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HER2^{Ile655Val} Polymorphism and Risk of Breast Cancer

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Abstract

HER2 plays a vital role in the development and progression of several types of human cancer, so the HER2 becomes one of major targets for HER2-positive breast cancer treatment. Several reports have shown that the HER2 oncogene expression relates to clinicopathological factors in cancer patients. HER2^{Ile655Val} single nucleotide polymorphism associates with malignant tumors, including prostate cancer, colorectal cancer, osteosarcoma, gastric cancer, uterine cervical carcinoma, fibroadenoma, and breast cancer. To understand the precise association, this chapter was described to estimate the association between HER2^{Ile655Val} single nucleotide polymorphism and susceptibility to breast cancer. Our findings suggest that the Val allele in HER2 codon 655 single nucleotide polymorphism is strongly associated with the risk of breast cancer. HER2^{Ile655Val} single nucleotide polymorphism might also be a susceptibility factor that favors early-onset breast cancer.

Keywords: single nucleotide polymorphism (SNP), HER2^{Ile655Val}, rs1136201, breast cancer, early-onset, meta-analysis

1. Introduction

Breast cancer is the most common cancer among women, increasing incidence in most countries, representing a public health threat [1, 2]. Breast cancer is considered the leading cause of women's deaths worldwide [3]. More than two million were newly diagnosed with breast cancer in women worldwide in 2018 [3, 4]. There will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. In the United States, breast cancer caused 42,000 deaths in 2017 [5]. There is a link with aging, especially among women aged 45 to 65, and it is increasing among younger women [6–8].

Human epidermal growth factor receptor 2 (HER2), also known as c-erbB2 and neu, is located on human chromosome 17q21 and is responsible for encoding a 185-kDa cross-membrane glycoprotein receptor. HER2 belongs to the ErbB family of growth factor receptors with intrinsic tyrosine kinase activity. The members of this family take the form of homodimer and heterodimer when activated via cell growth, specifically chemical and invasion [9, 10]. HER2 overexpression is seen in breast cancer, gastric cancer, and ovarian cancer [11]. HER2-targeted therapies have significantly enhanced HER2-positive breast cancer patients [12, 13]. Targets in downstream or resistant pathways of particular interest in HER2-positive breast

cancer include mTOR, PI3K, IGF-1R, Akt, HSP90, and VEGF that allow cell development, survival, and differentiation [14–17].

Several studies have independently discovered the association between HER2^{Ile655Val} single nucleotide polymorphism and different benign and malignant tumors. The association between HER2^{Ile655Val} SNP and the risk of breast cancer, especially early-onset breast cancer, has also been investigated; however, these results are inconclusive and controversial. Several articles have shown the association of HER2^{Ile655Val} SNP with an increased risk of early-onset breast cancer in Chinese, Australian, and Taiwanese women [18–21]. Nonetheless, the association has not been observed in other studies [22–24]. In the present chapter, we aimed to obtain a more reliable estimate of the association between HER2^{Ile655Val} SNP and the risk of breast cancer and susceptibility to early-onset breast cancer.

2. The role of HER2 in breast cancer

The proto-oncogene HER2/neu (C-erbB-2) has been localized to chromosome 17q21.1 and encodes a transmembrane tyrosine kinase growth factor receptor [25]. HER2 (human epidermal growth factor receptor 2) is a member of the epidermal growth factor receptor family, encodes a 185 kDa transmembrane glycoprotein with tyrosine kinase activity [26]. Most studies on HER2 found this gene was involved in inducing mammary carcinogenesis. HER2/neu gene amplification has been associated with the development of breast cancer [27].

HER2 is one of the biomarkers that play an essential role in breast cancer classification. Based on ER, PR, HER2, Ki-67 marker, breast cancer can be divided into five groups: Luminal A (ER+ or PR+; HER2-; Ki67 low), Luminal B HER2-negative (ER+ or PR+; HER2-; Ki67 high), Luminal B HER2-positive (ER+ or PR+; HER2+; Ki67 any), HER2-overexpression (ER-; PR-; HER2+; Ki67 any), Triple-negative (ER-; PR-; HER2-; Ki67 any) [28]. In addition, classification based on HER2 expression provides enhanced and essential therapeutic guidance [29]. Patients with subtype absence HER2 expression will have a poor prognosis and not receive the most benefit from chemotherapy [30].

HER2 is a human epidermal growth factor receptor (HER/EGFR/ERBB) family member. The basic structure of the epidermal growth factor receptor was described in **Figure 1**. In the extracellular domain, LD1 and LD2 are two repeated ligand-binding domains. CR1 and CR2 are two repeated cysteine-rich regions. TM indicates the short transmembrane spanning sequences. In the intracellular domain, TK is a catalytic tyrosine kinase, and CT is the carboxyl-terminal tail. Circled Ps are the phosphorylation sites within the TK and CT regions [31].

Schematic diagram of HER2 signaling pathways is shown in **Figure 1**. Upon ligand binding, dimerization between receptors of the EGFR family and HER2 receptor is induced. The homodimers or heterodimers after that, stimulate a serial of signaling cascades. Among various signaling pathways, the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways are the two major and most studied pathways which take a pivotal role in tumor proliferation and anti-apoptosis. The whole signal transduction process can be divided into three sections: signal input (ligand-binding and dimerization), signal processing (a series of signaling cascades), and signal output (corresponding cellular processes) [31].

HER2 molecular pathways approach for HER2-targeted therapeutic strategies have the potential to adopt the HER2 overexpression tumor cells. Drugs targeting HER2 may include monoclonal antibodies that downregulate HER2 expression by binding to the extracellular domain (such as Trastuzumab, Pertuzumab ...), small

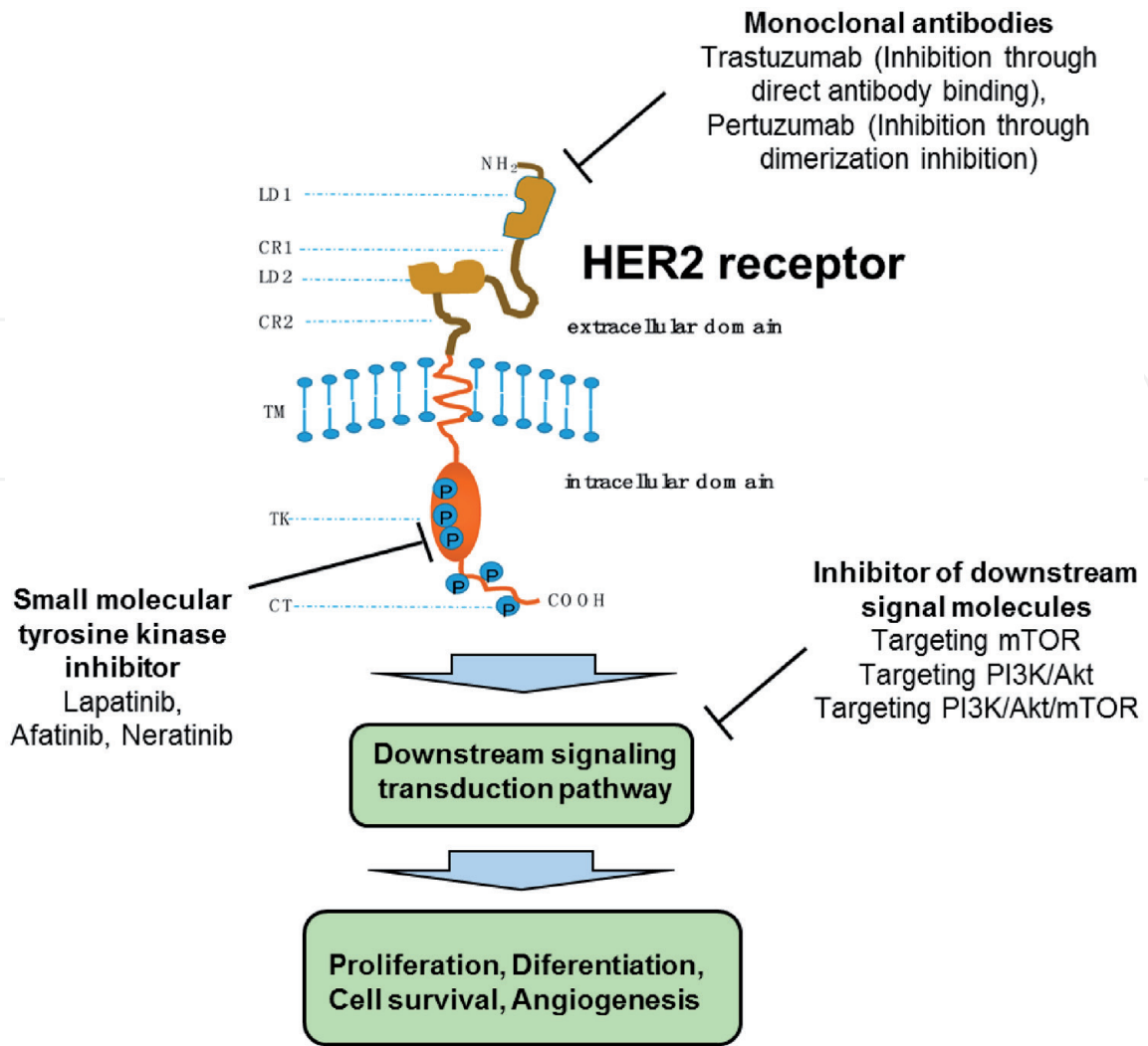


Figure 1.
HER2 molecular pathways approaches for HER2 positive breast cancer therapy (modified from Lv et al. 2016) [31].

molecular tyrosine kinase inhibitors (Lapatinib, Afatinib, Neratinib ...), which compete for ATP-binding to block HER2 signaling, antibody-drug conjugates (such as trastuzumab emtansine, called T-DM1), heat shock protein 90 inhibitors (hsp90) and inhibitors of downstream signal molecules (Targeting mTOR, PI3K/Akt ...) (Figure 1) [31, 32].

HER2 amplified or overexpressed in approximately 15–20% of breast cancer and associated with the aggressive clinical feature of absence therapy [33–35]. The IHC method of HER2 protein detection is advantageous, convenient, inexpensive, and only requires conventional microscopy. However, the results may be influenced by the time and the fixation protocol, the antibody clone, and it is challenging to apply the score sheet to have accurate conclusions. Therefore, for an ambiguous result obtained by immunohistochemical staining, the actual state of HER2 gene amplification should be assessed by performing fluorescent in situ hybridization (FISH) or dual chromogenic in-situ hybridization (DISH) because of its high accuracy and reliability, although expensive [36]. HER2 gene amplification and protein overexpression are important not only as a prognostic factor but also as a predictive clinical response to anti-HER2 therapeutic [37, 38]. Moreover, overall survival in patients treating with HER2-targeted therapy was higher than in patients without treatment [39].

The correlation between HER2 gene expression and breast cancer is not clear. According to most studies, it is thought that HER2 overexpression is a poor

prognostic factor [40]. The breast cancer parameters such as lymph node metastases, tumor grade, cell proliferation were reported that associated with the gene expression of HER2 [41, 42]. In the initial reports, HER2/neu amplification was a significant predictor of early relapse and death in breast cancer. HER2 gene amplification has a significant predictor of both disease-free survival and time to relapse in breast cancer patients [43, 44]. However, several authors demonstrated that amplification of the HER2 gene relate to ER, PR status but not correlate with age, tumor size, and lymph node [45].

3. HER2^{Ile655Val} single nucleotide polymorphism

Several studies have independently discovered the association between HER2^{Ile655Val} SNP and different types of benign and malignant tumors, including breast cancer, prostate cancer, colorectal cancer, osteosarcoma, gastric cancer, uterine cervical carcinoma, and fibroadenoma [46–53]. Riaz et al. conducted meta-analysis research and concluded that HER2^{Ile655Val} SNP is significantly correlated with six significant types of cancer (breast, ovarian, uterine, lung, thyroid, and gastric), suggesting that carriers of the Val allele and Val/Val genotype may be linked with an elevated risk of these cancers [54].

Single nucleotide polymorphisms residing in regulatory or functionally relevant gene regions may affect protein function [55]. HER2^{Ile655Val} SNP has been identified in the transmembrane domain-coding region of the HER2 gene at codon 655, encoding either isoleucine (Ile: ATC) or valine (Val: GTC) [53, 56]. Substitution of these two amino acids can alter the hydrophobicity of proteins, affecting the shape stability of the regions in the protein [57, 58]. Fleishman et al. found that substitution of Val for Ile in this position of the transmembrane region will destabilize the formation of active HER2 dimers, leading to reduced receptor activation and tyrosine kinase activity, even under conditions of HER2 overexpression [59]. The association between the HER2^{Ile655Val} SNP and the risk of breast cancer has been widely investigated in populations worldwide [18, 19, 23, 24, 53, 55, 60–92].

4. HER2^{Ile655Val} single nucleotide polymorphism contributes to breast cancer risk

Previous meta-analyses by Tao W et al. 2009 [93], Lu S et al. 2010 [94], Wang H et al. 2013 [95], Chen W et al. 2014 [47], and Krishna BM et al. 2018 [96] found that HER2^{Ile655Val} SNP is associated significantly with an increased risk of breast cancer, particularly in young women. However, a meta-analysis by Ma Y et al. 2011 revealed that HER2^{Ile655Val} SNP is not associated with breast cancer susceptibility [97].

Our recent meta-analyses further demonstrate the potential contribution of HER2^{Ile655Val} single nucleotide polymorphism to the oncogenesis of breast cancer [98]. The meta-analysis showed that the HER2 codon 655 Val allele was significantly associated with an increased risk of breast cancer in an allele genetic model (additive model, RR 1.21, 95% CI 1.07–1.36; $I^2 = 61.0\%$; $n = 16$). There was a 21% significant increase in the risk of breast cancer in subjects who were Val carriers (Ile/Val and Val/Val) (dominant model, RR 1.21, 95% CI 1.06–1.38; $I^2 = 58.0\%$; $n = 16$). The recessive model HER2 codon 655 was not associated with the risk of breast cancer (RR 1.26, 95% CI 0.99–1.60; $I^2 = 23.6\%$; $n = 15$). There was publication bias in the studies (Begg's funnel plot was symmetric; additive model, Egger's test $t = 5.44$, P for bias = 0.000, $n = 16$; dominant model, Egger's test $t = 4.92$, P for bias = 0.000, $n = 16$; recessive model, Egger's test $t = 4.35$, P for bias = 0.001, $n = 15$) (**Figure 2**).

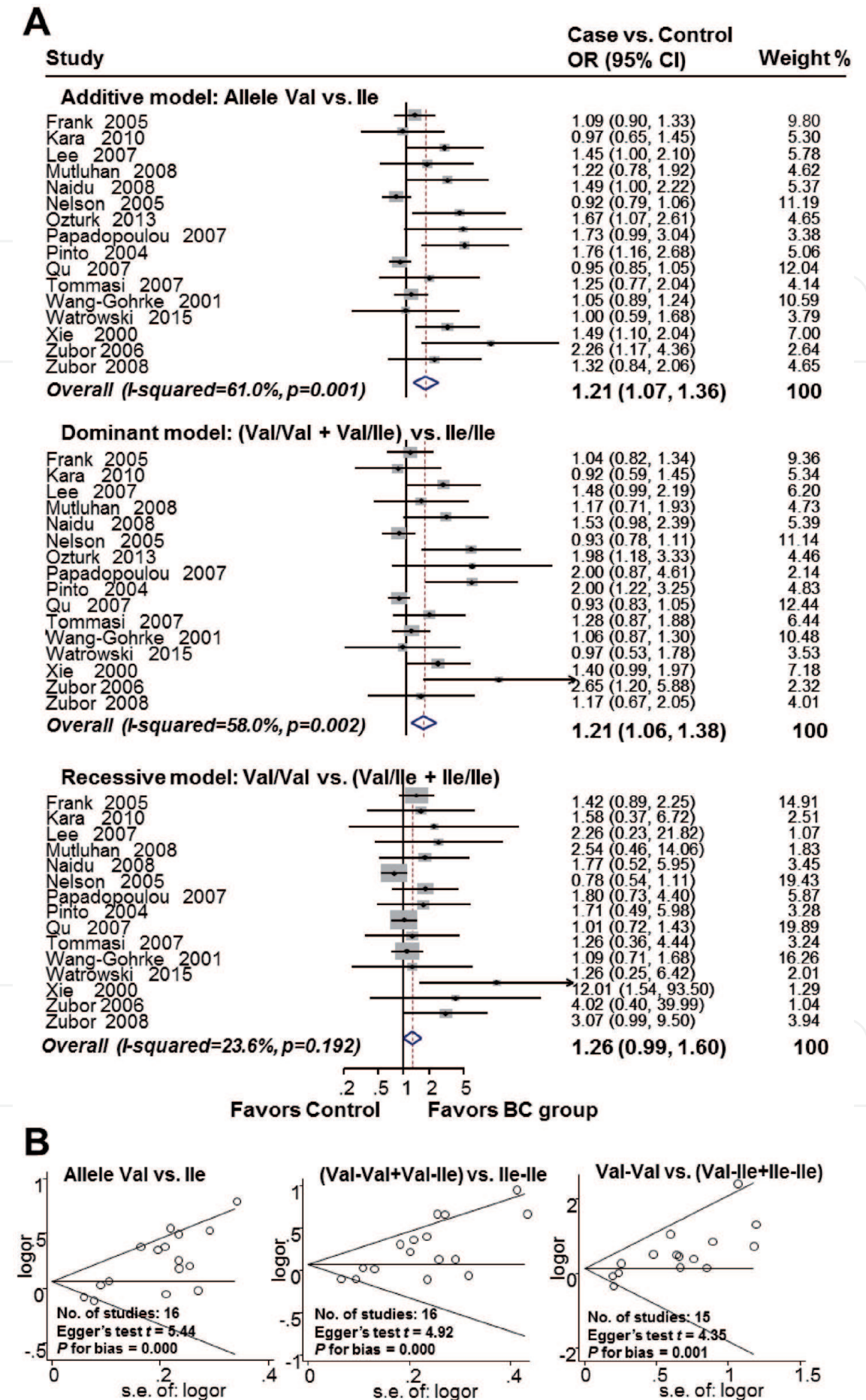


Figure 2.
The association between HER2^{Ile655Val} SNP and the risk of breast cancer in worldwide populations (modified from Nguyen Thanh et al. 2021) [98]. A. Forest plot for the association between HER2^{Ile655Val} SNP and breast cancer risk; B. Funnel plot evaluating publication bias among studies included in the meta-analysis.

The molecular mechanism of HER2^{Ile655Val} SNP, a non-polar to non-polar amino acid mutation, has been investigated in previous studies. Using computational exploration, Fleishman et al. 2002 proposed that the transmembrane region of the HER2 homodimer can exist in two stable conformations, either in an active or inactive form. The dimer mediated by the C-terminal dimerization motif is more durable than the dimer formed by the N-terminal motif. The authors found that substitution of Val for Ile in this position of the transmembrane region will destabilize the formation of active HER2 dimers mediated by the N-terminal dimerization motif and lead to reduced receptor activation and tyrosine kinase activity. However, the presence of the Val allele could reinforce the stabilization of the receptor's active state, which results in augmentation of autophosphorylation, hyper-active tyrosine kinase, and cellular proliferation [59]. Bocharov and colleagues researched the spatial structure of the dimeric transmembrane domain of the HER2 protein. They found that the Ile655Val variant can excessively stabilize the ErbB2 active dimeric state due to substituting the bulk side chain of Ile with the smaller Val, thus allowing tighter TM helix packing [99]. In another experiment, Tanaka et al. assessed the role of amino acid substitutions in the conformational stability of human lysozyme protein via thermodynamic analysis at high temperature and very low pH. They showed that in constructed isoleucine to valine mutants, the strength of mutant proteins was reduced compared to that of the wild-type protein [100].

5. Association between HER2^{Ile655Val} single nucleotide polymorphism and early-onset breast cancer susceptibility

Prior studies independently found a correlation between the high presence of the Val allele in the codon 655 of the HER2 gene and the onset of breast cancer [101–104]. Additionally, Millikan et al. 2003 and Tommasi et al. 2007 reported a strong association between the variant allele 655Val and breast cancer in younger women when combined with family history [105, 106]. However, other published data reveal the opposite results, with no significant correlation between the HER2^{Ile655Val} genotype and the risk of early-onset breast cancer in patients 40 to 50 years [63, 90, 107–109].

We conducted the meta-analysis, which collected 17 age-stratified articles with a cut-off age value from 40 to 55 years old (46.53 ± 3.84). We found that in young women, HER2 codon 655 polymorphism was strongly and significantly associated with breast cancer in all genetic models (additive, dominant, and recessive), which was in contrast to the results from a subgroup of older women (Data not shown).

Subgroup meta-analysis in the breast cancer population was utilized to investigate the association between HER2^{Ile655Val} SNP and the age at onset of breast cancer, calculating adjusted RRs comparing older and younger participants in the breast cancer population (**Figure 3**). There was a significant 17% increase in the risk of early onset of breast cancer in patients who were Val carriers (Ile/Val and Val/Val) (dominant model, RR 0.83, 95% CI 0.72 to 0.97; $I^2 = 36.5\%$; $n = 14$). Meanwhile, no significant association of HER2^{Ile655Val} SNP polymorphism with the age of onset was found in the subgroup of breast cancer women under an additive model (additive, RR 0.87, 95% CI 0.75–1.01, $I^2 = 39.8\%$; $n = 10$) and a recessive model (RR 0.96, 95% CI 0.73 to 1.26, $I^2 = 0.0\%$; $n = 9$). There was no publication bias in the studies (Begg's funnel plot was symmetric; additive model, Egger's test $t = -2.02$, P for bias = 0.078, $n = 10$; dominant model, Egger's test $t = -1.91$, P for bias = 0.08, $n = 14$; recessive model, Egger's test $t = -2.27$, P for bias = 0.057, $n = 9$). Furthermore, subgroup meta-analysis of the control population indicated no significant association between HER2^{Ile655Val} SNP and the age of participants was

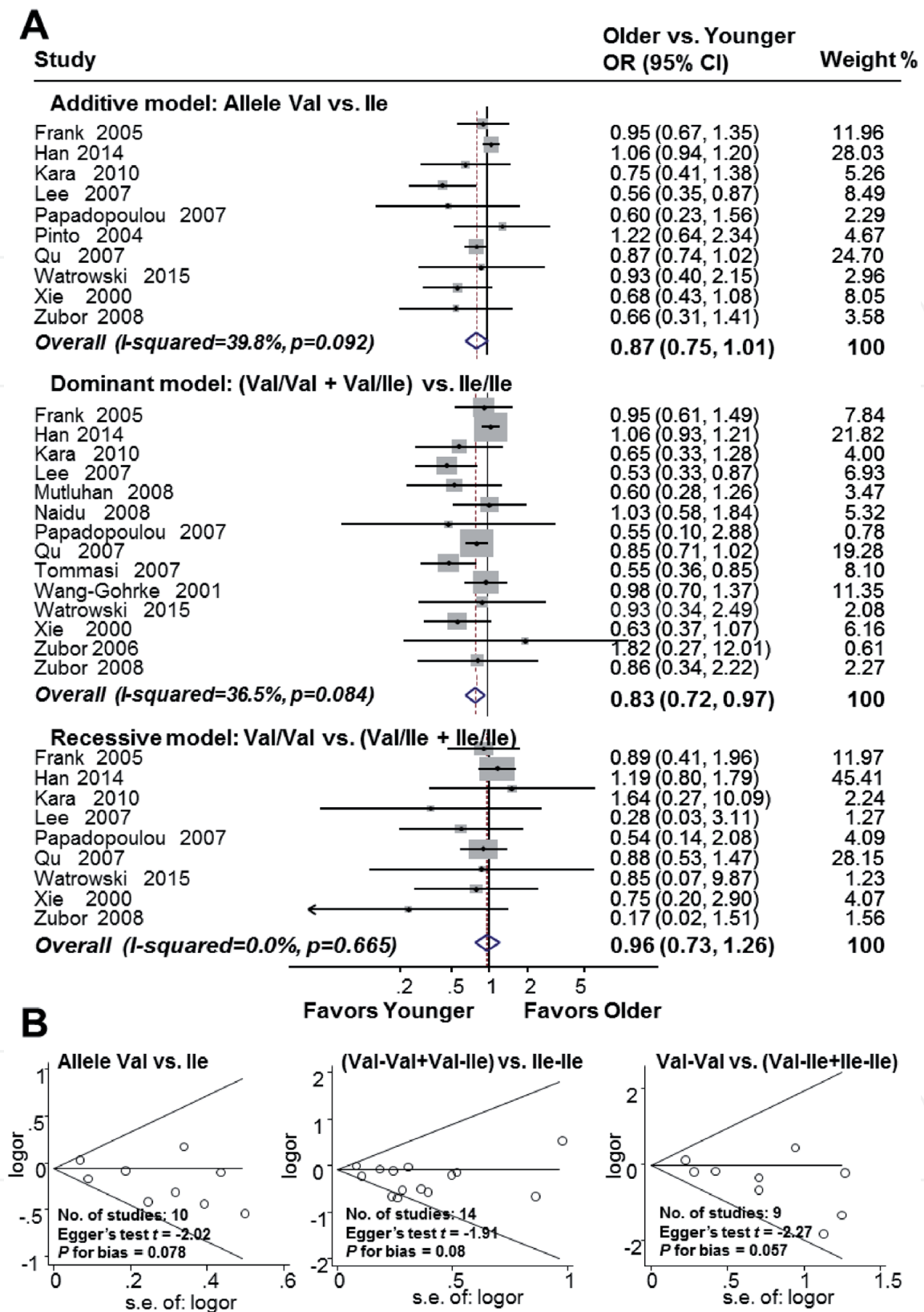


Figure 3. *HER2^{Ile655Val} SNP is associated with an increased risk of early-onset breast cancer (modified from Nguyen Thanh et al. 2021) [98]. (A) Forest plot for the association between *HER2^{Ile655Val} SNP and an increased risk of early-onset breast cancer; (B) Funnel plot evaluating for publication bias among studies included in the meta-analysis.**

found in control women under all genetic models (additive, RR 0.94, 95% CI 0.75 to 1.18; $I^2 = 28.1\%$; $n = 6$; dominant, RR 0.94, 95% CI 0.83 to 1.07; $I^2 = 0.0\%$; $n = 9$, and recessive, RR 1.19, 95% CI 0.70 to 2.02; $I^2 = 2.0\%$; $n = 3$) (Data not shown). In the breast cancer population, the dominant model of *HER2^{Ile655Val} SNP was shown*

to be significantly associated with younger age. Therefore, the high presence of the Val allele in codon 655 of the HER2 gene might explain the increasing frequency of younger age onset of breast cancer.

Molecular mechanisms of the early onset state have been studied in certain types of cancer. Several candidate genes and signaling pathways have been found in the early onset of colorectal cancer. REG1A, CK20, and MAP3K8 gene expression were related to early-onset colorectal cancer formation [110]. Using PPI network analysis, Zhao and colleagues suggested that early-onset colorectal cancer is associated with vascular smooth muscle contraction signaling pathways. They also identified seven hub genes, namely, ACTA2, ACTG2, MYH11, CALD1, MYL9, TPM2, and LMOD1, along with this signaling pathway [111]. Recently, using weighted gene co-expression network analysis and other analysis methods, Mo et al. identified seven genes (SPARC, DCN, FBN1, WWTR1, TAGLN, DDX28, and CSDC2) associated with the development and prognosis of early-onset colorectal cancer. These genes may serve as novel biomarkers for diagnosing early-onset colorectal cancer [112]. In prostate cancer, a study conducted by Weischenfeldt et al. found the genomic alteration landscapes of early-onset prostate cancer compared to older-onset cancer. They discovered that early-onset prostate cancer possesses a higher frequency of balanced structural rearrangements, with a specific abundance of androgen-regulated ETS gene fusions, and concluded that ETS fusion genes are signs of early-onset prostate cancer [113]. Furthermore, Gerhauser et al. demonstrated the role of androgen receptor-driven rearrangements, an early APOBEC-driven mutational mechanism, and ESRP1 gene duplication that contributed to the pathogenesis seen in early-onset prostate cancer [114]. Nevertheless, the molecular mechanism involved in the pathogenesis of early-onset breast cancer is, to date, poorly understood and needs to be studied further.

6. Conclusion

HER2 was involved in the development and progression of mammary carcinogenesis, including breast cancer. HER2-targeted therapies have significantly enhanced the clinical outcome for HER2-positive breast cancer patients. HER2^{Ile655Val} single nucleotide polymorphism associate with an increased risk of breast cancer. In addition, HER2^{Ile655Val} SNP might be considered as a susceptibility factor for early-onset breast cancer. Further molecular studies are required to reveal the mechanism of this correlation.

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