Polymorphisms in ERCC2 and ERCC5 and Risk of Prostate Cancer: A Meta-Analysis and Systematic Review

Yi Liu[1,2#], Yonghui Hu[3#], Meng Zhang[1,2], Runze Jiang[4*], Chaozhao Liang[1,2*]

[1]Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

[2]Institute of Urology, Anhui Medical University, Hefei, China

[3]Department of Endocrinology, The Second Hospital of Tianjin Medical University, Tianjin, China

[4]Department of Genetic Center, Jiangmen Maternity and Child Health Care Hospital

[*]**Corresponding authors:**

Chaozhao Liang: liang_chaozhao@ahmu.edu.cn (Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China. Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China);

Runze Jiang:solon.jiang@gmail.com (Department of Genetic Center, Jiangmen Maternity and Child Health Care Hospital)

[#]These authors contributed equally to the work.

Supplementary Information

Table S 1. Methodological quality of the included studies according to the Newcastle-Ottawa Scale

Table S 2. Details of the sensitivity analyses for the polymorphisms in ERCC2 and ERCC5 and PCa risk.

Table S 3. P values of the Egger's test for the polymorphisms in ERCCs.

Table S 4. Details of LD analysis for polymorphisms in ERCC2.

Figure S 1. Flow chart of studies selection process for polymorphisms in ERCC2-rs1799793genes.

Figure S 2. Flow chart of studies selection process for polymorphisms in ERCC2-rs238406genes.

Figure S 3. Flow chart of studies selection process for polymorphisms in ERCC2-rs13181genes.

Figure S 4. Flow chart of studies selection process for polymorphisms in ERCC5-rs17655genes.

Figure S 5. Forest plots of the association between ERCC2-rs13181 polymorphism and the risk of prostate cancer (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.

Figure S 6. Forest plots of the association between ERCC2-rs238406 polymorphism and the risk of prostate cancer (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.

Figure S 7. Sensitivity analysis for ERCC2-rs1799793 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

Figure S 8. Sensitivity analysis for ERCC2-rs13181 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

Figure S 9. Sensitivity analysis for ERCC5-rs17655 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

Figure S 10. Sensitivity analysis for ERCC2 rs238406 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

Figure S 11. Begg's funnel plot for publication bias under ERCC2-rs1799793 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall

estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

Figure S 12. Begg's funnel plot for publication bias under ERCC2-rs13181 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

Figure S 13. Begg's funnel plot for publication bias under ERCC5-rs17655 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

Figure S 14. Begg's funnel plot for publication bias under ERCC2-rs238406 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) =

log-transformed OR, OR = odds ratio.

Figure S 15. Linkage disequilibrium plot. The number of each cell represents r2 and white color cells shows no LD between polymorphisms. A. CHB (Han Chinese in Beijing, China); B. JPT (Japanese in Tokyo, Japan); C: CEU (Utah residents with ancestry from northern and western Europe); D: YRI (Yoruba in Ibadan, Nigeria). The "rs" numbers are SNP IDs taken from National Center for Biotechnology Information (NCBI).

Figure S 16. Forest plots of the association between *ERCC2*-rs1799793 polymorphism and the risk of prostate cancer (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.

Table S 1. Methodological quality of the included studies according to the Newcastle-Ottawa Scale

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
Rs1799793									
Rybicki*et al.*	Caucasian	*	*	NA	*	**	*	*	*
	Mixed	*	*	NA	*	**	*	*	*
Bau*et al.*	Asian	*	*	*	*	**	*	*	*
Agalliu *et al.*	Caucasian	*	*	NA	*	**	*	*	*
	African	*	*	NA	*	**	*	*	*
Mandal*et al.*	Asian	*	*	NA	*	**	*	*	*
Lavender*et al.*	Mixed	*	*	NA	NA	**	*	*	*
Dhillon*et al.*	Caucasian	*	*	NA	NA	**	*	*	*

Yeoh*et al.*	Oceania		*	*	NA	*	**	*	*	*
Mirecka*et al.*	Caucasian		*	*	*	*	**	*	*	*
Fachal*et al.*	Caucasian		*	*	NA	*	**	*	*	*
Rs238406										
Zhou*et al.*	Asian		*	*	NA	*	**	*	*	*
Mirecka*et al.*	Caucasian		*	*	*	*	**	*	*	*
Agalliu*et al.*	Caucasian		*	*	NA	*	**	*	*	*
	African		*	*	NA	*	**	*	*	*
Rs13181										
Rybicki*et al.*	Caucasian		*	*	NA	*	**	*	*	*
	Mixed		*	*	NA	*	**	*	*	*
Ritchey*et al.*	Asian		*	*	*	*	**	*	*	*
Bau*et al.*	Asian		*	*	*	*	**	*	*	*
Agalliu*et al.*	Caucasian	*		*	NA	*	**	*	*	*
	African	*		*	NA	*	**	*	*	*
Mandal*et al.*	Asian		*	*	NA	*	**	*	*	*
Gao*et al.*	America		*	*	NA	NA	**	*	*	*
Lavender*et al.*	Mixed		*	*	NA	NA	**	*	*	*
Sobti*et al.*	Asian		*	*	*	*	**	*	*	*
Mirecka*et al.*	Caucasian		*	*	*	*	**	*	*	*
Rs17655										
Hooker	African		*	*	NA	*	**	*	*	*
Berhane	Asian		*	*	*	*	**	*	*	*

Mirecka	Caucasian	*	*	*	*	**	*	*	*

This table identifies 'high' 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.

Table S 2. Details of the sensitivity analyses for the polymorphisms in *ERCC2* and *ERCC*5 and PCa risk.

Polymorphism	Comparison	Study Omitted	Estimate	95%CI	Effect Model
rs1799793	B vs. A	Rybicki *et al.* (2004)	1.276	0.957-1.701	Random
		Rybicki*et al.* (2004)	1.279	0.958-1.707	
		Bau*et al.* (2007)	1.228	0.939-1.608	
		Agalliu*et al.* (2009)	1.311	1.013-1.697	
		Agalliu*et al.* (2009)	1.248	0.959-1.624	
		Mandal*et al.* (2010)	1.237	0.944-1.622	
		Lavender*et al.* (2010)	1.251	0.956-1.639	
		Dhillon*et al.* (2011)	1.290	0.988-1.683	
		Yeoh*et al.* (2011)	1.290	0.988-1.683	
		Mirecka*et al.* (2014)	1.140	0.992-1.309	

	Fachal*et al.* (2012)	1.285	0.987-1.672	
BA vs. AA	Rybicki *et al.* (2004)	1.218	0.970-1.530	Random
	Rybicki*et al.* (2004)	1.224	0.976-1.534	
	Bau*et al.* (2007)	1.139	0.924-1.405	
	Agalliu*et al.* (2009)	1.206	0.944-1.540	
	Agalliu*et al.* (2009)	1.181	0.952-1.465	
	Mandal*et al.* (2010)	1.217	0.978-1.513	
	Lavender*et al.* (2010)	1.187	0.949-1.485	
	Dhillon*et al.* (2011)	1.203	0.967-1.495	
	Yeoh*et al.* (2011)	1.203	0.967-1.495	
	Mirecka*et al.* (2014)	1.052	0.948-1.167	
	Fachal*et al.* (2012)	1.180	0.952-1.462	
BA+BB vs. AA	Rybicki *et al.* (2004)	1.292	0.966-1.728	Random
	Rybicki*et al.* (2004)	1.297	0.970-1.735	
	Bau*et al.* (2007)	1.219	0.928-1.603	
	Agalliu*et al.* (2009)	1.306	0.980-1.740	
	Agalliu*et al.* (2009)	1.256	0.957-1.649	
	Mandal*et al.* (2010)	1.267	0.958-1.677	
	Lavender*et al.* (2010)	1.263	0.953-1.673	
	Dhillon*et al.* (2011)	1.293	0.983-1.701	
	Yeoh*et al.* (2011)	1.293	0.983-1.701	
	Mirecka*et al.* (2014)	1.087	0.970-1.218	
	Fachal*et al.* (2012)	1.271	0.969-1.667	
BB vs. AA	Rybicki *et al.* (2004)	1.657	0.884-3.105	Random
	Rybicki*et al.* (2004)	1.660	0.885-3.116	
	Bau*et al.* (2007)	1.622	0.885-2.975	

		Agalliu*et al.* (2009)	1.839	1.107-3.055	
		Agalliu*et al.* (2009)	1.609	0.912-2.838	
		Mandal*et al.* (2010)	1.557	0.862-2.814	
		Lavender*et al.* (2010)	1.543	0.873-2.727	
		Dhillon*et al.* (2011)	1.727	0.967-3.083	
		Yeoh*et al.* (2011)	1.727	0.967-3.083	
		Mirecka*et al.* (2014)	1.338	0.930-1.925	
		Fachal*et al.* (2012)	1.742	0.984-3.084	
	BB vs. AA + BA	Rybicki *et al.* (2004)	1.537	1.116-1.379	Random
		Rybicki*et al.* (2004)	1.538	1.141-1.436	
		Bau*et al.* (2007)	1.542	1.037-1.327	
		Agalliu*et al.* (2009)	1.733	1.111-1.366	
		Agalliu*et al.* (2009)	1.508	1.133-1.401	
		Mandal*et al.* (2010)	1.440	1.116-1.378	
		Lavender*et al.* (2010)	1.448	1.139-1.407	
		Dhillon*et al.* (2011)	1.606	1.130-1.388	
		Yeoh*et al.* (2011)	1.606	1.124-1.381	
		Mirecka*et al.* (2014)	1.304	1.126-1.380	
		Fachal*et al.* (2012)	1.638	1.102-1.360	
rs238406	B vs. A	Zhou*et al.* (2013)	1.029	0.940-1.127	Fixed
		Mirecka*et al.* (2014)	1.075	0.967-1.195	
		Agalliu*et al.* (2009)	1.061	0.918-1.229	
		Agalliu*et al.* (2009)	0.044	0.955-1.143	
	BA vs. AA	Zhou*et al.* (2013)	1.051	0.905-1.221	Fixed
		Mirecka*et al.* (2014)	1.137	0.960-1.346	
		Agalliu*et al.* (2009)	1.009	0.790-1.289	

		Agalliu*et al.* (2009)	1.076	0.926-1.249	
	BA + BB vs. AA	Zhou*et al.* (2013)	1.054	0.914-1.216	Fixed
		Mirecka*et al.* (2014)	1.140	0.972-1.338	
		Agalliu*et al.* (2009)	1.053	0.831-1.334	
		Agalliu*et al.* (2009)	1.080	0.937-1.245	
	BB vs. AA	Zhou*et al.* (2013)	1.053	0.871-1.274	Fixed
		Mirecka*et al.* (2014)	1.139	0.918-1.413	
		Agalliu*et al.* (2009)	1.151	0.830-1.597	
		Agalliu*et al.* (2009)	1.087	0.903-1.308	
	BB vs. AA + BA	Zhou*et al.* (2013)	1.022	0.870-1.201	Fixed
		Mirecka*et al.* (2014)	1.047	0.869-1.262	
		Agalliu*et al.* (2009)	1.145	0.874-1.500	
		Agalliu*et al.* (2009)	1.042	0.890-1.220	
rs13181	B vs. A	Rybicki*et al.* (2004)	1.001	0.934-1.073	Fixed
		Rybicki*et al.* (2004)	1.004	0.936-1.076	
		Ritchey*et al.* (2005)	1.016	0.951-1.084	
		Bau*et al.* (2007)	1.011	0.947-1.079	
		Agalliu*et al.* (2009)	1.060	0.980-1.146	
		Agalliu*et al.* (2009)	1.013	0.949-1.081	
		Mandal*et al.* (2010)	1.013	0.948-1.082	
		Gao*et al.* (2010)	1.012	0.947-1.082	
		Lavender*et al.* (2010)	1.011	0.946-1.081	
		Sobti*et al.* (2012)	1.007	0.943-1.076	
		Mirecka *et al.* (2014)	1.016	0.944-1.092	
	BA vs. AA	Rybicki*et al.* (2004)	0.961	0.870-1.062	Fixed
		Rybicki*et al.* (2004)	0.966	0.873-1.068	

	Ritchey*et al.* (2005)	0.965	0.878-1.060	
	Bau*et al.* (2007)	0.958	0.872-1.053	
	Agalliu*et al.* (2009)	0.964	0.862-1.077	
	Agalliu*et al.* (2009)	0.961	0.875-1.056	
	Mandal*et al.* (2010)	0.956	0.869-1.052	
	Gao*et al.* (2010)	0.968	0.880-1.065	
	Lavender*et al.* (2010)	0.957	0.869-1.054	
	Sobti*et al.* (2012)	0.958	0.872-1.054	
	Mirecka *et al.* (2014)	0.967	0.872-1.071	
BA+BB vs. AA	Rybicki*et al.* (2004)	0.978	0.890-1.075	Fixed
	Rybicki*et al.* (2004)	0.982	0.893-1.080	
	Ritchey*et al.* (2005)	0.988	0.904-1.081	
	Bau*et al.* (2007)	0.982	0.898-1.073	
	Agalliu*et al.* (2009)	1.013	0.911-1.126	
	Agalliu*et al.* (2009)	0.984	0.900-1.077	
	Mandal*et al.* (2010)	0.981	0.896-1.074	
	Gao*et al.* (2010)	0.988	0.903-1.082	
	Lavender*et al.* (2010)	0.981	0.895-1.075	
	Sobti*et al.* (2012)	0.980	0.895-1.072	
	Mirecka *et al.* (2014)	0.990	0.898-1.091	
BB vs. AA	Rybicki*et al.* (2004)	1.034	0.888-1.204	Fixed
	Rybicki*et al.* (2004)	1.035	0.888-1.205	
	Ritchey*et al.* (2005)	1.072	0.929-1.238	
	Bau*et al.* (2007)	1.070	0.927-1.236	
	Agalliu*et al.* (2009)	1.226	1.028-1.463	
	Agalliu*et al.* (2009)	1.070	0.926-1.237	

		Mandal*et al.* (2010)	1.076	0.929-1.245	
		Gao*et al.* (2010)	1.063	0.918-1.232	
		Lavender*et al.* (2010)	1.070	0.924-1.240	
		Sobti*et al.* (2012)	1.057	0.913-1.223	
		Mirecka *et al.* (2014)	1.084	0.919-1.279	
	BB vs. BA + AA	Rybicki*et al.* (2004)	1.057	0.917-1.218	Fixed
		Rybicki*et al.* (2004)	1.057	0.917-1.218	
		Ritchey*et al.* (2005)	1.095	0.958-1.252	
		Bau*et al.* (2007)	1.094	0.956-1.250	
		Agalliu*et al.* (2009)	1.250	1.061-1.473	
		Agalliu*et al.* (2009)	1.093	0.956-1.251	
		Mandal*et al.* (2010)	1.101	0.961-1.261	
		Gao*et al.* (2010)	1.082	0.943-1.240	
		Lavender*et al.* (2010)	1.094	0.955-1.254	
		Sobti*et al.* (2012)	1.081	0.944-1.239	
		Mirecka *et al.* (2014)	1.102	0.943-1.288	
rs17655	B vs. A	Hooker*et al.* (2008)	1.234	1.049-1.452	Random
		Berhane*et al.* (2011)	1.19	1.034-1.385	
		Mirecka*et al.* (2014)	1.226	1.009-1.489	
	BA vs. AA	Hooker*et al.* (2008)	1.200	0.976-1.476	Fixed
		Berhane*et al.* (2011)	1.203	0.988-1.466	
		Mirecka*et al.* (2014)	1.121	0.830-1.515	
	BA + BB vs. AA	Hooker*et al.* (2008)	1.244	1.020-1.516	Fixed
		Berhane*et al.* (2011)	1.234	1.023-1.489	
		Mirecka*et al.* (2014)	1.224	0.921-1.626	
	BB vs. AA	Hooker*et al.* (2008)	1.613	1.044-2.493	Fixed

	Berhane*et al.* (2011)	1.369	0.970-1.932	
	Mirecka*et al.* (2014)	1.587	1.056-2.385	
BB vs. BA + AA	Hooker*et al.* (2008)	1.535	1.002-2.349	Fixed
	Berhane*et al.* (2011)	1.272	0.928-1.744	
	Mirecka*et al.* (2014)	1.449	1.012-2.075	

B: mutated allele; A: wild allele.

Table S 3. *P* values of the Egger's test for the polymorphisms in *ERCCs*.

Polymorphism	Subgroup	N	Egger's test P>|t|	Trim and Fill Method
rs1799793	Overall	11	0.639	-
	Asian	2	-	-
	Caucasian	5	0.843	-
	Other	4	0.531	-
	H-B	5	**0.036**	Bias Not Existed
	P-B	4	0.622	-
	Other	2	-	-
	N	3	**0.001**	Bias Existed
	Y	8	0.791	-
rs238406	Overall	4	0.202	-
rs13181	Overall	11	0.095	-
	Asian	4	0.975	-

	Caucasian	4	0.304	-
	Other	3	0.462	-
	H-B	3	0.128	-
	P-B	6	0.275	-
	Other	2	-	-
	N	3	0.174	-
	Y	8	0.116	-
rs17655	Overall	3	0.460	-

H-B: hospital-based; P-B: population-based; Y: study conformed to HWE; N: study did not conform to HWE; N: number of studies.

Table S 4. Details of LD analysis for polymorphisms in *ERCC2*.

L1	L2	D'	LOD	r^2	CIlow	CIhi
JPT						
rs13181	rs1799793	0.605	5.77	0.34	0.38	0.77
rs13181	rs238406	1	2.32	0.066	0.42	1
rs1799793	rs238406	1	2.33	0.071	0.42	1
CHB						
rs13181	rs1799793	0.837	17.21	0.503	0.69	0.93
rs13181	rs238406	0.517	1.22	0.026	0.15	0.75
rs1799793	rs238406	1	4.77	0.07	0.67	1
CEU						
rs13181	rs1799793	0.787	17.73	0.619	0.68	0.86
rs13181	rs238406	0.836	8.28	0.331	0.65	0.93
rs1799793	rs238406	1	14.74	0.473	0.89	1
YRI						

rs13181	rs1799793	0.579	2.54	0.13	0.28	0.78

CIlow: Low confident interval; CIhi: High confident interval.

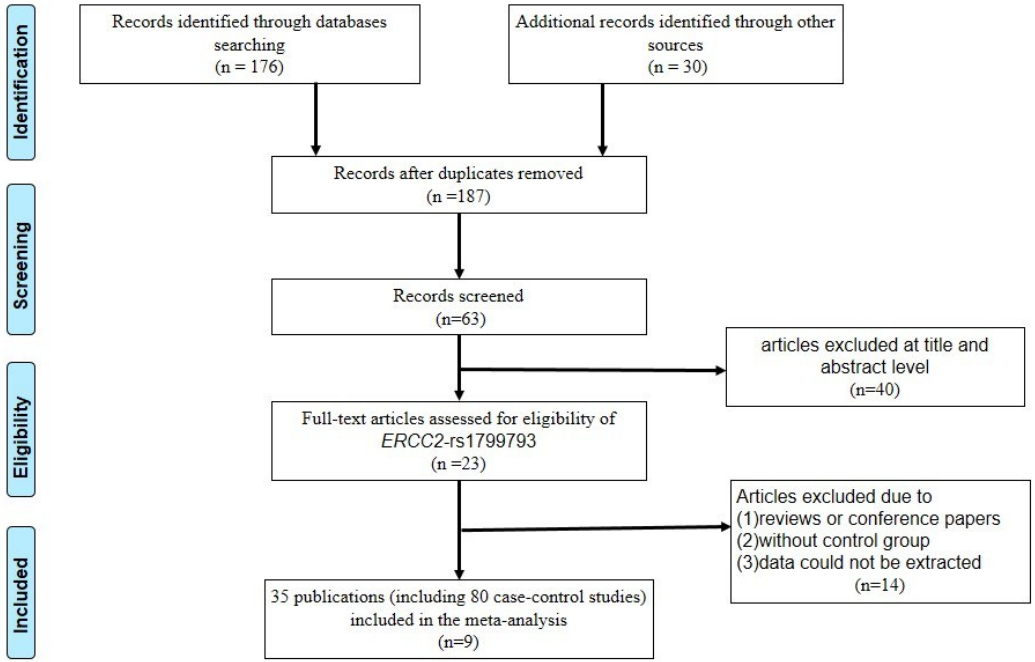

Figure S 1. Flow chart of studies selection process for polymorphisms in *ERCC2*-rs1799793genes.

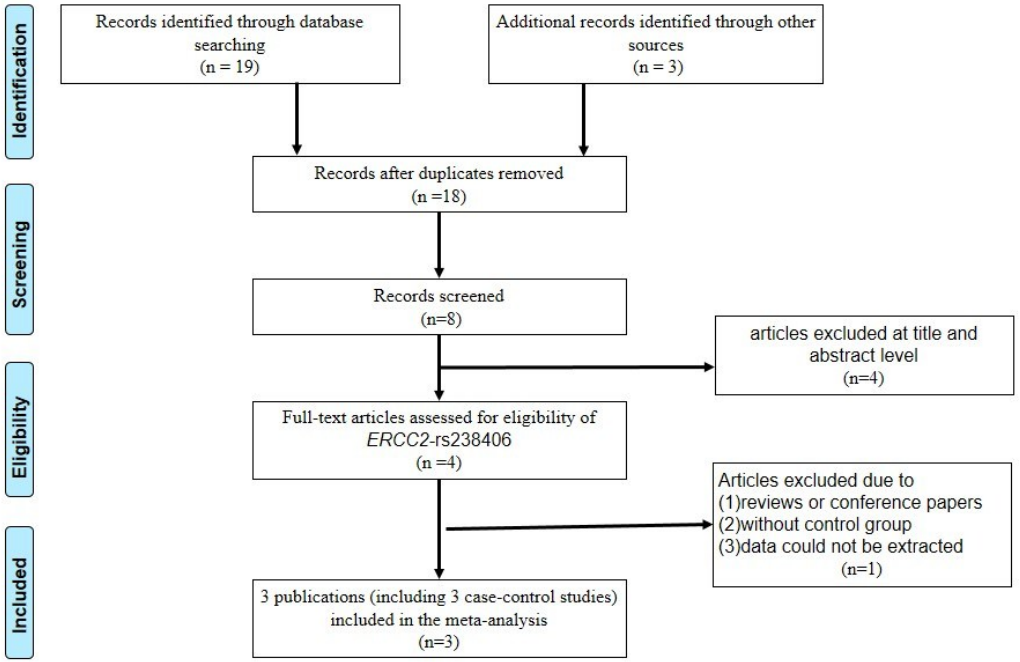

Figure S 2. Flow chart of studies selection process for polymorphisms in *ERCC2*-rs238406genes.

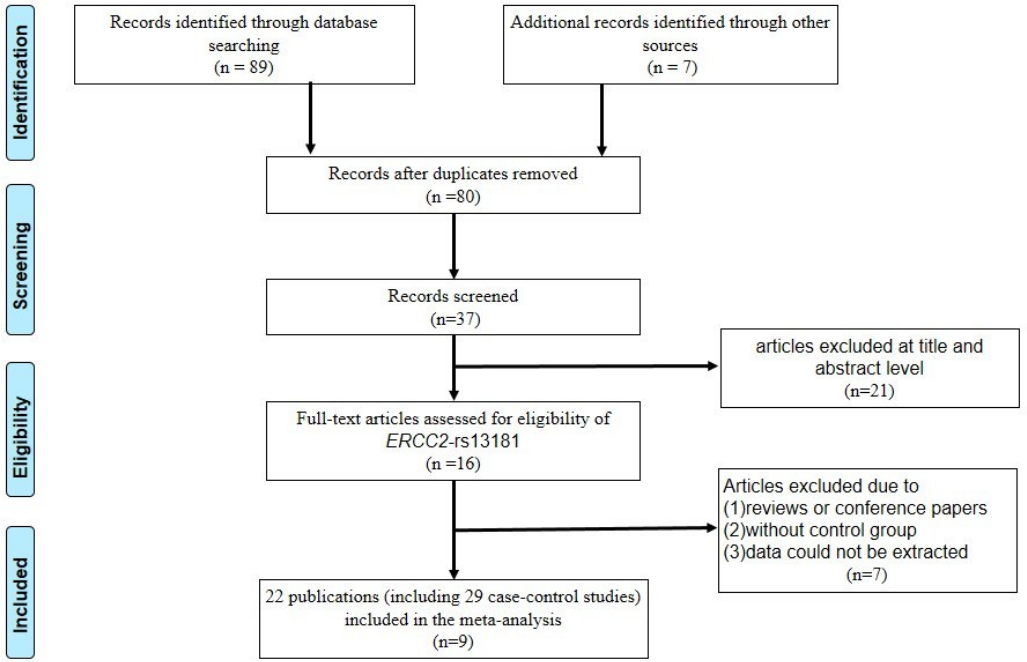

Figure S 3. Flow chart of studies selection process for polymorphisms in *ERCC2*-rs13181genes.

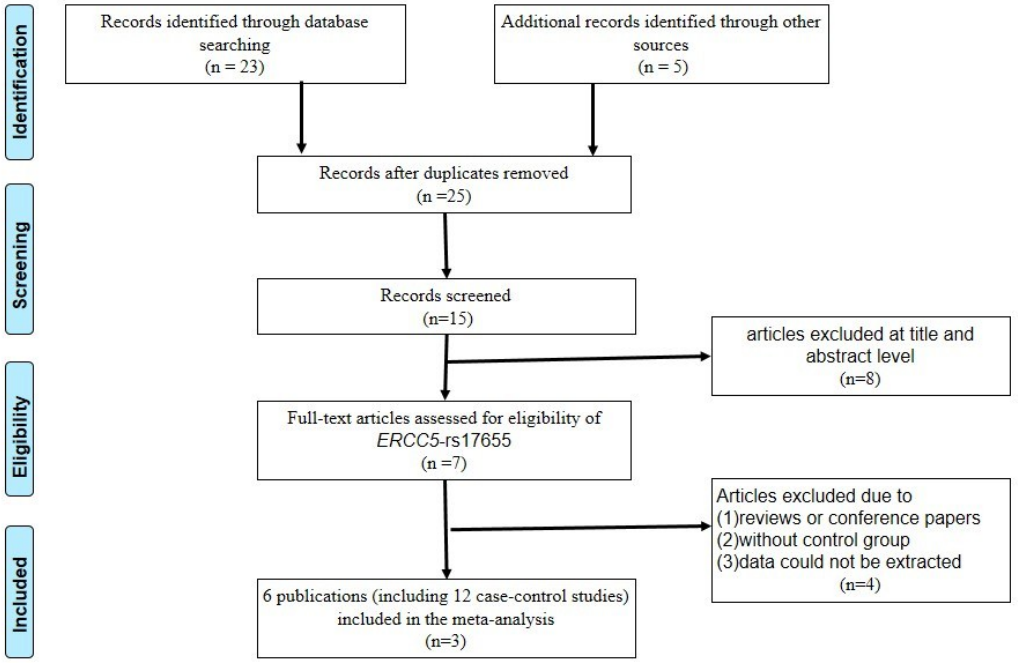

Figure S 4. Flow chart of studies selection process for polymorphisms in *ERCC5*-rs17655

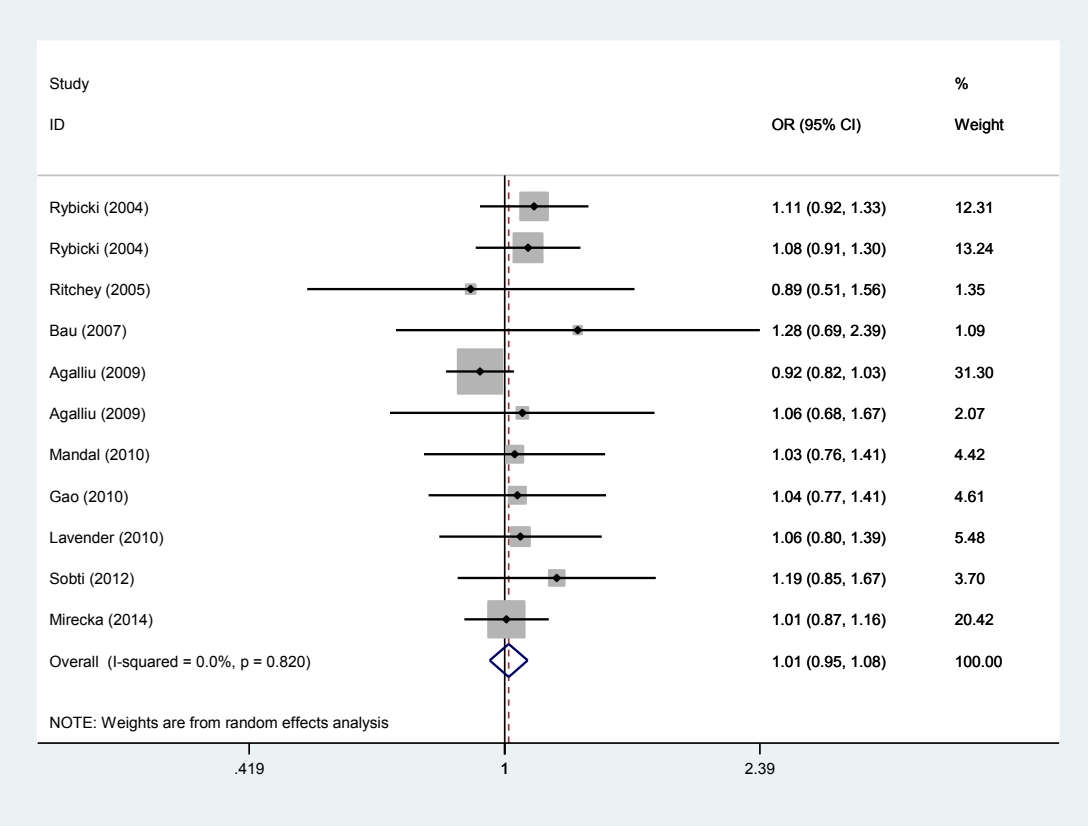

Figure S 5. Forest plots of the association between *ERCC2*-rs13181 polymorphism and the risk of prostate cancer (B vs. A). Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond

represents the summary OR and 95% CI. CI= confidence interval, OR= odds ratio.

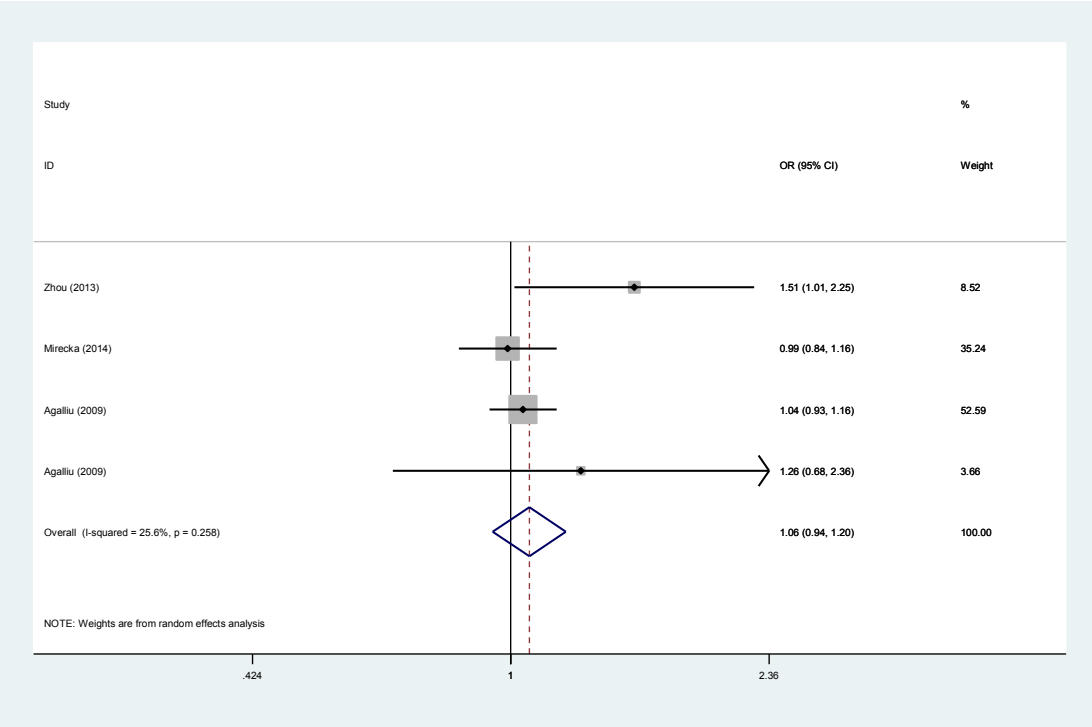

Figure S 6. Forest plots of the association between *ERCC2*-rs238406 polymorphism and the risk of prostate cancer (B vs. A). Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond

represents the summary OR and 95% CI. CI= confidence interval, OR= odds ratio.

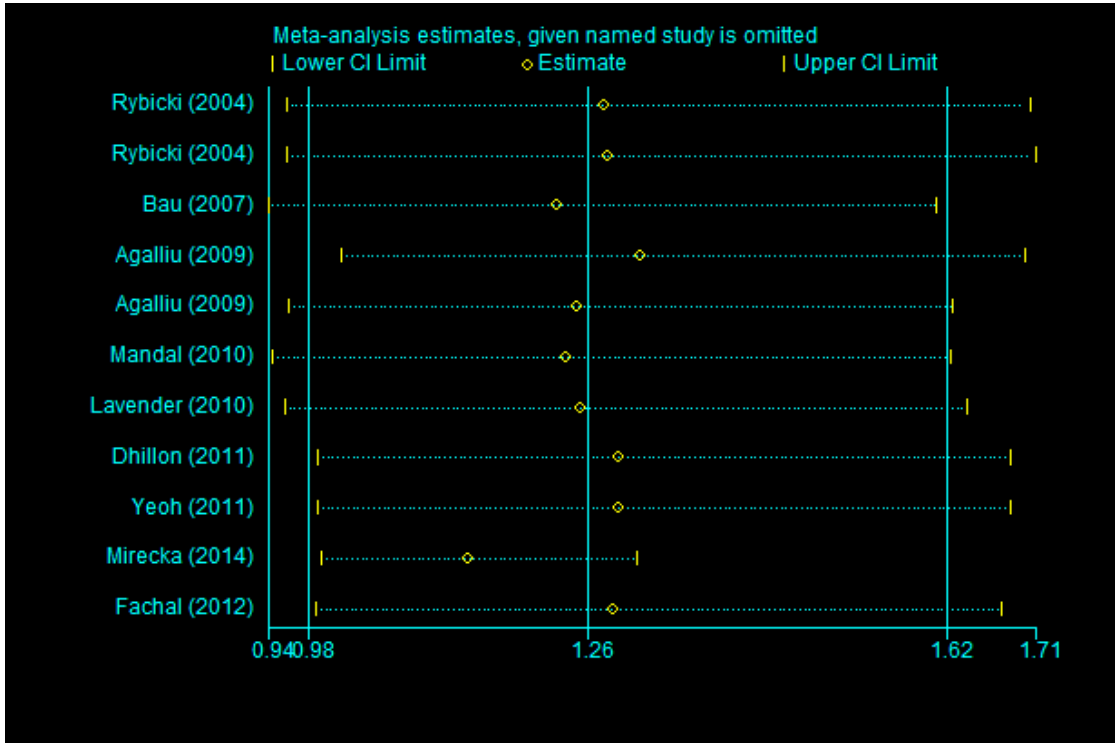

Figure S 7. Sensitivity analysis for *ERCC2*-rs1799793 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

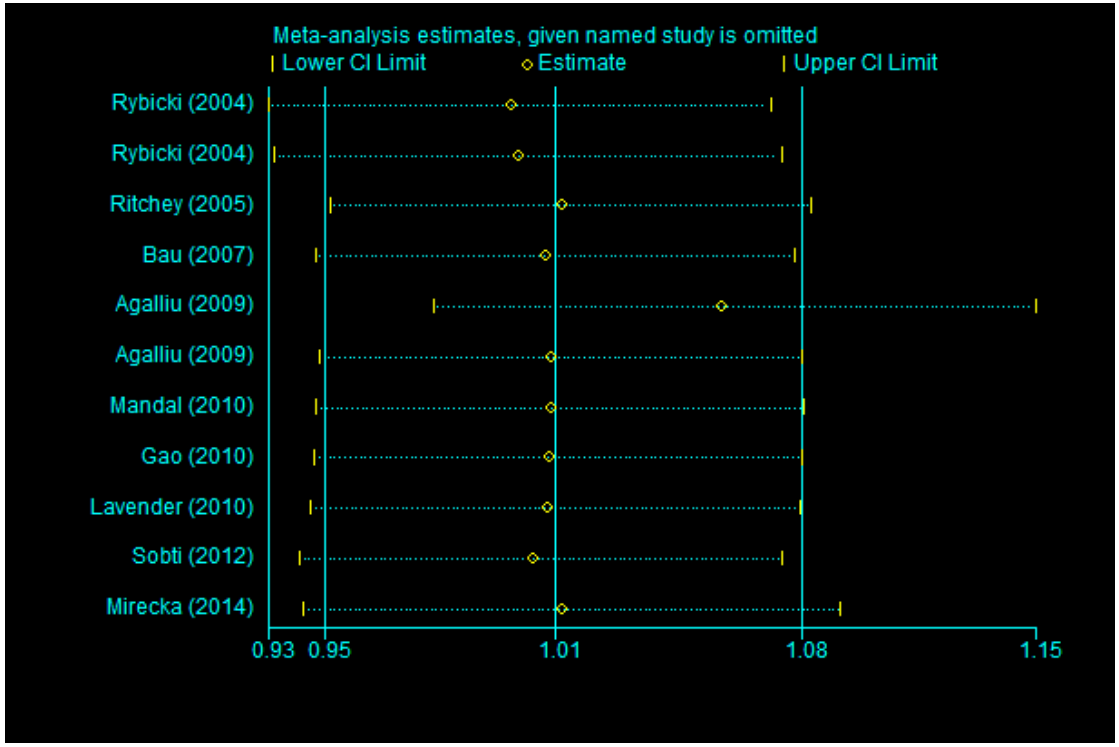

Figure S 8. Sensitivity analysis for *ERCC2*-rs13181 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

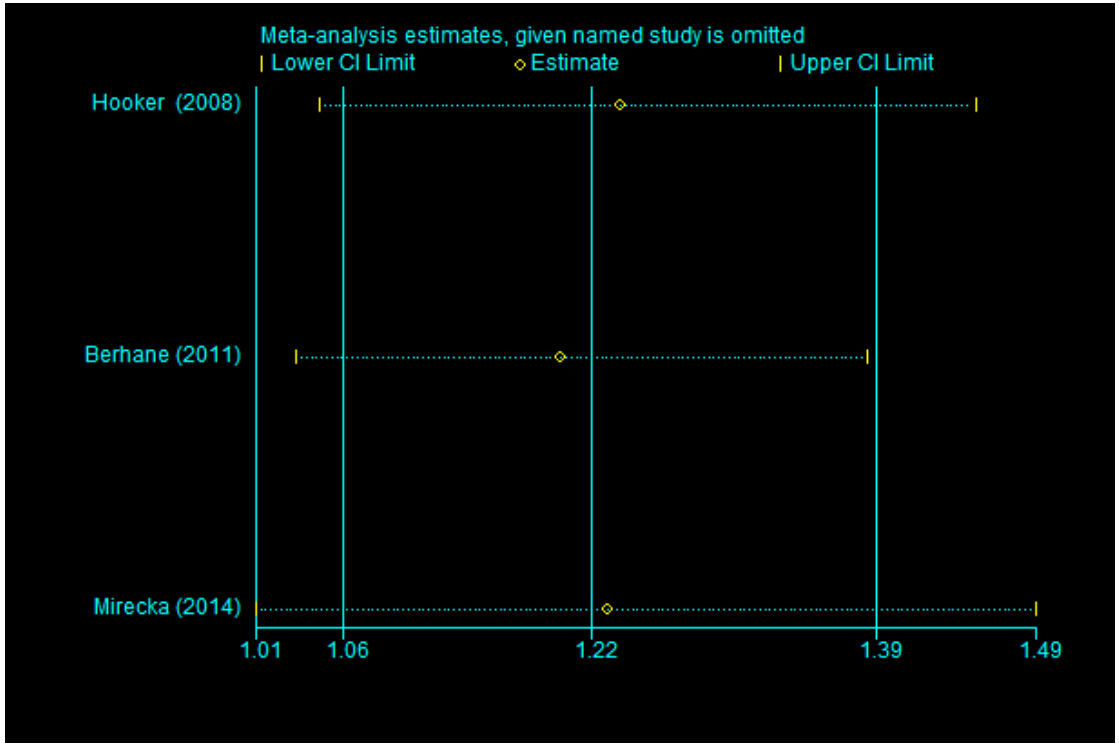

Figure S 9. Sensitivity analysis for *ERCC5*-rs17655 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

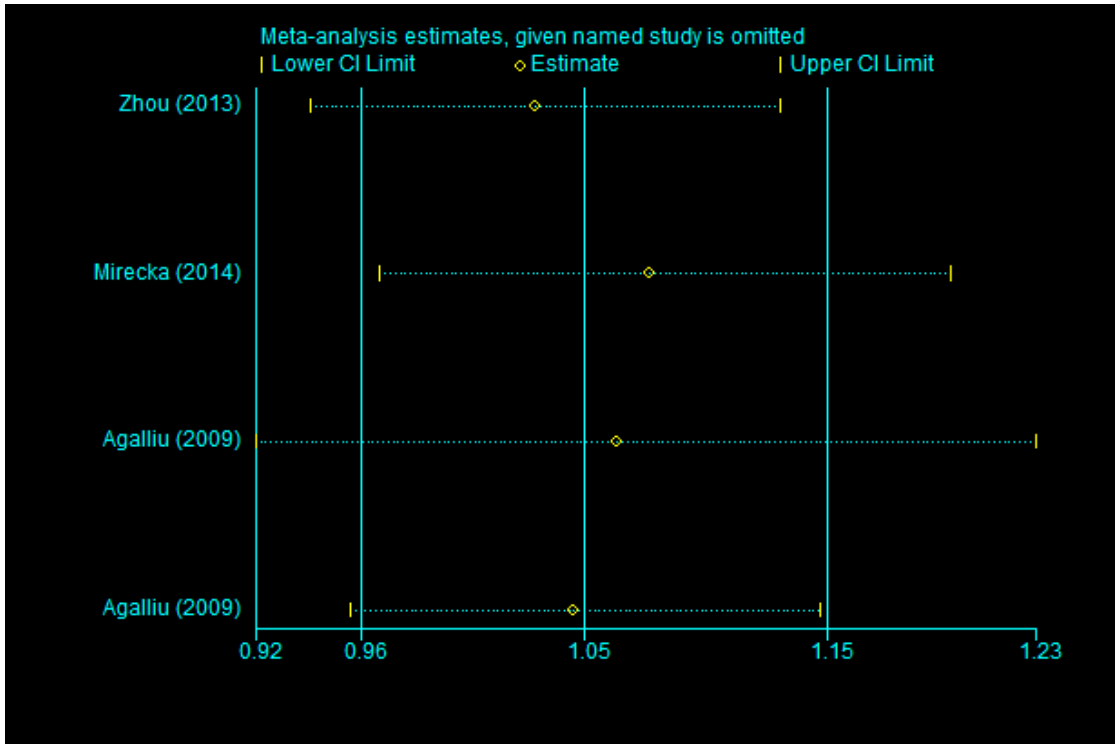

Figure S 10. Sensitivity analysis for *ERCC2* rs238406 polymorphism and the risk of prostate cancer (allelic comparison B vs. A).

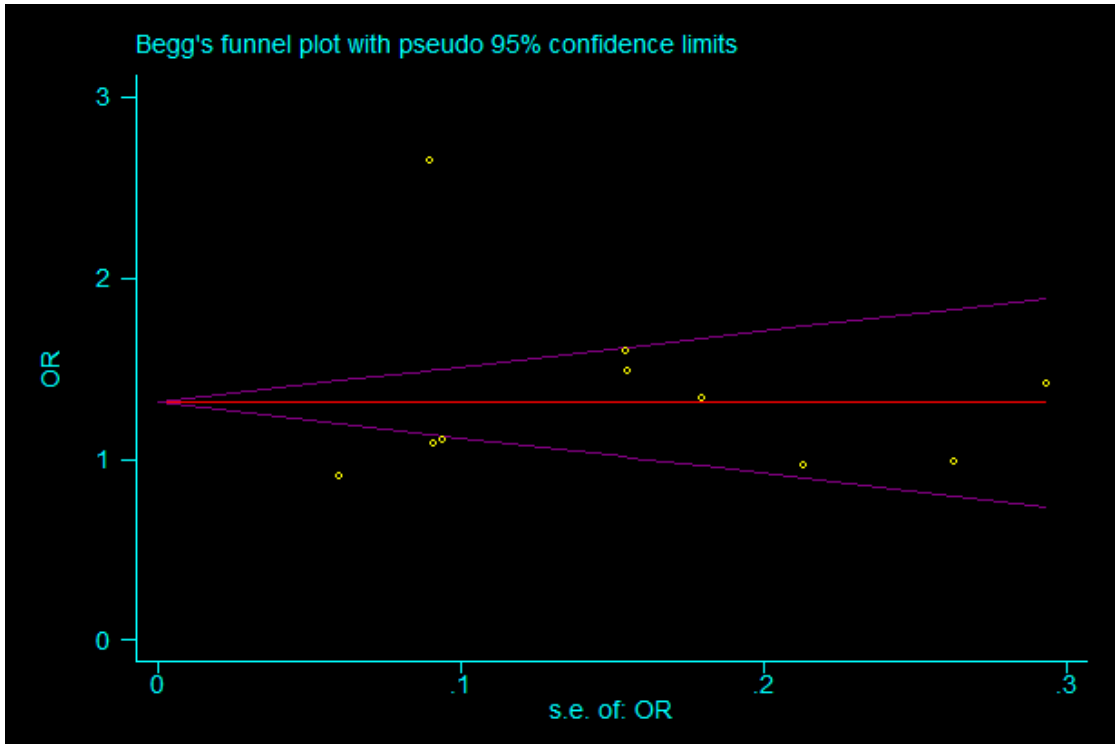

Figure S 11. Begg's funnel plot for publication bias under *ERCC2*-rs1799793 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

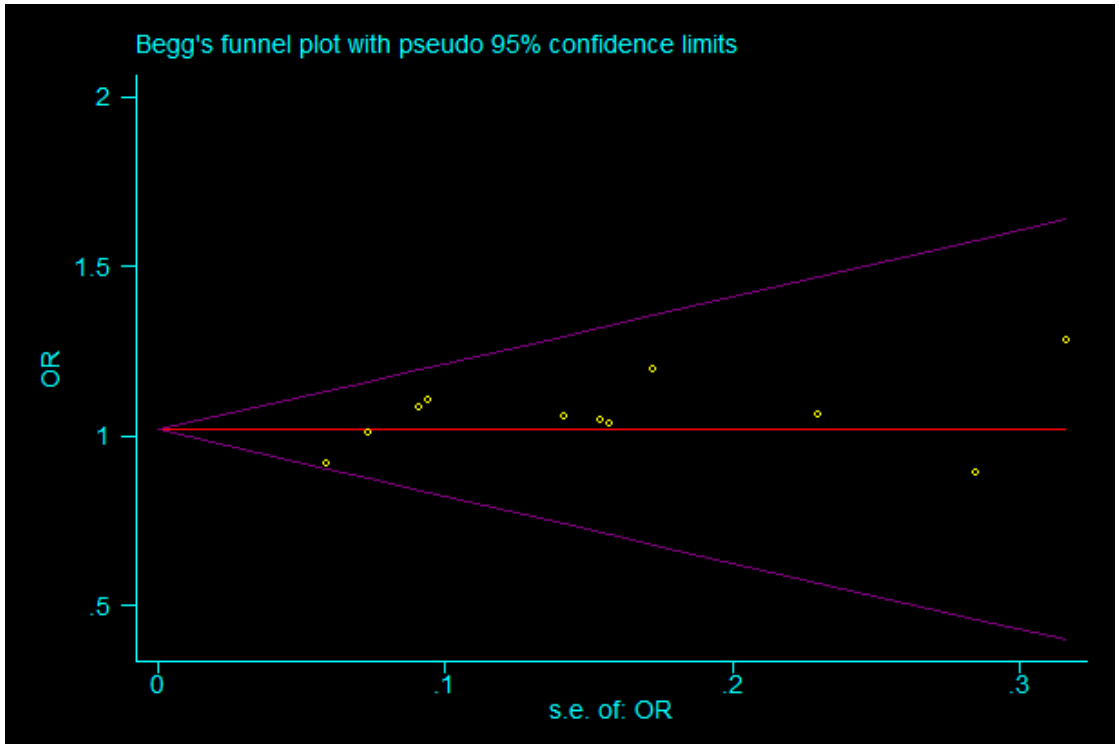

Figure S 12. Begg's funnel plot for publication bias under *ERCC2*-rs13181 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

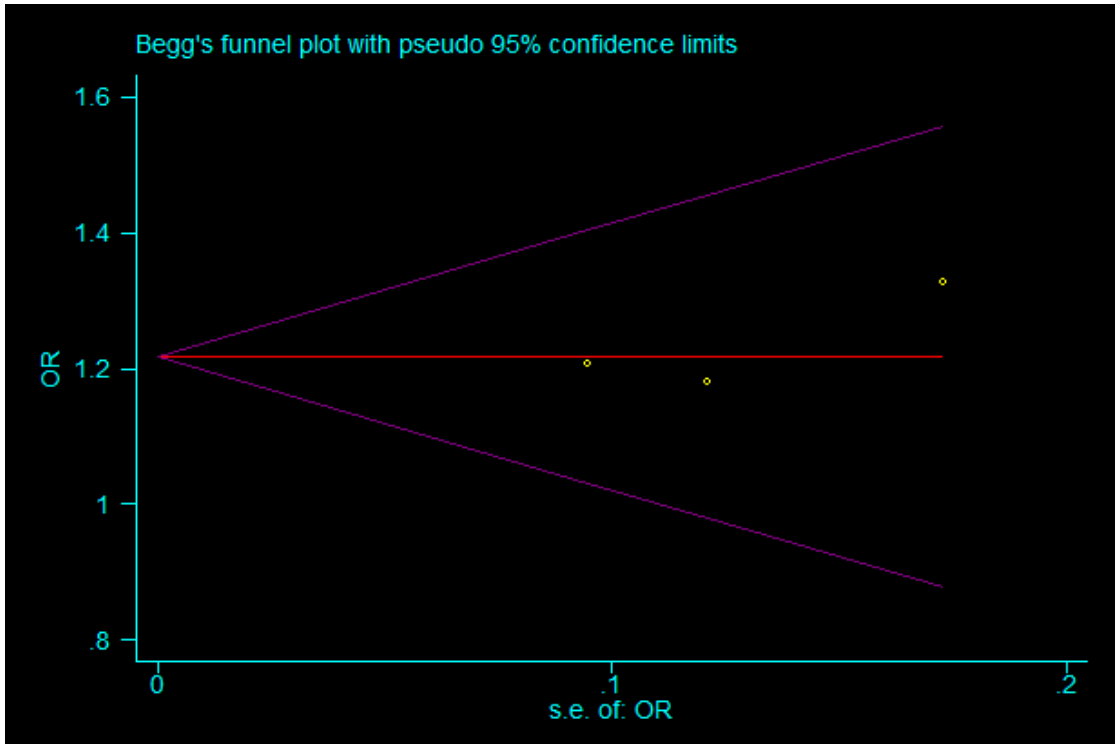

Figure S 13. Begg's funnel plot for publication bias under *ERCC5*-rs17655 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

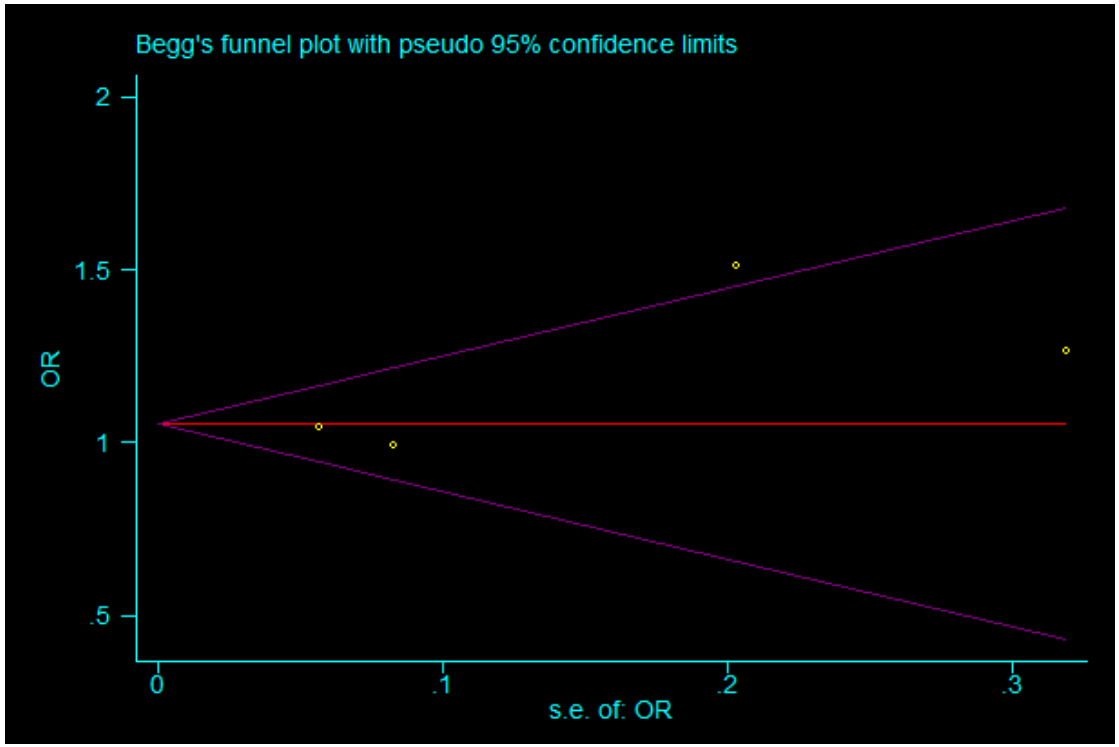

Figure S 14. Begg's funnel plot for publication bias under *ERCC2*-rs238406 polymorphism (allelic comparison B vs. A). The x-axis log (OR) and the y-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated log (OR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Log (OR) = log-transformed OR, OR = odds ratio.

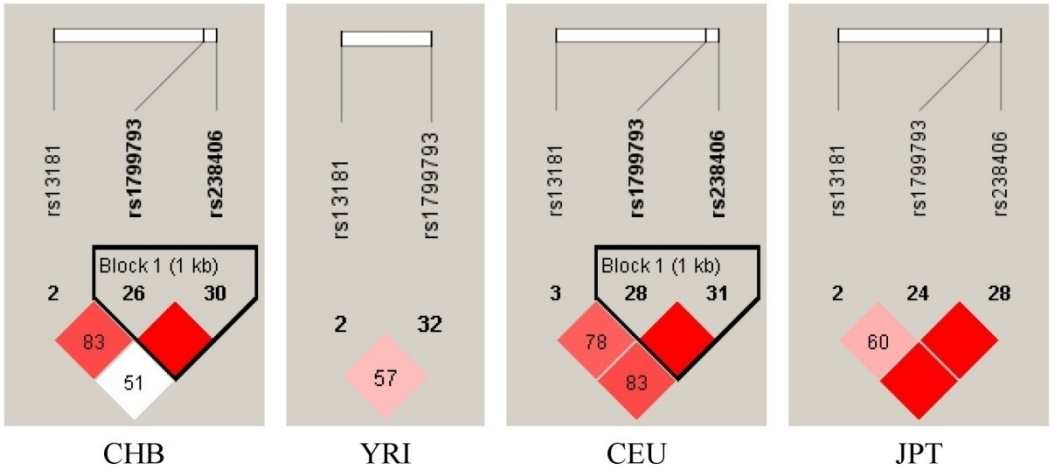

Figure S 15. Linkage disequilibrium plot. The number of each cell represents r2 and white color cells shows no LD between polymorphisms. A. CHB (Han Chinese in Beijing, China); B. JPT (Japanese in Tokyo, Japan); C: CEU (Utah residents with ancestry from northern and western Europe); D: YRI (Yoruba in Ibadan, Nigeria). The “rs” numbers are SNP IDs taken from National Center for Biotechnology Information (NCBI).

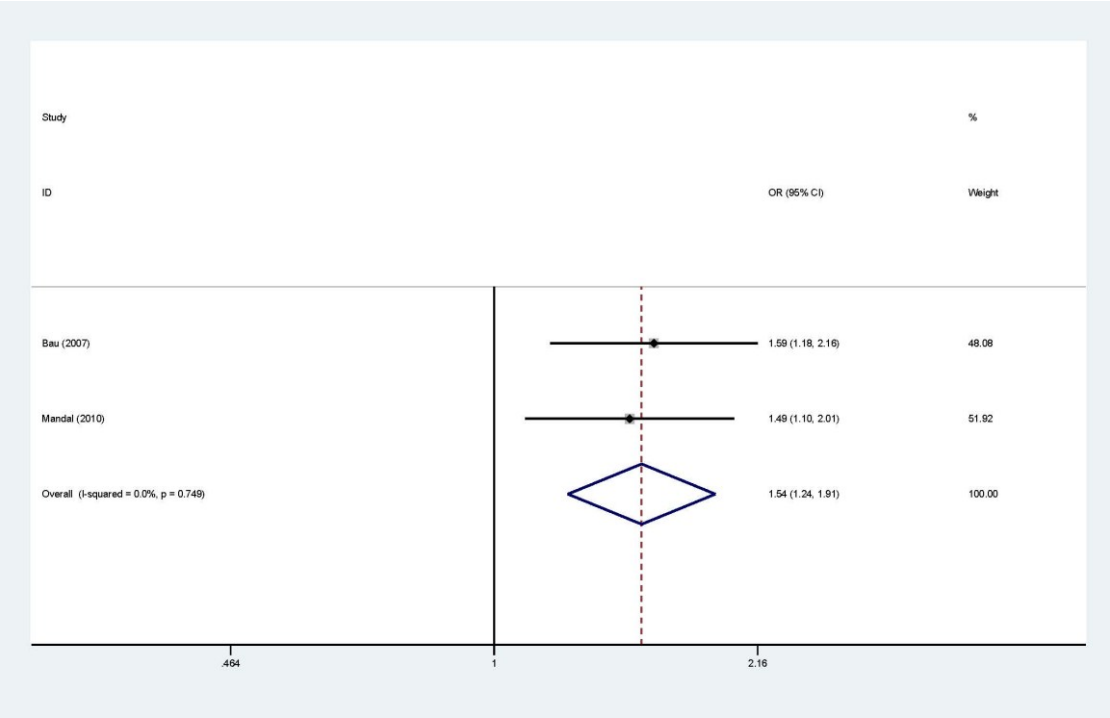

Figure S 16. Forest plots of the association between *ERCC2*-rs1799793 polymorphism and the risk of prostate cancer (B vs. A). Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the summary OR and 95% CI. CI= confidence interval, OR= odds ratio.