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OPEN Her2 ^{Ile}655^{Val} polymorphism and its association with breast cancer risk: an updated meta-analysis of casecontrol studies

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Breast cancer (BC) is one of the most common types of cancer in women worldwide. Several factors including genetic and environmental have been linked with susceptibility to development of BC. Her2 is a transmembrane protein with tyrosine kinase activity, overexpressed in several cancers including BC. Various studies in different populations have shown association of Her2 variants with susceptibility to BC, however these results were inconsistent, inconclusive and controversial. To obtain a common conclusive finding, we performed meta-analysis of 35 case-control studies reported earlier including 19, 220 cases and 22, 306 controls. We observed significant association of Her2 ^{IIe}655^{Val} polymorphism with susceptibility to development of breast cancer (Overall allele Val vs lle: OR = 1.130, 95% CI = 1.051-1.216, p = 0.001; lle-Val vs lle-lle: OR = 1.100, 95% Cl = 1.016–1.192, p = 0.019; Val-Val+lle-Val vs lle-lle: OR = 1.127, 95% Cl = 1.038–1.223, p = 0.004). Subgroup analysis indicated a significant association with susceptibility to breast cancer in African and Asian populations. However, such association was not observed in other ethnic groups. Our findings suggested that Her2^{lie}655^{val} polymorphism is associated with breast cancer risk in overall, Asian and African populations, and can be used as diagnostic marker for BC.

Breast cancer (BC) is second leading cause of cancer deaths worldwide and approximately 1.7 million new cases are being diagnosed every year and 521,900 deaths occurred in 2012 alone globally¹. It has been estimated that 252,710 new cases of invasive breast cancer will be diagnosed in 2017 among women in US alone. Although, breast cancer is most common in females it also rarely diagnosed in male individuals and 2,470 males are estimated to be diagnosed with breast cancer in 2017 in United States². Among the overall cancer deaths worldwide, approximately 60% of deaths occur in developing countries including India. In Indian woman, majority of cancer related deaths are due to breast cancer¹.

BC is highly heterogeneous and ~60-70% is of estrogen receptor positive which responds to anti-hormone therapy³. Estrogen receptor (ER) plays an important role in breast cancer progression and treatment. Approximately 20-30% breast cancers are of Human epidermal growth factor receptor2 (Her2) positive and are highly aggressive in nature⁴. High levels of Her2 expression was also observed in tamoxifen resistant breast cancers. Human epidermal growth factor receptor family members are a group of molecules having tyrosine kinase activity with no natural ligand found till date. Heterodimerization among the family members leads to autophosphorylation of cytoplasmic domain which leads to cell proliferation⁵⁻⁷. Her2 is highly expressed in various cancers types viz. breast, endometrial, ovarian, colon, lung, prostrate and cervical cancers. Role of ERBB2/Her2 in physiological processes (cell growth, differentiation and tissue development) as well as in carcinogenesis and metastasis has been well investigated⁸⁻¹⁰. Her2 plays major role in the regulation of several pathways such as Raf/Ras/MAPK and PI3K/AKT pathways¹¹. Receptor mediated signaling pathways has pivotal role in the regulation of normal cell function, growth and division. However disruption of these pathways might lead to several cancers¹²⁻¹⁵. Her2 positive breast cancers show poor survival rate, treatment with tyrosine inhibitors showing promising results in

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								Genotype Distribution		Allele	Distrib	ution (%	6)			
								Case	/1	Contr	rol	Case		Contr	· · · · · · · · · · · · · · · · · · ·	-
S. No	First Author	Year	Ethnic group	Cancer type	Case	Control	HWE	Ile/ Ile	Ile/Val + Val/Val	Ile/ Ile	Ile/Val + Val/Val	Ile	val	Ile	Val	Genotyping method
1	AbdRaboh NR et al.	2013	Egyptian	BC	64	86	Y	39	25	67	19	99	29	152	20	PCR-RFLP
2	Al-Janabi AM et al.	2015	Iraqi	BC	300	200	Y	141	159	120	80	407	193	308	92	PCR-RFLP
3	Akisik E et al.	2004	Turkish	BC	121	145	Y	98	23	117	28	218	24	260	30	PCR-RFLP
4	An HJ et al.	2005	Korean	BC	177	126	Y	139	38	96	30	311	43	221	31	PCR-RFLP
5	Baxter SW et al.	2001	Caucasian	BC	315	256	Y	190	125	138	118	489	141	377	135	PCR-RFLP
6	Benusiglio PR et al.	2006	British	BC	1989	2155	Y	1128	861	1230	925	3004	974	3251	1059	Taqman
7	Carrillo-Moreno DI <i>et al.</i>	2016	Mexican	BC	400	225	Y	312	88	191	34	709	91	415	35	Taqman
8	Cox DG et al.	2005	Cohort	BC	1313	1717	Y	766	505	980	687	1979	563	2551	783	Taqman
9	Frank B et al.	2005	German	BC	347	960	Y	186	161	525	435	504	190	1427	493	Taqman
10	GENICA et al.	2010	Caucasian	BC	3138	5486	Y	1856	1282	3072	2414	4795	1481	8227	2745	MALDI-TOF MSa and PCR- based fragment analyses
11	Hishida A et al.	2002	Japanese	BC	236	184	Y	182	54	136	48	415	57	313	55	Not reported
12	Kalemi TG et al.	2005	Greek	BC	42	51	N	32	10	36	15	74	10	87	15	PCR-RFLP
13	Kallel I et al.	2010	Tunician	BC	148	290	N	130	18	240	50	274	22	530	50	PCR-RFLP
14	Kamali-Sarvestani E <i>et al</i> .	2004	Iranian	BC	204	138	Y	145	59	102	36	347	61	236	40	PCR-RFLP
15	Kara N <i>et al</i> .	2010	Turkish	BC	204	192	Y	153	51	141	51	352	56	330	54	PCR-RFLP
16	Keshava C et al. (a)	2001	Caucasian	BC	89	180	Y	59	30	129	51	144	34	302	58	PCR-RFLP
17	Keshava C et al. (b)	2001	African- American	BC	34	63	Y	32	2	57	6	66	2	120	6	PCR-RFLP
18	Keshava C et al. (c)	2001	Latinos	BC	28	77	Y	17	11	58	19	44	12	134	20	PCR-RFLP
19	Lee SC et al.	2008	Taiwan	BC	424	318	Y	341	83	273	45	762	86	590	46	PCR-RFLP
20	Millikan R <i>et al</i> . (a)	2003	African- American	BC	754	676	N	658	96	606	70	1404	104	1282	70	Taqman
21	Millikan R et al. (b)	2003	Whites	BC	1261	1132	N	752	509	684	448	1933	589	1743	521	Taqman
22	Montgomery KG et al.	2003	Australian	BC	409	299	Y	240	169	196	103	618	200	486	112	Dual color allele- specific PCR assay
23	Mutluhan H et al.	2008	Turkish	BC	166	208	Y	128	38	166	42	290	42	372	44	PCR-RFLP
24	Naidu R <i>et al.</i>	2008	Malaysian	BC	230	200	Y	165	65	159	41	387	73	355	45	PCR-RFLP
25	Nelson SE et al.	2005	Europian	BC	1094	976	Y	637	457	551	425	1670	518	1458	494	Taqman
26	Ozturk O et al.	2013	Turkish	BC	118	118	N	61	57	87	41	179	57	215	41	PCR-RFLP
27	Papadopoulou E <i>et al.</i>	2007	Greek	BC	56	45	Y	15	41	19	26	52	60	54	36	PCR-RFLP
28	Parvin S et al.	2016	Asian	BC	310	250	Y	210	100	189	61	508	112	433	67	PCR-RFLP
29	Pinto D et al.	2004	Portuguese	BC	152	146	Y	88	64	107	39	233	71	249	43	PCR-RFLP
30	Qu S et al.	2008	Chineese	BC	3012	3004	Y	2298	714	2252	752	5244	780	5191	817	Taqman
31	Rajkumar T <i>et al</i> .	2008	South Indian	BC	250	500	Y	181	69	363	137	424	76	845	155	Taqman
32	Sezgin E et al.	2011	Turkish	BC	58	55	Y	44	14	37	18	102	14	91	19	PCR-RFLP
33	Siddig A et al.	2008	Sudan	BC	68	81	Y	56	12	75	6	123	13	155	7	Taqman
34	Tommasi S et al.	2007	Caucasian	BC	628	169	Y	433	195	125	44	947	209	291	47	Taqman
35	Wang-Gohrke S et al.	2001	Caucasian	BC	615	1078	Y	360	255	646	432	939	291	1666	490	PCR-RFLP
36	Watrowski R et al.	2015	Austrian	BC	80	100	Y	51	29	63	37	128	32	160	40	Taqman
37	Xie D et al.	2000	Chineese	BC	339	359	Y	243	96	280	79	571	107	638	80	PCR-RFLP
38	ŽÚBOR P et al.	2006	Slovak republican	BC	47	60	Y	22	25	42	18	66	28	101	19	PCR-RFLP

Table 1. Characteristics and distribution of Her2 polymorphism in each study involved in meta-analysis. Keshava *et al.* Caucasian ethnic group designated as (a), African-American ethnic group designated as (b) and Latinos ethnic group designated as (c). Millikan *et al.* African-American ethnic group designated as (a) and whites designated as (b).

harboring these aggressive tumors¹⁶. Trastuzumab a monoclonal antibody specifically binds to Her2 and disrupts the downstream pathways of Her2 and it is effectively used for the treatment of Her2 positive breast cancers^{17–19}. However several patients developed resistance to trastuzumab over a period of time²⁰. Recent studies suggested that Her2 ^{IIe}655^{Val} polymorphism is associated with cardiac toxicity. Moreover, it has been identified that both the Her2 ^{Ala}1170^{Pro} polymorphisms also responsible for increasing the risk of cardiac toxicity in women administrated with trastuzumab^{21,22}.

S.no	Model	Heteroger	neity analysis		Egger's reg	ression		Publication bias	Fixed/Random
1	Overall allele Val vs. Ile	Q-value	P heterogeneity	I ² value	Intercept	95% CI	p-value	Imputed	Random
1	Overall allele val vs. lie	95.232	0.000	61.147	1.46746	0.764-2.170	0.00015	Inputed	Kandoni
2	Homozygous Val-Val vs. Ile-Ile	54.756	0.014	37.906	0.88689	0.318-1.455	0.00324	Imputed	Fixed
3	Heterozygous Ile-Val vs. Ile-Ile	76.010	0.000	51.322	1.26086	0.593-1.928	0.00049	Imputed	Random
4	Recessive Val-Val vs. Ile-Ile+Ile-Val	47.555	0.061	28.503	0.74160	0.197-1.285	0.00907	Imputed	Fixed
5	Dominant Val-Val + Ile-Val vs. Ile-Ile	87.290	0.000	57.612	1.42523	0.730-2.119	0.00019	Imputed	Random

Table 2. Statistics for heterogeneity analysis and publication bias.

		Statisti	cs for eac	h study		Odds ratio and 95% Cl	
overall allele Val vs. lle	Odds ratio	Lower limit		Z-Value	p-Value		Rela we
bdRaboh NR et al 2013	2.226	1.194	4.153	2.516	0.012		
I-Janabi AM et al 2015	1.588	1.189	2.120	3.134	0.002		:
kisik E et al 2004 n HJ et al 2005	0.954 0.986	0.542	1.681 1.614	-0.163 -0.057	0.871 0.954		
axter SW et al 2005	0.986	0.602	1.014	-0.057	0.954		:
enusiglio PR et al 2006	0.995	0.900	1.100	-0.091	0.927	1 1 🛉 / 1	
arrillo-Moreno DI et al 2016	1.522	1.012	2.289	2.016	0.044		:
ox DG et al 2005	0.927	0.819 0.897	1.048 1.327	-1.209	0.227 0.382		:
rank B et al 2005 ENICA et al 2010	1.091 0.926	0.897	0.995	0.874 -2.086	0.382		
ishida A et al 2002	0.782	0.525	1.164	-1.212	0.226	-=7	
alemi TG et al 2005	0.784	0.332	1.849	-0.556	0.578		(
allel I et al 2010 amali-Sarvestani E et al 2004	0.851 1.037	0.505 0.674	1.435 1.597	-0.605 0.166	0.545 0.868		
anali-Sarvestani E et al 2004 ara N et al 2010	0.972	0.674	1.455	-0.137	0.881	I I I I I	
eshava C et al (a) Caucasian 2001	1.229	0.770	1.962	0.866	0.387	+=-	
eshava C et al (b) African -American 2001	0.606	0.119	3.088	-0.603	0.547		(
eshava C et al (c) Latinos 2001	1.827	0.827	4.037	1.491	0.136		(
ee SC et al 2008 lillikan R et al (a) African -American 2003	1.448 1.357	0.996 0.993	2.104 1.854	1.939 1.914	0.052 0.056		
lillikan R et al (b) Whites 2003	1.019	0.891	1.166	0.280	0.779		
lontgomery KG et al 2003	1.404	1.083	1.821	2.559	0.010		:
lutluhan H et al 2008	1.224	0.781	1.920	0.882	0.378		
aidu R et al 2008 elson SE et al 2005	1.488 0.915	0.999 0.794	2.216 1.055	1.955 -1.220	0.051 0.222		1
zturk O et al 2013	1.670	1.067	2.613	2.245	0.025	│ │ ी∎- │ │	
apadopoulou E et al 2007	1.731	0.987	3.036	1.913	0.056		
arvin S et al 2016	1.425	1.026	1.979	2.111	0.035		-
into D et al 2004 u S et al 2008	1.765 0.945	1.161 0.851	2.682 1.050	2.658	0.008		1
ajkumar T et al 2008	0.945	0.851	1.317	-0.152	0.293		
ezgin E et al 2011	0.657	0.312	1.386	-1.102	0.270	│ │ ─■┼ │ │	(
iddig A et al 2008	2.340	0.906	6.044	1.756	0.079		(
ommasi S et al 2007 /ang-Gohrke S et al 2001	1.366 1.054	0.970 0.893	1.925 1.243	1.786 0.619	0.074 0.536		1
/atrowski R et al 2015	1.000	0.595	1.682	0.000	1.000		
ie D et al 2000	1.494	1.095	2.039	2.533	0.011		:
ÚBOR P et al 2006 ombined	2.255 1.130	1.166 1.051	4.363 1.216	2.415 3.298	0.016 0.001		
al-Val vs. lle-lle							
bdRaboh NR et al 2013	6.872	0.741	63.689	1.697	0.090		C
bdRaboh NR et al 2013 I-Janabi AM et al 2015	2.411	1.195	4.864	2.459	0.014		1
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004	2.411 0.597	1.195 0.053	4.864 6.682	2.459 -0.419	0.014 0.675		1
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005	2.411 0.597 3.453	1.195 0.053 0.397	4.864 6.682 30.025	2.459 -0.419 1.123	0.014 0.675 0.261		1
bdRaboh NR et al 2013 I-Janabi AM et al 2015 Kisik E et al 2004 n HJ et al 2005 suter SW et al 2001	2.411 0.597	1.195 0.053	4.864 6.682	2.459 -0.419	0.014 0.675		1
bdRaboh NR et al 2013 -Janabi AM et al 2015 kisik E et al 2004 n JJ et al 2005 axter SW et al 2001 anusiglio PR et al 2006 armilo-Moreno DI et al 2016	2.411 0.597 3.453 0.684 0.920 1.837	1.195 0.053 0.397 0.334 0.707 0.190	4.864 6.682 30.025 1.400 1.196 17.782	2.459 -0.419 1.123 -1.040 -0.625 0.525	0.014 0.675 0.261 0.298		1 0 0
bdRaboh NR et al 2013 -Janabi AM et al 2015 iskik E et al 2004 n HJ et al 2005 axter SW et al 2001 anusiglio PR et al 2006 arrillo-Moreno Di et al 2016 ox DG et al 2005	2.411 0.597 3.453 0.684 0.920 1.837 0.773	1.195 0.053 0.397 0.334 0.707 0.190 0.551	4.864 6.682 30.025 1.400 1.196 17.782 1.085	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487	0.014 0.675 0.261 0.298 0.532 0.600 0.137		1 0 1 14 0 8
odRaboh NR et al 2013 Janabi AM et al 2015 disik E et al 2005 th JJ et al 2005 axter SW et al 2001 arrilio-Moreno DI et al 2016 ox DG et al 2005	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877	4.864 6.682 30.025 1.400 1.196 17.782 1.085 2.272	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156		1 0 1 14 0 8 4
bdRaboh NR et al 2013 -Janabi AM et al 2015 isiki E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 rank B et al 2005 ENICA et al 2010	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411 0.995	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877 0.827	4.864 6.682 30.025 1.400 1.196 17.782 1.085 2.272 1.197	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418 -0.052	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156 0.959		1 0 1 14 0 8 4 28
bdRaboh NR et al 2013 Janabi AM et al 2015 disik E et al 2004 1 HJ et al 2005 axter SW et al 2000 arrillo-Moreno DI et al 2016 xo DG et al 2005 ank B et al 2005 ENICA et al 2010 shida A et al 2002	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877	4.864 6.682 30.025 1.400 1.196 17.782 1.085 2.272	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156		1 0 1 14 0 8 4
addaboh NR et al 2013 Janabi AM et al 2015 sisk E et al 2004 H J et al 2005 satrer SW et al 2001 amusigito PR et al 2006 armice-Morenco DI et al 2016 ox D et al 2005 ank B et al 2005 ShiCA et al 2010 shida A et al 2010 shida A et al 2010	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411 0.995 0.320	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877 0.827 0.827 0.081 0.886 0.063	4.864 6.682 30.025 1.400 1.196 17.782 1.085 2.272 1.197 1.261	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418 -0.052 -1.628	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156 0.959 0.103		1 0 1 14 0 8 4 28 0
vdRaboh NR et al 2013 Janabi AM et al 2015 sisk E et al 2004 H J et al 2005 stuter SW et al 2001 musiglio PR et al 2006 armico-Moreno Di et al 2016 xx DG et al 2005 SNICA et al 2005 SNICA et al 2010 shida A et al 2010 liel I et al 2010 armali-Sarvestani E et al 2004 ara N et al 2010	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411 0.995 0.320 16.586 0.352 1.536	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877 0.827 0.081 0.886 0.063 0.360	4.864 6.682 30.025 1.400 1.196 17.782 1.085 2.272 1.197 1.261 310.466 1.957 6.545	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418 -0.052 -1.628 1.879 -1.193 0.580	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156 0.959 0.103 0.233 0.562		1 0 1 14 0 8 4 28 0 0 0 0 0 0 0 0 0
addaboh NR et al 2013 Janabi AM et al 2015 isik E et al 2004 H J et al 2005 witzer SW et al 2001 enusiglio PR et al 2006 arrillo-Morreno Di et al 2016 xx DG et al 2005 snx DG et al 2005 snk B et al 2005 SNICA et al 2010 shida A et al 2010 mail-Sarvestani E et al 2004 rar N et al 2010 shak 2 et al 2010 shak 2 et al 2010	2.411 0.597 3.453 0.684 0.920 1.837 0.773 1.411 0.995 0.320 16.586 0.352 1.536 1.249	1.195 0.053 0.397 0.334 0.707 0.190 0.551 0.877 0.827 0.827 0.827 0.886 0.063 0.360 0.352	4.864 6.682 30.025 1.400 17.782 1.085 2.272 1.197 1.261 310.466 1.957 6.545 4.433	2.459 -0.419 1.123 -1.040 -0.625 0.525 -1.487 1.418 -0.052 -1.628 1.879 -1.193 0.580 0.345	0.014 0.675 0.261 0.298 0.532 0.600 0.137 0.156 0.959 0.103 0.060 0.233 0.562 0.730		1 0 1 14 0 28 28 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
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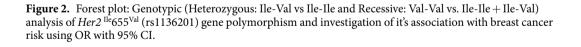
Figure 1. Forest plot: Overall allele and genotypic (Homozygous: Val-Val vs. Ile-Ile) analysis of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism and validation of it's association with breast cancer risk. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

Decrease

Increase

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Study name		Statist	ics for ead	ch study		Odds ratio and 95% Cl	
lle-Val vs. lle-lle	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	
AbdRaboh NR et al 2013	2.004	0.953	4.214	1.834	0.067		
Al-Janabi AM et al 2015	1.564	1.067	2.294	2.292	0.022		
Akisik E et al 2004	1.010	0.539	1.893	0.032	0.975	1.33	
An HJ et al 2005 Baxter SW et al 2001	0.786 0.784	0.448 0.553	1.379 1.110	-0.839 -1.370	0.401 0.171		
Benusiglio PR et al 2006	1.031	0.907	1.173	0.468	0.640	6.26	
Carrillo-Moreno DI et al 2016	1.577	1.015	2.450	2.026	0.043	2.28	
Cox DG et al 2005 Frank B et al 2005	0.968 0.988	0.829 0.763	1.130 1.281	-0.416 -0.089	0.678 0.929	5.83 4.18	
GENICA et al 2000	0.861	0.783	0.945	-3.153	0.002	4.10	
Hishida A et al 2002	0.930	0.583	1.483	-0.307	0.759		
Kalemi TG et al 2005	0.750	0.296	1.903	-0.606	0.545	0.67	
Kallel I et al 2010 Kamali-Sarvestani E et al 2004	0.517 1.253	0.275 0.759	0.970 2.069	-2.053 0.881	0.040 0.378		
Kara N et al 2010	0.883	0.555	1.406	-0.524	0.600		
Keshava C et al (a) Caucasian 2001	1.292	0.727	2.295	0.874	0.382	1.53	
Keshava C et al (b) African -American 2001 Keshava C et al (c) Latinos 2001	0.594 1.895	0.113 0.738	3.116 4.868	-0.616 1.329	0.538 0.184	0.22 0.65	
Lee SC et al 2008	1.525	1.016	2.289	2.037	0.042	2.55	
Millikan R et al (a) African -American 2003	1.158	0.830	1.615	0.863	0.388	3.25	
Millikan R et al (b) Whites 2003	1.041	0.875	1.237	0.450	0.652	5.53	
Montgomery KG et al 2003 Mutluhan H et al 2008	1.199 1.102	0.868 0.661	1.656 1.839	1.101 0.373	0.271 0.709	3.36	
Naidu R et al 2008	1.485	0.930	2.370	1.656	0.709	2.09	
Nelson SE et al 2005	0.962	0.801	1.155	-0.413	0.680	5.37	
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010	1.80	
Papadopoulou E et al 2007 Parvin S et al 2016	1.742 1.440	0.684 0.975	4.433 2.127	1.164 1.832	0.244 0.067	0.66	
Pinto D et al 2004	1.980	1.193	3.287	2.643	0.008		
Qu S et al 2008	0.924	0.818	1.044	-1.263	0.207	6.37	
Rajkumar T et al 2008	1.045	0.733	1.490	0.242	0.808	3.01	
Sezgin E et al 2011 Siddig A et al 2008	0.693 2.946	0.302	1.591 8.962	-0.866 1.904	0.386	0.82	
Tommasi S et al 2007	1.274	0.860	1.888	1.209	0.227		
Wang-Gohrke S et al 2001	1.051	0.851	1.297	0.460	0.645	4.91	
Watrowski R et al 2015 Xie D et al 2000	0.945 1.256	0.503 0.883	1.774 1.786	-0.177 1.267	0.859 0.205	1.32	
ZÚBOR P et al 2000	2.471	0.883	1.786	2.171	0.205	3.04	
Combined	1.100	1.016	1.192	2.350	0.019		
Val-Val vs. lle-lle + lle -Val							
AbdRaboh NR et al 2013	5.667	0.618	51.971	1.534	0.125	0.19	
Al-Janabi AM et al 2015 Akisik E et al 2004	2.003 0.596	1.010 0.053	3.969 6.652	1.989 -0.421	0.047	2.01	
Akisik E et al 2004 An HJ et al 2005	0.596 3.634	0.053	6.652 31.488	-0.421 1.171	0.674	0.16	
Baxter SW et al 2001	0.752	0.372	1.520	-0.793	0.428	1.90	
Benusiglio PR et al 2006	0.908	0.702	1.176	-0.729	0.466	14.13	
Carrillo-Moreno DI et al 2016	1.693	0.175	16.369	0.455	0.649	0.18	
Cox DG et al 2005 Frank B et al 2005	0.782 1.418	0.560 0.892	1.093 2.255	-1.437 1.477	0.151 0.140		
GENICA et al 2005	1.418	0.892	1.264	0.573	0.140	4.36	
Hishida A et al 2002	0.326	0.083	1.277	-1.609	0.108	0.50	
Kallel I et al 2010	18.093	0.968	338.355	1.938	0.053	0.11	
Kamali-Sarvestani E et al 2004	0.332	0.060	1.836	-1.264	0.206	0.32	
Kara N et al 2010	1.583 1.163	0.373 0.331	6.715 4.082	0.623	0.533 0.814	0.45	
Keshava C et al (a) Caucasian 2001 Keshava C et al (c) Latinos 2001	2.815	0.331	4.082	0.236	0.814	0.60	
Lee SC et al 2008	0.748	0.150	3.732	-0.354	0.724	0.36	
Millikan R et al (a) African -American 2003	15.406	0.888	267.418	1.878	0.060	0.12	
Millikan R et al (b) Whites 2003	0.983	0.708	1.364	-0.104	0.917	8.76	
Montgomery KG et al 2003	2.643	1.239	5.638	2.514	0.012		
Mutluhan H et al 2008 Naidu R et al 2008	2.543 1.766	0.460 0.524	14.059 5.954	1.070 0.917	0.285 0.359	0.32	
Nelson SE et al 2005	0.776	0.544	1.108	-1.395	0.163		
Papadopoulou E et al 2007	1.797	0.735	4.396	1.285	0.199	1.18	
Parvin S et al 2016	1.638	0.606	4.427	0.972	0.331	0.95	
Pinto D et al 2004 Qu S et al 2008	1.714 1.013	0.491	5.982 1.432	0.845	0.398		
Qu S et al 2008 Rajkumar T et al 2008	0.771	0.716	1.432	-0.574	0.942	1.20	
Sezgin E et al 2011	0.311	0.012	7.786	-0.711	0.477	0.09	
Siddig A et al 2008	1.194	0.073	19.455	0.125	0.901	0.12	
Tommasi S et al 2007	1.262	0.358	4.442	0.362	0.717	0.59	
Wang-Gohrke S et al 2001	1.093	0.713	1.678	0.409	0.683		
Watrowski R et al 2015 Xie D et al 2000	1.260 12.006	0.247 1.542	6.417 93.504	0.278 2.373	0.781 0.018		
ZÚBOR P et al 2006	4.023	0.405	39.987	1.188	0.235	0.22	
Combined	1.041	0.945	1.147	0.809	0.418		
						0.01 0.1 1 10 100	



Decrease

Increase

Genetic epidemiological studies indicated association between single nucleotide polymorphisms and different cancers²³⁻²⁵. Cell cycle regulatory role of Her2 and its importance in prognosis of breast cancer clearly indicates that polymorphism in coding region of *Her2* might be associated with either cancer susceptibility risk or resistance. One such single nucleotide transition mutation in transmembrane domain coding region of *Her2* at codon 655 [Isoleucine (Ile) to Valine (Val) mutation, *Her2* ^{1le}655^{Val}] was well investigated in different populations in relation to risk of breast cancer²⁶⁻⁶¹. Milikan *et al.*⁴⁰ reported the association of Valine allele at *Her2* 655 codon with breast cancer risk. Whereas, Baxter *et al.*²⁹ and Xie *et al.*⁶⁰ found no association with breast cancer risk in women aged <40 years, post menopausal respectively. However, few researchers performed meta-analysis and tried to conclude the possible correlation of *Her2* polymorphism with breast cancer risk. Tao *et al.*⁵⁶ showed no association in overall analysis, however mild association of *Her2* polymorphism with susceptibility to breast cancer in Asian ethnic group was suggested. Another meta-analysis by Chen *et al.*⁶² including 32 case control studies revealed comparable distribution of *Her2* ^{1le}655^{Val} variants among cases and controls in Caucasian, American and European population. Interestingly, Asian ethnic group showed significant association of breast cancer risk with *Her2* ^{1le}655^{Val} polymorphism with development of breast cancer risk with *Her2* ^{1le}655^{Val} polymorphism with development of possible association of *Her2* ^{1le}655^{Val} polymorphism with development of breast cancer. Furthermore, we subgrouped included reports according to ethnicity and the association was analyzed.

Study name		Statistics	s for each	study	
Val-Val + Ile-Val vs. Ile -Ile	Odds	Lower	Upper	7 1/-1	- Malua
	ratio	limit	limit	Z-Value	p-Value
AbdRaboh NR et al 2013	2.260	1.105	4.622	2.235	0.025
Al-Janabi AM et al 2015	1.691	1.177	2.431	2.842	0.004
Akisik E et al 2004	0.981	0.531	1.811	-0.062	0.950
An HJ et al 2005	0.875	0.507	1.508	-0.481	0.630
Baxter SW et al 2001	0.769	0.551	1.074	-1.540	0.124
Benusiglio PR et al 2006	1.015	0.897	1.148	0.237	0.813
Carrillo-Moreno DI et al 2016	1.584	1.026	2.447	2.075	0.038
Cox DG et al 2005	0.940	0.810	1.091	-0.809	0.419
Frank B et al 2005	1.045	0.817	1.336	0.348	0.728
GENICA et al 2010	0.879	0.804	0.961	-2.842	0.004
Hishida A et al 2002	0.841	0.537	1.316	-0.760	0.447
Kalemi TG et al 2005	0.750	0.296	1.903	-0.606	0.545
Kallel I et al 2010	0.665	0.372	1.186	-1.382	0.167
Kamali-Sarvestani E et al 2004	1.153	0.709	1.874	0.574	0.566
Kara N et al 2010	0.922	0.587	1.446	-0.355	0.722
Keshava C et al (a) Caucasian 2001	1.286	0.745	2.221	0.903	0.366
Keshava C et al (b) African -American 2001	0.594	0.113	3.116	-0.616	0.538
Keshava C et al (c) Latinos 2001	1.975	0.788	4.949	1.453	0.146
Lee SC et al 2008	1.477	0.994	2.195	1.928	0.054
Millikan R et al (a) African -American 2003	1.263	0.911	1.752	1.399	0.162
Millikan R et al (b) Whites 2003	1.033	0.877	1.217	0.393	0.694
Montgomery KG et al 2003	1.340	0.984	1.826	1.855	0.064
Mutluhan H et al 2008	1.173	0.715	1.926	0.632	0.527
Naidu R et al 2008	1.528	0.977	2.390	1.856	0.063
Nelson SE et al 2005	0.930	0.781	1.107	-0.814	0.416
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010
Papadopoulou E et al 2007	1.997	0.865	4.611	1.621	0.105
Parvin S et al 2016	1.475	1.015	2.145	2.037	0.042
Pinto D et al 2004	1.995	1.225	3.250	2.775	0.006
Qu S et al 2008	0.930	0.827	1.047	-1.200	0.230
Raikumar T et al 2008	1.010	0.719	1.419	0.058	0.230
Sezgin E et al 2011	0.654	0.287	1.419	-1.010	0.313
Siddig A et al 2008	2.679	0.287	7.573	1.858	0.063
0					
Tommasi S et al 2007	1.279	0.872	1.876	1.261	0.207
Wang-Gohrke S et al 2001	1.059	0.866	1.296	0.560	0.576
Watrowski R et al 2015	0.968	0.526	1.783	-0.104	0.917
Xie D et al 2000	1.400	0.993	1.975	1.919	0.055
ZÚBOR P et al 2006	2.652	1.197	5.876	2.402	0.016
Combined	1.127	1.038	1.223	2.856	0.004

Figure 3. Forest plot: Genotypic (Dominant: Val-Val + Ile-Val vs Ile-Ile) analysis of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism and evaluation of its association with increased risk of breast cancer. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

Decrease

Increase

S.no	Model	Odds Ratio(OR)	95% CI	p-value
,	Caucasian	0.053	0.005 1.015	0.126
1	Overall allele Val vs. Ile	0.953	0.895-1.015	0.136
2	Homozygous Val-Val vs. Ile-Ile	1.000	0.850-1.177	0.997
3	Heterozygous Ile-Val vs. Ile-Ile	0.903	0.833-0.979	0.013
4	Recessive Val-Val vs. Ile-Ile + Ile-Val	1.046	0.892-1.228	0.580
5	Dominant Val-Val + Ile-Val vs. Ile-Ile	0.917	0.850-0.990	0.027
<i>c</i>	American	0.007	0.012.1.000	0.026
6	Overall allele Val vs. Ile	0.996	0.912-1.088	0.936
7	HomozygousVal-Val vs. Ile-Ile	0.895	0.707-1.133	0.357
8	Heterozygous Ile-Val vs. Ile-Ile	1.038	0.929-1.160	0.511
9	Recessive Val-Val vs. Ile-Ile + Ile-Val	0.892	0.707-1.125	0.334
10	Dominant Val-Val + Ile-Val vs. Ile-Ile	1.019	0.917-1.133	0.725
11	Afro-American	1 210	0.970-1.792	0.077
11	Overall allele Val vs. Ile	1.318	0.970-1.792	0.077
12	Homozygous Ile-Val vs. Ile-Ile	1.128	0.814-1.563	0.469
13	Dominant Val-Val + Ile-Val vs. Ile-Ile	1.228	0.891-1.693	0.210
1.2	African	1.550	0.5(1, 0.100	0.005
13	Overall allele Val vs. Ile	1.558	0.761-3.192	0.225
14	Homozygous Val-Val vs. Ile-Ile	5.408	1.211-24.159	0.027*
15	Heterozygous Ile-Val vs. Ile-Ile	1.369	0.460-4.078	0.573
16	Recessive Val-Val vs. Ile-Ile + Ile-Val	4.907	1.103-21.839	0.037*
17	Dominant Val-Val + Ile-Val vs. Ile-Ile	1.505	0.588-3.858	0.394
10	European	1.100	0.050 1.000	0.140
18	Overall allele Val vs. Ile	1.128	0.958-1.328	0.149
19	Homozygous Val-Val vs. Ile-Ile	1.000	0.829-1.205	0.997
20	Heterozygous Ile-Val vs. Ile-Ile	1.042	0.949-1.143	0.390
21	Recessive Val-Val vs. Ile-Ile + Ile-Val	0.987	0.822-1.185	0.889
22	Dominant Val-Val + Ile-Val vs. Ile-Ile	1.137	0.941-1.374	0.184
	Asian	1.162	1 011 1 220	0.025*
23	Overall allele Val vs. Ile	1.163	1.011-1.338	0.035*
24	Homozygous Val-Val vs. Ile-Ile	1.176	0.916-1.510	0.203
25	Heterozygous Ile-Val vs. Ile-Ile	1.064	0.976-1.160	0.158
26	Recessive Val-Val vs. Ile-Ile + Ile-Val	1.149	0.897-1.473	0.272
27	Dominant Val-Val + Ile-Val vs. Ile-Ile	1.177	1.012-1.370	0.034*

Table 3. Subgroup analysis of Her2 Ile 655 Val polymorphism and its association with breast cancer risk.

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Study name		Statist	ics for e	ach study	,	Odds ratio and 95% Cl	
-	Odds	Lower	Upper	-		Relativ	
Overall allele Val vs. Ile	ratio	limit	limit	Z-Value	p-Value	weigi	
AbdRaboh NR et al 2013 Al-Janabi AM et al 2015	2.226 1.588	1.194 1.189	4.153 2.120	2.516 3.134	0.012 0.002	2.6	
Akisik E et al 2004	0.954	0.542	1.681	-0.163	0.871	3.0	01
An HJ et al 2005	0.986	0.602	1.614	-0.057	0.954	3.5	
Baxter SW et al 2001 GENICA et al 2010	0.805 0.926	0.614 0.861	1.056 0.995	-1.564 -2.086	0.118 0.037	5.7	
Kalemi TG et al 2005	0.784	0.332	1.849	-0.556	0.578		
Kallel I et al 2010	0.851	0.505	1.435	-0.605	0.545	3.3	
Kamali-Sarvestani E et al 2004 Kara N et al 2010	1.037 0.972	0.674 0.650	1.597 1.455	0.166 -0.137	0.868 0.891		
Keshava C et al (a) 2001 Caucasian	1.229	0.770	1.962	0.866	0.387		
Keshava C et al (b) 2001 African -American	0.606	0.119	3.088	-0.603	0.547	0.5	
Keshava C et al (c) 2001 Latinos Lee SC et al 2008	1.827 1.448	0.827 0.996	4.037 2.104	1.491 1.939	0.136 0.052		
Montgomery KG et al 2003	1.404	1.083	1.821	2.559	0.010		
Mutluhan H et al 2008	1.224	0.781	1.920	0.882	0.378	3.9	
Naidu R et al 2008 Ozturk O et al 2013	1.488 1.670	0.999 1.067	2.216 2.613	1.955 2.245	0.051 0.025		
Papadopoulou E et al 2007	1.731	0.987	3.036	1.913	0.025		
Parvin S et al 2016	1.425	1.026	1.979	2.111	0.035	5.1	
Pinto D et al 2004 Sezgin E et al 2011	1.765 0.657	1.161 0.312	2.682 1.386	2.658 -1.102	0.008 0.270		
Wang-Gohrke S et al 2001	1.054	0.893	1.243	0.619	0.536		
Xie D et al 2000	1.494	1.095	2.039	2.533	0.011	5.3	
ZÚBOR P et al 2006 Combined	2.255 1.236	1.166 1.091	4.363 1.400	2.415 3.338	0.016 0.001	2.4	-6
	1.200	1.001	1.400	0.000	0.001	0.1 0.2 0.5 1 2 5 10	
Val-Val vs. Ile-Ile	0.070	0.744	~~~~~	4 007	0.000		40
AbdRaboh NR et al 2013 Al-Janabi AM et al 2015	6.872 2.411	0.741 1.195	63.689 4.864	1.697 2.459	0.090 0.014		43 33
Akisik E et al 2004	0.597	0.053	6.682	-0.419	0.675	0.3	37
An HJ et al 2005 Baxter SW et al 2001	3.453 0.684	0.397 0.334	30.025 1.400	1.123 -1.040	0.261 0.298		46 14
GENICA et al 2010	0.995	0.827	1.197	-0.052	0.959		
Kallel I et al 2010	16.586		310.466	1.879	0.060		25
Kamali -Sarvestani E et al 2004 Kara N et al 2010	0.352 1.536	0.063 0.360	1.957 6.545	-1.193 0.580	0.233 0.562		72 01
Keshava C et al (a) 2001 Caucasian	1.249	0.352	4.433	0.345	0.730		33
Keshava C et al (c) 2001 Latinos Lee SC et al 2008	3.412 0.801	0.203 0.160	57.470 3.998	0.852 -0.271	0.394 0.786		27 82
Montgomery KG et al 2003	2.813	1.308	6.049	2.647	0.008		63
Mutluhan H et al 2008	2.594 1.927	0.468	14.383 6.527	1.091 1.054	0.275		73
Naidu R et al 2008 Papadopoulou E et al 2007	2.407	0.569 0.866	6.688	1.684	0.292 0.092		43 04
Parvin S et al 2016	1.800	0.663	4.890	1.153	0.249		13
Pinto D et al 2004 Sezgin E et al 2011	2.128 0.281	0.603 0.011	7.505 7.101	1.174 -0.770	0.240 0.441		34 20
Wang-Gohrke S et al 2001	1.114	0.721	1.721	0.485	0.628		
Xie D et al 2000	12.675	1.625	98.883	2.423	0.015		50
ZÚBOR P et al 2006 Combined	5.727 1.177	0.562 1.017	58.349 1.362	1.474 2.191	0.141 0.028	• 0.3	40
lle-Val vs. lle-lle						0.01 0.1 1 10 100	
AbdRaboh NR et al 2013	2.004	0.953	4.214	1.834	0.067		57
Al-Janabi AM et al 2015	1.564	1.067	2.294	2.292	0.022	5.2	
Akisik E et al 2004	1.010	0.539	1.893	0.032	0.975		
An HJ et al 2005 Baxter SW et al 2001	0.786 0.784	0.448 0.553	1.379 1.110	-0.839 -1.370	0.401 0.171		
GENICA et al 2010	0.861	0.784	0.945	-3.153	0.002	8.1	19
Kalemi TG et al 2005 Kallel I et al 2010	0.750 0.517	0.296 0.275	1.903 0.970	-0.606 -2.053	0.545		
Kamali-Sarvestani E et al 2004	1.253	0.275	2.069	-2.053	0.040		
Kara N et al 2010	0.883	0.555	1.406	-0.524	0.600	4.4	47
Keshava C et al (a) 2001 Caucasian Keshava C et al (b) 2001 African -American	1.292 0.594	0.727 0.113	2.295 3.116	0.874 -0.616	0.382 0.538		
Keshava C et al (c) 2001 African -Africian Keshava C et al (c) 2001 Latinos	1.895	0.738	4.868	1.329	0.538	1.8	
Lee SC et al 2008	1.525	1.016	2.289	2.037	0.042	5.0	03
Montgomery KG et al 2003	1.199	0.868	1.656	1.101	0.271		
Mutluhan H et al 2008 Naidu R et al 2008	1.102 1.485	0.661 0.930	1.839 2.370	0.373 1.656	0.709 0.098		
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010	4.0	01
Papadopoulou E et al 2007 Parvin S et al 2016	1.742 1.440	0.684 0.975	4.433 2.127	1.164 1.832	0.244 0.067		
Parvin S et al 2016 Pinto D et al 2004	1.440	1.193	3.287	2.643	0.067	5. I 4.1	
Sezgin E et al 2011	0.693	0.302	1.591	-0.866	0.386		19
Wang-Gohrke S et al 2001 Xie D et al 2000	1.051 1.256	0.851 0.883	1.297 1.786	0.460 1.267	0.645 0.205		
ZÚBOR P et al 2006	2.471	1.092	5.590	2.171	0.205		
Combined	1.183	1.026	1.364	2.308	0.021		
						0.1 0.2 0.5 1 2 5 10	
						\leftarrow	

Figure 4. Forest plot: Overall allele and genotypic (Homozygous: Val-Val vs. Ile-Ile and Heterozygous: Ile-Val vs Ile-Ile) analysis of studies in which RFLP used as detection method for *Her2*^{1le}655^{Val} (rs1136201) gene polymorphism and evaluation of its association with breast cancer risk. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

Decrease

Increase

Results

Characteristics of eligible studies. To understand association of *Her2*^{lle}655^{Val} polymorphism with breast cancer risk, we have performed meta-analysis using 35 case-control eligible studies including 19, 220 cases and 22, 306 controls. Genotype and allele frequency for case and control of each eligible study was extracted and the characteristics of each study are shown in Table 1. For subgroup analysis the identified studies were categorized based on their ethnicity viz. Caucasian, American, Afro-American, African, European and Asian respectively.

Study name		Statist	tics for e	ach study	,	Odds ratio and 95% Cl
Val-Val vs. lle-lle + lle-Val	Odds ratio	Lower limit	Upper limit	7-Value	p-Value	Relat weic
AbdRaboh NR et al 2013		0.618			•	
Al-Janabi AM et al 2015	5.667 2.003	1.010	51.971 3.969	1.534 1.989	0.125 0.047	
Akisik E et al 2004	0.596	0.053	6.652	-0.421	0.674	
An HJ et al 2005	3.634	0.419	31.488	1.171	0.242	
Baxter SW et al 2001	0.752	0.372	1.520	-0.793	0.428	
GENICA et al 2010	1.055	0.879	1.264	0.573	0.567	62.1
Kallel I et al 2010	18.093		338.355	1.938	0.053	0.2
Kamali-Sarvestani E et al 2004	0.332	0.060	1.836	-1.264	0.206	0.7
Kara N et al 2010 Keshava C et al (a) 2001 Caucasian	1.583	0.373	6.715	0.623	0.533	0.0
Keshava C et al (c) 2001 Latinos	1.163	0.331 0.170	4.082	0.236	0.814	
Lee SC et al 2008	2.815 0.748	0.170	46.585 3.732	0.723 -0.354	0.470 0.724	
Montgomery KG et al 2003	2.643	1.239	5.638	2.514	0.012	
Mutluhan H et al 2008	2.543	0.460	14.059	1.070	0.285	
Naidu R et al 2008	1.766	0.524	5.954	0.917	0.359	
Papadopoulou E et al 2007	1.797	0.735	4.396	1.285	0.199	2.5
Parvin S et al 2016	1.638	0.606	4.427	0.972	0.331	2.0
Pinto D et al 2004	1.714	0.491	5.982	0.845	0.398	1.3
Sezgin E et al 2011	0.311	0.012	7.786	-0.711	0.477	0.2
Wang-Gohrke S et al 2001	1.093	0.713	1.678	0.409	0.683	
Xie D et al 2000	12.006	1.542	93.504	2.373	0.018	
ZÚBOR P et al 2006	4.023	0.405 1.033	39.987	1.188	0.235	0.3
Combined	1.192	1.035	1.375	2.401	0.016	
Val-Val + lle-Val vs. lle -lle						
AbdRaboh NR et al 2013	2.260	1.105	4.622	2.235	0.025	2.6
Al-Janabi AM et al 2015	1.691	1.177	2.431	2.842	0.004	5.1
Akisik E et al 2004	0.981	0.531	1.811	-0.062	0.950	
An HJ et al 2005	0.875	0.507	1.508	-0.481	0.630	
Baxter SW et al 2001 GENICA et al 2010	0.769 0.879	0.551 0.804	1.074 0.961	-1.540 -2.842	0.124 0.004	
Kalemi TG et al 2005	0.879	0.804	1.903	-2.642	0.004	
Kallel I et al 2010	0.665	0.290	1.186	-1.382	0.343	
Kamali-Sarvestani E et al 2004	1.153	0.709	1.874	0.574	0.566	
Kara N et al 2010	0.922	0.587	1.446	-0.355	0.722	
Keshava C et al (a) 2001 Caucasian	1.286	0.745	2.221	0.903	0.366	
Keshava C et al (b) 2001 African -American	0.594	0.113	3.116	-0.616	0.538	0.6
Keshava C et al (c) 2001 Latinos	1.975	0.788	4.949	1.453	0.146	1.8
Lee SC et al 2008	1.477	0.994	2.195	1.928	0.054	4.9
Montgomery KG et al 2003	1.340	0.984	1.826	1.855	0.064	5.1
Mutluhan H et al 2008	1.173	0.715	1.926	0.632	0.527	4.0
Naidu R et al 2008	1.528	0.977	2.390	1.856	0.063	
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010	
Papadopoulou E et al 2007	1.997	0.865	4.611	1.621	0.105	
Parvin S et al 2016	1.475	1.015	2.145	2.037	0.042	5.
Pinto D et al 2004	1.995	1.225	3.250	2.775	0.006	
Sezgin E et al 2011	0.654	0.287	1.491	-1.010	0.313	
Wang-Gohrke S et al 2001 Xie D et al 2000	1.059 1.400	0.866 0.993	1.296 1.975	0.560 1.919	0.576 0.055	
				1.919	0.055	
ZÚROR R at al 2006					0.016	
ZÚBOR P et al 2006	2.652	1.197	5.876	2.402	0.016	
ZÚBOR P et al 2006 Combined					0.016 0.005	

Figure 5. Forest plot: Genotypic (Recessive: Val-Val vs. Ile-Ile + Ile-Val; Dominant: Val-Val + Ile-Val vs Ile-Ile) analysis of studies in which RFLP used as detection method for *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism and evaluation of its association with increased risk of breast cancer. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

Decrease

Increase

Heterogeneity test. To evaluate the heterogeneity among the studies Q test with I^2 statistics were used. I² more than 50 (I² > 50) with significant p-value (p < 0.05) considered to be presence of heterogeneity among included studies. Among the models tested, heterogeneity was observed in allele comparison, heterozygous and dominant genetic models. However, other genetic comparison models such as recessive and homozygous were homogeneous. Observations of heterogeneity Q test and I² statistics of each model are shown in Table 2. Based on results of heterogeneity test, fixed or random effect model was used for meta-analysis.

Publication bias. Begg's funnel plot and egger's regression test was performed to assess the publication bias within the studies included in meta-analysis. Results are imputed in Table 2. We observed significant publication bias in all genetic models tested and were resolved by "trim and fill" technique (Supplementary Fig. 1).

Statistical analysis. In the present study 35 case-control studies were included and cumulative analysis demonstrated the association of *Her2* polymorphism with increased risk of breast cancer. The overall allele model revealed association between *Her2* polymorphism and breast cancer risk with Odds ratio (OR) = 1.130, 95% confidence interval (CI) = 1.051-1.216, p = 0.001. Furthermore, both dominant and heterozygous models showed significant association of Her2 ^{Ile}655^{Val} polymorphism with increased risk of breast cancer (Dominant model Val-Val + Ile-Val vs Ile-Ile: OR = 1.127, 95% CI = 1.038-1.223, p = 0.004; Heterozygous Ile-Val vs Ile-Ile: OR = 1.100, 95% CI = 1.016-1.192, p = 0.019). However, comparison of genotypes in other genetics models didn't show significant association (Homozygous Val-Val vs Ile-Ile: OR = 1.034, 95% CI = 0.937-1.142, p = 0.503; Recessive Val-Val vs Ile-Ile + Ile-Val: OR = 1.041, 95% CI = 0.945-1.147, p = 0.418) (Figs 1–3). Furthermore, Studies were grouped based on the techniques used for the detection of polymorphism and were analyzed for the association with breast cancer. Studies which used RFLP method as genotypic detection were showing significant association with breast cancer risk in all the models (Overall allele Val vs Ile: OR = 1.236, 95% CI = 1.091-1.400, p = 0.001; Homozygous Val-Val vs Ile-Ile: OR = 1.177, 95% CI = 0.017-1.362, p = 0.028; Heterozygous Ile-Val vs Ile-Ile: OR = 1.183, 95% CI = 1.026-1.364, p = 0.021; Recessive Val-Val vs Ile-Ile + Ile-Val: OR = 1.192, 95%

Study name		Stati	stics for e	each stud	y		Odds ratio an	d 95% Cl		
	Odds	Lower	Upper							Relative
Overall allele Val vs. Ile	ratio	limit	limit		p-Value					weight
Benusiglio PR et al 2006 Carrillo-Moreno DI et al 2016	0.995 1.522	0.900 1.012	1.100 2.289	-0.091 2.016	0.927 0.044			_∎_		22.98 1.38
Cox DG et al 2005	0.927	0.819	1.048	-1.209	0.227					15.19
Frank B et al 2005	1.091	0.897	1.327	0.874	0.382		†	-		6.01
Hishida A et al 2002 Millikan R et al (a) 2003 African -American	0.782 1.357	0.525 0.993	1.164 1.854	-1.212 1.914	0.226 0.056			- I		1.45 2.36
Millikan R et al (b) 2003 Whites	1.019	0.891	1.166	0.280	0.030		+			12.74
Nelson SE et al 2005	0.915	0.794	1.055	-1.220	0.222		₫			11.45
Qu S et al 2008 Baikumar T at al 2008	0.945	0.851	1.050	-1.051	0.293			_		20.77
Rajkumar T et al 2008 Siddig A et al 2008	0.977 2.340	0.725 0.906	1.317 6.044	-0.152 1.756	0.879 0.079					2.59 0.26
Tommasi S et al 2007	1.366	0.970	1.925	1.786	0.074			•-		1.96
Watrowski R et al 2015	1.000	0.595	1.682	0.000	1.000			-		0.85
Combined	0.990	0.944	1.039	-0.392	0.695	I		1 1	I	
Val-Val vs lle-lle						0.1	0.2 0.5 1	2 5	10	
Benusiglio PR et al 2006 Carrillo-Moreno DI et al 2016	0.920 1.837	0.707 0.190	1.196 17.782	-0.625 0.525	0.532 0.600					25.97 0.35
Cox DG et al 2005	0.773	0.551	1.085	-1.487	0.137					15.60
Frank B et al 2005	1.411	0.877	2.272	1.418	0.156		_ ∙	⊷		7.93
Hishida A et al 2002	0.320	0.081	1.261	-1.628	0.103			_		0.96
Millikan R et al (a) 2003 African -American Millikan R et al (b) 2003 Whites	15.658 0.997	0.902 0.714	271.851 1.392	1.889 -0.019	0.059 0.985			-		0.22 16.14
Nelson SE et al 2005	0.765	0.532	1.099	-1.449	0.147					13.65
Qu S et al 2008	0.995	0.703	1.408	-0.028	0.978		- I †			14.89
Rajkumar T et al 2008	0.780 1.339	0.320 0.082	1.901 21.878	-0.547 0.205	0.585 0.838			-		2.26 0.23
Siddig A et al 2008 Tommasi S et al 2007	1.339	0.381	4.762	0.205	0.638					1.13
Watrowski R et al 2015	1.235	0.239	6.383	0.252	0.801		}•	<u> </u>		0.67
Combined	0.927	0.811	1.060	-1.103	0.270		€	I		
lle-Val vs lle-lle						0.01	0.1 1	10	100	
Benusiglio PR et al 2006	1.031	0.907	1.173	0.468	0.640			⊢		21.32
Carrillo-Moreno DI et al 2016	1.577	1.015	2.450	2.026	0.043					1.82
Cox DG et al 2005 Frank B et al 2005	0.968 0.988	0.829 0.763	1.130 1.281	-0.416 -0.089	0.678 0.929					14.66 5.24
Hishida A et al 2002	0.930	0.583	1.483	-0.307	0.329					1.61
Millikan R et al (a) 2003 African -American	1.158	0.830	1.615	0.863	0.388		-+	-		3.18
Millikan R et al (b) 2003 Whites	1.041	0.875	1.237	0.450	0.652			<u> </u>		11.77
Nelson SE et al 2005 Qu S et al 2008	0.962 0.924	0.801 0.818	1.155 1.044	-0.413 -1.263	0.680 0.207			_		10.52 23.64
Rajkumar T et al 2008	1.045	0.733	1.490	0.242	0.808					2.79
Siddig A et al 2008	2.946	0.969	8.962	1.904	0.057		+		>	0.28
Tommasi S et al 2007 Watrowski R et al 2015	1.274 0.945	0.860 0.503	1.888 1.774	1.209 -0.177	0.227 0.859	L		-	-	2.28 0.89
Combined	1.004	0.946	1.066	0.139	0.890					0.05
						0.5	1		2	
Val-Val vs IIe-IIe + IIe-Val	0.000	0 700	4.476	0 700	0.466	1	1	1	1	06.45
Benusiglio PR et al 2006 Carrillo-Moreno DI et al 2016	0.908 1.693	0.702 0.175	1.176 16.369	-0.729 0.455	0.466 0.649					26.15 0.34
Cox DG et al 2005	0.782	0.560	1.093	-1.437	0.151		-			15.57
Frank B et al 2005	1.418	0.892	2.255	1.477	0.140		t•	- ∣		8.10
Hishida A et al 2002 Millikan R et al (a) 2003 African -American	0.326 15.406	0.083	1.277 267.418	-1.609 1.878	0.108 0.060				_	0.93 0.21
Millikan R et al (b) 2003 Whites	0.983	0.708	1.364	-0.104	0.917		∔		1	16.20
Nelson SE et al 2005	0.776	0.544	1.108	-1.395	0.163		1 4			13.76
Qu S et al 2008 Rajkumar T et al 2008	1.013 0.771	0.716 0.318	1.432 1.872	0.073 -0.574	0.942 0.566			_		14.53 2.22
Siddig A et al 2008	1.194	0.073	19.455	0.125	0.901					0.22
Tommasi S et al 2007	1.262	0.358	4.442	0.362	0.717		_+	— I		1.10
Watrowski R et al 2015	1.260	0.247	6.417	0.278	0.781					0.66
Combined	0.928	0.813	1.059	-1.113	0.266	1		1	1	
lle-Val + Val-Val vs lle-lle + lle-Val + Val-Va	ıl					0.01	0.1 1	10	100	
Benusiglio PR et al 2006	1.015	0.897	1.148	0.237	0.813		🖷			21.40
Carrillo-Moreno DI et al 2016	1.584	1.026	2.447	2.075	0.038		_			1.71
Cox DG et al 2005 Frank B et al 2005	0.940 1.045	0.810 0.817	1.091 1.336	-0.809 0.348	0.419 0.728		🖡	-		14.64 5.34
Hishida A et al 2002	0.841	0.537	1.316	-0.760	0.447			·		1.62
Millikan R et al (a) 2003 African -American	1.263	0.911	1.752	1.399	0.162			-		3.03
Millikan R et al (b) 2003 Whites Nelson SE et al 2005	1.033 0.930	0.877 0.781	1.217 1.107	0.393 -0.814	0.694 0.416		1			12.07 10.64
Qu S et al 2008	0.930	0.827	1.047	-0.814	0.230		🖬			23.37
Rajkumar T et al 2008	1.010	0.719	1.419	0.058	0.954		 	-		2.80
Siddig A et al 2008	2.679	0.947	7.573	1.858	0.063			╾┼╸┼	-	0.30
Tommasi S et al 2007 Watrowski R et al 2015	1.279 0.968	0.872 0.526	1.876 1.783	1.261 -0.104	0.207 0.917					2.21 0.87
Combined	0.997	0.941	1.055	-0.121	0.904		∳			0.07
						0.1	0.2 0.5 1	2 5	10	
						\leftarrow		la contra	\rightarrow	
							Decrease	Increase		

Figure 6. Forest plot: Overall allele and genotypic analysis of studies in which Taqman used as detection method for *Her2*^{1le}655^{Val} (rs1136201) gene polymorphism and evaluation of its association with breast cancer risk. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR). Overall allele Val vs Ile: OR = 0.990, 95% CI = 0.944 - 1.039, p = 0.695; Homozygous Val-Val vs Ile-Ile: OR = 0.927, 95% CI = 0.811 - 1.060, p = 0.270; Heterozygous Ile-Val vs Ile-Ile: OR = 1.004, 95% CI = 0.946 - 1.066, p = 0.890; Recessive Val-Val vs Ile-Ile + Ile-Val: OR = 0.928, 95% CI = 0.813 - 1.059, p = 0.266; Dominant model Val-Val + Ile-Val vs Ile-Ile: OR = 0.997, 95% CI = 0.941 - 1.055, p = 0.904.

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CI = 1.033 - 1.375, p = 0.016; Dominant model Val-Val + Ile-Val vs Ile-Ile: OR = 1.233, 95% CI = 1.066 - 1.424, p = 0.005) (Figs 4 and 5). However, the studies in which Taqman used as detection method showed no association with increased risk of breast cancer (Fig. 6).

	Caucasian													
Overall allel Val Vs. Ile Imiti Imiti Itilitii Z-Value p-Value Baxter SW et al 2001 0.805 0.614 1.056 -1.564 0.118 Keshava C et al 2001 1.229 0.770 1.922 0.805 0.614 GENICA et al 2010 1.054 0.893 1.243 0.619 0.536 GENICA et al 2010 0.985 0.895 1.015 -1.491 0.136 Val-Val vs. Ile-Ile Baxter SW et al 2001 1.684 0.334 1.400 -1.040 0.298 Keshava C et al 2001 1.249 0.352 4.333 0.345 0.730 Tommasi S et al 2007 1.347 0.381 4.762 0.624 0.644 Wang-Gohrke S et al 2001 1.249 0.352 4.33 0.345 0.730 Cambined 1.000 0.850 1.177 0.045 0.628 0.644 Wang-Gohrke S et al 2001 1.249 0.653 1.107 0.0171 1.847 0.845 0.827 Keshava C et al 2001 1.262 0.727 2.955 0.874 0.382 0.381	Study name		Statistic	cs for ea	ich study			(Odds rat	tio an	d 95% C	21		
Keshava C et al 2001 1.229 0.770 1.962 0.866 0.387 Tommasi S et al 2007 1.066 0.970 1.925 1.786 0.074 Wang-Gohrke S et al 2010 0.926 0.861 0.995 -2.086 0.037 Combined 0.926 0.861 0.995 -2.086 0.037 Val-Val vs. Ile-Ile Baxter SW et al 2001 1.684 0.332 1.440 0.136 Wang-Gohrke S et al 2001 1.249 0.352 4.433 0.345 0.730 Tommasi S et al 2001 1.347 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2001 1.714 0.721 1.721 0.465 0.628 GENICA et al 2010 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.101 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.50 0.628 0.645 Combined 0.903 0.833 0.979 2.485 0.013 0.428 Keshava C et al 2001 1.651 0.272	Overall allele Val vs. lle				Z-Value	p-Value								Relativ weigh
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Baxter SW et al 2001	0.805	0.614	1.056	-1.564	0.118			-	+				5.36
Wang-Gohrke S et al 2001 1.054 0.893 1.243 0.619 0.536 GENICA et al 2010 0.926 0.861 0.995 2.066 0.037 Combined 0.953 0.895 1.015 -1.491 0.136 Val-Val vs. IIe-IIe Baxter SW et al 2001 1.644 0.334 1.400 -1.040 0.298 Keshava C et al 2001 1.249 0.552 4.433 0.443 0.644 Wang-Gohrke S et al 2001 1.347 0.381 4.762 0.483 0.644 Wang-Gohrke S et al 2001 1.347 0.550 1.177 0.052 0.997 Ile-Val vs. Ile-IIe Baxter SW et al 2001 0.784 0.553 1.107 -0.052 0.997 Ile-Val vs. Ile-IIe Baxter SW et al 2001 0.784 0.553 1.107 0.483 0.445 GENICA et al 2011 1.292 0.727 2.295 0.874 0.382 0.997 Vang-Gohrke S et al 2001 0.784 0.945 -3.153 0.002 0.001 0.903 0.833 0.979 -2.485 0.013 Vang-Gohrke S et al	Keshava C et al 2001	1.229	0.770	1.962	0.866	0.387				+	<u> </u>			1.8
GENICA et al 2010 0.926 0.861 0.995 -2.086 0.037 Combined 0.953 0.895 1.015 -1.491 0.136 Val-Val vs. IIe-IIe Baxter SW et al 2001 0.684 0.334 1.400 -1.040 0.298 Keshava C et al 2001 1.249 0.352 4.433 0.345 0.730 Tommasi S et al 2007 1.347 0.381 4.762 0.485 0.624 GENICA et al 2010 0.995 0.527 1.197 0.052 0.959 Combined 1.000 0.850 1.177 0.064 0.997 Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.784 0.553 1.1297 0.460 0.685 6 GENICA et al 2010 0.861 0.784 0.945 -3.153 0.002 0 Combined 0.903 0.833 0.979 -2.485 0.013 0 0 Val-Val vs. Ile-Ile Have SW et al 2001 0.752 0.573 0.567 0 0	Tommasi S et al 2007	1.366	0.970	1.925	1.786	0.074				+				3.37
Combined 0.953 0.895 1.015 -1.491 0.136 Val-Val vs. IIe-IIe Baxter SW et al 2001 0.684 0.334 1.400 -1.491 0.298 Keshava C et al 2001 1.147 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2001 0.995 0.827 1.117 -0.052 0.959 Genication 0.995 0.827 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.945 -3.153 0.002 0.002 Yang-Gohrke S et al 2001 0.550 0.372 1.229 0.428 0.845 0.136 Keshava C et al 2001 0.752 0.372 1.250 -0.793 0.428 0.833 0.997 2.485 0.013 Val-Val vs. IIe-IIe Baxter SW et al 2001 0.759 1.262 0.573 </td <td>Wang-Gohrke S et al 2001</td> <td>1.054</td> <td>0.893</td> <td>1.243</td> <td>0.619</td> <td>0.536</td> <td></td> <td></td> <td></td> <td>_ †=-</td> <td></td> <td></td> <td></td> <td>14.40</td>	Wang-Gohrke S et al 2001	1.054	0.893	1.243	0.619	0.536				_ †=-				14.40
Val-Val vs. III-IIe Baxter SW et al 2001 0.684 0.334 1.400 -1.040 0.298 Keshava C et al 2001 1.249 0.352 4.433 0.345 0.730 Tommasi S et al 2007 1.347 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2010 0.995 0.827 1.197 -0.052 0.959 Combined 1.000 0.850 1.177 0.004 0.997 Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 0.784 0.987 Yang-Gohrke S et al 2001 0.784 0.953 0.979 2.485 0.013 Val-Val vs. Ile-Ile Baxter SW et al 2001 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 1.765 0.879 1.264 0.573 0.567 Combined 1.046 0.892	GENICA et al 2010	0.926	0.861	0.995	-2.086	0.037								75.08
Baxter SW et al 2001 0.684 0.334 1.400 -1.040 0.298 Keshava C et al 2001 1.249 0.352 4.433 0.345 0.730 Tommasi S et al 2001 1.347 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2001 0.995 0.827 1.197 -0.052 0.959 Combined 1.000 0.850 1.177 0.004 0.997 Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.222 0.727 2.295 0.874 0.382 1 1.97 0.460 Wang-Gohrke S et al 2001 1.054 0.553 1.110 -1.370 0.171 1.540 0.645 GENICA et al 2010 0.861 0.784 0.945 -3.153 0.002 0.013 1 <t< td=""><td>Combined</td><td>0.953</td><td>0.895</td><td>1.015</td><td>-1.491</td><td>0.136</td><td></td><td></td><td></td><td>•</td><td></td><td></td><td></td><td></td></t<>	Combined	0.953	0.895	1.015	-1.491	0.136				•				
Keshava C et al 2001 1.249 0.352 4.433 0.345 0.730 Tommasi S et al 2007 1.347 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2001 1.114 0.721 1.721 0.485 0.628 GENICA et al 2010 0.995 0.827 1.197 -0.052 0.959 Combined 1.000 0.850 1.177 0.004 0.997 IIe-Val vs. IIe-IIe Baxter SW et al 2001 1.724 0.861 0.730 Yang-Gohrke S et al 2001 1.282 0.727 2.295 0.874 0.382 Tommasi S et al 2001 1.051 1.297 0.460 0.645 GENICA et al 2010 0.861 0.784 0.326 0.733 Vang-Gohrke S et al 2001 0.762 0.372 1.520 0.793 0.428 Keshava C et al 2001 1.63 0.331 4.082 0.771 Wang-Gohrke S et al 2001 1.655 0.372 1.520 0.773 0.428 Keshava C et al 2001 1.656 0.372 1.520 0.773 0.567 Combine	Val-Val vs. lle-lle													
Tommasi S et al 2007 1.347 0.381 4.762 0.463 0.644 Wang-Gohrke S et al 2001 1.114 0.721 1.721 0.485 0.628 GENICA et al 2010 0.995 0.827 1.197 -0.052 0.997 Ile-Val vs. Ile-Ile Baxter SW et al 2001 1.284 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.292 0.727 2.295 0.874 0.382 Tommasi S et al 2007 1.274 0.860 1.888 1.209 0.227 Wang-Gohrke S et al 2001 0.681 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 1.652 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.653 0.314 4.082 0.236 0.814 0.663 GENICA et al 2010 1.693 0.713 1.678 0.409 0.683 0.643 GENICA et al 2010 1.059 0.879 1.264 0.573 0.560 0	Baxter SW et al 2001	0.684	0.334	1.400	-1.040	0.298				-+-	-			5.1
Wang-Gohrke S et al 2001 1.114 0.721 1.721 0.485 0.628 GENICA et al 2010 0.995 0.827 1.197 -0.052 0.959 Combined 1.000 0.850 1.177 0.004 0.997 Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.292 0.727 2.295 0.874 0.382 Tommasi S et al 2001 1.274 0.860 1.888 1.209 0.227 Wang-Gohrke S et al 2001 1.051 0.851 1.297 0.460 0.645 GENICA et al 2010 0.861 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 -2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 1.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.055 0.879 1.264 0.553 0.567 Combined 1.046 0.822 1.228 0.553 0.567 Combined	Keshava C et al 2001	1.249	0.352	4.433	0.345	0.730				-				1.6
GENICA et al 2010 0.995 0.827 1.197 -0.052 0.959 Combined 1.000 0.850 1.177 0.004 0.997 IIe-Val vs. IIe-IIe Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.292 0.727 2.295 0.874 0.382 Tommasi S et al 2001 1.274 0.860 1.888 1.209 0.227 Wang-Gohrke S et al 2001 0.615 0.813 0.979 -2.485 0.013 Val-Val vs. IIe-IIe + IIe-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.051 0.811 1.074 0.563 0.814 Tommasi S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.056 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + IIe-Val vs. IIe-IIe Eaxter SW et al 2001 1.059 0.866 1.264 0.576 GENICA et al	Tommasi S et al 2007	1.347	0.381	4.762	0.463	0.644			-	-		_		1.6
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IIe-Val vs. IIe-IIe Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.292 0.727 2.295 0.874 0.382 Tommasi S et al 2001 1.292 0.727 2.295 0.874 0.382 GENICA et al 2011 1.051 0.851 1.297 0.460 0.645 GENICA et al 2010 0.861 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 -2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.635 0.373 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Eaxter SW et al 2001 1.059 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.268 0.745 2.221 0.903 0.366 <	GENICA et al 2010	0.995	0.827	1.197	-0.052	0.959				-				77.5
Baxter SW et al 2001 0.784 0.553 1.110 -1.370 0.171 Keshava C et al 2001 1.292 0.727 2.295 0.874 0.382 Tommasi S et al 2007 1.274 0.860 1.888 1.209 0.227 Wang-Gohrke S et al 2001 1.051 0.851 1.297 0.460 0.645 GENICA et al 2010 0.861 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 -2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.053 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027	Combined	1.000	0.850	1.177	0.004	0.997				•				
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GENCA et al 2010 0.861 0.784 0.945 -3.153 0.002 Combined 0.903 0.833 0.979 -2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 0.580 0.990 -2.211 0.027 0.1 0.2 0.5 <td>Tommasi S et al 2007</td> <td>1.274</td> <td>0.860</td> <td>1.888</td> <td>1.209</td> <td>0.227</td> <td></td> <td></td> <td></td> <td>+</td> <td></td> <td></td> <td></td> <td>4.1</td>	Tommasi S et al 2007	1.274	0.860	1.888	1.209	0.227				+				4.1
Combined 0.903 0.833 0.979 -2.485 0.013 Val-Val vs. Ile-Ile + Ile-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Image: the state s	Wang-Gohrke S et al 2001	1.051	0.851	1.297	0.460	0.645				-	-			14.5
Val-Val vs. lie-lie + lie-Val Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + lie-Val vs. lie-lie Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1<	GENICA et al 2010	0.861	0.784	0.945	-3.153	0.002								74.0
Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 Under Combined 0.917 </td <td>Combined</td> <td>0.903</td> <td>0.833</td> <td>0.979</td> <td>-2.485</td> <td>0.013</td> <td></td> <td></td> <td></td> <td>¢</td> <td></td> <td></td> <td></td> <td></td>	Combined	0.903	0.833	0.979	-2.485	0.013				¢				
Baxter SW et al 2001 0.752 0.372 1.520 -0.793 0.428 Keshava C et al 2001 1.163 0.331 4.082 0.236 0.814 Tommasi S et al 2007 1.262 0.358 4.442 0.362 0.717 Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 Under Combined 0.917 </td <td>Val-Val vs. lle-lle + lle-Val</td> <td></td>	Val-Val vs. lle-lle + lle-Val													
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Wang-Gohrke S et al 2001 1.093 0.713 1.678 0.409 0.683 GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Keshava C et al 2001	1.163	0.331	4.082	0.236	0.814					_	— I		1.62
GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Tommasi S et al 2007	1.262	0.358	4.442	0.362	0.717				\rightarrow		-1		1.6
GENICA et al 2010 1.055 0.879 1.264 0.573 0.567 Combined 1.046 0.892 1.228 0.553 0.580 Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Wang-Gohrke S et al 2001	1.093	0.713	1.678	0.409	0.683				-+-	-1			13.96
Val-Val + Ile-Val vs. Ile-Ile Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027	GENICA et al 2010	1.055	0.879	1.264	0.573	0.567				-				77.6
Baxter SW et al 2001 0.769 0.551 1.074 -1.540 0.124 Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027	Combined	1.046	0.892	1.228	0.553	0.580				•				
Keshava C et al 2001 1.286 0.745 2.221 0.903 0.366 Tommasi S et al 2007 1.279 0.872 1.876 1.261 0.207 Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Val-Val + lle-Val vs. lle-lle													
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Wang-Gohrke S et al 2001 1.059 0.866 1.296 0.560 0.576 GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Keshava C et al 2001	1.286	0.745	2.221	0.903	0.366				+				1.97
GENICA et al 2010 0.879 0.804 0.961 -2.842 0.004 Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Tommasi S et al 2007	1.279	0.872	1.876	1.261	0.207				+	-			4.01
Combined 0.917 0.850 0.990 -2.211 0.027 0.1 0.2 0.5 1 2 5 10	Wang-Gohrke S et al 2001	1.059	0.866	1.296	0.560	0.576	I			_ ≱=				14.48
0.1 0.2 0.5 1 2 5 10 <	GENICA et al 2010	0.879	0.804	0.961	-2.842	0.004	I							74.27
$\longleftrightarrow $	Combined	0.917	0.850	0.990	-2.211	0.027				۱				
							0.1	0.2	0.5	1	2	5	10	
							←	Decr			Inere		\rightarrow	

Figure 7. Forest plot: Analysis of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism data from Caucasian ethnic group and validation of its correlation with breast cancer susceptibility using OR with 95% CI. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

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Subgroup analysis. As the previous meta-analysis presented association of *Her2* gene polymorphism with susceptibility to breast cancer in Asian population only, in the present analysis we re-accessed possible link of *Her2* polymorphism with BC in different ethnic groups. In our study subgroup analysis with 15 case-control studies identified the association with increased risk of breast cancer in Asian ethnicity in overall allele and dominant models. Similarly, African group with 3 successful included case-control studies also showed association with breast cancer risk in recessive and homozygous models. However, 5 case control studies from Caucasian, 4 from American subgroup, 2 limited studies from Afro-American ethnic group and 8 studies from European ethnicity showed no association of *Her2* polymorphism with breast cancer risk in all the models (Table 3) (Figs 7–12).

Sensitivity analysis. We analyzed the influence of each individual study on the pooled OR by sensitivity analysis. One study was excluded each time and meta-analysis was performed. The results showed no individual study affected the pooled OR significantly, suggesting this meta-analysis is relatively credible, stable and not dependent on any individual study (Figs 13–15).

Discussion

Human epidermal growth factor family members are a group of receptors with tyrosine kinase activity which affects cell proliferation and survival^{63,64}. Dimerization of Her family members leads to autophosphorylation of tyrosine residues in the cytoplasmic domain and leads to cell proliferation and tumorigenesis⁵⁻⁷. Although Her family members lack natural ligand for signaling, various synthetic ligands have been developed and they are demonstrated to be efficientive in terms of drug delivery. Among the all-family members, Her2 is an important molecule and expression of *Her2* is elevated in various cancers⁸⁻¹⁰. Approximately 20–30% breast cancers

American													
Study name		Statist	tics for e	ach study	/		(Odds rat	tio an	d 95% (
Overall allele Val vs. Ile	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value								Relative weight
Carrillo-Moreno DI et al 2016	1.522	1.012	2.289	2.016	0.044				H	-•-+			4.66
Cox DG et al 2005	0.927	0.819	1.048	-1.209	0.227								51.17
Keshava C et al 2001	1.827	0.827	4.037	1.491	0.136				+		-		1.24
Millikan R et al 2003	1.019	0.891	1.166	0.280	0.779								42.94
Combined	0.996	0.912	1.088	-0.080	0.936				•				
Val-Val vs. lle-lle						0.1	0.2	0.5	1	2	5	10	
Carrillo-Moreno DI et al 2016	1.837	0.190	17.782	0.525	0.600						+		1.08
Cox DG et al 2005	0.773	0.551	1.085	-1.487	0.137								48.28
Keshava C et al 2001	3.412	0.203	57.470	0.852	0.394				-		+	-	0.70
Millikan R et al 2003	0.997	0.714	1.392	-0.019	0.985					•			49.94
Combined	0.895	0.707	1.133	-0.921	0.357				•				
lle-Val vs. lle-lle						0.01	0	.1	1	1	0	100	
Carrillo-Moreno DI et al 2016	1.577	1.015	2.450	2.026	0.043				H				6.34
Cox DG et al 2005	0.968	0.829	1.130	-0.416	0.678								51.18
Keshava C et al 2001	1.895	0.738	4.868	1.329	0.184				+				1.38
Millikan R et al 2003	1.041	0.875	1.237	0.450	0.652				- 🗰	+			41.10
Combined	1.038	0.929	1.160	0.658	0.511				•				
Val-Val vs. lle-lle + lle-Val						0.1	0.2	0.5	1	2	5	10	
Carrillo-Moreno DI et al 2016	1.693	0.175	16.369	0.455	0.649				-		⊢		1.05
Cox DG et al 2005	0.782	0.560	1.093	-1.437	0.151								48.16
Keshava C et al 2001	2.815	0.170	46.585	0.723	0.470			I —	-			-	0.68
Millikan R et al 2003	0.983	0.708	1.364	-0.104	0.917								50.11
Combined	0.892	0.707	1.125	-0.965	0.334				•				
Val-Val + lle-Val vs. lle-lle						0.01	0	.1	1	1	0	100	
Carrillo-Moreno DI et al 2016	1.584	1.026	2.447	2.075	0.038				-				5.95
Cox DG et al 2005	0.940	0.810	1.091	-0.809	0.419								50.82
Keshava C et al 2001	1.975	0.788	4.949	1.453	0.146				+		-		1.33
Millikan R et al 2003	1.033	0.877	1.217	0.393	0.694				-				41.90
Combined	1.019	0.917	1.133	0.352	0.725				•				
						0.1	0.2	0.5	1	2	5	10	
						←						\rightarrow	
							Decre	eased		increa	ase		

Figure 8. Forest plot: *Her2* ^{1le}655^{Val} (rs1136201) gene polymorphism data from American ethnic group showing OR and 95% CI for analyzing its association with breast cancer risk. Squares represents OR and horizontal line represents 95% Confidence Interval (CI) of odds ratio (OR).

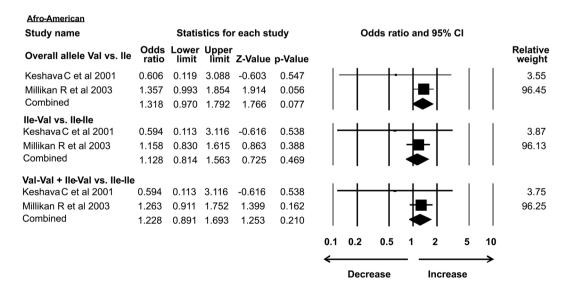


Figure 9. Forest plot: *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism data from Afro-American sub group population showing OR and 95% CI for validating its association with breast cancer risk. Black square represents OR and horizontal line representing 95% CI.

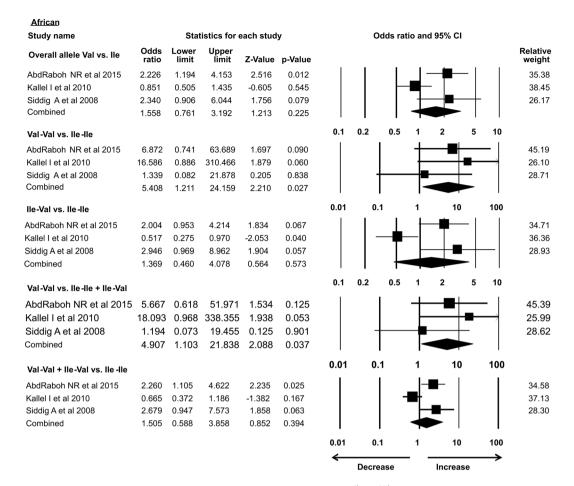


Figure 10. Forest plot: Overall analysis of African ethnic group *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism data for evaluation of its association with breast cancer susceptibility. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

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show 40-100 fold elevated levels of Her2, whereas other cancer types such as ovarian, endometrial, gastric and esophageal cancers were also detected with over-expressed Her2 protein levels⁶⁵⁻⁷¹. Single nucleotide polymorphisms (SNPs) are playing an important role in various cancer types and are capable of serving as diagnostic tools²³⁻²⁵. One such single nucleotide polymorphism with substitution of isoleucine with valine at codon 655 in transmembrane region of Her2 has been found to be playing an important role in development of cancer⁷². The transmembrane domain region of Her2 with valine at 655 domain region stabilizes the formation of protein dimer and thus predisposing to an auto-activity of the receptor⁷³. The hydrophobicity and conformational stability of the hydrophobic domains such as transmembrane domains may alter due to Isoleucine to valine change⁷⁴. Her2 ^{Ile}655^{Val} polymorphism was well studied for association with breast cancer risk, whereas other polymorphism at 1170 codon of Her2 (Pro1170Ala) was correlated with cardiotoxicity75. Her2 lle655Val polymorphism is not only associated with breast cancer risk but also associated with other cancers such as ovarian and endometrial cancers^{76,77}. However, these results are inconsistent and a stringent and powerful analysis is required to conclude the association with breast cancer. In the present study we have analyzed the association of Her2^{1le655Val} polymorphism with increased breast cancer susceptibility using powerful tool comprehensive meta-analysis (CMA). Overall allele comparison genetic model results suggest that valine allele in Her2 655 codon favors the development of breast cancer in worldwide population. Heterozygous, dominant models also prove that Her2 polymorphism is associated with increased risk of breast cancer. Whereas, subgroup analysis showing different results for different ethnic population. Earlier reports by Wang et al.⁵⁸ and Chen et al.⁶² demonstrated association of Her2 value allele with breast cancer risk in Caucasian population. In contrast, our study failed to show such link. The present study has several advantages over earlier reports. We have included more number of studies in the current meta-analysis including larger number of cases and controls.

Tao *et al.*⁵⁶ reported the association of *Her2* polymorphism with breast cancer risk in Asian population whereas later Wang *et al.*⁵⁸ and Chen *et al.*⁶² showed no such association with breast cancer. In this present meta-analysis, we have performed subgroup analysis and demonstrated that valine allele is associated with breast cancer risk in Asian population. In addition to that Val-Val + Ile-Val vs Ile-Ile model also prove the susceptibility of *Her2* polymorphism with breast cancer. We also observed that subjects with valine/valine genotype are susceptible for the development of breast cancer in African population. These results are in agreement with the study demonstrated by Wang *et al.*⁵⁸; however other studies failed to show such association with breast cancer

European												
Study name	name Statistics for each study								and 95%	CI		
Overall allele Val vs. lle	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value							Relative weight
Benusiglio PR et al 2006	0.995	0.900	1.100	-0.091	0.927							25.21
Frank B et al 2005	1.091	0.897	1.327	0.874	0.382				₽			19.90
Kalemi TG et al 2004	0.784	0.332	1.849	-0.556	0.578							3.21
Nelson SE et al 2005	0.915	0.794	1.055	-1.220	0.222							23.02
Papadopoulou E et al 2007	1.731	0.987	3.036	1.913	0.056				┝─■├	-		6.49
Pinto D et al 2004	1.765	1.161	2.682	2.658	0.008				╽──■┤─	-		9.85
Watrowski R et al 2015	1.000	0.595	1.682	0.000	1.000				† –			7.30
ZÚBOR P et al 2006	2.255	1.166	4.363	2.415	0.016							5.03
Combined	1.128	0.958	1.328	1.444	0.149		I	I		I	I	
Val-Val Vs lle-lle						0.1	0.2	0.5	12	5	10	
Benusiglio PR et al 2006	0.920	0.707	1.196	-0.625	0.532				₽_			50.53
Frank B et al 2005	1.411	0.877	2.272	1.418	0.156				† ■−			15.42
Nelson SE et al 2005	0.765	0.532	1.099	-1.449	0.147			-	t			26.56
Papadopoulou E et al 2007	2.407	0.866	6.688	1.684	0.092				— •—			3.35
Pinto D et al 2004	2.128	0.603	7.505	1.174	0.240			_		-		2.20
Watrowski R et al 2015	1.235	0.239	6.383	0.252	0.801				-			1.30
ZÚBOR P et al 2006 Combined	5.727	0.562	58.349	1.474	0.141						-	0.65
Combined	1.000	0.829	1.205	-0.004	0.997	1		•	7	I		
lle-Val vs lle-lle						0.01	0	.1 1	1	10	100	
Benusiglio PR et al 2006	1.031	0.907	1.173	0.468	0.640							52.42
Frank B et al 2005	0.988	0.763	1.281	-0.089	0.929			-	•			12.88
Kalemi TG et al 2004	0.750	0.296	1.903	-0.606	0.545				<u> </u>			1.00
Nelson SE et al 2005	0.962	0.801	1.155	-0.413	0.680							25.86
Papadopoulou E et al 2007	1.742	0.684	4.433	1.164	0.244			-				0.99
Pinto D et al 2004	1.980	1.193	3.287	2.643	0.008							3.37
Watrowski R et al 2015	0.945	0.503	1.774	-0.177	0.859				Γ			2.18
ZÚBOR P et al 2006 Combined	2.471 1.042	1.092 0.949	5.590 1.143	2.171 0.859	0.030 0.390							1.30
Combined	1.042	0.949	1.143	0.859	0.390					1		
Val-Val vs. lle-lle + lle-Val						0.01	0	.1 1	1 	10	100	
Benusiglio PR et al 2006	0.908	0.702	1.176	-0.729	0.466							50.01
Frank B et al 2005	1.418	0.892	2.255	1.477	0.140			· ·	┝╋╌			15.49
Nelson SE et al 2005	0.776	0.544	1.108	-1.395	0.163			-	t			26.31
Papadopoulou E et al 2007	1.797	0.735	4.396	1.285	0.199			-				4.16
Pinto D et al 2004	1.714	0.491	5.982	0.845	0.398			-				2.13
Watrowski R et al 2015	1.260	0.247	6.417	0.278	0.781				-			1.26
ZÚBOR P et al 2006	4.023	0.405	39.987	1.188	0.235							0.63
Combined	0.987	0.822	1.185	-0.139	0.889				7	I	1	
Val-Val + Ile-Val vs. Ile -Ile						0.01	0.	1 1		10	100	
	4	0.00-			0.010	ı	ı		. .	ı	ı	
Benusiglio PR et al 2006	1.015	0.897	1.148	0.237	0.813							26.44
Frank B et al 2005	1.045	0.817	1.336	0.348	0.728							19.79
Kalemi TG et al 2004	0.750	0.296	1.903	-0.606	0.545							3.63
Nelson SE et al 2005 Papadopoulou E et al 2007	0.930 1.997	0.781 0.865	1.107 4.611	-0.814 1.621	0.416 0.105							23.76 4.37
Papadopoulou E et al 2007 Pinto D et al 2004	1.997	1.225	4.611 3.250	2.775	0.105							4.37 9.99
Watrowski R et al 2015	0.968	0.526	3.250 1.783	-0.104	0.006				LT			9.99 7.27
ZÚBOR P et al 2006	2.652	1.197	5.876	2.402	0.917]			4.75
Combined	1.137	0.941	1.374	1.328	0.018			.				4.75
	1.107	0.041	1.574	1.020	0.104	1	0.0	0.5		-	10	
						0.1 ←	0.2	0.5 1	2	5	10	
						-	Decre			ease		
							Decre	ease	mer	ease		

Figure 11. Forest plot: Overall analysis of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism from European subgroup with OR and 95% CI for investigating the association with breast cancer risk. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

susceptibility. Ethnic groups such as American, European and Afro-American are not showing such association with breast cancer risk. Our present meta-analysis includes all the studies in which either Taqman or RFLP used as detection method. Frank *et al.* suggested the biasness in the methods used for the detection of polymorphism and suggested that Taqman method is capable of producing false results⁷⁸. We excluded the studies in which Taqman method used as detection method and performed the analysis. Studies which used other than Taqman method for the detection of polymorphism showed significant association with breast cancer risk in all models.

In conclusion, our present meta-analysis demonstrated that valine allele is susceptible in overall worldwide population and Asian ethnic group. *Her2* ^{Ile}655^{Val} polymorphism is associated with breast cancer risk in Asian, African population but not in other ethnic groups such as Caucasian, European, American and Afro-American. These results suggest that *Her2* ^{Ile}655^{Val} polymorphism could be considered as possible susceptible bio marker for the detection of breast cancer.

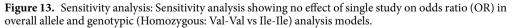
Asian							
Study name				r each stu	dy	Odds ratio and 95% CI	
Overall allele Val vs. lle	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		Relative weight
Al-Janabi AM et al 2015	1.588	1.189	2.120	3.134	0.002	│ │ │ │-■┤ │ │	8.49
Akisik E et al 2004	0.954	0.542	1.681	-0.163	0.871		4.20
An HJ et al 2005 Hisbida A et al 2002	0.986	0.602	1.614 1.164	-0.057 -1.212	0.954 0.226		5.03 6.41
Hishida A et al 2002 Kamali-Sarvestani E et al 2004	0.782 1.037	0.525 0.674	1.597	0.166	0.220		5.88
Kara N et al 2010	0.972	0.650	1.455	-0.137	0.891		6.34
Lee SC et al 2008	1.448	0.996	2.104	1.939	0.052		6.83
Mutluhan H et al 2008 Naidu R et al 2008	1.224 1.488	0.781 0.999	1.920 2.216	0.882 1.955	0.378 0.051		5.61 6.41
Ozturk O et al 2013	1.670	1.067	2.613	2.245	0.025		5.64
Parvin S et al 2016	1.425	1.026	1.979	2.111	0.035	│ │ │ <u></u> ==┤ │ │	7.68
Qu S et al 2007 Rajkumar T et al 2008	0.945 0.977	0.851 0.725	1.050 1.317	-1.051 -0.152	0.293 0.879		12.35 8.30
Sezgin E et al 2011	0.657	0.312	1.386	-1.102	0.270	│ │ ─┼∎┼╴│ │ │	2.79
Xie D et al 2000	1.494	1.095	2.039	2.533	0.011		8.04
Combined	1.163	1.011	1.338	2.111	0.035		
Val-Val vs. lle-lle							
Al-Janabi AM et al 2015 Akisik E et al 2004	2.411 0.597	1.195 0.053	4.864 6.682	2.459 -0.419	0.014 0.675		12.66 1.07
An HJ et al 2005	3.453	0.397	30.025	1.123	0.261		1.33
Hishida A et al 2002	0.320	0.081	1.261	-1.628	0.103		3.32
Kamali -Sarvestani E et al 2004 Kara N et al 2010	0.352 1.536	0.063 0.360	1.957 6.545	-1.193 0.580	0.233 0.562		2.12 2.97
Lee SC et al 2008	0.801	0.160	3.998	-0.271	0.786		2.41
Mutluhan H et al 2008	2.594	0.468	14.383	1.091	0.275		2.12
Naidu R et al 2008 Parvin S et al 2016	1.927 1.800	0.569 0.663	6.527 4.890	1.054 1.153	0.292 0.249		4.19 6.24
Qu S et al 2007	0.995	0.703	1.408	-0.028	0.978	🕈	51.65
Rajkumar T et al 2008	0.780 0.281	0.320 0.011	1.901 7.101	-0.547 -0.770	0.585 0.441		7.85 0.60
Sezgin E et al 2011 Xie D et al 2000	12.675	1.625	98.883	2.423	0.441		1.48
Combined	1.176	0.916	1.510	1.273	0.203		
lle-Val vs. lle-lle						0.01 0.1 1 10 100	
Al-Janabi AM et al 2015	1.564	1.067	2.294	2.292	0.022		5.06
Akisik E et al 2004 An HJ et al 2005	1.010	0.539	1.893	0.032	0.975		1.88
Hishida A et al 2002	0.786 0.930	0.448 0.583	1.379 1.483	-0.839 -0.307	0.401 0.759		2.34 3.39
Kamali-Sarvestani E et al 2004	1.253	0.759	2.069	0.881	0.378		2.94
Kara N et al 2000	0.883	0.555	1.406	-0.524	0.600		3.43
Lee SC et al 2008 Mutluhan H et al 2008	1.525 1.102	1.016 0.661	2.289 1.839	2.037 0.373	0.042 0.709		4.49 2.82
Naidu R et al 2008	1.485	0.930	2.370	1.656	0.098		3.39
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010		2.76
Parvin S et al 2016 Qu S et al 2007	1.440 0.924	0.975 0.818	2.127 1.044	1.832 -1.263	0.067 0.207		4.87 49.71
Rajkumar T et al 2008	1.045	0.733	1.490	0.242	0.808		5.88
Sezgin E et al 2011	0.693	0.302	1.591	-0.866	0.386		1.07
Xie D et al 2000 Combined	1.256 1.064	0.883 0.976	1.786 1.160	1.267 1.411	0.205 0.158		5.97
Val-Val vs. lle-lle + lle-Val	1.004	0.570	1.100	1.411	0.100	0.1 0.2 0.5 1 2 5 10	
Al-Janabi AM et al 2015	2.003	1.010	3.969	1.989	0.047	⊢⊷	13.16
Akisik E et al 2004	0.596	0.053	6.652	-0.421	0.674		1.06
An HJ et al 2005 Hishida A et al 2002	3.634 0.326	0.419 0.083	31.488 1.277	1.171 -1.609	0.242 0.108		1.32 3.30
Kamali-Sarvestani E et al 2004	0.332	0.060	1.836	-1.264	0.206		2.10
Kara N et al 2010 Lee SC et al 2008	1.583 0.748	0.373 0.150	6.715 3.732	0.623 -0.354	0.533 0.724		2.95 2.38
Mutluhan H et al 2008	2.543	0.460	14.059	1.070	0.285		2.30
Naidu R et al 2008	1.766	0.524	5.954	0.917	0.359		4.17
Parvin S et al 2016 Qu S et al 2007	1.638 1.013	0.606 0.716	4.427 1.432	0.972 0.073	0.331 0.942		6.23 51.35
Rajkumar T et al 2008	0.771	0.318	1.872	-0.574	0.566		7.83
Sezgin E et al 2011 Xie D et al 2000	0.311 12.006	0.012 1.542	7.786 93.504	-0.711 2.373	0.477 0.018		0.59 1.46
Combined	1.149	0.897	1.473	1.099	0.272		1.40
Val-Val + lle-Val vs. lle -lle						0.01 0.1 1 10 100	
Al-Janabi AM et al 2015	1.691	1.177	2.431	2.842	0.004	-=+	7.84
Akisik E et al 2004	0.981	0.531	1.811	-0.062	0.950		4.26
An HJ et al 2005 Hishida A et al 2002	0.875 0.841	0.507 0.537	1.508 1.316	-0.481 -0.760	0.630 0.447		5.00 6.34
Kamali-Sarvestani E et al 2004	1.153	0.709	1.874	0.574	0.566	│ │ │ ── 	5.77
Kara N et al 2010	0.922	0.587	1.446	-0.355	0.722		6.29
Lee SC et al 2008 Mutluhan H et al 2008	1.477 1.173	0.994 0.715	2.195 1.926	1.928 0.632	0.054 0.527		7.21 5.63
Naidu R et al 2008	1.173	0.977	2.390	1.856	0.527	│ │ │ ├─∎┼ │ │	6.34
Ozturk O et al 2013	1.983	1.181	3.328	2.591	0.010	┃ ┃ <u></u> +- ┃ ┃	5.34
Parvin S et al 2016	1.475 0.930	1.015 0.827	2.145 1.047	2.037 -1.200	0.042 0.230		7.61
Qu S et al 2007 Rajkumar T et al 2008	1.010	0.827	1.419	0.058	0.230		13.13 8.29
Sezgin E et al 2011	0.654	0.287	1.491	-1.010	0.313	│ │ ─┼■┼ <u>─</u> │ │ │	2.73
Xie D et al 2000 Combined	1.400 1.177	0.993 1.012	1.975 1.370	1.919 2.116	0.055 0.034		8.21
Combined	1.177	1.012	1.370	2.110	0.034		
						\longleftrightarrow	
						Decrease Increase	

Figure 12. Forest plot: Overall analysis of *Her2* ^{lle}655^{Val} (rs1136201) gene polymorphism data from Asian ethnic group for the evaluation of association with breast cancer susceptibility. Black squares represent the value of OR and horizontal line indicates 95% Confidence Interval (CI) of odds ratio (OR).

Materials and Methods

Literature search and identification of relevant studies. A systematic extensive search was performed to extract the appropriate published reports using online databases i.e., Pubmed, EMBASE and Google scholar. The publication search was performed by three independent authors (BMK, SC& DRM) using either single or combination of given keywords i.e., "*Her2* ^{IIc}655^{Val} polymorphism", "Herceptin receptor polymorphism", "rs1136201" and breast cancer. In addition to the preliminary online database search we have checked the cross references for the potential publications, those possibly missed in preliminary search. Our present study includes

Study name	s	Statistics	with stu	dy remove	ed	Odds ratio (95% CI) with a	study remov
Overall allele Val vs. lle	Point	Lower limit	Upper limit	Z-Value	p-Value		
odRaboh NR et al 2013	1.119	1.042	1.202	3.080	0.002	1 1 🖬	- I
I-Janabi AM et al 2015	1.113	1.036	1.195	2.943	0.003		
Akisik E et al 2004	1.134	1.053	1.221	3.335	0.001		
An HJ et al 2005	1.134	1.053	1.221	3.329	0.001		
Baxter SW et al 2001	1.143	1.062	1.231	3.558	0.000		
enusiglio PR et al 2006	1.145	1.058	1.238	3.375	0.001		
Carrillo-Moreno DI et al 2016	1.122	1.043	1.207	3.092	0.002		
ox DG et al 2005	1.146	1.061	1.237	3.490	0.000		
rank B et al 2005	1.134	1.052	1.223	3.264	0.001		
ENICA et al 2010	1.148	1.063	1.241	3.506	0.000		
ishida A et al 2002	1.140	1.059	1.227	3.482	0.000		
alemi TG et al 2005	1.134	1.053	1.220	3.350	0.001		
allel I et al 2010	1.136	1.055	1.223	3.387	0.001		
amali-Sarvestani E et al 2004	1.133	1.052	1.220	3.309	0.001		
ara N et al 2010	1.135	1.054	1.223	3.348	0.001		
eshava C et al (a) Caucasian 2001	1.135	1.034	1.225	3.227	0.001		
eshava C et al (b) African -American 2001	1.123	1.052	1.218	3.326	0.001		
eshava C et al (c) Latinos 2001	1.132	1.047	1.210	3.190	0.001		
es SC et al 2008	1.120	1.047	1.208	3.099	0.001		
lillikan R et al (a) African -American 2003	1.123	1.043	1.208	3.103	0.002		
illikan R et al (b) Whites 2003	1.123	1.044	1.209	3.347	0.002		
	1.141	1.056	1.232	3.347	0.001		
lontgomery KG et al 2003							
lutluhan H et al 2008 laidu R et al 2008	1.129 1.122	1.049 1.043	1.216 1.207	3.225 3.099	0.001 0.002		
lelson SE et al 2005	1.122	1.043	1.207	3.502	0.002		
Ozturk O et al 2013	1.120	1.042	1.204	3.071	0.002		
apadopoulou E et al 2007	1.123	1.044	1.207	3.125	0.002		
arvin S et al 2016	1.122	1.043	1.207	3.077	0.002		
into D et al 2004	1.117	1.039	1.200	3.019	0.003		
u S et al 2008	1.146	1.061	1.239	3.460	0.001		
ajkumar T et al 2008	1.137	1.055	1.225	3.366	0.001		
ezgin E et al 2011	1.135	1.055	1.222	3.406	0.001		
iddig A et al 2008	1.125	1.046	1.209	3.186	0.001		
ommasi S et al 2007	1.124	1.044	1.210	3.117	0.002		
/ang-Gohrke S et al 2001	1.137	1.054	1.227	3.304	0.001		
atrowski R et al 2015	1.133	1.053	1.220	3.321	0.001		
ie D et al 2000	1.118	1.040	1.202	3.023	0.003		
ÚBOR P et al 2006	1.120	1.042	1.203	3.096	0.002		
mbined	1.130	1.051	1.216	3.298	0.001	I I IV	I
ıl-Val vs. Ile-Ile							
odRaboh NR et al 2013	1.030	0.934	1.138	0.595	0.552	1 🖿	I
-Janabi AM et al 2015	1.017	0.920	1.123	0.327	0.743	∎	
kisik E et al 2004	1.035	0.938	1.143	0.688	0.492		
n HJ et al 2005	1.033	0.935	1.143	0.619	0.536		
axter SW et al 2001	1.032	0.935	1.159	0.819	0.338		
						I I I	
enusiglio PR et al 2006	1.054	0.948	1.173	0.976	0.329		
arrillo-Moreno DI et al 2016	1.033	0.936	1.141	0.648	0.517		
ox DG et al 2005	1.063	0.958	1.178	1.153	0.249		
rank B et al 2005	1.020	0.922	1.128	0.384	0.701		
ENICA et al 2010	1.050	0.935	1.180	0.825	0.409		
ishida A et al 2002	1.041	0.943	1.149	0.789	0.430	♥	
allel I et al 2010	1.031	0.934	1.138	0.607	0.544	♥	
amali-Sarvestani E et al 2004	1.038	0.940	1.146	0.740	0.459	1 1 🖬	
ara N et al 2010	1.032	0.935	1.140	0.632	0.527		
eshava C et al (a) Caucasian 2001	1.033	0.936	1.141	0.645	0.519		
eshava C et al (c) Latinos 2001	1.033	0.936	1.140	0.641	0.522		
e SC et al 2008	1.035	0.938	1.140	0.688	0.322		
						∎	
illikan R et al (a) African -American 2003	1.031	0.934	1.138	0.605	0.545	I I I	
Ilikan R et al (b) Whites 2003	1.038	0.936	1.151	0.707	0.479		1
ontgomery KG et al 2003	1.017	0.921	1.123	0.332	0.740		1
utluhan H et al 2008	1.031	0.934	1.138	0.608	0.543		1
aidu R et al 2008	1.030	0.933	1.137	0.587	0.557	♥	
elson SE et al 2005	1.060	0.956	1.174	1.106	0.269		1
apadopoulou E et al 2007	1.026	0.929	1.133	0.510	0.610		1
arvin S et al 2016	1.029	0.932	1.136	0.559	0.576		
nto D et al 2004	1.030	0.933	1.137	0.580	0.562	Ⅰ ∣ 董	
u S et al 2008		0.935	1.157	0.580	0.362	■	
	1.038					I I I	
ajkumar T et al 2008	1.038	0.940	1.146	0.735	0.462		
ezgin E et al 2011	1.036	0.938	1.143	0.694	0.488		
iddig A et al 2008	1.034	0.937	1.141	0.663	0.507		1
ommasi S et al 2007	1.033	0.935	1.140	0.636	0.525	♥	
Vang-Gohrke S et al 2001	1.030	0.931	1.140	0.575	0.565	1 1 🗰	
/atrowski R et al 2015	1.034	0.936	1.141	0.656	0.512		
ie D et al 2000	1.028	0.932	1.135	0.554	0.579		
ÚBOR P et al 2006	1.031	0.934	1.138	0.608	0.543	Ⅰ Ⅰ 董	
ombined	1.034	0.937	1.142	0.670	0.503	1 1	
						0.01 0.1 1	10
						←	
							Incr
						Decrease	Inci



recently published (earliest by 2017) 35 case-control studies with 19, 220 cases and 22, 306 controls for *Her2* ^{Ile}655^{Val} polymorphism (Supplementary Fig. 2).

Inclusion and exclusion of studies. The studies which met all the criteria given below have been included in the present meta-analysis: (a) studies published in English, (b) must have case-control or cohort design, (c) have available genotype frequency of both the cases and controls or have odds ratio (OR) and 95% confidence interval (CI) values, (d) evaluating the association of $Her2^{1le}655^{Val}$ polymorphism with breast cancer risk and (e) studies representing original data. The studies excluded based on the criteria given below: (a) studies published

	:	Statistics	s with stu	dy remove	ed	Odds ratio (95% CI) with study removed				
al-Val vs. lle-lle	Point	Lower limit	Upper limit	Z-Value	p-Value					
AbdRaboh NR et al 2013	1.092	1.009	1.182	2.184	0.029	1 1 🖬 1				
I-Janabi AM et al 2015	1.086	1.004	1.176	2.059	0.039					
kisik E et al 2004	1.103	1.017	1.196	2.367	0.018					
n HJ et al 2005	1.107	1.021	1.200	2.465	0.014					
axter SW et al 2001	1.112	1.026	1.206	2.574	0.010					
enusiglio PR et al 2006	1.110	1.019	1.210	2.393	0.017					
arrillo-Moreno DI et al 2016	1.089	1.006	1.179	2.109	0.035					
Cox DG et al 2005	1.113	1.023	1.211	2.477	0.013					
rank B et al 2005	1.108	1.020	1.203	2.420	0.016					
ENICA et al 2010	1.116	1.031	1.208	2.703	0.007					
ishida A et al 2002	1.105	1.019	1.199	2.417	0.016					
alemi TG et al 2005	1.104	1.019	1.196	2.408	0.016					
allel I et al 2010	1.108	1.025	1.199	2.568	0.010					
amali-Sarvestani E et al 2004	1.098	1.013	1.191	2.269	0.023					
ara N et al 2010	1.107	1.020	1.200	2.444	0.015					
eshava C et al (a) Caucasian 2001	1.098	1.013	1.190	2.273	0.023					
eshava C et al (b) African -American 2001	1.102	1.017	1.194	2.384	0.017					
eshava C et al (c) Latinos 2001	1.096	1.012	1.187	2.253	0.024					
ee SC et al 2008	1.089	1.006	1.179	2.102	0.036					
lillikan R et al (a) African -American 2003	1.099	1.013	1.193	2.275	0.023					
lillikan R et al (b) Whites 2003	1.107	1.018	1.205	2.374	0.018					
lontgomery KG et al 2003	1.098	1.012	1.191	2.241	0.025					
lutluhan H et al 2008	1.101	1.016	1.194	2.332	0.020					
aidu R et al 2008	1.092	1.008	1.183	2.165	0.030					
elson SE et al 2005	1.112	1.022	1.209	2.474	0.013					
zturk O et al 2013	1.084	1.003	1.172	2.044	0.041					
apadopoulou E et al 2007	1.097	1.013	1.188	2.267	0.023					
arvin S et al 2016	1.091	1.007	1.182	2.132	0.033					
into D et al 2004	1.084	1.003	1.171	2.033	0.042					
u S et al 2008	1.117	1.026	1.216	2.555	0.011					
ajkumar T et al 2008	1.104	1.017	1.198	2.359	0.018					
ezgin E et al 2011	1.105	1.020	1.197	2.435	0.015					
iddig A et al 2008	1.093	1.010	1.182	2.220	0.026					
ommasi S et al 2007	1.096	1.011	1.189	2.223	0.026					
Vang-Gohrke S et al 2001	1.105	1.017	1.202	2.358	0.018					
Vatrowski R et al 2015	1.104	1.018	1.197	2.388	0.017					
(ie D et al 2000	1.096	1.011	1.189	2.215	0.027					
CÚBOR P et al 2006 Combined	1.090 1.100	1.008 1.016	1.179 1.192	2.160 2.350	0.031 0.019					
al-Val vs. lle-lle + lle -Val										
/al-Val vs. Ile-Ile + Ile -Val	4 0 2 7	0.044	4 4 4 9	0.740	0.450					
bdRaboh NR et al 2013	1.037	0.941	1.143	0.743	0.458	=				
bdRaboh NR et al 2013 I-Janabi AM et al 2015	1.027	0.931	1.133	0.533	0.594	1				
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004	1.027 1.042	0.931 0.945	1.133 1.148	0.533 0.827	0.594 0.408					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005	1.027 1.042 1.038	0.931 0.945 0.942	1.133 1.148 1.144	0.533 0.827 0.757	0.594 0.408 0.449					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001	1.027 1.042 1.038 1.047	0.931 0.945 0.942 0.950	1.133 1.148 1.144 1.155	0.533 0.827 0.757 0.928	0.594 0.408 0.449 0.354					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006	1.027 1.042 1.038 1.047 1.064	0.931 0.945 0.942 0.950 0.959	1.133 1.148 1.144 1.155 1.182	0.533 0.827 0.757 0.928 1.169	0.594 0.408 0.449 0.354 0.242					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016	1.027 1.042 1.038 1.047 1.064 1.040	0.931 0.945 0.942 0.950 0.959 0.944	1.133 1.148 1.144 1.155 1.182 1.182	0.533 0.827 0.757 0.928 1.169 0.791	0.594 0.408 0.449 0.354 0.242 0.429					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006	1.027 1.042 1.038 1.047 1.064	0.931 0.945 0.942 0.950 0.959	1.133 1.148 1.144 1.155 1.182	0.533 0.827 0.757 0.928 1.169	0.594 0.408 0.449 0.354 0.242					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016	1.027 1.042 1.038 1.047 1.064 1.040	0.931 0.945 0.942 0.950 0.959 0.944	1.133 1.148 1.144 1.155 1.182 1.182	0.533 0.827 0.757 0.928 1.169 0.791	0.594 0.408 0.449 0.354 0.242 0.429					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005	1.027 1.042 1.038 1.047 1.064 1.040 1.069	0.931 0.945 0.942 0.950 0.959 0.944 0.966	1.133 1.148 1.144 1.155 1.182 1.182 1.146 1.183	0.533 0.827 0.757 0.928 1.169 0.791 1.281	0.594 0.408 0.449 0.354 0.242 0.429 0.200					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 rank B et al 2005	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512	0.594 0.408 0.449 0.354 0.242 0.429 0.200 0.609					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 rank B et al 2005 ENICA et al 2010 ishida A et al 2002	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595	0.594 0.408 0.449 0.354 0.242 0.429 0.200 0.609 0.552					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 rank B et al 2005 ENICA et al 2010 ishida A et al 2012 allel et al 2010	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035 1.047 1.038	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.950 0.942	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746	0.594 0.408 0.354 0.242 0.220 0.200 0.609 0.552 0.354 0.456					
bdRaboh NR et al 2013 -Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 amusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2005 ENICA et al 2010 shida A et al 2010 amali-Sarvestani E et al 2004	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035 1.047 1.038 1.045	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.923 0.950 0.942 0.948	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.151	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746 0.882	0.594 0.408 0.449 0.354 0.242 0.242 0.200 0.609 0.552 0.354 0.456 0.378					
bdRaboh NR et al 2013 -Janabi AM et al 2015 sisik E et al 2004 h J et al 2005 axter SW et al 2001 anusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 Tank B et al 2005 ENICA et al 2010 shida A et al 2020 allel I et al 2010 amali-Sarvestani E et al 2004 ara N et al 2010	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035 1.047 1.038 1.045 1.039	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.923 0.950 0.942 0.948 0.943	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.151 1.145	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.595 0.926 0.746 0.882 0.769	0.594 0.408 0.344 0.354 0.242 0.429 0.200 0.609 0.552 0.354 0.456 0.378 0.378					
bdRaboh NR et al 2013 -Janabi AM et al 2015 visik E et al 2004 h HJ et al 2005 axter SW et al 2001 anusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2005 ENICA et al 2005 ank B et al 2005 allel I et al 2010 amali-Sarvestani E et al 2004 ara N et al 2010 shava C et al (a) Caucasian 2001	1.027 1.042 1.038 1.047 1.064 1.040 1.040 1.026 1.035 1.047 1.038 1.045 1.039 1.040	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.923 0.950 0.942 0.948 0.943 0.944	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.151 1.145 1.145	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746 0.882 0.769 0.793	0.594 0.408 0.449 0.354 0.242 0.200 0.609 0.552 0.354 0.354 0.354 0.354 0.378 0.378 0.442					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2006 amillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2010 ishida A et al 2010 allel I et al 2010 amali-Sarvestani E et al 2004 ara N et al 2010 eshava C et al (a) Caucasian 2001 eshava C et al (c) Latinos 2001	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035 1.047 1.035 1.047 1.038 1.045 1.039 1.040 1.040	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.950 0.942 0.948 0.943 0.944 0.943	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.154 1.151 1.145 1.145 1.147 1.146	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746 0.882 0.769 0.793 0.785	0.594 0.408 0.354 0.242 0.200 0.609 0.552 0.354 0.456 0.378 0.378 0.378 0.442 0.427 0.433					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 rank B et al 2005 ENICA et al 2010 amali-Sarvestani E et al 2004 ara N et al 2010 eshava C et al (c) Latinos 2001 es C et al 2008	1.027 1.042 1.038 1.047 1.064 1.040 1.069 1.026 1.035 1.047 1.038 1.047 1.038 1.049 1.040 1.040 1.040	0.931 0.945 0.942 0.950 0.950 0.944 0.966 0.929 0.923 0.950 0.942 0.942 0.943 0.944 0.943 0.944	1.133 1.148 1.144 1.155 1.185 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.154 1.143 1.145 1.145 1.147 1.146 1.149	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.595 0.926 0.746 0.882 0.746 0.882 0.799 0.793 0.785 0.832	0.594 0.409 0.449 0.354 0.422 0.200 0.609 0.552 0.354 0.456 0.378 0.442 0.427 0.433 0.405					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2005 ENICA et al 2005 esitida A et al 2002 allel I et al 2010 amali-Sarvestani E et al 2004 ara N et al 2010 eshava C et al (a) Caucasian 2001 eshava C et al (c) Latinos 2001 ae SC et al 2008 illikan R et al (a) African -American 2003	1.027 1.042 1.038 1.047 1.064 1.040 1.026 1.026 1.035 1.047 1.038 1.045 1.039 1.040 1.040 1.042 1.038	0.931 0.945 0.942 0.950 0.950 0.944 0.966 0.929 0.923 0.942 0.948 0.943 0.944 0.943 0.944 0.943 0.944 0.943	1.133 1.148 1.144 1.155 1.185 1.146 1.183 1.161 1.154 1.143 1.151 1.145 1.145 1.145 1.146 1.149 1.143	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746 0.882 0.769 0.793 0.793 0.832 0.746	0.594 0.408 0.449 0.354 0.242 0.200 0.609 0.552 0.354 0.456 0.378 0.442 0.427 0.433 0.405 0.456					
bdRaboh NR et al 2013 Janabi AM et al 2015 sisik E et al 2004 h H J et al 2005 axter SW et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ank B et al 2005 ENICA et al 2010 Ishida A et al 2010 anali-Sarvestani E et al 2004 ara N et al 2010 sshava C et al (a) Caucasian 2001 sshava C et al (c) Latinos 2001 se SC et al 2008 illikan R et al (a) African -American 2003 illikan R et al (a) (b) Whites 2003	1.027 1.042 1.038 1.047 1.064 1.040 1.026 1.035 1.047 1.038 1.040 1.040 1.040 1.042 1.038 1.047	0.931 0.945 0.942 0.950 0.959 0.924 0.923 0.920 0.942 0.944 0.943 0.944 0.943 0.944 0.943 0.944 0.943 0.944 0.942 0.942	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.151 1.143 1.151 1.145 1.147 1.146 1.147 1.146 1.143 1.159	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.595 0.926 0.746 0.793 0.785 0.825 0.746 0.7746 0.880	0.594 0.408 0.354 0.242 0.200 0.552 0.354 0.456 0.378 0.378 0.378 0.433 0.433 0.433 0.435 0.339					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2005 ENICA et al 2010 sihida A et al 2020 allel I et al 2010 ara N et al 2010 eshava C et al (a) Caucasian 2001 eshava C et al (a) Caucasian 2001 eshava C et al (a) African -American 2003 illikan R et al (a) Africas 2003 antigometry KG et al 2003	1.027 1.042 1.038 1.047 1.064 1.040 1.026 1.035 1.047 1.038 1.047 1.040 1.040 1.040 1.042 1.038 1.047 1.025	0.931 0.945 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.923 0.942 0.948 0.943 0.944 0.943 0.944 0.943 0.946 0.942	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.154 1.145 1.147 1.146 1.149 1.149 1.149 1.159 1.130	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.595 0.926 0.746 0.882 0.769 0.785 0.832 0.785 0.832 0.785 0.832	0.594 0.409 0.449 0.354 0.422 0.200 0.609 0.552 0.354 0.456 0.378 0.442 0.427 0.433 0.405 0.433 0.405 0.433 0.405 0.623					
bdRaboh NR et al 2013 I-Janabi AM et al 2015 kisik E et al 2004 n HJ et al 2005 axter SW et al 2001 enusiglio PR et al 2006 arrillo-Moreno DI et al 2016 ox DG et al 2005 ENICA et al 2005 ENICA et al 2005 ENICA et al 2005 anal E al 2002 allel I et al 2010 aran N et al 2010 eshava C et al (a) Caucasian 2001 eshava C et al (a) African -American 2003 illilkan R et al (b) Whites 2003 ontgomery KG et al 2003	$\begin{array}{c} 1.027\\ 1.042\\ 1.034\\ 1.047\\ 1.064\\ 1.040\\ 1.026\\ 1.035\\ 1.047\\ 1.038\\ 1.045\\ 1.045\\ 1.045\\ 1.045\\ 1.045\\ 1.042\\ 1.038\\ 1.042\\ 1.038\\ 1.042\\ 1.038\\ 1.042\\ 1.025\\ 1.038\\ \end{array}$	0.931 0.945 0.942 0.959 0.959 0.944 0.966 0.923 0.950 0.942 0.948 0.948 0.944 0.943 0.944 0.943 0.946 0.942 0.946 0.929 0.929	$\begin{array}{c} 1.133\\ 1.148\\ 1.148\\ 1.145\\ 1.155\\ 1.182\\ 1.146\\ 1.183\\ 1.133\\ 1.161\\ 1.154\\ 1.145\\ 1.151\\ 1.145\\ 1.147\\ 1.146\\ 1.149\\ 1.143\\ 1.159\\ 1.130\\ 1.130\end{array}$	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.926 0.726 0.746 0.882 0.746 0.882 0.793 0.785 0.832 0.746 0.880 0.492 0.750	0.594 0.408 0.449 0.354 0.242 0.200 0.552 0.354 0.456 0.378 0.456 0.456 0.427 0.433 0.405 0.427 0.433 0.405 0.455 0.379 0.623 0.453					
bdRaboh NR et al 2013 Janabi AM et al 2015 sisik E et al 2004 In HJ et al 2005 axter SW et al 2001 anusiglio PR et al 2006 arrillo-Moreno DI et al 2016 xo DG et al 2005 shuña A et al 2005 ENICA et al 2010 anali-Sarvestani E et al 2004 ara N et al 2010 sshava C et al (a) Caucasian 2001 sshava C et al (a) African -American 2003 illikan R et al (b) Whites 2003 ontgomery KG et al 2008 utuhan H et al 2008 aldu R et al 2008	$\begin{array}{c} 1.027\\ 1.042\\ 1.038\\ 1.047\\ 1.064\\ 1.040\\ 1.069\\ 1.026\\ 1.038\\ 1.047\\ 1.038\\ 1.047\\ 1.038\\ 1.040\\ 1.040\\ 1.040\\ 1.042\\ 1.038\\ 1.047\\ 1.028\\ 1.037\\ \end{array}$	0.931 0.942 0.942 0.950 0.959 0.944 0.966 0.929 0.923 0.943 0.948 0.943 0.944 0.943 0.944 0.944 0.944 0.946 0.942 0.942 0.941	1.133 1.148 1.144 1.155 1.182 1.146 1.183 1.133 1.161 1.154 1.143 1.151 1.145 1.147 1.146 1.143 1.149 1.143 1.159 1.130	0.533 0.827 0.757 0.928 1.169 0.791 1.281 0.512 0.926 0.746 0.882 0.769 0.793 0.785 0.832 0.746 0.880 0.746 0.880 0.492 0.750	0.594 0.408 0.449 0.354 0.242 0.200 0.552 0.354 0.456 0.378 0.456 0.378 0.433 0.433 0.433 0.455 0.379 0.623 0.379 0.623 0.460					
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Figure 14. Sensitivity analysis: Sensitivity analysis with each study removal showing no effect on odds ratio (OR) in genotypic (Heterozygous: Ile-Val vs Ile-Ile and Recessive: Val-Val vs Ile-Ile + Ile-Val) analysis models of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism.

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in other languages except English, (b) studies having only case samples, (c) representing risk of other cancers, (d) without genotypic distribution and allele frequency data and (e) reviews and abstracts.

Data extraction. The data extraction was performed by three independent authors (BMK, SC & DRM) independently and the disagreement about the studies between the authors was resolved and came to a conclusion by conducting a group discussion within the authors. We followed previously established data form to extract the data from the studies and the following data was extracted from each article: first author's name, year

Study name	Statistics with study removed						Odds ratio (95% CI) with study removed					
/al-Val + lle-Val vs. lle -lle	Point	Lower limit	Upper limit	Z-Value	p-Value							
AbdRaboh NR et al 2013	1.116	1.029	1.210	2.657	0.008	1	- I			1	1	
Al-Janabi AM et al 2015	1.109	1.023	1.202	2.518	0.012							
Akisik E et al 2004	1.130	1.040	1.228	2.883	0.004							
An HJ et al 2005	1.133	1.042	1.231	2.935	0.003							
Baxter SW et al 2001	1.140	1.050	1.239	3,105	0.002							
Benusiglio PR et al 2006	1.140	1.044	1.245	2.911	0.004							
Carrillo-Moreno DI et al 2016	1.116	1.028	1.211	2.630	0.009							
Cox DG et al 2005	1.142	1.047	1.245	3.010	0.003							
rank B et al 2005	1.133	1.040	1.233	2.872	0.004							
GENICA et al 2010	1.144	1.052	1.245	3.151	0.002							
Hishida A et al 2002	1.135	1.044	1.234	2.982	0.003							
Kalemi TG et al 2005	1.131	1.041	1.228	2.914	0.004							
Kallel I et al 2010	1.136	1.046	1.233	3.030	0.002							
Kamali-Sarvestani E et al 2004	1.127	1.037	1.225	2.816	0.005							
Kara N et al 2010	1.133	1.042	1.232	2.932	0.003							
Keshava C et al (a) Caucasian 2001	1.125	1.035	1.222	2.778	0.005							
Keshava C et al (b) African -American 2001	1.129	1.040	1.226	2.889	0.004							
(eshava C et al (c) Latinos 2001	1.122	1.034	1.217	2.750	0.006							
ee SC et al 2008	1.117	1.029	1.213	2.647	0.008							
/illikan R et al (a) African -American 2003	1.123	1.033	1.220	2.720	0.007							
/illikan R et al (b) Whites 2003	1.136	1.042	1.239	2.889	0.004							
Montgomery KG et al 2003	1.119	1.030	1.216	2.661	0.008							
Mutluhan H et al 2008	1.127	1.037	1.225	2.809	0.005							
laidu R et al 2008	1.118	1.030	1.213	2.659	0.008							
Velson SE et al 2005	1.141	1.047	1.243	3.017	0.003							
Dzturk O et al 2013	1.112	1.026	1.204	2.579	0.010							
Papadopoulou E et al 2007	1.120	1.033	1.216	2.729	0.006							
Parvin S et al 2016	1.117	1.029	1.212	2.632	0.008							
Pinto D et al 2004	1.110	1.024	1.202	2.549	0.011							
Qu S et al 2008	1.145	1.049	1.249	3.031	0.002							
Rajkumar T et al 2008	1.132	1.041	1.232	2.893	0.004							
Sezgin E et al 2011	1.132	1.043	1.229	2.956	0.003							
Siddig A et al 2008	1.120	1.032	1.214	2.731	0.006							
Tommasi S et al 2007	1.123	1.033	1.221	2.734	0.006							
Vang-Gohrke S et al 2001	1.133	1.040	1.234	2.859	0.004							
Vatrowski R et al 2015	1.130	1.040	1.228	2.887	0.004							
Kie D et al 2000	1.118	1.029	1.214	2.648	0.008							
ÚBOR P et al 2006	1.115	1.029	1.208	2.655	0.008							
Combined	1.127	1.038	1.223	2.856	0.004				•			
						0.1	0.2	0.5	1	2	5	
						←						

Figure 15. Sensitivity analysis: Sensitivity analysis showing no effect of single study on OR of genotypic (Dominant: Val-Val + Ile-Val vs Ile-Ile) analysis model of *Her2* ^{Ile}655^{Val} (rs1136201) gene polymorphism.

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of publication, country, ethnicity, number of case and control samples, genotype distribution, allele frequency for each case and control.

Meta-analysis. The current meta-analysis was performed using comprehensive meta-analysis version 3 software (CMA v3) https://www.meta-analysis.com/pages/comparisons.php. CMA v3 is a powerful tool to analyze and has several advantages over other software available for computational meta-analysis. Combined odds ratio with 95% CI was calculated and was taken into consideration to apprise the association of *Her2* polymorphism with breast cancer risk. Chi-Squared based Q test was performed to analyze the heterogeneity and p-value < 0.05 was considered as significant. In case of no significant heterogeneity fixed effect model was used to assess the combined OR. In contrast, Random effect model was considered to calculate the combined odds ratio with 95% CI among the studies. I² statistics was used to quantify inter study variability, greater I² value depicts greater degree of heterogeneity. Publication bias was examined using Begg's funnel plot. Egger's linear regression test was employed to analyze and measure the asymmetry of Begg's funnel plot and the significance of intercept was assessed by t-test. Intercept considering p-value < 0.05 was considered as significant and the publication bias was reduced using "trim and fill" method.

Availability of data and materials. All those named as authors confirmed the availability of data and materials.

References

- Torre, L. A. *et al.* Global cancer statistics, 2012. *CA: a cancer journal for clinicians* 65, 87–108, https://doi.org/10.3322/caac.21262 (2015).
 https://www.cancer.org/cancer/breast-cancer.html.
- Lewis-Wambi, J. S. & Jordan, V. C. Treatment of Postmenopausal Breast Cancer with Selective Estrogen Receptor Modulators (SERMs). Breast disease 24, 93–105 (2005).
- 4. Slamon, D. J. *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235, 177–182 (1987).
- Olayioye, M. A. Update on HER-2 as a target for cancer therapy: intracellular signaling pathways of ErbB2/HER-2 and family members. Breast cancer research: BCR 3, 385–389 (2001).
- Moasser, M. M. The oncogene. HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene 26, 6469–6487, https://doi.org/10.1038/sj.onc.1210477 (2007).
- Citri, A. & Yarden, Y. EGF-ERBB signalling: towards the systems level. Nature reviews. Molecular cell biology 7, 505–516, https://doi. org/10.1038/nrm1962 (2006).
- Slichenmyer, W. J. & Fry, D. W. Anticancer therapy targeting the erbB family of receptor tyrosine kinases. Seminars in oncology 28, 67–79 (2001).

- Schmidt, M. et al. Long-term prognostic significance of HER-2/neu in untreated node-negative breast cancer depends on the method of testing. Breast cancer research: BCR 7, R256–266, https://doi.org/10.1186/bcr991 (2005).
- Ross, J. S. & Fletcher, J. A. The HER-2/neu Oncogene in Breast Cancer: Prognostic Factor, Predictive Factor, and Target for Therapy. Theoncologist 3, 237–252 (1998).
- Okines, A., Cunningham, D. & Chau, I. Targeting the human EGFR family in esophagogastric cancer. Nature reviews. Clinical oncology 8, 492–503, https://doi.org/10.1038/nrclinonc.2011.45 (2011).
- Casalini, P., Iorio, M. V., Galmozzi, E. & Menard, S. Role of HER receptors family in development and differentiation. *Journal of cellular physiology* 200, 343–350, https://doi.org/10.1002/jcp.20007 (2004).
- Feng, T. et al. Growth factor progranulin promotes tumorigenesis of cervical cancer via PI3K/Akt/mTOR signaling pathway. Oncotarget 7, 58381–58395, https://doi.org/10.18632/oncotarget.11126 (2016).
- Henson, E. S. & Gibson, S. B. Surviving cell death through epidermal growth factor (EGF) signal transduction pathways: implications for cancer therapy. *Cellular signalling* 18, 2089–2097, https://doi.org/10.1016/j.cellsig.2006.05.015 (2006).
- Leicht, D. T. et al. Raf kinases: function, regulation and role in human cancer. Biochimica et biophysica acta 1773, 1196–1212, https:// doi.org/10.1016/j.bbamcr.2007.05.001 (2007).
- English, D. P., Roque, D. M. & Santin, A. D. HER2 expression beyond breast cancer: therapeutic implications for gynecologic malignancies. Molecular diagnosis & therapy 17, 85–99, https://doi.org/10.1007/s40291-013-0024-9 (2013).
- 17. Carter, P. et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. Proceedings of the National Academy of Sciences of the United States of America 89, 4285-4289 (1992).
- Molina, M. A. et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer research 61, 4744–4749 (2001).
- Nahta, R. & Esteva, F. J. Trastuzumab: triumphs and tribulations. Oncogene 26, 3637–3643, https://doi.org/10.1038/sj.onc.1210379 (2007).
- Cobleigh, M. A. et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 17, 2639–2648, https://doi.org/10.1200/JCO.1999.17.9.2639 (1999).
- Lemieux, J. et al. Alcohol and HER2 polymorphisms as risk factor for cardiotoxicity in breast cancer treated with trastuzumab. Anticancer research 33, 2569–2576 (2013).
- 22. Roca, 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 research and treatment* **139**, 789–800, https://doi.org/10.1007/s10549-013-2587-x (2013).
- Hashemi, M. et al. Association between single nucleotide polymorphism in miR-499, miR-196a2, miR-146a and miR-149 and prostate cancer risk in a sample of Iranian population. Journal of advanced research 7, 491–498, https://doi.org/10.1016/j. jare.2016.03.008 (2016).
- Nahon, P. & Zucman-Rossi, J. Single nucleotide polymorphisms and risk of hepatocellular carcinoma in cirrhosis. *Journal of hepatology* 57, 663–674, https://doi.org/10.1016/j.jhep.2012.02.035 (2012).
- Multani, S. & Saranath, D. Genotypic distribution of single nucleotide polymorphisms in oral cancer: global scene. *Tumourbiology:* the journal of the International Society for Oncodevelopmental Biology and Medicine **37**, 14501–14512, https://doi.org/10.1007/ s13277-016-5322-5 (2016).
- AbdRaboh, N. R., Shehata, H. H., Ahmed, M. B. & Bayoumi, F. A. HER1 R497K and HER2 I655V polymorphisms are linked to development of breast cancer. Disease markers 34, 407–417, https://doi.org/10.3233/DMA-130989 (2013).
- Akisik, E. & Dalay, N. Estrogen receptor codon 594 and HER2 codon 655 polymorphisms and breast cancer risk. Experimental and molecular pathology 76, 260–263, https://doi.org/10.1016/j.yexmp.2003.12.005 (2004).
- An, H. J. et al. Her2 genotype and breast cancer progression in Korean women. Pathology international 55, 48–52, https://doi. org/10.1111/j.1440-1827.2005.01789.x (2005).
- Baxter, S. W. & Campbell, I. G. Re: Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. Journal of the National Cancer Institute 93, 557–559 (2001).
- Benusiglio, P. R. et al. Common ERBB2 polymorphisms and risk of breast cancer in a white British population: a case-control study. Breast cancer research: BCR 7, R204–209, https://doi.org/10.1186/bcr982 (2005).
- Cox, D. G., Hankinson, S. E. & Hunter, D. J. The erbB2/HER2/neu receptor polymorphism Ile655Val and breast cancer risk. Pharmacogenetics and genomics 15, 447–450 (2005).
- Frank, B. et al. The rare ERBB2 variant Ile654Val is associated with an increased familial breast cancer risk. Carcinogenesis 26, 643–647, https://doi.org/10.1093/carcin/bgh342 (2005).
- Hishida, A. et al. Re: Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. Journal of the National Cancer Institute 94, 1807–1808 (2002).
- 34. Kalemi, T. G. et al. The association of p53 mutations and p53 codon 72, Her 2 codon 655 and MTHFR C677T polymorphisms with breast cancer in Northern Greece. Cancer letters 222, 57–65, https://doi.org/10.1016/j.canlet.2004.11.025 (2005).
- Kallel, I. et al. HER2 polymorphisms and breast cancer in Tunisian women. Genetic testing and molecular biomarkers 14, 29–35, https://doi.org/10.1089/gtmb.2009.0069 (2010).
- Kamali-Sarvestani, E., Talei, A. R. & Merat, A. Ile to Val polymorphism at codon 655 of HER-2 gene and breast cancer risk in Iranian women. *Cancer letters* 215, 83–87, https://doi.org/10.1016/j.canlet.2004.04.007 (2004).
- Kara, N. et al. P53 codon 72 and HER2 codon 655 polymorphisms in Turkish breast cancer patients. DNA and cell biology 29, 387–392, https://doi.org/10.1089/dna.2009.0995 (2010).
- Keshava, C., McCanlies, E. C., Keshava, N., Wolff, M. S. & Weston, A. Distribution of *HER2*(V655) genotypes in breast cancer cases and controls in the United States. *Cancer letters* 173, 37–41 (2001).
- Lee, S. C. et al. A case-control study of the HER2 Ile655Val polymorphism and risk of breast cancer in Taiwan. Clinical biochemistry 41, 121–125, https://doi.org/10.1016/j.clinbiochem.2007.11.005 (2008).
- Millikan, R. et al. HER2 codon 655 polymorphism and risk of breast cancer in African Americans and whites. Breast cancer research and treatment 79, 355–364 (2003).
- Montgomery, K. G. *et al.* The HER2 I655V polymorphism and risk of breast cancer in women age 40 years. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. *Oncology* 12, 1109–1111 (2003).
- Mutluhan, H. *et al.* The influence of *HER2* genotypes as molecular markers on breast cancer outcome. *DNA and cell biology* 27, 575–579, https://doi.org/10.1089/dna.2007.0702 (2008).
- Naidu, R., Yip, C. H. & Taib, N. A. 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 55, 87–95 (2008).
- Nelson, S. E., Gould, M. N., Hampton, J. M. & Trentham-Dietz, A. A case-control study of the HER2 Ile655Val polymorphism in relation to risk of invasive breast cancer. Breast cancer research: BCR 7, R357–364, https://doi.org/10.1186/bcr1004 (2005).
- Ozturk, O. et al. HER2 Ile655Val and PTEN IVS4 polymorphisms in patients with breast cancer. Molecular biology reports 40, 1813–1818, https://doi.org/10.1007/s11033-012-2235-2 (2013).

- 46. Papadopoulou, 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* 54, 365–373 (2007).
- Parvin, S. et al. Association of BRCA1, BRCA2, RAD51, and HER2 gene polymorphisms with the breast cancer risk in the Bangladeshi population. Breast cancer 24, 229–237, https://doi.org/10.1007/s12282-016-0692-5 (2017).
- Pinto, D. et al. HER2 polymorphism and breast cancer risk in Portugal. European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation 13, 177–181 (2004).
- Qu, S. et al. ERBB2 genetic polymorphism and breast cancer risk in Chinese women: a population-based case-control study. Breast cancer research and treatment 110, 169–176, https://doi.org/10.1007/s10549-007-9691-8 (2008).
- Rajkumar, T. et al. TGFbeta1 (Leu10Pro), p53 (Arg72Pro) can predict for increased risk for breast cancer in south Indian women and TGFbeta1 Pro (Leu10Pro) allele predicts response to neo-adjuvant chemo-radiotherapy. Breast cancer research and treatment 112, 81–87, https://doi.org/10.1007/s10549-007-9821-3 (2008).
- Risk, M.-G. Co. G. Sf. M. H. T. R. B. C. Polymorphisms in the BRCA1 and ABCB1 genes modulate menopausal hormone therapy associated breast cancer risk in postmenopausal women. *Breast cancer research and treatment* 120, 727–736, https://doi.org/10.1007/ s10549-009-0489-8 (2010).
- Rutter, J. L., Chatterjee, N., Wacholder, S. & Struewing, J. The HER2 I655V polymorphism and breast cancer risk in Ashkenazim. Epidemiology 14, 694–700, https://doi.org/10.1097/01.ede.0000083227.74669.7b (2003).
- Sezgin, E., Sahin, F. I., Yagmurdur, M. C. & Demirhan, B. HER-2/neu gene codon 655 (Ile/Val) polymorphism in breast carcinoma patients. *Genetic testing and molecular biomarkers* 15, 143–146, https://doi.org/10.1089/gtmb.2010.0126 (2011).
- Siddig, A. et al. HER-2/neu Ile655Val polymorphism and the risk of breast cancer. Annals of the New York Academy of Sciences 1138, 84–94, https://doi.org/10.1196/annals.1414.014 (2008).
- Tommasi, S. et al. 655Val and 1170Pro ERBB2 SNPs in familial breast cancer risk and BRCA1 alterations. Cellular oncology: the official journal of the International Society for Cellular Oncology 29, 241–248 (2007).
- Tao, W., Wang, C., Han, R. & Jiang, H. HÉR2 codon 655 polymorphism and breast cancer risk: a meta-analysis. Breast cancer research and treatment 114, 371–376, https://doi.org/10.1007/s10549-008-0010-9 (2009).
- Wang-Gohrke, S. & Chang-Claude, J. Re: Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. Journal of the National Cancer Institute 93, 1657–1659 (2001).
- Wang, H. et al. Polymorphisms of ERBB2 and breast cancer risk: a meta-analysis of 26 studies involving 35,088 subjects. Journal of surgical oncology 108, 337–341, https://doi.org/10.1002/jso.23386 (2013).
- Watrowski, R. et al. HER2 Codon 655 (Ile/Val) Polymorphism and Breast Cancer in Austrian Women. Anticancer research 35, 5901–5904 (2015).
- Xie, D. et al. Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. Journal of the National Cancer Institute 92, 412–417 (2000).
- 61. Zubor, P. *et al.* HER-2 [Ile655Val] polymorphism in association with breast cancer risk: a population-based case-control study in Slovakia. *Neoplasma* 53, 49–55 (2006).
- 62. Chen, W., Yang, H., Tang, W. R., Feng, S. J. & Wei, Y. L. Updated meta-analysis on *HER2* polymorphisms and risk of breast cancer: evidence from 32 studies. *Asian Pacific journal of cancer prevention: APJCP* **15**, 9643–9647 (2014).
- Carpenter, G., King, L. Jr & Cohen, S. Epidermal growth factor stimulates phosphorylation in membrane preparations *in vitro*. *Nature* 276, 409–410 (1978).
- van der Geer, P., Hunter, T. & Lindberg, R. A. Receptor protein-tyrosine kinases and their signal transduction pathways. *Annual review of cell biology* 10, 251–337, https://doi.org/10.1146/annurev.cb.10.110194.001343 (1994).
- Kallioniemi, O. P. et al. ERBB2 amplification in breast cancer analyzed by fluorescence in situ hybridization. Proceedings of the National Academy of Sciences of the United States of America 89, 5321–5325 (1992).
- 66. Lohrisch, C. & Piccart, M. An overview of HER2. Seminars in oncology 28, 3-11 (2001).
- Mimura, K. et al. Frequencies of HER-2/neu expression and gene amplification in patients with oesophageal squamous cell carcinoma. British journal of cancer 92, 1253–1260, https://doi.org/10.1038/sj.bjc.6602499 (2005).
- Molina, M. A. et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer research 61, 4744–4749 (2001).
- 69. Slamon, D. J. et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244, 707-712 (1989).
- Venter, D. J., Tuzi, N. L., Kumar, S. & Gullick, W. J. Overexpression of the c-erbB-2 oncoprotein in human breast carcinomas: immunohistological assessment correlates with gene amplification. *Lancet* 2, 69–72 (1987).
- Yano, T. et al. Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. Oncology reports 15, 65–71 (2006).
- Papewalis, J., Nikitin, A. & Rajewsky, M. F. G to A polymorphism at amino acid codon 655 of the human erbB-2/HER2 gene. Nucleic acids research 19, 5452 (1991).
- Fleishman, S. J., Schlessinger, J. & Ben-Tal, N. A putative molecular-activation switch in the transmembrane domain of erbB2. Proceedings of the National Academy of Sciences of the United States of America 99, 15937–15940, https://doi.org/10.1073/ pnas.252640799 (2002).
- Takano, K. et al. Contribution of hydrophobic residues to the stability of human lysozyme: calorimetric studies and X-ray structural analysis of the five isoleucine to valine mutants. Journal of molecular biology 254, 62–76, https://doi.org/10.1006/jmbi.1995.0599 (1995).
- Stanton, S. E. et al. Pro1170 Ala polymorphism in HER2-neu is associated with risk of trastuzumab cardiotoxicity. BMC cancer 15, 267, https://doi.org/10.1186/s12885-015-1298-6 (2015).
- Mojtahedi, Z. et al. HER2 Ile655Val Single Nucleotide Polymorphism in Patients with OvarianCancer. Iranian Red Crescent medical journal 15, 1–3, https://doi.org/10.5812/ircmj.2173 (2013).
- Tong, S. Y. et al. The effects of obesity and HER-2 polymorphisms as risk factors for endometrial cancer in Korean women. BJOG: an international journal of obstetrics and gynaecology 116, 1046–1052, https://doi.org/10.1111/j.1471-0528.2009.02186.x (2009).
- Frank, B., Hemminki, K. & Burwinkel, B. A bias in genotyping the ERBB2 (HER2) Ile655Val variant. Carcinogenesis 26, 1649, https://doi.org/10.1093/carcin/bgi108 (2005).

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Author Contributions

B.M.K., S.C. and S.K.M. conceived and designed the study. B.M.K., S.C. and D.R.M. searched the suitable case control studies, extracted and analyzed the data. B.M.K., S.C. and A.K.P. performed Comprehensive meta-analysis. S.K.M. analyzed the data and approved the final version of manuscript before publication.

Additional Information

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