Degree project

UNIVERSITY OF SKÖVDE

A case control study on a population based on HER 2 genetic polymorphism and breast cancer

Master Degree Project in Bioscience

Second Cycle 30 credits

Spring semester 2025

Student: Sheeba Vazhuvadikadavil Kurian

a22sheva@student.his.se

Supervisor: Patric Nilsson

patric.nilsson@his.se

Examiner: Niclas Norrström

niclas.norrstrom@his.se

Abstract

Breast cancer is a complicated and diverse disease where cells in the breast tissue grow out of control. It is the most common type of cancer to affect women worldwide. Breast cancer can arise in the connective tissues, ducts, and lobules, among other places in the breast. Based on their morphological features, breast cancers are currently divided into two categories: invasive and non-invasive. This study aims to determine the relationship between HER2 gene changes and the development of breast cancer. Results could improve early detection, treatment strategies, and targeted medical interventions for individuals with diverse genetic backgrounds. The meta-analysis approach was used in this study. In order to conduct a meta-analysis, the literature must be thoroughly reviewed, and the results and theories that were investigated must be described. Data analysis techniques like funnel plots can be used to determine whether studies were missing, but if the majority of current research was not identified, the results may be inaccurate. The majority of research suggests that the HER2 Ile655Val polymorphism was strongly associated with an increased cancer of breast cancer, particularly among younger women and members of particular ethnic groups. No significant relationship was found in some studies, which may indicate sample size limitations or population-specific effects.

Keywords: Breast cancer, HER2 gene, HER2 Ile655Val polymorphism, Meta-analysis.

Popular Scientific Summary

One of the most common cancers to affect women worldwide is breast cancer. It is the outcome of breast cells growing out of control. Although environmental factors and lifestyle choices play a role, heredity also plays a significant role. One gene that scientists are currently studying is the HER2 gene, which helps control cell growth and division. A slight change in this gene called the Ile655Val polymorphism may increase the possibility of breast cancer. Therefore, the gene produce a different HER2 protein, which could cause excessive cell growth and ultimately cancer. A specific single nucleotide polymorphism (SNP) known as Ile655Val (rs1136201) was brought on by an A→G substitution in exon 17 of the HER2 gene, which causes an amino acid shift at codon 655 from isoleucine (Ile) to valine (Val). A lot of research has been done on this polymorphism because it was linked to an increased risk of breast cancer, particularly in younger women and certain ethnic groups. The Val allele has been shown to enhance HER2 receptor dimerization and activity, potentially resulting in cancer and uncontrolled cell division. In dominant or recessive genetic models, people with the Val/Val or Ile/Val genotype appear to be at a higher risk of developing breast cancer. However, there are differences between individual studies, most likely because of variations in sample size, ethnic background, exposure to the environment, and methodological approaches. Therefore, early HER2 polymorphism genetic screening was very helpful in identifying high-risk individuals, particularly those with an early-onset disease or a family history of cancer. Finding carriers of the HER2 Ile655Val variation could lead to better prevention tactics, more customized treatment regimens, and a possible decrease in the morbidity and death rate from breast cancer. In order to enhance precision medicine along with personalized interventions, this study aims to determine the degree to which the HER2 Ile655Val polymorphism contributes to breast cancer risk in different groups.

The association between breast cancer risk and HER2 genetic polymorphism, specifically the Ile655Val variation, has been studied in current, peer-reviewed, and scientifically mentioned literature from many relevant online databases, such as PubMed and Google Scholar. The selection of studies was guided by the following guidelines: population, intervention, and comparison. Only those articles that met strict eligibility and inclusion criteria, such as statistical clarity, relevance to the research question, and absence of duplicate data, were included in this meta-analysis. Data from ten different studies were analysed to determine the association between the HER2 Ile655Val polymorphism and breast cancer susceptibility. The statistical synthesis was conducted using R, a computer programming language. A forest plot of the odds ratios (OR) of breast cancer risk associated with the HER2 Val allele was used. The calculated odds ratio was odds ratio (OR) was 1.47 (95% CI = 1.07–1.87). The combined results showed a slight but significant increase in risk for Val allele carriers, although the odds ratio (OR) varied from study to study. To assess the presence of publication bias, the study used a funnel plot analysis. Given the small number of included studies, there is little possibility of bias going undetected; however, the relatively symmetrical distribution of studies indicated a low likelihood of significant publication bias. One genetic factor that may increase the risk of breast cancer, particularly in younger women and members of particular ethnic groups, is the HER2 Ile655Val polymorphism. Differences in sample size, ethnic origins, and environmental conditions are likely the cause of inconsistencies in individual studies. The findings indicate that, in addition to age, hormones, and lifestyle, HER2 genetic variation affects the biological behaviour of breast cancer. This has been taken into consideration in future risk prediction models and customized treatment regimens.

Acknowledgement

I would like to express my sincere gratitude to Patric Nilsson, who patiently guided and supported me throughout the research process for my thesis. Without his assistance, my work meta-analysis section would not have been possible, his kind manner and insightful advice were crucial. My sincere gratitude also goes out to my examiner, Niclas Norrström, for his wise and constructive criticism, which raised the standard and clarity of my report. His wise words motivated me to improve and produce work I am proud of.

I want to end by sincerely thanking my family for their continued trust, support, and encouragement during my entire journey.

Abbreviations

CIs	Confidence intervals
DCIS	Ductal carcinoma in situ
DNA	Deoxyribonucleic acid
ERα	Estrogen receptor
FISH	Fluorescent in situ hybridization
HER2	Human epidermal growth factor receptor 2
IBC	Inflammatory breast cancer
IDC	Invasive ductal carcinoma
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
Ile	Isoleucine
LCIS	Lobular carcinoma in situ
ORs	Odds ratios
PCR	Polymerase chain reaction
PR	Progesterone receptor
RFLP	Restriction fragment length polymorphism
SE	Standard error
SNP	Single nucleotide polymorphism
Val	Valine

List of Tables and Figures

Table 1	Systematic review of the selected studies
Table 2	Meta-analysis characteristics of the selected studies
Figure 1	The primary classifications of breast cancer
Figure 2	The normal breast cancer cells and HER2-positive breast cancer cells.
Figure 3	The flow chart for meta-analysis
Figure 4	Forest plot of the meta-analysis
Figure 5	Funnel plot

Table of Contents

1 Introduction 1
1.1 Breast cancer 1
1.2 Types of Breast Cancer 1
1.3 Human Epidermal Growth Factor Receptor 2 (HER2) 3
2 Aim and Objectives 5
3 Materials and Methords 5
3.1 Meta Analysis 5
3.2 Literature Review 6
3.3 Inclusion Criteria 6
3.4 Exclusion Criteria 6
3.5 Data Collection 7
3.6 Data Extraction 7
3.7 Statistical Analysis 7
4 Results 8
4.1 Study Search 8
4.2 Study characteristics 9
4.3 Studies Showing a Significant Association with Breast Cancer Risk 11
4.4 Studies Showing No Significant Association with Breast Cancer Risk 12
4.5 Publication Bias 13
5 Discussion 14
6 Conclusion 17
7 Ethical aspects and Impact on Society 17
8 Future Perspectives 18
9 Reference 19

1. Introduction

1.1 Breast cancer

The most common cause of cancer in women is breast cancer. Cancer cells have DNA and RNA that are extremely similar to those of the organism they originated from. The immune system does not frequently recognize them because of this. A DNA or RNA mutation causes cancer cells to grow from healthy cells. These mutations may occur naturally due to the Law of Thermodynamics' increase in entropy, or they can be caused by other things like nuclear radiation, electromagnetic radiation, viruses, bacteria, fungi, chemicals in the air, water, and food, free radicals, DNA and RNA evolution and aging, etc. Any of these could result in mutations that cause cancer (Sharma et al., 2010). Breast cancer is a diverse and complex condition where cells in the breast tissue grow uncontrollably, making it the most prevalent form of cancer affecting women globally and a primary contributor to cancer-related fatalities (Bray et al., 2018). Most cancerous cells will ultimately create a lump or mass known as a tumor. Cancer that originates from the breast tissue is known as breast cancer (Redhwan Ahmed Al-Naggar, 2013). Normal breasts are made up of fat, connective tissue, and mammary glands. These glands produce milk and are organized into lobes and tubes that link to the nipple (Elseaty & Taktash, 2020). During lactation, milk is produced by these glands. Breast cancer occurs when epithelial cells in the breast tissue grow uncontrollably (Nawaz et al., 2023). This can result in the development of a mass, which can be benign (non-cancerous) or malignant (cancerous). Breast cancer can develop in various locations within the breast, including the ducts, lobules, and connective tissues. Metastasis, the process by which malignant tumors enter and spread to distant organs of the body, is the ultimate reason for death. It is still unclear which particular mechanism leads breast cancer to develop. Breast tumors are categorized as malignant when they start spreading and break the basement membrane and myoepithelial cell layer. Breast cancers are currently classified based on their morphological characteristics into two groups: invasive or non-invasive (Govindasamy Muralidharan, 2017).

1.2 Types of breast cancer

Non-invasive breast cancer, also known as in situ breast cancer, is defined as having not spread outside of the original breast tissue. Precancers is a synonym for non-invasive breast cancers. These are two primary forms of non-invasive breast cancer: lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). 90% of non-invasive breast cancers are ductal carcinoma in situ (DCIS). Lobular carcinoma in situ (LCIS) is less frequent and is thought to be a sign of a higher risk of breast cancer (Sharma et al., 2010).Ductal carcinoma in situ (DCIS) is a non-invasive breast cancer that begins in the epithelial cell lining of the milk ducts. Because the cancer cells are yet to enter the basement membrane, it is commonly referred to as a premalignant lesion. DCIS raises the chance of getting invasive breast cancer later in life and is thought to be a precursor to the disease; however, it is not a life-threatening condition. Approximately 16% of all diagnoses of breast cancer are DCIS. Lobular carcinoma in situ (LCIS) is a non-invasive breast cancer that has not moved beyond the lobules where it first originated. LCIS is considered a benign breast condition and is not a true breast cancer, despite its name(E. Shelley Hwang et al., 2004).

Breast cancer that has spread into the surrounding breast tissue is referred to as invasive. Based on where in the breast they start to grow, invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) are the two most prevalent forms of invasive breast cancer (Govindasamy Muralidharan, 2017). Cells of invasive breast cancer enter the surrounding fatty and connective tissues of the breast after entering the duct and lobular wall. It is possible for cancer to be invasive without spreading to other organs or lymph nodes. Invasive breast cancer (IDC) begins in the milk ducts, which are the tubes that transport milk from the lobules to the nipple. About 80% of all breast cancers are invasive ductal carcinomas, making it the most prevalent kind. Invasive lobular breast cancer (ILC) begins in the breast's milk-producing glands called lobules. Invasive lobular carcinomas are the second most frequent kind of breast cancer, representing around 10% of all invasive breast cancers (Weigelt et al., 2010). The primary classifications of breast cancer are illustrated in Figure 1 below.

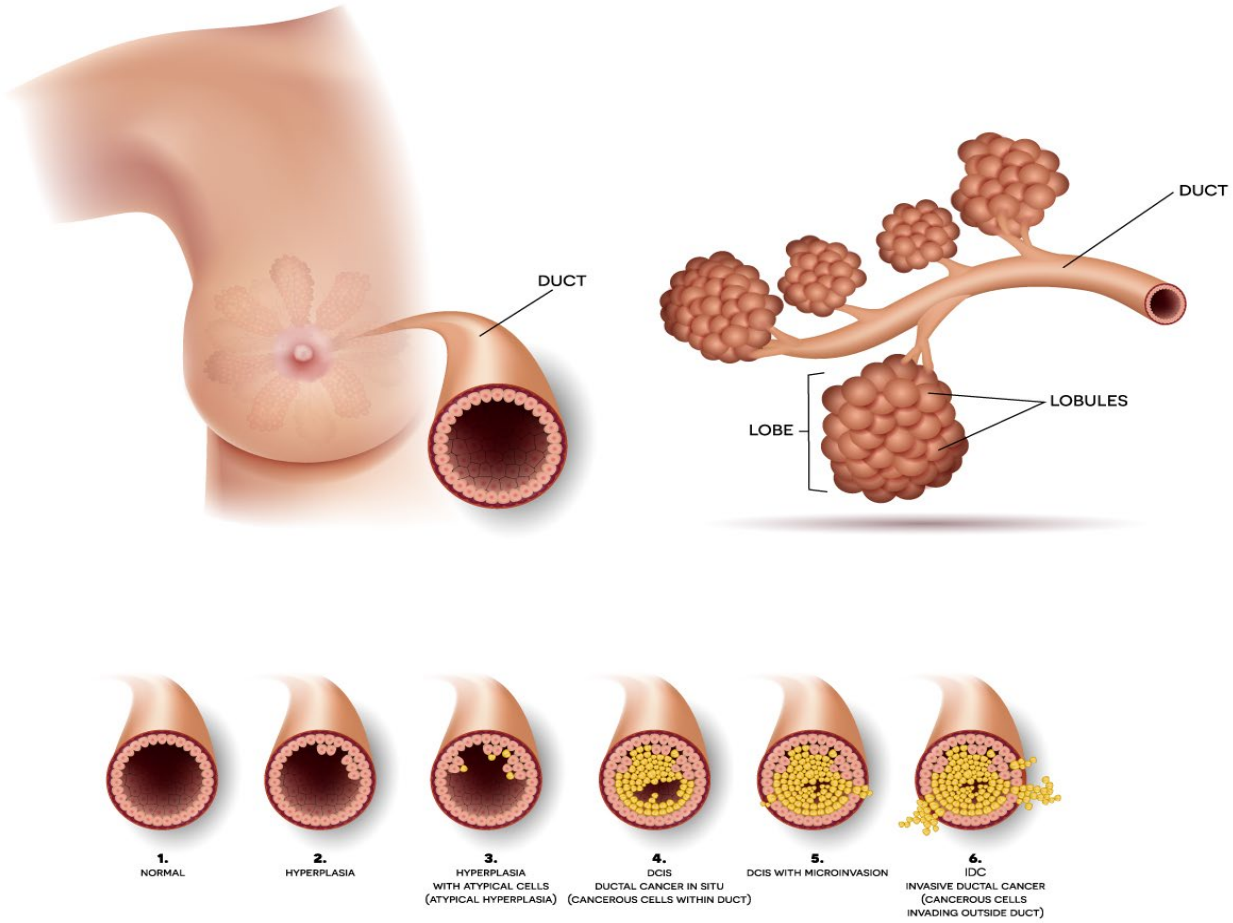

Figure 1. The primary classifications of breast cancer. The figure illustrates the primary types of breast cancer, including ductal carcinoma in situ (DCIS), and invasive ductal carcinoma (IDC), based on morphological characteristics (Anabia Sohail & Prof. Dr. Asifullah Khan, 2021).

The other types of invasive breast cancer are Paget's disease, Inflammatory breast cancer (IBC) and Triple-negative breast cancer. Paget's disease and inflammatory breast cancer (IBC) are two uncommon but different types of breast cancer that call for particular methods of diagnosis and care (Sharma et al., 2010). Paget's disease is a type of breast cancer that starts in the ducts and spreads to the nipples and areola, leading to symptoms that simulate eczema, including inflammation, itching, and scaling. This barely makes up 1–3% of all breast cancers, making it extremely uncommon. Inflammatory breast cancer (IBC) is represented by inflammatory signs in the breast, such as skin thickness, redness, and edema, which can occasionally resemble orange peel. Because it doesn't result in a breast lump and may not even be seen on a mammography, this type may be more difficult to diagnose. Breast cancer that tests negative for the estrogen receptor, progesterone receptor, and a protein known as HER2 is known as triple-negative breast cancer. This kind frequently has worse results, has few effective treatment options, and grows and spreads rapidly. Furthermore, there are subtypes like Luminal A and Luminal B(Sharma et al., 2010).

1.3 Human Epidermal Growth Factor Receptor 2 (HER2)

The human epidermal growth factor receptor 2 (HER2) has a major impact on the initiation and spread of breast cancer (Thanh et al., 2021). Breast tumors are categorized not only according to pathological characteristics but also according to the expression of the estrogen receptor (ERα), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The protein HER2/neu (ERBB2) is expressed on the surface of breast cancer cells and promotes growth and survival. Patients have a higher mortality and recurrence probability when targeted therapy against HER2 is not available. Gene amplification causes HER2 overexpression in 15% of breast tumours. HER2 status can be determined by the fluorescent in situ hybridization (FISH) technique or immunohistochemical (IHC) labelling (Slamon et al., 1987). Targeted HER2 medicines greatly increase patient survival. However, it has been demonstrated that anti-HER2 treatments only help patients who have HER2 overexpression or gene amplification. Lapatinib and trastuzumab (Herceptin) are examples of anti-HER2/neu medications (Lacruz et al., 2025). Patients with HER2-negative conditions are not given these medications (Carlos L Arteaga et al., 2011). Human epidermal growth factor receptor 2 (HER2) targeted therapy, endocrine therapy, and systemic chemotherapy are common treatments for breast cancer (Daniyal et al., 2021).

The Human Epidermal Growth Factor Receptor 2 (HER 2) gene, situated on chromosome 17q21, encodes a transmembrane protein (p185) with tyrosine kinase activity. About 15–25% of all breast tumors are HER2-enriched cancers. Only 70% of tumors with an overexpressed HER2 protein are categorized as HER2-enriched subtypes based on gene expression (Xie et al., 2000), (Coussens et al., 1985). The HER/erbB family consists of four cell surface receptors responsible for transmitting signals regulating normal cell growth and differentiation (Rubin & Yarden, 2001). Increased activity of the HER2 gene leads to excessive production of the receptor, which is associated with the formation of various types of human tumors, including breast, ovarian, and those in gastrointestinal tract tumors (Rubin & Yarden, 2001). The connection between HER2 genetic variations and breast cancer is crucial because it can offer valuable information about the genetic factors that contribute to the development of breast cancer, which can then be used to develop more effective risk assessment and personalized screening strategies (Antoniou et al., 2003).

The most researched HER2 polymorphism is Ile655Val. It results in the DNA changing from an A to a G in exon 17, which causes the position 655 to change from isoleucine (Ile) to valine (Val). This change may affect how the HER2 protein functions, which may affect how the tumour behaves and reacts to targeted treatments. Therefore, knowing the effects of this polymorphism is essential for developing individualized treatment plans for patients with breast cancer. The transmembrane domain polymorphism is believed to trigger downstream signalling pathways and improve receptor dimerization (Xie et al. 2000). Although the results vary by population, several studies have suggested that those who carry the Val allele may be at an increased chance of developing breast cancer. It has also been suggested that this polymorphism affects the effectiveness of anthracycline-based chemotherapy and trastuzumab. Ile655Val (rs1136201) is the HER2 gene polymorphism that has the most evidence of being associated with a higher risk of breast cancer along with different treatment outcomes (Isabel Blancas et al., 2024). The significance of other variants, such as rs1058808, rs2517951, and rs1810132, is still being investigated, although it is less certain. These polymorphisms also contribute to the advancement of pharmacogenomics and personalized medicine by potentially enabling better risk classification and customized treatment plans for patients with HER2-positive breast cancer. Figure 2 shows the image illustrating the differences between normal breast cancer cells and HER2-positive breast cancer cells.

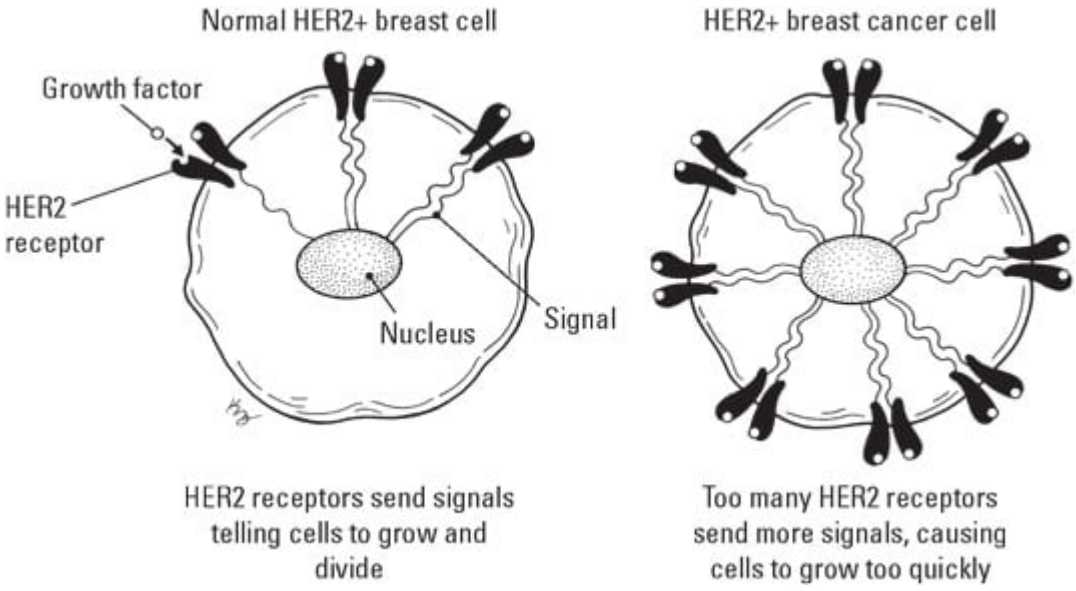

Figure 2. The image illustrates the differences between normal breast cancer cells and HER2-positive breast cancer cells (Mitri et al., 2012).

A meta-analysis is a type of statistical analysis that aggregates the findings of multiple scientific investigations (GLASS, 1976). The research papers focus on case-control studies that are carried out across various countries, involving diverse groups of people with breast cancer and non-

breast cancer patients (Krishna et al., 2018). In order to gather information from multiple sources with similar studies, I selected a few research papers that used the same methodology but presented different summaries. Some studies indicate that there is no link between breast cancer patients and HER2 gene variations (Asahi Hishida et al., 2002). While other research suggests a statistically significant increase in breast cancer due to HER2 gene mutations (Xie et al., 2000), (Zúbor et al., 2006). The odds ratio was the effect size that was consistently utilized in all these case-control studies.

The association between breast cancer and HER2 genetic variation and the Val655Ile polymorphism in genomic DNA samples from affected and control participants was investigated in this study. The evaluation of the distribution of HER2 polymorphisms by comparing breast cancer patients (cases) and healthy people (controls) includes genotyping and statistical analysis.

2. Aim and Objectives

This study aims to determine the relationship between HER2 gene changes and the development of breast cancer. It will include a wide range of people to determine whether specific changes in this gene increase the possibility of breast cancer. Findings may lead to better early identification, treatment plans, and specific medical approaches for people with different genetic backgrounds.

1. Investigate HER2 genetic polymorphism prevalence among breast cancer patients.
2. Compare HER2 polymorphism occurrence between breast cancer cases and controls.
3. Assess associations between HER2 polymorphisms and breast cancer risk, exploring interactions and implications for personalized prevention strategies.

3. Materials and Methods

3.1 Meta-Analysis

The present study employed the meta-analysis method. A meta-analysis is a formal, quantitative epidemiological study design that is used to evaluate prior research papers in a systematic manner in order to draw conclusions about that body of work, which was a collection of the results from different relevant studies. A meta-analysis's findings could provide a more accurate assessment of the impact of a treatment or risk factor for illness, among other outcomes, than any one study that contributed to the pooled analysis. Analyzing the variation or heterogeneity in research findings is another crucial consequence. One of the advantages of meta-analysis is that it provides a comprehensive, quantitative study of a sizable, frequently intricate, and occasionally seemingly contradictory body of literature. Meta-analyses need a sensitive literature search and the characterization of the result and hypotheses investigated. There are ways to analyze data to find the possibility that studies are missing, such as using funnel plots, but failing to identify the majority of extant studies can result in incorrect results (Rani & Shetty, 2010).

3.2 Literature Review

The purpose of this literature review was to find previous studies on the relationship between HER2 gene polymorphisms and the risk of breast cancer as well as to identify any missing information in the body of knowledge. Between February and March of 2025, searches were conducted in PubMed, Google Scholar, evaluated scientific journals, medical research papers, and other databases. A systematic review was performed, and the databases were collected from 2000 to 2021 using PubMed, Science Direct, and Google Scholar in search of English-language studies evaluating the severity of HER2 polymorphism in breast cancer patients. The keyword combinations such as "breast cancer," "HER2 gene", "genetic polymorphism", "breast cancer and HER2 genetic polymorphism", "breast cancer with HER2" and "types of breast cancer" were used to find relevant case-control studies. A meta-analysis then evaluated the efficacy of breast cancer. Peer-reviewed papers that evaluated HER2 gene variants in patients diagnosed with breast cancer and included statistical information such as odds ratios (ORs) and confidence intervals (CIs) completed the inclusion criteria. Participants in this study were patients with breast cancer and healthy people. Every patient was receiving treatment, including medication, therapy, and hospitalization. Outcome represented the patients pooled effect rating. One of the two effect models, the random effect model or the fixed effect model, was frequently used in meta-analysis. The fixed effect model assumes that all included studies will have the same effect size; therefore, any reported variations in effects are due to sampling error, in contrast to the random effect model, which takes into an account that effect sizes across included studies would vary from study to research (Borenstein et al., 2010). In this study, a random effect model and a fixed effect model were used for analysis.

3.3 Inclusion Criteria

Using inclusion and exclusion criteria, the publications were reviewed. Individuals with a diagnosis of breast cancer, including HER2-breast cancer. Diagnosis that has been confirmed by histopathology studies. Patients from different ethnic origins and age groups. Individuals in excellent health who have never experienced breast cancer or any other form of cancer are also included. Individuals who don't have any known hereditary susceptibility to breast cancer. Individuals who have been clinically tested for the HER2 Val655Ile polymorphism. Case-control investigations in which genomic DNA samples are used to assess HER2 polymorphisms. Peer-reviewed research with human subjects and transparent statistical analysis in case-control research (e.g., odds ratio) and research articles written in English. Studies carried out in a variety of geographical locations.

3.4 Exclusion Criteria

Patients undergoing therapy for secondary or metastatic breast cancer and those with other cancer diagnoses who do not have primary HER2-related data. Individuals without a clinical diagnosis of breast cancer but with a family history of the disease. Studies with unclear HER2 polymorphism genotyping results and studies that fail to distinguish between other subtypes of breast cancer and HER2-positive breast cancer. Research that lacks statistical significance and has limited sample sizes and studies without clinical validation that only use self-reported genetic or cancer status. Abstracts from conferences, unpublished reports, or non-peer-reviewed research and research articles written in languages other than English, unless they have been translated.

3.5 Data Collections

The HER2 Val655Ile polymorphism between breast cancer patients and healthy individuals had been the subject of this case-control investigation. Histopathological and genetic examinations are used to diagnose breast cancer, with an emphasis on HER2-breast cancer. Healthy people who have never had breast cancer, matched by age, race, and place of residence. In order to guarantee statistical power and significant findings, the study tried to involve an adequate number of participants. All participants had peripheral blood samples taken. Standard laboratory methods were used to obtain genomic DNA and analysis by restriction fragment length polymorphism (RFLP) after polymerase chain reaction (PCR). Odds ratios (ORs) with 95% CIs will be computed using logistic regression models and a comparison of the HER2 Val655Ile distribution between cases and controls. The names of the authors, the year of publication, the number of healthy individuals, the number of breast cancer patients in each study, and the number of healthy people used for the meta-analysis. Analysis was done on case-control studies from various countries. Both healthy people (controls) and breast cancer patients (cases) were included in the sample population.

3.6 Data Extraction

The relevant studies were independently reviewed based on their titles, abstracts, and methodologies in order to do the meta-analysis. In order to find suitable case-control studies, keywords such as "breast cancer," "HER2 gene," and "genetic polymorphism" were used. Ten relevant publications were chosen and the data was collected according the search, inclusion, and exclusion criteria. The table 1 below contains an overview of the ten selected studies.

Table 1. Systematic review of the selected studies. Given below is a l list of references on research studies of HER 2 genetic polymorphism and breast cancer risk.

First author	Year	Country	Cancer type	Control	Case
Al-Janabi et al	2015	Iran	Breast Cancer	200	300
Bhatt et al	2021	Indian	Breast Cancer	104	117
Karen G. Montgomery et al	2003	Australia	Breast Cancer	299	409
Kamali-Sarvestani et al	2004	Iran	Breast Cancer	138	204
Naglaa R. AbdRabo et al	2013	Egypt	Breast Cancer	86	64
Nelson et al	2005	United States	Breast Cancer	976	1094
Ozturk et al	2013	Turkey	Breast Cancer	118	118
WATROWSKI et al	2015	Austria	Breast Cancer	100	80
Xie, D., et al	2000	China	Breast Cancer	361	339
Zubor, P., et al	2006	Slovakia	Breast Cancer	60	47

3.7 Statistical Analysis

Data from several separate research studies on the same subject can be combined and analysed statistically using a meta-analysis. It offers a more thorough and accurate estimate of the effect size (risk, odds ratio, or treatment effect) than any one study might have provided on the subject. This study will use the widely used statistical program R to perform a meta-analysis. Both a fixed effect model and a random effect model were applied, with the standard error (SE) representing the 95% confidence interval (CI) and the effect size representing the odds ratio (OR). Using the R software, a funnel plot and a forest plot were generated to evaluate publication bias, the overall impacts of the investigation, and demonstrate heterogeneity among them. P-values < 0.05 were considered significant.

Graphical representations of the findings from both patients and controls investigations are called forest plots. By illustrating the combined outcomes of the studies and displaying their heterogeneity, the forest plot demonstrates the connections between the studies that are part of a meta-analysis. In meta-analyses, publication bias is investigated using a funnel plot. Individual study treatment effects are plotted against study size in such scatter plots. Statistical significance was defined as a p-value of less than 0.05.

4. Results

4.1 Study Search

The three major scientific databases that were extensively searched for this meta-analysis were PubMed, ScienceDirect, and Google Scholar. A total of 112 research articles were initially collected from these databases. However, it was found that many of the articles were duplicates, appearing in multiple databases. After removing these duplicate items, there were still 82 different studies. The researchers then reviewed the titles of these 82 studies. This was done to see if the topic of each study had anything to do with HER2 polymorphism and breast cancer. 45 papers were eliminated at this stage because their titles were clearly unrelated to the primary subject of the analysis. The next step was to read the abstracts of the final 37 papers. Abstracts give a brief overview of the aims, methods, and findings of the study. After the abstracts were reviewed, another set of studies was removed because they either lacked the necessary data or were irrelevant. At this point, only ten studies have been considered suitable for further review. The full texts of these 37 articles were also carefully reviewed to ensure that they met inclusion criteria. Currently, 27 studies have been eliminated for a number of reasons, such as lack of knowledge about the HER2 Ile655Val polymorphism, unclear methodology, low-quality data, or a focus on a different type of cancer. After this thorough and systematic screening process, ten papers were considered appropriate for inclusion in the meta-analysis. To evaluate the association between HER2 genetic variation and breast cancer risk, these studies provided clear and reliable information in the form of standard errors (SEs), odds ratios (ORs), and confidence intervals (CIs). Figure 3 shows the flowchart that shows how the studies were selected.

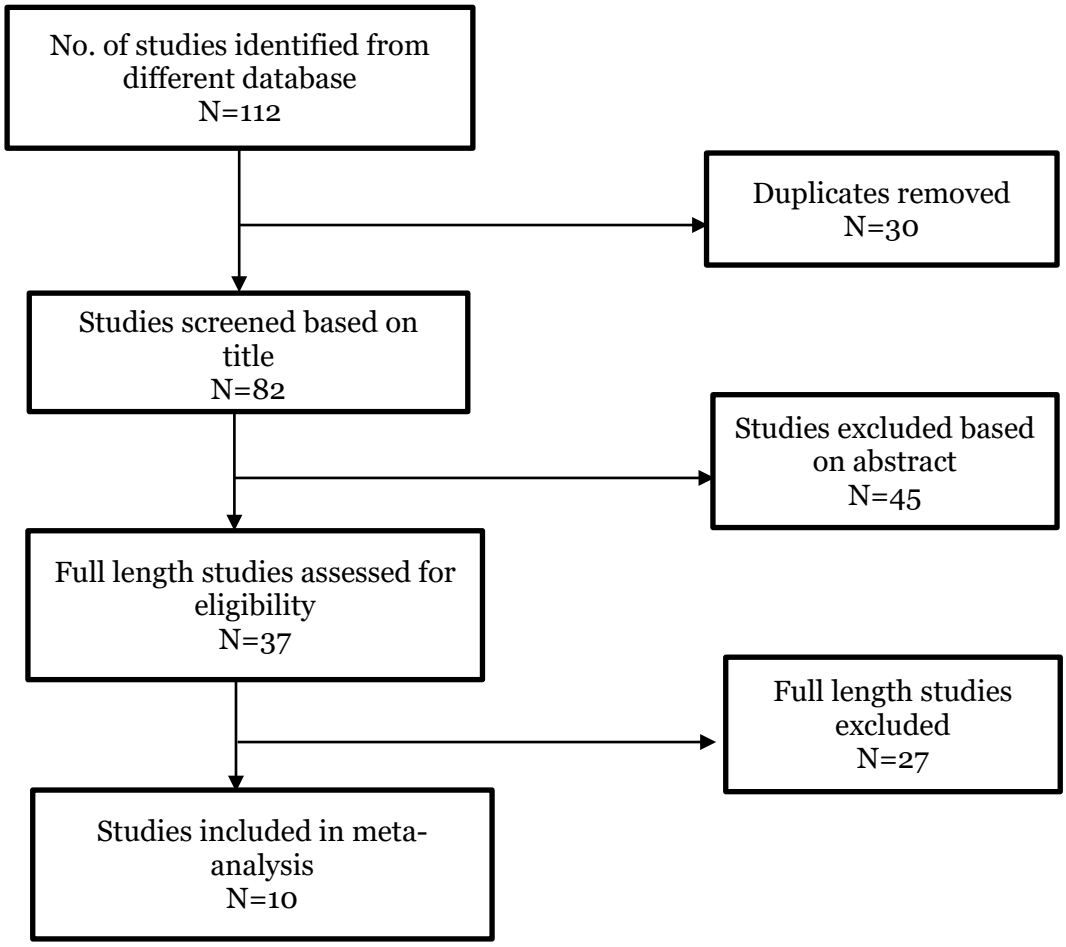

Figure 3. Flowchart of studies being included in meta-analysis.

4.2 Study characteristics

According to the meta-analysis's inclusion criteria, ten papers in total met the requirements. These studies clearly examined the relationship between the HER2 Ile655Val gene polymorphism and breast cancer possibility. Because the research was conducted in multiple countries, it provided an international population sample and strengthened the analysis overall. Of the selected studies, the United States had the highest number of reported cases of breast cancer, while Slovakia had the lowest number of cases. The research's two-decade duration of attention has been demonstrated by the different years of publication, ranging from 2000 to 2021.

Research indicated a significant correlation. For example, in Iran, people who carried the variation had a 2.44 odds ratio, indicating their possibility of breast cancer was more than doubled (CI: 1.23–5.1), according to Al-Janabi et al. (2015). Bhatt et al. (2021) in India found similar results, with an OR of 2.43 (CI: 1.32–4.46). Karen G. Montgomery et al. (2003) in Australia reported an OR of 2.8, demonstrating an important connection (CI: 1.3–6.2). According to a significant result (OR = 2.2, CI: 1.2–4.1) also discovered by Naglaa R. AbdRabo et al. (2013) in

Egypt, this gene variant may significantly increase the chance. In other studies, moderate relationships were found. For example, Ozturk et al. (2013) from Turkey found an OR of 1.9 (CI: 1.18–3.33), and Xie et al. (2000) from China showed an OR of 1.7 (CI: 1.1–2.6), both of which indicated increased possibility. Zubor et al. (2006) from Slovakia reported the highest odds ratio, 2.82 (CI: 1.05–7.6), particularly for older women. However, some studies found no significant association. In another instance, Nelson et al. (2005) found no increased chance in the United States, with an OR of 0.97 (CI: 0.79–1.18). Watrowski et al. (2015) in Austria and Kamali-Sarvestani et al. (2004) in Iran also reported non-statistically significant results, with an OR of 1.03 (CI: 0.56–1.9) and 1.16 (CI: 0.67–2.03), respectively. The range of findings demonstrates how the impact of the HER2 Ile655Val gene on the probability of breast cancer may differ depending on the community. The higher correlations found in other studies could be explained by differences in lifestyles, sample sizes, research methods, and genetic backgrounds. The combined results of these ten studies offer a thorough picture of the potential correlation between this specific gene variant and breast cancer across different countries and populations. The characteristics of the included studies were shown in Table 2.

Table 2. Meta-analysis characteristics of the selected studies

Study	Year	Country	Type of Cancer	Odds Ratio (OR	Confidence Interval (CI)	Standard Error (SE)
Al-Janabi et al	2015	Iran	Breast Cancer	2.44	5.1-1.23	0.99
Bhatt et al	2021	Indian	Breast Cancer	2.43	4.46-1.32	0.80
Karen G. Montgomery et al	2003	Australia	Breast Cancer	2.8	6.2-1.3	1.25
Kamali-Sarvestani et al	2004	Iran	Breast Cancer	1.16	2.03-0.67	0.35
Naglaa R. AbdRabo et al	2013	Egypt	Breast Cancer	2.2	4.1-1.2	0.74
Nelson et al	2005	United States	Breast Cancer	0.97	1.18-0.79	0.09
Ozturk et al	2013	Turkey	Breast Cancer	1.9	3.33-1.18	0.55
WATROWSKI et al	2015	Austria	Breast Cancer	1.03	1.9-0.56	0.34
Xie, D., et al	2015	Austria	Breast Cancer	1.03	1.9-0.56	0.34
Zubor, P., et al	2006	Slovakia	Breast Cancer	2.82	7.6-1.05	1.67

The pooled effect estimates for each of the ten studies included in this meta-analysis were shown using forest plots. Random effects models have been used to assess the connection between the HER2 Ile655Val genetic polymorphism and breast cancer probability. The included studies varied moderately, according to the meta-analysis's heterogeneity, which was found to be I^2 = 45.3% with a p-value of 0.058. This suggests that differences in study demographics, sample sizes, and research techniques may have had an impact on the observed heterogeneity. According to the random effects model, the overall odds ratio (OR) of 1.47 (95% CI = 1.07–1.87) indicates a statistically significant association between the HER2 Ile655Val genetic polymorphism and an increased probability of breast cancer. This indicates that compared to people without the variant, those who have this genetic variation have a roughly 47% chance of developing breast cancer. Even though the studies are not equal, this degree of variability suggests that the difference is not statistically significant. This could be due to differences in the techniques used to calculate or publish the odds ratio or confidence intervals. The results of the random effects model strongly show that the HER2 Ile655Val polymorphism is associated with an increased chance of breast cancer, suggesting that it may serve as a genetic probability factor in a range of populations. Figure 4 below shows the meta-analysis's forest plot.

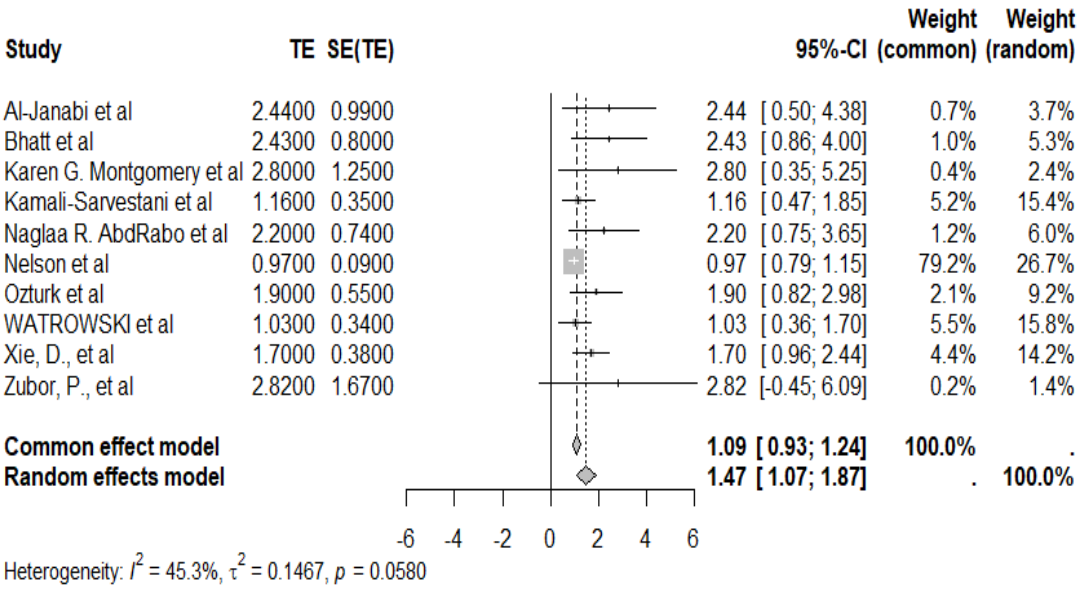

Figure 4: Forest plot of the meta-analysis.

4.3 Studies Showing a Significant Association with Breast Cancer Risk

Several of the studies that were part of this meta-analysis found that the HER2 Ile655Val genetic polymorphism was significantly linked to an increased chance of breast cancer. The findings consistently show that the Val allele, whether homozygous (Val/Val) or heterozygous (Ile/Val), may increase the probability of breast cancer. These correlations were found between different

populations and age groups. For example, Ozturk et al. (2013) found a significant correlation between the HER2 Ile655Val polymorphism and the chance of breast cancer in Turkey. Those with the Val allele had an odds ratio (OR) of 1.98 (95% CI: 1.18–3.33, $p < 0.009$), meaning their possibility was nearly doubled. In Iraq, the homozygous Val/Val genotype (GG) increased chance for breast cancer by more than 2.5 times (OR = 2.44, 95% CI: 1.23–5.1, $p = 0.014$), whereas the heterozygous Ile/Val (AG) genotype increased possibility by about 1.6 times (OR = 1.62, 95% CI: 1.15–2.4, $p = 0.022$) (Al-Janabi et al., 2015). According to Xie et al. (2000), the Val allele was found to significantly increase the possibility of breast cancer in younger women (OR = 1.7, 95% CI: 1.1–2.6) but not in older women ($p > 0.05$). This suggests that age may have an effect on the genetic risk. Additionally, Bhatt et al. (2021) found a significant correlation in India. Patients with the Val allele were more likely to be diagnosed ($p = 0.0016$), and those with the Ile/Val genotype were at significantly higher possibility (OR = 2.43, 95% CI: 1.32–4.46, $p = 0.004$) for breast cancer. Overall, there was a statistically significant relationship between the variables ($p = 0.0059$). In Australia, Karen G. Montgomery et al. (2003) discovered that breast cancer patients had a higher prevalence of the HER2 Ile655Val variant than controls ($p = 0.01$). Patients with the Val/Val genotype experienced a significant effect in the dominant model (OR = 2.8, 95% CI: 1.3–6.2, $p = 0.005$). The HER2 655Val variation significantly raised chance in Egypt (OR = 2.2, 95% CI: 1.2–4.1, $p < 0.05$), according to Naglaa R. AbdRabo et al. (2013). When paired with another polymorphism (HER1 497K), the chance increased significantly more (OR = 4.1, 95% CI: 1.58–10.57), indicating a possible gene-gene interaction. The effect of age on genetic susceptibility was highlighted by Zubor et al. (2006) in Slovakia, who found that women over 45 who had the Val/Val genotype had a significantly higher possibility of breast cancer (OR = 2.82, 95% CI: 1.05–7.6). The HER2 Ile655Val polymorphism, and more particularly the Val allele, may considerably increase the chance of breast cancer, according to all of these findings. The effect of this genetic variant appears to differ among populations and may also be influenced by age and interactions with other genes.

4.4 Studies Showing No Significant Association with Breast Cancer Risk

Other studies showed a strong association between the HER2 Ile655Val polymorphism and breast cancer possibility, but a few included in the meta-analysis did not find statistically significant results. These findings indicate that the effects of this genetic variation may vary by population or be impacted by other moderating factors. For example, Nelson et al. (2005) found no significant correlation between the Ile/Val genotype and breast cancer chance in the United States. Those with the Val allele were neither more nor less at threat than those with the Ile/Ile genotype, according to the published odds ratio (OR), which was 0.97 (95% CI: 0.79–1.18). The confidence interval contains 1.0, and the p-value was not statistically significant, indicating a neutral effect. Similarly, Watrowski et al. (2015) in Austria did not find a significant association between the HER2 codon 655 polymorphism and breast cancer. Their results showed that, with an OR of 1.03 (95% CI: 0.56–1.90), there was not a significant distinction in probability between Val allele carriers and non-carriers. Inaccurate effect estimation and data variability are indicated by the large confidence interval. A study by Kamali-Sarvestani et al. (2004) from Iran found no significant difference in allele frequencies of the HER2 Ile655Val polymorphism between breast cancer patients and healthy controls. It is clear that the p-value of 0.28 and the odds ratio of 1.16 (95% CI: 0.67–2.03) are not statistically significant. This indicates that the polymorphism might not play an important part in determining this population's chance of breast cancer. Nelson, Watrowski, and Kamali-Sarvestani found that population-specific effects,

environmental factors, or other genetic factors may reduce or hide the effect of the HER2 Ile655Val variation on breast cancer possibility. They also highlight the importance of examining a range of populations in genetic association research to gain a more comprehensive understanding of the connections between genes and diseases.

4.5 Publication bias

In order to better understand the possible correlation between the HER2 Ile655Val genetic polymorphism and breast cancer, ten studies have been included in this meta-analysis. A funnel plot was created in order to detect publication bias. The phenomenon known as publication bias states that studies with significant or positive results are more likely to be published than those with non-significant or negative results. This could affect the overall accuracy of the results of a meta-analysis. A funnel plot simplifies the identification of this bias by analyzing each study's odds ratio, which indicates chance, with its standard error, which indicates the study's size and accuracy. A symmetrical, inverted funnel shape is formed by the studies in a bias-free funnel plot. This indicates that the findings have not been influenced by missing or unpublished research and are uniformly distributed around the average. Most of the studies in this research paper were contained within the funnel's boundaries and evenly spaced around its center. This suggests that there isn't significant publication bias and that the data is generally symmetrical. However, since only ten research papers were taken into consideration, a very moderate amount of bias might still be present. The shape of the funnel plot, however, supports the reliability of the results by showing that they were not substantially impacted by unpublished or missing research. Figure 5 below shows the meta-analysis's funnel plot.

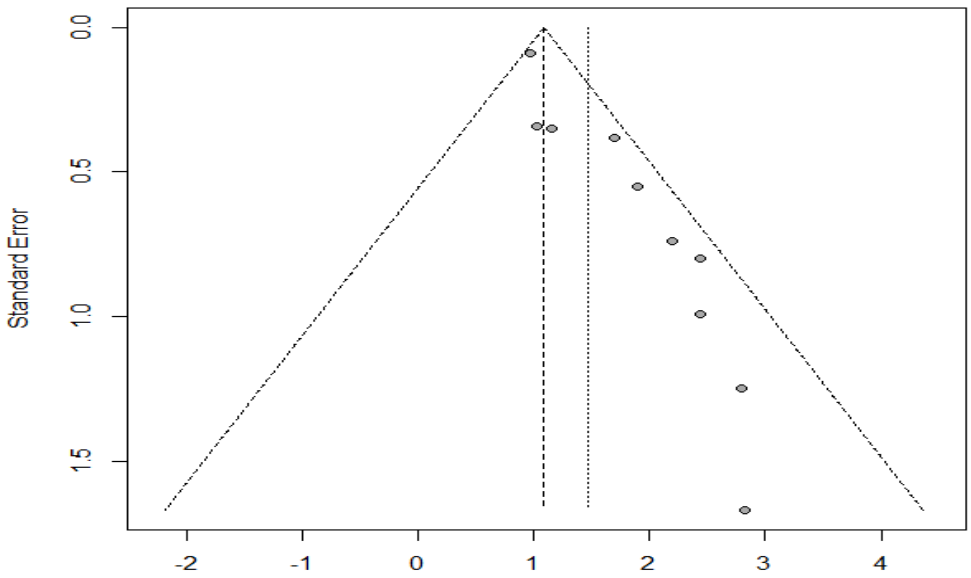

Figure 5. Funnel plot: To evaluate the meta-analysis's publication bias. There is some indication of publication bias when the data distribution is asymmetrical.

5. Discussion

The comprehensive screening process and systematic literature search in this meta-analysis were designed to evaluate the association between the HER2 Ile655Val polymorphism and breast cancer. At first, a comprehensive examination of the three main scientific databases, such as PubMed, ScienceDirect, and Google Scholar, turned up 112. However, it was found that many of the articles were duplicates, appearing in multiple databases. After removing these duplicate items, there were still 82 different studies. A multi-phase screening process that included title, abstract, and full-text reviews ultimately identified ten studies that met all inclusion criteria (Moher et al., 2009). Many studies were excluded because they included unrelated subjects, had poor data quality, or concentrated on other genetic markers or cancer types, which further supports the importance of exact inclusion and exclusion criteria (Egger et al., 1997). By maintaining that only studies with a clear methodological design and sufficient statistical reporting, such as odds ratios [ORs], confidence intervals [CIs], and standard errors [SEs], were included, the final selection of ten studies strengthened the validity and reliability of the overall findings. The research selection process flowchart explains reporting and shows how studies are frequently excluded. It is important to confirm the validity of the study's methodology, particularly when conducting meta-analyses where choices regarding inclusion may significantly affect outcomes (Liberati et al., 2009). The methodical approach needed for evidence synthesis is demonstrated by the selection of ten appropriate research articles from the initial collection of 112. The accuracy of the meta-analysis is strengthened by the inclusion of comprehensive genetic association data, international representation, and high methodological quality in the final dataset. This methodical selection process provides more convincing evidence for findings suggesting a potential association between the HER2 Ile655Val polymorphism and an increased chance of breast cancer.

This meta-analysis included ten eligible papers that evaluated the relationship between the HER2 Ile655Val (rs1136201) polymorphism and breast cancer possibility, providing a comprehensive review of studies conducted across a range of global populations. These studies show the two decades of continuous scientific interest in this polymorphism as a possible genetic risk factor, with a publication window comprising 2000 to 2021. The publication years 2000 to 2021 also demonstrate the evolution of research methodologies. One of the main advantages associated with this analysis is the geographical diversity of the included research. The papers chosen come from the following countries: Africa (Egypt), Europe (Austria, Slovakia), Australia, Asia (India, Iran, China, Turkey), and the United States. The outcomes are more widely applicable because this global representation allows the effects of the HER2 Ile655Val polymorphism to be evaluated across a variety of genetic and ethnic backgrounds. The strong association found in an Indian population by (Bhatt et al., 2021) (OR = 2.43; 95% CI: 1.32–4.46), along with similar findings reported in Iran (Al-Janabi et al., 2015) and Egypt (Naglaa R. AbdRabo et al., 2013), suggests that this polymorphism may be particularly significant in Middle Eastern and South Asian populations. Research on populations with greater genetic diversity, such as the US, did not reveal any meaningful association (Nelson et al., 2005). This may be due to the diverse nature of the participants in the study or to differences in lifestyle factors and environmental exposures. This heterogeneity provides support to the idea that genetic risk factors plus population-specific factors like ethnicity, environmental carcinogens, and access to healthcare may interact to influence the development of breast cancer (Xie et al., 2000). The majority of the studies may have used less effective genotyping technology and smaller sample sizes than more recent

studies. This temporal dispersion shows the importance of methodological consistency in genetic association studies, as previous studies could not have complied with modern requirements for data reporting and quality control (Lu et al., 2010). The sample sizes of the studies also were different. For example, (Zúbor et al., 2006) reported the highest odds ratio in Slovakia (OR = 2.82; 95% CI: 1.05–7.6), but their population size was smaller, and they exclusively looked at postmenopausal women, which could result in a higher effect estimate due to their weak statistical power. Although they did not find any significant association, larger studies, such as the one carried out in the United States by (Nelson et al., 2005), produced accurate estimates (OR = 0.97; 95% CI: 0.79–1.18). All ten included studies reported essential statistical measures, such as standard errors (SEs), odds ratios (ORs), and confidence intervals (CIs), which is important because it is recognized for quantitative synthesis. The specific characteristics of all the included research, especially their geographic variation, methodological diversity, and time span, improve the depth of the analysis. These factors introduce some variation, but they also show how complex genetic contributions to breast cancer are across populations.

The current meta-analysis combined data from ten appropriate research studies to evaluate the association between the HER2 Ile655Val (rs1136201) polymorphism and breast cancer chance. A random-effects model that considered inter-study heterogeneity was used to carefully and essentially estimate the overall genetic possibility. The study showed a statistically significant association between the Ile655Val polymorphism and a higher chance of breast cancer, with a pooled odds ratio (OR) of 1.47 (95% CI: 1.07–1.87). According to this study, individuals with the normal form genotype (Ile/Ile) have a 47% chance of getting a breast cancer diagnosis than those with the variable allele (Val). The importance of this study is supported by previous findings from several individual investigations, such as (Bhatt et al., 2021) in India and (Al-Janabi et al., 2015) in Iran, which both reported ORs above 2.0, indicating a more than twofold increased possibility. A p-value of 0.058 and 45.3% were found when the heterogeneity between the studies was evaluated using the I^2 statistic. This degree of heterogeneity is typically considered moderate (Higgins et al., 2003), indicating that it is not significant, even though there is a great deal of variation among the included studies. Because of the non-significant p-value for heterogeneity, the observed differences in results could have been caused by methodological and demographic diversity rather than just random error. Examples of this include different ethnic backgrounds, genotyping techniques, and sample sizes. The nature of this moderate heterogeneity makes the random-effects model particularly appropriate. As compared to a fixed-effect model that assumes a single real effect size, the random-effects approach accounts for both within-study and between-study variance, making it more robust when applied to genetically and ethnically different populations (Borenstein et al., 2010). This has strengthened the conclusion that the HER2 Ile655Val polymorphism is an ongoing factor in many geographic and population contexts. The publication bias has been reduced by evaluating both positive and negative results and by including papers including an extended time frame from 2000 to 2021. However, it is still important to consider the fact that studies with significant findings are more likely to be published, as this may have an impact on the overall impact size, a drawback that many meta-analyses share (Egger et al., 1997). The HER2 Ile655Val polymorphism raises the chance of breast cancer, according to the meta-analysis's results.

In this meta-analysis, the relationship between the HER2 Ile655Val (rs1136201) polymorphism and breast cancer possibility was evaluated across a range of international populations.

According to the results, people who carry the Val allele may be more susceptible to breast cancer, particularly if they have the Val/Val and Ile/Val genotypes. This result corresponds to earlier research showing that the amino acid substitution of valine (Val) for isoleucine (Ile) at codon 655 may enhance HER2 receptor dimerization, leading to abnormal cell signalling and tumour development (Qu et al., 2008). Several of the studies that were part of this analysis showed statistically significant correlations. Heterozygous carriers (Ile/Val) also showed increased susceptibility to breast cancer, even though those with the Val/Val genotype had a significantly higher possibility (OR = 2.44) for the disease Al-Janabi et al. (2015). Ozturk et al. (2013), for example, found that a Turkish cohort was more at risk (OR = 1.98; 95% CI: 1.18–3.33). These findings corroborate the conclusion that Chinese women, especially those under 50, who carried the Val allele had a significantly higher probability (OR = 1.7; 95% CI: 1.1–2.6) (Xie et al., 2000). The Indian population also displayed comparable relationships. HER2 polymorphisms were identified as hazard factors in South Asian populations, whereas Bhatt et al. (2021) discovered a strong correlation between the Val allele and the chance of breast cancer (Ile/Val OR = 2.43; p = 0.004). According to Karen G. Montgomery et al. (2003), the cancer frequency among Val/Val carriers in Australia (OR = 2.8) supports previous findings that suggested HER2 genetic variants might function as alleles with low-penetrance susceptibility (Breyer et al., 2009). In Egypt, Naglaa R. AbdRabo et al. (2013) also discovered a strong correlation between the 655Val allele and breast cancer (OR = 2.2; 95% CI: 1.2–4.1). The co-occurrence of the HER2 polymorphism with another cancer-causing mutation resulted in a significant gene–gene interaction, which significantly increased the chance (OR = 4.1), further confirming the findings that HER2 polymorphisms may interact with other genetic pathways in carcinogenesis (Daniyal et al., 2021). According to Zubor et al. (2006), women over 45 with the Val/Val genotype were significantly more likely to develop breast cancer. This is interesting because it draws attention to the potential moderating role that age and hormone levels may play in HER2-related cancer susceptibility. This is in accordance with studies that demonstrated the role HER2 plays in tumor aggressiveness and hormone receptor regulation (Han et al., 2014).

Although other studies in this meta-analysis demonstrated a strong correlation between the HER2 Ile655Val polymorphism and an increased chance of breast cancer, some of the research did not yield statistically significant results. For example, Nelson et al. (2005) conducted a large case-control study in the United States and found no evidence of a significant association between the Ile/Val genotype and breast cancer. With an odds ratio (OR) of 0.97 and a 95% CI of 0.79–1.18, they did not find any increased or decreased among Val allele carriers. In the same way, Watrowski et al. (2015) in Austria did not find a significant association between the HER2 codon 655 polymorphism and breast cancer. Their results showed that the Val allele had little to no effect on the development of breast cancer, with an OR of 1.03 (95% CI: 0.56–1.90). According to Kamali-Sarvestani et al. (2004), the HER2 Ile655Val polymorphism was not significantly associated with breast cancer in the Iranian study population. They also discovered a non-significant result with an OR of 1.16 (95% CI: 0.67–2.03, p = 0.28). The lack of connection in these studies may be due to genetic heterogeneity among populations, where linkage disequilibrium patterns, background genetic architecture, and environmental exposures differ. For example, different ethnic groups have different frequencies of HER2 polymorphism alleles, and gene-environment interactions, such as diet, hormone exposure, and reproductive history, may affect gene expression or disease penetrance (Ho et al., 2020).

The presence of publication bias in this meta-analysis examining the association between the HER2 Ile655Val polymorphism and breast cancer possibility was assessed using a funnel plot. A prevalent concern in meta-analyses is publication bias, which occurs when studies with statistically significant or positive results have a higher chance of being published than studies with null or negative results (Dwan et al., 2008). Impact sizes may be overestimated as a result of this bias, which may also have an effect on the actual connection being studied. The funnel plot used in this study plots the log odds ratios of different studies against their standard errors, which stand for sample size and precision (Terrin et al., 2005). In the absence of publication bias, the plot should display a symmetrical, inverted funnel shape, suggesting that the studies are spread equally around the pooled effect estimate (Sterne et al., 2011). The null effect, or no relationship, was represented by a solid vertical line at Log (OR) = 1). The log (odds ratio) of 1 shows that there is no increased or decreased chance if the odds ratio (OR) is 1. According to this line of investigation, the HER2 Ile655Val polymorphism has no impact on the possibility of developing breast cancer. The dashed vertical line is the pooled or overall effect size for the meta-analysis. After calculating each study's weight, which is usually based on sample size and precision, it shows the average log (OR) of all included studies. Moving this line away from the null (solid line) indicates a statistically significant overall effect in that direction (left = protective, right = negative). It is simpler to distinguish between the individual research impacts and the overall meta-analytic conclusion when both lines are present (Sterne & Egger, 2001).

6. Conclusion

The findings of this meta-analysis indicate that the HER2 Ile655Val polymorphism is strongly associated with an increased possibility of breast cancer, particularly for younger women and members of particular ethnic groups. The presence of the Val allele (G) and the heterozygous Ile/Val (A/G) genotype have been frequently linked to an increased chance of breast cancer in numerous studies. Significant associations were found in certain populations using both dominant and recessive genetic models, suggesting that the polymorphism may serve as a marker of genetic susceptibility. The lack of statistically significant relationships in some studies, however, raises the possibility that other variables like small sample sizes, community-specific genetic characteristics, and alternative research methodologies could have an impact on the effects that were observed. These differences indicate the importance of accounting for genetic and demographic variation in future research. The HER2 Ile655Val polymorphism appears to play a major role in the development of breast cancer overall, and it may help support more customized approaches to threat assessment and treatment.

7. Ethical aspects and Impact on Society

A meta-analysis combines data from multiple studies to present a clearer, more thorough understanding of a research topic. In a meta-analysis, researchers do not engage with participants directly. Even if researchers do not collect new data from participants in a meta-analysis, they still have some important ethical responsibilities. Meta-analyses depend on real research participants even though they use published findings. Researchers should only include studies that have received ethical approval, which indicates that the study was evaluated by an ethics committee and that participants gave their informed consent (Moher et al., 2009). Research that was carried out incorrectly or unethically may produce inaccurate or unfavourable results. Consequently, a meta-analyst's ethical duty includes carefully evaluating the morality and quality of the original research (Stroup et al., 2000). Another fundamental

ethical principle is transparency. Researchers should give concise explanations of the studies they choose, the data they used and their analysis techniques. Because it can be checked for bias or errors by others, the research gains credibility (Matthew J Page et al., 2021). Meta-analyses can have a big social impact since they help doctors, health officials, and politicians make decisions. The researchers conducting the meta-analysis must respect the participants in the original studies. These people gave their personal information, and while meta-analysis is often based on summary statistics rather than personal data, it is still based on the experiences of real people. Therefore, it is essential that the initial research be carried out ethically, with the consent of participants and the approval of ethical review boards. For example, a meta-analysis could identify the most effective cancer treatment, improving patient care and potentially saving lives. This helps to guide future research in a way that is more inclusive and equitable. However, if bias or low-quality studies are used in the meta-analyses, the results could be incorrect. This might lead to the use of ineffective treatments or uninformed laws. Therefore, meta-analyses need to be carried out very carefully and ethically (JOHN P.A. IOANNIDIS, 2016).

The researchers conducting the meta-analysis must respect the participants in the original studies. These people gave their personal information, and while meta-analysis is often based on summary statistics rather than personal data, it is still based on the experiences of real people. Therefore, it is essential that the initial research be carried out ethically, with the consent of participants and the approval of ethical review boards. Every paper that is considered for potential inclusion in this study will undergo a thorough review process to make sure it possesses the required ethical clearances. Most of the studies have been approved by an ethical board or review committee. Reducing biases and promoting transparency preserved the methodology's accuracy. There are ten research articles in the final stages of development that will be considered for inclusion in this review. The articles must have included hospital or medical treatment, have sufficient follow-up, be based entirely on data collected from randomized studies, and have informed consent from all participants. Researching the connection between HER2 genetic polymorphisms, specifically Ile655Val, and breast cancer will help medical professionals better understand how genetic variations affect cancer development and treatment response (Xie et al., 2000). The importance of early genetic screening and targeted treatments for improving patient outcomes should be highlighted by raising public awareness of the link between HER2 gene mutations and breast cancer. Individualized treatment plans based on genetic profiles are crucial, and patients and medical professionals should be aware of this, as individuals with particular HER2 polymorphisms may be more prone to aggressive tumor activity or respond less well to treatment. In order to prevent breast cancer, detect it early, and treat it individually, it may be essential to understand these genetic factors (Zúbor et al., 2006).

8. Future Perspectives

Research on HER2 gene polymorphisms, specifically Ile655Val, emphasizes the growing importance of personalized therapy in the identification and treatment of breast cancer, especially in Asian and African populations where this variant is more prevalent. Since the clinical implications of these variations are still unknown, more research is required. These genetic changes could affect the activity of the HER2 protein, which could affect the aggressiveness of the cancer and how patients respond to treatment (Krishna et al., 2001). Many studies have examined the relationship between HER2 polymorphisms and breast cancer, with

varying degrees of success (Xie et al., 2000). Therefore, larger population-based studies involving a range of ethnic groups are needed to better understand the occurrence and potential clinical significance of these variations. Laboratory-based functional studies are also required to comprehend the effects of these polymorphisms on HER2 signalling pathways, which are essential for the survival and growth of cancer cells (Asahi Hishida et al., 2002). If a strong correlation can be established, HER2 polymorphisms could serve as predictive biomarkers, enabling a more precise selection of therapies like trastuzumab or more recent HER2-targeted medications (Isabel Blancas et al., 2024). This would be in favour of the shift to precision oncology, where treatment is guided by the patient's unique genetic profile. Ultimately, more studies on HER2 polymorphisms could lead to improved breast cancer detection, diagnosis, and customized treatment regimens.

9. Reference

Al-Janabi, A. M., Hussein, A., Algenabi, A., Kamoona, T. H., & Alkhafaji, S. M. (2015). Association of HER2 [ILe655Val] gene polymorphism and Breast Cancer Risk in Iraqi females Population. In *International Journal of Advanced Research* (Vol. 3). http://quantspy.org.

Anabia Sohail, & Prof. Dr. Asifullah Khan. (2021). *Deep Convolutional Neural Networks based Mitosis Detection in Breast Histology Images and Challenges.*

Antoniou, A., Pharoah, P. D. P., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., Loman, N., Olsson, H., Johannsson, O., Borg, A. °, Pasini, B., Radice, P., Manoukian, S., Eccles, D. M., Tang, N., Olah, E., Anton-Culver, H., Warner, E., Lubinski, J., … Easton, D. F. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined. *Cell.ComA Antoniou, PDP Pharoah, S Narod, HA Risch, JE Eyfjord, JL Hopper, N Loman, H OlssonThe American Journal of Human Genetics, 2003•cell.Com*, *72*, 1117–1130. https://www.cell.com/ajhg/pdf/S0002-9297(07)60640-5.pdf

Asahi Hishida, Nobuyuki Hamajima, Hiroji Iwata, Keitaro Matsuo, Kaoru Hirose, Nobuhiko Emi, & Kazuo Tajima. (2002). Population based, case-control study of HER2 genetic polymorphism and breast cancer. *Journal of the National Cancer Institute*, *94*(23), 1807–1808.

Bhatt, D., Verma, A. K., Bharti, P. S., Goyal, Y., Alsahli, M. A., Almatroudi, A., Rahmani, A. H., Almatroodi, S., Joshi, P. C., Alam, M. M., Ahmad, I., Zaman, G. S., & Dev, K. (2021). BCL-2 (-938C>A), BAX (-248G>A), and HER2 Ile655Val Polymorphisms and Breast Cancer Risk in Indian Population. *Journal of Oncology*, *2021*, 8865624. https://doi.org/10.1155/2021/8865624

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97–111. https://doi.org/10.1002/JRSM.12

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). 394 CA: A Cancer Journal for Clinicians Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA CANCER J CLIN*, *68*, 394–424. https://doi.org/10.3322/caac.21492

Breyer, J. P., Sanders, M. E., Airey, D. C., Cai, Q., Yaspan, B. L., Schuyler, P. A., Dai, Q., Boulos, F., Olivares, M. G., Bradley, K. M., Gao, Y. T., Page, D. L., Dupont, W. D., Zheng, W., & Smith, J. R. (2009). Heritable variation of ERBB2 and breast cancer risk. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *18*(4), 1252–1258. https://doi.org/10.1158/1055-9965.EPI-08-1202

Carlos L Arteaga, Mark X Sliwkowski, C kent Osborne, Edith A perez, Fabio puglisi, & Luca Gianni. (2011). Treatment of HER2- positive breast cancer: current status and future perspectives. *Review Article*, *9*, 16–32.

Coussens, L., Yang-Feng, T. L., Liao, Y. C., Chen, E., Gray, A., McGrath, J., Seeburg, P. H., Libermann, T. A., Schlessinger, J., Francke, U., Levinson, A., & Ullrich, A. (1985). Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with neu Oncogene. *Science*, *230*(4730), 1132–1139. https://doi.org/10.1126/SCIENCE.2999974

Daniyal, A., Santoso, I., Gunawan, N. H. P., Barliana, M. I., & Abdulah, R. (2021). Genetic influences in breast cancer drug resistance. *Breast Cancer: Targets and Therapy*, *13*, 59–85. https://doi.org/10.2147/BCTT.S284453/ASSET/78903D26-553E-4553-A707-B874205F5DF8/ASSETS/IMAGES/DBCT_A_33603458_ILG0006.JPG

Dwan, K., Altman, D. G., Arnaiz, J. A., Bloom, J., Chan, A.-W., Cronin, E., Decullier, E., Easterbrook, P. J., Elm, E., Gamble, C., Ghersi, D., Ioannidis, J. P. A., Simes, J., & Williamson, P. R. (2008). *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias*. https://doi.org/10.1371/journal.pone.0003081

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634. https://doi.org/10.1136/BMJ.315.7109.629

Elseaty, A., & Taktash, M. (2020). *Do Birth control pills increase the chance of getting breast cancer*. http://dr.limu.edu.ly/bitstream/handle/123456789/1300/cancer.pdf?sequence=1&isAllowed=y

E. Shelley Hwang, Sandy DeVries, Karen L. Chew, Dan H. Moore, Karla Kerlikowske, Ann Thor, Britt-Marie Ljung, & Frederic M. Waldman. (2004). Patterns of Chromosomal Alterations in Breast Ductal Carcinoma In situ. Clin Cancer Res 1 August 2004; 10 (15): 5160–5167. *Clinical Cancer Research*, *10*(5), 5160–5167.

GLASS, G. V. (1976). Primary, Secondary, and Meta-Analysis of Research1. *Educational Researcher*, *5*(10), 3–8. https://doi.org/10.3102/0013189X005010003

Govindasamy Muralidharan, K. (2017). *Biological and therapeutic aspects of breast cancer progression*. https://openarchive.ki.se/xmlui/handle/10616/45895

Han, X., Diao, L., Xu, Y., Xue, W., Ouyang, T., Li, J., Wang, T., Fan, Z., Fan, T., Lin, B., & Xie, Y. (2014). Association between the HER2 Ile655Val polymorphism and response to trastuzumab in women

with operable primary breast cancer. *Annals of Oncology*, *25*(6), 1158–1164. https://doi.org/10.1093/ANNONC/MDU111

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557–560. https://doi.org/10.1136/BMJ.327.7414.557

Ho, P. J., Ow, S. G. W., Sim, Y., Liu, J., Lim, S. H., Tan, E. Y., Tan, S. M., Lee, S. C., Tan, V. K. M., Yap, Y. S., Chay, W. Y., Tan, B. K. T., Wong, F. Y., Li, J., & Hartman, M. (2020). Impact of deviation from guideline recommended treatment on breast cancer survival in Asia. *Scientific Reports 2020 10:1*, *10*(1), 1–12. https://doi.org/10.1038/s41598-020-58007-5

Isabel Blancas, Marina Linares-Rodriguez, Cella Martin- Bravo, Cella Gomez-Peria, & Fernando Rodriguez-Serrano. (2024). HER2/neu 655 polymorphism, trastuzumab-induced cardiotoxicity, and survival in HER2-positive breast cancer patients. *Research Article*.

JOHN P.A. IOANNIDIS. (2016). The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *The Milbank Quarterly*, *94*(3), 485–514. https://doi.org/10.1111/1468-0009.12210

Kamali-Sarvestani, E., Talei, A. R., & Merat, A. (2004). Ile to Val polymorphism at codon 655 of HER-2 gene and breast cancer risk in Iranian women. *Cancer Letters*, *215*(1), 83–87. https://doi.org/10.1016/J.CANLET.2004.04.007

Karen G. Montgomery, Dorota M. Gertig, Simon W. Baxter, Roger L. Milne, Gillian S. Dite, Margaret R. E. McCredie, Graham G. Giles, Melissa C. SoutheZ, John L. Hoppe, & Ian G. Campbell. (2003, October). *The HER2 I655V Polymorphism and Risk of Breast Cancer in Women < Age 40 Years1 | Cancer Epidemiology, Biomarkers & Prevention | American Association for Cancer Research*. https://aacrjournals.org/cebp/article/12/10/1109/253630/The-HER2-I655V-Polymorphism-and-Risk-of-Breast

Krishna, B. M., Chaudhary, S., Panda, A. K., Mishra, D. R., & Mishra, S. K. (2001). *Her2 Ile 655 Val polymorphism and its association with breast cancer risk: an updated meta-analysis of case-control studies*. https://doi.org/10.1038/s41598-018-25769-y

Krishna, B. M., Chaudhary, S., Panda, A. K., Mishra, D. R., & Mishra, S. K. (2018). Her2 Ile655Val polymorphism and its association with breast cancer risk: an updated meta-analysis of case-control studies. *Scientific Reports*, *8*(1), 7427. https://doi.org/10.1038/s41598-018-25769-y

Lacruz, M. E., Thies, S., Schmidt-Pokrzywniak, A., Wittenberg, I., Engler, T., Reinwald, F., Klinkhammer-Schalke, M., Zeissig, S. R., Franke, B., Weitmann, K., & Ignatov, A. (2025). Clinical characteristics, metastasis patterns, and treatment outcomes of HER2-low breast cancer. *Scientific Reports 2025 15:1*, *15*(1), 1–11. https://doi.org/10.1038/s41598-025-88394-6

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*, *339*. https://doi.org/10.1136/BMJ.B2700

Lu, S., Wang, Z., Liu, H., & Hao, X. (2010). HER2 Ile655Val polymorphism contributes to breast cancer risk: evidence from 27 case–control studies. *Breast Cancer Research and Treatment*, *124*(3), 771–778. https://doi.org/10.1007/s10549-010-0886-z

Matthew J Page, Joanne E McKenzie, Patrick M Bossuyt, Isabelle Boutron, Tammy C Hoffmann, Cynthia D Mulrow, Larissa Shamseer, Jennifer M Tetzlaff, Elie A Akl, Sue E Brennan, Roger Chou, Julie Glanville, Jeremy M Grimshaw, & Asbjørn Hróbjartsson. (2021). *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*.

Mitri, Z., Constantine, T., & O'Regan, R. (2012). The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemotherapy Research and Practice*, *2012*, 1–7. https://doi.org/10.1155/2012/743193

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*, *339*(7716), 332–336. https://doi.org/10.1136/BMJ.B2535

Naglaa R. AbdRabo, Hanan H. Shehata, Manal B. Ahme, & Fatehia A. Bayoumi. (2013). *HER1 R497K and HER2 I655V Polymorphisms Are Linked to Development of Breast Cancer*. https://onlinelibrary.wiley.com/doi/epdf/10.3233/dma-130989.

Nawaz, Y., Nazar, I., Ali, U., Ahmad, H., & Iqbal, N. (2023). *Research Journal of Applied Medical Sciences*. https://www.researchgate.net/profile/Umer-Ali-4/publication/376678618_A_review_on_probability_of_breast_cancer_in_women_under_a_Creative_Commons_Attribution-Non_Commercial_40_CC_BY-NC_40_International_License/links/6582f01d2468df72d3be9d0e/A-review-on-probability-of-breast-cancer-in-women-under-a-Creative-Commons-Attribution-Non-Commercial-40-CC-BY-NC-40-International-License.pdf

Nelson, S. E., Gould, M. N., Hampton, J. M., & Trentham-Dietz, A. (2005). A case-control study of the HER2 Ile655Val polymorphism in relation to risk of invasive breast cancer. *Breast Cancer Research*, *7*(3). https://doi.org/10.1186/BCR1004

Ozturk, O., Canbay, E., Kahraman, O. T., Fatih Seyhan, M., Aydogan, F., Celik, V., & Uras, C. (2013). HER2 Ile655Val and PTEN IVS4 polymorphisms in patients with breast cancer. *Molecular Biology Reports*, *40*(2), 1813–1818. https://doi.org/10.1007/S11033-012-2235-2/METRICS

Qu, S., Cai, Q., Gao, Y. T., Lu, W., Cai, H., Su, Y., Wang, S. E., Shu, X. O., & Zheng, W. (2008). ERBB2 genetic polymorphism and breast cancer risk in Chinese women: a population-based case-control study. *Breast Cancer Research and Treatment*, *110*(1), 169–176. https://doi.org/10.1007/S10549-007-9691-8

Rani, S., & Shetty, D. N. (2010). Meta-analysis in medical research. *Hippokratia*, *14*(Suppl 1), 29. https://doi.org/10.4018/979-8-3693-2655-8.ch013

Redhwan Ahmed Al-Naggar. (2013). *Principles and practice of Cancer prevention and control*. OMICS Group eBooks.

Rubin, I., & Yarden, Y. (2001). The basic biology of HER2. *Annals of Oncology*, *12*(SUPPL. 1), S3–S8. https://doi.org/10.1093/ANNONC/12.SUPPL_1.S3

Sharma, Ganesh N., Dave, R., Sanadya, Jyostana., Sharma, Piush, & .Sharma K. (2010). VARIOUS TYPES AND MANAGEMENT OF BREAST CANCER AN OVERVIEW. *Journal of Advanced Pharmaceutical Technology & Research*, *1*(2), 109–126.

Slamon, D. J., Clark, G. M., Wong, S. G., Levin, W. J., Ullrich, A., & McGuire, W. L. (1987). Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene. *Science*, *235*(4785), 182–191. https://doi.org/10.1126/SCIENCE.3798106

Sterne, J. A. C., & Egger, M. (2001). Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of Clinical Epidemiology*, *54*(10), 1046–1055. https://doi.org/10.1016/S0895-4356(01)00377-8

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., Carpenter, J., Rücker, G., Harbord, R. M., Schmid, C. H., Tetzlaff, J., Deeks, J. J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D. G., Moher, D., & Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, *343*(7818). https://doi.org/10.1136/BMJ.D4002

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A., & Thacker, S. B. (2000). Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *JAMA*, *283*(15), 2008–2012. https://doi.org/10.1001/JAMA.283.15.2008

Terrin, N., Schmid, C. H., & Lau, J. (2005). In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *Journal of Clinical Epidemiology*, *58*(9), 894–901. https://doi.org/10.1016/J.JCLINEPI.2005.01.006

Thanh, T. N., Nguyen Tran, B. S., Hoang Thi, A. P., Binh, T. T., Nguyen, T. B., Minh, T. Le, Nguyen Vu, Q. H., & Cong, T. D. (2021). HER2Ile655Val Single Nucleotide Polymorphism Associated with Early-Onset Breast Cancer Susceptibility: A Systematic Review and Meta-Analysis. *Asian Pacific Journal of Cancer Prevention : APJCP*, *22*(1), 11. https://doi.org/10.31557/APJCP.2021.22.1.11

WATROWSKI, R., CASTILLO-TONG, D. C., WOLF, A., SCHUSTER, E., FISCHER, M. B., SPEISER, P., & ZEILLINGER, R. (2015). HER2 Codon 655 (Ile/Val) Polymorphism and Breast Cancer in Austrian Women. *Anticancer Research*, *35*(11).

Weigelt, B., Geyer, F. C., & Reis-Filho, J. S. (2010). *Histological types of breast cancer: How special are they?* https://doi.org/10.1016/j.molonc.2010.04.004

Xie, D., Shu, X. O., Deng, Z., Wen, W. Q., Creek, K. E., Dai, Q., Gao, Y. T., Jin, F., & Zheng, W. (2000). Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. *Journal of the National Cancer Institute*, *92*(5), 412–417. https://doi.org/10.1093/jnci/92.5.412

Zúbor, P., Vojvodová, A., Danko, J., Kajo, K., Szunyogh, N., Lasabová, Z., Biringer, K., Visnovský, J., Dókus, K., Galajda, P., & Plank, L. (2006). HER-2 [Ile655Val] polymorphism in association with breast cancer risk: a population-based case-control study in Slovakia. *Neoplasma*, *53*(1), 49–55.