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Review Article

Relationship of BRCA2 N372H polymorphism and risk of cancer: a systematic meta-analysis under PRISMA guidelines

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Abstract: Objective: Many studies have investigated the association between BRCA2 N372H polymorphism and the risk of several cancers. However, the results were inconsistent. The aim of this meta-analysis was to elucidate whether BRCA2 N372H polymorphism was associated with cancer risk. Methods: We identified eligible studies, published from 2000 through 2016, by searching PubMed, Web of knowledge and Chinese National Knowledge Infrastructure (CNKI). Odds ratios (ORs) and 95% confidence interval (CI) were used to assess the strength of association between BRCA2 N372H polymorphism and cancer risk. Heterogeneity among studies was evaluated using Cochran's Q and I^2 statistics. Results: A total of forty six case-control studies were included in the meta-analysis. The pooled analysis indicated that BRCA2 N372H polymorphism was significantly associated with an increased risk of overall cancer (dominant model: OR = 1.06, 95% CI = 1.01-1.12; recessive model: OR = 1.13, 95% CI = 1.03-1.17). In subgroup analysis, we also found significantly increased risk of BRCA2 N372H polymorphism with ovarian cancer, non-Hodgkin lymphoma, population-based controls and Africans. Conclusions: This research study showed a major role of polymorphism in shaping over cancer risk. Future large-scale studies performed in multiple populations are warranted to confirm the results.

Keywords: BRCA2, polymorphism, cancer, meta-analysis

Introduction

In 2012 about 14.1 million new cases of cancer occurred globally [1]. It caused about 8.2 million deaths or 14.6% of all human deaths [2]. With research development, it is becoming clear that carcinogenesis is caused by mutation and epimutation of the genetic material of normal cells, which upsets the normal balance between proliferation and cell death. Recently, it has become evident that genetic variation plays a significant role in the development and progression of cancer. More studies based on gene polymorphisms have proved that polymorphisms may contribute to the cancer risk [3]. Identification of the key gene polymorphisms that are associated with cancer risk is essential for predicting individual at risk.

BRCA2 is a human tumor suppressor gene [4, 5] (specifically, a caretaker gene), found in all humans; its protein, also called the synonym breast cancer type 2 susceptibility protein, is responsible for repairing DNA. The gene was first cloned by scientists at Myriad Genetics, Endo Recherche, Inc., HSC Research & Development Limited Partnership, and the University of Pennsylvania [6]. In addition to breast cancer in men and women, mutations in BRCA2 also lead to an increased risk of ovarian, fallopian, prostate, and pancreatic cancers, as well as malignant melanoma.

As we know, the N372H could induce the single amino acid to substite histidine (His, H) for asparagine (Asn, N), which is the only common non-synonymous polymorphism in the BRCA2 gene. Moreover, Fuks F et al. [7] proposed that the consequential amino acid substitution falls into residues 290-453 of BRCA2, which mediates interaction between BRCA2 and the histone acetyltransferase P/CAF and transcription-

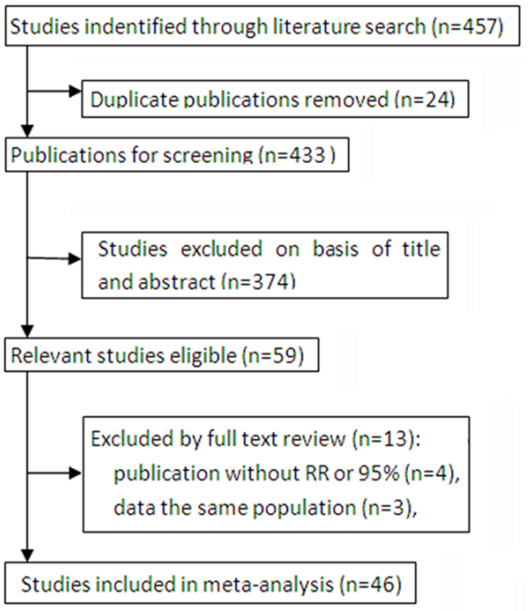

Figure 1. Flow chat of the study screening process in this meta-analysis.

al activation of target genes. So BRCA2 N372H polymorphism may have an effect on the transcriptional activation function of BRCA2 protein.

Most recently, increasing studies investigated the association between BRCA2 N372H polymorphism and risk of various types of cancer, In addition to breast cancer in men and women, mutations in BRCA2 also lead to an increased risk of ovarian, fallopian tube, prostate, and pancreatic cancers, as well as malignant melanoma. However, the results from individual studies were inconclusive. To explore whether BRCA2 N372H polymorphism was associated with risk of cancer and specific cancer subtypes, we performed a meta-analysis on the association between BRCA2 N372H polymorphism and cancer risk in present study.

Materials and methods

Literature search strategy

Literatures of electronic databases including PubMed and Web of Science were systematically searched using the search terms of "BRCA2", "polymorphism/mutation/variant" and "cancer/malignancy/neoplasm". References cited in each identified literatures were further searched manually to find potential available studies. We contacted the author for specific raw data if the data presented in the article were not sufficient. When overlapping data exists, only the latest study with the largest sample was selected for this meta-analysis. The last search date was June 1, 2016. We also searched for ongoing studies via ClinicalTrials.gov and checked the reference lists of relevant reviews and trials.

Selection criteria

Study eligibility was determined independently by two reviewers. Disagreements were solved by consensus. Studies were considered for inclusion if they meet the following criteria: (i) studies evaluated BRCA2 N372H polymorphism and cancer susceptibility, (ii) case-control studies, and (iii) reported data necessary to calculate the OR with corresponding 95% CI. If such data were unavailable, attempts were made to contact the first author and/or corresponding author via e-mail to provide the missing data before the study was excluded from the final analysis. When several reports were published on the same subject, only the most recent and informative one was included.

Data extraction and quality assessment

Two reviewers independently assessed articles for inclusion, extracted data, and assessed quality. Any disagreement was presented to a third author resolved by discussion among the investigators. The general information extracted included first author, publication year, ethnicity of the studied population, cancer type, numbers of each genotype in cases and controls, genotyping methods for BRCA2 N372H polymorphism, and source of controls. In accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS), the quality assessment of all included studies were performed by 2 reviewers independently. Any disagreement was resolved by a third reviewer. The scores of each study ranged between 1 and 9, and studies with the scores >6 were recognized as of high quality. All studies in this study are higher than 6 scores.

Statistical analysis

The statistical analysis was performed by Stata software (Version 11.0; StataCorp, College Station, TX). ORs and their 95% CI were used to assess the strength of association between

Table 1. Characteristics of eligible studies

First author	Year	Cancer	Race	Source of control	Case	Control	Method	Quality
Healey	2000	Breast	Caucasian	PB	234	266	TaqMan	7
Healey	2000	Breast	Caucasian	PB	449	453	TaqMan	7
Healey	2000	Breast	Caucasian	PB	659	866	TaqMan	6
Spurdle	2002	Breast	Caucasian	PB	1397	775	TaqMan	8
Ishitobi	2003	Breast	Asian	HB	149	154	PCR-SSPC	7
Menzel	2004	Breast	Caucasian	PB	94	152	Pyrosequencingt	6
Menzel	2004	Breast	Caucasian	PB	211	912	Pyrosequencingt	7
Freedman	2004	Breast	Mixed	PB	1715	2602	Unknown	6
Cox	2005	Breast	Caucasian	Nested	1285	1660	Taqman	7
Millikan	2005	Breast	African	PB	849	675	Taqman	7
Millikan	2005	Breast	Caucasian	PB	1265	1135	Taqman	8
Jenkins	2005	Breast	Caucasian	Family	1400	800	Unknown	8
HBBCS	2006	Breast	Caucasian	HB	274	273	Restriction enzyme-based assays	6
HBCS	2006	Breast	Caucasian	HB	807	697	Taqman	6
Sheffield	2006	Breast	Caucasian	HB	973	956	Taqman	6
LSHTM	2006	Breast	Caucasian	Nested	585	598	Restriction enzyme-based assays	7
Madrid	2006	Breast	Caucasian	HB	712	767	Taqman and illumina	8
USRTS	2006	Breast	Caucasian	Nested	707	1046	Taqman	7
SEARCH	2006	Breast	Caucasian	PB	4454	4537	Taqman	6
KBCP	2006	Breast	Caucasian	HB	446	452	Taqman	6
GESBC	2006	Breast	Caucasian	PB	602	851	Various	7
Garcia-Closas	2006	Breast	Caucasian	PB	3161	2701	Taqman	8
Garcia-Closas	2006	Breast	Caucasian	PB	1968	2276	Taqman	7
Johnson	2007	Breast	Caucasian	NA	473	2461	Illumina Sentrix Bead Arrays	6
Seymour	2008	Breast	Caucasian	HB	263	60	PCR	8
Hu R	2008	Breast	Asian	NA	71	85	PCR	7
Dombernowsky	2009	Breast	Caucasian	PB	1200	4119	TaqMan	7
Sun	2009	Breast	Asian	PB	512	541	PCR	7
Li	2011	Breast	Asian	HB	152	165	PCR	6
Silva	2011	Breast	Mixed	NA	54	20	PCR	7
Auranen	2003	Ovarian	Caucasian	PB	680	1546	TaqMan	7
Wenham	2003	Ovarian	Caucasian	PB	312	398	TaqMan	7
Beesley	2007	Ovarian	Caucasian	PB	492	948	MALDIF mass spectrophotometric	6
Beesley	2007	Ovarian	Caucasian	PB	930	825	MALDIF mass spectrophotometric	7
Hill	2006	NHL	Mixed	PB	1116	926	illumina	7
Shen	2006	NHL	Mixed	PB	476	555	TaqMan	6
Scoff	2007	NHL	Caucasian	PB	676	757	TaqMan	8
shen	2007	NHL	Caucasian	PB	556	498	TaqMan	6
Salagovic	2012	NHL	Caucasian	HB	107	127	PCR	7
Rudd	2006	CLL	Caucasian	HB	962	2695	illumina	8
Hu	2003	ESCC	Asian	PB	120	231	PCR-SSCP	7
Wu	2006	Bladder	Caucasian	PB	604	595	TaqMan	7
Debniak	2008	Melanoma	Caucasian	PB+HB	627	3819	RTPCR	6
Agalliu	2010	Prostate	Caucasian	PB	1269	1243	SNPLEXtm	7
Agalliu	2010	Prostate	African	PB	142	79	SNPLEXtm	6
Kotnis	2012	Overall	Asian	HB	109	186	PCR	8

HB, hospital-based; PB, population-based; CLL, chronic lymphocytic leukemia; ESCC, esophageal squamous cell carcinoma.

PTEN gene polymorphisms and cancer risks. *P* value <0.05 was considered as statistically significant. Heterogeneity was measured by using Q statistic (P<0.10 indicates significant heterogeneity between studies) and I-squared (I^2) value [8]. A fixed-effects model using Mantel-Haenszel method [9] was performed to calculate the pooled ORs when heterogeneity between studies was not significant. Otherwise, a random-effects model using DerSimonian and Laird method [10] was applied. Sensitivity analysis was performed to explore heterogene-

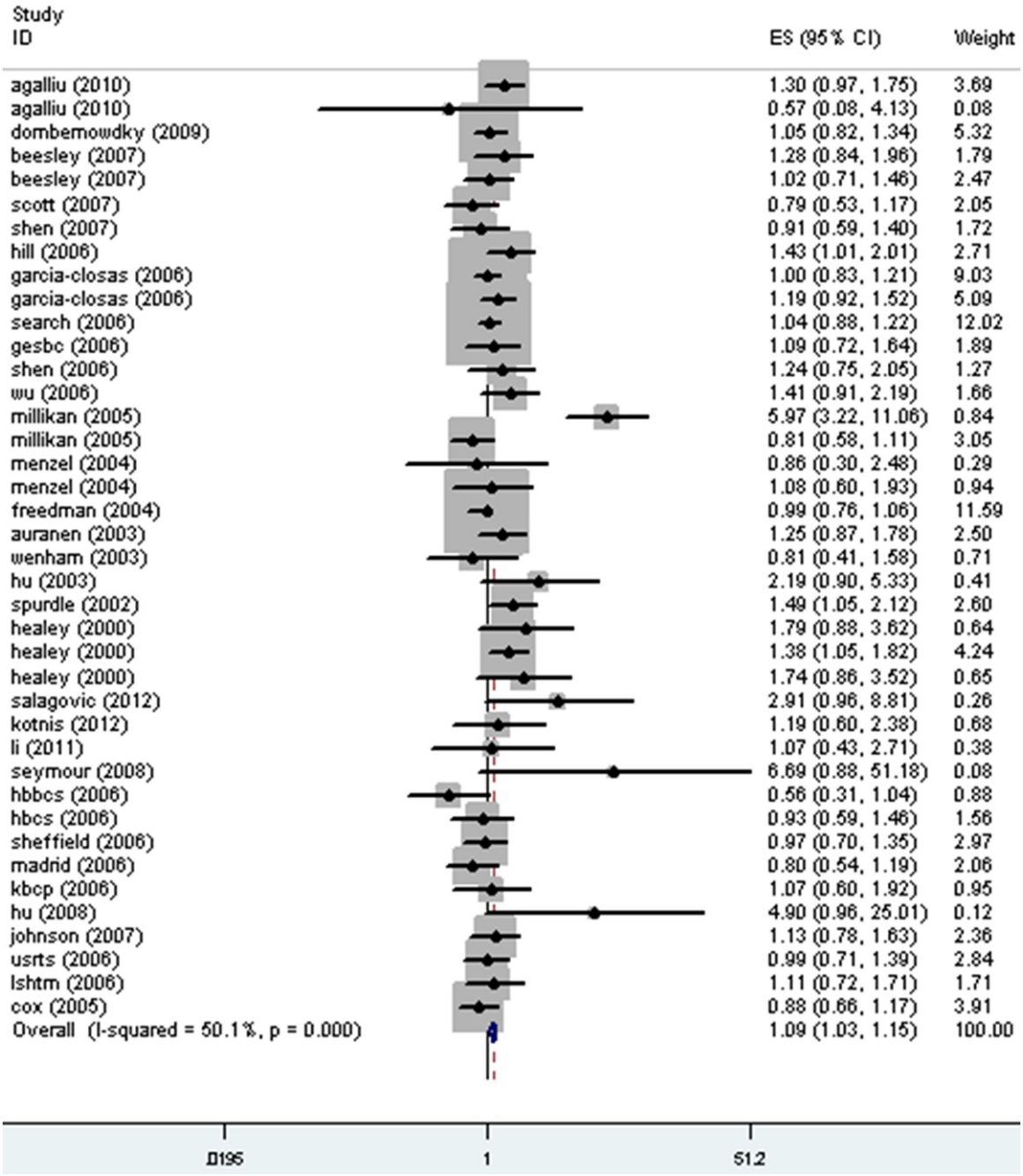

Figure 2. Forest plot of recessive model.

ity when significant heterogeneity was indicated. Subgroup analyses were performed to explore the effects of cancer type and source of controls. Additionally, publication bias were evaluated qualitatively by performing funnel plots and assessed quantitatively by Begg's test [11] and Egger's test [12], respectively. *P* value <0.05 for Begg's and Egger's tests indicates significant publication bias.

Results

Study characteristics

The meta-analysis was organized based on PRISMA statement (PRISMA Checklist). A total of 457 literatures were obtained from electronic databases after duplicates removal. After reviewing the titles and abstracts, 398 articles

Table 2. The association between PTEN IVS4 polymorphism and cancer risk

Variables	Homozygous	*P* value	Heterozygous	*P* value	Dominant	*P* value	Recessive	*P* value
All	1.09 (1.03, 1.15)	<0.01	1.03 (0.99, 1.06)	0.52	1.06 (1.01, 1.12)	<0.01	1.13 (1.02, 1.17)	<0.01
Cancer type								
Breast	1.11 (0.99, 1.23)	<0.01	1.01 (0.97, 1.05)	0.81	1.05 (0.98, 1.14)	<0.01	1.10 (0.98, 1.24)	<0.01
Ovarian	1.13 (0.92, 1.38)	0.52	1.12 (1.02, 1.22)	0.07	1.14 (1.02, 1.24)	0.18	1.06 (0.87, 1.30)	0.34
NHL	1.14 (0.83, 1.57)	0.08	1.01 (0.90, 1.12)	0.56	1.03 (0.92, 1.14)	0.31	1.18 (1.0, 1.33)	0.07
Others	1.34 (1.09, 1.68)	0.58	1.05 (0.95, 1.17)	0.37	1.08 (0.96, 1.22)	0.36	1.33 (0.99, 1.65)	0.59
Ethnicity								
African	2.24 (0.23, 21.77)	0.03	1.06 (0.84, 1.33)	0.29	1.28 (1.08, 1.71)	0.42	2.19 (0.22, 21.72)	0.02
Asian	1.53 (0.99, 2.35)	0.45	1.02 (0.81, 1.27)	0.16	1.33 (0.81, 2.17)	<0.01	1.48 (0.85, 2.59)	0.18
Caucasian	1.07 (0.99, 1.16)	0.13	1.02 (0.99, 1.06)	0.62	1.03 (0.99, 1.07)	0.18	1.08 (1.00, 1.16)	0.04
Mixed	1.15 (0.90, 1.48)	0.14	1.06 (0.91, 1.23)	0.89	1.13 (1.02, 1.25)	0.69	1.33 (0.99, 1.72)	0.67
Source of control								
HB	0.85 (0.69, 1.02)	0.20	0.94 (0.86, 1.04)	0.42	0.96 (0.86, 1.07)	0.27	1.07 (0.86, 1.33)	0.06
PB	1.07 (0.99, 1.16)	<0.01	0.99 (0.84, 1.17)	0.76	1.09 (1.02, 1.16)	<0.01	1.11 (1.01, 1.27)	<0.01
Quality Score								
Low	1.06 (0.94, 1.20)	0.28	1.04 (0.98, 1.10)	0.15	1.04 (0.98, 1.10)	0.28	1.16 (1.06, 1.26)	0.04
High	1.16 (1.03, 1.30)	<0.01	1.02 (0.98, 1.06)	0.93	1.06 (0.99, 1.14)	<0.01	1.08 (1.00, 1.15)	<0.01

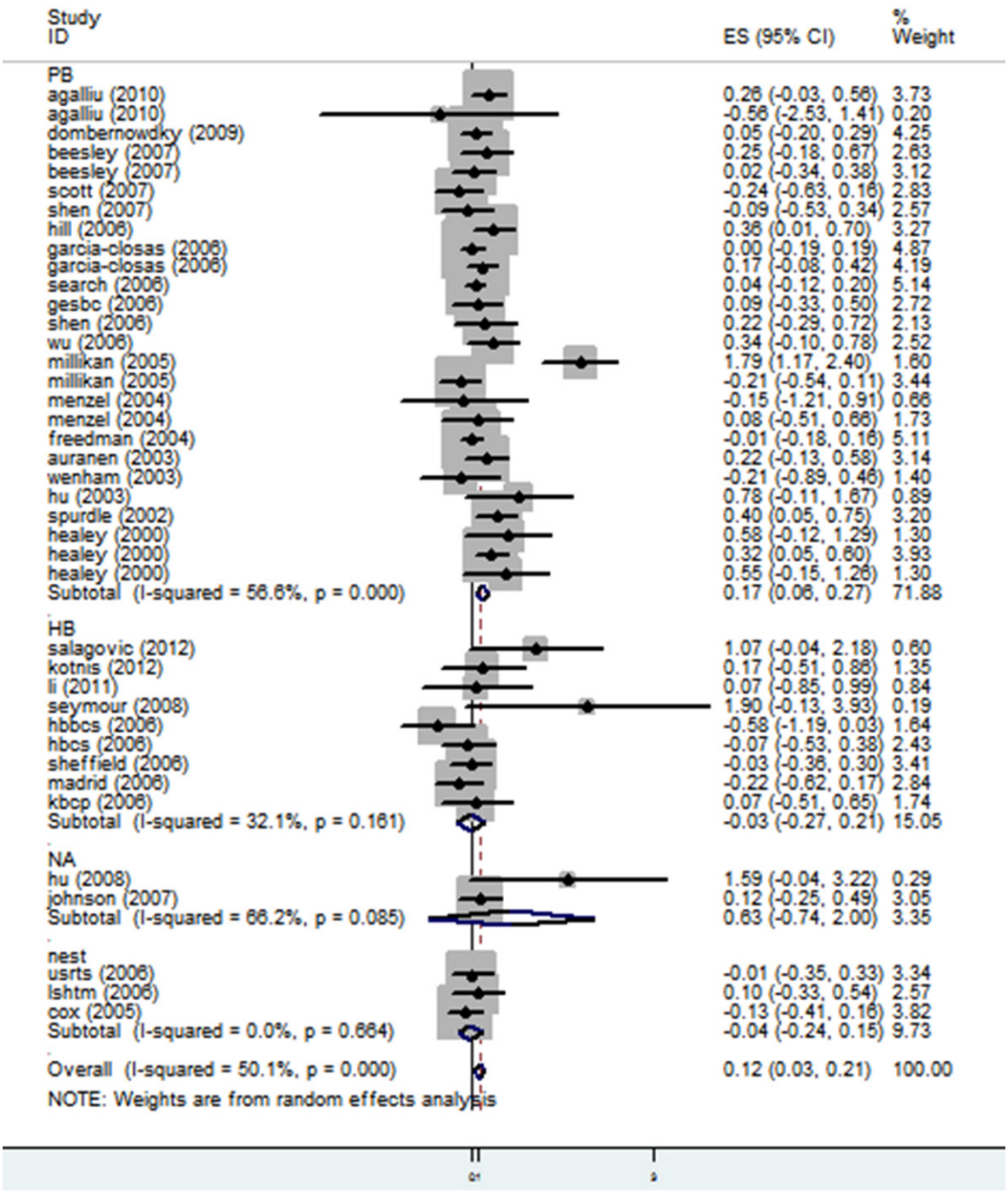

Figure 3. Forest plot of recessive model among different source control.

were excluded mainly due to no relevance, reviews, animal experiments or not about cancer. Subsequently, the left 59 publications were further evaluated for eligibility. Thirteen literatures were removed because of not in English or Chinese, no raw data, or not concerning IVS4 polymorphism. Finally, 46 full-text articles were included in the present meta-analysis. The detailed flow chart of study selection was shown in **Figure 1**. And the baseline characteristics of the studies were summarized in **Table 1**.

Overall analysis

Our study indicated that there was a statistically significant association between BRCA2 N372H and cancer risk, and three models

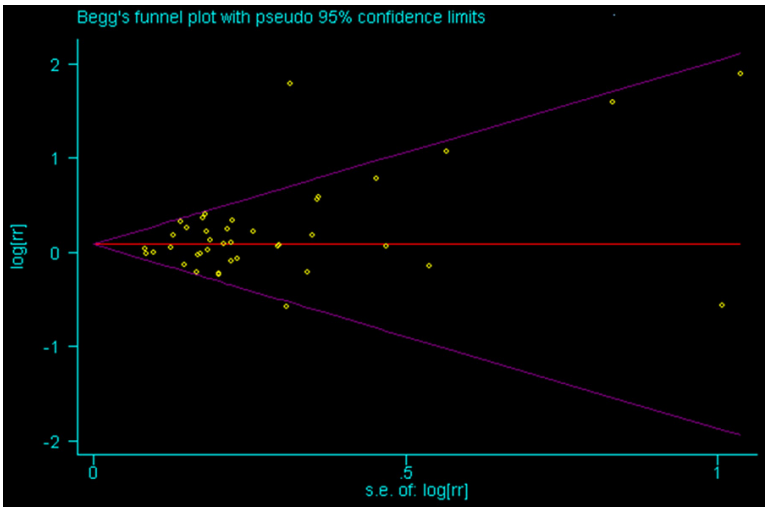

Figure 4. Funnel plot analysis of recessive model.

showed definite association. The overall ORs and 95% CIs were as follows: [homozygous model: OR (95% CI) = 1.09 (1.03-1.15) (**Figure 2**), dominant model: OR (95% CI) = 1.06 (1.01-1.12); and recessive model: OR (95% CI) = 1.13 (1.02-1.17)] (**Table 2**).

Subgroup analysis

As for cancer type, we found that the risk of cancer was increased among ovarian cancer patients [heterozygous: OR (95% CI) = 1.12 (1.02-1.22); dominant: OR (95% CI) = 1.14 (1.02-1.24)] and NHL [recessive: OR (95% CI) = 1.18 (1.00-1.33)] and other cancers [homozygous: OR (95% CI) = 1.34 (1.09-1.68)]. As for ethnicity type, there was a statistically significant association among Africans [dominant: OR (95% CI) = 1.28 (1.08-1.71)] and Mixed group [dominant: OR (95% CI) = 1.13 (1.02-1.25)]. As for source of control, our study proposed a statistically significant association in PB group [dominant: OR (95% CI) = 1.09 (1.02-1.16); recessive: OR (95% CI) = 1.11 (1.01-1.27)]. But no significant association was found in PB group in any model (**Figure 3**). As for quality score, there was a statistically significant association in low score subgroup, significant association was only observed under recessive model [OR (95% CI) = 1.14 (1.04-1.23)], while in the high score subgroup, the significant association were observed under two models [homozygous model: OR (95% CI) = 1.16 (1.03-1.31); recessive model: OR (95% CI) = 1.08 (1.00-1.15)] (**Table 2**).

Heterogeneity test, sensitivity analysis and publication bias

We conducted a meta-regression analysis to investigate the impact of heterogeneous factors on the OR estimates. The cancer type, ethnicity type, and source of control were chosen as the potential heterogeneous factors (data not shown). We observed that ethnicity contributed to the heterogeneity in the meta-analysis.

Sensitivity analysis was subsequently performed to detect the influence of individual study on the pooled estimate by omitting one study from the pooled analysis each time. The exclusion of each single study did not significantly change the pooled OR (data not shown), suggesting that the results of the meta-analysis were robust.

Among techniques to minimize the effects of publication bias, we have performed a thorough search for unpublished studies, and to use such analytical tools as a funnel plot to quantify the potential presence of publication bias. Begg's test was carried out to access the publication bias in our studies. There was no evidence of publication bias for the association between polymorphism of BRCA2 N372H and overall cancer risk under the homozygous, heterozygous, dominant, or recessive model (P = 0.823, P = 0.918, P = 0.451, P = 0.237) (**Figure 4**).

Discussion

Summary

The identification of genetic variants capable of modulating cancer development could be helpful for the early detection and design of targeted treatment and prevention strategies. With high interest in gene susceptibility to carcinogenesis, increasing efforts have been devoted to the study of genetic variants and cancer risk.

Most recently, increasing studies investigated the association between BRCA2 N372H polymorphism and risk of various types of cancer.

For instance, a research based on the Breast Cancer Association Consortium concluded no significant association was observed under all the models [13]. And, a pooled analysis issued by Cancer Hospital of Fudan University [14] also showed the null association with breast cancer in a whole. But, when stratified by study design, significantly elevated risk was found for 372H allele based on population-based studies (HH versus NN: OR = 1.11, 95% CI = 1.01-1.21; dominant model: OR = 1.05, 95% CI = 1.00-1.10; recessive model: OR = 1.09, 95% CI = 1.00-1.18).

Our pooled analysis indicated that BRCA2 N372H polymorphism had a big effect on the risk of cancer. More specifically, BRCA2 N372H polymorphism increased the 1.09, 1.06, and 1.13 fold excess risk of cancer under the homozygous, dominant and recessive models, respectively. Next, ovarian cancer, non-Hodgkin lymphoma and other cancers (a combination of prostate cancer, bladder cancer and esophageal cancer) were observed with statistically significant association in stratified analysis. Moreover, Africans and mixed groups as well as PB controls subgroup were also with definite association.

Mechanism

BRCA2 gene is located on the long (q) arm of chromosome 13 at position 12.3 (13q12.3) [15]. The human reference BRCA2 gene contains 27 exons, and the cDNA has 10,254 base pairs [16] coding for a protein of 3418 amino acids [17]. BRCA2 contains a number of 39 amino acid repeats that are critical for binding to RAD51 (a key protein in DNA recombination repair) and resistance to methyl methane sulphonate treatment [18-20].

The proteins made by BRCA2 gene are essential for repairing damaged DNA. BRCA2 binds the single strand DNA and directly interacts with the recombinase RAD51 to stimulate strand invasion a vital step of homologous recombination. The localization of RAD51 to the DNA double-strand break requires the formation of BRCA1-PALB2-BRCA2 complex. PALB2 (Partner and localizer of BRCA2) [21] can function synergistically with a BRCA2 chimera (termed piccolo, or piBRCA2) to further promote strand invasion [22]. These breaks can be caused by natural and medical radiation or other environmental exposures, but also occur when chromosomes exchange genetic material during a special type of cell division that creates sperm and eggs (meiosis). Double strand breaks are also generated during repair of DNA cross links. By repairing DNA, these proteins play a role in maintaining the stability of the human genome and prevent dangerous gene rearrangements that can lead to hematologic and other cancers.

They are involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double strand breaks [23]. If BRCA1 or BRCA2 itself is damaged by a BRCA mutation, damaged DNA is not repaired properly, and this increases the risk for cancer.

Limitations

There are, however, several limitations of the meta-analysis. First, some residual confounding is inevitable. For instance, we are unable to investigate the underlying effect of the covariates in the original studies, such as living environment, education background, family history, age and sex which may influence the results. Second, publication bias is always an important issue in the meta-analyses. Publication bias is a problem when interpreting our results. Negative studies are less likely to be published in indexed journals, leading to potential publication bias. We found no evidence of such publication bias in the Egger's linear regression test, but the funnel plot seemed asymmetrical. However, according to the Cochrane Handbook for Systematic Reviews of Interventions, Egger's teat typically has low power. Finally, although we made our best to track and acquire unpublished work and grey literature, especially university theses or conference proceedings, there were inevitability some researches left. As a result, publication bias may have influenced the results. And only English literatures were included in this study, it was possible that our findings were biased for many non-English literatures.

Conclusion

To be concluded, this meta-analysis suggested that BRCA2 N372H polymorphism significantly conferred with an increased risk of overall cancer. No significant association was observed

between NOD2 rs2066842 C/T polymorphism and cancer risk. Further randomized trials with larger sample size, different ethnicities and longer follow-up duration remain required to confirm our conclusion.

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Disclosure of conflict of interest

None.

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