RESEARCH ARTICLE

Updated Meta-analysis on HER2 Polymorphisms and Risk of Breast Cancer: Evidence from 32 Studies

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Abstract

<u>Background</u>: Several studies have been performed to investigate the association of the HER2 Ile655Val polymorphism and breast cancer risk. However, the results were inconsistent. To understand the precise relationship, a meta-analysis was here conducted. <u>Materials and Methods</u>: A search of PubMed conducted to investigate links between the HER2 Ile655Val polymorphism and breast cancer, identified a total of 32 studies, of which 29, including 14,926 cases and 15,768 controls, with odds ratios (ORs) with 95% confidence intervals were used to assess any association. <u>Results</u>: In the overall analysis, the HER2 Ile655Val polymorphism was associated with breast cancer in an additive genetic model (OR=1.136, 95% CI 1.043-1.239, $p=0.004$) and in a dominant genetic (OR=1.118, 95% CI 1.020-1.227, $p=0.018$), while no association was found in a recessive genetic model. On subgroup analysis, an association with breast cancer was noted in the additive genetic model (OR=1.111, 95% CI: 1.004-1.230, $p=0.042$) for the Caucasian subgroup. No significant associations were observed in Asians and Africans in any of the genetic models. <u>Conclusions</u>: In summary, our meta-analysis findings suggest that the HER2 Ile655Val polymorphism is marginally associated with breast cancer susceptibility in worldwide populations with additive and dominant models, but not a recessive model.

Keywords: HER2 - polymorphism - breast cancer - meta-analysis - additive - dominant - recessive - models

Introduction

Breast cancer has a wide distinct range of clinical, pathological and molecular features that makes it a heterogeneous disease (Sorlie et al., 2001). It has been progressively increased with estimated 229,060 new diagnoses and 39,510 deaths per year in the United States, and its incidence is currently increasing in the world (Linos et al., 2008; Ziegler et al., 2008; Siegel et al., 2012). Molecular genetic factors indicated the various structural and functional genetic alterations play an important role in the development and progression of breast cancer.

HER2 (Human epidermal growth factor receptor 2, ERBB2/neu/EGFP2) gene is located on chromosome 17q12-21q, spans 38kb, a 1255 amino acid glycoprotein of 185 kDa, comprises 27 coding exons, and over expressed in 20%-30% of breast cancer (Tommasi et al., 2004). Sequence analysis identified a common genetic variant at codon 655 in the transmembrane coding region of HER2 gene, an Ile-to-Val single-nucleotide polymorphism was found, resulting in the substitution of isoleucine (Ile: ATC) with valine (Val: GTC) (Cooke et al., 2001; Uzan et al., 2009). Isoleucine to valine changes might alter the hydrophobicity of the protein which affects the conformational stability of the domains (Papewalis et

al., 1991). Meanwhile, there is evidence suggesting that changing the existing isoleucine (Ile: ATC) to valine (Val: GTC) at codon 655 suggests an increased dimerization, autophosphorylation of HER2, and tyrosine kinase activity, which may cause the transformation of cells (Takano et al., 1995). Clinically, HER2 is an important biomarker and target of therapy of breast cancer (Nakajima et al., 1999).

Since the first study of the association between HER2 Ile655Val polymorphism and breast cancer was carried out by Xie (Ross et al., 2003), a number of studies have been conducted (Xie et al., 2000; Mutluhan et al., 2008; Naidu et al., 2008; Tao et al., 2009; Kallel et al., 2010; Kara et al., 2010; Zhang et al., 2011; AbdRaboh et al., 2013; Lemieux et al., 2013; Ozturk et al., 2013; Roca et al., 2013; Wang et al., 2013). The HER2 Ile655Val polymorphism is the most extensively studied in the literatures (Keshava et al., 2001; Millikan et al., 2003; Montgomery et al., 2003; Akisik et al., 2004; Kamali-Sarvestani et al., 2004; Marie-Genica et al., 2004; Pinto et al., 2004; An et al., 2005; Cox et al., 2005; Frank et al., 2005; Kalemi et al., 2005; Nelson et al., 2005; Benusiglio et al., 2006; Zubor et al., 2006; Papadopoulou et al., 2007; Tommasi et al., 2007; Lee et al., 2008; Mutluhan et al., 2008; Naidu et al., 2008; Qu et al., 2008; Kallel et al., 2010; Kara et al., 2010).

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But previous studies have produced inconsistent results. Therefore, we conducted a meta-analysis to estimate the possible influence of HER2 Ile655Val polymorphism on the risk of breast cancer.

Materials and Methods

Publication search

PubMed was searched using the search terms "HER2 (or ERBB2, or neu, or EGFP2)", "polymorphism" and "breast cancer" (last search update was on December, 2013). Case-control studies containing available genotype Ile655Val (rs 1136201) were chosen. Additional studies were identified by a manual search of the references of original studies.

Data extraction

Information was carefully extracted from all investigators independently by two of the authors (Chen and Yang) a consensus on inclusion criteria listed above. Disagreement was resolves by discussion between the two authors. Otherwise, other authors (Tang and Wei) were consulted to resolve. A final decision was made by the majority of the votes. The following data were sought for: first author's surname, publication year, country origin, ethnicity (categorized as African, Asian and Caucasian), genotyping total number of cases and controls.

Statistic analysis

Information was carefully extracted from each study, the following date of HER2 Ile655Val polymorphism was assessed for Hardy-Weinberg equilibrium in control group using the *p* text, and a P-value of <0.05 were not considered. The strength of association between HER2 Ile655Val polymorphism and canner was accessed by calculating crude ORs (odds rations) with 95%CIs (confidence intervals). The pooled ORs were performed for additive genetic model, dominant model and recessive model, respectively. Heterogeneity assumption was checked by a chi-square based Q-test. A significant Q-statistic ($p<0.05$) indicated heterogeneity among studies. The pooled OR estimate of each study was calculated by the fixed-effects mode (Mantel et al., 1959) if there was not significant heterogeneity. Otherwise, the random-effects model was used (DerSimonian et al., 1986).

The potential for publication bias was carried out by a Begg's test (funnel plot method) and Egger's linear regression test ($p<0.05$ considered representative of statistical significance) (Egger et al., 1997).

Meanwhile, to assess the influence of definition criteria on the pooled result, sensitivity analysis was performed in the meta-analysis. Sensitivity analysis was performed by methods to examine the impact of methodological quality, statistical models and types of study design on the results. First, leave-one-out to repeat analyses to test the influence of single studies on the summary effect; Second, reanalyze under different effects models; Third, reanalyze data categorized by study design.

All statistical analyses were performed with Stata version (version9.0; Stata Corporation, College Station, TX).

Results

Eligible studies

We identified 32 cases-control studies on the association between HER2 Ile655Val polymorphism and breast cancer, including 14,926 cases and 15,768 controls (Table 1). The distribution of genotypes in the controls of all the studies was in agreement with Hardy-Weinberg equilibrium, except three studies (Millikan et al., 2003; Kallel et al., 2010; Ozturk et al., 2013).
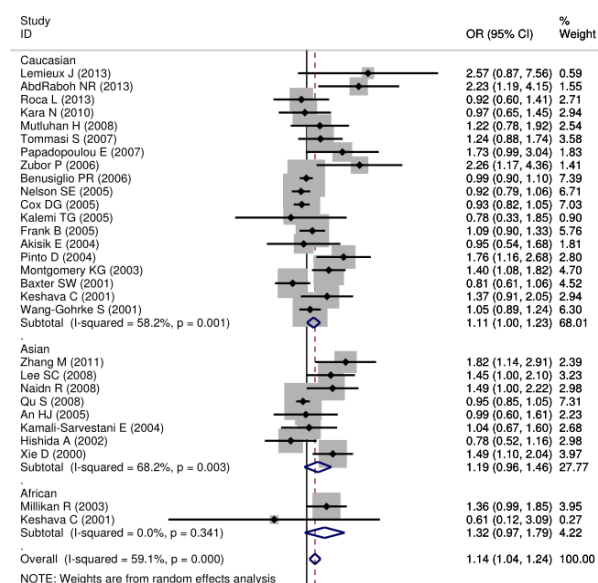

Figure 1. Forest Plot of ORs of Breast Cancer Risk Val Allele when Compared to the Ile Allele (Additive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI

Figure 2. Forest plot of ORs of Breast Cancer Risk Val Allele Carries (Val/Val+Val/Ile) when Compared to the Ile/Ile Genotype (Dominant model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI
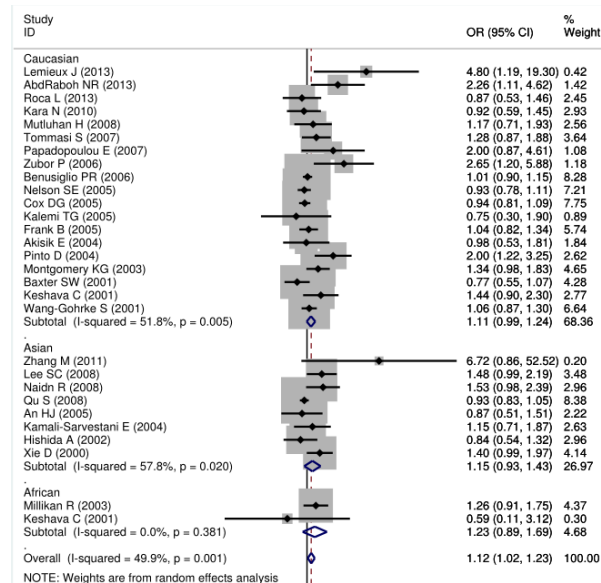
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Meta analysis

The results of the association between the HER2 Ile655Val polymorphism and breast cancer and the heterogeneity test were shown in Table 2 (Figure. 1-3). In additive model, the results suggested that the evidence of an association between the breast cancer risk in worldwide populations (OR=1.136, 95% CI 1.043-1.239, *p*=0.004), especially in Caucasian subgroup (OR=1.111, 95% CI: 1.004-1.230, *p*=0.042), but not in African (OR=1.318, 95% CI: 0.970-1.792, *p*=0.077) nor Asian (OR=1.188, 95% CI: 0.965-1.462, *p*=0.105).

Similarly, in dominant model, we also find the HER2 Ile655Val polymorphism was associated with the breast cancer risk in worldwide populations (OR=1.118, 95% CI 1.020-1.227, *p*=0.018), but not in Caucasian (OR=1.110, 95% CI 0.991-1.243, *p*=0.072), African (OR=1.228, 95% CI: 0.891-1.693, *p*=0.210) nor Asian (OR=1.154, 95% CI: 0.930-1.431, *p*=0.195).

Table 1. Characteristics of Studies Included the Association between HER2 Ile655Val Polymorphism and Breast Cancer

No.	Case			Control			Author	year	pop	population	*p**
	Ile/Ile	Val/Ile	Val/Val	Ile/Ile	Val/Ile	Val/Val					
1	39	21	4	67	18	1	AbdRaboh NR	2013	Caucasian	Egyptians	0.86
2	75	39	5	79	48	5	Roca L	2013	Caucasian	French	0.49
3	4	6	0	48	12	3	Lemieux J	2013	Caucasian	Canadians	0.08
4	61	57	0	87	41	0	Ozturk O	2012	Caucasian	Turkish	0.03
5	67	26	1	104	62	12	Zhang M	2011	Asian	Chinese	0.51
6	144	55	11	226	46	6	Feng D	2010	Asian	Chinese	0.06
7	153	46	5	141	48	3	Kara N	2010	Caucasian	Turkish	0.63
8	55	2	0	34	4	2	Kallel I	2010	Caucasian	Tunisian	0.004
9	165	57	8	159	37	4	Naidn R	2008	Asian	Malaysia	0.3
10	2298	648	66	2252	687	65	Qu S	2008	Asian	Chinese	0.14
11	128	34	4	166	40	2	Mutluhan H	2008	Caucasian	Turkish	0.81
12	341	80	3	273	44	1	Lee SC	2008	Asian	Taiwanese	0.58
13	15	22	19	19	16	10	Papadopoulou	2007	Caucasian	Greeks	0.08
14	433	181	14	125	41	3	Tommasi S	2007	Caucasian	Italian	0.86
15	1134	752	113	1229	791	134	Benusiglio PR	2006	Caucasian	French	0.66
16	22	22	3	42	17	1	Zubor P	2006	Caucasian	Slovakia	0.63
17	637	396	61	551	356	69	Nelson SE	2005	Caucasian	American	0.27
18	139	33	5	96	29	1	An HJ	2005	Asian	Korean	0.45
19	766	447	58	980	591	96	Cox DG	2005	Caucasian	American	0.58
20	186	132	29	525	377	58	Frank B	2005	Caucasian	German	0.37
21	32	10	0	36	15	0	Kalemi TG	2005	Caucasian	Greeks	0.22
22	88	57	7	107	35	4	Pinto D	2004	Caucasian	Portuguese	0.58
23	98	22	1	117	26	2	Akisik E	2004	Caucasian	Turkish	0.69
24	145	57	2	102	32	4	Kamali-Sarvestani E	2004	Asian	Iranian	0.45
25	658	88	8	606	70	0	Millikan R	2003	African	African-American	0.16
26	752	429	80	684	375	73	Millikan R	2003	Caucasian	White	0.03
27	240	138	31	196	94	9	Montgomery KG	2003	Caucasian	Australian	0.57
28	182	51	3	136	41	7	Hishida A	2002	Asian	Japanse	0.09
29	32	2	0	57	6	0	Keshava C	2001	African	African-American	0.69
30	76	36	5	187	62	8	Keshava C	2001	Caucasian	American	0.31
31	190	109	16	138	101	17	Baxter SW	2001	Caucasian	British	0.8
32	360	219	36	646	374	58	Wang-Gohrke S	2001	Caucasian	German	0.69
33	243	85	11	280	78	1	Xie D	2000	Asian	Chinese	0.07

*P value for Hardy-Weinberg equilibrium in control group

Table 2. ORs and 95%CI for Breast Cancer and the HER2 Ile655Val Polymorphism under different Genetic Models

| Genetic model	Population	Pooled OR [95% CI] P	Heterogeneity P-value	Begg's test P-value	Egger's test P-value
Additive	Caucasian	1.111 [1.004-1.230] 0.042	0.001	0.046	0.006
(Val vs. Ile)	African	1.318 [0.970-1.792] 0.077	0.341	0.317	
	Asian	1.188 [0.965-1.462] 0.105	0.003	0.805	0.11
	Overall	1.136 [1.043-1.239] 0.004	0	0.051	0
Dominant	Caucasian	1.110 [0.991-1.243] 0.072	0.005	0.054	0.008
(Val-carriers vs. Ile/Ile)	African	1.228 [0.891-1.693] 0.210	0.381	0.317	
	Asian	1.154 [0.930-1.431] 0.195	0.02	0.805	0.066
	Overall	1.118 [1.020-1.227] 0.018	0.001	0.08	0
Recessive	Caucasian	1.077 [0.891-1.302] 0.445	0.175	0.421	0.014
(Val/Val vs. Ile-carriers)	African	15.406 [0.888-267.418] 0.060		0.317	
	Asian	1.303 [0.744-2.282] 0.355	0.033	0.805	0.595
	Overall	1.176 [0.964-1.435] 0.111	0.023	0.419	0.006
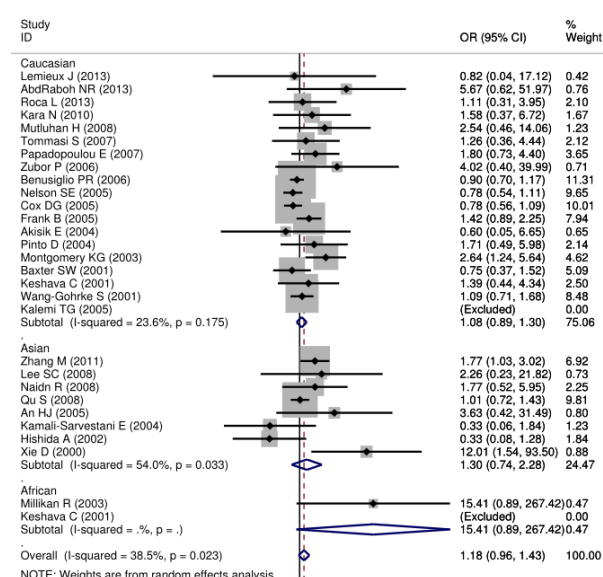
Figure 3. Forest Plot of ORs of Breast Cancer Risk Val/Val Genotype when Compared to the Ile Allele Carriers (Ile/Ile+Ile/Val) (Recessive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI

However, in recessive model, finding the HER2 Ile655Val polymorphism was not associated with the breast cancer risk in worldwide populations (OR=1.176, 95% CI 0.964-1.435, p=0.011), Caucasian (OR=1.077, 95% CI 0.891-1.302, p=0.445), African (OR=15.406, 95% CI: 0.888-267.418, p=0.060) nor Asian (OR=1.303, 95% CI: 0.744-2.282, p=0.355).

Publication bias

Funnel plot, Egger's test and the Begg's test were done to estimate the publication bias of literatures. The results of the Egger's test (p>0.05), and the Begg's test (p>0.05) provided statistical evidence for funnel plot symmetry in Table 2.

Sensitivity analysis ensured all the data analysis was stability and dependability in Figure 4.

Discussion

It is biologically plausible that exposure to cancer is a result of the accumulation of genetic variation and a combination often environmental exposure. The genetic susceptibility to cancer may be attributed to the SNP of major genetic pathways. And genetic susceptibility to cancer has been a research focus on scientific community. HER2 gene variants in the etiology of breast cancer have drawn increasing attention. Some studies have attempted to discover a possible association between the HER2 Ile655Val polymorphism and the risk of breast cancer in population. It is possible that point HER2 Ile655Val polymorphism might be found in breast cancer.

In subgroup analysis, we found that HER2 Ile655Val polymorphism was significantly correlated with breast cancer in overall in additive and dominant models. The Val allele causes an increase susceptibility to breast cancer in worldwide populations, especially in Caucasian. However,
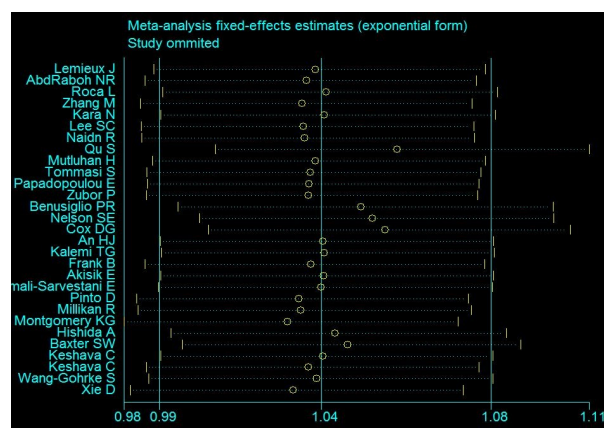
Figure 4. Sensitivity Analysis for HER2 Ile655Val Polymorphism and Breast Cancer Association in our Paper Dates

we did not found Ile allele and Ile-carriers such association risk in African nor Asian. Maybe several factors contribute to these. Fist, the presence of Val in 655position stabilized the formation of an active dimer of the protein, thus predisposing to an auto-activity of the receptor (Fleishman et al., 2002). Second, clinical heterogeneity contribute to the discrepancy in different. Third, our dates did not evaluate enough African subgroup for lack of studies.

In conclusion, this meta-analysis suggests that allele contrast (Val vs Ile) of HER2 Ile655Val polymorphism is associated with the breast cancer risk, especially in Caucasian subgroups. Future well designed large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of singleness cancer.

Acknowledgements

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