Original Article Association of three common BARD1 variants with cancer susceptibility: a system review and meta-analysis

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Abstract: BARD1 has been shown to play tumor suppressive roles in human cancer. We performed this meta-analysis and firstly evaluated the association between three common BARD1 polymorphisms (Arg378Ser, Val507Met and Pro24Ser) and cancer susceptibility. We performed this meta-analysis following PRISMA guidelines. A comprehensive search of PubMed, EMBASE, Cochrane Library, OVID and Web of Science databases was done from database inception to August 2014. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were combined to measure the association between BARD1 polymorphisms and cancer risk. On the basis of 10 studies about BARD1 polymorphisms and cancer, we found that BARD1 Val507Met (G/A) polymorphism was associated with decreased cancer susceptibility (allelic model: OR = 0.76, 95% CI: 0.66-0.87, P < 0.00001; dominant model: OR = 0.77, 95% CI: 0.65-0.91, P < 0.00001; recessive model: OR = 0.64, 95% CI: 0.55-0.74, P < 0.00001; homozygote comparison: OR = 0.58, 95% CI: 0.49-0.70, P < 0.00001; heterozygote comparison: OR = 0.85, 95% CI: 0.74-0.99 , P = 0.0008). BARD1 Pro24Ser (C/T) polymorphism was also associated decreased cancer risk in allelic model (OR = 0.72, 95% CI: 0.60-0.88, P = 0.0009), dominant model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), recessive model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), homozygote comparison (OR = 0.55, 95% CI: 0.39-0.78, P = 0.0007) and heterozygote comparison (OR = 0.75, 95% CI: 0.62-0.91, P = 0.004). And in our sensitivity analysis, when deleting the study performed by Capasso in 2009, we found that BARD1 Arg378Ser polymorphism was associated with decreased cancer risk in allelic model (OR = 0.81, 95% CI: 0.67-0.97, P = 0.02), dominant model (OR = 0.72, 95% CI: 0.56-0.91, P = 0.007) and heterozygote comparison (OR = 0.72, 95% CI: 0.57-0.91, 0 = 0.006). In conclusion, BARD1 Arg378Ser, Val507Met and Pro24Ser may be associated with decreased cancer risk. More studies with larger samples and gene-environment interactions are needed to confirm our findings.

Keywords: BARD1, polymorphism, cancer risk, meta-analysis

Introduction

BRCA1-associated RING domain protein-1 (BARD1) is firstly identified through a yeast twohybrid screen using a BRCA1 RING domain as bait. The BARD1 gene has been localized to the distal end of chromosome 2q and shares homology with two highly conserved domains of BRCA1 [1]. BRCA1 and BARD1 interact via their respective amino terminal RING finger domains, and both proteins have BRCT domains at their C-terminal [2]. The interaction between BRCA1 and BARD1 is mediated via their RINGfinger motifs [3]. Functional studies have demonstrated that disruption of the endogenous BRCA1–BARD1 complex decreases homologydirected repair, which is important to the tumorsuppressor activity of BRCA1 [4].

Since BARD1 stabilizes BRCA1 by binding with it and participates with BRCA1 in mediating tumor suppressor functions, BARD1 is also regarded as a kind of tumor suppressor [5]. BARD1 has been implicated in multiple crucial cellular processes including DNA repair [6], RNA processing [7], apoptosis [8], cell cycle regulation [9] and transcription [10]. The tumor suppressor functions of BARD1 may be affected by functional single nucleotide polymorphisms (SNPs) [11]. Some BARD1 polymorphism like Arg378Ser (rs2229571), Val507Met (rs2070-094), and Pro24Ser (rs1048108) were reported to be associated with cancer susceptibility recently.

As BARD1 plays important roles in some types of cancer in which these mutations occur [12], the aim of this meta-analysis was to assess whether combined evidence showed the association between three BARD1 polymorphisms (Arg378Ser, Val507Met and Pro24Ser) and cancer risk.

Materials and methods

Literature search

The PRISMA statement (Checklist S1) was followed in our meta-analysis. A comprehensive search of EMBASE, PubMed, Web of Science, OVID, Cochrane Library and China National Knowledge Infrastructure (CNKI) was performed from database inception to August 10, 2014 without language restriction. The search strategy was "BRCA1-associated RING domain protein-1 or BARD1 or BARD-1" and "polymorphism or variant or mutation or genotype". We also read the review articles and reference lists of retrieved articles manually to complete our research. The database search was performed by X. Zhang and X. Liu respectively and the disagreements were resolved through consensus by all of the authors.

Selection criteria

Studies were included in the meta-analysis if the following inclusion criteria were satisfied:1) case-control studies focused on association between the BARD1 polymorphisms (Arg-378Ser, Val507Met, Pro24Ser) and cancer risk: 2) more than 30 patients were enrolled in each study; 3) studies provided sufficient data to estimate the odds ratio (OR) and 95% confidence intervals (CI) according to BARD1 polymorphisms; 4) when study patients overlapped with patients in other included studies, we selected the study firstly published. The two researchers (X. Liu and X. Zhang) read the titles and abstracts and excluded the uncorrelated studies, respectively; then the full-texts were examined by our review team. The studies would be included due to the inclusion criteria.

Data abstraction

Two reviewers (X. Zhang and X. Liu) independently extracted the following information: authors, year of publication, country, tumor type, number of cases and controls analyzed, mean value of age, source of controls (hospitalbased controls or population-based controls), genotyping method. If insufficient data (missing data, inconsistencies, or any other uncertainties) were reported in articles, we tried our best to ask the first and corresponding authors for necessary information by telephone or E-mail.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were combined to measure the association between BARD1 polymorphisms and cancer susceptibility. The pooled ORs were calculated for the allelic model (mutation [M] allele versus [vs] wild [W] allele), dominant model (WM + MM vs WW), recessive model (MM vs WM + WW), homozygote comparison (MM vs WW) and heterozygote comparison (WM vs WW), respectively. And P values < 0.05 indicated statistical significance. Statistical heterogeneity among the studies was evaluated using the Q test and I² test. When heterogeneity among the studies was observed, the pooled OR was calculated by randomeffects models. Sensitivity analyses were performed to identify the potential influence of the individual data set to the pooled ORs. Subgroup analyses were performed with respect to ethnicity, tumor type and source of controls. These analyses were performed by Review Manager Version 5.1 software (http://ims.cochrane.org/ revman). The Begg's and Egger's test was performed by R (http://cran.r-project.org/bin/windows/base).

Results

Characteristics of identified studies

Following an initial search, 131 studies were searched in PubMed, 158 studies were searched in EMBASE, 375 studies were searched in OVID, 156 studies were searched in Web of Science, 0 were searched in Cochrane Library. 288 published studies were identified after duplicates were removed. 213 studies were excluded by reading titles and abstracts. Next, full-text of the remaining 75 studies were downloaded and the unrelated studies were exclud-



ed. We tried our best to communicate with the first and corresponding author to get the complete data in some articles. Some authors were kind to provide the data for us. Eventually, ten studies were included in our meta-analysis [13-22]. The selection process was showed in **Figure 1.** These ten studies were published between 2003 and 2013. There were eight studies evaluating BARD1 Arg378Ser polymorphism, eight studies evaluating Val507Met polymorphism and eight studies evaluating Pro24Ser polymorphism and cancer susceptibility, respectively. Studies were carried out in China, France, Japan, Finland, Canada and USA. The control of two studies was hospitalbased [15, 19] and population-based control was in the other eight studies [13, 14, 16-18, 20-22]. Seven studies assessed breast cancer [13-17, 19, 22], two studies assessed neuroblastoma [18, 21] and one studies assessed cervical cancer [20]. The main characteristics of all the included studies is shown in <u>Table S1</u>.

Meta-analysis

A significant association between BARD1 Val507Met (G/A) polymorphism and cancer susceptibility was found in allelic model (OR = В

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A Val50	7Met (G/A) allelic model	(A allele vs	G allele)
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	Experim	ental	Contr	lo		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Capasso 2009	363	1078	890	2012	16.3%	0.64 [0.55, 0.75]	•	
Capasso 2013	131	652	465	1550	13.4%	0.59 [0.47, 0.73]	-	
Gunerd 2009	60	192	71	196	7.0%	0.80 [0.52, 1.22]		
Huo 2007	348	1014	399	1078	15.2%	0.89 [0.74, 1.06]	-	
Ishitobi 2003	31	106	113	304	5.9%	0.70 [0.43, 1.13]		
Liu 2013	461	1610	484	1590	16.4%	0.92 [0.79, 1.07]	+	
Sun 2012	88	288	108	272	8.8%	0.67 [0.47, 0.95]		
Vahteristo 2006	804	1734	716	1436	16.9%	0.87 [0.76, 1.00]	1	
Total (95% CI)		6674		8438	100.0%	0.76 [0.66, 0.87]	•	
Total events	2286		3246					
Heterogeneity: Tau*=	0.02; Chi ^a	= 22.44	, df = 7 (P = 0.0	02); I [#] = 6	9%		
Test for overall effect	Z = 3.89 (< 0.00	01)				Favours experimental Favours control	ol

C Val507Met (G/A) recessive model (AA vs GA+GG)

	Experim	ental	Contr	lor		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	_
Capasso 2009	101	539	282	1006	26.4%	0.59 [0.46, 0.77]	•	
Capasso 2013	24	326	109	775	9.9%	0.49 [0.31, 0.77]		
Gunerd 2009	10	96	12	98	2.9%	0.83 [0.34, 2.03]		
Huo 2007	49	507	69	539	13.5%	0.73 [0.49, 1.07]	-	
Ishitobi 2003	7	53	27	152	2.8%	0.70 [0.29, 1.73]		
Liu 2013	31	805	55	795	10.4%	0.54 [0.34, 0.85]		
Sun 2012	12	144	27	136	4.3%	0.37 [0.18, 0.76]		
Vahteristo 2006	178	867	179	718	29.8%	0.78 [0.61, 0.99]	•	
Total (95% CI)		3337		4219	100.0%	0.64 [0.55, 0.74]	•	
Total events	412		760					
Heterogeneity: Tau* =	0.01; Chi*	= 7.97	df = 7 (P	= 0.34)	; I ² = 129	6		d
Test for overall effect	Z= 5.75 (F	P < 0.00	001)				avours experimental Favours control	,

E Val507Met (G/A) heterozygote comparison (GA vs GG)

	Experim	ental	Contr	lo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Capasso 2009	161	438	326	724	17.1%	0.71 [0.56, 0.90]	+
Capasso 2013	83	302	247	666	13.8%	0.64 [0.48, 0.87]	
Gunerd 2009	40	86	47	86	5.0%	0.72 [0.40, 1.31]	
Huo 2007	250	458	261	470	16.1%	0.96 [0.74, 1.25]	+
Ishitobi 2003	17	46	59	125	3.9%	0.66 [0.33, 1.31]	
Liu 2013	399	774	374	740	20.0%	1.04 [0.85, 1.27]	+
Sun 2012	64	132	54	109	6.6%	0.96 [0.58, 1.59]	+
Vahteristo 2006	448	689	355	539	17.5%	0.96 [0.76, 1.22]	+
Total (95% CI)		2925		3459	100.0%	0.85 [0.74, 0.99]	•
Total events	1462		1723				
Heterogeneity: Tau* =	0.02; Chi ²	= 12.17	7, df = 7 (P = 0.1	0); I [#] = 42	%	
Test for overall effect	Z= 2.14 (8	P = 0.03	9			F	avours experimental Favours control

Val507Met (G/A) dominant model (AA+AG vs GG)

	Experim	ental	Contr	lo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Capasso 2009	262	539	608	1006	16.8%	0.62 [0.50, 0.76]	•
Capasso 2013	107	326	356	775	14.3%	0.58 [0.44, 0.75]	-
Gunerd 2009	50	96	59	98	6.3%	0.72 [0.41, 1.27]	
Huo 2007	299	507	330	539	15.3%	0.91 [0.71, 1.17]	+
Ishitobi 2003	24	53	86	152	5.4%	0.64 [0.34, 1.19]	
Liu 2013	430	805	429	795	17.4%	0.98 [0.80, 1.19]	+
Sun 2012	76	144	81	136	8.1%	0.76 [0.47, 1.22]	
Vahteristo 2006	626	867	534	718	16.3%	0.90 [0.72, 1.12]	1
Total (95% CI)		3337		4219	100.0%	0.77 [0.65, 0.91]	•
Total events	1874		2483				
Heterogeneity: Tau* =	0.03; Chi ^a	= 17.99	9, df = 7 (P = 0.01	1); 2 = 61	%	
Test for overall effect	Z = 3.08 (P = 0.00	2)		F	avours experimental Favours control	

D Val507Met (G/A) homozygote comparison (AA vs GG)

	Experim	ental	Control			Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI		
Capasso 2009	101	378	282	680	25.7%	0.51 (0.39, 0.68	•		
Capasso 2013	24	243	109	528	11.6%	0.42 [0.26, 0.67			
Gunerd 2009	10	56	12	51	3.3%	0.71 [0.28, 1.81			
Huo 2007	49	257	69	278	14.4%	0.71 [0.47, 1.08			
Ishitobi 2003	7	36	27	93	3.4%	0.59 [0.23, 1.51	+		
Liu 2013	31	406	55	421	12.0%	0.55 [0.35, 0.87			
Sun 2012	12	80	27	82	4.9%	0.36 [0.17, 0.77			
Vahteristo 2006	178	419	179	363	24.8%	0.76 [0.57, 1.01	•		
Total (95% CI)		1875		2496	100.0%	0.58 [0.49, 0.70	· •		
Total events	412		760						
Heterogeneity: Tau* =	0.01; Chi*	= 8.63,	df = 7 (P	= 0.28	; I ² = 199	6			
Test for overall effect Z = 5.99 (P < 0.00001)							Favours experimental Favours control		

Figure 2. Forest plot of BARD1 Val507Met polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Val507Met polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Val507Met polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Val507Met polymorphism and cancer risk in recessive model; D. Forest plot of BARD1 Val507Met polymorphism and cancer risk in homozygote comparison; E. Forest plot of BARD1 Val507Met polymorphism and cancer risk in heterozygote comparison.

В

D

A Pro24Ser (C/T) allelic model (T allele vs C allele)

Pro24Ser (C/T) dominant model (TT+CT vs CC)

	Experim	ental	Contr	lo		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Rand	om, 95% CI
Capasso 2009	308	1122	798	2182	14.0%	0.66 (0.56, 0.77	1 •	
Capasso 2013	154	564	553	1500	13.0%	0.64 [0.52, 0.80	i •	
Gunerd 2009	55	192	59	190	8.6%	0.89 [0.57, 1.38	1 -	-
Huo 2007	311	1014	392	1078	13.6%	0.77 [0.65, 0.93	•	
Liu 2013	521	1610	542	1590	14.2%	0.93 [0.80, 1.07	i ·	
Onay 2006	260	796	276	744	13.1%	0.82 [0.67, 1.01	i -	
Sun 2012	108	288	181	272	10.3%	0.30 [0.21, 0.43		
Zhou 2009	287	808	291	808	13.2%	0.98 [0.80, 1.20	i '	•
Total (95% CI)		6394		8364	100.0%	0.72 [0.60, 0.88	ı •	
Total events	2004		3092					
Heterogeneity: Tau*:	= 0.06; Chi ²	= 46.82	2, df = 7 (P < 0.0	0001); P	= 85%		10 10
Test for overall effect	Z = 3.31 (P = 0.00	09)				Favours experimental	Favours control

C Pro24Ser (C/T) recessive model (TT vs CT+CC)

Experimental		Contr	lo		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Capasso 2009	45	561	155	1091	14.4%	0.53 [0.37, 0.75]	-	
Capasso 2013	28	282	99	750	13.0%	0.72 [0.47, 1.13]		
Gunerd 2009	11	96	10	95	7.1%	1.10 [0.44, 2.73]	-	
Huo 2007	52	507	71	539	13.9%	0.75 [0.52, 1.10]		
Liu 2013	52	805	78	795	14.1%	0.63 [0.44, 0.91]	-	
Onay 2006	36	398	46	372	12.7%	0.70 [0.44, 1.12]		
Sun 2012	21	144	66	136	11.0%	0.18 [0.10, 0.32]		
Zhou 2009	59	404	59	404	13.8%	1.00 [0.68, 1.48]	+	
Total (95% CI)		3197		4182	100.0%	0.63 [0.46, 0.86]	•	
Total events	304		584					
Heterogeneity: Tau* =	0.14; Chi ^a	= 27.50	0, df = 7 (P = 0.0	003); I [#] =	75%	has also in the second	-
Test for overall effect	7 = 2 91 (5	P = 0.00	4)				0.01 0.1 1 10 10	0

E Pro24Ser (C/T) heterozygote comparison (CT vs CC)

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Capasso 2009	218	516	488	936	15.9%	0.67 [0.54, 0.83]	•
Capasso 2013	98	254	355	651	13.5%	0.52 [0.39, 0.70]	-
Gunerd 2009	33	85	39	85	6.5%	0.75 [0.41, 1.38]	
Huo 2007	207	455	250	468	14.6%	0.73 [0.56, 0.94]	-
Liu 2013	417	753	386	717	16.3%	1.06 [0.87, 1.31]	+
Onay 2006	188	362	184	326	13.4%	0.83 [0.62, 1.13]	-
Sun 2012	66	123	49	70	6.4%	0.50 [0.27, 0.92]	
Zhou 2009	169	345	173	345	13.4%	0.95 [0.71, 1.29]	+
Total (95% CI)		2893		3598	100.0%	0.75 [0.62, 0.91]	•
Total events	1396		1924				
Heterogeneity: Tau* =	0.05; Chi*	= 21.84	4, df = 7 ()	P = 0.0	03); I [#] = 68	%	
Test for overall effect: Z = 2.90 (P = 0.004)						0.01 0.1 1 10 100	

Experimental Control Odds Ratio Odds Ratio M-H, Random, 95% CI Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Capasso 2009 263 561 643 1091 14.9% 0.61 [0.50, 0.75] Capasso 2013 126 282 454 750 13.5% 0.53 [0.40, 0.69] -Gunerd 2009 44 96 49 95 7.9% 0.79 [0.45, 1.40] 507 321 539 14.1% 0.71 [0.56, 0.91] Huo 2007 259 Liu 2013 469 805 464 795 15.0% 1.00 [0.82, 1.21] Onay 2006 224 398 230 372 13.2% 0.79 [0.60, 1.06] Sun 2012 87 144 115 136 7.9% 0.28 [0.16, 0.49] 228 404 232 404 13.4% Zhou 2009 0.96 [0.73, 1.27] Total (95% CI) 3197 4182 100.0% 0.70 [0.56, 0.87] Total events 1700 2508 Heterogeneity. Tau# = 0.07; Chi# = 32.45, df = 7 (P < 0.0001); I# = 78% 0.01 0.1 10 100 Test for overall effect Z = 3.26 (P = 0.001) Favours experimental Favours control

Pro24Ser (C/T) homozygote comparison (TT vs CC)

	Experim	ental	Contr	rol		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Rando	m, 95% Cl	
Capasso 2009	45	343	155	603	14.4%	0.44 [0.30, 0.63]			
Capasso 2013	28	184	99	395	13.2%	0.54 [0.34, 0.85	·		
Gunerd 2009	11	63	10	56	7.6%	0.97 (0.38, 2.50	i —		
Huo 2007	52	300	71	289	13.9%	0.64 [0.43, 0.96]	i		
Liu 2013	52	388	78	409	14.2%	0.66 [0.45, 0.96]	i		
Onay 2006	36	210	46	188	12.8%	0.64 [0.39, 1.04	·		
Sun 2012	21	78	66	87	10.1%	0.12 [0.06, 0.24			
Zhou 2009	59	235	59	231	13.7%	0.98 [0.64, 1.48]	i –	-	
Total (95% CI)		1801		2258	100.0%	0.55 [0.39, 0.78]	•		
Total events	304		584						
Heterogeneity: Tau*:	= 0.19; Chi ²	= 30.43	3, df = 7 (P < 0.0	001); l ^a =	77%		10	100
Test for overall effect	Z = 3.37 (P = 0.00	07)				Favours experimental	Favours contro	100

Figure 3. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in recessive model; D. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in homozygote comparison; E. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in heterozygote comparison.

В

A Arg378Ser (G/C) allelic model (C allele vs G allele)

Study or Subgroup	Events	Total	Events	Total	Weight	Odds Ratio M-H, Random, 95% C	Odds Rat M-H, Random,	io 95% CI
Capasso 2009	568	1124	928	2206	14.9%	1.41 [1.22, 1.63	•	
Capasso 2013	246	700	779	1618	14.4%	0.58 [0.49, 0.70	•	
Gunerd 2009	119	192	106	176	10.8%	1.08 [0.71, 1.64	i +	
Huo 2007	334	1014	396	1078	14.4%	0.85 [0.71, 1.01	i •	
Ishitobi 2003	6	120	19	304	4.7%	0.79 [0.31, 2.03	i —+-	
Liu 2013	474	1610	551	1590	14.8%	0.79 [0.68, 0.91	· •	
Sun 2012	85	288	105	272	11.9%	0.67 [0.47, 0.95	i	
Zhou 2009	307	834	286	808	14.2%	1.06 [0.87, 1.30	i t	
Total (95% CI)		5882		8052	100.0%	0.88 [0.69, 1.12	ı 🔶	
Total events	2139		3170					
Heterogeneity: Tau* =	0.10; Ch	#= 67.5	91, df = 7	(P < 0.	00001);1	*= 90%		
Test for overall effect	Z=1.03	(P = 0.3	(0)	<i>.</i>			Favours experimental Fa	10 10 wours control

C Arg378Ser (G/C) recessive model (CC vs GC+GG)

	Experim	ental	Contr	Control		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1 M-H, Random, 95% CI	
Capasso 2009	145	562	188	1103	16.8%	1.69 [1.32, 2.16	1 +	
Capasso 2013	61	350	208	809	16.0%	0.61 [0.44, 0.84	á 🗕	
Gunerd 2009	35	96	30	88	12.3%	1.11 [0.61, 2.03	i —	
Huo 2007	44	507	68	539	15.0%	0.66 [0.44, 0.98	i —	
Liu 2013	74	805	65	795	15.6%	1.14 [0.80, 1.61	i 🛨	
Sun 2012	9	144	19	136	9.6%	0.41 [0.18, 0.94	i —	
Zhou 2009	59	417	44	404	14.8%	1.35 [0.89, 2.05	a 🕂	
Total (95% CI)		2881		3874	100.0%	0.94 [0.65, 1.37	i 🔶	
Total events	427		622					
Heterogeneity: Tau*:	0.20; Chi ^a	= 37.5	0, df = 6 (P < 0.0	0001); P:	= 84%		
Test for overall effect	Z=0.32 (P = 0.75)				Favours experimental Favours control	

E Arg378Sr (G/C) heterozygote comparison (GC vs GG)

	Contr	ol		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Capasso 2009	278	417	552	915	15.6%	1.32 [1.03, 1.68]	•
Capasso 2013	124	289	363	601	14.9%	0.49 [0.37, 0.65]	+
Gunerd 2009	49	61	46	58	6.3%	1.07 [0.43, 2.61]	
Huo 2007	246	463	260	471	15.4%	0.92 [0.71, 1.19]	i +
Ishitobi 2003	6	60	19	152	5.6%	0.78 [0.29, 2.05]	·
Liu 2013	326	731	421	730	16.1%	0.59 [0.48, 0.73]	•
Sun 2012	67	135	67	117	11.3%	0.74 [0.45, 1.21]	
Zhou 2009	189	358	198	360	14.8%	0.92 [0.68, 1.23]	· +
Total (95% CI)		2514		3404	100.0%	0.80 [0.61, 1.06]	•
Total events	1285		1926				
Heterogeneity: Tau ^a =	0.12; Chi ^a	= 37,88	8, df = 7 (P < 0.00	0001); l ^a =	82%	
Test for overall effect	Z = 1.53 (F	P = 0.13)				Favours experimental Favours control

Arg378Ser (G/C) dominant model (CC+GC vs GG)

Study or Subgroup	Events	Total	Events	Total	Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
Capasso 2009	423	562	740	1103	15.0%	1.49 [1.19, 1.88]	-
Capasso 2013	185	350	571	809	14.7%	0.47 [0.36, 0.61]	-
Gunerd 2009	84	96	76	88	7.4%	1.11 [0.47, 2.61]	
Huo 2007	290	507	328	539	14.8%	0.86 [0.67, 1.10]	-
Ishitobi 2003	6	60	19	152	6.4%	0.78 [0.29, 2.05]	
Liu 2013	400	805	486	795	15.3%	0.63 [0.51, 0.77]	-
Sun 2012	76	144	86	136	11.9%	0.65 [0.40, 1.05]	
Zhou 2009	248	417	242	404	14.5%	0.98 [0.74, 1.30]	+
Total (95% CI)		2941		4026	100.0%	0.81 [0.59, 1.11]	•
Total events	1712		2548				
Heterogeneity: Tau* =	0.16; Ch	P = 54.	44, df = 7	(P < 0.	00001); (*= 87%	
Test for overall effect	Z=1.29	(P = 0.2	20)				0.01 0.1 1 10 100 Favours experimental Favours control



Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Capasso 2009 145 284 188 551 16.1% 2.01 [1.50, 2.70] Capasso 2013 61 226 208 446 15.7% 0.42 [0.30, 0.60] 35 47 30 42 10.9% Gunerd 2009 1.17 [0.46, 2.98] 44 261 68 279 15.2% 0.63 [0.41, 0.96] Huo 2007 Liu 2013 74 479 65 374 15.6% 0.87 [0.60, 1.25] 9 77 0.35 [0.15, 0.83] Sun 2012 19 69 11.4% Zhou 2009 59 228 44 206 15.0% 1.29 [0.82, 2.01] Total (95% CI) 1602 1967 100.0% 0.83 [0.50, 1.40] Total events 427 622 Heterogeneity: Tau² = 0.41; Chi² = 57.18, df = 6 (P < 0.00001); P = 90% 0.01 0.1 10 100 Test for overall effect: Z = 0.69 (P = 0.49) Favours experimental Favours control

Figure 4. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in recessive model; D. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in homozygote comparison; E. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in heterozygote comparison.

BARD1 polymorphism	Genetic model	Begg's fun	nel plot	Egger'	s test
		Z test for plot asymmetry	P value	Kendall's tau	P value
Arg378Ser	allelic model	-0.2797	0.7797	0	1
	dominant model	0.1585	0.8741	0	1
	recessive model	-0.3596	0.174	-0.1429	0.7726
	homozygote comparison	-0.6312	0.5279	-0.0476	1
	heterozygote comparison	0.2421	0.8087	-0.1429	0.7195
Val507Met	allelic model	-0.6832	0.4945	-0.2143	0.5484
	dominant model	-0.6896	0.4905	-0.2857	0.3988
	recessive model	-0.841	0.4003	-0.3571	0.2751
	homozygote comparison	-0.6139	0.5393	-0.0714	0.9049
	heterozygote comparison	-0.9299	0.3524	-0.5	0.1087
Pro24Ser	allelic model	-0.9753	0.3294	-0.2857	0.3988
	dominant model	-1.5398	0.1236	-0.2857	0.3988
	recessive model	0.0157	0.9874	0.1429	0.7195
	homozygote comparison	-0.5005	0.6167	0	1
	heterozygote comparison	-1.0237	0.306	-0.1429	0.7195

Table 1. Begg's funnel plot and Egger's test of publication bias on the relationships between BARD1

 polymorphisms and cancer susceptibility in five genetic models

0.76, 95% CI: 0.66-0.87, P < 0.00001), dominant model (OR = 0.77, 95% CI: 0.65-0.91, P < 0.00001), recessive model (OR = 0.64, 95% CI: 0.55-0.74, P < 0.00001), homozygote comparison (OR = 0.58, 95% CI: 0.49-0.70, P < 0.00001), heterozygote comparison (OR = 0.85, 95% CI: 0.74-0.99, P = 0.0008) (Figure 2). BARD1 Pro24Ser (C/T) polymorphism was also associated decreased cancer risk in allelic model (OR = 0.72, 95% CI: 0.60-0.88, P = 0.0009), dominant model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), recessive model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), homozygote comparison (OR = 0.55, 95% CI: 0.39-0.78, P = 0.0007) and heterozygote comparison (OR = 0.75, 95% CI: 0.62-0.91, P = 0.004) (Figure 3). No significant association was found between Arg378Ser polymorphism and cancer risk under five genetic models (allelic model: OR = 0.88, 95% CI: 0.69-1.12, P = 0.30; dominant model: OR = 0.81, 95% CI: 0.59-1.11, P = 0.20; recessive model: OR = 0.94, 95% CI: 0.65-1.37, P = 0.75; homozygote comparison: OR = 0.83, 95% CI: 0.50-1.40, P = 0.49; heterozygote comparison: OR = 0.80, 95% CI: 0.61-1.06, P = 0.13) (Figure 4).

Subgroup analysis

In our subgroup analysis, we evaluated BARD1 Arg378Ser, Val507Met and Pro24Ser polymorphisms with respect to ethnicity, tumor type and source of control in five different genotypes. We found that BARD1 Arg378Ser polymorphism was associated with decreased cancer risk in breast cancer (allelic model: OR = 0.81, 95% CI: 0.73-0.90, P < 0.0001; dominant model: OR = 0.73, 95% CI: 0.61-0.87, P = 0.0005; heterozygote comparison: OR = 0.75, 95% CI: 0.58-0.97, P = 0.03) and in Asians (allelic model: OR = 0.85, 95% CI: 0.73-0.98, P = 0.03; dominant model: OR = 0.77, 95% CI: 0.63-0.95, P = 0.02; heterozygote comparison: OR = 0.77, 95% CI: 0.61-0.98, P = 0.03) (Table S2). BARD1 Val507Met polymorphism (allelic model: OR = 0.87, 95% CI: 0.80-0.94, P = 0.0007; dominant model: OR = 0.90, 95% CI: 0.80-1.01, P = 0.01; recessive model: OR = 0.69, 95% CI: 0.59-0.82, P < 0.0001; homozygote comparison: OR = 0.66, 95% CI: 0.55-0.80, P < 0.0001) (Table S3) and Pro24Ser (allelic model: OR = 0.70, 95% CI: 0.52-0.95, P = 0.02; dominant model: OR = 0.70, 95% CI: 0.52-0.96, P = 0.03; recessive model: OR = 0.57, 95% CI: 0.35-0.94, P = 0.03; homozygote comparison: OR = 0.50, 95% CI: 0.29-0.87, P = 0.01) was also associated with decreased breast cancer risk (Table S4).

Sensitivity analysis

Sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs again. When the study performed by

A Arg378Ser (G/C) allelic model (C allele vs G allele)

В

D

Arg378Ser (G/C) dominant model (CC+GC vs GG)

Study or Subaroup	Deprete	Total	Dente	Total	Weight	Odds Ratio	Odds Ratio	4
Study of Study Oup	CVEIRS	10101	Lyeins	2000	WYCODIN .	M-D, Nation, 227 C	m-n, Kalidolli, 23% (
Capasso 2009	268	1124	928	2206	0.0%	1.41 [1.22, 1.63]		
Capasso 2013	246	700	779	1618	18.4%	0.58 [0.49, 0.70]	•	
Gunerd 2009	119	192	106	176	10.2%	1.08 [0.71, 1.64]	+	
Huo 2007	334	1014	396	1078	18.5%	0.85 [0.71, 1.01]		
Ishitobi 2003	6	120	19	304	3.2%	0.79 [0.31, 2.03]		
Liu 2013	474	1610	551	1590	19.7%	0.79 [0.68, 0.91]	•	
Sun 2012	85	288	105	272	12.2%	0.67 [0.47, 0.95]		
Zhou 2009	307	834	286	808	17.7%	1.06 [0.87, 1.30]	· • •	
Total (95% CI)		4758		5846	100.0%	0.81 [0.67, 0.97]	•	
Total events	1571		2242					
Heterogeneity: Tau* =	0.04; Ch	= 22.	38, df = 6	(P = 0.	001); I [#] =	73%		1 100
Test for overall effect	Z= 2.34	(P = 0.0	02)				Favours experimental Favours	control

C Arg378Ser (G/C) recessive model (CC vs GC+GG)

	Experim	Contr	lo		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Capasso 2009	145	562	188	1103	0.0%	1.69 [1.32, 2.16	1
Capasso 2013	61	350	208	809	20.4%	0.61 [0.44, 0.84	· · ·
Gunerd 2009	35	96	30	88	13.7%	1.11 [0.61, 2.03	i +-
Huo 2007	44	507	68	539	18.4%	0.66 [0.44, 0.98	·
Liu 2013	74	805	65	795	19.7%	1.14 [0.80, 1.61	i +
Sun 2012	9	144	19	136	9.8%	0.41 [0.18, 0.94	i —
Zhou 2009	59	417	44	404	18.0%	1.35 [0.89, 2.05	i †•-
Total (95% CI)		2319		2771	100.0%	0.84 [0.60, 1.17]	ı 🔶
Total events	282		434				
Heterogeneity: Tau* =	0.11; Chi*	= 16.83	3, df = 5 (P = 0.0	05); I [#] = 7	0%	
Test for overall effect	Z=1.01 (F	P = 0.31)				Favours experimental Favours control

E Arg378Ser (G/C) heterozygote comparison (GC vs GG)

	Experimental Control					Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Capasso 2009	278	417	552	915	0.0%	1.32 [1.03, 1.68]	
Capasso 2013	124	289	363	601	18.7%	0.49 [0.37, 0.65]	+
Gunerd 2009	49	61	46	58	5.3%	1.07 [0.43, 2.61]	
Huo 2007	246	463	260	471	19.7%	0.92 [0.71, 1.19]	+
Ishitobi 2003	6	60	19	152	4.7%	0.78 [0.29, 2.05]	
Liu 2013	326	731	421	730	21.5%	0.59 [0.48, 0.73]	•
Sun 2012	67	135	67	117	11.8%	0.74 [0.45, 1.21]	
Zhou 2009	189	358	198	360	18.3%	0.92 [0.68, 1.23]	1
Total (95% CI)		2097		2489	100.0%	0.72 [0.57, 0.91]	•
Total events	1007		1374				
Heterogeneity: Tau* =	0.05; Chi ^a	= 16.88	8, df = 6 (P = 0.0	10); I* = 6	4%	
Test for overall effect	Z= 2.74 (P = 0.00	6)			1	Favours experimental Favours control

						Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Capasso 2009	423	562	740	1103	0.0%	1.49 [1.19, 1.88]	
Capasso 2013	185	350	571	809	18.8%	0.47 [0.36, 0.61]	•
Gunerd 2009	84	96	76	88	5.9%	1.11 [0.47, 2.61]	-
Huo 2007	290	507	328	539	19.2%	0.86 [0.67, 1.10]	+
Ishitobi 2003	6	60	19	152	4.9%	0.78 [0.29, 2.05]	
Liu 2013	400	805	486	795	20.7%	0.63 [0.51, 0.77]	•
Sun 2012	76	144	86	136	12.3%	0.65 [0.40, 1.05]	-
Zhou 2009	248	417	242	404	18.2%	0.98 [0.74, 1.30]	†
Total (95% CI)		2379		2923	100.0%	0.72 [0.56, 0.91]	•
Total events	1289		1808				
Heterogeneity: Tau* =	0.06; Ch	= 20.0	06, df = 6	(P = 0.	003); 17 =	70%	
Test for overall effect	Z= 2.71	(P = 0.0)	007)				Favours experimental Favours control

Arg378Ser (G/C) homozygote comparison (CC vs GG)



Figure 5. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in sensitivity analysis. A. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in allelic model when study performed by Capasso in 2009 was omitted; B. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in dominant model when study performed by Capasso in 2009 was omitted; C. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in recessive model when study performed by Capasso in 2009 was omitted; D. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in homozygote comparison when study performed by Capasso in 2009 was omitted; E. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in heterozygote comparison when study performed by Capasso in 2009 was omitted; E. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in heterozygote comparison when study performed by Capasso in 2009 was omitted. Capasso in 2009 was deleted, BARD1 Arg378Ser polymorphism was associated with decreased cancer risk in allelic model (OR = 0.81, 95% CI: 0.67-0.97, P = 0.02), dominant model (OR = 0.72, 95% CI: 0.56-0.91, P = 0.007) and heterozygote comparison (OR = 0.72, 95% CI: 0.57-0.91, 0 = 0.006) (Figure 5).

Publication bias

Both Begg's funnel plot and Egger's test were carried out to evaluate the publication bias of the studies. The result was displayed in **Table 1**. Begg's funnel plot and Egger's test didn't suggest any evidence of publication bias.

Discussion

In our meta-analysis, we firstly evaluated whether three common BARD1 polymorphisms (Arg378Ser, Val507Met and Pro24Ser) was associated with cancer susceptibility. And we found that BARD1 Val507Met (G/A) polymorphism was associated with decreased cancer susceptibility (allelic model: OR = 0.76, 95% CI: 0.66-0.87, P < 0.00001; dominant model: OR = 0.77, 95% CI: 0.65-0.91, P < 0.00001; recessive model: OR = 0.64, 95% CI: 0.55-0.74, P < 0.00001; homozygote comparison: OR = 0.58, 95% CI: 0.49-0.70, P < 0.00001; heterozygote comparison: OR = 0.85, 95% CI: 0.74-0.99, P = 0.0008). BARD1 Pro24Ser (C/T) polymorphism was also associated decreased cancer risk in allelic model (OR = 0.72, 95% CI: 0.60-0.88, P = 0.0009), dominant model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), recessive model (OR = 0.70, 95% CI: 0.56-0.87, P = 0.004), homozygote comparison (OR = 0.55, 95% CI: 0.39-0.78, P = 0.0007) and heterozygote comparison (OR = 0.75, 95% CI: 0.62-0.91, P = 0.004). And in our sensitivity analysis, when deleting the study performed by Capasso in 2009, we found that BARD1 Arg378Ser polymorphism was associated with decreased cancer risk in allelic model (OR = 0.81, 95% CI: 0.67-0.97, P = 0.02), dominant model (OR = 0.72, 95% CI: 0.56-0.91, P = 0.007) and heterozygote comparison (OR = 0.72, 95% CI: 0.57-0.91, 0 = 0.006).

BARD1 interacts with BRCA1 via their RING finger domains [23]. This important interaction is required for BRCA1 stability, nuclear localization and the E3 ubiquitin ligase activity of the BRCA1-BARD1 complex which has a crucial function in cell cycle check point control [24]. Some mutations in BARD1 will disrupt the ubiquitin ligase activity of the BRCA1-BARD1 heterodimer and lead to ER- α upregulation, causing even more BARD1 isoform expression [25]. Some mutations in BARD1 will promote the tumor-suppressive role of BARD1 compared to the wild type genotypes [13]. Mutations in BARD1 are apparently likely to have an influence on susceptibility to cancer, as they are often found, along with their products, in patients with breast [26], uterine [27], or endometrial cancers [28]. The Arg378Ser, Val-507Met and Pro24Ser polymorphisms in BARD1 are located directly on BRCA1 binding domain [13, 14, 29, 30], so the associated residue changes probably affect the E3 ligase activity of the BRCA1-BARD1 interaction. These mutations may have a protective function compared to the wild type genotype.

We performed subgroup analysis with respect to tumor type, ethnicity and the source of control. Breast cancer is the leading cause of cancer death in women [31]. BRCA1 and BRCA2 are identified as two highly penetrant breast cancer susceptibility genes [32]. The mutations in BARD1 might have an impact on the interaction between BARD1 and BRCA1/2 and have an impact on the breast cancer susceptibility [33]. We found that these three polymorphisms were all associated decreased susceptibility of breast cancer. So we speculated that these three polymorphisms might play a tumor suppressive role compared to the wild type genotype.

In our sensitivity analysis, the study performed by Capasso 2009 evaluating the association between BARD1 Arg378Ser polymorphism and neuroblastoma susceptibility was omitted by us. When deleting this study, we found BARD1 Arg378Ser polymorphism was significantly associated with decreased cancer risk in allelic model (OR = 0.81, 95% CI: 0.67-0.97, P = 0.02), dominant model (OR = 0.72, 95% CI: 0.56-0.91, P = 0.007) and heterozygote comparison (OR = 0.72, 95% CI: 0.57-0.91, 0 = 0.006). Moreover, the study performed by Capasso 2009 evaluating the association between BARD1 Arg378Ser polymorphism and neuroblastoma susceptibility reported the completely opposite result compared to the study performed Capasso 2013. We read these two papers carefully and didn't find the interpretation about this phenomenon by the author.

Although the association between BARD1 polymorphisms and cancer susceptibility was found in our meta-analysis, the limitations should be acknowledged. Firstly, studies included in our meta-analysis were not sufficient, which leads to the relative insufficiency of studies in subgroup analyses. If more studies are included in our meta-analysis especially studies evaluating BARD1 polymorphism and breast cancer susceptibility, more representative conclusions will get. Secondly, some genome-wide association studies reported that these BARD1 polymorphisms were investigated. However, when we communicated with the authors, they informed us that the specific data couldn't be found and provide for us. It's a shame that these studies are not able to be included in our metaanalysis.

Despite these limitations, our meta-analysis concluded that BARD1 Val507Met and Pro24Ser polymorphisms were both associated with decreased cancer susceptibility. Moreover, Arg378Ser might also be associated with decreased cancer susceptibility. Since BARD1 has a tumor-suppressive function and has been implicated in multiple crucial cellular processes including DNA repair, RNA processing, apoptosis, cell cycle regulation and transcription. With more studies in the future emerging, some effective tumor prevention methods may be generated according to these BARD1 polymorphisms which play a tumor suppressive role compared to the wild type genotype.

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Disclosure of conflict of interest

None.

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References

[1] Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, Yang MC, Hwang LY, Bowcock AM and Baer R. Identification of a RING protein that can interact in vivo with the BRCA1 gene product. Nat Genet 1996; 14: 430-440.

- [2] Irminger-Finger I. BARD1, a possible biomarker for breast and ovarian cancer. Gynecol Oncol 2010; 117: 211-215.
- [3] Birrane G, Varma AK, Soni A and Ladias JA. Crystal structure of the BARD1 BRCT domains. Biochemistry 2007; 46: 7706-7712.
- [4] Westermark UK, Reyngold M, Olshen AB, Baer R, Jasin M and Moynahan ME. BARD1 participates with BRCA1 in homology-directed repair of chromosome breaks. Mol Cell Biol 2003; 23: 7926-7936.
- [5] Simons AM, Horwitz AA, Starita LM, Griffin K, Williams RS, Glover JN and Parvin JD. BRCA1 DNA-binding activity is stimulated by BARD1. Cancer Res 2006; 66: 2012-2018.
- [6] Reidt W, Wurz R, Wanieck K, Chu HH and Puchta H. A homologue of the breast cancer-associated gene BARD1 is involved in DNA repair in plants. EMBO J 2006; 25: 4326-4337.
- [7] Kim HS, Li H, Cevher M, Parmelee A, Fonseca D, Kleiman FE and Lee SB. DNA damage-induced BARD1 phosphorylation is critical for the inhibition of messenger RNA processing by BRCA1/BARD1 complex. Cancer Res 2006; 66: 4561-4565.
- [8] Tembe V and Henderson BR. BARD1 translocation to mitochondria correlates with Bax oligomerization, loss of mitochondrial membrane potential, and apoptosis. J Biol Chem 2007; 282: 20513-20522.
- [9] Schuchner S, Tembe V, Rodriguez JA and Henderson BR. Nuclear targeting and cell cycle regulatory function of human BARD1. J Biol Chem 2005; 280: 8855-8861.
- [10] Dechend R, Hirano F, Lehmann K, Heissmeyer V, Ansieau S, Wulczyn FG, Scheidereit C and Leutz A. The Bcl-3 oncoprotein acts as a bridging factor between NF-kappaB/Rel and nuclear co-regulators. Oncogene 1999; 18: 3316-3323.
- [11] Johnatty SE, Beesley J, Chen X, Hopper JL, Southey MC, Giles GG, Goldgar DE, Chenevix-Trench G, Spurdle AB, Australian Ovarian Cancer Study G and Kathleen Cuningham Consortium for Research in Familial Breast C. The BARD1 Cys557Ser polymorphism and breast cancer risk: an Australian case-control and family analysis. Breast Cancer Res Treat 2009; 115: 145-150.
- [12] Zhang YQ, Pilyugin M, Kuester D, Leoni VP, Li L, Casula G, Zorcolo L, Schneider-Stock R, Atzori L and Irminger-Finger I. Expression of oncogenic BARD1 isoforms affects colon cancer progression and correlates with clinical outcome. Br J Cancer 2012; 107: 675-683.
- [13] Liu H, Zhang H, Sun X, He Y, Li J and Guo X. A cross-sectional study of associations between

nonsynonymous mutations of the BARD1 gene and breast cancer in Han Chinese women. Asia Pac J Public Health 2013; 25: 8S-14S.

- [14] Vahteristo P, Syrjakoski K, Heikkinen T, Eerola H, Aittomaki K, von Smitten K, Holli K, Blomqvist C, Kallioniemi OP and Nevanlinna H. BARD1 variants Cys557Ser and Val507Met in breast cancer predisposition. Eur J Hum Genet 2006; 14: 167-172.
- [15] Sun G, Wang JT, Ma BL, Geng ZL, Ren GH, Shan MH, Ma B, Ma LL and Wang Y. [Association between single nucleotide polymorphisms of BARD 1 gene and susceptibility of early-onset breast cancer in Uygur women in Xinjiang]. Zhonghua Zhong Liu Za Zhi 2012; 34: 341-347.
- [16] Ishitobi M, Miyoshi Y, Hasegawa S, Egawa C, Tamaki Y, Monden M and Noguchi S. Mutational analysis of BARD1 in familial breast cancer patients in Japan. Cancer Lett 2003; 200: 1-7.
- [17] Huo X, Hu Z, Zhai X, Wang Y, Wang S, Wang X, Qin J, Chen W, Jin G, Liu J, Gao J, Wei Q, Wang X and Shen H. Common non-synonymous polymorphisms in the BRCA1 Associated RING Domain (BARD1) gene are associated with breast cancer susceptibility: a case-control analysis. Breast Cancer Res Treat 2007; 102: 329-337.
- [18] Capasso M, Devoto M, Hou C, Asgharzadeh S, Glessner JT, Attiyeh EF, Mosse YP, Kim C, Diskin SJ, Cole KA, Bosse K, Diamond M, Laudenslager M, Winter C, Bradfield JP, Scott RH, Jagannathan J, Garris M, McConville C, London WB, Seeger RC, Grant SF, Li H, Rahman N, Rappaport E, Hakonarson H and Maris JM. Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. Nat Genet 2009; 41: 718-723.
- [19] Guenard F, Labrie Y, Ouellette G, Beauparlant CJ, Durocher F and BRCAs I. Genetic sequence variations of BRCA1-interacting genes AURKA, BAP1, BARD1 and DHX9 in French Canadian families with high risk of breast cancer. J Hum Genet 2009; 54: 152-161.
- [20] Zhou X, Han S, Wang S, Chen X, Dong J, Shi X, Xia Y, Wang X, Hu Z and Shen H. Polymorphisms in HPV E6/E7 protein interacted genes and risk of cervical cancer in Chinese women: a case-control analysis. Gynecol Oncol 2009; 114: 327-331.
- [21] Capasso M, Diskin SJ, Totaro F, Longo L, De Mariano M, Russo R, Cimmino F, Hakonarson H, Tonini GP, Devoto M, Maris JM and Iolascon A. Replication of GWAS-identified neuroblastoma risk loci strengthens the role of BARD1 and affirms the cumulative effect of genetic variations on disease susceptibility. Carcinogenesis 2013; 34: 605-611.
- [22] Onay VU, Briollais L, Knight JA, Shi E, Wang Y, Wells S, Li H, Rajendram I, Andrulis IL and

Ozcelik H. SNP-SNP interactions in breast cancer susceptibility. BMC Cancer 2006; 6: 114.

- [23] Meza JE, Brzovic PS, King MC and Klevit RE. Mapping the functional domains of BRCA1. Interaction of the ring finger domains of BRCA1 and BARD1. J Biol Chem 1999; 274: 5659-5665.
- [24] Irminger-Finger I, Busquets S, Calabrio F, Lopez-Soriano FJ and Argiles JM. BARD1 content correlates with increased DNA fragmentation associated with muscle wasting in tumourbearing rats. Oncol Rep 2006; 15: 1425-1428.
- [25] Wu JY, Vlastos AT, Pelte MF, Caligo MA, Bianco A, Krause KH, Laurent GJ and Irminger-Finger I. Aberrant expression of BARD1 in breast and ovarian cancers with poor prognosis. Int J Cancer 2006; 118: 1215-1226.
- [26] Mahdi KM, Nassiri MR and Nasiri K. Hereditary genes and SNPs associated with breast cancer. Asian Pac J Cancer Prev 2013; 14: 3403-3409.
- [27] Thai TH, Du F, Tsan JT, Jin Y, Phung A, Spillman MA, Massa HF, Muller CY, Ashfaq R, Mathis JM, Miller DS, Trask BJ, Baer R and Bowcock AM. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. Hum Mol Genet 1998; 7: 195-202.
- [28] Alshatwi AA, Hasan TN, Syed NA, Shafi G and Grace BL. Identification of functional SNPs in BARD1 gene and in silico analysis of damaging SNPs: based on data procured from dbSNP database. PLoS One 2012; 7: e43939.
- [29] Atipairin A, Canyuk B and Ratanaphan A. Substitution of aspartic acid with glutamic acid at position 67 of the BRCA1 RING domain retains ubiquitin ligase activity and zinc(II) binding with a reduced transition temperature. J Biol Inorg Chem 2011; 16: 217-226.
- [30] Al Abo M, Dejsuphong D, Hirota K, Yonetani Y, Yamazoe M, Kurumizaka H and Takeda S. Compensatory functions and interdependency of the DNA-binding domain of BRCA2 with the BRCA1-PALB2-BRCA2 complex. Cancer Res 2014; 74: 797-807.
- [31] Bhatelia K, Singh K and Singh R. TLRs: Linking Inflammation and Breast cancer. Cell Signal 2014; 26: 2350-7.
- [32] Hasan TN, Shafi G, Syed NA, Alsaif MA, Alsaif AA and Alshatwi AA. Lack of association of BRCA1 and BRCA2 variants with breast cancer in an ethnic population of Saudi Arabia, an emerging high-risk area. Asian Pac J Cancer Prev 2013; 14: 5671-5674.
- [33] Gonzalez-Hormazabal P, Reyes JM, Blanco R, Bravo T, Carrera I, Peralta O, Gomez F, Waugh E, Margarit S, Ibanez G, Santos JL and Jara L. The BARD1 Cys557Ser variant and risk of familial breast cancer in a South-American population. Mol Biol Rep 2012; 39: 8091-8098.

Study	Year	Country	Tumor Type	BARD1 polymorphism	Cases	Controls	Mean Age	Source of controls	Genotyping method
Liu [13]	2013	China	breast cancer	Arg378Ser (G/C)	805	795	Cases: 51.22 controls 51.85	PB	PCR-PIRA
Liu [13]	2013	China	breast cancer	Val507Met (G/A)	805	795	Cases: 51.22 controls 51.85	PB	PCR-PIRA
Liu [13]	2013	China	breast cancer	Pro24Ser (C/T)	805	795	Cases: 51.22 controls 51.85	PB	PCR-PIRA
Vahteristo [14]	2006	Finland	breast cancer	Val507Met (G/A)	867	718	NR	PB	PCR and BigDye Terminator v3.1 Cycle Sequencing Kit and ABI 310 Sequencer
Ishitobi [16]	2003	Japan	breast cancer	Arg378Ser (G/C)	60	152	NR	PB	PCR-SSCP
Ishitobi [16]	2003	Japan	breast cancer	Val507Met (G/A)	53	152	NR	PB	PCR-SSCP
Sun [15]	2012	China	breast cancer	Arg378Ser (G/C)	144	136	≤ 40	HB	PCR-RFLP
Sun [15]	2012	China	breast cancer	Val507Met (G/A)	144	136	≤ 40	HB	PCR-RFLP
Sun [15]	2012	China	breast cancer	Pro24Ser (C/T)	144	136	≤ 40	HB	PCR-RFLP
Huo [17]	2007	China	breast cancer	Arg378Ser(G/C)	507	539	cases: 52.31 \pm 11.58 controls: 52.34 \pm 10.73	PB	PCR-RFLP and PCR-PIRA
Huo [17]	2007	China	breast cancer	Val507Met (G/A)	507	539	cases: 52.31 ± 11.58 controls: 52.34 ± 10.74	PB	PCR-RFLP and PCR-PIRA
Huo [17]	2007	China	breast cancer	Pro24Ser (C/T)	507	539	cases: 52.31 \pm 11.58 controls: 52.34 \pm 10.75	PB	PCR-RFLP and PCR-PIRA
Capasso [18]	2009	USA	neuroblastoma	Arg378Ser (G/C)	397	2043	NR	PB	genome-wide genotyping
Capasso [18]	2009	USA	neuroblastoma	Val507Met (G/A)	397	2043	NR	PB	genome-wide genotyping
Capasso [18]	2009	USA	neuroblastoma	Pro24Ser (C/T)	397	2043	NR	PB	genome-wide genotyping
Gunerd [19]	2009	France	breast cancer	Arg378Ser (G/C)	96	88	NR	HB	PCR, Big Dye fluorescent method, Staden preGap4 and Gap4 programs
Gunerd [19]	2009	France	breast cancer	Val507Met (G/A)	96	98	NR	HB	PCR, Big Dye fluorescent method, Staden preGap4 and Gap4 programs
Gunerd [19]	2009	France	breast cancer	Pro24Ser (C/T)	96	95	NR	HB	PCR, Big Dye fluorescent method, Staden preGap4 and Gap4 programs
Zhou [20]	2009	China	cervical cancer	Pro24Ser (C/T)	404	404	cases: 54.89 ± 12.89 controls: 54.62 ± 11.22	PB	PCR-PIRA
Zhou [20]	2009	China	cervical cancer	Arg378Ser (G/C)	404	404	cases: 54.89 ± 12.89 controls: 54.62 ± 11.22	PB	PCR-PIRA
Capasso [21]	2013	USA	neuroblastoma	Arg378Ser (G/C)	350	809	NR	PB	genome-wide genotyping
Capasso [21]	2013	USA	neuroblastoma	Val507Met (G/A)	326	775	NR	PB	genome-wide genotyping
Capasso [21]	2013	USA	neuroblastoma	Pro24Ser (C/T)	282	750	NR	PB	genome-wide genotyping
Onay [22]	2006	Canada	breast cancer	Pro24Ser (C/T)	398	372	Cases: 44.8 control: 45.2	PB	PCR and ABI PRISM 7900 HT Sequence Detection System

Table S1. Baseline characteristics of studies included in the met	a-anal	VSIS
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HB: hospital based; PB: population based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; NR: no report; PCR-PIRA : polymerase chain reaction-primer introduced restriction analysis; PCR-SSCP: polymerase chain reaction -single-strand conformation polymorphism.

Subgroups	Dominant model (ORs)	number of studies	95% CI	P value	Recessive Model (ORs)	number of studies	95% CI	P value	Allelic model (ORs)	number of studies	95%CI	P value
breast cancer	0.73	5	0.61-0.87	0.0005	0.82	4	0.54-1.23	0.34	0.81	5	0.73-0.90	< 0.0001
neuroblastoma	0.84	2	0.84-2.61	0.76	1.02	2	0.38-2.78	0.97	0.91	2	0.38-2.15	0.83
cervical cancer	0.98	1	0.74-1.30	0.9	1.35	1	0.89-2.05	0.16	1.06	1	0.87-1.30	0.55
Caucasians	0.9	3	0.36-2.24	0.83	0.87	4	0.57-1.35	0.54	0.96	3	0.50-1.82	0.89
Asians	0.77	5	0.63-0.95	0.02	1.05	3	0.51-2.16	0.9	0.85	5	0.73-1.98	0.03
PB	0.82	6	0.57-1.18	0.28	1.01	5	0.66-1.55	0.95	0.89	6	0.67-1.19	0.43
НВ	0.75	2	0.47-1.19	0.22	0.7	2	0.27-1.86	0.48	0.83	2	0.52-1.34	0.45
Subgroups	Homozygote com- parison (ORs)	number of studies	95% CI	P value	Heterozygote comparison (ORs)	number of studies	95% CI	P value				
breast cancer	0.71	4	0.49-1.03	0.07	0.75	5	0.58-0.97	0.03				
neuroblastoma	0.93	2	0.20-4.28	0.92	0.81	2	0.31-2.11	0.66				
cervical cancer	1.29	1	0.82-4.01	0.27	0.92	1	0.68-1.23	0.55				
Caucasians	0.99	3	0.31-3.22	0.99	0.87	3	0.40-1.88	0.72				
Asians	0.77	4	0.51-1.18	0.23	0.77	5	0.61-0.98	0.03				
PB	0.9	5	0.50-1.64	0.74	0.8	5	0.55-1.16	0.23				
НВ	0.63	2	0.19-2.06	0.44	0.88	2	0.70-1.10	0.26				

Table S2. A summary of odds ratios (ORs) for the subgroup analyses of BARD1 Arg378Ser polymorphism and cancer susceptibility

ORs: odds ratios; CI: confidence interval; PB: population based; HB: hospital based.

Table S3. A summary of odds ratios (ORs) for the subgroup analyses of BARD1 Val507Met polymorphism and cancer sus	ceptibility
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Subgroups	Dominant model (ORs)	number of studies	95% CI	P value	Recessive Model (ORs)	number of studies	95% CI	P value	Allelic model (ORs)	number of studies	95%CI	P value
breast cancer	0.9	6	0.80-1.01	0.01	0.69	6	0.59-0.82	< 0.0001	0.87	6	0.80-0.94	0.0007
neuroblastoma	0.6	2	0.51-0.71	< 0.00001	0.56	2	0.45-0.70	< 0.00001	0.62	2	0.55-0.70	< 0.00001
Caucasians	0.69	4	0.61-0.79	< 0.00001	0.66	4	0.56-0.77	< 0.00001	0.72	4	0.66-0.79	< 0.00001
Asians	0.91	4	0.79-1.05	0.23	0.6	4	0.46-0.78	0.0001	0.87	4	0.78-0.97	0.01
PB	0.79	6	0.71-0.87	< 0.00001	0.65	6	0.57-0.75	< 0.00001	0.72	6	0.55-0.94	0.02
HB	0.74	2	0.52-1.07	0.11	0.5	2	0.29-0.88	0.02	0.79	2	0.73-0.84	< 0.00001
Subgroups	Homozygote com- parison (ORs)	number of studies	95% CI	P value	Heterozygote com- parison (ORs)	number of studies	95% CI	P value				
breast cancer	0.66	6	0.55-0.80	< 0.0001	0.97	6	0.86-1.19	0.59				
neuroblastoma	0.49	2	0.38-0.62	< 0.0001	0.68	2	0.56-0.82	< 0.0001				
Caucasians	0.58	4	0.49-0.70	< 0.0001	0.77	4	0.67-0.89	0.0005				
Asians	0.59	4	0.45-0.77	0.0001	0.99	4	0.85-1.14	0.85				
PB	0.59	6	0.51-0.69	< 0.00001	0.87	6	0.78-0.97	0.01				
НВ	0.47	2	0.26-0.84	0.01	0.85	2	0.58-1.25	0.42				

ORs: odds ratios; CI: confidence interval; PB: population based; HB: hospital based.

Subgroups	Dominant model (ORs)	number of studies	95% CI	P value	Recessive Model (ORs)	number of studies	95% CI	P value	Allelic model (ORs)	number of studies	95%CI	P value
breast cancer	0.7	5	0.52-0.96	0.03	0.57	5	0.35-0.94	0.03	0.7	5	0.52-0.95	0.02
neuroblastoma	0.58	2	0.49-0.69	< 0.00001	0.6	2	0.44-0.81	0.001	0.65	2	0.57-0.74	< 0.00001
cervical cancer	0.96	1	0.73-1.27	0.78	1	1	0.68-1.48	1	0.98	1	0.80-1.20	0.84
Caucasians	0.65	4	0.54-0.78	< 0.00001	0.65	4	0.51-0.81	0.0002	0.71	4	0.62-0.82	< 0.00001
Asians	0.72	4	0.50-1.03	0.08	0.56	4	0.31-1.02	0.06	0.7	4	0.49-1.00	0.05
PB	0.75	6	0.61-0.92	0.006	0.7	6	0.52-0.84	0.0001	0.51	2	0.18-1.49	0.22
НВ	0.47	2	0.17-1.31	0.15	0.43	2	0.07-2.52	0.35	0.79	6	0.69-0.91	0.001
Subgroups	Homozygote com- parison (ORs)	number of studies	95% CI	P value	Heterozygote com- parison (ORs)	number of studies	95% CI	P value				
breast cancer	0.5	5	0.29-0.87	0.01	0.81	5	0.65-1.02	0.07				
neuroblastoma	0.47	2	0.35-0.63	< 0.00001	0.61	2	0.48-0.77	< 0.0001				
cervical cancer	0.98	1	0.64-1.48	0.91	0.95	1	0.71-1.29	0.76				
Caucasians	0.54	4	0.42-0.69	< 0.00001	0.67	4	0.55-0.82	< 0.0001				
Asians	0.5	4	0.25-0.97	0.04	0.84	4	0.65-1.09	0.2				
PB	0.62	6	0.50-0.78	< 0.0001	0.78	6	0.63-0.96	0.02				
НВ	0.33	2	0.04-2.62	0.29	0.61	2	0.40-0.95	0.03				

Table S4. A summary of odds ratios (ORs) for the subgroup analyses of BARD1 Pro24Ser polymorphism and cancer susceptibility

ORs: odds ratios; CI: confidence interval; PB: population based; HB: hospital based.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registra- tion number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Literature search and Selection criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Literature search and Selection criteria
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Literature search and Selection criteria
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Data abstraction
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, indepen- dently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data abstraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Statistical analysis
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (includ- ing specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Data abstraction
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	Statistical analysis
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Statistical analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Statistical analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Tables 2-4, Figure 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion

Checklist S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgment

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6 (6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.