Clinical Research Paper

Polymorphisms in BER genes and risk of breast cancer: evidences from 69 studies with 33760 cases and 33252 controls

Lele Qiao^{1,*}, Xiaoshan Feng^{1,*}, Gongping Wang¹, Bo Zhou¹, Yantong Yang¹ and Mengxiang Li²

¹The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, 471003, China

²Henan University of Science and Technology, LuoYang, Henan, 471023, China

 * These authors contributed equally to this work and should be considered as co-first authors

Correspondence to: Lele Qiao, email: lianghe201610@163.com Xiaoshan Feng, email: samfeng137@hotmail.com

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ABSTRACT

Recently, numerous studies have reported an association between single nucleotide polymorphisms in base-excision repair genes and the risk of developing breast cancer, however there is no consensus. The aim of this meta-analysis was to review and quantitatively assess the relationship between single nucleotide polymorphisms in base-excision repair genes and breast cancer risk. The results suggested that a mutation of T to G in rs1760944 may lead to a higher risk of developing breast cancer in the Mongoloid population, and G to A of rs25487 significantly reduced the risk of breast cancer in Mongoloid and Caucasoid populations. In contrast to the CC and CG genotypes, the GG genotype of rs1052133 located on theOGG1 gene appeared to be a protective factor against developing breast cancer in both Mongoloid and Caucasoid populations. There was no evidence to suggest that rs25489, rs1799782, rs1130409, rs1805414 and rs1136410 were associated with breast cancer risk. In conclusion, this study provides evidence to support the theory that DNA repair genes are associated with breast cancer risk, providing information to further understand breast cancer etiology. and The potential biological pathways linking DNA repair, ethnic background, environment and breast cancer require further investigation.

INTRODUCTION

-Breast cancer (BC) affects about 12% of women worldwide. Statistics indicate that almost 3 million women suffers from BC in 2015 in the United States [1]. Risk factors for developing breast cancer include unhealthy lifestyles, other medical conditions and genetic susceptibility [2, 3]. Epidemiologic studies suggest that women with family history of BC could be more vulnerable to develop BC cancer than those not [4, 5].

Environmental factors and metabolic processes are the two main causes of DNA damage. Ionizing radiation has been confirmed as an environmental risk factor for the development of cancer, which can cause DNA damage of different kinds.[6] Base-excision repair (BER), one of DNA repair pathways, mainly repairs single base in damaged DNA molecule. Mutations occurred in BER related genes can lead to change its repair function, and then increases the probability of developing cancer greatly [7, 8].

Numerous studies have widely explored the relationship between susceptibility to BC and single nucleotide polymorphisms (SNPs) in Base-excision repair genes. However, the conclusions remain indecisive as a result of insufficient samples and/or race diversity. These studies include human apurinic/apyrimidinic endonuclease (APE1), x-ray repair cross-complementing 1 (XRCC1), human 8-oxoguanine DNA glycosylase (OGG1, also known as hOGG1), and poly (ADP-ribose) polymerase-1 (ADPAT1, also known as PARP1). Among these, the relationships between risk of BC and mutations of

rs25487 and rs1799782 on the XRCC1 gene have caused the greatest controversy among researchers. Positive association between rs25487 mutation [9–14] and the risk of BC have been reported in single race population studies, but others did not even in the same race [15–21]. Most studies suggest that the rs1799782 mutation is not associated with developing BC, while other studies report it is positively correlated. [9, 11–15, 17, 19] Inconsistent results have also been reported in studies using populations consisting of mixed race. Duell *et al.* (2001) reported a positive association for rs25487 with BC was found among African Americans but not Caucasian Americans [22]. VIEIRAL *et al.* (2015) demonstrates genetic background can influence BC developing, even an inverse association [23].

Meta-analysis is an authoritative way to improve authenticity and provides quantitative pooled values for different races. Previous meta-analysis studies adopted the continental location as the classification standard to discuss the relationship between susceptibility to BC and SNPs in BER genes [24, 25]. However, there are numerous races distributed on the same continent. For example, the Mongoloid race is mainly located in the East and Southeast of Asia, and the Caucasoid race mainly located in Europe, the Americas, Oceania, North Africa, South and West Asia. Therefore, using human race as the standard of classification to use in stratification analysis may be more appropriate. The purpose of this study is to discuss the relationship between risk of developing BC and BER genes based on genetic ancestry.

MATERIALS AND METHODS

Literature search strategy

The Medline, PubMed, Embase, Web of Science were searched (the last search was updated on October 20th 2016) using the search terms "breast cancer", "polymorphism" or "SNP", "DNA Repair Gene" or "base excision DNA repair gene" or "BER gene". All searches were retrieved and their references were checked for other relevant publications. Only published studies with full-text articles were included. When more than one of the same patient populations was included in several studies, only the study with the largest sample size or the complete study was used for this meta-analysis. A flow diagram of the study selection process was shown in Figure 1.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were established on the basis of discussion and consensus. The inclusion criteria for studies were as follows: (1) casecontrol studies; (2) the aim was to examine the association of the polymorphisms in BER genes with susceptibility of breast cancer; (3) data provided met the requirements of meta-analysis method; (4) genotype distribution in healthy controls complied with the Hardy–Weinberg equilibrium (HWE).

The exclusion criteria were as follows: (1) did not fit the diagnostic criteria; (2) animal study; (3) the aim of the study didn't focus on susceptibility to breast cancer or not BER genes; (5) genotype distribution healthy controls deviated from the HWE.

Racial classification

According to the Meyers Konversations-Lexikon (1885–90), human beings can be divided into three major races: Mongoloid race, Caucasoid race, and Negroid race. The Mongoloid race is a term used for all or some people who are indigenous to East Asia, Central Asia, Southeast Asia, North Asia, South Asia, the Arctic, the Americas, the Pacific Islands and other lesser regions, and are the minority group worldwide (https://en.wikipedia.org/ wiki/Mongoloid). The Caucasoid race usually includes some or all of the ancient and modern populations of Europe, the Caucasus, Asia Minor, North Africa, the Horn of Africa, Western Asia, Central Asia and South Asia (https://en.wikipedia.org/wiki/Caucasian race#cite note-Pickering-8). The Negroid race populations are found in most of Sub-Saharan Africa and isolated parts of Southeast Asia (Negritos) (https://en.wikipedia.org/wiki/Negroid).

The information included in this meta-analysis was arranged and divided into Mongoloid population, Caucasoid population and Negroid population using the criteria above. If the racial origin of the samples could not be clearly defined, the data was assigned to a mixed race group.

Statistical analysis

A χ^2 test was used to determine if observed frequencies of genotypes corresponded to the HWE. Statistical analysis was conducted using R software and a *P*-value ≤ 0.05 was considered statistically significant. Dichotomous data was presented as the odds ratio (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the Q-statistic (P \leq 0.10 was considered to be representative of statistically significant heterogeneity). Effect of heterogeneity quantified by the I^2 statistic, a fixed effects model was used when there was no heterogeneity in the results of the trials; otherwise, the random effects model was used. Egger's weighted regression method were used to statistically assess the publication bias ($P \le 0.05$ was considered to indicate statistically significant publication bias). The methods of "Influence analysis" and "Trim and Filled analysis" were both conducted to investigate the sensitivity of the pooled ORs.

RESULTS

183 relevant studies with 69 SNPs on 20 BER related genes were retrieved in this research. 114 articles describing 19 genes were excluded from this study due to insufficient publication number (not more than 3 researches). Finally, this study included 69 papers with 33760 BC cases and 33252 controls, and the information was summarized in Table 1. The flow process was shown in Figure 1.

Three SNPs on the XRCC1 gene were analysed in this meta-analysis. As Supplementary Table 1 show, this meta-analysis didn't find any evidence to suggest that mutations in rs25489 and rs1799782 were associated with the susceptibility to develop BC in any race population. But, rs25487 with A allele significantly reduced the risk of developing BC in Mongoloid and Caucasoid populations, but not in the Negroid population (Figures 2 and 3).

Two SNPs on the ADPRT1 gene were analysed in this meta-analysis. As Table 2 shows, there is no evidence which indicates that mutations in SNPs of rs1805414 and rs1136410 were significantly associated with BC. The relationship between two SNPs (rs1130409 and rs1760944) on the APEX1 gene and risk of developing BC was analysed in this meta-analysis (Figures 4 and 5).

The mutations in rs1130409 did not relate to the risk of developing BC, but T mutated to G in rs1760944 could increase the risk of developing BC in the Mongoloid race. There are insufficient studies which are focused on the relationship of rs1760944 and BC susceptibility outside the Mongoloid population, which restricted the meta-analysis on Mongoloid populations, compared to that done for the Caucasoid and Negroid populations (Table 3).

Table 4 shows a CC genotype of rs1052133 played a protective role in the development of BC in Mongoloid and Caucasoid race populations (Figures 6, 7 and 8).

Sensitivity analysis demonstrated all the results were robust, and no significant publication bias was found.

DISCUSSION

This study quantitatively summarized the association between 8 SNPs on 4 BER genes and the risk of developing BC, by pooling the data from 69 papers



Figure 1: A flow diagram of the studies selection process.

Genes in BER pathway	SNPs	n. of studies included	n. of Cases	n. of Controls	References included
XRCC1	rs1799782	33	14991	15624	[9, 10, 12, 13, 16–23, 26–46]
	rs25487	47	20995	22964	[9–13, 15–22, 26, 27, 29–45, 47–60]
	rs25489	10	7509	7403	[16, 19, 21, 28, 32, 34, 36, 43, 47, 57]
ADPRT1	rs1805414	3	236	269	[61-63]
	rs1136410	7	3128	2805	[28, 32, 53, 61, 62, 64, 65]
APEX1	rs1130409	12	5154	5858	[13, 14, 28, 32, 35, 36, 51, 66–70]
	rs1760944	4	1415	1827	[13, 14, 68, 69]
OGG1	rs1052133	16	11038	12799	[14, 32, 34, 36, 44, 46, 57, 67, 71–78]

 Table 1: Summary of the SNPs studied in this meta-analysis

SNP	Genetic	Race	п		OR (95% CI)		Homog	eneity	P for Publication
	Models	1000		OR	CI	P value	Q	I ² (%)	Bias test
	TT + CT vs. CC (Dominant)	Caucasoid	3	0.411	0.134-1.256	0.119	5.000	61.541	0.628
	TT vs. CT + CC (Recessive)	Caucasoid	3	0.576	0.195-1.702	0.318	17.000	88.241	0.758
Rs1805414 TT/ CT/ CC	T vs. C (Allele)	Caucasoid	3	0.582	0.255-1.33	0.200	16.000	87.383	0.332
	TT vs. CT (Co-Dominant)	Caucasoid	3	0.650	0.207-2.038	0.460	17.000	87.892	0.566
	CT vs. CC (Co-Dominant)	Caucasoid	3	0.519	0.169–1.595	0.252	5.000	57.083	0.659
	CT+CC vs. TT	Overall	7	1.004	0.787-1.282	0.971	5.000	0.000	0.188
	(Dominant)	Caucasoid	6	1.075	0.776-1.487	0.665	4.970	0.000	0.314
	CC vs. CT+ TT	Overall	7	0.996	0.781-1.272	0.971	5.000	0.000	0.683
D 4406440	(Recessive)	Caucasoid	6	0.931	0.672-1.288	0.665	4.970	0.000	0.547
Rs1136410	C vs. T	Overall	8	0.975	0.822-1.157	0.772	14.000	48.680	0.147
CC / CT/ TT	(Allele)	Caucasoid	6	0.999	0.802-1.247	0.628	11.014	54.605	0.721
	CC vs. CT	Overall	8	0.981	0.811-1.186	0.841	11.000	35.808	0.590
	Co-Dominant	Caucasoid	6	1.021	0.813-1.283	0.857	9.283	40.354	0.918
	CT vs. TT	Overall	7	1.031	0.798-1.331	0.817	4.000	0.000	0.182
	Co-Dominant	Caucasoid	6	1.093	0.778-1.534	0.609	4.087	0.000	0.536

with 33760 BC cases and 33252 control individuals. To the best of our knowledge, this paper is novel in its discussion in terms of the difference to the susceptibility to BC in different races. Overall, the results of this paper found that the mutations of rs25487 on the XRCC1 gene, rs1760944 on APEX1 and rs1052133 on the OGG1 gene were significantly related with susceptibility to BC.

Rs25487 on the XRCC1 gene (also known as Gln399Arg, and A allele encodes the Gln amino acid) was the polymorphism most studied in the risk of cancers. Rs25487 participates in coding of BRCT I domains of XRCC 1, which is one of the interaction domains of BRCA 1 protein [79]. BRCA 1 has been proved to be a predict gene for hereditary BC, it can suppress developing

SNP	Genetic	Race	п		OR (95% CI)		Homogeneity				
	Models		-	OR	CI	P value	Q	I ² (%)	Publicatior Bias		
Rs1130409	TT + CT vs.	Overall	13	1.012	0.773-1.325	0.932	74.000	83.730	0.412		
TT/ TG/ GG	CC (Dominant)	Caucasoid	7	0.942	0.604-1.469	0.794	60.567	90.094	0.778		
		Mongoloid	5	1.076	0.779-1.486	0.658	13.195	69.684	0.747		
	TT vs. CT+CC	Overall	13	0.918	0.783-1.075	0.288	37.000	67.181	0.703		
	(Recessive)	Caucasoid	7	0.840	0.623-1.132	0.251	30.948	80.613	0.144		
		Mongoloid	5	0.966	0.837-1.115	0.637	5.348	25.199	0.342		
	T vs. C	Overall	13	0.967	0.831-1.124	0.658	75.000	83.977	0.363		
	(Allele)	Caucasoid	7	0.908	0.688-1.199	0.4-95	69.148	91.323	0.786		
		Mongoloid	5	1.005	0.903-1.118	0.928	5.635	29.015	0.073		
	TT vs. CT	Overall	13	0.878	0.753-1.026	0.101	30.000	60.592	0.133		
	Co-Dominant	Caucasoid	7	0.799	0.61-1.047	0.104	21.625	72.254	0.739		
		Mongoloid	5	0.937	0.775-1.133	0.503	8.105	50.650	0.295		
	CT vs. CC	Overall	13	1.074	0.812-1.421	0.615	69.000	82.658	0.944		
	Co-Dominant	Caucasoid	7	1.042	0.665-1.633	0.858	53.503	88.786	0.978		
		Mongoloid	5	1.111	0.764-1.614	0.582	15.600	74.359	0.972		
Rs1760944	TT+CT vs. CC	Overall	4	1.000	0.840-1.192	0.996	7.000	55.865	0.899		
TT/CT/CC	(Dominant)	Mongoloid	3	1.021	0.854-1.221	0.816	5.387	62.873	0.609		
	TT vs. CT+CC	Overall	4	1.265	1.086-1.474	0.003	4.000	23.638	0.763		
	(Recessive)	Mongoloid	3	1.227	1.044-1.441	0.013	2.511	20.344	0.943		
	T vs. C	Overall	4	1.106	1.001-1.222	0.049	6.000	50.892	0.638		
	(Allele)	Mongoloid	3	1.098	0.989-1.219	0.081	5.909	66.153	0.609		
	TT vs. CT	Overall	4	1.067	0.772-1.478	0.122	3.000	4.848	0.359		
	Co-Dominant	Mongoloid	3	1.241	1.045-1.473	0.014	1.201	0.000	0.727		
	CT vs. CC	Overall	4	0.913	0.757-1.101	0.337	6.000	46.736	0.882		
	Co-Dominant	Mongoloid	3	0.938	0.775-1.135	0.511	3.641	45.072	0.279		

Table 3: Summary about meta-analysis results of SNPs in APEX1 gene and risk of breast cancer

Table 4: Summary about meta-analysis results of SNPs in OGG1 gene and risk of breast cancer

SNP	Genetic	Race	п		OR(95% CI)			ogeneity	<i>P</i> for Publication
	Models			OR	CI	P value	Q	I ² (%)	Bias
rs1052133	CC+CG vs. GG	Overall	20	0.767	0.611-0.962	0.021	128	85.21	0.478
CC/CG/GG	(Dominant)	Caucasoid	11	0.646	0.376-1.107	0.112	111.303	91.016	0.735
		Mongoloid	8	0.877	0.770-0.998	0.047	11.056	36.687	0.425
	CC vs .CG+GG	Overall	22	1.215	0.819-1.802	0.334	133	84.168	0.665
	(Recessive)	Caucasoid	13	1.224	0.962-1.556	0.100	112.479	89.331	0.139
		Mongoloid	8	0.955	0.749-1.217	0.709	11.056	36.687	0.391
	C vs. G	Overall	20	1.002	0.897-1.119	0.968	115	83.47	0.841
	(Allele)	Caucasoid	11	0.994	0.818-1.208	0.954	87.007	88.507	0.211
		Mongoloid	8	1.006	0.880-1.149	0.932	26.557	73.642	0.480
	CC vs.CG	Overall	20	0.818	0.677-0.987	0.036	59	67.958	0.488
	Co-Dominant	Caucasoid	11	0.734	0.492-1.093	0.128	51.521	80.591	0.577
		Mongoloid	8	0.855	0.749-0.976	0.020	7.037	0.521	0.583
	CG vs. GG	Overall	20	0.752	0.595-0.951	0.017	122	84.455	0.289
	Co-Dominant	Caucasoid	11	0.613	0.352-1.070	0.085	105.605	90.531	0.131
		Mongoloid	8	0.886	0.777-1.010	0.052	10.097	30.673	0.735

Study	C Events	ASES Total		TROL Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
race = Negroid					2				
Eric J. Duell 2001	246	253	262	266		0.54	[0.16; 1.86]	0.3%	0.8%
Tasha R.Smith 2008	52	75	74	112			[0.62; 2.17]	0.8%	1.8%
Brian F. Pachkowski 2006	739	761	665	676		0.56	[0.27; 1.15]	0.9%	1.5%
Fixed effect model		1089		1054			[0.51; 1.23]	1.9%	4.1%
Random effects model Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.0611$,	p = 0.26					0.70	[0.45; 1.33]		4.1%
race = Mixed									
Jiali Han 2003	851	986	1161	1337	1		[0.75; 1.22]	5.7%	2.7%
Jing Shen 2005 Dawei Bu 2006	951 168	1067 190	980 85	1110 95			[0.83; 1.42] [0.41; 1.98]	4.4% 0.6%	2.6% 1.4%
Raguel A. Santos 2010	63	65	77	85	<u></u>		[0.67; 15.97]	0.0%	0.6%
Fixed effect model		2308		2627		1.03	[0.86; 1.22]	10.7%	
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.2$	14					1.02	[0.86; 1.21]		7.3%
race = Caucasoid									
Eric J. Duell 2001	337	386	322	381		1.26	[0.84; 1.90]	1.7%	2.3%
Mazhar S. Al Zoubi 2015	36	46	26	31		0.69		0.3%	0.9%
Nelly M. Mac?as-Gomez 2015	308	345	326	341			[0.21; 0.71]	1.5%	1.8%
Alexandra S. Shadrina 2014	559	658	507	564	- B		[0.45; 0.90]	3.5%	2.5%
Ragaa A. Ramadan 2014	74	100	69	75			[0.10; 0.64]	0.9%	1.2%
Norman Moullan 2003 Tasha R.Smith 2008	222	254	273	312			[0.60; 1.63]	1.3%	2.1%
Tasha R.Smith 2008 Tasha R. Smith 2002	177 142	312 162	360 269	406 300			[0.11; 0.24] [0.45; 1.49]	5.7% 1.0%	2.4% 1.8%
U gur D eligezer 2004	142	151	116	133			[0.38; 1.49]	0.9%	1.7%
Priya Chacko 2005	106	123	114	123			[0.21; 1.15]	0.7%	1.3%
Alpa V Patel 2005	391	452	396	452		0.91		2.3%	2.4%
A.M. Brewster 2006	282	322	270	321		1.33	[0.85; 2.08]	1.4%	2.2%
Brian F. Pachkowski 2006	1085	1244	974	1122		1.04		5.5%	2.7%
Bharat Thyagarajan MBBS 2006	133	193	275	322			[0.25; 0.58]	2.7%	2.2%
Yawei Zhang 2005	2647	3039	2227	2587	i		[0.94; 1.27]	13.1%	2.9%
Susana N. Silva MSc 2007 Maria A. Loizidou 2008	215 985	240 1107	400 1036	453 1176			[0.69; 1.89] [0.84; 1.41]	1.2% 4.7%	2.1% 2.7%
Amit Kumar Mitra 2008	96	150	1030	225	I		[0.20; 0.54]	2.3%	2.1%
Silvia Sterpone 2010	60	71	26	31			[0.33; 3.32]	0.2%	0.9%
ASTA F?RSTI 2003	203	223	267	298			[0.65; 2.13]	0.9%	1.9%
Karolina Przybylowska-Sygut 2012	162	185	174	205		1.25	[0.70; 2.24]	0.9%	1.9%
Jennifer Zipprich 2010	241	271	280	323	<u>8</u>	1.23	[0.75; 2.03]	1.2%	2.1%
Fatima Masoud Al Mutairi 2013	90	100	92	100			[0.30; 2.07]	0.4%	1.1%
Katja Metsola 2005	433	479	441	478			[0.50; 1.24]	1.8%	2.2%
Lívia Kipika?ová 2008 Mostafa Saada 2007	99 153	114 186	96 171	113 187		1.17	[0.55; 2.47] [0.23; 0.82]	0.5% 1.3%	1.5% 1.7%
K. Jelonek 2010	81	94	352	409			[0.23, 0.82]	0.8%	1.7%
Sandra Costa 2007	151	175	191	220			[0.53; 1.71]	1.0%	1.9%
HANNA ROMANOWICZ 2010	170	220	196	220			[0.25; 0.71]	1.9%	2.0%
Michelle Roberts 2011	246	268	455	506	<u></u>	1.25	[0.74; 2.12]	1.1%	2.0%
Yousry Mostafa Hussien 2011	88	100	90	100		0.81		0.5%	1.3%
Irina Mordukhovich-1 2016	276	307	274	305		1.01		1.2%	2.0%
Irina Mordukhovich-2 2016	241	275	303	347	- it		[0.64; 1.66]	1.4%	2.1%
Irina Mordukhovich-3 2016 Ana M. Krivokuca 2016	288 79	323 106	270 68	306 104		1.10	[0.67; 1.80] [0.85; 2.81]	1.3% 0.7%	2.1% 1.8%
Fixed effect model	15	12781	00	13576	\$		[0.80; 2.01]	67.4%	1.0 %
Random effects model		12101		10070			[0.67; 0.95]		67.2%
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.203$,	0.01 < 0.01						<u></u>		
race = Mongoloid									
Sook-Un Kim 2002	171	205	191	205		0.37	[0.19; 0.71]	1.3%	1.7%
Gongjian Zhu 2015	87	101	93	101			[0.21; 1.34]	0.5%	1.2%
Peijian Ding 2014	527	606	601	633			[0.23; 0.54]	3.2%	2.3%
Hao Luo 2014	98	111	119	128			[0.23; 1.39]	0.5%	1.3%
Suleeporn Sangrajrang 2007	251	268	234	244			[0.28; 1.41]	0.7%	1.4%
Ming-Shiean Hsu 2009	347	395	478	531	<u></u>		[0.53; 1.21]	2.1%	2.3%
Li Liu 2011 Xiao Qu Shu 2003	920	1004	914	995	3		[0.71; 1.33]	3.2%	2.5%
Xiao-Ou Shu 2003 XIANGJUN ZHAI 2006	1003 274	1088 302	1108 587	1182 639			[0.57; 1.09] [0.54; 1.40]	3.5% 1.5%	2.5% 2.1%
Yun Qian 2010	604	666	716	789	5		[0.54, 1.40]	2.6%	2.1%
Iric Tzyy Jiann Chon 2016	58	71	228	260			[0.31; 1.27]	0.8%	1.6%
Fixed effect model		4817		5707	4		[0.64; 0.84]	19.9%	
Random effects model					\$		[0.55; 0.86]		21.3%
Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.0761$,	p = 0.01				\$				
Fixed effect model		20995		22964			[0.80; 0.90]	100.0%	100.0%
Random effects model Heterogeneity: $I^2 = 74\%$, $\tau^2 = 0.1509$,	n < 0.01				♦	0.79	[0.69; 0.90]		100.0%
	- 0.01				0.1 0.5 1 2	10			

Figure 2: Forest plot of RS25487 polymorphism in XRCC1 and risk to breast cancer (GA+GG vs. AA) (the model adopted was marked by black frame).

race = Negroid Eric J. Duell 2001 Tasha R.Smith 2008									(random)
Eric J. Duell 2001					3				
	410	506	460	532		0.67	[0.48; 0.93]	0.9%	1.5%
	90	150	132	224			[0.69; 1.59]	0.4%	1.2%
Brian F. Pachkowski 2006	1275	1522	1158	1352			[0.71; 1.06]	2.0%	2.3%
Fixed effect model		2178		2108	\diamond		[0.68; 1.03]	3.4%	
Random effects model Heterogeneity: $I^2 = 31\%$, $\tau^2 = 0.0115$,	p = 0.23				A	0.83	[0.68; 1.03]		5.0%
in a second second					5				
race = Mixed Jiali Han 2003	1242	1972	1706	2674	<u>81</u>	0.07	[0.86; 1.09]	5.5%	2.8%
Jing Shen 2005	1363	2134	1424	2220	<u> </u>		[0.87; 1.12]	5.2%	2.8%
Dawei Bu 2006	252	380	1424	190			[0.67; 1.41]	0.6%	1.4%
Raguel A. Santos 2010	87	130	101	170			[0.86; 2.23]	0.3%	1.0%
Fixed effect model	•.	4616		5254	*		[0.91; 1.07]	11.6%	
Random effects model					\$		[0.91; 1.07]		8.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.5$	56				5				
race = Caucasoid									
Eric J. Duell 2001	499	772	486	762			[0.84; 1.28]	1.8%	2.2%
Mazhar S. Al Zoubi 2015	58	92	41 527	62			[0.44; 1.72]	0.2%	0.6%
Nelly M. Mac?as-Gomez 2015	491 838	690 1316	527 778	682 1128			[0.57; 0.93] [0.67; 0.93]	1.6%	2.0%
Alexandra S. Shadrina 2014 Ragaa A. Ramadan 2014	838	200	106	150 -			[0.67; 0.93]	3.1% 0.7%	2.5% 1.1%
Norman Moullan 2003	331	508	400	624			[0.82; 1.34]	1.3%	2.0%
Tasha R.Smith 2008	318	624	539	812			[0.42; 0.65]	2.4%	2.2%
Tasha R. Smith 2002	212	324	388	600			[0.78; 1.37]	1.0%	1.8%
U gur D eligezer 2004	184	302	166	266			[0.67: 1.32]	0.7%	1.5%
Priva Chacko 2005	162	246	193	246	I		[0.35; 0.79]	0.7%	1.2%
Alpa V Patel 2005	587	904	590	904			[0.81; 1.20]	2.1%	2.3%
A.M. Brewster 2006	397	644	400	642			[0.78; 1.22]	1.6%	2.1%
Brian F. Pachkowski 2006	1589	2488	1454	2244	<u>21</u>	0.96	[0.85; 1.08]	5.7%	2.8%
Bharat Thyagarajan MBBS 2006	190	386	410	644	_ *	0.55	[0.43; 0.71]	1.6%	1.9%
Yawei Zhang 2005	3861	6078	3281	5174		1.00	[0.93; 1.09]	13.3%	3.1%
Susana N. Silva MSc 2007	326	480	590	906		1.13	[0.90; 1.43]	1.3%	2.1%
Maria A. Loizidou 2008	1491	2214	1556	2352		1.05	[0.93; 1.19]	5.1%	2.8%
Amit Kumar Mitra 2008	140	300	273	450			[0.42; 0.76]	1.2%	1.7%
Silvia Sterpone 2010	96	142	42	62			[0.53; 1.88]	0.2%	0.6%
ASTA F?RSTI 2003	303	446	405	596			[0.77; 1.30]	1.1%	1.9%
Karolina Przybylowska-Sygut 2012		370	260	410			[0.76; 1.36]	0.9%	1.7%
Jennifer Zipprich 2010	367	542	419	646			[0.89; 1.45]	1.3%	2.0%
Fatima Masoud Al Mutairi 2013	148	200	150	200			[0.61; 1.49]	0.4%	1.1%
Katja Metsola 2005	670	958	697	956			[0.71; 1.05]	2.2%	2.3%
Lívia Kipika?ová 2008	148	228 372	149	226			[0.65; 1.41]	0.5%	1.3%
Mostafa Saada 2007 K. Jelonek 2010	236 122	188	252 490	374 818	3		[0.62; 1.14] [0.89; 1.72]	0.9% 0.7%	1.7% 1.5%
Sandra Costa 2007	235	350	266	440			[1.00; 1.72]	0.8%	1.7%
HANNA ROMANOWICZ 2010	233	440	200	440			[0.47; 0.81]	1.4%	1.9%
Michelle Roberts 2011	372	536	682	1012	- <u>i</u>		[0.88; 1.38]	1.5%	2.1%
Yousry Mostafa Hussien 2011	125	200	140	200			[0.47; 1.08]	0.5%	1.2%
Irina Mordukhovich-1 2016	398	614	410	610			[0.71; 1.14]	1.5%	2.1%
Irina Mordukhovich-2 2016	346	550	424	694			[0.86; 1.36]	1.4%	2.1%
Irina Mordukhovich-3 2016	408	646	405	612			[0.70; 1.10]	1.6%	2.1%
Ana M. Krivokuca 2016	126	212	103	208			[1.02; 2.20]	0.4%	1.3%
Fixed effect model		25562		27152	\$		[0.90; 0.97]	62.5%	
Random effects model					\$	0.89	[0.83; 0.97]		64.8%
Heterogeneity: $I^2 = 75\%$, $\tau^2 = 0.0379$,	p < 0.01				2				
race = Mongoloid					0 0 0				
Sook-Un Kim 2002	263	410	281	410		0.82	[0.61; 1.10]	1.0%	1.8%
Gongjian Zhu 2015	100	202	139	202			[0.30; 0.67]	0.7%	1.2%
Peijian Ding 2014	845	1212	948	1266			[0.65; 0.92]	2.9%	2.5%
Hao Luo 2014	152	222	190	256			[0.51; 1.12]	0.6%	1.2%
Suleeporn Sangrajrang 2007	401	536	376	488			[0.66; 1.18]	1.0%	1.8%
Ming-Shiean Hsu 2009	545	790	754	1062	- <u>#</u>		[0.74; 1.11]	2.0%	2.3%
Li Liu 2011	1438	2008	1461	1990			[0.79; 1.05]	4.3%	2.7%
Xiao-Ou Shu 2003	1564	2176	1718	2364			[0.84; 1.09]	4.8%	2.8%
XIANGJUN ZHAI 2006	447	604	934	1278			[0.84; 1.31]	1.6%	2.2%
Yun Qian 2010	953	1332	1128	1578			[0.85; 1.18]	3.0%	2.6%
Iric Tzyy Jiann Chon 2016	83	142	342	520			[0.50; 1.07]	0.6%	1.3%
Fixed effect model Random effects model		9634		11414	<u>\$</u>		[0.84; 0.95] [0.79; 0.96]	22.6%	22.3%
Heterogeneity: $I^2 = 53\%$, $\tau^2 = 0.0128$,	p = 0.02					0.07	"211 01 010 0]		
Fixed effect model		41990		45928	80	0.93	[0.90; 0.95]	100.0%	
Random effects model							[0.85; 0.95]		100.0%
Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.0258$,	p < 0.01				0.5 1 2				

Figure 3: Forest plot of RS25487 polymorphism in XRCC1 and risk to breast cancer (G allele vs. A allele) (the model adopted was marked by black frame).

of breast cancer in humans [80, 81] This meta-analysis found populations with A allele could significantly reduce the risk of developing BC. Similar findings are presented in other cancers studies. For instance, in two studies carried on Americans and Koreans, the rs25487(A/A) genotype significantly reduces the risk of both basal cell and squamous cell cancers [82, 83]. A meta-analysis found the G allele is one of the risk factors in developing of Glioma in Asians [84]. Another meta-analysis carried out on a Chinese population found XRCC1 Arg399Gln polymorphism is not associated with BC (at the 5% level) but indicated a borderline association [85].

In human cells, APE1 gene, located on chromosome 14, encodes the primar AP endonuclease. AP sites is frequently happened in DNA molecules, which can help cells to recognize and repair DNA damage [86]. Rs1130409 and rs1760944 on the APE1 gene has been widely researched with respect to its role in cancer susceptibility [87–89]. By pooling 4 studies (3 on Chinese populations and 1 on an Iran population),

	C	ASES	CONT	ROL	Odds Ratio				
Study	Events	Total I	Events 1	Total		OR	95%-CI	W(fixed)	W(random)
race = Caucasoid									
Mashayekhi 2015	41	143	58	138		0.55	[0.34; 0.91]	15.2%	19.9%
Fixed effect model		143		138		0.55	[0.34; 0.91]	15.2%	
Random effects model						0.55	[0.34; 0.91]		19.9%
Heterogeneity: not applical	ble for a si	ngle stu	dy						
					i i				
race = Mongoloid									
Peijian Ding 2014	177	470	177	503		1.11	[0.86; 1.44]	38.6%	29.9%
Hao Luo 2014	44	130	47	175		1.39	[0.85; 2.28]	9.6%	20.0%
Huafeng Kang 2013	180	387	248	629			[1.03; 1.73]	36.6%	30.2%
Fixed effect model		987		1307		1.24	[1.05; 1.47]	84.8%	
Random effects model					$\langle \rangle$	1.24	[1.05; 1.47]		80.1%
Heterogeneity: I-squared=0	%, tau-squ	ared=0,	p=0.5486						
Fixed effect model		1130		1445		1.14	[0.97; 1.34]	100%	
Random effects model						1.07	[0.77; 1.48]		100%
Heterogeneity: I-squared=7	0.8%, tau-s	squared	=0.0743, p	=0.016	4				
					0.5 1 2				

Figure 4: Forest plot of rs1760944 polymorphism in APEX1 and risk to breast cancer (TT vs. CT) (the model adopted was marked by black frame).

	C	ASES	CONT	ROL	Odds Ratio				
Study	Events	Total I	Events	Total		OR	95%-CI	W(fixed)	W(random)
					¢				
race = Caucasoid									
Mashayekhi 2015	58	150	41	150	- <u>c</u> =	— 1.68	[1.03; 2.73]	8.6%	12.5%
Fixed effect model		150		150		- 1.68	[1.03; 2.73]	8.6%	
Random effects model						- 1.68	[1.03; 2.73]		12.5%
Heterogeneity: not applicat	ble for a sir	ngle stu	dy		4				
0 1 11		0	2						
race = Mongoloid					Č C				
Peijian Ding 2014	177	606	177	633		1.06	[0.83; 1.36]	42.0%	36.2%
Hao Luo 2014	44	194	47	245			[0.78; 1.96]	11.0%	13.7%
Huafeng Kang 2013	180	465	248	799			[1.10; 1.78]	38.3%	37.6%
Fixed effect model		1265		1677				91.4%	
Random effects model					\diamond	1.23	[1.02; 1.48]		87.5%
Heterogeneity: I-squared=2	0.3%. tau-s	auared	=0.0058. (0=0.2850	4 4				
	,	,							
Fixed effect model		1415		1827	\diamond	1.27	[1.09: 1.47]	100%	
Random effects model				50 0000 B	\diamond		[1.06; 1.53]		100%
Heterogeneity: I-squared=2	3.6%. tau-s	auared	=0.0085. i	o=0.2693	l l		,		
5) (,		,						
					0.5 1 2				

Figure 5: Forest plot of rs1760944 polymorphism in APEX1 and risk to breast cancer (TT vs. CT+CC) (the model adopted was marked by black frame).

Fixed effect model 1041 1093 1.03 [0.70; 1.52] 3.7 Random effects model 103 403 425 1.03 [0.70; 1.52] 3.7 Heterogeneity: not applicable 1041 1093 1.03 [0.70; 1.52] 3.7 race = Caucasoid 1184 1244 0.88 [0.48; 1.65] 1.6 Yawei Zhang 2006 1499 1571 1184 1244 1.06 [0.74; 1.50] 4.5 Hanna Romanowicz-Makowska 2008 66 100 72 106 0.92 [0.51; 1.64] 1.8 Patricia Rodrigues-2 2014 .408 .800 0.0 0.07 [0.04; 0.49] 1.2 Mada Cuchra 2015 154 169 219 222 0.14 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.95 [0.68; 1.34] 5.1 Inia Mordukhovich-2 2016 254 268 321 340 1.07 [0.53; 2.18] 1.1 Iria Mordukhovich-3 2016 298 315 289 302	nt Weight d) (random)	Weight (fixed)	5%-CI	95	OR	Ratio	Odds	TROL Total	CON Events	ASES Total		Study
Pavel Rossner 2006 990 1041 1038 1093 1.03 [0.70], 1.52] 3.7 Random effects model 1041 1093 1.03 [0.70], 1.52] 3.7 Random effects model 1041 1093 1.03 [0.70], 1.52] 3.7 Random effects model 1041 1093 1.03 [0.70], 1.52] 3.7 Random effects model 1499 1571 1184 1244 1.06 [0.74], 1.50] 4.5 Yawei Zhang 2006 1499 1571 1184 1244 1.06 [0.74], 1.50] 4.5 Patricia Rodrigues-2 2014 .408 .800 0.0 0.01 0.0 0.01 Hanna Romanowicz 2016 47 200 164 200 0.75 0.66; 1.34] 4.9 Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 10.66; 1.34] 51 0.0 Irina Mordukhovich-3 2016 258 302 20 0.76 10.98 1.43 1.10 Irina Mordukhovich-3 2016 258 315 289 302 0.77							8					race = Mixed
Random effects model 1.03 [0.70; 1.52] Heterogeneity: not applicable 1.03 [0.70; 1.52] race = Caucasoid 0.88 [0.48; 1.65] 1.6 Ulla Vogel 2003 403 425 414 434 0.88 [0.48; 1.65] 1.6 Yawei Zhang 2006 1499 1571 1184 1244 1.06 [0.74; 1.50] 4.5 Hanna Romanowicz-Makowska 2008 66 100 72 106 0.92 [0.51; 1.64] 1.8 Patricia Rodrigues-2 2014 .408 .800 0.07 Hanna Romanowicz 2016 47 200 164 200 0.07 Magda Cuchra 2015 154 169 219 222 0.14 [0.49; 0.49] 1.2 Michelle R.Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 5.1 Irina Mordukhovich-1 2016 288 302 290 302 0.85 [0.39; 1.87] 1.0 Irina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53; 2.18] 1.1 Irina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53; 1.65] 1.2 Fixed effect model 6337 7746 0.68 [0.58; 0.78] 32.4 Random effects model 0.65 [0.38; 1.11] 1.2 Heterogeneity: $f^* = 918, \tau^* = 0.7208, \rho < 0.01$ 1.82 245 1.12 [0.62; 1.80] 3.3 Guyin Cai 2	% 5.5%	3.7%	1.52]	[0.70;	1.03	←		1093	1038	1041	990	Pavel Rossner 2006
Heterogeneity: not applicable race = Caucasoid Ulla Vogel 2003 403 425 414 434 0.88 [0.48; 1.65] 1.6 Yawei Zhang 2006 1499 1571 1184 1244 1.06 [0.74; 1.50] 4.5 Patricia Rodrigues-1 2014 .347 .665 0.02 [0.51; 1.64] 1.8 Patricia Rodrigues-2 2014 .408 .800 0.07 [0.04; 0.11] 9.3 Madda Cuchra 2015 154 164 200 0.07 [0.04; 0.11] 9.3 Michelle R. Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 290 302 0.79 [0.38; 1.65] 1.2 Fixed effect model 6337 7746 0.68 [0.58; 0.78] 32.4 Alerogeneity: /* = 91%, r* = 0.7		3.7%				>	4	1093		1041		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	5.5%		1.52]	[0.70;	1.03	>	*					Random effects model
Ulla Vogel 2003 403 425 414 434 0.88 [0.48; 1.65] 1.6 Yawei Zhang 2006 1499 1571 1184 1244 1.06 [0.74; 1.50] 4.5 Hanna Romnowicz-Makowska 2008 66 100 72 106 0.92 [0.51; 1.64] 1.8 Patricia Rodrigues-1 2014 .347 665 0.00 0.07 [0.40; 0.11] 9.3 Magda Cuchra 2015 154 169 219 222 0.14 [0.04; 0.49] 1.2 Michelle R. Roberts 2011 1000 1054 1795 1887 0.95 [0.68; 1.34] 5.1 Michelle R. Roberts 2011 1000 1054 1795 1887 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.95 [0.68; 1.34] 5.1 1.0 1.11 1.0 1.0 1.03 1.0 1.174 0.95 [0.58; 1.20] 4.7 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0												Heterogeneity: not applicable
Yawei Zhang 2006 1499 1571 1184 1244 106 0.72 106 0.72 106 0.92 0.51 1.66 0.02 0.51 1.64 1.68 0.00 0.02 0.51 1.64 1.68 0.00 0.02 0.51 1.64 1.68 0.00 0.02 0.51 1.64 1.68 0.00 0.00 0.02 0.51 1.64 1.68 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.01 0.92 0.51 1.64 1.03 0.01 0.92 0.51 1.64 1.00 0.00 0.00 0.00 0.07 10.04 0.01 0.03 0.03 1.03 1.03 0.07 10.04 0.01 1.03 1.0												
Hanna Romanowicz-Makowska 2008 66 100 72 106 0.92 0.51 1.64 1 1 Patricia Rodrigues-1 2014 .347 .665 0.0 0.0 0.0 Hanna Romanowicz 2016 47 200 164 200 0.0 0.0 Hanna Romanowicz 2016 47 200 164 200 0.07 0.04; 0.01 9.3 Mada Cuchra 2015 154 169 219 22 0.14 10.04; 0.49 1.2 Michelle Roberts 2011 1000 1054 1795 1887 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.99 Irina Mordukhovich-2016 288 302 290 302 0.85 0.39; 1.87] 1.0 Irina Mordukhovich-2016 288 312 240 1.07 0.53; 2.18 1.1 Irina Mordukhovich-3 2016 288 315 289 302 0.79 0.38; 1.651 1.2 Irina Mordukhovich-3 2003 152 201 151	% 4.4%	1.6%	1.65]	[0.48;	0.88	-		434	414		403	Ulla Vogel 2003
Patricia Rodrigues-1 2014	% 5.7%	4.5%	1.50]	[0.74;	1.06	÷	1	1244	1184	1571	1499	Yawei Zhang 2006
Patricia Rodrigues-2 2014 .408 .800 0.0 Hanna Romanowicz 2016 47 200 164 200 0.07 [0.04; 0.11] 9.3 Magda Cuchra 2015 154 169 219 222 0.14 [0.07; [0.04; 0.11] 9.3 Michelle R. Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 200 302 0.85 [0.39; 1.87] 1.0 Irina Mordukhovich-3 2016 298 315 289 302 0.79 [0.38; 1.65] 1.2 Fixed effect model 6337 7746 0.68 [0.58; 0.78] 32.4 Heterogeneity: I* = 91%, r* = 0.7208, p < 0.01	% 4.6%	1.8%	1.64]	[0.51;	0.92	-		106	72	100	66	Hanna Romanowicz-Makowska 2008
Hanna Romanowicz 2016 47 200 164 200 - 0.07 [0.04; 0.11] 9.3 Magda Cuchra 2015 154 169 219 222 0.14 [0.04; 0.11] 9.3 Michelle R.Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 5.1 Beata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 290 302 0.65 [0.39; 1.87] 1.0 Irina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53; 2.18] 1.1 Heterogeneity: /* = 91%, * 6337 7746 0.68 [0.58; 1.20] 4.7 Heterogeneity: /* = 91%, * * = 0.7208, $\rho < 0.01$ 1102 151 184 0.68 [0.64] 1.01 12.7 Ji-Yeob Choi-2 2003 152 201 151 184 0.68 [0.64] 1.01 17.7 <	% 0.0%	0.0%					8	665		347		Patricia Rodrigues-1 2014
Michelle R, Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A, Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 4.9 Maria A, Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 51 Jeata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 290 302 0.85 [0.39; 1.87] 1.0 Irina Mordukhovich-3 2016 298 315 299 302 0.79 [0.38; 1.65] 1.2 Fixed effect model 6337 7746 0.68 [0.58; 0.78] 32.4 Random effects model 0.65 204 284 0.66 [0.38; 1.11] Heterogeneity, 1 ² = 91%, x ² = 0.7208, p < 0.01		0.0%					8	800		408		Patricia Rodrigues-2 2014
Michelle R, Roberts 2011 1000 1054 1795 1887 0.95 [0.67; 1.34] 4.9 Maria A, Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 4.9 Maria A, Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 51 Jeata Smolarz 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 290 302 0.85 [0.39; 1.87] 1.0 Irina Mordukhovich-3 2016 298 315 299 302 0.79 [0.38; 1.65] 1.2 Fixed effect model 6337 7746 0.68 [0.58; 0.78] 32.4 Random effects model 0.65 204 284 0.66 [0.38; 1.11] Heterogeneity, 1 ² = 91%, x ² = 0.7208, p < 0.01	% 5.0%	9.3%	0.11]	[0.04;	0.07		- 1	200	164	200	47	Hanna Romanowicz 2016
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	% 2.2%	1.2%	0.49]	[0.04;	0.14			222	219	169	154	Magda Cuchra 2015
Maria A. Loizidou 2009 1037 1108 1102 1174 0.95 [0.68; 1.34] 5.1 Beata Smolary 2013 55 70 54 70 1.09 [0.49; 2.41] 0.9 Irina Mordukhovich-1 2016 288 302 290 302 0.85 [0.39; 1.87] 1.0 Irina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53; 2.18] 1.1 Irina Mordukhovich-3 2016 298 315 289 302 0.85 [0.58; 1.078] 32.4 Random effects model 6337 7746 0.65 0.88 [0.58; 1.20] 4.7 Ji-Yeob Choi-1 2003 152 201 151 184 0.65 [0.48; 1.11] 1.8 Velop Choi-2 2003 152 201 151 184 0.68 [0.41; 1.11] 2.8 Ji-Yeob Choi-2 2003 152 201 151 184 0.68 [0.41; 1.11] 8.7 Mig-Shiean Hsu 2010 229 401 318 533 0.90 [0.69; 1.17] 8.7 Myoung-Yeon Kim 2013 406	% 5.7%	4.9%	1.34]	[0.67;	0.95	-		1887	1795	1054	1000	Michelle R.Roberts 2011
trina Mordukhovich-1 2016 288 302 290 302 0.85 [0.39] 1.87] 1.0 trina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53] 1.87] 1.0 trina Mordukhovich-2 2016 254 268 321 340 1.07 [0.53] 1.87] 1.0 Tina Mordukhovich-3 2016 298 315 289 302 0.79 [0.38] 1.65] 1.2 Fixed effect model 6337 7746 0.68 0.68 0.58: 0.78] 32.4 Random effects model 6337 7746 0.65 0.38 1.11 Heterogeneity: $l^* = 91\%$, $t^* = 0.7208$, $p < 0.01$ 720 1167 1.04 0.68 10.41 11.11 Trace = Mongoloid Ji-Yeob Choi-2 2003 152 201 151 184 0.68 10.41 11.2 Gluyin Cai 2006 720 1102 751 1167 1.04 0.88; 1.20] 4.7 Hai Luo 2014 129 194 152 245 1.21 10.84; 1.01 12.7 Suleeporn Sangrajrang 2008 344	% 5.7%	5.1%	1.34]	[0.68;	0.95	-		1174	1102	1108	1037	Maria A. Loizidou 2009
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	% 3.6%	0.9%	2.41]	[0.49;	1.09			70	54	70	55	Beata Smolarz 2013
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	% 3.7%	1.0%	1.87]	[0.39;	0.85	<u> </u>		302	290	302	288	Irina Mordukhovich-1 2016
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	% 4.0%	1.1%	2.18]	[0.53;	1.07	-		340	321	268	254	Irina Mordukhovich-2 2016
Random effects model 0.65 [0.38; 1.11] Heterogeneity: I* = 91%, s* = 0.7208, p < 0.01	% 3.9%	1.2%	1.65]	[0.38;	0.79	<u> </u>		302	289	315	298	Irina Mordukhovich-3 2016
Heterogeneity: $l^{\mu} = 91\%$, $z^{*} = 0.7208$, $p < 0.01$ race = Mongoloid Ji-Yeob Choi-1 2003 180 265 204 284 Qiuyin Cai 2003 152 201 151 184 0.68 [0.41; 1.11] 2.8 Qiuyin Cai 2006 720 1102 751 1167 1.04 [0.88; 1.24] 18.7 Ming-Shiean Hsu 2010 229 401 318 533 0.90 [0.69; 1.17] 8.7 Hao Luo 2014 129 194 152 245 1.21 [0.82; 1.80] 3.3 Kyoung-Yeon Kim 2013 275 361 273 346 0.68 [0.60; 1.22] 4.9 Suleeporn Sangrajrang 2008 344 506 321 424 0.68 [0.51; 0.91] 8.3 Fixed effect model 3660 3960 0.89 [0.81; 0.98] 64.0 Random effects model 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 0.77 [0.61; 0.96] 0.77 [0.61; 0.96] 100.0	%	32.4%	0.78]	[0.58;	0.68			7746		6337		Fixed effect model
race = Mongoloid Ji-Yeob Choi-1 2003 180 265 204 284 0.83 [0.58; 1.20] 4.7 Ji-Yeob Choi-2 2003 152 201 151 184 0.68 [0.41; 1.11] 2.8 Qiuyin Cai 2006 720 1102 751 1167 1.04 [0.88; 1.24] 18.7 Ming-Shiean Hsu 2010 229 401 318 533 0.90 [0.69; 1.17] 8.7 Hui Xie 2013 406 630 538 777 0.81 [0.64; 1.01] 12.7 Hao Luo 2014 129 194 152 245 1.21 [0.82; 1.80] 3.3 Kyoung-Yeon Kim 2013 275 361 273 346 0.68 [0.51; 0.91] 8.3 Suleeporn Sangrajrang 2008 344 506 321 424 0.68 [0.51; 0.91] 8.3 Random effects model 3660 3860 0.89 [0.77; 1.00] 0.88 [0.77; 1.00] Heterogeneity: $I^2 = 37\%$, $s^2 = 0.0122$, $p = 0.14$ Fixed effects model 0.83 [0.76; 0.90] 100.0 Random effects model	48.4%		1.11]	[0.38;	0.65	•	, ()					Random effects model
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $											< 0.01	Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.7208$, p
Ji-Yeob Choi-2 2003 152 201 151 184 -2 0.68 [0.41, 1.11] 2.8 Qiuyin Cai 2006 720 1102 751 1167 1.04 [0.88, 1.24] 18.7 Ming-Shiean Hsu 2010 229 401 318 533 0.90 [0.69; 1.17] 8.7 Hui Xie 2013 406 630 538 777 0.81 [0.64; 1.01] 12.7 Hao Luo 2014 129 194 152 245 1.21 [0.82; 1.80] 3.3 Kyoung-Yeon Kim 2013 275 361 273 346 0.68 [0.64; 1.01] 8.3 Fixed effect model 3660 3960 0.88 [0.51; 0.91] 8.3 Fixed effect model 0.88 0.77; 1.00] 0.88 [0.76; 0.90] 100.0 Hetrogeneity: $I^2 = 37\%$, $z^2 = 0.0122$, $p = 0.14$ 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 11038 12799 0.83 [0.76; 0.90] 100.0												race = Mongoloid
Qiuyin Cai 2006 720 1102 751 1167 1.04 [0.88, 1.24] 18.7 Ming-Shiean Hsu 2010 229 401 318 533 0.90 [0.68, 1.17] 8.7 Hui Xie 2013 406 630 538 777 0.81 [0.64; 1.01] 12.7 Hao Luo 2014 129 194 152 245 1.21 [0.82; 1.80] 3.3 Kyoung-Yeon Kim 2013 275 361 273 346 0.86 [0.60; 1.22] 4.9 Suleeporn Sangrajrang 2008 344 506 321 424 0.68 [0.51; 0.91] 8.3 Fixed effect model 3660 3960 0.89 [0.81; 0.98] 64.0 Random effects model 3660 3960 0.88 [0.77; 1.00] Heterogeneity: $I^2 = 37\%, \tau^2 = 0.0122, p = 0.14$ 0.88 [0.76; 0.90] 100.0 Random effects model 0.83 [0.76; 0.90] 100.0 Random effects model 11038 12799 0.83 [0.76; 0.90] 100.0 0.87 [0.76; 0.90] 100.0 0	% 5.6%	4.7%	; 1.20]	[0.58;	0.83	-			204		180	Ji-Yeob Choi-1 2003
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	% 5.0%	2.8%	; 1.11]	[0.41;	0.68	-		184	151	201	152	Ji-Yeob Choi-2 2003
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	% 6.3%	18.7%	1.24]	[0.88;	1.04	+-		1167	751	1102	720	Qiuyin Cai 2006
Hui Xie 2013 406 630 538 777 0.81 [0.64] (1.01] 12.7 Hao Luo 2014 129 194 152 245 1.21 [0.82] (1.80] 3.3 Kyoung-Yeon Kim 2013 275 361 273 346 0.86 [0.65] (1.22] 4.9 Suleeporn Sangrajrang 2008 344 506 321 424 0.68 [0.51] (0.91] 8.3 Fixed effect model 3660 3960 0.89 [0.81] (0.41 (1.0.98) 64.0 Random effects model 0.86 0.92 (p = 0.14 0.88 [0.77; 1.00] 0.88 [0.77; 1.00] Fixed effect model 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 0.77 [0.61] 0.96] 0.77 [0.61] 0.96]	% 6.0%	8.7%	1.17]	[0.69;	0.90	+	-	533	318	401	229	Ming-Shiean Hsu 2010
Hab Lub 2014 129 194 102 245 106 1.21 [0.62], 1.80] 3.3. Kyoung-Yeon Kim 2013 275 361 273 346 1 0.86 [0.60], 1.22] 4.9 Suleeporn Sangrajrang 2008 344 506 321 424 1 0.68 [0.51], 0.91] 8.3 Fixed effect model 3660 3960 9 0.88 [0.77; 1.00] 8.4 Heterogeneity: $l^2 = 37\%$, $\tau^2 = 0.0122$, $p = 0.14$ 0.88 [0.77; 1.00] 44.0 1038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 11038 12799 0.77 [0.61; 0.96] 100.0	% 6.2%	12.7%	1.01]	[0.64;	0.81			777	538	630	406	Hui Xie 2013
Suleeport Sangrajrang 2008 344 506 321 424 8.3 Fixed effect model 3660 3960 0.89 [0.81; 0.91] 8.3 Random effects model 0.88 0.77; 1.00] 0.88 [0.77; 1.00] Heterogeneity: l ² = 37%, r ² = 0.0122, p = 0.14 0.83 [0.76; 0.90] 100.0 0.83 [0.77; 1.00] Fixed effect model 11038 12799 0.83 [0.77; 10.61] .0.90] 100.0 Random effects model 0.77 [0.61] 0.96] 0.77 [0.61] 0.96] 0.77	% 5.5%	3.3%	1.80]	[0.82;	1.21	*	5	245	152	194	129	Hao Luo 2014
Suleeport Sangrajrang 2008 344 506 321 424	% 5.7%	4.9%	1.221	[0.60;	0.86	-		346	273	361	275	Kyoung-Yeon Kim 2013
Random effects model 0.88 [0.77; 1.00] Heterogeneity: /² = 37%, τ² = 0.0122, p = 0.14 0.83 [0.76; 0.90] 100.0 Fixed effect model 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 0.77 [0.61: 0.96] 0.77 [0.61: 0.96]	% 5.9%	8.3%	0.91	[0.51;	0.68		-	424	321	506	344	Suleeporn Sangrajrang 2008
Heterogeneity: <i>I</i> ² = 37%, <i>z</i> ² = 0.0122, <i>p</i> = 0.14 Fixed effect model 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 0.77 [0.61: 0.96]	%	64.0%	0.98]	[0.81;	0.89			3960		3660		Fixed effect model
Fixed effect model 11038 12799 0.83 [0.76; 0.90] 100.0 Random effects model 0.77 [0.61: 0.96]	46.1%		1.00]	[0.77;	0.88		¢.					
Random effects model 0.77 [0.61; 0.96]											= 0.14	Heterogeneity: $I^2 = 37\%$, $\tau^2 = 0.0122$, $p =$
		100.0%						12799		11038		
	100.0%		0.961	[0.61;	0.77							
Heterogeneity: J ² = 85%, τ ² = 0.2035, ρ < 0.01 0.1 0.5 1 2 10							I I .				< 0.01	Heterogeneity: / ² = 85%, τ ² = 0.2035, p ·

Figure 6: Forest plot of rs1052133 polymorphism in OGG1 and risk to breast cancer (CC+CG vs. GG) (the model adopted was marked by black frame).

Study		ASES Total	CON Events	TROL Total	Odds Ratio	OR		Weight (fixed)	Weight (random)
race = Mixed									
Pavel Rossner 2006	375	426	385	440		1.05	[0.70; 1.58]	3.8%	5.5%
Fixed effect model		426		440		1.05	[0.70; 1.58]	3.8%	
Random effects model					\diamond	1.05	[0.70; 1.58]		5.5%
Heterogeneity: not applicable									
race = Caucasoid									
Ulla Vogel 2003	147	169	169	189	<u> </u>	0.79	[0.42; 1.51]	1.7%	4.4%
Yawei Zhang 2006	532	604	424	484		1.05	[0.73; 1.51]	4.6%	5.7%
Hanna Romanowicz-Makowska 2008	34	68	52	86		0.65	[0.34; 1.24]	1.9%	4.4%
Patricia Rodrigues-1 2014								0.0%	0.0%
Patricia Rodrigues-2 2014								0.0%	0.0%
Hanna Romanowicz 2016	24	177	120	156		0.05	[0.03; 0.08]	9.1%	4.8%
Magda Cuchra 2015	54	69	65	68		0.17	[0.05; 0.60]	1.2%	2.2%
Michelle R.Roberts 2011	366	420	670	762	1	0.93	[0.65; 1.33]	5.1%	5.7%
Maria A. Loizidou 2009	422	493	455	527		0.94	[0.66; 1.34]	5.2%	5.8%
Beata Smolarz 2013	39	54	38	54	<u> </u>	1.09	[0.48; 2.52]	0.9%	3.6%
Irina Mordukhovich-1 2016	100	114	96	108		0.89	[0.39; 2.03]	1.0%	3.7%
Irina Mordukhovich-2 2016	108	122	120	139		1.22	[0.58; 2.55]	1.1%	4.0%
Irina Mordukhovich-3 2016	114	131	113	126		0.77	[0.36; 1.66]	1.2%	3.9%
Fixed effect model		2421		2699	A	0.66	[0.57; 0.77]	33.1%	
Random effects model						0.61	[0.35; 1.07]		48.2%
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.7623$, p	< 0.01								
race = Mongoloid									
Ji-Yeob Choi-1 2003	132		155	235			[0.55; 1.18]	4.8%	5.6%
Ji-Yeob Choi-2 2003	95		89	122	- <u></u>	0.72	[0.42; 1.22]	2.7%	5.0%
Qiuyin Cai 2006	534		537	953			[0.90; 1.30]	18.2%	6.4%
Ming-Shiean Hsu 2010	165		231	446	蓋		[0.67; 1.18]	8.4%	6.0%
Hui Xie 2013	310		401	640			[0.65; 1.04]	12.7%	6.2%
Hao Luo 2014	87	152	107	200			[0.76; 1.78]	3.3%	5.4%
Kyoung-Yeon Kim 2013	185	271	181	254			[0.60; 1.26]	4.9%	5.7%
Suleeporn Sangrajrang 2008	232		217	320			[0.50; 0.93]	8.2%	5.9%
Fixed effect model		2965		3170	ø		[0.82; 1.00]	63.2%	
Random effects model					8	0.89	[0.78; 1.01]		46.3%
Heterogeneity: $I^2 = 31\%$, $\tau^2 = 0.0105$, p	= 0.18								
Fixed effect model		5812		6309	0		[0.76; 0.90]		,
Random effects model						0.75	[0.59; 0.95]		100.0%
Heterogeneity: $I^2 = 84\%$, $\tau^2 = 0.2155$, p	< 0.01								
					0.1 0.5 1 2 10				

Figure 7: Forest plot of rs1052133 polymorphism in OGG1 and thus risk to breast cancer (CG vs. GG) (the model adopted was marked by black frame).

this meta-analysis found the rs1760944 (also known as -656T > G) variants was associated with an incaresed risk of developing BC in Mongoloid populations, or more specifically, in the Chinese population. Rs1760944 polymorphism is located on Polymorphisms in a promoter region and is located –141bp upstream from the transcription initiation site. Variants in the promoter region, or 3'UTR, of a gene may influence its function and lead to abnormal protein expression. Function studies have proved that Rs1760944 mutation can influence its activity of communicating to other BER proteins [69].

The key role of OGG1 protein is to cleave 8-hydroxyguanine. [90] Rs1052133, also known as Ser326Cys, is a SNP on the OGG1 gene, and the minor (G) allele, encoding the cysteine. This paper found that in contrast to the GG genotype, people who carried the CC or CG genotype had a lower risk of developing BC in both the Mongoloid and Caucasoid race populations. This study indicated that rs1052133 may follow a recessive inheritance pattern in BC susceptibility, because the OR of CC vs. GG genotypes was similar to CG vs. GG genotypes (results shown in Table 4). Lee et al. (2015) found that ability of oxidative DNA damage repair was significant lower in GG genotype individuals than non-GG genotype individuals [91].

CONCLUSIONS

This study suggests that rs1052133, rs25487 and rs1760944 polymorphisms may influence individual susceptibility to risk of developing BC, and provides evidence which supports the idea that mutations of the DNA repair genes are associated to BC risk. The understanding of BC etiology and roles in the potential biological pathways linking DNA repair, ethnic background, environment and BC need to be studied further.

Study	-	ASES Total	CON Events	TROL Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
race = Mixed	045		050	700		4 00	10 00 4 541	F 00/	0.40/
Pavel Rossner 2006	615	666	653	708			[0.68; 1.51]	5.6%	6.1%
Fixed effect model		666		708	Ĭ		[0.68; 1.51]	5.6%	C 40/
Random effects model						1.02	[0.68; 1.51]		6.1%
Heterogeneity: not applicable									
race = Random	050	070	045	005		0.05	10 54. 4 701	0.00/	4.00/
Ulla Vogel 2003	256	278 1039	245	265			[0.51; 1.78]	2.3%	4.3%
Yawei Zhang 2006	967		760	820	3		[0.74; 1.51]	6.8%	6.4%
Hanna Romanowicz-Makowska 2008	32	66	20	54	3	1.60	[0.77; 3.33]	1.3% 0.0%	3.7% 0.0%
Patricia Rodrigues-1 2014 Patricia Rodrigues-2 2014				•	3			0.0%	0.0%
Hanna Romanowicz 2016	23	176	44	80	1	0 12	[0.07; 0.23]	6.0%	4.4%
Magda Cuchra 2015	100	115		157			[0.07; 0.23]	2.0%	4.4%
Michelle R.Roberts 2011	634	688	1125	1217	<u>1</u>		[0.68; 1.36]	7.3%	6.5%
Maria A. Loizidou 2009	615	686		719	<u>=</u>		[0.68; 1.36]	7.5%	6.5%
Beata Smolarz 2013	16	31	16	32	<u> </u>		[0.40; 2.87]	0.9%	2.5%
Irina Mordukhovich-1 2016	188	202		206			[0.37; 1.84]	1.5%	3.3%
Irina Mordukhovich-2 2016	146	160		220			[0.48; 2.03]	1.7%	3.7%
Irina Mordukhovich-3 2016	184	201	176	189			[0.38; 1.69]	1.8%	3.6%
Fixed effect model	101	3642		3959	à		[0.70; 0.96]	39.0%	0.070
Random effects model		0011			\sim		[0.49; 1.09]	==	46.6%
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.3335$, p	< 0.01								
race = Mongoloid									
Ji-Yeob Choi-1 2003	48	133	49	129		0.92	[0.56; 1.52]	3.7%	5.2%
Ji-Yeob Choi-2 2003	57	106	62	95	<u></u>	0.62	[0.35; 1.09]	3.5%	4.7%
Qiuyin Cai 2006	186	568	214	630	÷	0.95	[0.74; 1.20]	15.7%	7.3%
Ming-Shiean Hsu 2010	64	236	87	302	- <u>+</u> -		[0.63; 1.34]	6.4%	6.2%
Hui Xie 2013	96	320	137	376		0.75	[0.54; 1.03]	10.1%	6.7%
Hao Luo 2014	42	107	45	138	<u>}</u>	1.34	[0.79; 2.26]	2.7%	5.0%
Kyoung-Yeon Kim 2013	90	176		165		0.83	[0.54; 1.27]	5.3%	5.8%
Suleeporn Sangrajrang 2008	112		104	207		0.68	[0.48; 0.99]	8.0%	6.3%
Fixed effect model		1920		2042	<u> </u>	0.86	[0.75; 0.98]	55.4%	
Random effects model Heterogeneity: $I^2 = 1\%$, $\tau^2 = 0.0002$, $p =$	0.43					0.85	[0.75; 0.98]		47.3%
Fixed effect model		6228		6709		0.85	[0.77; 0.94]	100 0%	
Random effects model				5.05			[0.68; 0.99]		100.0%
Heterogeneity: $I^2 = 68\%$, $\tau^2 = 0.1112$, p	< 0.01					3102	[0.00, 0.00]		1001070
	5.01				0.1 0.5 1 2 10				

Figure 8: Forest plot of rs1052133 polymorphism in OGG1 and thus risk to breast cancer (CC vs. GG) (the model adopted was marked by black frame).

CONFLICTS OF INTEREST

The authors state that there are no conflicts of interest to disclose.

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