Review Article

Role of HER-2 Ile655Val Polymorphism as Universal Cancer Susceptibility Marker among Different Cancers

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Abstract

Background: Genetic and expression anomaly of HER-2 have been frequently observed in different cancers. However, an overall association of HER-2 polymorphism (Ile655Val) with available cancer studies has not yet been explored. In the present study, a probable correlation of HER-2 Ile655Val polymorphism with 6 major types of cancers including breast, lung, gastric, ovarian, thyroid and uterine has been collectively assessed.

Methodology: Extensive data mining was performed using online available medical research databanks including Pubmed, Ovid, Medline and Embase. Research articles were retrieved based on common keywords "HER-2, polymorphism, (SNP) and cancer (including breast, gastric, lung, ovarian, thyroid and uterine). A database was maintained and updated for case control studies of HER-2 genotype Ile655Val (rs1136201) information until February 2015. Based on selection criteria, a total of 41 studies containing 37,111 subjects (17845 patients, 19266 controls) were selected for thorough insight about HER-2.

Results: A significant risk association of HER-2 Ile655Val polymorphism was observed in different types of cancer using various genetic models (co-dominant heterogeneous Ile/Val vs. Ile/Ile; OR=1.1, 95% CI = 1.01–1.16, *P* = 0.01 and dominant; OR = 1.12, 95% CI = 1.03–1.20, *P* = 0.0003). Interestingly, a strong correlation of Ile655Val heterogeneity was seen in the stratified subgroup of different population including African-American (co-dominant homogenous Val/Val vs. Ile/Ile; OR = 8.7, 95% CI = 2.5–30.4, *P* = 0.0001, dominant; OR = 1.3, 95% CI = 1.03–1.7, *P* = 0.003; recessive; OR = 8.3, 95% CI = 2.4–28, *P* = 0.0002), Caucasians (co-dominant heterogeneous Ile/Val vs Ile/Ile; OR = 1.1, 95% CI = 1.0 – 1.2, *P* = 0.03, dominant; OR = 1.12, 95% CI = 1.0–1.2, *P* = 0.01). However, in Asian ethnic group, Ile655Val polymorphism lacked a significant association with cancer. This may be attributed to limited studies explored so far.

Conclusion: In summary, the current study reveals a significant association between cancer susceptibility and the HER-2 Ile655Val polymorphism in all genetic models.

Keywords: HER-2 polymorphism, breast cancer, metanalysis

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Introduction

Cancer is a leading cause of death worldwide alongside heart diseases. In 2012, approximately 14 million new cancer cases and 8.2 million cancer deaths have been reported across the globe.[1] Both genetic and non-genetic factors significantly contribute to cancer initiation, promotion and progression. Interestingly, involvement of oncogenes in initiation and progression of various cancers is well established.

HER-2 is a proto-oncogene located at chromosomal position 17q21. It retains an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain.[2] HER-2 overexpression is observed in 30% of invasive breast cancers,[3] along with several other cancers namely lung,[4] ovarian,[5] thyroid,[6] gastric,[7] and uterine cancers.[8] Trastuzumab (Herceptin), humanized monoclonal antibody was the first drug designed to restrict HER-2 activation. At present, molecular mechanistic details of trastuzumab induced cellular toxicity upon binding with HER-2 extracellular ligands are lacking. Based on efficient response rate, trastuzumab conjugated chemotherapy with doxorubicin and cyclophosphamide or paclitaxel led to its formal approval from the US food and drug administration (FDA). Later on, several other compounds have also been developed which target either HER-2 or HER-1 molecules (lapatinib, afatinib, and neratinib). Despite the wide range of inhibitors targeting HER-family, resistance against these drugs has been observed in HER-2 expressing tumors.[9] Both genetic and epigenetic alteration of HER-2, like loss of trastuzumab binding region (p95-HER-2), splice variants, activating mutations in extra or intracellular portions are few plausible reasons for drug resistance induced by HER-2 expressing cancer cells.[10]

Based on the earlier findings, an association has been frequently observed between HER-2 polymorphism and different forms of cancer. Involvement of Ile655Val (rs1136201) present at the codon 655 (ATC to GTC) in transmembrane domain of the receptor has been extensively reported in the literature.[11–13] Presence of valine at given 655 site significantly enhances tumorigenic behavior of the respective cancer.[11] Earlier, several reports have independently deciphered the association of HER-2 Ile655Val polymorphism with different types of cancer.[14–58]

Due to inconsistencies in previous studies, there is a need to elucidate HER-2 Ile655Val polymorphism with most commonly

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encountered cancers. Hence, a meta-analysis study was designed on the basis of all the relevant published case–control studies to explore any probable association of rs1136201 among different cancers.

Materials and Methods

Publication search

PubMed, Ovid, Medline and Embase were searched using multiple keywords like "HER-2 or ERBB2, Neu, or EGFP2", "polymorphism, SNP, variants" and "cancer" (last search update was in February 2015). 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. All research articles exploring association of HER-2 polymorphism Ile655Val and major cancers published from 2000 to 2015 were selected based on the following criteria.

Inclusion and exclusion criteria

Only those research articles satisfying the following inclusion criteria were selected for this study:

1. Included articles had followed a case-control study design.
2. For genotyping, molecular techniques like allele-specific PCR, RFLP-PCR, Taq Man assay and DNA sequencing was used in those research articles.
3. Tumors were also confirmed histologically in all these studies.
4. For estimation of odds ratios (OR) and 95% confidence intervals (CI), genotypic distributions were available in all studies.
5. These research articles were published in English.

Following exclusion criteria was used for this meta-analysis:

1. Research articles which failed to follow Hardy-Wienberg equilibrium were not included.
2. Research articles lacking complete information about allelic distribution were also excluded.
3. Those research articles lacking healthy controls were also not included.
4. All articles in which source of DNA isolation was different from blood origin like fresh tissue biopsies, paraffin embedded tissue blocks, saliva, cell line or any other *in vivo* model were not considered.
5. Review articles and HapMap analysis were not considered.

The studies found eligible for inclusion after following the inclusion and exclusion criteria are represented in Figure 1.

Data extraction

Information was carefully extracted from all studies independently by two authors (Riaz and Malik). Disagreement was resolved either by discussion or consultation with other authors (Kayani and Rashid). A majority of votes made the final decision. The following data were sought for: first author's surname, publication year, country origin, ethnicity (categorized as African-American, Asian and Caucasian), genotyping method, sources of controls, total number of cases and controls genotyped and p values of Hardy- Wienberg equilibrium reported in the paper.

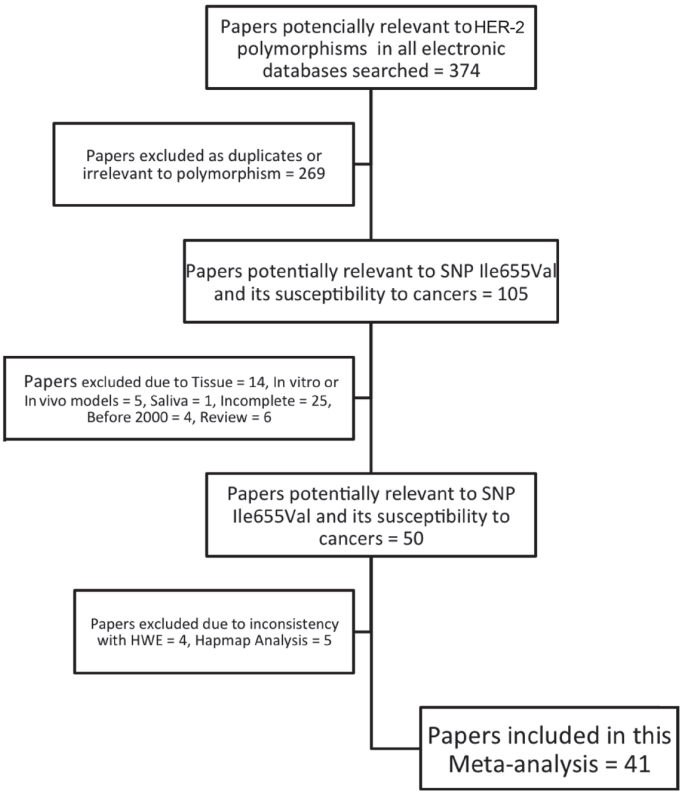

Figure 1. Flow diagram of the strategy of inclusion and exclusion criterion following which 41 potential studies were included for HER-2 I655V polymorphism with cancer.

Statistical analysis

After extracting the information from all the included studies, meta-analysis was performed as described previously.[34,59,60] Initially, data obtained was evaluated for Hardy-Weinberg equilibrium in the control group using online software (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Crude odd ratios with 95% confidence interval were used to evaluate any probable association among HER-2 Ile655Val polymorphism and six major types of cancers (breast, ovarian, lung, uterine, thyroid and gastric) on the basis of genotypic distribution and minor allele frequencies. Pooled odd ratios were calculated to estimate the risk in co-dominant models (Val/Val vs. Ile/Ile; Ile/Val vs. Ile/Ile), dominant model (Ile/Val + Val/Val vs. Ile/ Ile) and recessive model (Val/Val vs. Ile/Ile + Ile/Val). I^2 statistics were used to check the heterogeneity among the studies and P value less than 0.1 was considered as statistically significant. The pooled odd ratios were estimated under random effect model for significant P values of heterogeneity otherwise fixed effect model was used. Subgroup analysis was conducted by stratifying genotypic distribution data of world population into ethnic groups and assessment of summary of odd ratios in all genetic models. Impact of individual studies was also verified by sensitivity analysis.

Publication bias was detected by Egger's linear regression test where $P < 0.05$ was considered significant[58] and funnel plots were generated by applying Begg's test to the data. Statistical analyses were performed using software RevMan and StatsDirect version 2.

Results

Distribution of study cohort

Based on selection criteria, 41 case-control studies were found relevant for HER-2 Ile655Val polymorphism reported in 6 cancers, including 17845 patients and 19266 controls (Table 1). These studies were selected out of total 374 papers retrieved earlier from various databases. A total of 269 articles were excluded as duplicates or unrelated to HER-2 polymorphism while 105 studies were found relevant. Upon careful screening out of these 105 studies, 64 were not included due to the following reasons: 25 were incomplete with reference to the absence of genotypic allelic distribution among cases and controls, 15 studies were performed on tissue or saliva samples rather than blood, 11 were reviews and HapMap analysis, 5 studies were performed *in vitro* or *in vivo*, 4 studies were conducted before 2000 and 4 studies were not in Hardy-Weinberg equilibrium. Of the 41 included studies, 4 were conducted on African-American population.[29,35,46,49] Twelve were performed on Asian population,[16,22,23-25,30,32,36,39,45,51,52] and 25 were conducted on the Caucasian ethnic group.[14,15,17–21,26–29,31,33,35,37,38,40–44,47,48,50,52] The majority of these studies were performed on women affected by breast cancer. Out of 41 total studies, 34 studies were performed on breast cancer,[14–23,25–29,32,33,35,37–43,45,47,48,50,51,52,53] 2 studies were conducted on ovarian[36,44] and uterine cancer[30,31] and 1 on lung,[24] thyroid,[46] and gastric cancers.[49] In context to source of controls, 13 studies were hospital-based[14,20,23,24,29,30,33,36,39,42,47,48] 27 were population-based[15–19,21,22,25–28,31,32,35,37,38,40,41,43–46,50–53] while 1 study[49] was a mix of both methods as 121 control samples were hospital based and 103 DNA samples were extracted from healthy individuals who participated in the study voluntarily from a general Mexican population. For the included studies, genotyping methods such as TaqMan, PCR-RFLP and dual-color allele specific PCR assays were used. The minor allele frequency between the studies ranged from 0.048 for the American population[29] to 0.66 in the Egyptian population[14]. The genotypic distribution, P-values and minor allele frequencies of individual studies are also summarized in Table 2.

Meta-analysis

The conclusions drawn from the heterogeneity test for assessing the correlation of HER-2 Ile655Val polymorphism and 6 different types of cancers are summarized in Table 3.

In the co-dominant homogenous model (Val/Val vs Ile/Ile), an association of HER-2 Ile655Val and cancer risk ($I^2 = 42.4\%$, OR = 1.16, 95% CI = 0.96–1.4, $P = 0.13$) in the worldwide population was observed. Similar results were obtained in the subgroup analysis for Asian ($I^2 = 43.2\%$, OR = 1.01, 95% CI = 0.58–1.76, $P = 0.98$) and Caucasian populations ($I^2 = 36.9\%$, OR = 1.11, 95% CI = 0.92–1.33, $P = 0.27$). However, for the African-American population, a significant association was observed ($I^2 = 32.8\%$, OR = 8.68, 95% CI = 2.48 – 30.39, $P = 0.0001$).

Likewise in the co-dominant heterogeneous model (Ile/Val vs Ile/Ile), the risk of cancer was significantly higher compared to Ile/Ile in the worldwide population ($I^2 = 31.9\%$, OR = 1.09, 95% CI = 1.01–1.16, $P = 0.02$) as shown in Figure 2. In the subgroup analysis, a similar association was also observed in the Caucasian population ($I^2 = 42.8$, OR = 1.10, 95% CI = 1.01–1.21, $P = 0.03$). However, no significant risk of cancer with heterogeneity was observed in Asian ($I^2 = 20.2\%$, OR = 0.99, 95% CI = 0.91–1.09, $P = 0.99$) or African-American populations ($I^2 = 0\%$, OR = 1.19, 95% CI = 0.92–1.54, $P = 0.22$).

In the same way, in Dominant model, a significant increased risk association of these cancers was found with the HER-2 Ile655Val polymorphism in the worldwide population ($I^2 = 49\%$, OR = 1.12, 95% CI = 1.03–1.21, $P = 0.005$) (Figure 4), Caucasians ($I^2 = 55.1\%$, OR = 1.13, 95% CI = 1.02–1.24, $P = 0.01$), and African-Americans ($I^2 = 0\%$, OR = 1.32, 95% CI = 1.03–1.70, $P = 0.03$) but not in Asians ($I^2 = 41.7$, OR = 1.06, 95% CI = 0.91–1.23, $P = 0.46$).

In the recessive model, findings proposed that the HER-2 Ile655Val polymorphism was significantly associated with cancer risk in African-Americans only ($I^2 = 34\%$, OR = 8.27, 95% CI = 2.38–28.77, $P = 0.0002$) while it was not significant in worldwide population ($I^2 = 35.1\%$, OR = 1.11, 95% CI = 0.93–1.31, $P = 0.24$), Asians ($I^2 = 40.4\%$, OR = 0.99, 95% CI = 0.58–1.72, $P = 0.99$) or Caucasians ($I^2 = 23.6\%$, OR = 0.99, 95% CI = 0.89–1.12, $P = 0.96$).

Publication bias

The Begg's test, Funnel plot and Egger's test were performed to assess the publication bias of the included studies. The P values of the Egger's test and the Begg's test furnished statistical confirmation for the symmetry of funnel plot as shown in the Figure 3 and 5. Stability of the data analysis was ensured by sensitivity analysis.

Discussion

HER-2 belongs to the human epidermal growth factor receptor family, commonly expressed on the surface of epithelial cells.[54] Besides contribution to cell proliferation and differentiation, activation of HER-2 in normal cells promotes cell adhesion and motility.[55] The role of genetic aberrations in kinase binding domain

Table 1. List of all studies included in this meta-analysis.

No.	Author	Year	Ethnicity	Country	Source	Genotyping Method	Cancer Type	Total Cases	Total Controls
1	Haghshenas L[22]	2014	Asian	Iran	PB	PCR-RFLP	Breast Cancer	113	120
2	AbdRaboh NR[14]	2013	Caucasian	Egypt	HB	PCR-RFLP	Breast Cancer	64	86
3	Roca L[47]	2013	Caucasian	France	HB	PCR-RFLP	Breast Cancer	119	132
4	Lemieux J[33]	2013	Caucasian	Canada	HB	Taq Man Assay	Breast Cancer	10	63
5	Ozturk O[41]	2012	Caucasian	Turkey	PB	PCR-RFLP	Breast Cancer	118	128
6	Zhang M[52]	2011	Asian	Chinese	PB	PCR-RFLP	Breast Cancer	94	178
7	Kara N[28]	2010	Caucasian	Turkey	PB	PCR-RFLP	Breast Cancer	204	192
8	Kallel I[26]	2010	Caucasian	Tunisia	PB	PCR-RFLP	Breast Cancer	57	40
9	Naidu R[39]	2008	Asian	Malaysia	HB	PCR-RFLP	Breast Cancer	230	200
10	Qu S[45]	2008	Asian	China	PB	Taq Man Assay	Breast Cancer	3012	3004
11	Mutluhan H[38]	2008	Caucasian	Turkey	PB	PCR-RFLP	Breast Cancer	166	208
12	Lee SC[32]	2008	Asian	Taiwan	PB	PCR-RFLP	Breast Cancer	424	318
13	Papadopoulou E[42]	2007	Caucasian	Greece	HB	PCR-RFLP	Breast Cancer	56	45
14	Tommasi S[48]	2007	Caucasian	Italy	HB	Taq Man Assay	Breast Cancer	628	169
15	Benusiglio PR[18]	2006	Caucasian	Britian	PB	Taq Man Assay	Breast Cancer	1999	2154
16	Zubor P[53]	2006	Caucasian	Slovakia	PB	PCR-RFLP	Breast Cancer	47	60
17	Nelson SE[40]	2005	Caucasian	America	PB	Taq Man Assay	Breast Cancer	1094	976
18	An HJ[16]	2005	Asian	Korea	PB	PCR-RFLP	Breast Cancer	177	126
19	Cox DG[20]	2005	Caucasian	America	HB	Taq Man Assay	Breast Cancer	1271	1667
20	Frank B[21]	2005	Caucasian	Germany	PB	Taq Man Assay	Breast Cancer	347	960
21	Kalemi TG[27]	2005	Caucasian	Greece	PB	PCR-RFLP	Breast Cancer	42	51
22	Benusiglio PR[19]	2004	White British	United Kingdom	PB	Taq Man Assay	Breast Cancer	1989	2155
23	Pinto D[43]	2004	Caucasian	Portugal	PB	PCR-RFLP	Breast Cancer	152	146
24	Akisik E[15]	2004	Caucasian	Turky	PB	PCR-RFLP	Breast Cancer	121	145
25	Kamali-Sarvestani E[25]	2004	Asian	Iran	PB	PCR-RFLP	Breast Cancer	204	138
26	Millikan R[35]	2003	African-American	America	PB	Taq Man Assay	Breast Cancer	754	676
27	Millikan R 2[35]	2003	Caucasian	America	PB	Taq ManAssay	Breast Cancer	1261	1132
28	Montgomery KG[37]	2003	Caucasian	Australia	PB	Dual color allele-specific PCR assay	Breast Cancer	409	299
29	Hishida A[23]	2002	Asian	Japan	HB	Not Reported	Breast Cancer	236	184
30	Keshava C[29]	2001	African-American	America	HB	PCR-RFLP	Breast Cancer	34	63
31	Keshava C[29]	2001	Caucasian	America	HB	PCR-RFLP	Breast Cancer	117	257
32	Baxter SW[17]	2001	Caucasian	Britian	PB	PCR-RFLP	Breast Cancer	315	256
33	Wang-Gohrke S[50]	2001	Caucasian	Germany	PB	PCR-RFLP	Breast Cancer	615	1078
34	Xie D[51]	2000	Asian	China	PB	PCR-RFLP	Breast Cancer	339	359
35	Mojtahedi Z[36]	2013	Asian	Iran	HB	PCR-RFLP	Ovarian Cancer	107	130
36	Pinto D[44]	2005	Caucasian	Portugal	PB	PCR-RFLP	Ovarian Cancer	111	146
37	Kruszyna L[31]	2010	Caucasian	Poland	PB	PCR-RFLP	Uterine Cancer	109	220
38	Jo UH[24]	2008	Asian	Korea	HB	PCR-RFLP	Lung Cancer	406	403
39	Rebai M[46]	2009	African	Tunisia	PB	PCR-RFLP	Thyroid Cancer	106	286
40	Torres-Jasso JH[49]	2013	American	Mexico	Mix	PCR-RFLP	Gastric Cancer	72	103
41	Kitao K[30]	2007	Asian	Japan	HB	PCR-RFLP	Uterine Cancer	116	213

Table 2. Genotypic distribution, *P*-values and minor allele frequency (Val) of included studies.

No.	Author	Year	Cases				Controls				*P*-Value of HWE	Minor allele frequency (Val)
			Total	Ile/Ile	Ile/ Val	Val/Val	Total	Ile/Ile	Ile/Val	Val/ Val		
1	Haghshenas L[22]	2014	113	81	28	4	120	93	26	1	0.01	0.117
2	AbdRaboh NR[14]	2013	64	39	21	4	86	67	18	1	0.86	0.661
3	Roca L[47]	2013	119	75	39	5	132	79	48	5	0.49	0.220
4	Lemieux J[33]	2013	10	4	6	0	63	48	12	3	0.18	0.300
5	Ozturk O[41]	2012	118	61	57	0	128	87	41	0	0.03	0.160
6	Zhang M[52]	2011	94	67	26	1	178	104	62	12	0.51	0.242
7	Kara N[28]	2010	204	153	46	5	192	141	48	3	0.63	0.141
8	Kallel I[26]	2010	57	55	2	0	40	34	4	2	0.004	0.100
9	Naidu R[39]	2008	230	165	57	8	200	159	37	4	0.3	0.113
10	Qu S[45]	2008	3012	2298	648	66	3004	2252	687	65	0.14	0.136
11	Mutluhan H[38]	2008	166	128	34	4	208	166	40	2	0.81	0.106
12	Lee SC[32]	2008	424	341	80	3	318	273	44	1	0.58	0.072
13	Papadopoulou E[42]	2007	56	15	22	19	45	19	16	10	0.08	0.400
14	Tommasi S[48]	2007	628	433	181	14	169	125	41	3	0.86	0.139
15	Benusiglio PR[18]	2006	1999	1134	752	113	2154	1229	791	134	0.66	0.246
16	Zubor P[53]	2006	47	22	22	3	60	42	17	1	0.63	0.158
17	Nelson SE[40]	2005	1094	637	396	61	976	551	356	69	0.28	0.253
18	An HJ[16]	2005	177	139	33	5	126	96	29	1	0.45	0.123
19	Cox DG[20]	2005	1271	766	447	58	1667	980	591	96	0.58	0.235
20	Frank B[21]	2005	347	186	132	29	960	525	377	58	0.37	0.257
21	Kalemi TG[27]	2005	42	32	10	0	51	36	15	0	0.22	0.147
22	Benusiglio PR[19]	2004	1989	1128	748	113	2155	1230	791	134	0.69	0.246
23	Pinto D[43]	2004	152	88	57	7	146	107	35	4	0.58	0.147
24	Akisik E[15]	2004	121	98	22	1	145	117	26	2	0.69	0.103
25	Kamali-Sarvestani E[25]	2004	204	145	57	2	138	102	32	4	0.28	0.145
26	Millikan R[35]	2003	754	658	88	8	676	606	70	0	0.16	0.052
27	Millikan R 2[35]	2003	1261	752	429	80	1132	684	375	73	0.03	0.230
28	Montgomery KG[37]	2003	409	240	138	31	299	196	94	9	0.57	0.187
29	Hishida A[23]	2002	236	182	51	3	184	136	41	7	0.09	0.149
30	Keshava C[29]	2001	34	32	2	0	63	57	6	0	0.69	0.048
31	Keshava C 2[29]	2001	117	76	36	5	257	187	62	8	0.31	0.152
32	Baxter SW[17]	2001	315	190	109	16	256	138	101	17	0.8	0.264
33	Wang-Gohrke S[50]	2001	615	360	219	36	1078	646	374	58	0.69	0.227
34	Xie D[51]	2000	339	243	85	11	359	280	78	1	0.07	0.111
35	Mojtahedi Z[36]	2013	107	81	25	1	130	97	30	3	0.71	0.138
36	Pinto D[44]	2005	111	73	34	4	146	107	35	4	0.853	0.147
37	Kruszyna L[31]	2010	109	53	49	7	220	138	78	4	0.046	0.195
38	Jo UH[24]	2008	406	304	97	5	403	300	97	6	0.98	0.135
39	Rebai M[46]	2009	106	78	23	5	286	235	51	0	0.059	0.089
40	Torres-Jasso JH[49]	2013	72	49	20	3	103	76	25	2	0.965	0.141
41	Kitao K[30]	2007	116	91	23	2	213	169	39	5	0.99	0.115

Table 3. Stratified pooled OR with 95% Confidence Interval for HER-2 Ile655Val polymorphism and cancer risk.

Models	No. of studies	Total cases	Total controls	OR (95% CI)	P*	I^2 (%)	Analysis model
CODOMINANT (Val/Val vs Ile/Ile)							
African-American	4	849	978	8.7(2.5–30.4)	0.226	32.8	Fixed Effect
Asian	12	4359	4281	1.0 (0.6–1.8)	0.055	43.2	Random Effect
Caucasian	25	8028	9079	1.1 (0.9–1.3)	0.040	36.9	Random Effect
Overall	41	13236	14338	1.2 (0.95–1.4)	0.004	42.4	Random Effect
CODOMINANT (Ile/Val vs. Ile/Ile)							
African-American	4	1083	1278	1.2 (0.9–1.5)	0.817	0	Fixed Effect
Asian	12	6557	6465	0.99 (0.9–1.1)	0.245	20.2	Fixed Effect
Caucasian	25	14814	16451	1.1 (1.0–1.2)	0.013	42.8	Random Effect
Overall	41	22454	24194	1.1 (1.0–1.2)	0.028	31.9	Random Effect
DOMINANT (Ile/Val + Val/Val vs. Ile/ Ile)							
African-American	4	1115	1282	1.3 (1.0–1.7)	0.645	0	Fixed Effect
Asian	12	6779	6685	1.1 (0.9–1.2)	0.064	41.7	Random Effect
Caucasian	25	16044	17851	1.1 (1.0–1.3)	0.0005	55.1	Random Effect
Overall	41	23938	25818	1.1 (1.0–1.2)	0.0003		Random Effect
RECESSIVE (Val/Val vs. Ile/Ile + Ile/ Val)							
African-American	4	982	1130	8.3 (2.4–28.8)	0.220	34	Fixed Effect
Asian	12	5569	5483	0.99 (0.6–1.7)	0.072	40.4	Random Effect
Caucasian	25	12036	13465	0.99 (0.9–1.1)	0.151	23.6	Fixed Effect
Overall	41	18587	20078	1.1 (0.9–1.3)	0.019	35.1	Random Effect

* *P*-value of heterogeneity; Values in bold are significant either in random or fixed effect models.

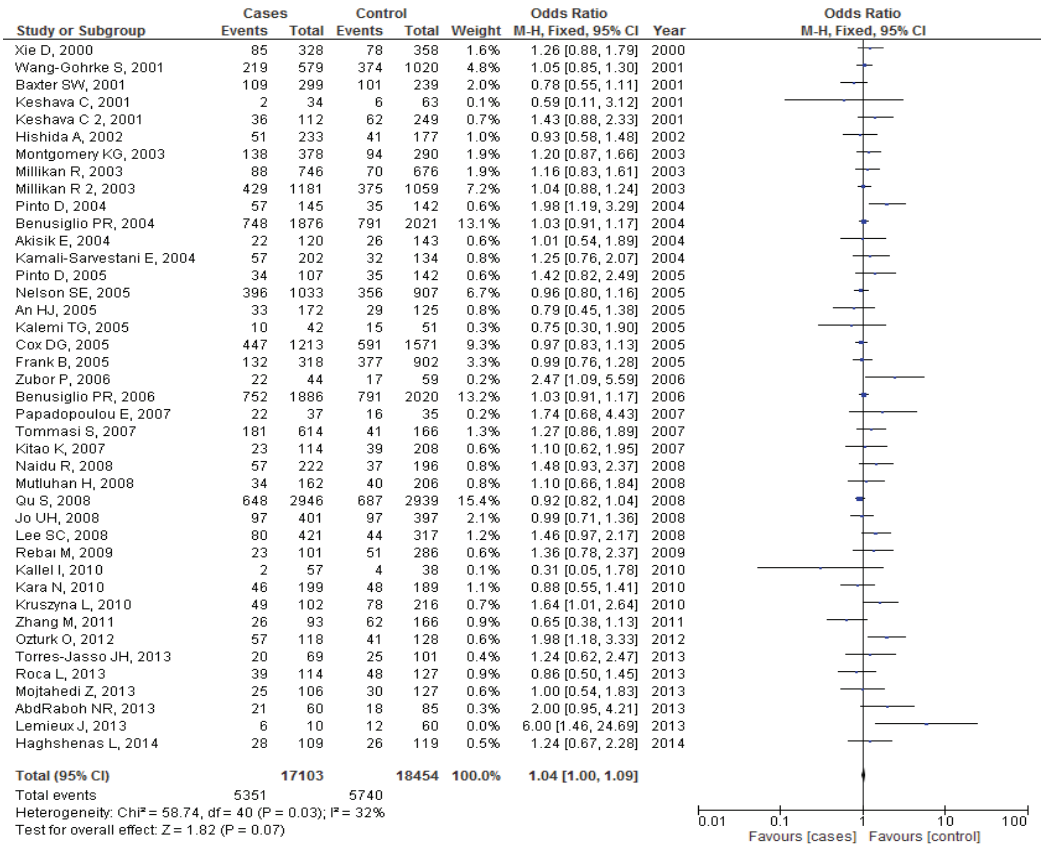

Figure 2. Forest plot of the codominant heterogeneous model (Ile/Val vs Ile/Ile) showing association of HER-2 I655V polymorphism with cancer risk in world-wide population.

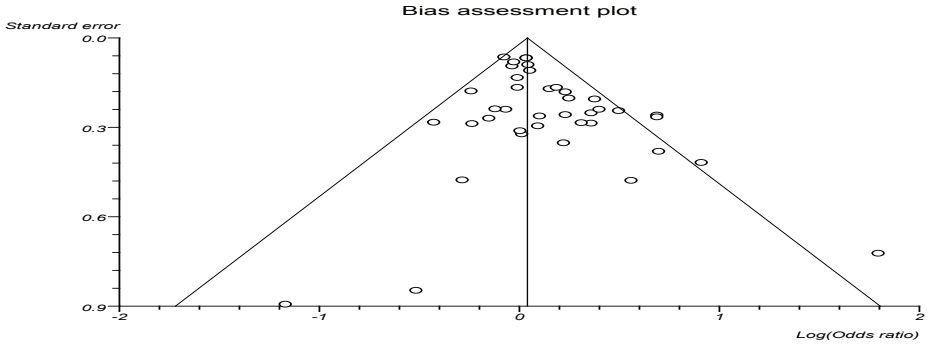

Figure 3. Funnel plot of the co-dominant heterogeneous model (Ile/Val vs Ile/Ile) for publication bias. Each included study is represented by a point for the association.

Study or Subgroup	Cases Events	Cases Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Xie D, 2000	96	339	79	359	1.5%	1.40 [0.99, 1.97]	2000
Keshava C 2, 2001	41	117	70	257	0.8%	1.44 [0.90, 2.30]	2001
Keshava C, 2001	2	34	6	63	0.1%	0.59 [0.11, 3.12]	2001
Baxter SW, 2001	125	315	118	256	2.1%	0.77 [0.55, 1.07]	2001
Wang-Gohrke S, 2001	255	615	432	1078	4.9%	1.06 [0.87, 1.30]	2001
Hishida A, 2002	54	236	48	184	1.1%	0.84 [0.54, 1.32]	2002
Millikan R 2, 2003	509	1261	448	1132	7.4%	1.03 [0.88, 1.22]	2003
Millikan R, 2003	96	754	70	676	1.7%	1.26 [0.91, 1.75]	2003
Montgomery KG, 2003	169	409	103	299	1.8%	1.34 [0.98, 1.83]	2003
Kamali-Sarvestani E, 2004	59	204	36	138	0.8%	1.15 [0.71, 1.87]	2004
Benusiglio PR, 2004	861	1989	925	2155	13.3%	1.01 [0.90, 1.15]	2004
Akisik E, 2004	23	121	28	145	0.5%	0.98 [0.53, 1.81]	2004
Pinto D, 2004	64	152	39	146	0.6%	2.00 [1.22, 3.25]	2004
Kalemi TG, 2005	10	42	15	51	0.3%	0.75 [0.30, 1.90]	2005
Frank B, 2005	161	347	435	960	3.3%	1.04 [0.82, 1.34]	2005
Cox DG, 2005	505	1271	687	1667	9.5%	0.94 [0.81, 1.09]	2005
An HJ, 2005	38	177	30	126	0.7%	0.87 [0.51, 1.51]	2005
Pinto D, 2005	38	111	39	146	0.6%	1.43 [0.83, 2.44]	2005
Nelson SE, 2005	457	1094	425	976	6.9%	0.93 [0.78, 1.11]	2005
Benusiglio PR, 2006	865	1999	925	2154	13.4%	1.01 [0.90, 1.15]	2006
Zubor P, 2006	25	47	18	60	0.2%	2.65 [1.20, 5.88]	2006
Kitao K, 2007	25	116	44	213	0.6%	1.06 [0.61, 1.83]	2007
Papadopoulou E, 2007	41	56	26	45	0.2%	2.00 [0.87, 4.61]	2007
Tommasi S, 2007	195	628	44	169	1.3%	1.28 [0.87, 1.88]	2007
Lee SC, 2008	83	424	45	318	1.1%	1.48 [0.99, 2.19]	2008
Jo UH, 2008	102	406	103	403	2.0%	0.98 [0.71, 1.34]	2008
Qu S, 2008	714	3012	752	3004	15.2%	0.93 [0.83, 1.05]	2008
Naidu R, 2008	65	230	41	200	0.8%	1.53 [0.98, 2.39]	2008
Mutluhan H, 2008	38	166	42	208	0.8%	1.17 [0.71, 1.93]	2008
Rebai M, 2009	28	106	51	286	0.5%	1.65 [0.98, 2.80]	2009
Kruszyna L, 2010	56	109	82	220	0.7%	1.78 [1.12, 2.83]	2010
Kallel I, 2010	2	57	6	40	0.2%	0.21 [0.04, 1.08]	2010
Kara N, 2010	51	204	51	192	1.0%	0.92 [0.59, 1.45]	2010
Zhang M, 2011	27	94	74	178	1.0%	0.57 [0.33, 0.97]	2011
Ozturk O, 2012	57	118	41	128	0.5%	1.98 [1.18, 3.33]	2012
AbdRaboh NR, 2013	25	64	19	86	0.3%	2.26 [1.11, 4.62]	2013
Torres-Jasso JH, 2013	23	72	27	103	0.4%	1.32 [0.68, 2.56]	2013
Roca L, 2013	44	119	53	132	0.8%	0.87 [0.53, 1.46]	2013
Mojtahedi Z, 2013	26	107	33	130	0.6%	0.94 [0.52, 1.71]	2013
Lemieux J, 2013	6	10	15	63	0.0%	4.80 [1.19, 19.30]	2013
Haghshenas L, 2014	32	113	27	120	0.5%	1.36 [0.75, 2.46]	2014
Total (95% CI)		**17845**		**19266**	**100.0%**	**1.04 [1.00, 1.09]**	
Total events	6093		6552				

Heterogeneity: Chi² = 78.38, df = 40 (P = 0.0003); I² = 49%
Test for overall effect: Z = 1.92 (P = 0.05)

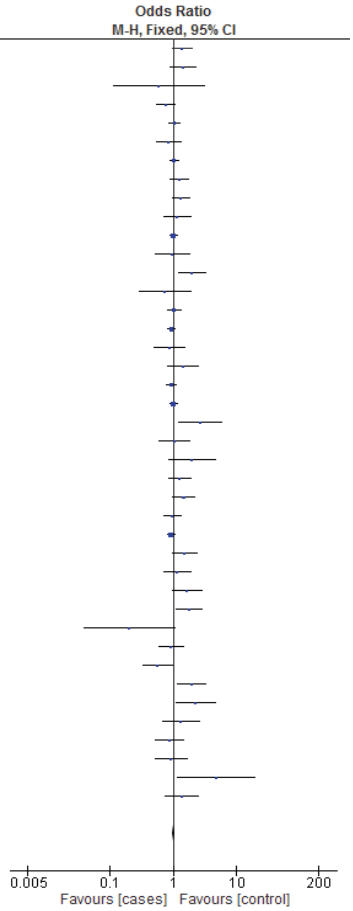

Figure 4. Forest plot of the dominant model (Ile/Val + Val/Val vs Ile/Ile) indicating association of HER-2 I655V polymorphism with cancer risk in worldwide population.

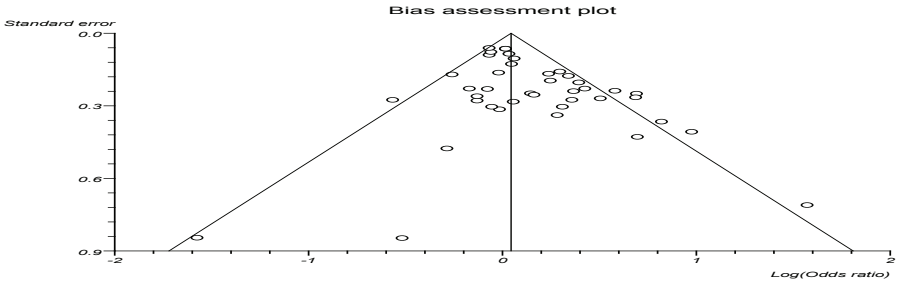

Figure 5. Funnel plot of the dominant model (Ile/Val + Val/Val vs Ile/Ile) for publication bias. Each included study is represented by a point for the association.

of HER-2 also contributes to tumorigenesis and has also been reported in many cancer types[3,56] Ile655Val (rs1136201) is the most extensively studied polymorphism associated with different cancers.[11] This change results in stabilization of homodimerized HER-2 complex which enhances tyrosine kinase activity for activation of several downstream pathways leading to increased cell proliferation.[57]

This meta-analysis revealed a significant association of cancer and HER-2 Ile655Val polymorphism in worldwide population. A significant association was observed in the worldwide analysis (Ile/Val vs.. Ile/Ile; OR = 1.1, 95% CI = 1.0–1.2, *P* = 0.01, Ile/Val + Val/Val vs.. Ile/Ile; OR = 1.12, 95% CI = 1.0–1.2, *P* = 0.005). Significant heterogeneity was also found in the stratified subgroup analysis in which moderate risk association was observed for African-Americans (Val/Val vs. Ile/Ile; OR = 8.7, 95% CI = 2.5–30.4, *P* = 0.0001, Ile/Val+Val/Val vs. Ile/Ile; OR = 1.3, 95% CI = 1.03–1.7, *P* = 0.003; Val/Val vs. Ile/Val+Ile/Ile; OR = 8.3, 95% CI = 2.4–28, *P* = 0.0002), Caucasians (Ile/Val vs. Ile/Ile; OR = 1.1, 95% CI = 1.0–1.2, *P* = 0.03, Ile/Val + Val/Val vs. Ile/Ile; OR = 1.12, 95% CI = 1.0–1.2, *P* = 0.03). No associations were observed in the Asian ethnic group in any of the 4 models.

The initial positive association of HER-2 Ile655Val polymorphism and breast cancer risk was reported by Xie in a Chinese population.[51] Since then, many studies have been performed in different populations and different cancers which have provided conclusive evidence of correlation.[14,22,24,31,32,37,38,42,43,46,48,53] Interestingly, quite contrasting findings stating lack of any association between cancer risk and HER-2 Ile655Val polymorphism have also been reported.[19,25,30,36,49,50] Furthermore, Cox[20] and Nelson[40] demonstrated an inverse association stating that valine present at 655 reduced the risk of breast cancer. Based on these contrasting results, there was an immense need for a meta-analysis to establish a significant association between allele contrast (Val vs. Ile) of HER-2 Ile655Val polymorphism and risk of all major cancers with worldwide population, especially Caucasians and Asians. Previously, several meta-analyses have been conducted to assess this association in breast cancer but the results are quite ambiguous, especially in stratified analysis. A significant effect of valine substitution on increased tumorigenicity and cardiomyopathies is established.

Lu *et al.* (2010)[34] found association of HER-2 Ile655Val polymorphism with the Asian and African sub-groups in breast cancer and no correlation was observed for Caucasians. On the contrary, Chen (2014) suggested an inverse relationship.[59] In this meta-analysis, no association was observed in the Asian ethnic group but with African-American and Caucasian groups. This could be due to lack of studies and clinical heterogeneity, which plays a vital role in genetic susceptibility to cancer. Based on these findings, Ile655Val polymorphism significantly elevates cancer risk across Caucasians and African-American populations. These polymorphisms significantly attribute in designing a personalized medication as evidenced by a recent approval of Kalydeco drug by FDA destined against cystic fibrosis (CF) gene polymorphism G551D.

There are certain limitations in this article which should be considered. As cancer is a multifactorial disease, there are several exogenous factors involved in the initiation and progression of cancer. Gender, age, stage of cancer, occupational hazards, lifestyle, obesity and co-morbidity are certain factors that affect the onset of several types of cancers and the penetration of polymorphisms. As information regarding these confounders was unavailable in the included studies, the analysis was performed using unadjusted odd ratios. Secondly, studies included in the African-American subgroup are fewer compared to other ethnic groups; hence studies with large sample size will further elaborate this plausible association of HER-2 with all salient types of cancer.

In conclusion, it is the first report suggesting a significant association between HER-2 Ile655Val polymorphism and all major types of cancers (Breast, Ovarian, Uterine, Lung, Thyroid and Gastric) suggesting that carriers of Valine allele and Val/Val genotype may be linked with elevated risk of cancer. In future, further well-designed studies are warranted, especially addition of more studies for other cancers besides breast cancer to validate these findings.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. *CA: A Cancer J Clin*. 2015; 65(2): 87 – 108.
2. Hynes NE, Stern DF. The Biology of erbB-2/neu/HER-2 and Its Role in Cancer. *Biochim Biophys Acta*. 1994; 1198(2-3): 165 – 84.
3. Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB Signaling Network: Receptor Heterodimerization in Development and Cancer. *EMBO*. 2000; 19(13): 3159 – 67.
4. Harpole DH Jr, Marks JR, Richards WG, Herndon JE, Sugarbaker DJ. Localized Adenocarcinoma of the Lung: Oncogene Expression of erbB-2 and p53 in 150 Patients. *Clin Cancer Res*. 1995; 1(6): 659 – 64.
5. Meden H, Marx D, Rath W, Kron M, Fattahi-Meibodi A, Hinney B, et al. Overexpression of the Oncogene c-Erb B2 in Primary Ovarian Cancer: Evaluation of the Prognostic Value in a Cox Proportional Hazards Multiple Regression. *Int J Gynecol Pathol*. 1994; 13(1): 45 – 53.
6. Kremser R, Obrist P, Spizzo G, Erler H, Kendler D, Kemmler G, et al. Her2/neu Overexpression in Differentiated Thyroid Carcinomas Predicts Metastatic Disease. *Virchows Arch*. 2003; 442(4): 322 – 28.
7. Roh JK, Paik S, Chung HC, Yang W, Kim HK, Choi IJ, et al. Overexpression of erbB-2 Protein in Gastric Adenocarcinoma--a Potential Role in Therapeutic Response to Adjuvant 5-FU-Doxorubicin Regimen. *Gan To Kagaku Ryoho*. 1992; 19(8 Suppl): 1207 – 19.
8. Berchuck A, Rodriguez G, Kinney RB, Soper JT, Dodge RK, Clarke-Pearson Dl, et al. Overexpression of HER-2/neu in Endometrial Cancer Is Associated with Advanced Stage Disease. *Am J Obstet Gynecol*. 1994; 164(1Pt1): 15 – 21.
9. Rimawi MF, Schiff R, Osborne CK. Targeting HER2 for the treatment of breast cancer. *Annu Rev Med*. 2015; 66: 111 – 28.
10. Herter-Sprie GS, Greulich H, Wong KK. Activating mutations in ERBB2 and their impact on diagnostics and treatment. *Front Oncol*. 2013; 3: 86.
11. Han X, Diao L, Xu Y, Xue W, Ouyang T, Li J, et al. Association between the HER2 Ile655Val Polymorphism and Response to Trastuzumab in Women with Operable Primary Breast Cancer. *Ann Oncol*. 2014; 25(6): 1158 – 64.
12. Kuraoka K, Matsumura S, Hamai Y, Nakachi K, Imai K, Matsusaki K, et al. A Single Nucleotide Polymorphism in the Transmembrane Domain Coding Region of HER-2 Is Associated with Development and Malignant Phenotype of Gastric Cancer. *Int J Cancer*. 2003; 107(4): 593 – 96.
13. Papewalis J, Nitin AYu, Rajewsky MF. G to A Polymorphism at Amino Acid Codon 655 of the Human erbB-2/HER2 Gene. *Nucleic Acids Res*. 1991; 19(19): 54 – 52.
14. AbdRaboh NR, Shehata HH, Ahmed MB, Bayoumi FA. HER1 R497K and HER2 I655V polymorphisms are linked to development of breast cancer. *Dis Markers*. 2013; 34(6): 407 –17.
15. Akisik E, Dalay N. Estrogen Receptor Codon 594 and HER2 Codon 655 Polymorphisms and Breast Cancer Risk. *Exp Mol Pathol*. 2004; 76(3): 260 – 3.
16. An HJ, Kim NK, Oh D, Kim SH, Park MJ, Jung MY, et al. Her2 Genotype and Breast Cancer Progression in Korean Women. *Pathol Int*. 2005; 55(2): 48 – 52.
17. Baxter SW, Campbell IG. Re: Population-Based, Case-Control Study of HER2 Genetic Polymorphism and Breast Cancer Risk. *J Natl Cancer Inst*. 2001; 93(7): 557 – 59.
18. Benusiglio PR, Pharoah PD, Smith PL, Lesueur F, Conroy D, Luben

RN, et al. HapMap-based study of the 17q21 ERBB2 amplicon in susceptibility to breast cancer. *Br J Cancer*. 2006; 95(12): 1689 – 95.
19. Benusiglio PR, Lesueur F, Luccarini C, Conroy DM, Shah M, Easton DF, et al. Common ERBB2 polymorphisms and risk of breast cancer in a white British population: A case-control study. *Breast Cancer Res*. 2005; 7(2): R204 – 9.
20. Cox DG, Hankinson SE, Hunter DJ. The erbB2/HER2/neu Receptor Polymorphism Ile655Val and Breast Cancer Risk. *Pharmacogenet Genomics*. 2005; 15(7): 447 – 50.
21. Frank B, Hemminki K, Wirtenberger M, Bermejo JL, Bugert P, Klaes R, et al. The rare ERBB2 variant Ile654Val is associated with an increased familial breast cancer risk. *Carcinogenesis*. 2005; 26(3): 643 – 47.
22. Haghshenas L, Khandouzi M. HER2 Ile655Val SNP and Risk of Breast Cancer. *IJMER*. 2014; 3(7): 1 – 10.
23. Hishida A, Hamajima N, Iwata H, Matsuo K, Hirose K, Emi N, et al. Re: Population-Based, Case-Control Study of HER2 Genetic Polymorphism and Breast Cancer Risk. *J Natl Cancer Inst*. 2002; 94(23): 1807 – 8.
24. Jo UH, Han SG, Seo JH, Park KH, Lee JW, Lee HJ, *et al*. The Genetic Polymorphisms of HER-2 and the Risk of Lung Cancer in a Korean Population. *BMC Cancer*. 2008; 8: 359.
25. Kamali-Sarvestani E, Talei AR, Merat A. Ile to Val Polymorphism at Codon 655 of HER-2 Gene and Breast Cancer Risk in Iranian Women. *Cancer Lett*. 2004; 215(1): 83 – 7.
26. Kallel I, Kharrat N, Al-fadhly S, Rebai M, Khabir A, Boudawara TS, et al. HER2 polymorphisms and breast cancer in Tunisian women. *Genet Test Mol Biomarkers*. 2010; 14(1): 29 – 35.
27. Kalemi T, Lambropoulos AF, Gueorguiev M, Chrisafi S, Papazisis KT, Kotsis A. The Association of p53 Mutations and p53 Codon 72, Her 2 Codon 655 and MTHFR C677T Polymorphisms with Breast Cancer in Northern Greece. *Cancer Lett.* 2005; 222(1): 57 – 65.
28. Kara N, Karakus N, Ulusoy AN, Ozaslan C, Gungor B, Bagci H. P53 Codon 72 and HER2 Codon 655 Polymorphisms in Turkish Breast Cancer Patients. *DNA Cell Biol*. 2010; 29(7): 387 – 92.
29. Keshava C, McCanlies EC, Keshava N, Wolff MS, Weston A. Distribution of HER2(V655) genotypes in breast cancer cases and controls in the United States. *Cancer Lett.* 2001; 173(1): 37 – 41.
30. Kitao K, Yoshida S, Kennedy S, Takemura N, Sugimoto M, Deguchi M, et al. Epidermal growth factor receptor and human epidermal growth factor receptor 2 gene polymorphisms in endometrial cancer in a Japanese population. *Reprod Sci.* 2007; 14(4): 349 – 57.
31. Kruszyna L, Lianeri M, Roszak A, Jagodziński PP. HER2 Codon 655 Polymorphism Is associated with advanced uterine cervical carcinoma. *Clin Biochem*. 2010; 43(6): 545 – 48.
32. Lee SC, Hou MF, Hsieh PC, Wu SH, Hou LA, Ma H, et al. A case-control study of the HER2 Ile655Val polymorphism and risk of breast cancer in Taiwan. *Clin Biochem*. 2008; 41(3): 121 – 5.
33. Lemieux J, Diorio C, Cote MA, Provencher L, Barabé F, Jacob S, et al. Alcohol and HER2 polymorphisms as risk factor for cardiotoxicity in breast cancer treated with Trastuzumab. *Anticancer Res*. 2013; 33(6): 2569 – 76.
34. Lu Su, Wang Z, Liu H, Hao X. HER2 Ile655Val Polymorphism Contributes to Breast Cancer Risk: Evidence from 27 case-control studies. *Breast Cancer Res Treat*. 2010; 124(3): 771 – 8.
35. Millikan R, Eaton A, Worley K, Biscocho L, Hodgson E, Huang WY, et al. HER2 Codon 655 Polymorphism and Risk of Breast Cancer in African Americans and Whites. *Breast Cancer Res Treat*. 2003; 79(3): 355 – 64.
36. Mojtahedi Z, Erfani N, Malekzadeh M, Haghshenas MR, Ghaderi A, Samsami Dehaghani A. HER2 Ile655Val Single Nucleotide Polymorphism in Patients with Ovarian Cancer. *Iran Red Crescent Med J.* 2013; 15(1): 1 – 3.
37. Montgomery KG, Gertig DM, Baxter SW, Milne RL, Dite GS, McCredie MR, et al. The HER2 I655V Polymorphism and Risk of Breast Cancer in Women < Age 40 Years. *Cancer Epidemiol Biomarkers Prev.* 2003; 12(10): 1109 – 11.
38. Mutluhan H, Akbas E, Erdogan NE, Soylemez F, Senli MS, Polat A, et al. The Influence of HER2 Genotypes as Molecular Markers on Breast Cancer Outcome. *DNA Cell Biol*. 2008; 27(10): 575 – 9.
39. Naidu R, Yip CH, Taib NA. Polymorphisms of HER2 Ile655Val and Cyclin D1 (CCND1) G870A are not associated with breast cancer risk but polymorphic allele of HER2 Is Associated with Nodal Metastases. *Neoplasma*. 2008; 55(2): 87 – 95.
40. Nelson, SE, Gould MN, Hampton JM, Trentham-Dietz A. A Case-Control Study of the HER2 Ile655Val polymorphism in relation to risk of Invasive Breast Cancer. *Breast Cancer Res*. 2005; 7(3): R357 – 64.
41. Ozturk O, Canbay E, Kahraman OT, Fatih Seyhan M, Aydogan F, Celik V, et al. HER2 Ile655Val and PTEN IVS4 polymorphisms in patients with breast cancer. *Mol Biol Rep*. 2013; 40(2): 1813 – 18.
42. Papadopoulou E, Simopoulos K, Tripsianis G, Tentes I, Anagnostopoulos K, Sivridis E, et al. Allelic Imbalance of HER-2 Codon 655 Polymorphism among Different Religious/ethnic Populations of Northern Greece and its association with the development and the malignant phenotype of breast cancer. *Neoplasma*. 2007; 54(5): 365 – 73.
43. Pinto D, Vasconcelos A, Costa S, Pereira D, Rodrigues H, Lopes C, et al. HER2 polymorphism and breast cancer risk in Portugal. *Eur J Cancer Prev*. 2004; 13(3): 177–81.
44. Pinto D, Pereira D, Portela C, da Silva JL, Lopes C, Medeiors R. The Influence of HER2 Genotypes as Molecular Markers in Ovarian Cancer Outcome. *Biochem Biophys Res Commun.* 2005; 335(4): 1173 – 78.
45. Qu S, Cai Q, Gao YT, Lu W, Cai H, Su Y, et al. ERBB2 genetic polymorphism and breast cancer risk in Chinese women: A population-based case-control study. *Breast Cancer Res Treat*. 2008; 110(1): 169 – 76.
46. Rebaï M, Kallel I, Hamza F, ChrfeddineS, Kaffel R, Guermazi F, et al. Association of EGFR and HER2 polymorphisms with risk and clinical features of Thyroid Cancer. *Genet Test Mol Biomarkers.* 2009; 13(6): 779 – 84.
47. Roca, L, Dieras V, Roche H, Lappartient E, Kerbrat P, Cany L, et al. Correlation of HER2, FCGR2A, and FCGR3A gene polymorphisms with Trastuzumab related cardiac toxicity and efficacy in a subgroup of patients from UNICANCER-PACS 04 Trial. *Breast Cancer Res Treat*. 2013; 139(3): 789 – 800.
48. Tommasi S, Fedele V, Lacalamita R, Bruno M, Schittuli F, Ginzinger D, et al. 655Val and 1170Pro ERBB2 SNPs in familial breast cancer risk and BRCA1 alterations. *Cell Oncol*. 2007; 29(3): 241 – 8.
49. Torres-Jasso JH, Bustos-Carpinteyro AR, Marin ME, Santiago E, Leoner C, Flores-Luna L, et al. Analysis of the polymorphisms EGFR-R521K and ERBB2-I655V in Mexican patients with gastric cancer and premalignant gastric lesions. *Rev Invest Clin*. 2013; 65(2): 150 – 55.
50. Wang-Gohrke S, Chang-Claude J. Re: Population-Based, Case-Control Study of HER2 Genetic Polymorphism and Breast Cancer Risk. *J Natl Cancer Inst*. 2001; 93(21): 1657 – 9.
51. Xie D, Shu XO, Deng Z, Wen WQ, Creek KE, Dai Q, et al. Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. *J Natl Cancer Inst*. 2000; 92(5): 412 – 17.
52. Zhang M, Guo LL, Cheng Z, Liu RY, Lu Y, Qian Q, et al. A functional polymorphism of TGFBR2 is associated with risk of breast cancer with ER+, PR+, ER+PR+ and HER2- expression in women. *Oncol Lett*. 2011; 2(4): 653 – 58.
53. Zúbor P, Vojvodova A, Danko J, Kajo K, Szunyogh N, Lasabova Z, et al. HER-2 [Ile655Val] polymorphism in association with breast cancer risk: A population-based case-control Study in Slovakia. *Neoplasma.* 2006; 53(1): 49 – 55.
54. O-charoenrat P, Rhys-Evans PH, Modjtahedi H, Eccles SA. The role of c-erbB receptors and ligands in head and neck squamous cell carcinoma. *Oral Oncol*. 2002; 38(7): 627 – 40.
55. Meyer D, Birchmeier C. Multiple Essential Functions of Neuregulin in Development. *Nature*. 1995; 378(6555): 386 – 90.
56. Fan YX, Wong L, Ding J, Spiridonov NA, Johnson RC, Johnson GR. Mutational activation of ErbB2 reveals a new Protein Kinase autoinhibition mechanism. *J Biol Chem*. 2008; 283(3): 1588 – 96.
57. Fleishman SJ, Schlessinger J, Ben-Tal N. A Putative molecular-activation switch in the transmembrane domain of erbB2. *Proc Natl Acad Sci U S A*. 2002; 99(25): 15937 – 40.
58. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315(7109): 629 – 34.
59. Chen W, Yang H, Tang WR, Feng SJ, Wei YL. Updated meta-analysis on HER2 polymorphisms and risk of breast cancer: evidence from 32 Studies. *Asian Pac J Cancer Prev.* 2014; 15(22): 9643 – 47.
60. Lin H, Lin D, Zheng C. Association of XPD Lys751Gln polymorphism with head and neck cancer susceptibility: evidence from 11,443 subjects. *Diagn Pathol.* 2014; 9: 15.