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Research Paper

Association Between Twelve Polymorphisms in Five X-ray Repair Cross-complementing Genes and the Risk of Urological Neoplasms: A Systematic Review and Meta-Analysis

Meng Zhang [1], Wanzhen Li [1], Zongyao Hao, Jun Zhou, Li Zhang *, Chaozhao Liang *

Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
Institute of Urology, Anhui Medical University, Hefei, China
Graduate School of Anhui Medical University, Hefei, China

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ABSTRACT

Polymorphisms in X-ray repair cross-complementing (*XRCC*) genes have been implicated in altering the risk of various urological cancers. However, the results of reported studies are controversial. To ascertain whether polymorphisms in *XRCC* genes are associated with the risk of urological neoplasms, we conducted present updated meta-analysis and systematic review. Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to estimate the association. Finally, 54 publications comprising 129 case-control studies for twelve polymorphisms in five *XRCC* genes were enrolled. We identified that *XRCC1*-rs25489 polymorphism was associated with an increased risk of urological neoplasms in heterozygote and dominant models. Moreover, in the subgroup analysis by cancer type, we found that *XRCC1*-rs25489 polymorphism was associated with an increased risk of bladder cancer (BC) in heterozygote model. Although overall analyses suggested a null result for *XRCC1*-rs25487 polymorphism, in the stratified analysis by ethnicity, an increased risk of urological neoplasms for Asians in allelic and homozygote models was identified. While for other polymorphisms in *XRCC* genes, no significant association was uncovered. To sum up, our results indicated that *XRCC1*-rs25489 polymorphism is a risk factor for urological neoplasms, particularly for BC. Further studies with large sample size are needed to validate these findings.

1. Introduction

Deoxyribonucleic acid (DNA) in a normal cell is capable of withstanding internal and external damage to prevent the damage or death of the cell (Alli et al., 2009; Orlow et al., 2008). The direct reversal, base excision, nucleotide excision in the main DNA repair pathways of human beings' function as restoring lost gene information and maintaining DNA integrity (Rajaraman et al., 2010). Some research studies have already showed that polymorphisms in DNA-repair genes are an integral part of cancer risk, apart from environmental factors, diet, intake of non-steroidal and anti-inflammatory drugs, and endogenous factors (Spitz et al., 2003). At the cellular level, checkpoints activated by the DNA-repair genes can regulate the cell cycle and transcription to make the choice of the damage or the apoptosis (Vispe et al., 2000). In addition, DNA repair-gene is also critical in defending the cellular genome from the risk of environmental factors (Hoeijmakers, 2001). Therefore, making certain of the genetic mechanisms of DNA repair system might take an insight into the pathogenesis of relevant cancers. X-ray repair cross-complementing (*XRCC*) genes are members of the family of DNA repair system (Dizdaroglu, 2015), which are polymorphic with several non-synonymous polymorphisms, such as Arg194Trp (rs1799782), Arg280His (rs25489), Arg399Gln (rs25487) in *XRCC1*, Arg188His (rs3218536) polymorphisms in *XRCC2*, IVS6-14 (rs1799796) and Thr241Met (rs861539) polymorphisms in *XRCC3*, rs1805377, rs6869366 and rs28360071 polymorphisms in *XRCC4* and rs7003908 in *XRCC7*. To date, plenty of evidences have indicated that more than one hundred proteins encoded by *XRCC* genes are implicated in four DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR) and mismatch repair (MMR), working as tumor suppressors or oncogenes for the sake of participating in tumorigenesis through posting expression regulation of homologous target genes (Liesegang, 2001). Recently, studies have highlighted the ambivalent association between polymorphisms in *XRCC* genes and risk of urological neoplasms. In the study conducted by Agalliu et al. (2010), they have proved that there was no significant association between *XRCC1* polymorphisms

* Corresponding authors at: Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China.
E-mail addresses: lzhang@ahmu.edu.cn (L. Zhang), liang_chaozhao@ahmu.edu.cn (C. Liang).
[1] These authors contributed equally to the work.

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(rs1799782, rs25487, rs25489 and rs915927) and prostate cancer (PCa) risk. Consistent with Agalliu et al.'s conclusion, Lavender et al. (2010) also confirmed that no significant influence of *XRCC1*-rs25487 polymorphism on PCa risk was identified for African population. While in another population-based case-control dataset, Lan et al. (2006) suggested that *XRCC1*-rs25487 polymorphism was significantly associated with the development of PCa. Both Matullo (2005) and Nowacka-Zawisza et al. (2015) have not revealed a significant association between *XRCC2*-rs3218536 polymorphism and urological neoplasms risk in their work, respectively. As for polymorphisms in *XRCC3* gene, Wu et al. (2006) indicated that there was no association between *XRCC3*-rs861539 polymorphism and bladder cancer (BC) risk, while Narter et al. (2009) reported the conflicting results that there was a 4.87-fold protective role of *XRCC3* T allele against BC. In 2011, Mandal et al. (2011) conducted a case-control study comprising 192 PCa cases and 224 age-matched healthy controls and obtained a conclusion that *XRCC4* promoter-1394 (rs6869366) heterozygote was associated with a lower risk of PCa, a result inconsistent with Chang et al.'s (2008) work. In addition, Mandal et al. (2010) provided a strong supportive evidence that common sequence variants genotype of *XRCC7* gene might increase the risk of PCa.

As mentioned above, although many studies have conducted to investigate the associations between one or multiple polymorphism (s) and the risk of urological neoplasms, but there results were not consistent or even contradictory, which was partially due to the heterogeneity within cancer subtypes, the diverse ethnicities of patient cohorts and the small sample sizes. Therefore, we conducted the current updated meta-analysis and systematic review at the aim of precisely determines the association between genetic variants in five *XRCC* genes and the susceptibility to urological neoplasms.

2. Materials and Methods

2.1. Literature Search

We conducted a systematic literature search on PubMed, Medline, Google Scholar and Web of Science to retrieve all eligible publications on the association between polymorphisms in all *XRCC* genes and the risk of all urological cancer types (up to December 27, 2016) with the following keywords: (*XRCC1-9* OR X-Ray Repair Cross Complementing 1-9) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (carcinoma OR cancer OR neoplasm OR adenocarcinoma OR tumor OR malignancy) (Supplementary Table 1). The language of enrolled studies was restricted to English. Moreover, we identified additional articles by screening the references of enrolled eligible articles and Reviews. We would contact authors for critical data not mentioned in the eligible articles. If data or datasets were published in several articles, the publication with largest sample sizes was selected. However, after carefully screening, twelve polymorphisms in five *XRCC* genes were left for further investigation, and the cancer types were restricted to PCa, BC and renal cell carcinoma (RCC).

2.2. Inclusion Criteria and Exclusion Criteria

Publications satisfied the following inclusion criteria would be enrolled: (1) case-control studies that evaluated the association between polymorphisms in *XRCC* genes and urological neoplasms risk; (2) publications focusing on population genetic polymorphisms (3) articles with sufficient genotype data to assess ORs and the corresponding 95%CIs; (4) the control subjects satisfied Hardy-Weinberg equilibrium (HWE). The major exclusion criteria were: (1) case-only studies, case reports, or Reviews; (2) studies without raw data for the *XRCC* genotype (or contacted the corresponding author also cannot obtain the necessary original data): (3) studies that compared the *XRCC* variants in precancerous lesions and other cancers.

2.3. Data Extraction

Our investigators extracted the data from each study. All the case-control studies satisfied the inclusion criteria and consensus for any controversy was achieved. The data from the eligible articles was composed of the first author's name, year of publication, ethnicity, source of controls, cancer type and numbers of cases and controls in the *XRCC1*, *XRCC2*, *XRCC3*, *XRCC4*, *XRCC7* genotypes. Ethnicity was categorized as "Caucasian", "Asian", and "Mixed". The cancer type was categorized as PCa and BC. With the regard to the sources of controls, all eligible case-control studies were defined as either population-based or hospital-based.

2.4. Statistical Analysis

The strength of association between the polymorphisms in *XRCC* genes and the risk of urological neoplasms were evaluated using summary ORs and the corresponding 95%CIs in allelic (B vs. A), recessive (BB vs. BA + AA), dominant (BA + BB vs. AA), homozygous (BB vs. AA), and heterozygous (BA vs. AA) models (A: wild allele; B: mutated allele). The *P* values of our study were adjusted by Bonferroni correction method to compensate for that increased by testing each individual hypothesis at a significance level of **a**/**m** (**a**: the desired overall alpha level; **m**: the number of the hypothesis), and the Bonferroni correction rejects the null hypothesis with the value of *P* less than **a**/**m** ($P_A = P_Z * 60 < 0.05$, was considered as statistical significant) (Bonferroni, 1935). The Cochrane's Q-statistic test was used to assess the heterogeneity between studies (Davey Smith and Egger, 1997), and the inconsistency was quantified with the I^2 statistic. The substantial heterogeneity was considered significant when $I^2 > 50\%$ or $P_Q \leq 0.1$, then, a random effects model (DerSimonian-Laird method) was used; otherwise, the fixed-effects model (Mantel-Haenszel method) was applied (Mantel and Haenszel, 1959). When it came to the comparison among studies, we performed subgroup analyses categorized by cancer type, ethnicity, HWE and the source of control. Last but not least, we also conducted sensitivity analysis to assess stability of the results by omitting one study each time to exclude studies. HWE was estimated by the asymptotic test using the "sampsi command" in the Stata 12.0 software (version 12.0; State Corporation, College Station, Texas, USA), and deviation was considered when $P < 0.05$. The potential publication bias of the eligible studies was evaluated by Begg's funnel plots (Begg and Mazumdar, 1995) graphically and Egger's linear regression test (Seagroatt and Stratton, 1998) quantitatively. Moreover, the trim and fill algorithm which trim off the asymmetric outlying part of the funnel and estimate the true center of the funnel further provide effective and relatively powerful tests for evaluating the existence of such publication bias (Sue and Richard, 2000). The data was analyzed using the Stata 12.0 software (version 12.0; State Corporation, College Station, Texas, USA).

2.5. Linkage Disequilibrium (LD) Analysis Across Populations

Data were extracted from the 1000 genomes Project (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r2_B36/) comprising the polymorphisms in *XRCC1*, *XRCC3* and *XRCC4* evaluated in present study. Briefly, populations enrolled in the project including CHB (Han Chinese in Beijing, China), CEU (Utah residents with Northern and Western European ancestry from the CEPH collection), JPT (Japanese in Tokyo, Japan) and YRI (Yoruba in Ibadan, Nigeria). Then, Haploview software was applied to conduct analyses and LD was assessed by r^2 statistics in each of the above-mentioned populations.

3. Results

3.1. Main Characteristics of the Enrolled Studies

Table 1 showed the characteristics of all the eligible studies and genotype frequency distributions of twelve polymorphisms in five

Table 1
Characteristics of the enrolled studies.

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Cancer type	Case			Control			
						AA	AB	BB	AA	AB	BB	Y (HWE)
	Figueroa et al.	2007	Caucasian	H-B	BC	434	494	133	433	453	110	Y
	Matullo et al.	2001	Mixed	H-B	BC	53	58	13	31	41	12	Y
	Stern et al.	2001	African	H-B	BC	9	10	0	9	4	0	Y
	Stern et al.	2001	Caucasian	H-B	BC	87	106	21	79	92	26	Y
	Mittal et al.	2012	Asian	H-B	BC	67	106	39	102	109	39	Y
	Arizono et al.	2008	Asian	H-B	BC	139	102	10	140	90	21	Y
	Mittal et al.	2008	Asian	H-B	BC	37	76	27	73	81	36	Y
	Sak et al.	2007	Caucasian	H-B	BC	218	248	66	226	259	75	Y
	Sanyal et al.	2003	Caucasian	H-B	BC	124	155	32	113	110	23	Y
	Matullo et al.	2005	Caucasian	H-B	BC	136	135	40	120	145	47	Y
	Fontana et al.	2008	Caucasian	H-B	BC	21	25	5	18	18	9	Y
	Broberg et al.	2005	Caucasian	H-B	BC	26	31	4	80	62	13	Y
	Matullo et al.	2006	Caucasian	P-B	BC	54	53	17	484	482	128	Y
	Shen et al.	2003	Caucasian	H-B	BC	93	87	21	92	98	24	Y
	Ramaniuk et al.	2014	Caucasian	H-B	BC	141	154	37	151	165	48	Y
	Zhi et al.	2012	Asian	P-B	BC	121	151	30	148	143	20	Y
	Wang et al.	2010	Asian	P-B	BC	113	102	19	105	126	22	Y
	Andrew et al.	2006	Mixed	H-B	BC	412	456	122	533	536	184	N
	Kelsey et al.	2004	Mixed	P-B	BC	132	187	36	228	230	86	N
XRCC1-rs25487	Huang et al.	2007	Caucasian	H-B	BC	266	276	71	267	264	65	Y
	Gao et al.	2010	Mixed	H-B	PCa	145	151	56	49	47	10	Y
	Hamano et al.	2008	Asian	H-B	PCa	16	54	72	11	50	58	Y
	Berhane et al.	2012	Asian	H-B	PCa	50	60	40	62	64	24	Y
	Mittal et al.	2012	Asian	P-B	PCa	84	62	49	105	102	43	N
	Abe et al.	2010	Caucasian	P-B	PCa	326	329	98	154	161	44	Y
	vanGils et al.	2002	Caucasian	P-B	PCa	37	30	9	77	78	27	Y
	Xu et al.	2009	Asian	P-B	PCa	108	85	14	153	72	10	Y
	Ritchey et al.	2005	Asian	P-B	PCa	85	53	17	132	99	12	Y
	Hirata et al.	2007	Asian	H-B	PCa	87	63	15	86	69	10	Y
	Dhillon et al.	2011	Caucasian	H-B	PCa	38	49	28	37	60	33	Y
	Kuasne et al.	2010	Caucasian	P-B	PCa	73	52	47	65	73	34	Y
	Zhu et al.	2015	Asian	H-B	PCa	249	245	78	276	243	53	Y
	Chen et al.	2005	African	H-B	PCa	90	30	3	84	28	3	Y
	Chen et al.	2005	Caucasian	H-B	PCa	95	104	29	109	87	21	Y
	Rybicki et al.	2003	Caucasian	H-B	PCa	245	257	70	179	203	55	Y
	Rybicki et al.	2003	Mixed	H-B	PCa	291	274	72	216	208	56	Y
	Agalliu et al.	2010	Caucasian	H-B	PCa	522	576	159	481	590	169	Y
	Agalliu et al.	2010	Mixed	H-B	PCa	103	37	4	53	27	2	Y
	Hirata et al.	2006	Asian	H-B	RCC	64	32	16	102	68	10	Y
	Huang et al.	2007	Caucasian	H-B	BC	539	73	2	524	74	2	Y
	Andrew et al.	2006	Mixed	H-B	BC	857	115	6	1041	152	10	Y
	Figueroa et al.	2007	Caucasian	H-B	BC	967	124	5	906	115	1	Y
	Matullo et al.	2007	Caucasian	P-B	BC	108	16	0	951	141	2	Y
	Stern et al.	2001	African	H-B	BC	18	1	0	10	3	0	Y
	Stern et al.	2001	Caucasian	H-B	BC	189	24	0	163	34	0	Y
	Mittal et al.	2008	Asian	H-B	BC	111	27	2	159	30	1	Y
	Mittal et al.	2012	Asian	H-B	BC	172	37	3	207	41	2	Y
	Fontana et al.	2008	Caucasian	H-B	BC	0	4	47	0	5	40	Y
XRCC1-rs1799782	Wang et al.	2010	Asian	H-B	BC	109	102	23	142	102	9	Y
	Sak et al.	2007	Caucasian	H-B	BC	476	56	3	498	61	3	Y
	Matullo et al.	2005	Caucasian	H-B	BC	275	40	0	260	51	0	Y
	Agalliu et al.	2010	Mixed	H-B	PCa	131	15	0	72	9	0	Y
	Hamano et al.	2008	Asian	H-B	PCa	70	62	10	79	32	8	Y
	Hirata et al.	2007	Asian	H-B	PCa	70	74	21	85	62	18	Y
	Zhu et al.	2015	Asian	H-B	PCa	310	208	54	340	203	29	Y
	vanGils et al.	2002	Caucasian	P-B	PCa	67	9	0	152	28	0	Y
	Xu et al.	2007	Asian	P-B	PCa	103	84	20	92	117	26	Y
	Agalliu et al.	2010	Caucasian	H-B	PCa	1098	143	5	1071	158	6	Y
	Mittal et al.	2012	Asian	P-B	PCa	157	29	9	203	43	4	Y
	Sak et al.	2007	Caucasian	H-B	BC	456	54	3	516	41	3	N
	Stern et al.	2001	Caucasian	H-B	BC	198	16	0	180	13	0	Y
	Stern et al.	2001	African	H-B	BC	17	2	0	13	0	0	N
	Figueroa et al.	2007	Caucasian	H-B	BC	955	122	4	911	101	4	Y
	Mittal et al.	2012	Asian	H-B	BC	112	58	42	146	41	63	N
	Mittal et al.	2008	Asian	H-B	BC	72	39	29	105	28	57	N
XRCC1-rs25489	Wang et al.	2010	Asian	P-B	BC	140	88	6	201	52	0	Y
	Xu et al.	2008	Asian	P-B	PCa	165	40	2	193	39	3	Y
	vanGils et al.	2002	Caucasian	P-B	PCa	66	10	0	164	18	0	Y
	Agalliu et al.	2010	Caucasian	H-B	PCa	1120	121	3	1145	106	2	Y
	Agalliu et al.	2010	Mixed	H-B	PCa	137	9	0	76	7	0	Y
	Mittal et al.	2012	Asian	H-B	PCa	82	76	37	131	47	72	N
	Zhu et al.	2015	Asian	H-B	PCa	380	120	73	394	116	62	N
XRCC1-rs915927	Sak et al.	2007	Caucasian	H-B	BC	162	260	93	170	270	105	Y
	Matullo et al.	2006	Caucasian	P-B	BC	27	56	41	243	508	342	N

Table 1 (*continued*)

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Cancer type	Case			Control			
						AA	AB	BB	AA	AB	BB	Y (HWE)
	Matullo et al.	2005	Caucasian	H-B	BC	87	139	60	116	125	49	Y
	Agalliu et al.	2010	Caucasian	H-B	PCa	238	622	400	220	618	409	Y
	Agalliu et al.	2010	Mixed	H-B	PCa	29	54	62	11	38	30	Y
	Wang et al.	2010	Asian	P-B	BC	174	56	4	178	73	2	Y
	Sak et al.	2007	Caucasian	H-B	BC	90	266	174	94	275	187	Y
XRCC1-rs3213245	Zhi et al.	2012	Asian	P-B	BC	232	61	9	229	76	6	Y
	Nowacka-Zawisza et al.	2015	Caucasian	H-B	PCa	90	11	0	196	20	0	Y
	Matullo et al.	2005	Caucasian	H-B	BC	133	22	1	94	13	2	Y
	Figueroa et al.	2007	Caucasian	H-B	BC	924	208	6	908	208	13	Y
	Nowacka-Zawisza et al.	2015	Caucasian	H-B	PCa	90	11	0	196	20	0	Y
XRCC2-rs3218536	Matullo et al.	2005	Caucasian	H-B	BC	133	22	1	94	13	2	Y
	Figueroa et al.	2007	Caucasian	H-B	BC	924	208	6	908	208	13	Y
	Narter et al.	2009	Caucasian	H-B	BC	23	5	27	5	2	32	N
	Fontana et al.	2008	Caucasian	H-B	BC	8	28	15	4	23	18	Y
	Matullo et al.	2001	Caucasian	H-B	BC	33	64	27	42	27	16	N
	Zhu et al.	2012	Asian	H-B	BC	91	44	15	96	49	5	Y
	Andrew et al.	2008	Mixed	P-B	BC	397	477	172	482	617	176	Y
	Gangwar et al.	2009	Asian	H-B	BC	135	68	9	159	80	11	Y
	Figueroa et al.	2007	Caucasian	H-B	BC	392	524	167	398	468	144	Y
	Mittle et al.	2012	Asian	H-B	BC	134	68	9	154	79	11	Y
	Matullo et al.	2005	Caucasian	H-B	BC	99	155	63	117	148	52	Y
	Sanyal et al.	2004	Caucasian	H-B	BC	131	129	51	107	109	30	Y
	Shen et al.	2003	Caucasian	H-B	BC	89	87	25	71	116	27	Y
XRCC3-rs861539	Narter et al.	2009	Caucasian	H-B	BC	23	5	27	5	2	32	N
	Wu et al.	2006	Caucasian	H-B	BC	230	290	92	250	261	85	Y
	Broberg et al.	2005	Caucasian	P-B	BC	23	33	5	60	72	21	Y
	Stern et al.	2002	Mixed	H-B	BC	90	110	33	94	91	24	Y
	Matullo et al.	2006	Caucasian	P-B	BC	46	61	17	383	544	167	Y
	Hao et al.	2008	Asian	H-B	BC	268	37	2	292	23	1	Y
	Nowacka-Zawisza et al.	2015	Caucasian	H-B	PCa	54	34	13	119	75	52	N
	Ritchey et al.	2005	Asian	P-B	PCa	139	17	3	214	31	2	Y
	Dhillon et al.	2011	Mixed	H-B	PCa	60	44	12	54	72	6	N
	Mandal et al.	2010	Caucasian	H-B	PCa	103	77	12	137	78	9	Y
	Hamano et al.	2008	Asian	H-B	PCa	121	18	3	97	20	2	Y
	Dhillon et al.	2011	Mixed	H-B	PCa	60	44	12	54	72	6	N
	Matullo et al.	2005	Caucasian	H-B	BC	171	117	21	166	126	19	Y
	Mittle et al.	2012	Asian	H-B	BC	122	83	6	160	77	7	Y
XRCC3-rs1799796	Wu et al.	2006	Caucasian	H-B	BC	279	258	63	256	261	75	Y
	Broberg et al.	2005	Caucasian	P-B	BC	25	30	3	57	74	21	Y
	Matullo et al.	2006	Caucasian	P-B	BC	60	47	17	554	447	91	Y
	Chang et al.	2008	Asian	H-B	PCa	113	21	0	126	8	0	Y
XRCC4-rs6869366	Mandal et al.	2011	Asian	H-B	PCa	117	70	5	112	98	14	Y
	Mittal et al.	2011	Asian	H-B	BC	120	83	8	121	106	17	Y
	Chang et al.	2009	Asian	H-B	BC	105	53	0	127	31	0	Y
	Mandal et al.	2011	Asian	H-B	PCa	124	49	19	168	48	8	Y
XRCC4-rs28360071	Mittal et al.	2011	Asian	H-B	BC	153	47	11	188	50	6	Y
	Chang et al.	2009	Asian	H-B	BC	95	61	2	98	57	3	Y
	Mandal et al.	2011	Asian	H-B	PCa	131	55	6	149	65	10	Y
	Luedeke et al.	2009	Caucasian	H-B	PCa	8	107	422	8	89	410	Y
XRCC4-rs1805377	Broberg et al.	2005	Caucasian	H-B	BC	44	9	1	103	23	1	Y
	Mittal et al.	2011	Asian	H-B	BC	140	70	1	156	79	9	Y
	Figueroa et al.	2007	Caucasian	H-B	BC	13	232	841	12	168	852	Y
	Hirata et al.	2006	Asian	H-B	PCa	74	79	12	86	67	12	Y
	Mandal et al.	2010	Asian	H-B	PCa	48	82	62	75	105	44	Y
XRCC7-rs7003908	Wang et al.	2008	Asian	H-B	BC	129	80	4	118	103	14	Y
	Gangwar et al.	2009	Asian	H-B	BC	32	81	99	80	116	54	Y
	Zhi et al.	2012	Asian	H-B	BC	185	105	12	152	134	25	Y
	Hirata et al.	2006	Asian	H-B	RCC	57	40	15	90	76	14	Y

PCa: prostate cancer; BC: bladder cancer; RCC: renal cell carcinoma; H-B: hospital-based; P-B: population-based; HWE: Hardy Weinberg equilibrium; Y: controls conformed to HWE; N: controls were not conformed to HWE; Mixed: more than two ethnicities.

XRCC genes (*XRCC1*-rs915927, *XRCC1*-rs25489, *XRCC1*-rs25487, *XRCC1*-rs1799782, *XRCC1*-rs3213245, *XRCC2*-rs3218536, *XRCC3*-rs1799796, *XRCC3*-rs861539, *XRCC4*-rs6869366, *XRCC4*-rs28360071, *XRCC4*-rs1805377, *XRCC7*-rs7003908) included in current meta-analysis (Agalliu et al., 2010; Andrew et al., 2015, 2007, 2006; Arizono et al., 2008; Berhane et al., 2012; Broberg et al., 2005; Chang et al., 2009; Lan et al., 2006; Lavender et al., 2010; Chang et al., 2008; Dhillon et al., 2009; Figueroa et al., 2007a,b; Fontana et al., 2008; Gangwar et al., 2009; Hamano et al., 2008; Hirata et al., 2006, 2007; Huang et al., 2007; Abe et al., 2011; Mittal et al., 2008; Narter et al., 2009; Nowacka-Zawisza et al., 2015; Ramaniuk et al., 2014; Ritchey et al., 2005; Rybicki et al., 2004; Sak et al., 2007; Sanyal et al., 2004; Shen et al., 2003; Stern et al., 2002, 2001; van Gils et al., 2002; Wang et al., 2010, 2008; Wen et al., 2009, 2013; Wu et al., 2006; Xu et al., 2007; Zhi et al., 2012; Hao et al., 2008; Zhou et al., 2012; Zhu et al., 2014, 2012; Kelsey et al., 2004; Kuasne et al., 2011; Luedeke et al., 2009; Mandal et al., 2010, 2011; Matullo, 2005; Matullo et al., 2006, 2001; Mittal et al., 2012a, b). The study selection processes were presented in Supplementary Figs. 1–5.

For polymorphisms in *XRCC1* gene (*XRCC1*-rs915927, *XRCC1*-rs25489, *XRCC1*-rs25487, *XRCC1*-rs1799782, *XRCC1*-rs3213245), a total of 80 case-control studies with 28,095 cases and 31,363 controls met the inclusion criteria. 37 studies of them were performed in Caucasians, 29 studies in Asians, four in Africans and the others were in mixed ethnic groups (including at least one race). Controls of 60 studies were hospital-based controls, and the others were population-based controls. Additionally, the distributions of polymorphisms in *XRCC1* for control groups were consistent with HWE, except for ten studies (Andrew et al., 2006; Mittal et al., 2008; Sak et al., 2007; Stern et al., 2001; Zhu et al., 2014; Kelsey et al., 2004; Matullo et al., 2006; Mittal et al., 2012b). For *XRCC2*-rs3218536 polymorphism, three eligible studies comprising1395 cases and 1454 controls were enrolled. All the studies were performed on subjects in Caucasians. Controls of studies were hospital-based. All of the studies were consistent with HWE. For polymorphisms in *XRCC3* (*XRCC3*-rs1799796 and *XRCC3*-rs861539), we analyzed 28 studies with 7283 cases and 9773 controls, which were published between 2002 and 2016. 17 of the studies were performed in Caucasians, seven studies in Asians and the other four in Mixed group. Controls of 23 studies were hospital-based controls, and others were population-based controls. There are six case-control studies that were not consistent with HWE (Nowacka-Zawisza et al., 2015; Narter *et al*., 2009; Dhillon et al., 2009; Matullo et al., 2001). For polymorphisms in *XRCC4* (*XRCC4*-rs6869366, *XRCC4*-rs28360071 and *XRCC4*-rs1805377), 12 case-control studies comprising 3336 cases and 3520 controls were considered eligible. Nine studies were conducted in Asians and the others were in Caucasians. Controls of all studies were hospital-based controls and no study was deviated from HWE. For *XRCC7*-rs7003908, six studies with 1196 cases and 1365 controls were enrolled. All the six studies were performed in Asians. Source of control of all enrolled studies were hospital-based controls and no study was deviated from HWE. In addition, we applied a Newcastle-Ottawa scale (NOS) to evaluate the quality of these enrolled studies (Wells et al., 2000), which was presented in Table 2, and employed a PRISMA 2009 checklist to present our meta-analysis work (Supplementary Table 4).

3.2. Quantitative Synthesis

Table 3 listed the main results of the meta-analysis of polymorphisms in *XRCC* genes and risk of urological neoplasm.

3.2.1. XRCC1-rs25489

The pooled results based on 13 included studies indicated that the *XRCC1*-rs25489 polymorphism conferred a significantly increased overall risk to urological neoplasms in heterozygote (BA vs. AA: OR = 1.455, 95%CI = 1.198–1.768, $P_A < 0.001$, Fig. 1) and dominant models (BA + BB vs. AA: OR = 1.281, 95%CI = 1.148–1.428, $P_A < 0.001$), respectively. Further subgroup analysis by cancer type indicated that the 'B' allele was significantly related to an increased risk of BC in heterozygote model (BA vs. AA: OR = 1.611, 95%CI = 1.242–2.090, $P_A < 0.001$). Moreover, when the subgroup analyses were performed based on source of controls, ethnicity and HWE status, null result was uncovered (Table 3).

3.2.2. XRCC1-rs1799782

Overall, no significant association was uncovered for the association between *XRCC1*-rs1799782 polymorphism and urological neoplasms risk. However, in the stratification analysis by source of control, we observed hospital-based controls groups were one of the heterogeneity sources in homozygote model (BB vs. AA: OR = 1.648, 95%CI = 1.252–2.170, $P_A < 0.001$) instead of population-based controls groups.

3.2.3. XRCC1-rs25487

With regard to the *XRCC1*-rs25487 polymorphism, overall results revealed a null association between the polymorphism and risk of urological neoplasms (Fig. 2). However, in the stratification analysis by ethnicity, a significant increased risk of urological neoplasms risk was uncovered for Asians in allelic (B vs. A: OR = 1.176, 95%CI = 1.089–1.271, $P_A < 0.001$) and homozygote models (BB vs. AA: OR = 1.464, 95%CI = 1.232–1.740, $P_A < 0.001$). However, in the stratified analysis by HWE status, source of controls and cancer type, null result was obtained.

3.2.4. XRCC1-rs3213245, XRCC1-rs915927, XRCC2-rs3218536, XRCC3-rs1799796, XRCC3-rs861539, XRCC4-rs1805377, XRCC4-rs28360071, XRCC4-rs6869366 and XRCC7-rs7003908

There was no significant association between *XRCC1*-rs3213245, *XRCC1*-rs915927, *XRCC2*-rs3218536, *XRCC3*-rs1799796, *XRCC3*-rs861539, *XRCC4*-rs1805377, *XRCC4*-rs28360071 and *XRCC4*-rs6869366, *XRCC7*-rs7003908 polymorphisms and risk of urological neoplasms. Furthermore, in the subgroup analysis by ethnicity, HWE status, source of controls and cancer type, similar results were also obtained (Table 3).

3.3. Sensitivity Analysis and Publication Bias

Sensitivity analyses were performed to evaluate the influence of the separate case-control study on the integrated data. The results showed that there was no material alteration in corresponding pooled ORs for *XRCC1*-rs915927, *XRCC1*-rs25489, *XRCC1*-rs25487, *XRCC1*-rs1799782, *XRCC1*-rs3213245, *XRCC2*-rs3218536, *XRCC3*-rs1799796, *XRCC3*-rs861539, *XRCC4*-rs6869366, *XRCC4*-rs28360071, *XRCC4*-rs1805377, *XRCC7*-rs7003908 polymorphisms (Supplementary Table 2 and Figs. 6–17). Additionally, Begg's funnel plot and Egger's regression test were performed to evaluate the publication bias. If the tests indicated significant publication bias existed in several genetic models, it might reflect differences in the selection of controls, age distributions, and some other lifestyle characteristics. As for *XRCC1*-rs915927, *XRCC1*-rs25489, *XRCC1*-rs3213245, *XRCC1*-rs25487, *XRCC1*-rs1799782, *XRCC2*-rs3218536, *XRCC3*-rs1799796, *XRCC3*-rs861539, *XRCC4*-rs1805377, *XRCC4*-rs6869366, and *XRCC7*-rs7003908 polymorphisms, no evidence of publication bias was identified by viewing the shape of Begg's funnel plot, which was further validated by Egger's regression test (Supplementary Table 3 and Figs. 18–29). However, for *XRCC4*-rs28360071 polymorphism in overall ($P > |t| = 0.043$), publication bias was existed. Therefore, we conducted a sensitivity analysis using the trim and fill method (Sue and Richard, 2000). The imputed results provide a symmetrical funnel plot, which indicated that no publication bias for *XRCC4*-rs28360071 polymorphism was identified after adjusting.

3.4. LD Analyses Across Populations

In order to better understand the quantitative synthesis, LD analysis was performed to test for the existence of bins in the region comprising these polymorphisms in each *XRCC* genes, respectively (polymorphisms including *XRCC1*-rs915927, *XRCC1*-rs25489, *XRCC1*-rs25487, *XRCC1*-rs1799782, *XRCC1*-rs3213245, *XRCC1*-rs3218536, *XRCC3*-rs1799796, *XRCC3*-rs861539, *XRCC4*-rs6869366, *XRCC4*-rs28360071, *XRCC4*-rs1805377, *XRCC7*-rs7003908). Finally, only *XRCC4*-rs28360071 polymorphism cannot be matched from the database. LD plots for polymorphisms in each gene were presented in Supplementary Figs. 30–31. Highlighted, for the two significant risk factors (*XRCC1*-rs25489 and *XRCC1*-rs25487), no significant LD was identified in all the four populations (CHB: $r^2 = 0.03$; CEU: $r^2 = 0.02$; JPT: $r^2 = 0.04$; YRI: $r^2 = 0$).

4. Discussion

Tumors of the urinary system were reported to make significant threaten to the overall human cancer burden (Parkin, 2008). A wide variable incidence of urological neoplasms indicates its multi-factorial aetiology that involves the interactions between genetic and ethnic backgrounds, as well as the environmental factors. In human beings, *XRCC* genes that are relevant to DNA repair and damage prevention

Table 2
Methodological quality of the included studies according to the Newcastle-Ottawa scale.

Gene-polymorphism	Author	Ethnicity	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Matullo et al.	Mixed	*	*	NA	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Arizono et al.	Asian	*	*	NA	*	**	*	*	*
	Mittal et al.	Asian	*	*	NA	*	*	NA	*	*
	Sak et al.	Caucasian	*	*	NA	*	**	*	*	*
	Sanyal et al.	Caucasian	*	*	NA	*	**	NA	*	*
	Matullo et al.	Mixed	*	*	NA	*	**	*	*	*
	Fontana et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Broberg et al.	Asian	*	*	NA	*	**	NA	*	*
	Matullo et al.	Caucasian	*	*	NA	*	*	*	*	*
	Shen et al.	Caucasian	*	*	NA	*	**	*	*	*
	Ramaniuk et al.	Caucasian	*	*	NA	*	**	*	*	*
	Zhi et al.	Asian	*	*	*	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Andrew et al.	Mixed	*	*	NA	*	**	*	*	*
	Kelsey et al.	Mixed	*	*	*	*	**	*	*	*
XRCC1-rs25487	Huang et al.	Caucasian	*	*	NA	*	**	*	*	*
	Gao et al.	Mixed	NA	*	NA	*	*	NA	*	-
	Hamano et al.	Asian	*	*	NA	*	**	*	*	*
	Berhane et al.	Asian	*	*	NA	*	**	NA	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Abe et al.	Caucasian	*	*	NA	*	**	*	*	*
	vanGils et al.	Caucasian	*	*	*	*	**	NA	*	*
	Xu et al.	Asian	*	*	*	*	**	*	*	*
	Ritchey et al.	Asian	*	*	*	*	**	*	*	*
	Hirata et al.	Asian	*	*	NA	*	**	NA	*	*
	Dhillon et al.	Caucasian	*	*	NA	*	**	NA	*	*
	Kuasne et al.	Caucasian	*	*	*	*	**	NA	*	*
	Zhu et al.	Asian	*	*	NA	*	**	NA	*	*
	Chen et al.	Mixed	*	*	NA	*	**	*	*	*
	Chen et al.	Mixed	*	*	NA	*	**	*	*	*
	Rybicki et al.	Mixed	*	*	NA	*	*	*	*	*
	Rybicki et al.	Mixed	*	*	NA	*	*	*	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Hirata et al.	Asian	*	*	NA	*	**	NA	*	*
	Huang et al.	Caucasian	*	*	NA	*	**	*	*	*
	Andrew et al.	Mixed	*	*	NA	*	**	*	*	*
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Matullo et al.	Caucasian	*	*	*	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Mittal et al.	Asian	*	*	NA	*	*	NA	*	*
	Fontana et al.	Caucasian	*	*	NA	*	*	NA	*	*
XRCC1-rs1799782	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Sak et al.	Caucasian	*	*	NA	*	**	*	*	*
	Matullo et al.	Caucasian	*	*	NA	*	*	*	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Hamano et al.	Asian	*	*	NA	*	**	*	*	*
	Hirata et al.	Asian	*	*	NA	*	**	NA	*	*
	Zhu et al.	Asian	*	*	NA	*	**	NA	*	*
	vanGils et al.	Caucasian	*	*	*	*	**	NA	*	*
	Xu et al.	Asian	*	*	*	*	**	*	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Mittal et al.	Asian	*	*	NA	*	*	NA	*	*
	Sak et al.	Mixed	*	*	NA	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Mittal et al.	Asian	*	*	NA	*	*	NA	*	*
XRCC1-rs25489	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Xu et al.	Asian	*	*	*	*	**	*	*	*
	vanGils et al.	Caucasian	*	*	*	*	**	NA	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Zhu et al.	Asian	*	*	NA	*	**	NA	*	*
XRCC1-rs915927	Sak et al.	Caucasian	*	*	NA	*	**	*	*	*

(continued on next page)

Table 2 (*continued*)

Gene-polymorphism	Author	Ethnicity	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
	Matullo et al.	Caucasian	*	*	*	*	**	*	*	*
	Matullo et al.	Caucasian	*	*	NA	*	*	*	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Agalliu et al.	Mixed	*	*	NA	*	**	NA	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
XRCC1-rs3213245	Sak et al.	Caucasian	*	*	NA	*	**	*	*	*
	Zhi et al.	Asian	*	*	*	*	**	*	*	*
XRCC2-rs3218536	Nowacka-Zawisza et al.	Caucasian	NA	*	NA	*	**	*	*	*
	Matullo et al.	Caucasian	*	*	NA	*	*	*	*	*
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Narter et al.	Caucasian	*	*	NA	*	**	*	*	*
	Fontana et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Matullo et al.	Caucasian	*	*	*	*	**	*	*	*
	Zhu et al.	Asian	*	*	NA	*	**	NA	*	*
	Andrew et al.	Mixed	*	*	NA	*	**	*	*	*
	Gangwar et al.	Asian	*	*	NA	*	*	*	*	*
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Mittle et al.	Asian	*	*	NA	*	**	*	*	*
XRCC3-rs861539	Matullo et al.	Caucasian	*	*	NA	*	*	*	*	*
	Sanyal et al.	Caucasian	*	*	NA	*	**	NA	*	*
	Shen et al.	Caucasian	*	*	NA	*	**	*	*	*
	Narter et al.	Caucasian	*	*	NA	*	**	*	*	*
	Wu et al.	Caucasian	*	*	NA	*	**	*	*	*
	Broberg et al.	Asian	*	*	NA	*	**	NA	*	*
	Stern et al.	Mixed	*	*	NA	*	**	*	*	*
	Matullo et al.	Mixed	*	*	NA	*	**	*	*	*
	Yang et al.	Asian	*	*	NA	*	**	*	*	*
	Hao et al.	Asian	NA	*	NA	*	**	NA	*	*
	Nowacka-Zawisza et al.	Caucasian	NA	*	NA	*	**	*	*	*
	Ritchey et al.	Asian	*	*	*	*	**	*	*	*
XRCC3-rs861539	Dhillon et al.	Caucasian	*	*	NA	*	**	NA	*	*
	Mandal et al.	Asian	*	*	NA	*	**	*	*	*
	Hamano et al.	Asian	*	*	NA	*	**	*	*	*
	Dhillon et al.	Caucasian	*	*	NA	*	**	NA	*	*
	Matullo et al.	Caucasian	*	*	*	*	**	*	*	*
	Mittle et al.	Asian	*	*	NA	*	**	*	*	*
XRCC3-rs1799796	Wu et al.	Caucasian	*	*	NA	*	**	*	*	*
	Broberg et al.	Asian	*	*	NA	*	**	NA	*	*
	Matullo et al.	Mixed	*	*	NA	*	**	*	*	*
	Mandal et al.	Asian	*	*	NA	*	*	*	*	*
	Luedeke et al.	Caucasian	*	*	NA	*	**	NA	*	*
XRCC4-rs1805377	Broberg et al.	Asian	*	*	NA	*	**	NA	*	*
	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Figueroa et al.	Caucasian	*	*	NA	*	*	NA	*	*
	Chang et al.	Asian	*	*	NA	*	**	*	*	*
XRCC4-rs6869366	Mandal et al.	Asian	*	*	NA	*	*	*	*	*
	Mittal et al.	Asian	*	*	NA	*	*	NA	*	*
	Chang et al.	Asian	*	*	NA	*	**	*	*	*
	Mandal et al.	Asian	*	*	NA	*	**	*	*	*
XRCC4-rs28360071	Mittal et al.	Asian	*	*	NA	*	**	*	*	*
	Chang et al.	Asian	*	*	NA	*	**	*	*	*
	Hirata et al.	Asian	*	*	NA	*	**	NA	*	*
	Mandal et al.	Asian	*	*	NA	*	**	*	*	*
XRCC7-rs7003908	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Gangwar et al.	Asian	*	*	NA	*	*	*	*	*
	Zhi et al.	Asian	*	*	*	*	**	*	*	*
	Hirata et al.	Asian	*	*	NA	*	**	NA	*	*

H′ quality choices with a 'star'. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

pathways are critical for preventing cancer initiation and progression. The *XRCC1*, situated at chromosome 19q13.3, can produce *XRCC*1 enzyme that involved in BER pathway. It may be particularly important for urological neoplasms, functioning as repairing uracil and oxidative DNA damage (Taylor et al., 2002). The *XRCC*2 protein encoded by the *XRCC2* genes, one of homologue of the RecA protein, displaces replication protein A (RPA) on the exposed single-stranded DNA, which takes responsibility for repairing the DNA double-strand breaks (DBS) (Riha et al., 2006). Similarly, the *XRCC*3 protein is involved in the homologous recombination repair (HR) pathway and the *XRCC*4, *XRCC*7 protein in the non-homologous end joining (NHEJ), also responsible for repairing DBS.

It is hypothesized that polymorphisms in *XRCC* genes of BER, NER, DSBR and MMR pathways may be important risk factors for the development of urological neoplasms. Some investigators have conducted case-control studies to evaluate the association between polymorphisms in *XRCC* genes and the risk of urological tumors. However, most of former studies stressed on limited polymorphisms in *XRCC* genes while neglected potential multiple genes' influence on carcinogenesis. In current study, we presented a comprehensive meta-

Table 3
Results of meta-analysis for polymorphisms in *XRCC* genes and risk of urological neoplasms.

SNP	Comparison	Subgroup	N	Cases	Controls	P_H	P_Z	P_A	Random	Fixed
XRCC1-rs25487	B vs. A	Overall	39	12,565	13,362	0.068	0.103	1.000	1.040 (0.992–1.090)	1.031 (0.993–1.070)
	B vs. A	African	2	142	128	0.330	0.718	1.000	1.084 (0.676–1.738)	1.090 (0.682–1.743)
	B vs. A	Asian	13	2837	3169	0.168	0.000	**0.000**	1.174 (1.069–1.288)	1.176 (1.089–1.271)
	B vs. A	Caucasian	18	6984	7516	0.582	0.795	1.000	0.993 (0.945–1.044)	0.993 (0.945–1.044)
	B vs. A	Mixed	6	2602	2549	0.515	0.617	1.000	0.978 (0.900–1.064)	0.979 (0.900–1.064)
	B vs. A	H-B	29	9992	9719	0.120	0.317	1.000	1.029 (0.977–1.084)	1.022 (0.980–1.066)
	B vs. A	P-B	10	2573	3643	0.125	0.123	1.000	1.072 (0.966–1.191)	1.066 (0.983–1.157)
	B vs. A	N	3	1540	2047	0.508	0.902	1.000	0.994 (0.902–1.096)	0.994 (0.902–1.095)
	B vs. A	Y	36	11,025	11,315	0.051	0.093	1.000	1.046 (0.993–1.101)	1.037 (0.996–1.080)
	B vs. A	BC	20	6438	7928	0.266	0.535	1.000	1.016 (0.959–1.075)	1.016 (0.966–1.068)
	B vs. A	PCa	18	6015	5254	0.046	0.090	1.000	1.072 (0.989–1.160)	1.046 (0.988–1.107)
	BA vs. AA	Overall	39	12,565	13,362	0.095	0.331	1.000	1.033 (0.967–1.104)	1.033 (0.978–1.090)
	BA vs. AA	African	2	142	128	0.261	0.638	1.000	1.217 (0.582–2.542)	1.141 (0.659–1.974)
	BA vs. AA	Asian	13	2837	3169	0.024	0.339	1.000	1.082 (0.920–1.272)	1.093 (0.979–1.221)
	BA vs. AA	Caucasian	18	6984	7516	0.568	0.747	1.000	0.988 (0.919–1.062)	0.988 (0.919–1.062)
	BA vs. AA	Mixed	6	2602	2549	0.256	0.186	1.000	1.074 (0.924–1.249)	1.084 (0.962–1.223)
	BA vs. AA	H-B	29	9992	9719	0.493	0.278	1.000	1.034 (0.973–1.099)	1.034 (0.973–1.099)
	BA vs. AA	P-B	10	2573	3643	0.008	0.934	1.000	0.992 (0.820–1.200)	1.027 (0.914–1.154)
	BA vs. AA	N	3	1540	2047	0.061	0.515	1.000	1.095 (0.832–1.442)	1.121 (0.971–1.293)
	BA vs. AA	Y	36	11,025	11,315	0.172	0.532	1.000	1.022 (0.955–1.094)	1.019 (0.961–1.080)
	BA vs. AA	BC	20	6438	7928	0.227	0.014	0.840	1.097 (1.008–1.193)	1.095 (1.019–1.177)
	BA vs. AA	PCa	18	6015	5254	0.271	0.401	1.000	0.968 (0.881–1.063)	0.966 (0.890–1.048)
	BA + BB vs. AA	Overall	39	12,565	13,362	0.145	0.134	1.000	1.044 (0.983–1.109)	1.040 (0.988–1.094)
	BA + BB vs. AA	African	2	142	128	0.255	0.663	1.000	1.211 (0.576–2.543)	1.125 (0.662–1.914)
	BA + BB vs. AA	Asian	13	2837	3169	0.076	0.036	1.000	1.160 (1.010–1.333)	1.165 (1.050–1.293)
	BA + BB vs. AA	Caucasian	18	6984	7516	0.577	0.760	1.000	0.989 (0.924–1.059)	0.989 (0.924–1.059)
	BA + BB vs. AA	Mixed	6	2602	2549	0.473	0.525	1.000	1.037 (0.926–1.162)	1.038 (0.926–1.162)
	BA + BB vs. AA	H-B	29	9992	9719	0.315	0.249	1.000	1.038 (0.974–1.105)	1.034 (0.977–1.095)
	BA + BB vs. AA	P-B	10	2573	3643	0.066	0.540	1.000	1.048 (0.901–1.219)	1.060 (0.949–1.183)
	BA + BB vs. AA	N	3	1540	2047	0.517	0.335	1.000	1.068 (0.934–1.222)	1.068 (0.934–1.222)
	BA + BB vs. AA	Y	36	11,025	11,315	0.106	0.221	1.000	1.041 (0.974–1.114)	1.035 (0.980–1.093)
	BA + BB vs. AA	BC	20	6438	7928	0.210	0.066	1.000	1.067 (0.984–1.157)	1.066 (0.996–1.142)
	BA + BB vs. AA	PCa	18	6015	5254	0.170	0.831	1.000	1.020 (0.928–1.122)	1.008 (0.934–1.089)
	BB vs. AA	Overall	39	12,565	13,362	0.040	0.176	1.000	1.077 (0.967–1.199)	1.053 (0.970–1.143)
	BB vs. AA	African	2	142	128	0.968	0.942	1.000	0.949 (0.229–3.933)	0.949 (0.229–3.933)
	BB vs. AA	Asian	13	2837	3169	0.131	0.000	**0.000**	1.456 (1.170–1.812)	1.464 (1.232–1.740)
	BB vs. AA	Caucasian	18	6984	7516	0.778	0.729	1.000	0.981 (0.880–1.094)	0.981 (0.880–1.094)
	BB vs. AA	Mixed	6	2602	2549	0.354	0.212	1.000	0.890 (0.725–1.093)	0.890 (0.742–1.068)
	BB vs. AA	H-B	29	9992	9719	0.072	0.443	1.000	1.049 (0.929–1.184)	1.031 (0.940–1.130)
	BB vs. AA	P-B	10	2573	3643	0.121	0.150	1.000	1.171 (0.928–1.478)	1.140 (0.954–1.363)
	BB vs. AA	N	3	1540	2047	0.116	0.314	1.000	0.930 (0.667–1.297)	0.900 (0.733–1.105)
	BB vs. AA	Y	36	11,025	11,315	0.074	0.097	1.000	1.101 (0.983–1.233)	1.085 (0.992–1.186)
	BB vs. AA	BC	20	6438	7928	0.247	0.610	1.000	0.971 (0.853–1.105)	0.971 (0.869–1.086)
	BB vs. AA	PCa	18	6015	5254	0.111	0.038	1.000	1.194 (1.015–1.403)	1.138 (1.007–1.287)
	BB vs. BA + AA	Overall	39	12,565	13,362	0.022	0.233	1.000	1.064 (0.961–1.179)	1.039 (0.963–1.121)
	BB vs. BA + AA	African	2	142	128	0.853	0.842	1.000	0.865 (0.211–3.546)	0.866 (0.211–3.548)
	BB vs. BA + AA	Asian	13	2837	3169	0.087	0.002	0.120	1.378 (1.120–1.695)	1.376 (1.176–1.609)
	BB vs. BA + AA	Caucasian	18	6984	7516	0.828	0.941	1.000	0.997 (0.900–1.104)	0.996 (0.900–1.103)
	BB vs. BA + AA	Mixed	6	2602	2549	0.161	0.049	1.000	0.860 (0.666–1.109)	0.843 (0.710–0.999)
	BB vs. BA + AA	H-B	29	9992	9719	0.140	0.758	1.000	1.025 (0.922–1.139)	1.014 (0.931–1.104)
	BB vs. BA + AA	P-B	10	2573	3643	0.021	0.166	1.000	1.202 (0.926–1.560)	1.145 (0.969–1.353)
	BB vs. BA + AA	N	3	1540	2047	0.006	0.701	1.000	0.910 (0.563–1.473)	0.857 (0.709–1.037)
	BB vs. BA + AA	Y	36	11,025	11,315	0.170	0.074	1.000	1.088 (0.986–1.200)	1.079 (0.993–1.172)
	BB vs. BA + AA	BC	20	6438	7928	0.343	0.129	1.000	0.924 (0.824–1.035)	0.922 (0.831–1.024)
	BB vs. BA + AA	PCa	18	6015	5254	0.180	0.006	0.360	1.215 (1.057–1.397)	1.172 (1.047–1.312)
XRCC1-rs25489	B vs. A	Overall	13	4854	5050	0.040	0.028	1.000	1.168 (1.017–1.343)	1.156 (1.053–1.268)
	B vs. A	Asian	6	1561	1750	0.001	0.204	1.000	1.168 (0.919–1.484)	1.141 (1.017–1.280)
	B vs. A	Caucasian	5	3128	3204	0.900	0.028	1.000	1.197 (1.020–1.405)	1.197 (1.020–1.405)
	B vs. A	H-B	10	4337	4380	0.820	0.089	1.000	1.090 (0.987–1.204)	1.090 (0.987–1.204)
	B vs. A	P-B	3	517	670	0.030	0.097	1.000	1.580 (0.921–2.711)	1.715 (1.322–2.223)
	B vs. A	N	6	1652	1835	0.539	0.262	1.000	1.071 (0.949–1.209)	1.071 (0.950–1.208)
	B vs. A	Y	7	3202	3215	0.027	0.054	1.000	1.289 (0.995–1.670)	1.291 (1.116–1.494)
	B vs. A	BC	7	2413	2475	0.003	0.118	1.000	1.246 (0.946–1.641)	1.206 (1.054–1.381)
	B vs. A	PCa	6	2441	2575	0.899	0.102	1.000	1.112 (0.979–1.264)	1.112 (0.979–1.264)
	BA vs. AA	Overall	13	4854	5050	0.010	0.000	**0.000**	1.455 (1.198–1.768)	1.388 (1.233–1.563)
	BA vs. AA	Asian	6	1561	1750	0.003	0.001	0.060	1.738 (1.244–2.428)	1.615 (1.364–1.912)
	BA vs. AA	Caucasian	5	3128	3204	0.870	0.025	1.000	1.213 (1.025–1.437)	1.213 (1.025–1.437)
	BA vs. AA	H-B	10	4337	4380	0.035	0.002	0.120	1.393 (1.133–1.712)	1.323 (1.162–1.506)
	BA vs. AA	P-B	3	517	670	0.076	0.050	1.000	1.653 (1.000–2.735)	1.764 (1.322–2.354)
	BA vs. AA	N	6	1652	1835	0.031	0.002	0.120	1.667 (1.211–2.295)	1.526 (1.272–1.830)
	BA vs. AA	Y	7	3202	3215	0.061	0.037	1.000	1.309 (1.016–1.686)	1.294 (1.107–1.513)
	BA vs. AA	BC	7	2413	2475	0.082	0.000	**0.000**	1.611 (1.242–2.090)	1.540 (1.298–1.827)
	BA vs. AA	PCa	6	2441	2575	0.032	0.077	1.000	1.304 (0.971–1.750)	1.260 (1.068–1.485)
	BA + BB vs. AA	Overall	13	4854	5050	0.153	0.000	**0.000**	1.297 (1.129–1.491)	1.281 (1.148–1.428)

(continued on next page)

Table 3 (*continued*)

SNP	Comparison	Subgroup	N	Cases	Controls	P_H	P_Z	P_A	Random	Fixed
	BA + BB vs. AA	Asian	6	1561	1750	0.019	0.010	0.600	1.392 (1.083–1.790)	1.352 (1.168–1.564)
	BA + BB vs. AA	Caucasian	5	3128	3204	0.882	0.024	1.000	1.211 (1.025–1.431)	1.211 (1.025–1.431)
	BA + BB vs. AA	H-B	10	4337	4380	0.918	0.002	0.120	1.207 (1.073–1.359)	1.207 (1.073–1.359)
	BA + BB vs. AA	P-B	3	517	670	0.034	0.080	1.000	1.666 (0.942–2.947)	1.802 (1.357–2.394)
	BA + BB vs. AA	N	6	1652	1835	0.791	0.004	0.240	1.258 (1.078–1.468)	1.258 (1.078–1.468)
	BA + BB vs. AA	Y	7	3202	3215	0.025	0.051	1.000	1.316 (0.999–1.733)	1.304 (1.118–1.521)
	BA + BB vs. AA	BC	7	2413	2475	0.052	0.008	0.480	1.403 (1.091–1.804)	1.378 (1.177–1.614)
	BA + BB vs. AA	PCa	6	2441	2575	0.718	0.020	1.000	1.197 (1.029–1.392)	1.197 (1.029–1.392)
	BB vs. AA	Overall	13	4854	5050	0.773	0.933	1.000	0.978 (0.790–1.209)	0.991 (0.803–1.223)
	BB vs. AA	Asian	6	1561	1750	0.202	0.879	1.000	0.959 (0.716–1.285)	0.983 (0.790–1.223)
	BB vs. AA	Caucasian	5	3128	3204	0.975	0.678	1.000	1.194 (0.524–2.719)	1.190 (0.524–2.703)
	BB vs. AA	H-B	10	4337	4380	0.936	0.664	1.000	0.954 (0.769–1.184)	0.954 (0.769–1.182)
	BB vs. AA	P-B	3	517	670	0.232	0.094	1.000	2.33 (0.508–10.683)	2.554 (0.852–7.657)
	BB vs. AA	N	6	1652	1835	0.674	0.647	1.000	0.950 (0.762–1.186)	0.950 (0.762–1.184)
	BB vs. AA	Y	7	3202	3215	0.640	0.243	1.000	1.360 (0.638–2.898)	1.527 (0.751–3.107)
	BB vs. AA	BC	7	2413	2475	0.548	0.561	1.000	0.878 (0.635–1.215)	0.910 (0.662–1.251)
	BB vs. AA	PCa	6	2441	2575	0.779	0.688	1.000	1.060 (0.800–1.405)	1.059 (0.800–1.401)
	BB vs. BA + AA	Overall	13	4854	5050	0.361	0.096	1.000	0.830 (0.657–1.048)	0.843 (0.689–1.031)
	BB vs. BA + AA	Asian	6	1561	1750	0.036	0.277	1.000	0.811 (0.556–1.183)	0.828 (0.671–1.020)
	BB vs. BA + AA	Caucasian	5	3128	3204	0.976	0.715	1.000	1.169 (0.513–2.661)	1.165 (0.513–2.646)
	BB vs. BA + AA	H-B	10	4337	4380	0.454	0.048	1.000	0.815 (0.662–1.003)	0.812 (0.661–0.998)
	BB vs. BA + AA	P-B	3	517	670	0.298	0.150	1.000	2.034 (0.515–8.037)	2.260 (0.744–6.863)
	BB vs. BA + AA	N	6	1652	1835	0.143	0.042	1.000	0.779 (0.574–1.057)	0.804 (0.651–0.992)
	BB vs. BA + AA	Y	7	3202	3215	0.742	0.321	1.000	1.298 (0.609–2.765)	1.436 (0.703–2.935)
	BB vs. BA + AA	BC	7	2413	2475	0.537	0.083	1.000	0.740 (0.542–1.010)	0.763 (0.562–1.036)
	BB vs. BA + AA	PCa	6	2441	2575	0.215	0.492	1.000	0.892 (0.578–1.378)	0.910 (0.696–1.191)
XRCC1-rs1799782	B vs. A	Overall	20	7280	8577	0.013	0.468	1.000	1.044 (0.930–1.171)	1.055 (0.977–1.139)
	B vs. A	Asian	8	1867	2034	0.036	0.020	1.000	1.227 (1.033–1.458)	1.223 (1.096–1.365)
	B vs. A	Caucasian	9	4270	5246	0.756	0.193	1.000	0.923 (0.816–1.043)	0.922 (0.816–1.042)
	B vs. A	Mixed	2	1124	1248	0.964	0.383	1.000	0.903 (0.719–1.135)	0.903 (0.719–1.135)
	B vs. A	H-B	16	6678	6818	0.019	0.260	1.000	1.075 (0.948–1.220)	1.086 (1.000–1.179)
	B vs. A	P-B	4	602	1759	0.324	0.229	1.000	0.893 (0.707–1.127)	0.881 (0.716–1.083)
	B vs. A	BC	12	4531	5740	0.123	0.661	1.000	1.017 (0.881–1.174)	1.024 (0.920–1.141)
	B vs. A	PCa	8	2749	2837	0.011	0.440	1.000	1.081 (0.887–1.319)	1.086 (0.974–1.210)
	BA vs. AA	Overall	20	7280	8577	0.080	0.833	1.000	0.987 (0.878–1.111)	0.986 (0.902–1.077)
	BA vs. AA	Asian	8	1867	2034	0.020	0.230	1.000	1.153 (0.914–1.455)	1.132 (0.983–1.305)
	BA vs. AA	Caucasian	9	4270	5246	0.862	0.111	1.000	0.901 (0.791–1.026)	0.900 (0.790–1.025)
	BA vs. AA	Mixed	2	1124	1248	0.994	0.503	1.000	0.919 (0.717–1.177)	0.919 (0.717–1.177)
	BA vs. AA	H-B	16	6678	6818	0.097	0.653	1.000	1.029 (0.907–1.168)	1.019 (0.926–1.120)
	BA vs. AA	P-B	4	602	1759	0.592	0.054	1.000	0.774 (0.597–1.002)	0.774 (0.596–1.004)
	BA vs. AA	BC	12	4531	5740	0.555	0.607	1.000	0.971 (0.861–1.094)	0.969 (0.860–1.092)
	BA vs. AA	PCa	8	2749	2837	0.011	0.836	1.000	1.026 (0.802–1.314)	1.007 (0.880–1.151)
	BA + BB vs. AA	Overall	20	7280	8577	0.023	0.783	1.000	1.018 (0.897–1.154)	1.018 (0.934–1.110)
	BA + BB vs. AA	Asian	8	1867	2034	0.018	0.083	1.000	1.218 (0.975–1.523)	1.207 (1.055–1.381)
	BA + BB vs. AA	Caucasian	9	4270	5246	0.819	0.136	1.000	0.908 (0.798–1.032)	0.907 (0.798–1.031)
	BA + BB vs. AA	Mixed	2	1124	1248	0.984	0.435	1.000	0.908 (0.713–1.157)	0.908 (0.713–1.157)
	BA + BB vs. AA	H-B	16	6678	6818	0.032	0.399	1.000	1.060 (0.925–1.215)	1.051 (0.958–1.153)
	BA + BB vs. AA	P-B	4	602	1759	0.398	0.103	1.000	0.813 (0.634–1.042)	0.813 (0.634–1.043)
	BA + BB vs. AA	BC	12	4531	5740	0.290	0.886	1.000	0.992 (0.868–1.134)	0.991 (0.882–1.114)
	BA + BB vs. AA	PCa	8	2749	2837	0.006	0.621	1.000	1.064 (0.832–1.360)	1.051 (0.924–1.196)
	BB vs. AA	Overall	20	7280	8577	0.459	0.001	0.060	1.486 (1.158–1.908)	1.502 (1.178–1.916)
	BB vs. AA	Asian	8	1867	2034	0.099	0.014	0.840	1.676 (1.111–2.530)	1.659 (1.259–2.187)
	BB vs. AA	Caucasian	9	4270	5246	0.907	0.424	1.000	1.278 (0.657–2.486)	1.303 (0.681–2.492)
	BB vs. AA	Mixed	2	1124	1248	0.852	0.476	1.000	0.705 (0.271–1.832)	0.706 (0.271–1.839)
	BB vs. AA	H-B	16	6678	6818	0.749	0.000	**0.000**	1.625 (1.227–2.154)	1.648 (1.252–2.170)
	BB vs. AA	P-B	4	602	1759	0.107	0.826	1.000	1.583 (0.563–4.450)	1.061 (0.625–1.802)
	BB vs. AA	BC	12	4531	5740	0.653	0.016	0.960	1.706 (1.066–2.731)	1.735 (1.106–2.722)
	BB vs. AA	PCa	8	2749	2837	0.198	0.019	1.000	1.357 (0.918–2.006)	1.415 (1.060–1.890)
	BB vs. BA + AA	Overall	20	7280	8577	0.673	0.002	0.120	1.443 (1.134–1.837)	1.461 (1.155–1.850)
	BB vs. BA + AA	Asian	8	1867	2034	0.212	0.001	0.060	1.570 (1.108–2.226)	1.583 (1.210–2.071)
	BB vs. BA + AA	Caucasian	9	4270	5246	0.910	0.321	1.000	1.335 (0.723–2.467)	1.355 (0.743–2.470)
	BB vs. BA + AA	Mixed	2	1124	1248	0.851	0.489	1.000	0.712 (0.274–1.850)	0.714 (0.274–1.857)
	BB vs. BA + AA	H-B	16	6678	6818	0.781	0.002	0.120	1.509 (1.150–1.980)	1.534 (1.176–2.001)
	BB vs. BA + AA	P-B	4	602	1759	0.195	0.453	1.000	1.615 (0.683–3.820)	1.217 (0.729–2.032)
	BB vs. BA + AA	BC	12	4531	5740	0.758	0.017	1.000	1.660 (1.061–2.598)	1.688 (1.097–2.598)
	BB vs. BA + AA	PCa	8	2749	2837	0.356	0.027	1.000	1.340 (0.977–1.838)	1.374 (1.037–1.821)
XRCC1-rs915927	B vs. A	Overall	5	2330	3254	0.170	0.895	1.000	1.028 (0.915–1.154)	1.005 (0.927–1.090)
	B vs. A	Caucasian	4	2185	3175	0.094	0.584	1.000	1.038 (0.908–1.188)	1.007 (0.927–1.094)
	B vs. A	H-B	4	2206	2161	0.097	0.675	1.000	1.031 (0.893–1.191)	1.001 (0.920–1.090)
	B vs. A	Y	4	2206	2161	0.097	0.675	1.000	1.031 (0.893–1.191)	1.001 (0.920–1.090)
	B vs. A	BC	3	925	1928	0.108	0.254	1.000	1.093 (0.904–1.322)	1.074 (0.950–1.214)
	B vs. A	PCa	2	1405	1326	0.926	0.408	1.000	0.956 (0.858–1.064)	0.956 (0.858–1.064)
	BA vs. AA	Overall	5	2330	3254	0.133	0.897	1.000	1.019 (0.823–1.261)	1.010 (0.874–1.165)
	BA vs. AA	Caucasian	4	2185	3175	0.198	0.676	1.000	1.054 (0.869–1.280)	1.032 (0.891–1.194)
	BA vs. AA	H-B	4	2206	2161	0.070	0.878	1.000	1.021 (0.785–1.327)	1.011 (0.870–1.175)
	BA vs. AA	Y	4	2206	2161	0.070	0.878	1.000	1.021 (0.785–1.327)	1.011 (0.870–1.175)

Table 3 (*continued*)

SNP	Comparison	Subgroup	N	Cases	Controls	P_H	P_Z	P_A	Random	Fixed
	BA vs. AA	BC	3	925	1928	0.223	0.236	1.000	1.139 (0.882–1.471)	1.129 (0.924–1.379)
	BA vs. AA	PCa	2	1405	1326	0.201	0.298	1.000	0.819 (0.520–1.288)	0.896 (0.729–1.102)
	BA + BB vs. AA	Overall	5	2330	3254	0.104	0.853	1.000	1.032 (0.836–1.273)	1.013 (0.885–1.160)
	BA + BB vs. AA	Caucasian	4	2185	3175	0.099	0.561	1.000	1.066 (0.860–1.320)	1.029 (0.897–1.181)
	BA + BB vs. AA	H-B	4	2206	2161	0.053	0.810	1.000	1.032 (0.797–1.336)	1.011 (0.878–1.166)
	BA + BB vs. AA	Y	4	2206	2161	0.053	0.810	1.000	1.032 (0.797–1.336)	1.011 (0.878–1.166)
	BA + BB vs. AA	BC	3	925	1928	0.128	0.194	1.000	1.152 (0.867–1.530)	1.133 (0.938–1.367)
	BA + BB vs. AA	PCa	2	1405	1326	0.378	0.277	1.000	0.898 (0.739–1.093)	0.897 (0.738–1.091)
	BB vs. AA	Overall	5	2330	3254	0.238	0.913	1.000	1.017 (0.822–1.258)	0.991 (0.841–1.168)
	BB vs. AA	Caucasian	4	2185	3175	0.158	0.992	1.000	1.045 (0.820–1.332)	1.001 (0.846–1.184)
	BB vs. AA	H-B	4	2206	2161	0.145	0.831	1.000	1.018 (0.779–1.331)	0.981 (0.825–1.167)
	BB vs. AA	Y	4	2206	2161	0.145	0.831	1.000	1.018 (0.779–1.331)	0.981 (0.825–1.167)
	BB vs. AA	BC	3	925	1928	0.167	0.348	1.000	1.153 (0.821–1.618)	1.125 (0.880–1.439)
	BB vs. AA	PCa	2	1405	1326	0.743	0.322	1.000	0.895 (0.717–1.116)	0.895 (0.717–1.116)
	BB vs. BA + AA	Overall	5	2330	3254	0.596	0.974	1.000	1.002 (0.882–1.138)	1.002 (0.882–1.139)
	BB vs. BA + AA	Caucasian	4	2185	3175	0.517	0.897	1.000	0.991 (0.870–1.130)	0.991 (0.870–1.130)
	BB vs. BA + AA	H-B	4	2206	2161	0.457	0.919	1.000	0.993 (0.868–1.136)	0.993 (0.868–1.136)
	BB vs. BA + AA	Y	4	2206	2161	0.457	0.919	1.000	0.993 (0.868–1.136)	0.993 (0.868–1.136)
	BB vs. BA + AA	BC	3	925	1928	0.422	0.617	1.000	1.055 (0.855–1.302)	1.055 (0.855–1.302)
	BB vs. BA + AA	PCa	2	1405	1326	0.408	0.734	1.000	0.972 (0.828–1.142)	0.973 (0.828–1.142)
XRCC1-rs3213245	B vs. A	Overall	3	1066	1120	0.835	0.504	1.000	0.954 (0.830–1.096)	0.954 (0.830–1.096)
	B vs. A	Asian	2	536	564	0.891	0.388	1.000	0.899 (0.706–1.145)	0.899 (0.706–1.145)
	B vs. A	P-B	2	536	564	0.891	0.388	1.000	0.899 (0.706–1.145)	0.899 (0.706–1.145)
	BA vs. AA	Overall	3	1066	1120	0.537	0.212	1.000	0.873 (0.705–1.081)	0.873 (0.705–1.081)
	BA vs. AA	Asian	2	536	564	0.973	0.095	1.000	0.789 (0.597–1.042)	0.789 (0.597–1.042)
	BA vs. AA	P-B	2	536	564	0.973	0.095	1.000	0.789 (0.597–1.042)	0.789 (0.597–1.042)
	BA + BB vs. AA	Overall	3	1066	1120	0.697	0.297	1.000	0.897 (0.730–1.101)	0.896 (0.730–1.101)
	BA + BB vs. AA	Asian	2	536	564	0.916	0.180	1.000	0.831 (0.635–1.089)	0.831 (0.635–1.089)
	BA + BB vs. AA	P-B	2	536	564	0.916	0.180	1.000	0.831 (0.635–1.089)	0.831 (0.635–1.089)
	BB vs. AA	Overall	3	1066	1120	0.555	0.795	1.000	1.042 (0.749–1.449)	1.045 (0.752–1.451)
	BB vs. AA	Asian	2	536	564	0.752	0.288	1.000	1.617 (0.661–3.955)	1.622 (0.664–3.958)
	BB vs. AA	P-B	2	536	564	0.752	0.288	1.000	1.617 (0.661–3.955)	1.622 (0.664–3.958)
	BB vs. BA + AA	Overall	3	1066	1120	0.454	0.946	1.000	1.006 (0.789–1.283)	1.008 (0.791–1.285)
	BB vs. BA + AA	Asian	2	536	564	0.743	0.234	1.000	1.711 (0.702–4.172)	1.715 (0.705–4.175)
	BB vs. BA + AA	P-B	2	536	564	0.743	0.234	1.000	1.711 (0.702–4.172)	1.715 (0.705–4.175)
XRCC2-rs3218536	B vs. A	Overall	3	1395	1454	0.815	0.524	1.000	0.943 (0.788–1.130)	0.943 (0.787–1.130)
	B vs. A	BC	2	1294	1238	0.856	0.446	1.000	0.930 (0.773–1.120)	0.930 (0.773–1.120)
	BA vs. AA	Overall	3	1395	1454	0.798	0.925	1.000	1.010 (0.828–1.230)	1.010 (0.828–1.230)
	BA vs. AA	BC	2	1294	1238	0.615	0.984	1.000	0.998 (0.813–1.224)	0.998 (0.814–1.224)
	BA + BB vs. AA	Overall	3	1395	1454	0.815	0.796	1.000	0.975 (0.803–1.184)	0.975 (0.803–1.184)
	BA + BB vs. AA	BC	2	1294	1238	0.728	0.703	1.000	0.962 (0.787–1.175)	0.962 (0.787–1.175)
	BB vs. AA	Overall	3	1395	1454	0.552	0.116	1.000	0.510 (0.216–1.203)	0.507 (0.217–1.183)
	BB vs. AA	BC	2	1294	1238	0.851	0.073	1.000	0.438 (0.178–1.079)	0.438 (0.178–1.080)
	BB vs. BA + AA	Overall	3	1395	1454	0.556	0.115	1.000	0.509 (0.216–1.199)	0.506 (0.217–1.180)
	BB vs. BA + AA	BC	2	1294	1238	0.835	0.073	1.000	0.438 (0.178–1.078)	0.438 (0.178–1.079)
XRCC3-rs861539	B vs. A	Overall	23	5979	7382	0.000	0.914	1.000	0.994 (0.890–1.110)	1.044 (0.988–1.102)
	B vs. A	Asian	6	1181	1326	0.314	0.265	1.000	1.102 (0.916–1.326)	1.099 (0.931–1.297)
	B vs. A	Caucasian	13	3287	4308	0.000	0.326	1.000	0.914 (0.765–1.093)	1.031 (0.961–1.106)
	B vs. A	Mixed	4	1511	1748	0.463	0.351	1.000	1.049 (0.948–1.161)	1.049 (0.948–1.161)
	B vs. A	H-B	19	4589	4613	0.000	0.807	1.000	0.983 (0.855–1.130)	1.051 (0.986–1.121)
	B vs. A	P-B	4	1390	2769	0.801	0.643	1.000	1.025 (0.924–1.137)	1.025 (0.924–1.137)
	B vs. A	N	6	567	673	0.000	0.094	1.000	0.637 (0.376–1.081)	0.788 (0.663–0.936)
	B vs. A	Y	17	5412	6709	0.301	0.011	0.660	1.076 (1.007–1.150)	1.077 (1.017–1.141)
	B vs. A	BC	17	5153	6282	0.000	0.918	1.000	1.007 (0.884–1.146)	1.056 (0.997–1.119)
	B vs. A	PCa	6	826	1100	0.277	0.534	1.000	0.945 (0.784–1.139)	0.950 (0.807–1.117)
	BA vs. AA	Overall	23	5979	7382	0.005	0.823	1.000	1.014 (0.894–1.151)	1.031 (0.952–1.116)
	BA vs. AA	Asian	6	1181	1326	0.392	0.830	1.000	1.020 (0.830–1.253)	1.022 (0.837–1.249)
	BA vs. AA	Caucasian	13	3287	4308	0.031	0.304	1.000	1.093 (0.922–1.296)	1.108 (0.997–1.232)
	BA vs. AA	Mixed	4	1511	1748	0.021	0.244	1.000	0.815 (0.577–1.150)	0.896 (0.772–1.040)
	BA vs. AA	H-B	19	4589	4613	0.002	0.764	1.000	1.024 (0.876–1.198)	1.064 (0.970–1.167)
	BA vs. AA	P-B	4	1390	2769	0.882	0.473	1.000	0.945 (0.811–1.102)	0.945 (0.811–1.102)
	BA vs. AA	N	6	567	673	0.001	0.686	1.000	0.880 (0.473–1.637)	0.878 (0.676–1.141)
	BA vs. AA	Y	17	5412	6709	0.226	0.273	1.000	1.046 (0.947–1.156)	1.048 (0.964–1.138)
	BA vs. AA	BC	17	5153	6282	0.029	0.271	1.000	1.076 (0.944–1.227)	1.065 (0.978–1.160)
	BA vs. AA	PCa	6	826	1100	0.068	0.184	1.000	0.808 (0.590–1.106)	0.839 (0.678–1.039)
	BA + BB vs. AA	Overall	23	5979	7382	0.000	0.997	1.000	1.000 (0.873–1.145)	1.041 (0.966–1.122)
	BA + BB vs. AA	Asian	6	1181	1326	0.412	0.508	1.000	1.065 (0.878–1.292)	1.067 (0.881–1.292)
	BA + BB vs. AA	Caucasian	13	3287	4308	0.000	0.906	1.000	0.987 (0.796–1.224)	1.075 (0.974–1.186)
	BA + BB vs. AA	Mixed	4	1511	1748	0.061	0.492	1.000	0.905 (0.681–1.203)	0.963 (0.837–1.109)
	BA + BB vs. AA	H-B	19	4589	4613	0.000	0.940	1.000	0.994 (0.838–1.178)	1.063 (0.975–1.160)
	BA + BB vs. AA	P-B	4	1390	2769	0.969	0.808	1.000	0.982 (0.849–1.135)	0.982 (0.849–1.136)
	BA + BB vs. AA	N	6	567	673	0.000	0.173	1.000	0.646 (0.345–1.211)	0.768 (0.609–0.970)
	BA + BB vs. AA	Y	17	5412	6709	0.228	0.061	1.000	1.077 (0.979–1.184)	1.078 (0.997–1.167)
	BA + BB vs. AA	BC	17	5153	6282	0.000	0.535	1.000	1.050 (0.899–1.227)	1.070 (0.987–1.159)
	BA + BB vs. AA	PCa	6	826	1100	0.157	0.203	1.000	0.855 (0.658–1.110)	0.877 (0.716–1.073)

(*continued on next page*)

Table 3 (*continued*)

SNP	Comparison	Subgroup	N	Cases	Controls	P_H	P_Z	P_A	Random	Fixed
	BB vs. AA	Overall	23	5979	7382	0.004	0.479	1.000	1.076 (0.878–1.318)	1.119 (0.995–1.258)
	BB vs. AA	Asian	6	1181	1326	0.527	0.140	1.000	1.397 (0.853–2.289)	1.434 (0.888–2.315)
	BB vs. AA	Caucasian	13	3287	4308	0.000	0.485	1.000	0.900 (0.669–1.210)	1.035 (0.894–1.198)
	BB vs. AA	Mixed	4	1511	1748	0.729	0.035	1.000	1.263 (1.014–1.572)	1.265 (1.016–1.574)
	BB vs. AA	H-B	19	4589	4613	0.002	0.554	1.000	1.079 (0.839–1.387)	1.123 (0.978–1.291)
	BB vs. AA	P-B	4	1390	2769	0.420	0.363	1.000	1.111 (0.890–1.388)	1.108 (0.888–1.381)
	BB vs. AA	N	6	567	673	0.000	0.474	1.000	0.728 (0.306–1.733)	0.751 (0.535–1.056)
	BB vs. AA	Y	17	5412	6709	0.617	0.009	0.540	1.181 (1.041–1.341)	1.182 (1.043–1.340)
	BB vs. AA	BC	17	5153	6282	0.002	0.710	1.000	1.044 (0.833–1.307)	1.117 (0.988–1.264)
	BB vs. AA	PCa	6	826	1100	0.201	0.535	1.000	1.264 (0.743–2.151)	1.135 (0.762–1.690)
	BB vs. BA + AA	Overall	23	5979	7382	0.004	0.641	1.000	1.046 (0.867–1.261)	1.087 (0.976–1.212)
	BB vs. BA + AA	Asian	6	1181	1326	0.505	0.126	1.000	1.407 (0.863–2.295)	1.447 (0.901–2.324)
	BB vs. BA + AA	Caucasian	13	3287	4308	0.002	0.294	1.000	0.875 (0.683–1.122)	0.980 (0.857–1.120)
	BB vs. BA + AA	Mixed	4	1511	1748	0.371	0.009	0.540	1.320 (1.053–1.654)	1.308 (1.069–1.600)
	BB vs. BA + AA	H-B	19	4589	4613	0.002	0.711	1.000	1.044 (0.831–1.313)	1.068 (0.939–1.214)
	BB vs. BA + AA	P-B	4	1390	2769	0.289	0.209	1.000	1.081 (0.795–1.470)	1.138 (0.930–1.394)
	BB vs. BA + AA	N	6	567	673	0.000	0.468	1.000	0.743 (0.333–1.658)	0.725 (0.527–0.997)
	BB vs. BA + AA	Y	17	5412	6709	0.724	0.019	1.000	1.147 (1.021–1.288)	1.148 (1.023–1.288)
	BB vs. BA + AA	BC	17	5153	6282	0.006	0.957	1.000	1.005 (0.826–1.224)	1.078 (0.962–1.207)
	BB vs. BA + AA	PCa	6	826	1100	0.075	0.250	1.000	1.437 (0.775–2.665)	1.203 (0.822–1.761)
XRCC3-rs1799796	B vs. A	Overall	5	1302	2391	0.116	0.693	1.000	0.998 (0.845–1.180)	0.977 (0.872–1.095)
	B vs. A	Caucasian	4	1091	2147	0.204	0.335	1.000	0.951 (0.808–1.119)	0.942 (0.834–1.064)
	B vs. A	H-B	3	1120	1147	0.155	0.535	1.000	0.990 (0.818–1.197)	0.960 (0.843–1.092)
	B vs. A	P-B	2	182	1244	0.069	0.893	1.000	0.967 (0.597–1.568)	1.040 (0.819–1.322)
	BA vs. AA	Overall	5	1302	2391	0.396	0.828	1.000	0.984 (0.841–1.151)	0.983 (0.842–1.148)
	BA vs. AA	Caucasian	4	1091	2147	0.992	0.320	1.000	0.918 (0.775–1.087)	0.918 (0.775–1.087)
	BA vs. AA	H-B	3	1120	1147	0.133	0.909	1.000	1.018 (0.786–1.317)	0.990 (0.832–1.178)
	BA vs. AA	P-B	2	182	1244	0.898	0.801	1.000	0.957 (0.682–1.344)	0.957 (0.682–1.344)
	BA + BB vs. AA	Overall	5	1302	2391	0.276	0.780	1.000	0.991 (0.833–1.179)	0.979 (0.845–1.135)
	BA + BB vs. AA	Caucasian	4	1091	2147	0.735	0.308	1.000	0.920 (0.784–1.080)	0.920 (0.784–1.080)
	BA + BB vs. AA	H-B	3	1120	1147	0.118	0.736	1.000	1.006 (0.779–1.299)	0.972 (0.823–1.148)
	BA + BB vs. AA	P-B	2	182	1244	0.372	0.966	1.000	1.006 (0.732–1.383)	1.007 (0.733–1.384)
	BB vs. AA	Overall	5	1302	2391	0.088	0.913	1.000	0.976 (0.627–1.518)	0.927 (0.708–1.214)
	BB vs. AA	Caucasian	4	1091	2147	0.046	0.844	1.000	0.949 (0.565–1.596)	0.917 (0.694–1.210)
	BB vs. AA	H-B	3	1120	1147	0.611	0.329	1.000	0.856 (0.626–1.170)	0.856 (0.626–1.170)
	BB vs. AA	P-B	2	182	1244	0.020	0.824	1.000	0.830 (0.160–4.302)	1.171 (0.694–1.977)
	BB vs. BA + AA	Overall	5	1302	2391	0.082	0.974	1.000	0.993 (0.645–1.529)	0.948 (0.732–1.228)
	BB vs. BA + AA	Caucasian	4	1091	2147	0.040	0.948	1.000	0.983 (0.592–1.634)	0.946 (0.725–1.234)
	BB vs. BA + AA	H-B	3	1120	1147	0.668	0.408	1.000	0.881 (0.653–1.189)	0.881 (0.654–1.189)
	BB vs. BA + AA	P-B	2	182	1244	0.017	0.843	1.000	0.848 (0.167–4.320)	1.175 (0.712–1.939)
XRCC4-rs1805377	B vs. A	Overall	5	2080	2134	0.813	0.005	0.300	0.827 (0.725–0.944)	0.827 (0.725–0.943)
	B vs. A	Asian	2	403	468	0.734	0.238	1.000	0.863 (0.676–1.102)	0.863 (0.676–1.102)
	B vs. A	Caucasian	3	1677	1666	0.524	0.009	0.540	0.812 (0.694–0.951)	0.812 (0.694–0.950)
	B vs. A	BC	3	1351	1403	0.693	0.005	0.300	0.789 (0.668–0.931)	0.789 (0.668–0.931)
	B vs. A	PCa	2	729	731	0.963	0.326	1.000	0.897 (0.721–1.115)	0.897 (0.721–1.115)
	BA vs. AA	Overall	5	2080	2134	0.969	0.949	1.000	1.009 (0.784–1.298)	1.008 (0.784–1.297)
	BA vs. AA	Asian	2	403	468	0.931	0.869	1.000	0.976 (0.730–1.305)	0.976 (0.730–1.305)
	BA vs. AA	Caucasian	3	1677	1666	0.847	0.675	1.000	1.116 (0.672–1.854)	1.114 (0.672–1.847)
	BA vs. AA	BC	3	1351	1403	0.827	0.917	1.000	1.018 (0.734–1.412)	1.017 (0.734–1.411)
	BA vs. AA	PCa	2	729	731	0.693	0.981	1.000	0.995 (0.670–1.478)	0.995 (0.670–1.478)
	BA + BB vs. AA	Overall	5	2080	2134	0.998	0.567	1.000	0.931 (0.729–1.189)	0.931 (0.729–1.189)
	BA + BB vs. AA	Asian	2	403	468	0.921	0.518	1.000	0.911 (0.687–1.208)	0.911 (0.687–1.208)
	BA + BB vs. AA	Caucasian	3	1677	1666	0.989	0.981	1.000	0.994 (0.608–1.626)	0.994 (0.608–1.626)
	BA + BB vs. AA	BC	3	1351	1403	0.975	0.618	1.000	0.922 (0.670–1.269)	0.922 (0.669–1.270)
	BA + BB vs. AA	PCa	2	729	731	0.803	0.766	1.000	0.944 (0.646–1.380)	0.944 (0.646–1.380)
	BB vs. AA	Overall	5	2080	2134	0.376	0.216	1.000	0.799 (0.471–1.357)	0.735 (0.451–1.197)
	BB vs. AA	Asian	2	403	468	0.139	0.050	1.000	0.367 (0.070–1.918)	0.413 (0.171–1.000)
	BB vs. AA	Caucasian	3	1677	1666	0.814	0.984	1.000	0.996 (0.545–1.821)	0.994 (0.544–1.816)
	BB vs. AA	BC	3	1351	1403	0.139	0.211	1.000	0.630 (0.151–2.629)	0.652 (0.333–1.275)
	BB vs. AA	PCa	2	729	731	0.575	0.641	1.000	0.847 (0.414–1.733)	0.844 (0.414–1.721)
	BB vs. BA + AA	Overall	5	2080	2134	0.338	0.001	0.060	0.764 (0.617–0.946)	0.753 (0.635–0.894)
	BB vs. BA + AA	Asian	2	403	468	0.136	0.051	1.000	0.370 (0.070–1.948)	0.418 (0.174–1.006)
	BB vs. BA + AA	Caucasian	3	1677	1666	0.466	0.004	0.240	0.774 (0.650–0.921)	0.773 (0.649–0.921)
	BB vs. BA + AA	BC	3	1351	1403	0.175	0.001	0.060	0.585 (0.181–1.889)	0.706 (0.571–0.872)
	BB vs. BA + AA	PCa	2	729	731	0.676	0.280	1.000	0.853 (0.638–1.140)	0.852 (0.638–1.139)
XRCC4-rs6869366	B vs. A	Overall	4	695	760	0.000	0.590	1.000	1.163 (0.672–2.015)	0.916 (0.758–1.107)
	B vs. A	BC	2	369	402	0.002	0.731	1.000	1.165 (0.488–2.780)	0.987 (0.770–1.265)
	B vs. A	PCa	2	326	358	0.002	0.717	1.000	1.291 (0.324–5.146)	0.828 (0.618–1.108)
	BA vs. AA	Overall	4	695	760	0.000	0.476	1.000	1.253 (0.674–2.328)	1.030 (0.819–1.295)
	BA vs. AA	BC	2	369	402	0.003	0.634	1.000	1.258 (0.490–3.230)	1.120 (0.828–1.514)
	BA vs. AA	PCa	2	326	358	0.002	0.683	1.000	1.345 (0.324–5.585)	0.918 (0.646–1.306)
	BA + BB vs. AA	Overall	4	695	760	0.000	0.553	1.000	1.216 (0.637–2.320)	0.974 (0.778–1.218)
	BA + BB vs. AA	BC	2	369	402	0.002	0.694	1.000	1.222 (0.450–3.318)	1.065 (0.792–1.430)
	BA + BB vs. AA	PCa	2	326	358	0.001	0.726	1.000	1.304 (0.295–5.773)	0.862 (0.611–1.216)
	BB vs. AA	Overall	4	695	760	0.762	0.015	0.900	0.462 (0.244–0.875)	0.458 (0.244–0.861)
	BB vs. AA	BC	2	369	402	0.530	0.118	1.000	0.516 (0.224–1.192)	0.515 (0.224–1.183)

Table 3 (*continued*)

SNP	Comparison	Subgroup	N	Cases	Controls	P_H	P_Z	P_A	Random	Fixed
	BB vs. AA	PCa	2	326	358	0.436	0.060	1.000	0.396 (0.148–1.062)	0.393 (0.149–1.039)
	BB vs. BA + AA	Overall	4	695	760	0.882	0.032	1.000	0.509 (0.271–0.954)	0.505 (0.271–0.942)
	BB vs. BA + AA	BC	2	369	402	0.666	0.159	1.000	0.557 (0.244–1.267)	0.555 (0.245–1.260)
	BB vs. BA + AA	PCa	2	326	358	0.546	0.100	1.000	0.449 (0.169–1.188)	0.445 (0.170–1.166)
XRCC4-rs28360071	B vs. A	Overall	3	561	626	0.148	0.004	0.240	1.359 (1.010–1.829)	1.369 (1.106–1.695)
	B vs. A	BC	2	369	402	0.350	0.206	1.000	1.189 (0.909–1.554)	1.189 (0.909–1.554)
	BA vs. AA	Overall	3	561	626	0.772	0.162	1.000	1.207 (0.927–1.571)	1.207 (0.927–1.571)
	BA vs. AA	BC	2	369	402	0.890	0.458	1.000	1.130 (0.819–1.558)	1.130 (0.819–1.558)
	BA + BB vs. AA	Overall	3	561	626	0.406	0.027	1.000	1.325 (1.032–1.701)	1.325 (1.032–1.700)
	BA + BB vs. AA	BC	2	369	402	0.611	0.295	1.000	1.180 (0.866–1.608)	1.180 (0.866–1.608)
	BB vs. AA	Overall	3	561	626	0.318	0.005	0.300	2.298 (1.169–4.519)	2.358 (1.289–4.312)
	BB vs. AA	BC	2	369	402	0.263	0.234	1.000	1.592 (0.553–4.586)	1.690 (0.712–4.011)
	BB vs. BA + AA	Overall	3	561	626	0.337	0.009	0.540	2.194 (1.146–4.198)	2.230 (1.224–4.061)
	BB vs. BA + AA	BC	2	369	402	0.259	0.262	1.000	1.533 (0.528–4.454)	1.635 (0.692–3.863)
XRCC7-rs7003908	B vs. A	Overall	6	1196	1365	0.000	0.567	1.000	1.133 (0.738–1.741)	1.148 (1.020–1.293)
	B vs. A	BC	3	727	796	0.000	0.978	1.000	1.012 (0.430–2.383)	1.044 (0.894–1.219)
	B vs. A	PCa	2	357	389	0.259	0.003	0.180	1.376 (1.081–1.752)	1.384 (1.119–1.711)
	BA vs. AA	Overall	6	1196	1365	0.004	0.979	1.000	0.996 (0.719–1.379)	0.937 (0.789–1.112)
	BA vs. AA	BC	3	727	796	0.003	0.717	1.000	0.903 (0.520–1.567)	0.822 (0.658–1.026)
	BA vs. AA	PCa	2	357	389	0.725	0.116	1.000	1.295 (0.938–1.789)	1.295 (0.938–1.789)
	BA + BB vs. AA	Overall	6	1196	1365	0.000	0.643	1.000	1.113 (0.708–1.749)	1.021 (0.868–1.199)
	BA + BB vs. AA	BC	3	727	796	0.000	0.994	1.000	1.003 (0.430–2.341)	0.881 (0.715–1.086)
	BA + BB vs. AA	PCa	2	357	389	0.698	0.023	1.000	1.423 (1.049–1.929)	1.423 (1.050–1.929)
	BB vs. AA	Overall	6	1196	1365	0.000	0.677	1.000	1.195 (0.517–2.763)	1.584 (1.219–2.057)
	BB vs. AA	BC	3	727	796	0.000	0.830	1.000	0.809 (0.117–5.612)	1.422 (1.000–2.023)
	BB vs. AA	PCa	2	357	389	0.214	0.007	0.420	1.755 (0.964–3.196)	1.845 (1.178–2.888)
	BB vs. BA + AA	Overall	6	1196	1365	0.000	0.628	1.000	1.180 (0.603–2.308)	1.630 (1.293–2.054)
	BB vs. BA + AA	BC	3	727	796	0.000	0.795	1.000	0.811 (0.166–3.957)	1.570 (1.152–2.140)
	BB vs. BA + AA	PCa	2	357	389	0.165	0.010	0.600	1.537 (0.820–2.879)	1.677 (1.133–2.482)

*P*H: *P* value of Q test for heterogeneity test; P_Z: means statistically significant; *P* (Adjust): Multiple testing *P* value according to Bonferroni correction (*P* value less than 0.05/(12 polymorphisms * 5 models) was considered as statistically significant, which was marked with bold font in the P_A column); PCa: Prostate cancer; BC: Bladder cancer; H-B: hospital-based; P-B: population-based; HWE: Hardy Weinberg equilibrium; **Note:** Heterogeneity was considered to be significant when the P-value was less than 0.1. If there was no significant heterogeneity, a fixed effect model (Der-Simonian Laird) was used to evaluate the point estimates and 95% CI; otherwise, a random effects model (Der-Simonian Laird) was used. And the P_Z was calculated based on the actual model adopted.

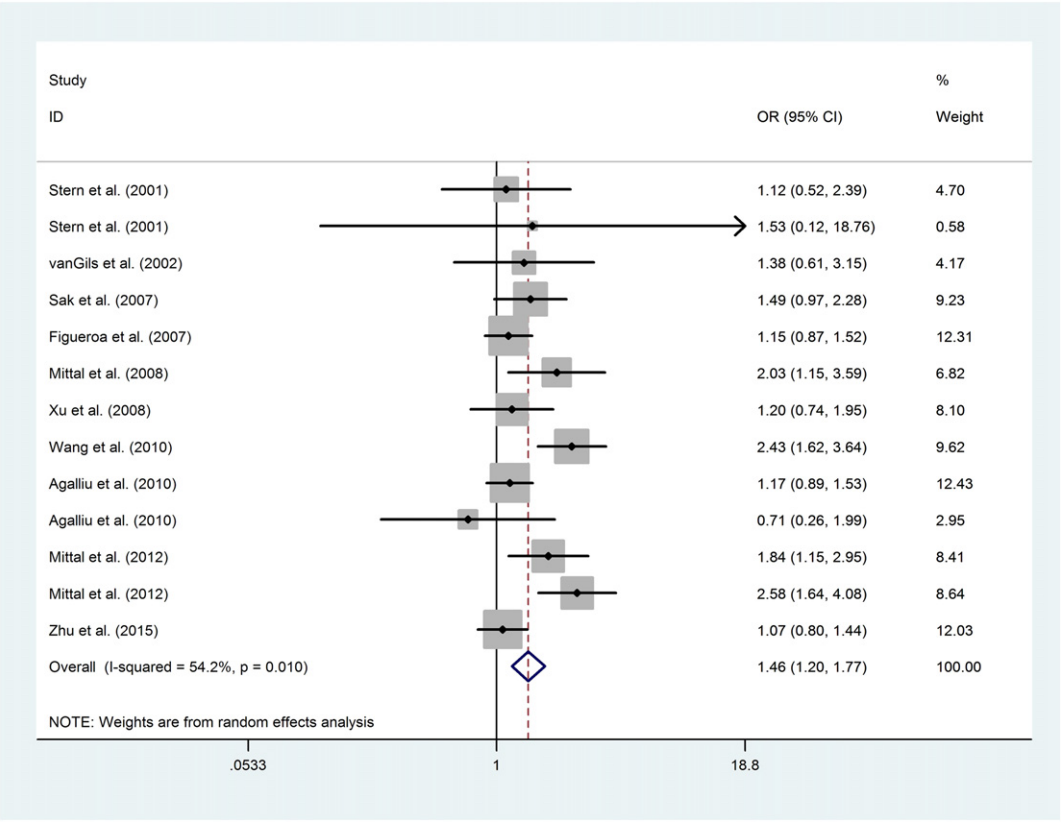

Fig. 1. Forest plots of the association between *XRCC1*-rs25489 polymorphism and the risk of urological neoplasms (BA vs. AA). Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. CI = confidence interval, OR = odds ratio.

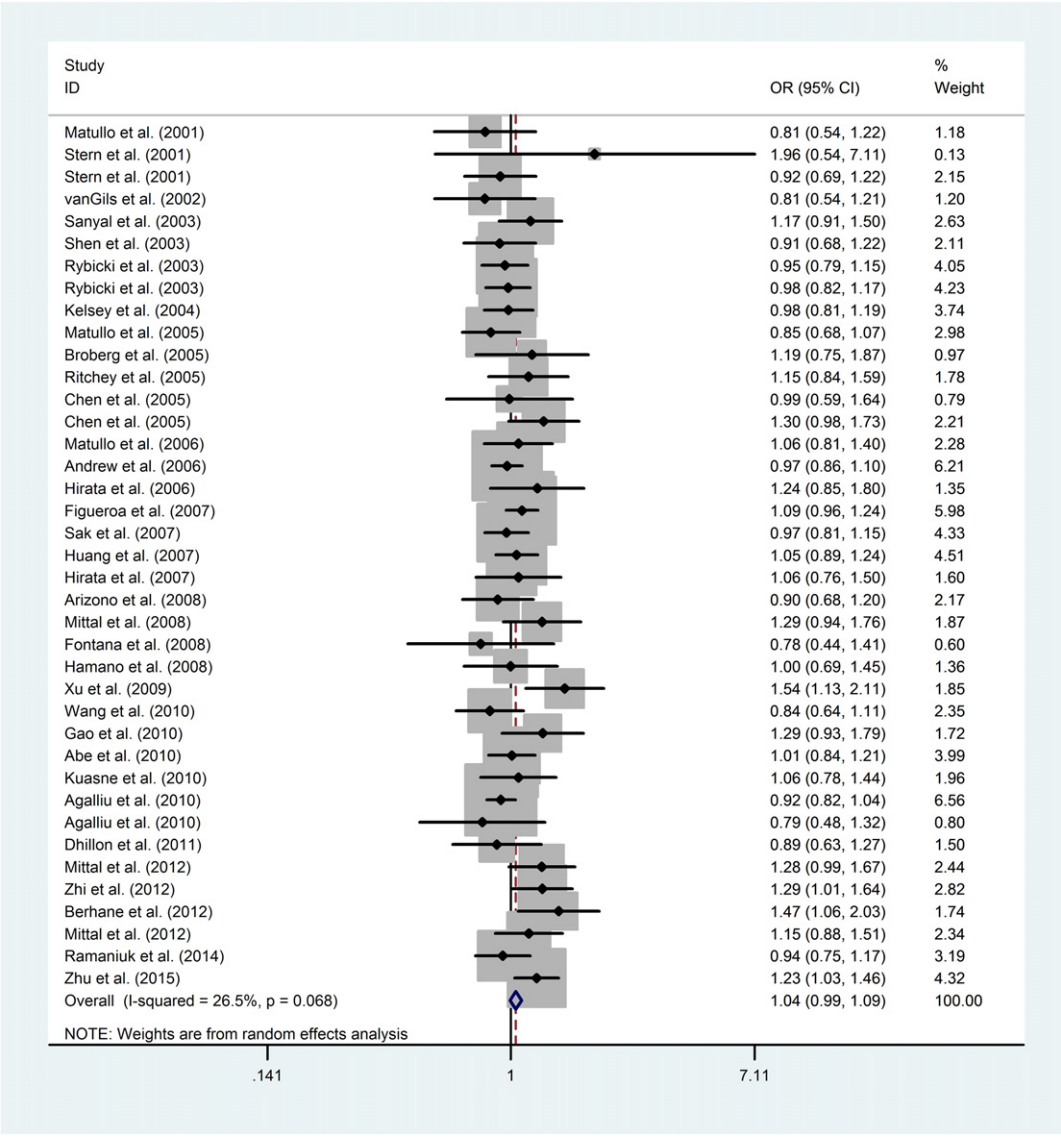

Fig. 2. Forest plots of the association between *XRCC1*-rs25487 polymorphism and the risk of urological neoplasms (B vs. A). Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. CI = confidence interval, OR = odds ratio.

analysis and systematic review for five DNA repair genes (*XRCC1*, *XRCC2*, *XRCC3*, *XRCC4* and *XRCC7*) to examine the association between these polymorphisms and the risk of urological neoplasms. Overall, our findings suggested that *XRCC1*-rs25489 polymorphism was associated with an increased risk of urological neoplasms in heterozygote and dominant models, a result consistent with Mittal et al.'s (2012b) work. However, in the research conducted by Zhu et al. (2014), they did not uncover a significant association between *XRCC1* polymorphisms and urological neoplasms risk. In further subgroup analyses categorized by cancer type, *XRCC1*-rs25489 polymorphism was identified as a risk factor for BC in heterozygote model. In addition, significantly increased risk of urological neoplasms in Asians was also identified for *XRCC1*-rs25487 polymorphism in allelic and homozygote models, while no significant association was revealed for the overall, a result consistent with previous study conducted by Fontana et al. (2008). Furthermore, we also performed LD analysis to find the potential LD association between the two significant risk factors in *XRCC1* (rs25487 and rs25489), however, an extremely lower LD was identified for them in all the four commonly researched populations ($r^2 < 0.10$). Moreover, subgroup analysis based on source of controls suggests a significant association between *XRCC1*-1799782 polymorphism and the risk of urological neoplasms in homozygote model for hospital-based group. The existence of this phenomenon may be due to the inconsistencies in control groups. Although majority of the controls were selected from healthy populations, many individuals may have suffered from other non-cancer diseases. While for other polymorphisms, no significant association was found.

It is worth noting that our data for *XRCC3*-rs861539 was not consistent with several previously published studies. In the study performed by Shen et al. (2003), they found that the *XRCC3* rs861539 variant genotype exhibited a protective effect against BC (OR = 0.63; 95% CI = 0.42–0.93), which was further validated by Narter et al. (2009). On the contrary, Zhu et al. (2012) genotyped a comprehensive case-control studies of 150 BC cases and 150 controls and identified an elevated BC risk among individuals who carry at least one mutated variant allele (OR = 3.22, 95% CI = 1.14–9.11, $P = 0.030$), and similar results was also obtained by Andrew et al. (2007) Moreover, the frequency of *XRCC3*-rs861539 genotype distributions in some of the control groups were departed from HWE and thus we cannot rule out the possibility that such an association occurred as a result of bias. Then, we conducted a subgroup analysis by HWE status, and identified that HWE status did not give rise to the bias of results. In addition, the stability of meta-results was further enhanced by sensitivity analysis.

In the present study, we have put considerable effort on carefully searching for published studies, setting strict criteria for study inclusion. There are some advantages that should be illustrated. Firstly, we have conducted a comprehensive search to identify more eligible studies thus, makes our analysis more persuasive and substantial. Secondly, we assessed quality of enrolled studies by NOS, excluding low quality studies to raise the overall quality. Thirdly, we performed various subgroup analysis by ethnicity, source of controls and so on, in order to provide the sources of heterogeneity and the tumor and/or race markers. Fourthly, results were adjusted according to the recognized formula, ensuring the accuracy of the results. In addition, the stability of these studies was further confirmed by sensitivity analysis, and publication bias was tested by Egger's test and Begg's funnel plot. However, several drawbacks in our study should also be noted. Firstly, for *XRCC1*-rs1799782 polymorphism, relatively heterogeneity existed between some studies, although we conducted this analysis with severe inclusion criteria and explicit extraction for data. Therefore, after stratified analysis by source of control, we observed that the subgroup heterogeneity reduced significantly. It can be assumed that the heterogeneity possibly derived from differenced of ethnicity, source of control, HWE status and cancer type. Secondly, we did not obtain sufficient published studies for several polymorphisms, and some small sample sizes studies may not have enough statistical power to prove authentic associations. Thirdly, all of the studies were published in English, exclusion of studies in other languages may influence effects of polymorphisms tested here. Fourthly, although we want to explore the association between all eligible polymorphisms in *XRCC* genes and the risk of all urological cancers, however, eligible studies were only identified for the three most commonly researched cancer types (PCa, BC and RCC). Follow-up studies will continue to focus on this issue. Last but not least, our unadjusted estimated results were lacking in information for data analysis, which might lead to failure to confirm marginal association. Hence, result presented here should be interpreted with care, and future studies with more covariates are required.

In conclusion, our meta-analysis suggests that *XRCC1*-rs25489 polymorphism is a risk factor for urological neoplasms, particularly for BC. Further studies with larger sample size are needed to validate our findings.

Conflicts of Interests

The authors declare no competing financial interests.

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Author Contributions

M.Z., W.L., Z.H., J.Z., L.Z. and C.L. contributed to the conception and design of the study, or acquisition of data, or analysis and interpretation of data; M.Z., W.L. and L.Z. drafting the article or revising it critically for important intellectual content; C.L. final approval of the version to be submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2017.03.009.

References

Abe, M., Xie, W., Regan, M.M., King, I.B., Stampfer, M.J., Kantoff, P.W., Oh, W.K., Chan, J.M., 2011. Single-nucleotide polymorphisms within the antioxidant defence system and associations with aggressive prostate cancer. BJ. Int. 107, 126–134.

Agalliu, I., Kwon, E.M., Salinas, C.A., Koopmeiners, J.S., Ostrander, E.A., Stanford, J.L., 2010. Genetic variation in DNA repair genes and prostate cancer risk: results from a population-based study. Cancer Causes Control 21, 289–300.

Alli, E., Sharma, V.B., Sunderesakumar, P., Ford, J.M., 2009. Defective repair of oxidative dna damage in triple-negative breast cancer confers sensitivity to inhibition of poly(ADP-ribose) polymerase. Cancer Res. 69, 3589–3596.

Andrew, A.S., Gui, J., Hu, T., Wyszynski, A., Marsit, C.J., Kelsey, K.T., Schned, A.R., Tanyos, S.A., Pendleton, E.M., Ekstrom, R.M., 2015. Genetic polymorphisms modify bladder cancer recurrence and survival in a USA population-based prognostic study. BJ. Int. 115, 238–247.

Andrew, A.S., Karagas, M.R., Nelson, H.H., Guarrera, S., Polidoro, S., Gamberini, S., Sacerdote, C., Moore, J.H., Kelsey, K.T., Demidenko, E., 2007. DNA Repair Polymorphisms Modify Bladder Cancer Risk: A Multi-factor Analytic Strategy. Hum. Hered. 65, 105–118.

Andrew, A.S., Nelson, H.H., Kelsey, K.T., Moore, J.H., Meng, A.C., Casella, D.P., Tosteson, T.D., Schned, A.R., Karagas, M.R., 2006. Concordance of multiple analytical approaches demonstrates a complex relationship between DNA repair gene SNPs, smoking and bladder cancer susceptibility. Carcinogenesis 27, 1030–1037.

Arizono, K., Osada, Y., Kuroda, Y., 2008. DNA repair gene hOGG1 Codon 326 and XRCC1 Codon 399 polymorphisms and bladder cancer risk in a Japanese population. Jpn. J. Clin. Oncol. 38, 186–191.

Begg, C.B., Mazumdar, M., 1995. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Berhane, N., Sobti, R.C., Mahdi, S.A., 2012. DNA repair genes polymorphism (XPG and XRCC1) and association of prostate cancer in a north Indian population. Mol. Biol. Rep. 39, 2471–2479.

Bonferroni, C.E., 1935. Teoria Statistica Delle Classi e Calcolo Delle Probabilità. Comm. Firenze 216–218.

Broberg, K., Björk, J., Paulsson, K., Höglund, M., Albin, M., 2005. Constitutional short telomeres are strong genetic susceptibility markers for bladder cancer. Carcinogenesis 26, 1263–1271.

Chang, C.H., Chang, C.L., Tsai, C.W., Wu, H.C., Chiu, C.F., Wang, R.F., Liu, C.S., Lin, C.C., Bau, D.T., 2009. Significant association of an XRCC4 single nucleotide polymorphism with bladder cancer susceptibility in Taiwan. Anticancer Res. 29, 1777–1782.

Chang, C.H., Chiu, C.F., Wu, H.C., Tseng, H.C., Wang, C.H., Lin, C.C., Tsai, C.W., Liang, S.Y., Wang, C.L., Bau, D.T., 2008. Significant association of XRCC4 single nucleotide polymorphisms with prostate cancer susceptibility in Taiwanese males. Mol. Med. Rep. 1, 525–530.

Davey Smith, G., Egger, M., 1997. Meta-analyses of randomised controlled trials. Lancet 350 (9085), 1182 (PubMed PMID: 9343537).

Dhillon, V.S., Yeoh, E., Fenech, M., 2009. DNA repair gene polymorphisms and prostate cancer risk in South Australia—results of a pilot study. Urol. Oncol. 29, 641–646.

Dizdaroglu, M., 2015. Oxidatively induced DNA damage and its repair in cancer. Mutat. Res. Rev. Mutat. Res. 763, 212–245.

Figueroa, J.D., Malats, N., Real, F.X., Silverman, D., Kogevinas, M., Chanock, S., Welch, R., Dosemeci, M., Tardón, A., Serra, C., 2007a. Genetic variation in the base excision repair pathway and bladder cancer risk. Hum. Genet. 121, 233–242.

Figueroa, J.D., Malats, N., Rothman, N., Real, F.X., Silverman, D., Kogevinas, M., Chanock, S., Yeager, M., Welch, R., Dosemeci, M., 2007b. Evaluation of genetic variation in the double-strand break repair pathway and bladder cancer risk. Carcinogenesis 28, 1788–1793.

Fontana, L., Bosviel, R., Delort, L., Guy, L., Chalabi, N., Kwiatkowski, F., Satih, S., Rabiau, N., Boiteux, J.P., Chamoux, A., 2008. DNA repair gene ERCC2, XPC, XRCC1, XRCC3 polymorphisms and associations with bladder cancer risk in a French cohort. Anticancer Res. 28, 1853–1856.

Gangwar, R., Ahirwar, D., Mandhani, A., Mittal, R.D., 2009. Do DNA repair genes OGG1, XRCC3 and XRCC7 have an impact on susceptibility to bladder cancer in the North Indian population? Mutat. Res. 680, 56–63.

Hamano, T., Matsui, H., Ohtake, N., Nakata, S., Suzuki, K., 2008. Polymorphisms of DNA repair genes, XRCC1 and XRCC3, and susceptibility to familial prostate cancer in a Japanese population. Asia-Pacific J. Clin. Oncol. 4, 21–26.

Hao, G.Y., Zhang, Y.Y., Zhang, W.D., Yang, M.S., Jia, Q., 2008. Relationship between XRCC3 gene polymorphism and bladder cancer in the Han population. J. Shandong Univ. 46, 612–615.

Hirata, H., Hinoda, Y., Matsuyama, H., Tanaka, Y., Okayama, N., Suehiro, Y., Zhao, H., Urakami, S., Kawamoto, K., Kawakami, T., 2006. Polymorphisms of DNA repair genes are associated with renal cell carcinoma. Biochem. Biophys. Res. Commun. 342, 1058–1062.

Hirata, H., Hinoda, Y., Tanaka, Y., Okayama, N., Suehiro, Y., Kawamoto, K., Kikuno, N., Majid, S., Vejdani, K., Dahiya, R., 2007. Polymorphisms of DNA repair genes are risk factors for prostate cancer. Eur. J. Cancer 43, 231–237.

Hoeijmakers, J.H.J., 2001. Genome maintenance mechanisms for preventing cancer. Nature 411, 366–374.

Huang, M., Dinney, C.P., Lin, X., Lin, J., Grossman, H.B., Wu, X., 2007. High-order interactions among genetic variants in DNA base excision repair pathway genes and smoking in bladder cancer susceptibility. Cancer Epidemiol. Biomark. Prev. 16, 84–91.

Kelsey, K.T., Park, S., Nelson, H.H., Karagas, M.R., 2004. A population-based case-control study of the XRCC1 Arg399Gln polymorphism and susceptibility to bladder cancer. Cancer Epidemiol. Biomark. Prev. 13, 1337–1341.

Kuasne, H., Rodrigues, I.S., Losi-Guembarovski, R., Reis, M.B., Fuganti, P.E., Gregório, E.P., Libos, J.F., Matsuda, H.M., Rodrigues, M.A., Kishima, M.O., 2011. Base excision repair

genes XRCC1 and APEX1 and the risk for prostate cancer. Mol. Biol. Rep. 38, 1585–1591.
Lan, C., Ambrosone, C.B., Lee, J., Sellers, T.A., Pow-Sang, J., Park, J.Y., 2006. Association between polymorphisms in the DNA repair genes XRCC1 and APE1, and the risk of prostate cancer in white and black Americans. J. Urol. 175, 108–112.
Lavender, N.A., Komolafe, O.O., Benford, M., Brock, G., Moore, J.H., Vancleave, T.T., States, J.C., Kittles, R.A., Kidd, L.C.R., 2010. No association between variant DNA repair genes and prostate cancer risk among men of African descent †. Prostate 70, 113–119.
Liesegang, T.J., 2001. Human DNA repair genes. Am J. Ophthalmol. 132, 298.
Luedeke, M., Linnert, C.M., Hofer, M.D., Surowy, H.M., Rinckleb, A.E., Hoegel, J., Kuefer, R., Rubin, M.A., Vogel, W., Maier, C., 2009. Predisposition for TMPRSS2-ERG fusion in prostate cancer by variants in DNA repair genes. Cancer Epidemiol. Biomark. Prev. 18, 3030–3035.
Mandal, R.K., Kapoor, R., Mittal, R.D., 2010. Polymorphic variants of DNA repair gene XRCC3 and XRCC7 and risk of prostate cancer: a study from North Indian population. DNA Cell Biol. 29, 669–674.
Mandal, R.K., Singh, V., Kapoor, R., Mittal, R.D., 2011. Do polymorphisms in XRCC4 influence prostate cancer susceptibility in North Indian population? Biomarkers 16, 236–242.
Mantel, N., Haenszel, W., 1959. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natil Cancer Inst. 22, 719–748.
Matullo, G., 2005. Polymorphisms/haplotypes in DNA repair genes and smoking: a bladder cancer case-control study. Cancer Epidemiol. Biomark. Prev. 14, 2569–2578.
Matullo, G., Dunning, A.M., Guarrera, S., Baynes, C., Polidoro, S., Garte, S., Autrup, H., Malaveille, C., Peluso, M., Airoldi, L., 2006. DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. Carcinogenesis 27, 997–1007.
Matullo, G., Guarrera, S., Carturan, S., Peluso, M., Malaveille, C., Davico, L., Piazza, A., Vineis, P., 2001. DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case-control study. Int. J. Cancer 92, 562–567.
Mittal, R.D., Gangwar, R., Mandal, R.K., Srivastava, P., Ahirwar, D.K., 2012a. Gene variants of XRCC4 and XRCC3 and their association with risk for urothelial bladder cancer. Mol. Biol. Rep. 39, 1667–1675.
Mittal, R.D., Mandal, R.K., Gangwar, R., 2012b. Base excision repair pathway genes polymorphisminprostate and bladder cancer risk in North Indian population. Mech. Ageing Dev. 133 (4), 127–132 (PubMed PMID: 22019847).
Mittal, R.D., Singh, R., Manchanda, P.K., Ahirwar, D., Gangwar, R., Kesarwani, P., Mandhani, A., 2008. XRCC1 codon 399 mutant allele: a risk factor for recurrence of urothelial bladder carcinoma in patients on BCG immunotherapy. Cancer Biol. Ther. 7, 645–650.
Narter, K.F., Ergen, A., Ağaçhan, B., Görmüş, U., Timirci, Ö., Isbir, T., 2009. Bladder Cancer and Polymorphisms of DNA Repair Genes (XRCC1, XRCC3, XPD, XPG, APE1, hOGG1). Anticancer Res. 29, 1389–1393.
Nowacka-Zawisza, M., Wiśnik, E., Wasilewski, A., Skowrońska, M., Forma, E., Bryś, M., Różański, W., Krajewska, W.M., 2015. Polymorphisms of Homologous Recombination RAD51, RAD51B, XRCC2, and XRCC3 Genes and the Risk of Prostate Cancer. Anal. Cell. Pathol. 2015, 2087–2095.
Orlow, I., Park, B.J., Mujumdar, U., Patel, H., Siu-Lau, P., Clas, B.A., Downey, R., Flores, R., Bains, M., Rizk, N., 2008. DNA damage and repair capacity in patients with lung cancer: prediction of multiple primary tumors. J. Clin. Oncol. 26, 3560–3566.
Parkin, D.M., 2008. The global burden of urinary bladder cancer. Scand. J. Urol. 42, 1–9.
Rajaraman, P., Hutchinson, A., Wichner, S., Black, P.M., Fine, H.A., Loeffler, J.S., Selker, R.G., Shapiro, W.R., Rothman, N., Linet, M.S., 2010. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro-Oncology 12, 37–48.
Ramaniuk, V.P., Nikitchenko, N.V., Savina, N.V., Kuzhir, T.D., Rolevich, A.I., Krasny, S.A., Sushinsky, V.E., Goncharova, R.I., 2014. Polymorphism of DNA repair genes OGG1, XRCC1, XPD and ERCC6 in bladder cancer in Belarus. Biomarkers 19, 1–8.
Riha, K., Heacock, M.L., Shippen, D.E., 2006. The role of the nonhomologous end-joining DNA double-strand break repair pathway in telomere biology. Genetics 40, 237–277.
Ritchey, J.D., Huang, W.Y., Chokkalingam, A.P., Gao, Y.T., Deng, J., Levine, P., Stanczyk, F.Z., Hsing, A.W., 2005. Genetic variants of DNA repair genes and prostate cancer: a population-based study. Cancer Epidemiol. Biomark. Prev. 14, 1703–1709.
Rybicki, B.A., Conti, D.V., Moreira, A., Cicek, M., Casey, G., Witte, J.S., 2004. DNA repair gene XRCC1 and XPD polymorphisms and risk of prostate cancer. Cancer Epidemiol. Biomark. Prev. 13, 23–29.
Sak, S.C., Barrett, J.H., Paul, A.B., Bishop, D.T., Kiltie, A.E., 2007. DNA repair gene XRCC1 polymorphisms and bladder cancer risk. BMC Genet. 8, 1–8.
Sanyal, S., Festa, F., Sakano, S., Zhang, Z., Steineck, G., Norming, U., Wijkström, H., Larsson, P., Kumar, R., Hemminki, K., 2004. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis 25, 729–734.
Seagroatt, V., Stratton, I., 1998. Bias in meta-analysis detected by a simple, graphical test. Test had 10% false positive rate. BMJ 315, 629–634.
Shen, M., Hung, R.J., Brennan, P., Malaveille, C., Donato, F., Placidi, D., Carta, A., Hautefeuille, A., Boffetta, P., Porru, S., 2003. Polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, interaction with environmental exposures, and bladder cancer risk in a case-control study in northern Italy. Cancer Epidemiol. Biomark. Prev. 12, 1234–1240.
Spitz, M.R., Wei, Q., Dong, Q., Amos, C.I., Wu, X., 2003. Genetic susceptibility to lung cancer: the role of DNA damage and repair. Cancer Epidemiol. Biomark. Prev. 12, 689–698.
Stern, M.C., Umbach, D.M., Lunn, R.M., Taylor, J.A., 2002. DNA repair gene XRCC3 codon 241 polymorphism, its interaction with smoking and XRCC1 polymorphisms, and bladder cancer risk. Cancer Epidemiol. Biomark. Prev. 11, 939–943.
Stern, M.C., Umbach, D.M., Van Gils, C.H., Lunn, R.M., Taylor, J.A., 2001. DNA repair gene XRCC1 polymorphisms, smoking, and bladder cancer risk. Cancer Epidemiol. Biomark. Prev. 10, 125–131.
Sue, D., Richard, T., 2000. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.
Taylor, R.M., Thistlethwaite, A., Caldecott, K.W., 2002. Central role for the XRCC1 BRCT I domain in mammalian DNA single-strand break repair. Mol. Cell. Biol. 22, 2556–2563.
Van Gils, C.H., Bostick, R.M., Stern, M.C., Taylor, J.A., 2002. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene. Cancer Epidemiol. Biomark. Prev. 11, 1279–1284.
Vispe, S., Yung, T.M., Ritchot, J., Serizawa, H., Satoh, M.S., 2000. A cellular defense pathway regulating transcription through poly(ADP-ribosyl)ation in response to DNA damage. Proc. Natl. Acad. Sci. U. S. A. 97, 185–189.
Wang, M., Qin, C., Zhu, J., Yuan, L., Fu, G., Zhang, Z., Yin, C., 2010. Genetic variants of XRCC1, APE1, and ADPRT genes and risk of bladder cancer. DNA Cell Biol. 29, 303–311.
Wang, S.Y., Peng, L., Li, C.P., Li, A.P., Zhou, J.W., Zhang, Z.D., Liu, Q.Z., 2008. Genetic variants of the XRCC7 gene involved in DNA repair and risk of human bladder cancer. Int. J. Urol. 15, 534–539.
Wells, G.A., Shea, B.J., O'connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2000. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl. Eng. Agric. 18, 727–734.
Wen, H., Ding, Q., Fang, Z.J., Xia, G.W., Fang, J., 2009. Population study of genetic polymorphisms and superficial bladder cancer risk in Han-Chinese smokers in Shanghai. Int. Urol. Nephrol. 41, 855–864.
Wen, H., Feng, C.C., Fang, Z.J., Xia, G.W., Jiang, H.W., Xu, G., Huang, X.D., Ding, Q., 2013. Estudio sobre susceptibilidad de cáncer de vejiga y polimorfismos genéticos de XPC, XPG y CYP en fumadores y no fumadores. Actas Urol. Esp. 37, 259–265.
Wu, X., Gu, J., Grossman, H.B., Amos, C.I., Etzel, C., Huang, M., Zhang, Q., Millikan, R.E., Lerner, S., Dinney, C.P., 2006. Bladder cancer predisposition: a multigenic approach to dna-repair and cell-cycle–control genes. Am. J. Hum. Genet. 78, 464–479.
Xu, Z., Qian, H.L.X., Yang, J., Wang, X.R., Zhang, W., Wu, H.F., 2007. Relationship between XRCC1 polymorphisms and susceptibility to prostate cancer in men from Han, Southern China. Asian J. Androl. 9, 331–338.
Zhi, Y., Yu, J., Liu, Y., Wei, Q., Yuan, F., Zhou, X., Song, B., Chen, Z., Yang, J., 2012. Interaction between polymorphisms of DNA repair genes significantly modulated bladder cancer risk. Int. J. Med. Sci. 9, 498–505.
Zhou, Y.F., Zhang, G.B., Qu, P., Zhou, J., Pan, H.X., Hou, J.Q., 2012. Association between single nucleotide polymorphisms in the XRCC1 gene and susceptibility to prostate cancer in Chinese men. Asian Pac. J. Cancer Prev. 13, 5241–5243.
Zhu, H., Jiu, T., Wang, D., 2014. Impact of polymorphisms of the DNA repair gene XRCC1 and their role in the risk of prostate cancer. Pak. J. Med. Sci. 31.
Zhu, X., Zhong, Z., Zhang, X., Zhao, X., Xu, R., Ren, W., Li, S., 2012. DNA repair gene XRCC3 T241M polymorphism and bladder cancer risk in a Chinese population. Genet. Test. Mol. Biomarkers 16, 640–643.