
Ethnicity		P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)
Asian	6	0.03	0.83[a]	0.99(0.86–1.13)[a]	0.77	0.19	1.13(0.94–1.37)	0.01	0.60[a]	0.94(0.77–1.17)[a]
Caucasian	3	0.12	0.43	1.05(0.94–1.17)	0.75	0.006	1.45(1.11–1.90)	0.13	0.68	0.97(0.85–1.11)
Other	2	0.31	0.15	0.90(0.79–1.04)	0.77	0.20	0.80(0.57–1.13)	0.19	0.26	0.91(0.77–1.07)
Tumor site										
Lung cancer	4	0.16	0.31	1.05(0.95–1.16)	0.67	0.22	1.15(0.92–1.45)	0.08	0.56[a]	1.07(0.86–1.33)[a]
Bladder cancer	2	0.07	0.51[a]	1.09(0.85–1.38)[a]	0.47	0.02	1.49(1.06–2.09)	0.10	0.71	1.03(0.87–1.22)
Other cancers	5	0.32	0.03	0.91(0.83–0.99)	0.29	0.81	1.03(0.83–1.26)	0.19	0.004	0.85(0.76–0.95)
Overall	11	0.03	0.74[a]	0.99(0.90–1.07)[a]	0.40	0.06	1.14(1.00–1.32)	0.01	0.16[a]	0.94(0.84–1.06)[a]
Subgroup	Studies	Contrast								
C21151T		TT vs. CC			TC vs. CC			TT vs. TC		
Ethnicity		P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)
Asian	6	0.40	0.43	1.08(0.89–1.31)	0.007	0.46[a]	0.92(0.74–1.15)[a]	0.89	0.07	1.20(0.98–1.46)
Caucasian	3	0.54	0.02	1.41(1.07–1.85)	0.21	0.19	0.91(0.79–1.05)	0.94	0.004	1.52(1.15–2.01)
Other	2	0.99	0.13	0.77(0.54–1.09)	0.16	0.43	0.93(0.78–1.11)	0.48	0.37	0.85(0.59–1.22)
Tumor site										
Lung cancer	4	0.45	0.23	1.16(0.91–1.47)	0.08	0.66[a]	1.05(0.84–1.32)[a]	0.76	0.24	1.15(0.91–1.47)
Bladder cancer	2	0.33	0.02	1.49(1.05–2.11)	0.19	0.73	0.97(0.81–1.16)	0.76	0.03	1.49(1.05–2.13)
Other cancers	5	0.33	0.52	0.93(0.75–1.16)	0.13	0.002	0.83(0.74–0.93)	0.23	0.20	1.15(0.93–1.44)
Overall	11	0.20	0.21	1.10(0.95–1.27)	0.02	0.15[a]	0.92(0.81–1.03)[a]	0.58	0.01	1.21(1.04–1.40)
Subgroup	Studies	Contrast								
PAT +/−		+ vs. −			++ vs. (+− and –)			(++ and +−) vs. –		
Ethnicity		P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)	P_{hetero}	*P** value	OR (95%CI)
Asian	5	0.83	0.14	0.90(0.79–1.03)	0.15	0.69	0.94(0.72–1.24)	0.97	0.08	0.85(0.71–1.02)
Caucasian	7	0.06	0.05[a]	1.13(1.00–1.18)[a]	0.37	0.02	1.20(1.03–1.40)	0.07	0.12[a]	1.15(0.97–1.37)[a]
Other	2	0.77	0.15	0.92(0.82–1.03)	0.17	0.33	0.90(0.72–1.12)	0.58	0.18	0.89(0.76–1.05)
Tumor site										
Lung cancer	3	0.05	0.55[a]	1.08(0.84–1.38)[a]	0.40	0.13	1.21(0.94–1.55)	0.03	0.69[a]	1.09(0.71–1.66)[a]
Head–neck cancer	2	0.15	0.02	1.29(1.04–1.59)	0.31	0.10	1.41(0.93–2.12)	0.19	0.04	1.36(1.02–1.82)
Oral cancer	2	0.71	0.89	0.98(0.77–1.26)	0.27	0.58	1.15(0.69–1.93)	1.00	0.59	0.91(0.65–1.27)

Table 3 continued

Subgroup	Studies	Contrast								
PAT +/−		+ vs. −			++ vs. (+− and −)			(++ and +−) vs. −		
Ethnicity		P_{hetero}	P* value	OR (95%CI)	P_{hetero}	P* value	OR (95%CI)	P_{hetero}	P* value	OR (95%CI)
Bladder cancer	2	0.73	0.51	0.96(0.85–1.08)	0.45	0.94	1.01(0.80–1.27)	0.29	0.32	0.92(0.77–1.09)
Other cancers	5	0.08	0.85[a]	0.99(0.85–1.14)[a]	0.02	0.81[a]	0.96(0.68–1.35)[a]	0.34	0.62	0.97(0.85–1.10)
Overall	14	0.03	0.60[a]	1.02(0.94–1.11)[a]	0.10	0.30	1.06(0.95–1.19)	0.09	0.94[a]	1.00(0.90–1.12)[a]
Subgroup	Studies	Contrast								
PAT +/−		++ vs. −−			+− vs. −−			++ vs. +−		
Ethnicity		P_{hetero}	P* value	OR (95%CI)	P_{hetero}	P* value	OR (95%CI)	P_{hetero}	P* value	OR (95%CI)
Asian	5	0.26	0.33	0.86(0.64–1.16)	0.82	0.08	0.84(0.69–1.02)	0.10	0.85	1.03(0.77–1.37)
Caucasian	7	0.13	0.008	1.26(1.06–1.50)	0.21	0.36	1.06(0.94–1.20)	0.72	0.06	1.17(0.99–1.39)
Other	2	0.41	0.18	0.85(0.67–1.08)	0.31	0.27	0.91(0.76–1.08)	0.11	0.58	0.94(0.75–1.18)
Tumor site										
Lung cancer	3	0.16	0.13	1.24(0.94–1.65)	0.07	0.94[a]	0.99(0.69–1.41)[a]	0.70	0.12	1.24(0.95–1.61)
Head–neck cancer	2	0.19	0.03	1.61(1.03–2.50)	0.32	0.10	1.29(0.95–1.76)	0.53	0.33	1.24(0.80–1.93)
Oral cancer	2	0.32	0.72	1.11(0.63–1.93)	0.74	0.42	0.86(0.61–1.23)	0.23	0.46	1.23(0.72–2.10)
Bladder cancer	2	0.89	0.71	0.95(0.74–1.23)	0.17	0.28	0.91(0.76–1.09)	0.24	0.42	1.05(0.83–1.34)
Other cancers	5	0.02	0.80[a]	0.95(0.66–1.39)[a]	0.57	0.74	0.98(0.85–1.12)	0.04	0.81[a]	0.96(0.68–1.35)[a]
Overall	14	0.03	0.40[a]	1.08(0.90–1.31)[a]	0.27	0.73	0.97(0.88–1.06)	0.23	0.24	1.08(0.95–1.21)

[a] Random effect estimate

* The P value of OR determined by the Z test

The CC genotype contributed to an elevated risk of lung cancer under both the recessive genetic model ($P = 0.04$, OR = 1.20, 95% CI 1.00–1.45, $P_{\text{heterogeneity}} = 0.88$, Fig. 1) and homozygote–heterozygote (CC vs. CA) comparison ($P = 0.05$, OR = 1.21, 95% CI 1.00–1.46, $P_{\text{heterogeneity}} = 0.96$). An increased risk of colorectal cancer was found when the CA genotype was compared with the AA genotype ($P = 0.002$, OR = 1.32, 95% CI 1.11–1.56,

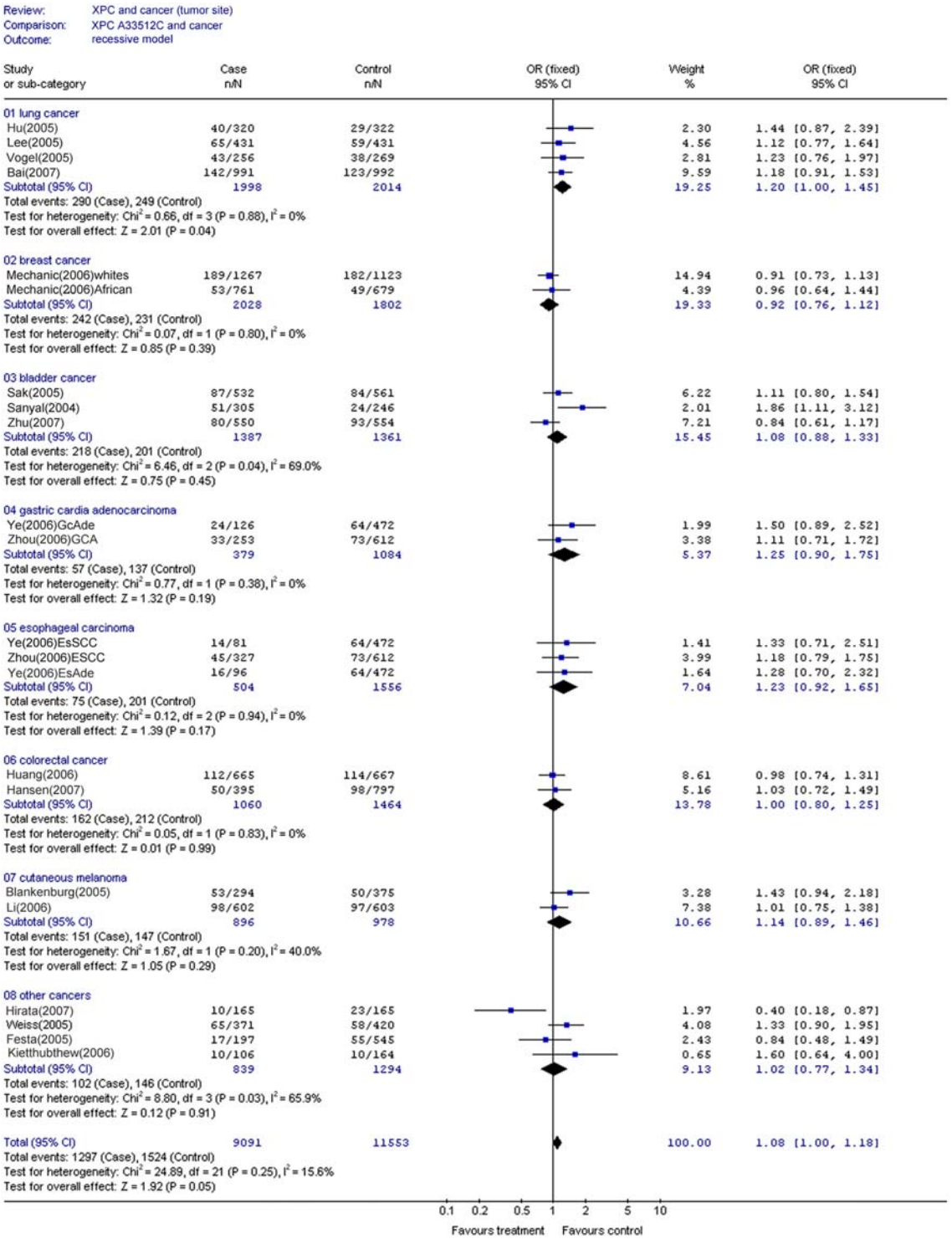

Fig. 1 Meta-analysis for the xeroderma pigmentosum group C (*XPC*) A33512C polymorphisms and cancer stratified according to different tumor sites: CC vs. (CA + AA). The study is shown by a point estimate of the odds ratio (OR) and the accompanying 95% confidence interval (CI) using a fixed-effects model. *n* indicates the total number of CC; *N* indicates the total number of individuals

$P_{heterogeneity} = 0.14$). No evidence of association between 33512C and other cancers was found (Table 3).

XPC *C21151T*

Significant between-study heterogeneity existed in 11 studies when we compared C21151T C and the T allele in different kinds of cancers ($P_{heterogeneity} = 0.03$). The random-effects model was used to pool the result. There was no significant association between the 21151T allele and cancer risk ($P = 0.74$, OR = 0.99, 95% CI 0.90–1.07). An elevated but not significant association between 21151T and cancer risk was found under the recessive genetic model in all subjects ($P = 0.06$, OR = 1.14, 95% CI 1.00–1.32, $P_{heterogeneity} = 0.40$), and a significantly elevated association was found in analysis of TT vs. TC contrast in all subjects ($P = 0.01$, OR = 1.21, 95% CI 1.04–1.40, $P_{heterogeneity} = 0.58$). In Caucasians, the association was significant under the recessive genetic model ($P = 0.006$, OR = 1.45, 95% CI 1.11–1.90, $P_{heterogeneity} = 0.75$, Fig. 3a), homozygote comparison ($P = 0.02$, OR = 1.41, 95% CI 1.07–1.85, $P_{heterogeneity} = 0.54$), and TT vs. TC contrast ($P = 0.004$, OR = 1.52, 95% CI 1.15–2.01, $P_{heterogeneity} = 0.94$) (Table 3).

In the subgroup analysis for different tumor sites, 21151T had an effect of increasing the bladder cancer risk under the recessive genetic model ($P = 0.02$, OR = 1.49, 95% CI 1.06–2.09, $P_{heterogeneity} = 0.47$, Fig. 2a), homozygote comparison ($P = 0.02$, OR = 1.49, 95% CI 1.05–2.11, $P_{heterogeneity} = 0.33$), and TT vs. TC contrast ($P = 0.03$, OR = 1.49, 95% CI 1.05–2.13, $P_{heterogeneity} = 0.76$) in all subjects. No evidence of association between 21151T and other cancers was found (Table 3).

XPC *PAT*

Significant heterogeneity existed in 14 studies when we compared *XPC* PAT − and + allele in different kinds of cancers. The random-effects model was used to pool the result. There was no significant association between the PAT + allele and cancer risk in all subjects ($P = 0.72$, OR = 1.02, 95% CI 0.94–1.11, $P_{heterogeneity} = 0.03$, Fig. 2 b). The PAT + allele appeared to increase the cancer risk under tje recessive genetic model ($P = 0.02$, OR = 1.20, 95% CI 1.03–1.40, $P_{heterogeneity} = 0.37$, Fig. 3b) and homozygote comparison ($P = 0.008$, OR = 1.26, 95% CI 1.06–1.50, $P_{heterogeneity} = 0.13$) in Caucasians (Table 3).

In the subgroup analysis for different tumor sites, PAT + allele contributed to an increased head and neck cancer risk ($P = 0.02$, OR = 1.29, 95% CI 1.04–1.59, $P_{heterogeneity} = 0.15$, Fig. 2b), as well as under dominant genetic model and homozygote comparison in all subjects (Table 3).

Publication bias

The funnel plot was applied for comparison of 33512C vs. 33512A in the OR analysis of *XPC* A33521C, and Egger's test provided no evidence for funnel-plot asymmetry ($t = 1.87$, $P = 0.076$). Similarly, no publication bias was detected for C21151T and PAT −/+ polymorphisms ($t = -0.60$, $P = 0.565$; $t = 0.64$, $P = 0.671$, respectively; Fig. 4).

Discussion

Sanyal et al. first reported that the frequency of the variant C allele of *XPC* A33512C polymorphism was significantly higher in bladder cancer cases of Caucasian than in controls ($P = 0.001$, OR = 1.49, 95% CI 1.16–1.92) in 2004 (Sanyal et al. 2004). Thereafter, more and more studies were conducted to further access the association in different tumor sites across different nations. However, the results were fairly confusing rather than conclusive. Most studies could not confirm a significantly increased risk between cancers and 33512C allele. Khan et al. studied the function of the *XPC* A33512C alteration in an allele-specific post-UV reaction assay in fibroblast cell (Khan et al. 2000). They found that *XPC* 33512C allele was equally as efficient as A33512 allele, indicating both polymorphisms were fully functional in DNA repair. Our meta-analysis did not reveal a significant association between the 33512C and cancer risk compared with 33512A. However, the CC genotype contributed to an elevated risk of cancer.

No functional data of the *XPC* C21151T polymorphism was reported. Our meta-analysis indicated 21151T had an effect of increasing the bladder cancer risk under the recessive-genetic model and homozygote comparison, and contributed to an increased cancer risk under the recessive genetic model and homozygote comparison in Caucasians. We found that the cancer risk in Caucasians with *XPC* PAT + allele increased under the recessive genetic model and homozygote comparison, and *XPC* PAT + carriers had an elevated head and neck cancer risk under the dominant genetic model and homozygote comparison. The same polymorphism may play different roles in cancer susceptibility in different tumor sites. The *XPC* PAT + allele might contribute to a higher risk of head and neck cancer but had no effect on the susceptibility of lung cancer, oral cancer, and bladder cancer.

It is interesting that none of the three *XPC* polymorphisms had a significant effect in Asians, and the variant

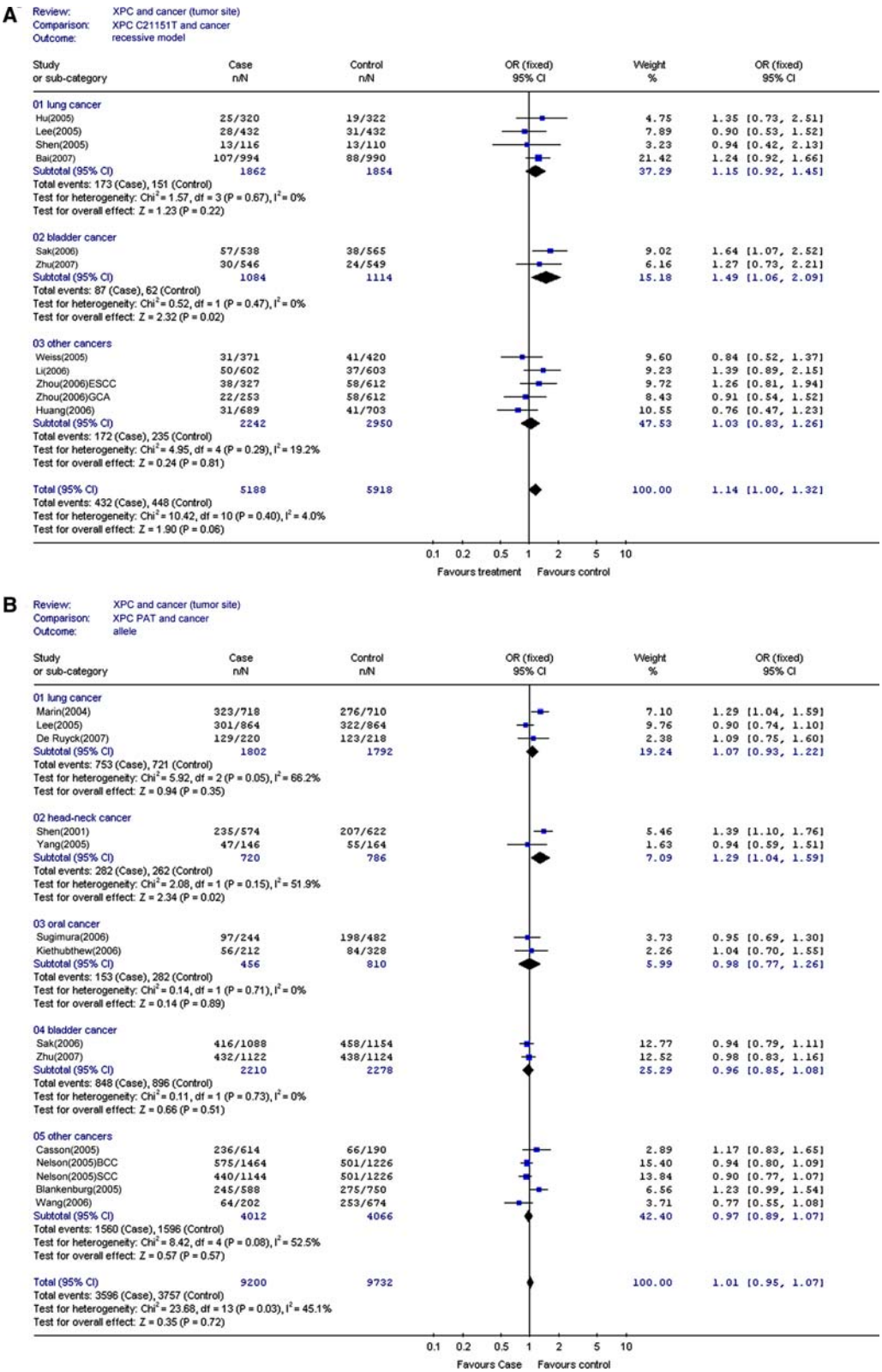

Fig. 2 Meta-analysis for the xeroderma pigmentosum group C (*XPC*) C21151T and poly (AT) insertion/deletion polymorphism (PAT) −/+ polymorphisms and cancer stratified according to different tumor sites. **a** C21151T: TT vs. (TC + CC). **b** PAT −/+: + vs. −. The study is shown by a point estimate of the odds ratio (OR) and the accompanying 95% confidence interval (CI) using a fixed-effects model. *n* indicates the total number of TT (**a**) or + (**b**); *N* indicates the total number of individuals (**a**) or alleles (**B**)

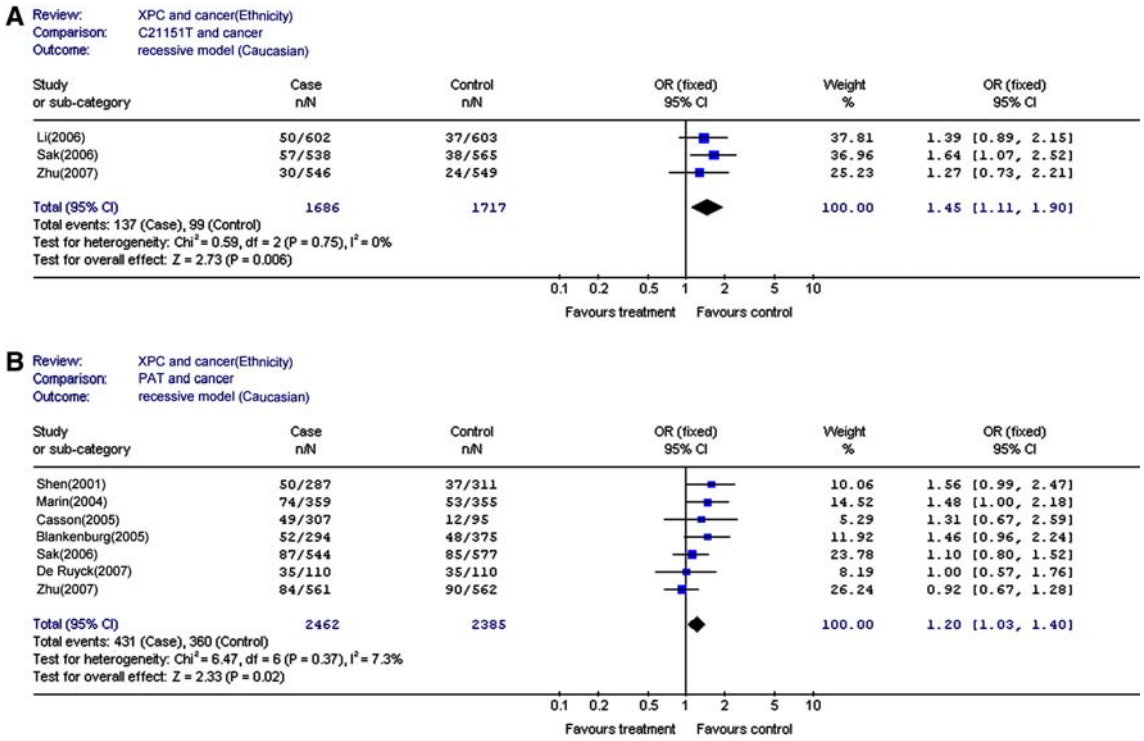

Fig. 3 Meta-analysis for the xeroderma pigmentosum group C (*XPC*) C21151T and poly (AT) insertion/deletion polymorphism (PAT) −/+ polymorphisms and cancer in Caucasians. **a** C21151T: TT vs. (TC + CC). **b** PAT −/+: ++ vs. (+− and − −). The study is shown by a point estimate of the odds ratio (OR) and the accompanying 95% confidence interval (CI) using a fixed-effects model. *n* indicates the total number of TT (**a**) or ++ (**b**); *N* indicates the total number of individuals

homozygote genotypes of *XPC* C21151T and *XPC* PAT −/+ might increase cancer risk in Caucasians. Due to the difference in different populations, it is necessary to stratify the ethnicity in the tumor-sites analysis. The same polymorphism may play different roles across different ethnicities because of different genetic background.

The PAT + allele is in linkage disequilibrium with the A allele of an intronic SNP (IVS11-6) in intron 11. It appears that IVS11 6A affects alternative splicing and increases the frequency of deletion of exon 12. The *XPC* splicing isoform without exon 12 had reduced DNA repair activity (Khan et al. 2002). PAT −/+ might not be a causal SNP, and the increased cancer susceptibility of PAT + carriers may arise from the linkage with IVS11-6 A. Blankenburg et al.(2005) performed a hospital-based case–control study with 294 cutaneous melanoma cases and 375 gender-matched controls. They found *XPC* intron 9, PAT +, intron 11-6A, and exon 15 33512C polymorphisms were in linkage disequilibrium. The role of PAT + in head and neck cancer still needs further investigation, as the cases and controls involved is too small; analysis of 33512C did not provide data on head and neck cancer. We could not make a comparison between PAT + and 33512C because the studies included in the meta-analysis of these two polymorphisms were different, which should have the same results due to the linkage disequilibrium.

A single polymorphism likely has weak effects on the individual's phenotype. It may not be measurable except in the context of some supporting environmental factors, such as smoking. We tried to evaluate the effect of smoking on the susceptibility of *XPC* A33512C polymorphism on cancer risk. Three studies from two articles (Hansen et al. 2007; Zhou et al. 2006) (esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma, colorectal cancer) were recruited for analysis, as their stratification data on smoking were available. We found the cancer risk in smokers carrying the 33512C allele was not higher ($P = 0.86$, OR = 1.01, 95% CI 0.87–1.18, $P_{\text{heterogeneity}} = 0.47$) than that of the nonsmokers ($P = 0.05$, OR = 1.18, 95% CI 1.00–1.40, $P_{\text{heterogeneity}} = 0.83$). However, smoking has different effects on different cancer types. It is still necessary to stratify cancer types; the study size was relatively small (975 cancer patients and 1,409 controls). So, this conclusion should be treated as preliminary.

It is necessary to access the combined effect of several polymorphisms, as interaction of different polymorphisms in the same gene or between different genes might contribute to cancer risk. Several articles in our meta-analysis

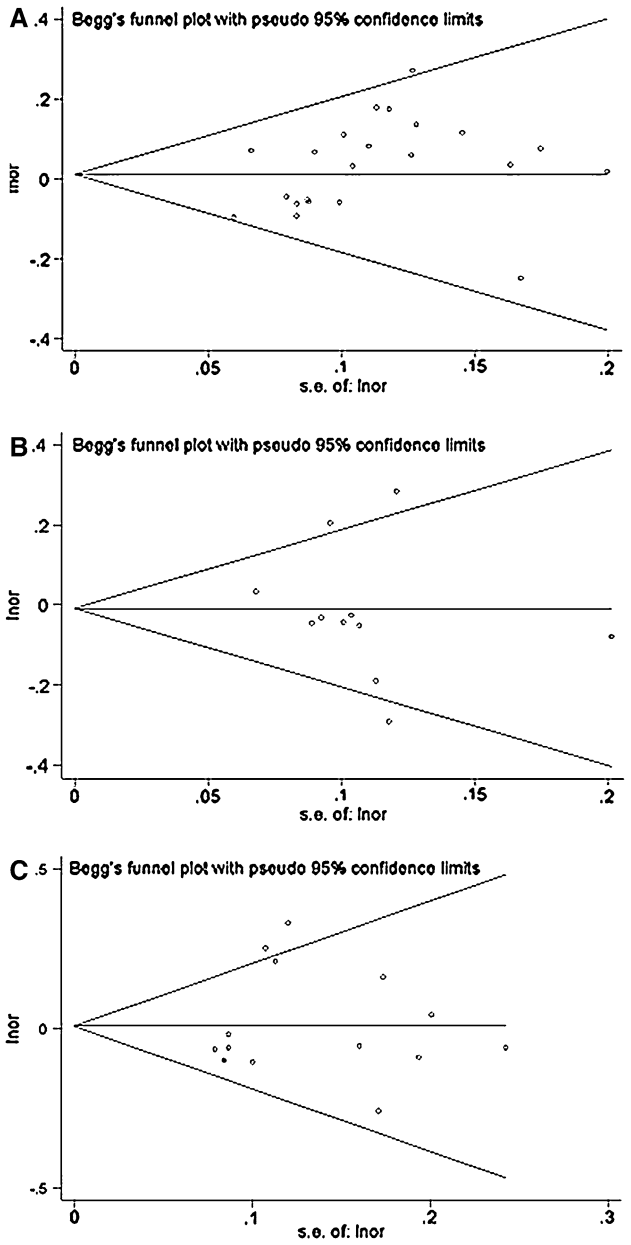

Fig. 4 Begg's funnel plot of the Egger's test of allele comparison for publication bias. **a** Funnel plot for C vs. A allele comparison in A33512C polymorphism; **b** funnel plot for T vs. C allele in C21151T polymorphism; **c** funnel plot for + vs. − allele in poly (AT) insertion/deletion polymorphism (PAT). No asymmetry was found as indicated by the *P* value of Egger's test

evaluated the combined effect of *XPC* A33512C, C21151T, and PAT −/+ or two of these three polymorphisms (Blankenburg et al. 2005; Hu et al. 2005; Huang et al. 2006; Li et al. 2006; Sak et al. 2005; Shen et al. 2005; Weiss et al. 2005; Zhu et al. 2007). Hu et al. (2005) examined the combined effect of *XPC* A33512C and C21151T on lung cancer risk. They found that cases with both 21151CT/TT and 33512AC/CC variant genotypes had a significantly increased lung cancer risk compared with those having both wild-type genotypes (21151CC and 33512AA); smokers with both variant genotypes (21151CT/TT and 33512AC/CC) had the highest lung cancer risk (adjusted OR = 7.36; 95% CI 3.19–17.00) compared with that of nonsmokers. Zhu et al. (2007) evaluated the combined effect of the there polymorphisms and found a protective effect of the haplotype 21151C-PAT− -33512C. We tried to evaluate the combined effect of these polymorphisms on the susceptibility of cancer. Unfortunately, the available data was not compatible. More studies should be carried out to examine the combined effect of these three polymorphisms in different kinds of cancers.

Chance effects, as with false negatives (underpowered studies) and false positives (type I error), together with the true variability among populations, might lead to conflicting conclusions across different studies. In our meta-analysis, false negative and false positive findings would neutralize each other, as a relatively large number of studies were included. However, publication of the findings may depend on the expectation of the researchers. False-negative results may be suppressed and false-positive results magnified (Salanti et al. 2005). Thus, the validity of conclusions in our meta-analysis may be affected. The inclusion of unpublished data is commonly suggested as a means of reducing the impact of false-positive and publication bias. However, in practice, most of the unpublished studies were not available. Although there was no significant publication bias in our meta-analysis, the results may still be affected by the false positive (type I error).

Five genetic contrasts (dominant genetic model, recessive genetic model, and three pairwise comparisons) were considered, as were allelic association; the results under different models were inconsistent. As shown in Table 3, there was an interesting tendency that most significant associations found in our study were under the recessive genetic model, homozygote comparison, and homozygote–heterozygote comparison. The excess of allele homozygotes but not heterozygotes was considered a risk among cancer patients.

In conclusion, our meta-analysis investigated the associations between the three *XPC* polymorphisms and cancer risk with a total of 12,408 cancer patients and 14,984 controls from 32 case–control studies. Overall, our meta-analysis suggested no significant associations between *XPC* 33512C, 21151T, and PAT + in Asians. However, 21151TT and PAT ++ might increase cancer risk in Caucasians, which indicated a big difference among different populations. In all subjects, *XPC* 33512C, 21151T, and PAT + might increase lung cancer, bladder cancer, and head and neck cancer risks under different genetic models, respectively. The present results suggest

association only in particular ethnic backgrounds and/or tumor sites, and more studies based on larger, stratified case–control populations are still needed to clarify the different effects of these polymorphisms in Asians and Caucasians. Studies investigating the combined effect of *XPC* A33512C, C21151T, and PAT will be very important to further evaluate the role of these polymorphisms in different cancers.

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