Int J Clin Exp Med 2015;8(1):311-321
www.ijcem.com /ISSN:1940-5901/IJCEM0003341

Original Article

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

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Received October 23, 2014; Accepted December 31, 2014; Epub January 15, 2015; Published January 30, 2015

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 two-hybrid 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 RING-finger motifs [3]. Functional studies have demonstrated that disruption of the endogenous BRCA1–BARD1 complex decreases homology-directed repair, which is important to the tumor-suppressor 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 (rs2070094), 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 (Arg378Ser, 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 (hospital-based 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 I^2 test. When heterogeneity among the studies was observed, the pooled OR was calculated by random-effects 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-

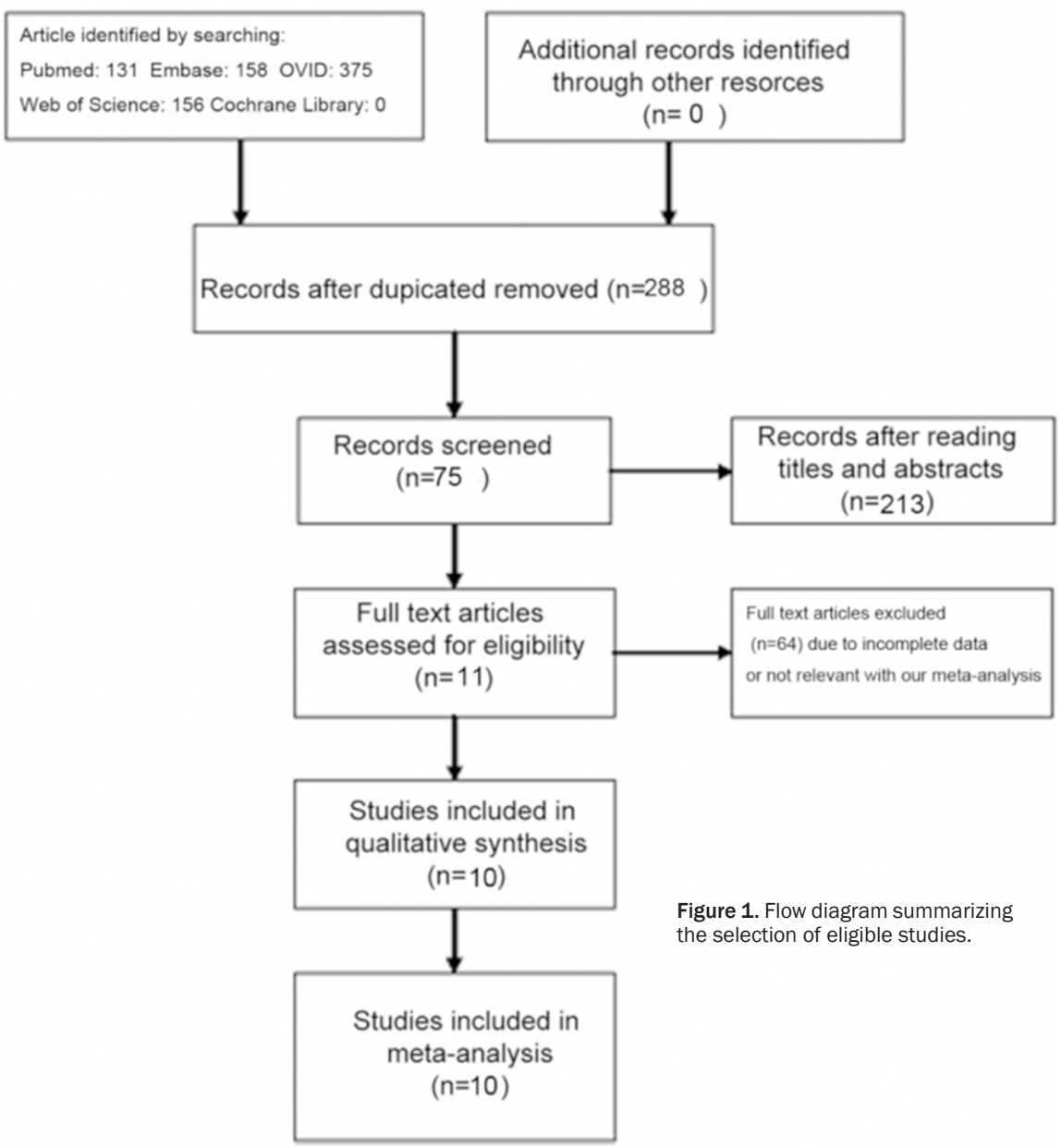

Figure 1. Flow diagram summarizing the selection of eligible studies.

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 hospital-based [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 Table S1.

Meta-analysis

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

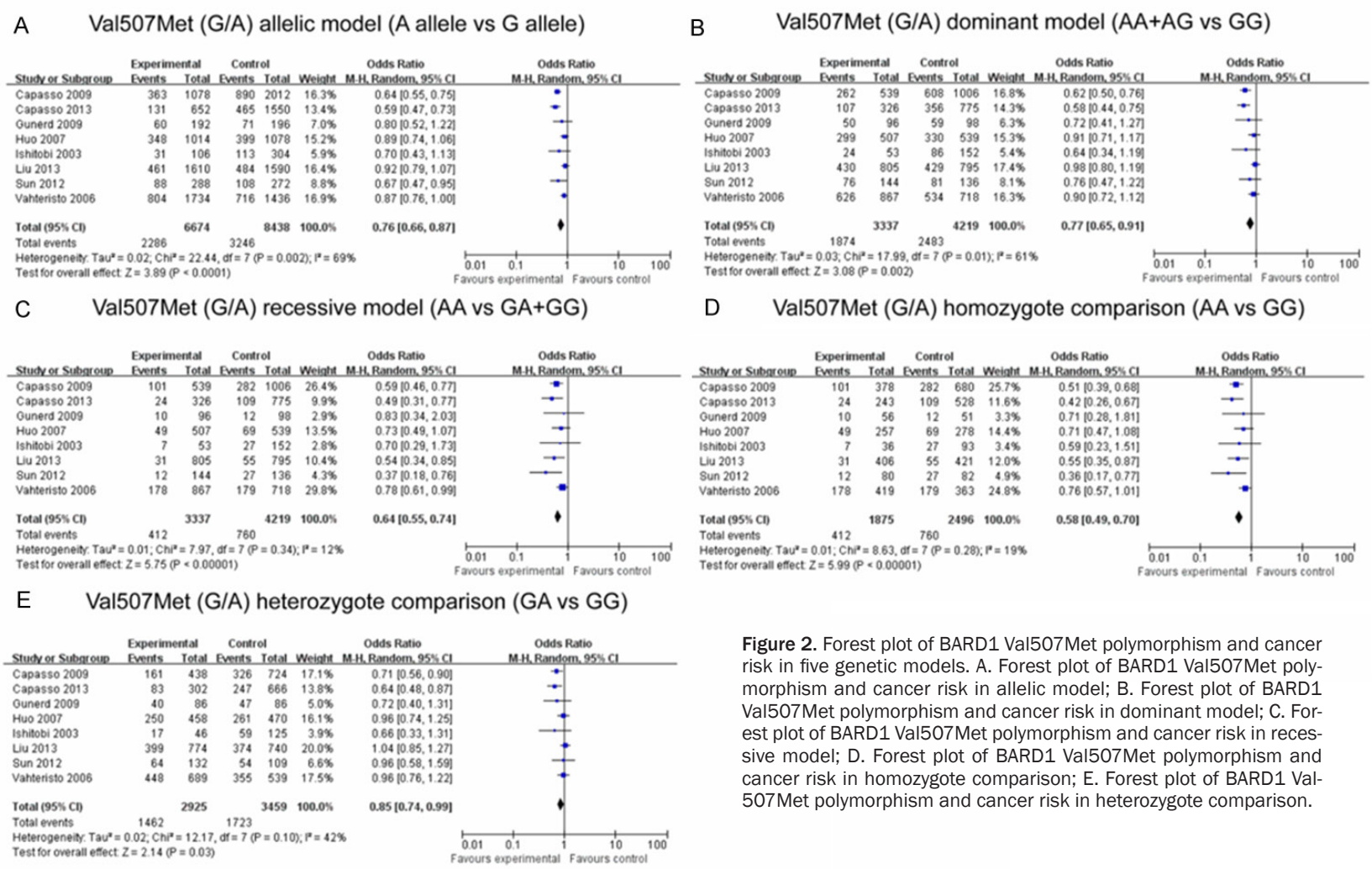

Figure 2. Forest plot of BARD1 Val507Met polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Val507Met polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Val507Met polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Val507Met polymorphism 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.

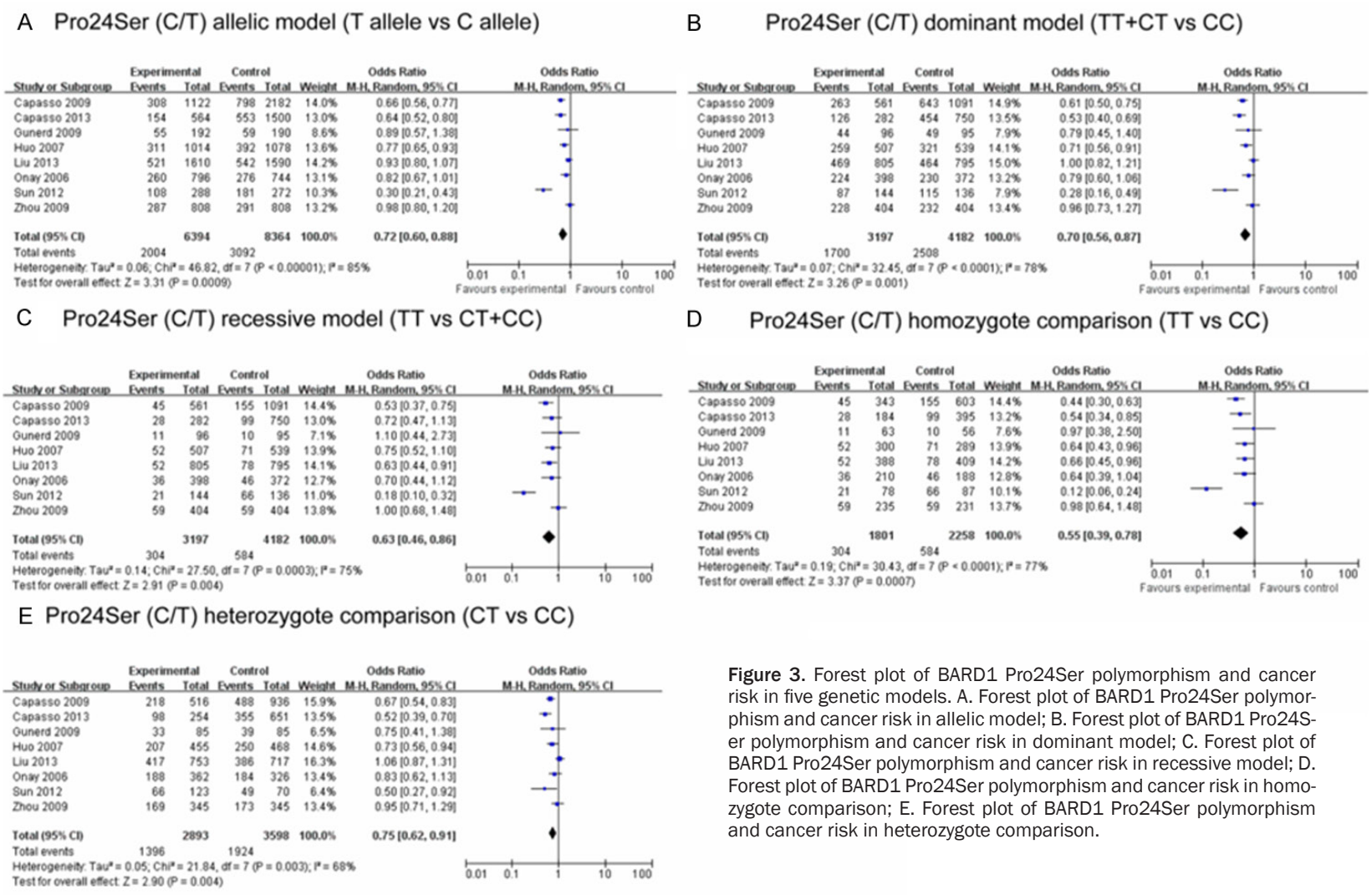

Figure 3. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Pro24Ser polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Pro24Ser polymorphism and 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.

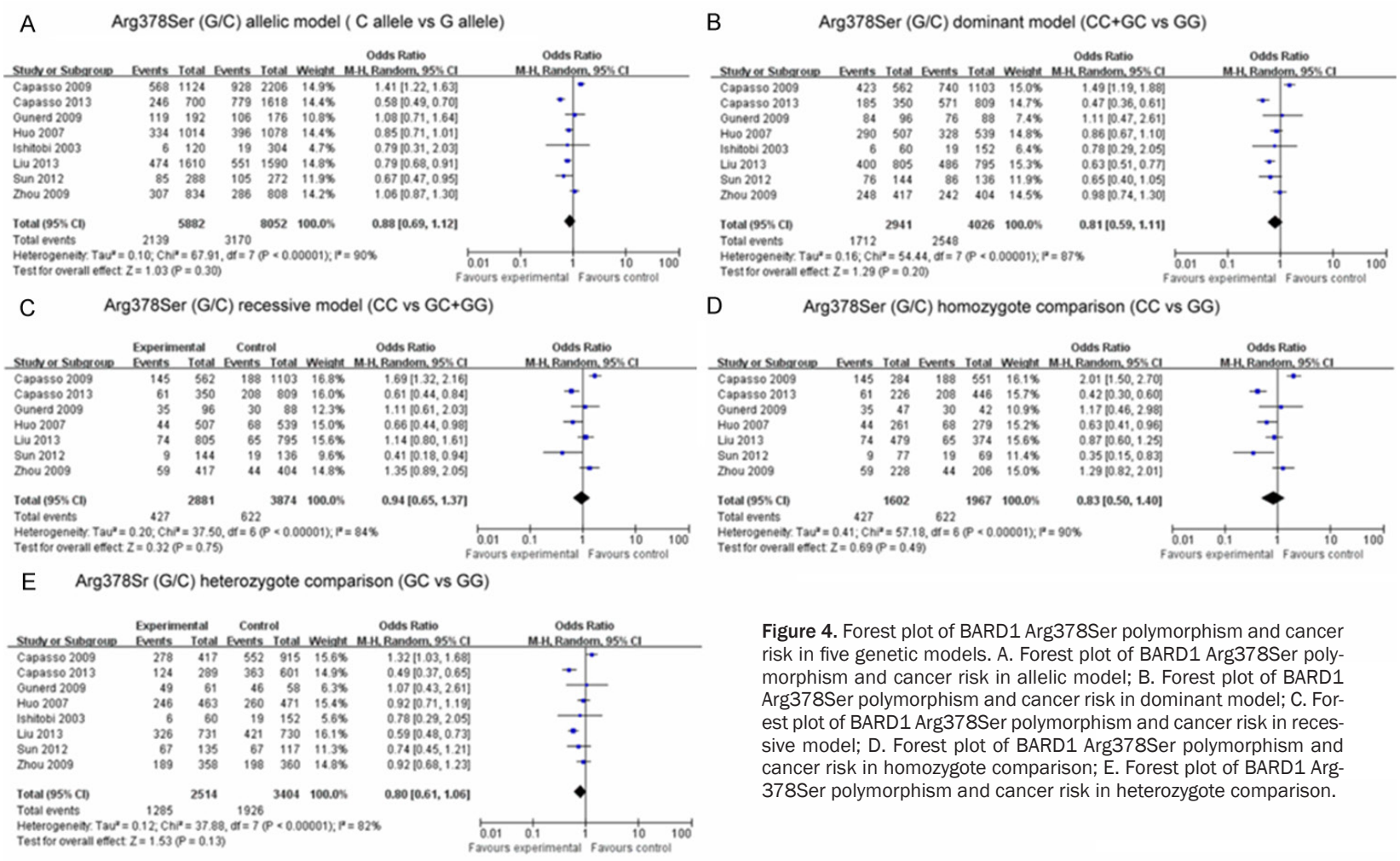

Figure 4. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in five genetic models. A. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in allelic model; B. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in dominant model; C. Forest plot of BARD1 Arg378Ser polymorphism 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.

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

BARD1 polymorphism	Genetic model	Begg's funnel 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

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

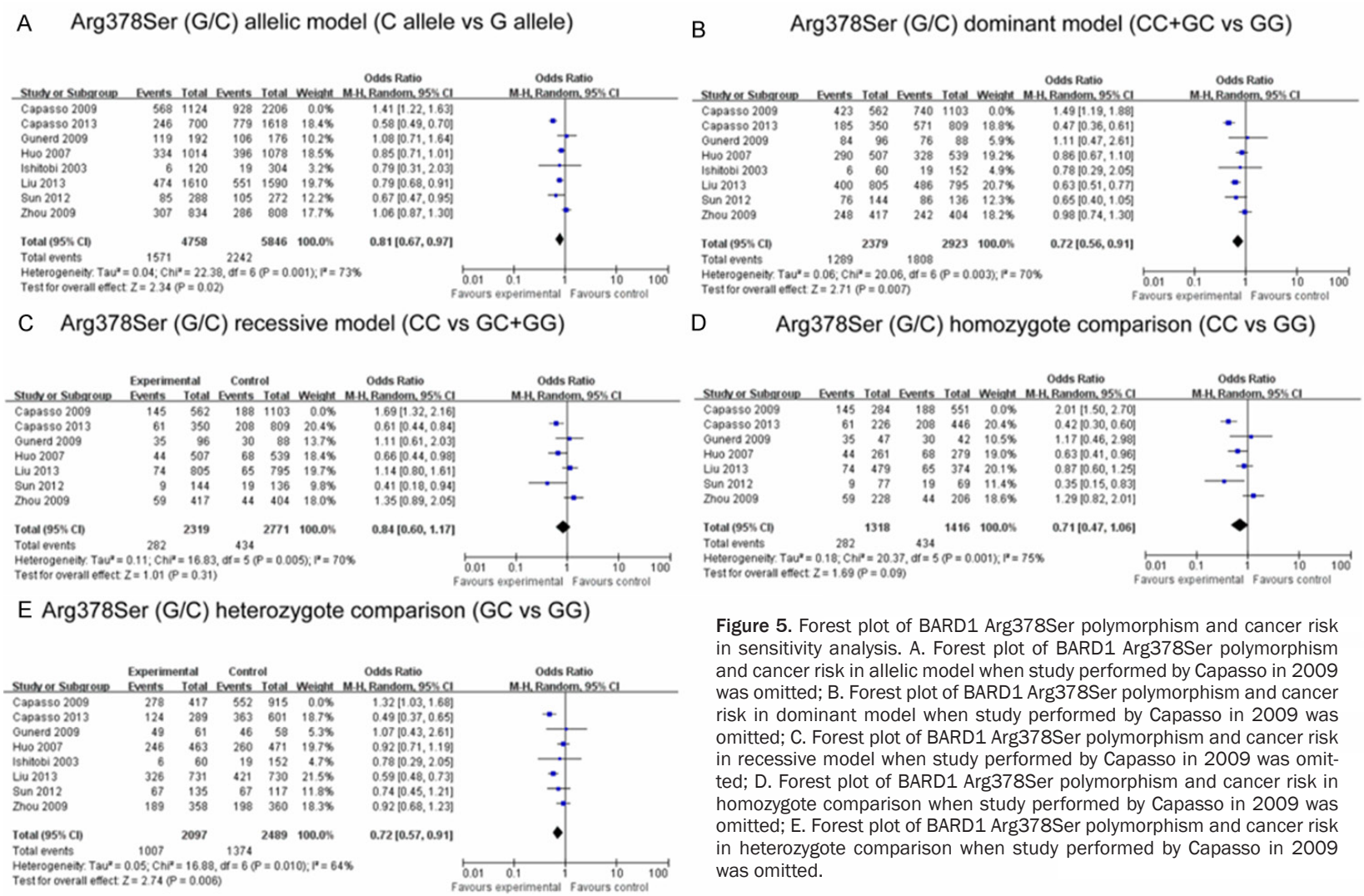

Figure 5. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in sensitivity analysis. A. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in allelic model when study performed by Capasso in 2009 was omitted; B. Forest plot of BARD1 Arg378Ser polymorphism and cancer risk in dominant 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.

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, Val507Met 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 meta-analysis.

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.

Acknowledgements

This study was supported by Natural science foundation of China (Grant No.: 81201913).

Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of studies included in the meta-analysis

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 ± 11.58 controls: 52.34 ± 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 ± 11.58 controls: 52.34 ± 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

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.

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

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
HB	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 comparison (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				
HB	0.63	2	0.19-2.06	0.44	0.88	2	0.70-1.10	0.26				

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 susceptibility

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 comparison (ORs)	number of studies	95% CI	*P* value	Heterozygote comparison (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				
HB	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.

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

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
HB	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 comparison (ORs)	number of studies	95% CI	*P* value	Heterozygote comparison (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				
HB	0.33	2	0.04-2.62	0.29	0.61	2	0.40-0.95	0.03				

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

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

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 registration 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, independently, 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 (including 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

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.