Breast Cancer: Targets and Therapy

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REVIEW

Genetic Influences in Breast Cancer Drug Resistance

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Abstract: Breast cancer is the most common cancer in adult women aged 20 to 50 years. The therapeutic regimens that are commonly recommended to treat breast cancer are human epidermal growth factor receptor 2 (HER2) targeted therapy, endocrine therapy, and systemic chemotherapy. The selection of pharmacotherapy is based on the characteristics of the tumor and its hormone receptor status, specifically, the presence of HER2, progesterone receptors, and estrogen receptors. Breast cancer pharmacotherapy often gives different results in various populations, which may cause therapeutic failure. Different types of congenital drug resistance in individuals can cause this. Genetic polymorphism is a factor in the occurrence of congenital drug resistance. This review explores the relationship between genetic polymorphisms and resistance to breast cancer therapy. It considers studies published from 2010 to 2020 concerning the relationship of genetic polymorphisms and breast cancer therapy. Several gene polymorphisms are found to be related to longer overall survival, worse relapse-free survival, higher pathological complete response, and increased disease-free survival in breast cancer patients. The presence of these gene polymorphisms can be considered in the treatment of breast cancer in order to shape personalized therapy to yield better results.

Keywords: breast cancer, genetic polymorphisms, resistance therapy

Introduction

Breast cancer is the most widespread cancer in women aged 20–50 years. Annually, approximately 2.1 million women are suffering from this disease, including those who have new diagnoses and received treatment.[1] In 2018, a study estimated that 11.6% of cancer patients were classified as having breast cancer, with a mortality rate of 6.6% of all cancer-related deaths. Breast cancer has the highest rate of new cases among 154 countries and is the leading cause of mortality for 103 countries.[2] It can be estimated that the incidence of breast cancer will increase by 26.1% by 2030, based on incident cases of the disease in 2018.[3]

Several medications are widely available for treating breast cancer. Characteristics of the tumor and its hormone receptor (HR) status, such as estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) in the tumor, determine the recommendations for more specific treatment choices, such as systemic chemotherapy, endocrine therapy, or HER2-targeted therapy, to yield a better disease prognosis.[4] According to the Clinical Practice Guidelines of Breast Cancer of the National Comprehensive Cancer Network, anthracycline and cyclophosphamide are usually chosen for a recommended chemotherapy regimen. The HER2-targeting

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drug trastuzumab suppresses the mitogen activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways in cell cycle arrest[5] and is also considered as an addition to the main chemotherapy regimens[6] such as taxane,[7–9] and thus increases early-stage breast cancer patient survival rate. Tamoxifen is usually given as monotherapy for early-stage breast cancer[10–12] or as a replacement for an aromatase inhibitor (AI) regimen after 2 to 3 years.[13,14] The use of AIs such as anastrozole, letrozole, and exemestane demonstrated better efficacy in lowering the risk of recurrence of breast cancer when compared with tamoxifen in postmenopausal women with HER2-positive breast cancer.[15–17]

Despite improvements in disease prognosis and the overall benefits of using chemotherapy and adjuvants, therapy in breast cancer often produces different results in selected populations. Such differences are a result of innate resistance to some of the drugs employed.[18] Drug resistance is a major source of cancer therapy failure.[19] The drug response differs from person to person mainly because of mutations in DNA that can alter drug efficacy.[20] Resistance may be explained by different mechanisms, such as alteration of drug pharmacokinetics,[21,22] amplification or reduction in cell signaling,[23] changes in pharmacodynamic-related receptor numbers,[24] and so on. It is highly relevant to explore further gene polymorphisms that may affect therapy responses in breast cancer, in order to identify drug resistance and provide information that enables development of personalized medicine.

Methodology

For this review, the PubMed database was searched for relevant literature. The search terms were "polymorphism breast cancer therapy" with added filters specific to articles that were published during the 10 years from 2010 to 2020. The search was made in May 2020, and scrutiny of eligible articles was conducted manually by excluding non-English studies, reviews, and unrelated studies, such as those not discussing breast cancer pharmacotherapy outcome and genetic polymorphisms. A flowchart for the literature search procedure is presented in Figure 1.

From the 210 articles identified in May 2020, this review evaluates the results of 36 studies[18,25–60] that particularly focused on the pharmacogenetic influences in breast cancer drug resistance (Table 1). The data that discussed in this review article was extracted from each identified study. These studies reported an association with breast cancer drug resistance for several genes, including

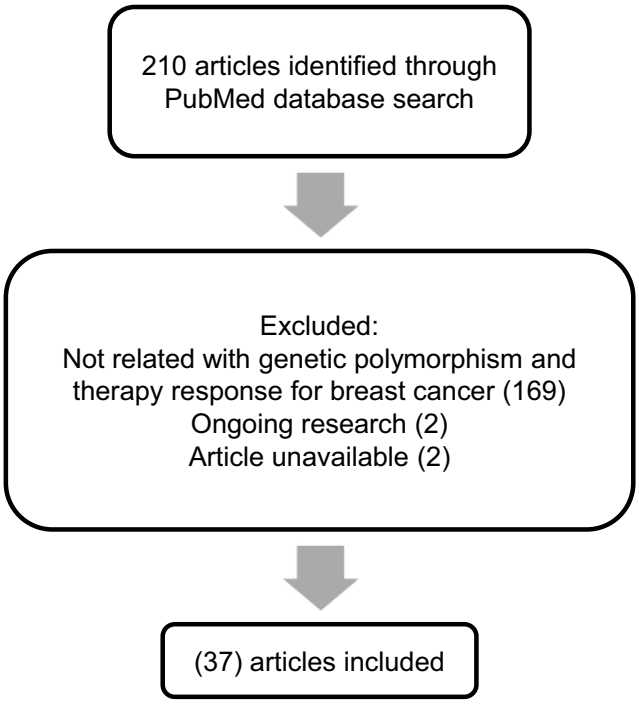

Figure 1 Flowchart representing the literature search process.

ABCB1, BARD1, BRCA1, BRCA2, CD24, CYBA, CYP19A1, CYP2C19, CYP2C9, CYP2D6, CYP3A4, FCGR2A, FCGR2B, FCGR3A, FGFR4, GSTM1, GSTP1, GSTT1, HER2, HER3, IL12B, KDR, MDM2, MEG3, SLC, TGFBR2, TP53, UGT1A8, UGT2B15, and *UGT2B7*.

Clinical endpoints included in this article are BCSS, breast-cancer-specific survival; BCFI, breast-cancer-free interval; DFS, disease-free survival; DSS, disease-specific survival CR, complete response; EFS, event-free survival; OR, overall response; ORR, overall response rate; OS, overall survival; pCR, progression complete response; PFS, progression-free survival; PR, partial response; RFS, recurrence-free survival; SD, stable disease; TTF, time-to-treatment failure; and TTP, time to progression.

ABCB1

ATP-binding cassette (ABC) is a transporter for various types of drug molecules, and among them are drugs for chemotherapy. By expending energy, this gene transporter helps drug molecules to pass through biological membranes. The subfamily of *ABC* is classified as *ABCB, ABCG, ABCD, ABCF, ABCCI*, and *ABCCII*.[61] Polymorphism in the transporter gene can contribute to multidrug resistance because it may be responsible for changes that induce differences in therapy for different individuals.

Table 1 Association Between Genetic Polymorphism and Therapy Response

Genes	Therapy	Study Population	Ethnic	Clinical Setting	Method Used for Genotyping	Results	References
ABCB1							
rs2032582 GT	FEC	991 breast cancer patients	–	Belgium	Sequenom MassARRAY	Had a significant association with better BCSS HR 0.5, 95% CI 0.3–0.9, p = 0.021	Vulsteke et al, 2014.
3435 C>T	Anthracycline-based, Anthracycline + Paclitaxel, FAC, FEC	770 patients (9 studies)	German (Caucasian), Indonesian (Asian), Korean (Asian), Indian, Slovak (Caucasian), Chinese (Asian), Chinos (Asian), Indiann, Spanish (Caucasian)		PCR-SEQ, PCR-RFLP, TAQMAN	Had no significant association with response to chemotherapy Dominant OR 0.888, 95% CI 0.558–1.413	Madrid-Paredes et al, 2017
3435 C>T	FEC/FAC	100 patients		India	PCR-RFLP	Had no significant association with better treatment response p = 0.110	Chaturvedi et al, 2013.
1236 C>T	Anthracycline-based, FAC, FEC	566 patients (6 studies)	Chinese (Asian), Chinos (Asian), Arabic, Indian, Spanish (Caucasian)		PCR-RFLP, TAQMAN	No significant association with response to chemotherapy Dominant OR: 1.968, 95% CI 0.609–6.362	Madrid-Paredes et al, 2017.
1236 C>T	FEC/FAC	100 patients		India	PCR-RFLP	Better treatment response compared with TT OR: 5.17 95% CI 1.3–20.2, p = 0.018	Chaturvedi et al, 2013.
2677 G>T/A	Anthracycline-based, Anthracycline +Paclitaxel	367 patients (3 studies)	Korean (Asian), Chinos (Asian), Indian		PCR-SEQ, PCR-RFLP	Had no significant association with response to chemotherapy OR 0.854. 95% CI 0.418–1.744	Madrid-Paredes et al, 2017.
2677 G>T/A	FEC/FAC	100 patients		India	PCR-RFLP	Had no significant association with better treatment response p = 0.421	Chaturvedi et al, 2013.
rs1045642	Cyclophosphamide, doxorubicin, TA/TAC, FAC, Gemcitabine, paclitaxel, Docetaxel, doxorubicin	684 patients (4 studies)		UK, China, Korea	Genes were extracted from 555,117 genotyped SNPs in the Affymetrix Genome-Wide Human SNP array 6.0 chip	Had a significant association with worse progression-free survival HR 1.33, 95% CI 1.07–1.64	Kim et al, 2018
BARD1							
rs2070096	TCH	157 primary breast cancer patients		Ireland	Mass Spectrometry based Genotyping	Had a significant association with worse RFS p = 0.05	Coté et al, 2018
rs2229571	TCH	157 primary breast cancer patients		Ireland	Mass Spectrometry based Genotyping	Had no significant association with OS and RFS Carboplatin p = 0.04, cisplatin p = 0.02	Coté et al, 2018

(*Continued*)

Table 1 (Continued).

Genes	Therapy	Study Population	Ethnic	Clinical Setting	Method Used for Genotyping	Results	References
BRCA1 & BRCA2							
90 SNPs	Carboplatin	291 patients			SNP Type Assay	Had no significant association in overall pCR and DFS OR 3.50, 95% CI, 1.39–8.84, p = 0.008	Hahnen et al, 2017.
CD24							
Ala/Val genotype	Anthracycline	257 patients		Germany	TaqMan	Had a significant association with better pCR OR 4.97, 95% CI 1.72–14.33, P = 0.003	Marmé et al, 2010.
	Taxane	257 Patients		Germany	TaqMan	Had a significant association with better pCR OR 4.97, 95% CI 1.72–14.33, P = 0.003	Marmé et al, 2010.
CYBA							
rs4673 CT	FEC	991 breast cancer patients		Belgium	Sequenom MassARRAY	Had a significant association with worse RFI HR 1.8, 95% CI 1.2–2.7; p = 0.006	Vulsteke et al, 2014.
CYP19A1							
rs4646	Aromatase Inhibitor	2646 patients (12 studies)	Caucasian, Asian, Black, Others	Netherlands, China, Italy, USA, UK, Korea, Spain		Had a significant association with increased TTP compared with wild type gene HR = 0.51, 95% CI = 0.33–0.78, p = 0.002	Artigalás et al, 2015
CYP2C19							
CYP2C19*2	Tamoxifen	494 patients		Netherlands	Taqman Allelic Discrimination Assay	Had a significant association with better TTF HR 0.26, p = 0.001	Beelen et al, 2013.
CYP2C19*2 and *17	Tamoxifen	787 patients (6 studies)	Netherland, USA, Germany, Switzerland	Caucasians		Had a significant association with better survival of disease OR 0.46 95% CI 0.21–1.01, p = 0.233	Bai et al, 2014
CYP2C9							
rs1057910	FEC	991 breast cancer patients		Belgium	Sequenom MassARRAY	Had a significant association with worse RFI HR 30.4, 95% CI 6.1–151.5, p<0.001	Vulsteke et al, 2014.
CYP2D6							

CYP2D6*4	Tamoxifen	4861 postmenopausal women with hormone receptor and breast cancer without previous therapy		Worldwide	PCR-based GenomeLab SNPstream Geontyping System & 7900HT Fast Real-Time PCR System	No significant association with BCFI p = 0.35	Regan et al, 2012.
5 SNPs	Tamoxifen	731 patients	Dutch		TAQMAN, *3 with pyrosequencing	No significant association in DFS compared with extensive metabolizers Unadjusted HR 1.33, 95% CI 0.52–3.43, p = 0.55	Dezentjé et al, 2013.
12 SNPs	Tamoxifen	297 patients	Caucasian,	Belgium & Switzerland	Sequenom MassARRAY	No significant association with endoxifen concentration and ORR and PFS p = 0.56	Neven et al, 2018.
CYP2D6*10	Tamoxifen	667 patients		Belgium & Netherlands	Amplichip CYP450 Test	No significant association with endoxifen concentration and RFS HR 0.989, 95% CI 0.945–1.035, p = 0.627	Sanchez-Spitman et al, 2019.
Poor Metabolizers (two inactive alleles: *3-*8, *11-*16, *19-*21, *38, *40, *42)	Endoxifen	13,001 patients (29 studies)	NA	NA	TAQMAN, Tag-It, Amplichip, SNaPshot, BioTools Taq, BeadChip SNP, 9700 Thermal Cycler	Had a significant association with lower endoxifen concentration and/or clinical outcomes compared with *extensive metabolizers* Mean ± s.d endoxifen concentration 8.8±,7.2 versus 22.3±,11.8, p < 0.05	Hwang, et al, 2018.
CYP2D6*1,*10, *17,*41,*4, dan *5	Tamoxifen	5183 patients (10 studies)	Asian and Caucasians		PCR-based method, TAQMAN, PCR-RFLP	Had a significant association with increased risk of disease recurrence. HRs (95% CIs) were 1.44 (1.15–1.80) in the fixed effect model and 1.60 (1.04–2.47) in the random effect model	Jung, et al, 2014
CYP3A4							
1B/*1A	CAF	350 patients	White, Black, Other		PyroSequencing & TAQMAN Real-Time PCR	Had a significant association with worse DFS compared with *1A/*1A' HR 2.44, 95% CI 1.52–5.14	Gor, et al, 2010.
FCGR							
FCGR2A 131H/H	Trastuzumab	76 patients			Goldgate Genotyping	Had a significant association with better PFS compared with 131R/R p = 0.034	Tamura, et al, 2011
FCGR2A 131H/H	Trastuzumab	1189 patient with HER2-positive, invasive, high-risk, node-negative or node-positive adenocarcinoma		Worldwide	Sanger sequencing and Sequenom mass spectrometry	No significant association with DFS compared with 131R/R p = 0.76	Hurvitz et al, 2012

(*Continued*)

Table 1 (Continued).

Genes	Therapy	Study Population	Ethnic	Clinical Setting	Method Used for Genotyping	Results	References
FCGR2A 131H/H	Trastuzumab	1325 patients			TaqMan Real-Time PCR	No significant association with DFS compared with 131R/R p = 0.64	Norton et al, 2014
FCGR2A 131H/H	Trastuzumab	1251 patients		United States	iPLEX Pro Chemistry & Mass Spectrometry	Had a significant association with better DFS compared with 131R/R HR 0.31, 95% CI 0.19–0.49, P < 0.001	Gavin et al, 2017.
FCGR2A 131H/H	Trastuzumab	132 patients			Fluorogenic PCR with GeneAmp	Had a significant association with better EFS compared with 131R/R p = 0.027	Roca et al, 2013.
FCGR2B 232I/I	Trastuzumab	1325 patients			TaqMan Real-Time PCR	Had a significant association with better DFS compared with 232T/T p = 0.03	Norton et al, 2014
FCGR3A 158V/V	Trastuzumab	76 patients			Goldgate Genotyping	No significant association with PFS compared with 158F/V and 158F/F, but showed overall higher response rate p = 0.37	Tamura, et al, 2011.
FCGR3A 158V/V	Trastuzumab	1189 patient with HER2-positive, invasive, high-risk, node-negative or node-positive adenocarcinoma		Worldwide	Sanger sequencing and Sequenom mass spectrometry	No significant association with DFS compared with 158F/F p = 0.98	Hurvitz et al, 2012
FCGR3A 158V/V	Trastuzumab	1325 patients			TaqMan Real-Time PCR	No significant association with DFS compared with 158F/F p = 0.77	Norton et al, 2014
FCGR3A 158V/V	Trastuzumab (ACT Arm)	1251 patients		United States	iPLEX Pro Chemistry & Mass Spectrometry	Had a significant association with worse prognosis compared with 158 F/F HR 1.57, 95% CI 1.15–2.14, p = 0.005	Gavin et al, 2017.
FCGR3A 158V/V	Trastuzumab (ACTH Arm)	1251 patients		United States	iPLEX Pro Chemistry & Mass Spectrometry	Had a significant association with better prognosis compared with 158 F/F HR 0.68, 95% CI 0.48–0.96, p = 0.03	Gavin et al, 2017.
FCGR3A 158V/V	Trastuzumab	132 patients			Fluorogenic PCR with GeneAmp	No significant association with EFS compared with 158F/F p = 0.08	Roca et al, 2013.
FGFR4							
arg388	AC-Doc	257 patients diagnosed with T2-4, N0-2, M0 breast cancer		Germany	TaqMan Genotyping Assay	Had a significant association with better pCR rate OR 3.79, p = 0.03	Marmé et al, 2010.

arg388	AP-Doc	257 patients diagnosed with T2-4, N0-2, M0 breast cancer		Germany	TaqMan Genotyping Assay	No significant association with pCR rate OR 3.18, p = 0.018	Marmé et al, 2010.
GSTP1 & GSTT1							
GSTP1 c.313A>G	Doxorubicin	159 patients		Spain	TaqMan	Had an association with lower chemoresistance risk OR 0.106, CI95% 0.012–0.898, p = 0.040	Romero et al, 2012.
GSTP1 c.313A>G	Docetaxel	159 patients		Spain	TaqMan	No significant association with chemoresistance risk p = 0.016	Romero et al, 2012.
GSTP1 105Val/Val genotype	CTX	120 patients			PCR-RFLP	Had a significant association with worse DFS PR = 0.35, 95% CI = 0.13–0.78, p = 0.006	Zhang et al, 2011.
GSTP1 GG genotype	Cyclophosphamide	1332 patients		North America	MALDI-TOF	No significant association with treatment outcome p = 0.83	Yao et al, 2010.
GSTT1 *null* genotype	CAF	350 patients	White, Black, Other		PyroSequencing & TAQMAN Real-Time PCR	Had a significant association with better DFS and OS compared with other variant Adjusted DFS HR 1.95 p = 0.053	Gor, et al, 2010.
GSTM *null* genotype	Anthracycline based chemotherapy	1468 patients (11 studies)	Asians, Caucasians, Mixed	Tunisia, China, Brasil, USA, Spain, Iran, India	PCR-RFLP	Had a significant association with worse responsiveness to chemotherapy OR 0.74, CI 0.60–0.92, p = 0.006	Kong et al, 2016
HER2							
−3444C>T	Trastuzumab-Lapatinib-Bevacizumab	94 metastatic breast cancer patients		United States	Sanger Sequencing	No significant association with SD≥6 months/PR/CR rate and TTF p = 0.038	Falchook et al, 2015.
−1985G>T	Trastuzumab-Lapatinib-Bevacizumab	94 metastatic breast cancer patients		United States	Sanger Sequencing	No significant association with SD≥6 months/PR/CR rate and TTF p = 0.038	Falchook et al, 2015.
1655A A>G	Trastuzumab-Lapatinib-Bevacizumab	94 metastatic breast cancer patients		United States	Sanger Sequencing	No significant association with SD≥6 months/PR/CR rate and TTF p = 0.038	Falchook et al, 2015.
P1170A C>G	Trastuzumab-Lapatinib-Bevacizumab	94 metastatic breast cancer patients		United States	Sanger Sequencing	No significant association with SD≥6 months/PR/CR rate and TTF p = 0.038	Falchook et al, 2015.
rs1810132 (STR C>T)	Trastuzumab-Lapatinib-Bevacizumab	94 metastatic breast cancer patients		United States	Sanger Sequencing	No significant association with SD≥6 months/PR/CR rate and TTF p = 0.038	Falchook et al, 2015.
HER3							

(*Continued*)

Table 1 (Continued).

Genes	Therapy	Study Population	Ethnic	Clinical Setting	Method Used for Genotyping	Results	References
rs2229046	TCH	157 primary breast cancer patients	Caucasian	Ireland	Mass spectrometry-based genotyping	Had a significant association with worse RFS p = 1.51×10^{-3}	Coté et al, 2018
rs77123	TCH	157 primary breast cancer patients	Caucasian	Ireland	Mass spectrometry-based genotyping	Had a significant association with worse RFS p = 0.05	Coté et al, 2018
KDR/VEGFR2							
rs2071559 (A>G)	Bevacizumab	113 HER2 positive patients	Caucasian	Italia	TaqMan	No significant association with PFS p=0.03	Allegrini et al, 2014.
rs2071559	Capecitabine	70 TN breast cancer patient	Caucasian	Rusia	TaqMan	Had a significant association with better pCR rate p = 0.016	Babyshkina et al, 2018.
rs11133360 (T>C)	Bevacizumab	113 HER2 positive patients	Caucasian	Italia	TaqMan	Had a significant association with worse PFS and OS for patients carrying SNP IL-8 rs4073 p=0.73	Allegrini et al, 2014.
IL12B							
rs2546892 (G > A)	Chemotherapy	499 patients	Caucasians	Eropa	iCOGS	Had a significant association with worse OS HR 1.50 95% CI 1.21–1.86, p = 1.81×10^{-4}	Lei et al, 2015
rs2853694 (A > C)	Chemotherapy	499 patients	Caucasians	Eropa	iCOGS	Had a significant association with better OS HR 0.73 95% CI 0.61–0.87, p = 3.67×10^{-4}	Lei et al, 2015
MDM2							
rs2279744 (309 T>G)	Paclitaxel & Epirubicin	223 patients with primary stage III breast cancers	Caucasian	Norwegian	PCR	No significant association with RFS p= 0.012	Chrisanthar et al, 2011
MEG3							
rs10132552 TT genotype	Cisplatin	144 patients			Mass Array	Had a significant association with worse DFS HR = 0.257, 95% CI 0.069–0.951, p = 0.042	Bayarmaa et al, 2019.
SLC							
rs7867504 (CC and CT genotype)	Paclitaxel & Gemcitabine	324 MBC Patients	Asian	Korea	MassArray	Had a significant association with better OS HR 2.6, 95% CI 1.1–6.3, p = 0.027	Lee et al, 2014

rs747199 and rs760370 (GA haplotype)	Paclitaxel & Gemcitabine	324 MBC paients	Asian	Korea	MassArray	Had a significant association with better OS p = 0.030, HR 3.391, 95% CI 1.13–10.19	Lee et al, 2014
rs4149056	Aromatase Inhibitors	503 patients		US	PCR	Had a significant association with worse outcome OR 1.84; 95% CI 1.08–2.14; p = 0.025)	Dempsey et al, 2019.
rs10841753	Aromatase Inhibitors	503 patients		US	PCR	Had a significant association with lower risk of detectable estrone OR: 0.61, 95% CI 0.41–0.90, p = 0.013	Dempsey et al, 2019.
TGFBR2							
rs1367610 (G > C)	Chemotherapy	499 patients	Caucasians	Eropa	iCOGS	Had a significant association with worse OS 95% CI 1.22–1.95, $p = 3.08 \times 10^{-4}$	Lei et al, 2015
TP53							
	Paclitaxel & Epirubicin	223 patients with primary stage III breast cancers	Caucasian	Norwegian	PCR	Had a significant association with worse RFS and DSS p= 0.007	Chrisanthar et al, 2011
UGT							
UGT2B15*2	Tamoxifen	9799 postmenopause early stage breat cancer	Caucasian	Netherland	Taqman	May be associated with worse DFS 95% CI 0.25–0.89; p = 0.015)	Dezentjé et al, 2013.
UGT2B15*2	Tamoxifen	541 breast cancer recurrent cases	Caucasian	Denmark	Taqman Kit	Had no significant association with OR OR 1.0, 95% CI 0.70–1.5	Ahern et al, 2011
UGT2B7*2	Tamoxifen	541 breast cancer recurrent cases	Caucasian	Denmark	Taqman Kit	Had no significant association with OR OR 0.96, 95% CI 0.65–1.4	Ahern et al, 2011
UGT2B7 rs3924194	FEC	991 breast cancer patients	Caucasian	Belgium	Sequenom MassARRAY	Had an association with worse RFI HR 3.4, 95% CI 1.2–9.7, p = 0.023.	Vulsteke et al, 2014.
UGT1A8*3	Tamoxifen	541 breast cancer recurrent cases	Caucasian	Denmark	Taqman Kit	Had no significant association with OR OR = 0.95, 95% CI, 0.49–1.9	Ahern et al, 2011

Abbreviations: ACT, doxorubicin-cyclophosphamide-paclitaxel; AC-Doc, doxorubicin-cyclophosphamide-docetaxel; AP-Doc, doxorubicin-permetrexed-docetaxel; BCSS, breast cancer specific survival; BCFI, breast cancer free inteval; CMF, cyclophosphamide-metothrexate-fluorouracil; CTX, anthracycline-cyclophosphamide; DFS, disease-free survival; DSS, disease specific survival; CR, complete response; EFS, event free survival; FEC, fluorouracil-epirubicin-cyclophosphamide; OR, overall response; ORR, overall response rate; OS, overall survival; pCR, progression complete response; PFS, progression-free survival; PR, partial response; RFS, recurrence-free survival; SD, stable disease; TCH, docetaxel, cisplatin, trastuzumab; TTF, time-to-treatment failure; TTP, time to progression.

The *ABCB1* gene is located at chromosome 7 and expresses a 45-kB mRNA.[62] It encodes an active transporter of drugs involved in secreting cytotoxic agents from cells.[25] A study conducted by Vulsteke et al[25] suggests that the *ABCB1* GT genotype gene polymorphism gave better therapeutic effects in patients with early breast cancer treated with 5-fluorouracil (FU), eirenicon, and cyclophosphamide (FEC), compared with patients who had the *ABCB1* GG/GA genotype. Another study reported different results, such that polymorphisms in the *ABCB1* 2677 GG genotype demonstrated resistance to paclitaxel and anthracycline treatment. It is possible that in metastatic breast cancer treatment this gene polymorphism contributes to cross-resistance between paclitaxel and anthracycline. In addition, cases of resistance were found for the *ABCB1* 3435 CT genotype, which resulted in shorter overall survival (OS) and lower disease control rate when using anthracycline treatment.[63] Many studies had shown that the *ABCB1* 3435 C>T polymorphism is associated with anthracycline resistance, such as in a Chinese study where patients with the CT genotype were associated with poor prognosis[64] and patients with the TT genotype were associated with worse clinical response.[65]

In studies by Zhang et al[60] and Ji et al[64] polymorphism at ABCB1 1236 C>T showed association with poor response to anthracycline regiment chemotherapy, which is about dose delay in patients. In response evaluation, 1236C > T polymorphism was significantly associated with treatment response for CT genotype [OR = 5.17 (1.3–20.2), P = 0.018] and in dominant model (CC vs CT + TT) [OR = 4.63 (1.25–17.0), P = 0.021] and the T allele of 1236C>T was found to be associated with grade 2–4 toxicity [OR 1.48 (1.00–2.20), P = 0.049]. This may due to the variant allele in ABCB1 gene may lead to P-gp lower expression and resulted accumulation of drugs inside the cell, thus altering the distribution profile of the chemotherapeutic drugs inside cells. Therefore, ABCB1 polymorphisms do exert significant effects on breast cancer chemotherapy responses.[44] The meta-analysis results conducted by Kim et al[45] polymorphism *ABCB1* in rs1045642 (C>T) was associated with poor progression-free survival (PFS), especially in Asian patients (Hazard Ratio (HR) = 1.56, 95%, Confidence Interval (CI): 1.07–2.27). The association of rs1045642 with PFS was significant in observational studies (HR = 1.28, 95% CI: 1.05–1.56); however, this association was not significant in clinical trials (HR = 1.47, 95% CI: 0.96–2.27).

BARD1

Several genes may encode proteins that can interact with breast cancer gene-1 (*BRCA1*) and breast cancer gene-2 (*BRCA2*), thus inducing DNA and tumor suppressor damage. One such gene is *BRCA1*-associated RING domain 1 (*BARD1*) gene.[66] The *BARD1* gene produces a protein that is similar to the BRCA1 protein in terms of structure and function.[67] BRCA1 and BARD1 can be transformed into homodimer and heterodimer structures, where the former can be constructed through interaction with the really interesting new gene (RING) finger domain in the N-terminal portion, and the latter is made stable with bonds of 26–119 amino acid residues from BARD1 and 1–109 amino acid residues from BRCA1.[68] These interactions have an important function in the manifestation of breast cancer tumor suppression.[67] Generally, BARD1 has a function of regulating the stability of genotype and phenotype, and also has a role in DNA repair and ubiquitination.

The gene *BARD1* is located at chromosome region 2q34-35 with a size of 80 kB.[66] Minor alleles of *BARD1* (rs2229571) exhibit higher sensitivity to platinum-based treatments, such as carboplatin and cisplatin, in HER2 breast cancer patients. A study found no significant relationship between the polymorphism of *BARD1* in rs2229571 and the response of patients using docetaxel, carboplatin, and trastuzumab (TCH) compared with non-TCH treatment, but it also proved that there is a significant association such that patients who carry SNP in *BARD1* rs2070096 with minor alleles had worse relapse-free survival compared to patients who received non-TCH treatment. This thus suggests possible chemoresistance.[18]

BRCA1 and BRCA2

Mutation in the *BRCA* gene, which is classified as *BRCA1* and *BRCA2*, is related to 20% of breast cancer cases.[69] The main function of BRCA1 is to repair DNA through interaction with cell cycle regulators, tumor suppressors, and DNA repair proteins.[70,71] BRCA1 contains the domain of BRCA C-Terminal and RING, which are known to suppress the initiation of breast and ovarian cancer,[72] and therefore mutations at this domain are often observed in breast cancer patients. In contrast to BRCA1, BRCA2 has a major function in homologous recombination for repairing DNA damage.[73] BRCA2 is directly involved in the DNA repair process by involving RAD51, and RAD51 is carried by BRCA2 to sites of double-strand breaks.[74]

The *BRCA1* gene is located at chromosome region 17q21.3,[75] functioning as a tumor suppressor gene in terms of the appearance of wild-type alleles that are somatically mutated.[76] Mutations in this gene are more often found in triple-negative breast cancer (TNBC) patients.[77] The *BRCA2* gene is located at chromosome region 13q12-13.[78] More than 1800 mutations are known in the *BRCA2* gene, including insertion, frameshift deletion, and nonsense mutation.[79] BRCA1 and BRCA2 have essential roles in the process of DNA repair in order to maintain genome integrity through the presence of homologous recombination. The presence of polymorphism in *BRCA1* and *BRCA2* genes can affect the efficacy of breast cancer treatment. It is known that TNBC patients with a variation in *BRCA1* and *BRCA2* genes did not show significant changes in overall part and disease-free survival (DFS) values between treatment regimens without carboplatin and with carboplatin. However, patients without a variation in *BRCA1* and *BRCA2* genes showed significant changes in the overall pathological complete response (pCR) value for treatment regimens without carboplatin compared to treatments with carboplatin. Therefore, patients with *BRCA1* and *BRCA2* gene mutations respond better if standard neoadjuvant therapy (paclitaxel, doxorubicin, and cyclophosphamide) is given.[28] The lack of BRCA1 and BRCA2 proteins is associated with high sensitivity to DNA-damaging agents, so those TNBC patients who exhibit variations in the *BRCA1* and *BRCA2* genes exhibit more sensitivity to standard chemotherapy agents. This also means that TNBC patients with variations in the *BRCA1* and *BRCA2* genes have higher immune cell activity.[80]

The poly ADP ribose polymerase (PARP) inhibitors may be candidates for use in treatment of *BRCA*-mutated cancer patients.[81] However, there have been therapeutic failures in clinical trials of the PARP inhibitor Iniparib. In TNBC patients, Iniparib failed to prolong survival in Phase III. This failure is known to be associated with a secondary *BRCA2* mutation.[82] Secondary mutations in *BRCA1* or *BRCA2* may also play a role in drug resistance to platinum therapy. This is caused by prolonged drug exposure, which exerts selection pressure and may lead to PARP inhibitors, as well as to resistance to platinum drugs. Mutation in c.9106 C>T translates into the BRCA2 protein without the C-terminal OB-fold and thus may impair binding with single-stranded (ss) DNA, as well as nuclear localization sequences and the TR2 RAD51-binding domain.[83]

CD24

The cluster of differentiation 24 (*CD24*) gene is located at chromosome region 6q21, encoding sialoglycoprotein, which can induce growth and signal differences in cells.[84] CD24 is a protein on the cell surface, providing linkage to the cell membrane via glycosylphosphatidylinositol.[85] Overexpressed CD24 protein has been found in cases of various cancers, including breast cancer. In breast cancer, CD24 expression was usually found in HER2-positive and luminal breast cancer cells.[86] Prognosis in breast cancer patients is related to CD24 expression, which can regulate tumor cell proliferation[87] and increase the likelihood of metastasis.[88]

So far, no convincing correlations have been found between differentiation of genotype and CD24 expression level. *CD24* Val has been reported to be associated with higher susceptibility, more autoreactive immunity, and faster disease progression, and it contributes to chemotherapy response. In a previous study, *CD24* Val demonstrated a high sensitivity to anthracycline-based and taxane-based therapy in primary breast cancer. The study showed that *CD24* Ala/Val is the only single-factor predictor of pCR in breast cancer patients subsequent to neoadjuvant chemotherapy (NCT) treatment. *CD24* Ala/Val may be able to modulate the antitumor immune response of the host so that this becomes more autoreactive. The response to NCT therapy is influenced by differences in the *CD24* genotype, which was demonstrated by a significant relationship between *CD24* Val/Val with intratumoral lymphocytic.[37] However, a study conducted by Zhou et al[89] showed that *CD24* polymorphisms in rs3838646 and rs52812045 could not predict pCR in breast cancer patients who had received NCT treatment.

CYBA

The *CYBA* gene is used to produce cytochrome b-245 alpha chain (p22-phox), which is a subunit of proteins that can take part in constructing NADPH oxidase, an enzyme complex that had an essential role in the immune system, when bonded with a beta chain that is expressed by the *CYBB* gene. NADPH oxidase functions as a regulator of neutrophil activity, and its primary function in phagocytes is to produce reactive oxygen species.[90] In cancer therapy, the presence of CYBA may be related to anthracycline metabolism.[25]

In a study conducted by Vulsteke et al,[25] the T-allele carriers in rs4673 were significantly associated with a

shorter recurrence-free interval (RFI), but the results were not significant for homozygous C-allele carriers. In this case, resistance may be caused by a missense mutation of His72Tyr that could cause decreased activity of the enzyme due to a change in the heme-binding site that is essential for protein stability, with further impaired reactive oxygen species (ROS) defense capacity and thus an increased ROS level.[91] In several studies,[92–94] the mutation was found to be caused by 242C>T. Hoffman et al[95] suggested that 640A>G reduced the enzyme activity, but a contrary study conducted by Schirmer et al[96] found an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity instead.

CYP

Cytochrome P450 (CYP450) is an enzyme that serves as a xenobiotic metabolizer by drawing the xenobiotic into an oxidation reaction that changes the drug into its metabolites. In breast cancer therapy, this process is important in treatments using drugs such as tamoxifen, where the drug must be subsequently converted into a more active metabolite such as 4-hydroxy-tamoxifen (4-HT) and endoxifen by CYP450 3A4 and CYP2D6, thus developing a higher binding affinity for the ER.[97]

In a study conducted by Artigalás et al[46] finds that rs4646 polymorphism in the *CYP19A1* may be a predictive factor in aromatase inhibitor (AI) therapy. Among metastatic BC patients treated with AI, SNP rs4646 were associated with increased time to progression (TTP) compared with the wild-type gene (hazard ratio (HR) = 0.51 [95% confidence interval (CI), 0.33–0.78], $P = 0.002$). Furthermore, Liu et al[98] reported a statistically significant association between rs4646 T alleles (G/T or T/T) and increased OS in women with metastatic BC (HR, 2.37 [95% CI, 1.20–4.65], P = 0.001). However, Miron et al[99] did not find any significant association with OS in the same SNP. Henry et al[100] also did not find any statistically significant association between 127 SNPs in CYP19A1 related to estrogen metabolism and modulation of breast density. These data suggest that *CYP19A1* genotypes may be associated with OS in BC patients treated with AIs. However, this association appears very variable between patients.

Gor et al[50] conducted a retrospective cohort study to determine chemoresistance caused by CYP3A4 polymorphisms, and found that patients having at least of CYP3A4 *1B variant allele had a significant association with worse disease-free survival (DFS) compared with those having a wild-type *1A/*1A. The mechanism underlying this chemoresistance is that *1B polymorphism leads to reduced Phase I enzyme activity and thus having suboptimal 4-hydroxy-cyclophosphamide concentration. Due to the nature of cyclophosphamide pharmacokinetics, it needs to be activated to 4-hydroxy-cyclophosphamide to be able to diffuse into cancer cells through Phase I metabolisms CYP enzymes and one of them is 3A4.

Previous studies by Beelen et al[38] showed a significant relation between *CYP2C19* variant alleles and time to treatment failure (TTF) in patients using tamoxifen, where *CYP2C19*2* carriers were associated with longer TTF, and those who had the *CYP2C19*17* allele showed a shorter TTF, but not to a statistically significant degree. The inhibition of CYP2C19 effectively influences tamoxifen metabolism, where conversion to its active metabolites such as endoxifen is seen (shown later in Figure 2). The tamoxifen resistance mechanism may be related to lower concentrations of tamoxifen and trans-4-OH-tamoxifen that were triggered by isomerization to the cis isomer, and this isomerization may also occur for endoxifen.[101] Vulsteke et al[25] also suggested that resistance was caused by *CYP2C9* rs1057910 polymorphism in his study, where there was a significantly worse RFI, but the C-allele variant carrier was only present in 3 subjects, and thus this suggestion needs further research.

Regan et al[39] did not find any association with tamoxifen therapy for differences in *CYP2D6* phenotype metabolism. Endoxifen, a tamoxifen metabolite with higher affinity for ER, is suspected to be related to disease control, while the polymorphism of *CYP2D6*, an enzyme that could metabolize tamoxifen into its active metabolite, was hypothesized to be related to lower endoxifen concentrations and thus worse disease control and higher side effects. Regan et al[39] indicated that *CYP2D6* metabolism phenotype failed to predict tamoxifen efficacy and that there was thus a need for further study regarding tamoxifen metabolism and its mechanism of disease control. Dezentjé et al[40] suspected incorrect interpretation in that study and replicated it while considering whether the loss of heterozygosity (LOH) could explain a Hardy–Weinberg equilibrium deviation that might exclude false genotype by LOH in tumor tissues. However, their study failed to find any association between *CYP2D6* genotype differences and tamoxifen efficacy. Studies by Neven et al[41] and Sanchez-Spitman et al[42] also support these findings, reporting that there were no associations for low-activity

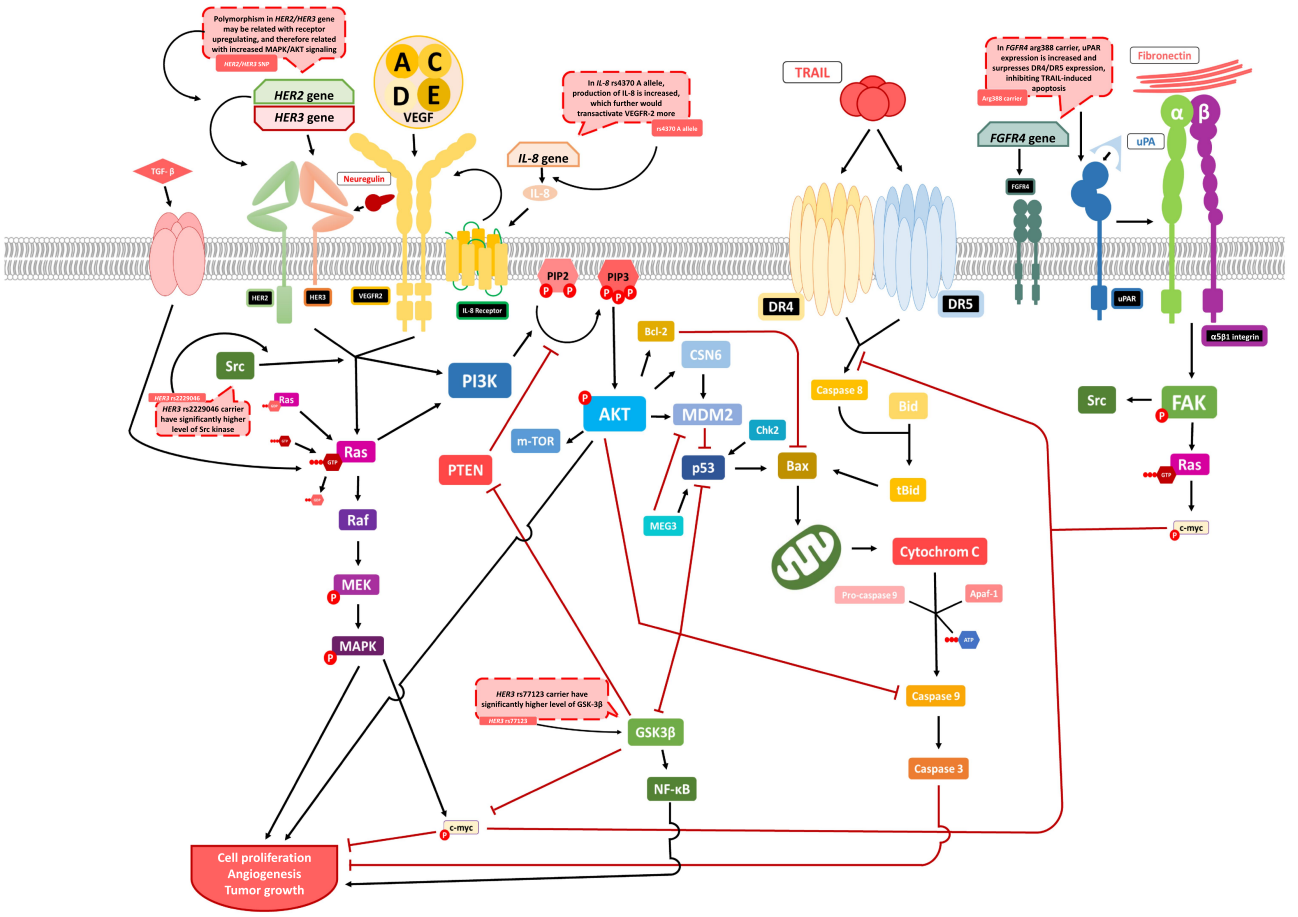

Figure 2 Influences of gene polymorphism with tamoxifen metabolism. Some of the chemoresistance mentioned in the paper are involving changes in drug metabolism and further decreased drug concentration in some individu. The decreased drug concentration may leads to suboptimal concentration needed to have therapeutic effect. *CYP2C19* polymorphism may decrease CYP2C19 expression, which an enzyme that have a function in Phase I metabolism of tamoxifen needed to activate the substance into 4-hydroxy-tamoxifen and endoxifen, a more active metabolite in inhibiting estrogen-ER binding to halt tumor growth.
Notes: P Activates/transactivates/upregulates/expresses. ↑ Inhibits/downregulates. T Converted into.

CYP2D6 genotypes and low concentrations of endoxifen with clinical outcomes.

Two meta-analysis related with the impact of *CYP2D6* polymorphisms on therapy effectiveness are included in this article. Hwang et al[48] found that poor endoxifen metabolizers, stated as having two inactive alleles of *3-*8, *11-*16, *19-*21, *38, *40, and *42 was found to have a significant association with lower endoxifen concentration compared with those having extensive metabolizers ($p < 0.05$). Jung et al[49] also found that those having alleles of *1, *10, *17, *41, *4, and *5 had a significantly increased risk of disease recurrence. These studies suggest that endoxifen dose may need to be adjusted for those with poor metabolizer alleles to have optimal efficacy.

FCGR

One mechanism of action for trastuzumab in treating breast cancer cells is known as antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). Both mechanisms include the Fc fragment of IgG receptor (FCGR) on its process. In ADCC, the FCGR located on natural killer (NK) cells binds to the Fc part of trastuzumab and triggers release of a factor such as interferon-γ (IFN-γ) or one of the perforins or granzymes, which could induce apoptosis of tumor cells, while ADCP is initiated when the FCGR on a macrophage binds instead with trastuzumab and induces phagocytosis of tumor cells.[56]

Gavin et al[56] found that patients who had the 158F/F genotype had better prognosis when treated with the doxorubicin–cyclophosphamide–paclitaxel (ACT) regimen and less benefit when trastuzumab was added, while patients with 158F/V or V/V gained more benefit from adding trastuzumab to ACT. These findings suggest that changes in ADCC mechanism may alter the efficacy of trastuzumab. Furthermore, *FCGR2A*-131 polymorphism

showed no evidence of differential trastuzumab treatment effects because of the lack of expression of FCGR2A on natural killer (NK) cells, which are the main effectors of ADCC. These findings may reflect the mechanism of *FCGR3A*-158V, not *FCGR3A*-158F, as *FCGR3A*-158V has been found to bind at low concentration to immunoglobulin (Ig) G1 immune complexes.[102]

Norton et al[55] found no association between the *FCGR2A* and *FCGR3A* genes in relation to DFS, but demonstrated that *FCGR2B* I/I patients had better DFS when trastuzumab was added in the therapy combination. The results differed for patients having *FCGR2B* with T alleles, as they did not show any improvement in DFS when adding trastuzumab. Immune response inhibition by FCGR2B may be reduced in the minor allele (232T) and increased in response to infection and autoimmunity; it is possible that the T-allele may be related to this escalation of immunity response to tumor mechanism like the one that was triggered by trastuzumab, and thus that the T-allele carrier may have better survival but less response to trastuzumab. Hurvitz et al[47] also did not find any significant correlation between *FCGR3A* and *FCGR2A* genotype differences with DFS.

In a study conducted by Tamura et al,[36] there was a significant association of the *FCGR2A*-131H/H genotype with greater tumor response and longer FPS, whereas the *FCGR3A*-158V/V genotype was usually correlated with tumor response after trastuzumab was given. The metastatic cancer patient's immune system is usually suppressed and therefore the trastuzumab-induced immune response was decreased in such patients. Roca et al[57] also found that in breast cancer patients treated with trastuzumab the *FCGR2A*-131R/R genotype is significantly associated with worse event-free survival (EFS), and found that considering *FCGR3A* genotype polymorphism yielded no predictive value toward clinical outcome.

The different outcomes in multiple studies may be influenced by distinctions in intrinsic to the populations or in the chemotherapy regimens conducted, by different levels of aggressiveness of the disease, and by different sample sizes, sampling bias, and methodologies. However, these lead to conclusions that substitution of valine into phenylalanine in *FCGR3A* at position 158 may amplify ADCC activity due to stronger IgG_1 binding compared with the wild-type (F)[103,104] and that the change from histidine to arginine in *FCGR2A* at position 131 causes less efficient binding to IgG_2, hence causing therapy resistance.[105]

FGFR4

The fibroblast growth factor receptors (FGFRs) are classified as tyrosine kinase receptors, which are growth-stimulating transducers and play decisive roles in regulation of cell growth. The *FGFR* family consists of more than 20 ligands that are important in cell cycle processes such as cell migration, cell differentiation, and tumorigenesis.[106]

Normally, fibroblast growth factors (FGFs) signaling takes part in multiple biological processes such as angiogenesis, inflammation, and regeneration of cells. The release of FGFs in wound repair may be triggered during wound creation by endothelial cells in response to mechanical force as a stimulus. FGF-1 and FGF-4 stimulate the production of inflammatory regulators such as interleukin-2 (IL-2) and megakaryocyte progenitor cells.[107]

FGF may activate many transduction cascades, which could promote cell cycle progression and halt the cell death process. A disruption of any of this regulation process may result in uncontrollable cell growth. The exact tumor growth-promoting mechanism resulting from mutation in the gene expressing *FGFR4* is unknown. However, it may be related to autocrine FGF signaling, as FGF is usually observed alongside FGFR in FGFR overexpression. FGFs may be secreted by tumor cells or neighboring stromal cells and could act on either of these sources.[107]

An SNP, the transmembrane domain missense mutation from glycine to arginine at codon 388, is associated with breast cancer disease outcome. This polymorphism occurs in one of every two persons. There is speculation that the *FGFR4* Arg388 genotype is not involved in tumor induction, as *FGFR4* alleles are homogeneously distributed. *FGFR4* Arg388 is overexpressed in node-positive breast cancer patients, but there is no evidence of it being significantly associated with DFS.[108] Another study confirmed that *FGFR4* Arg388 could be used as a disease progression predictor and suggests that it could also be used to predict chemotherapy resistance.[24]

In a study conducted by Marmé et al,[58] the *FGFR4* Gly388Arg polymorphism showed application as a specific predictive factor for therapy response to doxorubicin–cyclophosphamide–docetaxel (AC-Doc) as NCT with an odds ratio of 3.79, and there were no significant associations of pCR rates between patients with different HR status using AP-Doc treatment (42.9% versus 7.8% to 17.8% versus 15.6%). This thus suggests that regimens of drugs may affect two biological subgroups differently.

The study also showed that *FGFR4* Arg388 carriers have a higher risk of breast cancer involving the axillary lymph nodes, and thus supports a previous report linking the *FGFR4* Arg388 allele with worse disease progression but better responses to NCT.[58] The exact molecular mechanism that leads to *FGFR4* Arg388 being a more hostile phenotype is not yet clearly understood. There may be a linkage disequilibrium with other mutations that could affect breast cancer prognosis. There was no observation of elevated tyrosine phosphorylation in *FGFR4* Arg388 compared with Gly388 in tumor cells, which further indicated that any change in the kinase activity may be too minuscule to be detected.[24]

A contrary result was found in a study conducted by Thussbas et al,[24] who reported that the *FGFR4* Arg388 allele is significantly associated with worse DFS and poorer overall survival (OS). Chemotherapy failure may result from tumor cells resisting the induction of apoptosis. Urokinase-type plasminogen activator-receptor (uPAR) downregulation increases the susceptibility of tumor cells in chemotherapy-induced apoptosis; thus, it could be that because uPAR expression is escalated in cells producing *FGFR4* Arg388 allele compared with Gly388, this increases the release of anti-apoptotic factors or downregulates proapoptotic factors in cells expressing the Gly388 allele.[24] uPAR increases miR-17-5p/20a, a microRNA involved in inhibition of apoptosis by suppressing death receptor 4 (DR4) and death receptor 5 (DR5). If mechanism applies, upregulation of c-myc by uPAR may further increase miR-17-5p/20a expression. If c-myc is suppressed, uPAR concentration would decrease and the expression of DR4 and DR5 would be enhanced, activating TRAIL-induced apoptosis. These findings suggest that miR-17-5p/20a may offer a potential target therapy for breast cancer treatment and should be considered in preventing chemoresistance (Figure 3).[109]

GST

The glutathione S-transferases (GSTs) are a superfamily of dimeric Phase II metabolic enzymes. The family plays a vital role in cell defense by catalyzing the conjugation reaction of oncogenic substances with glutathione and thus preventing cellular damage.[60] Any mutation in a gene expressing this enzyme could change the catalysis process, which in turn could alter the bioavailability of the drug and may amplify or decrease drug efficacy and toxicity.[60]

Genetic variability in *GSTP1* is significantly associated with therapy effectiveness. Zhang et al[60] conducted a study that revealed in patients with *GSTP1* 105Val/Val genotype a statistically significant relationship with resistance of breast cancer chemotherapy, especially epirubicin. This mutation is known to occur via an SNP in the coding sequence of *GSTP1* (1578 A>G), which then gives rise to Ile105Val substitutions in the substrate-binding site of GSTP1. This was supported by a study that demonstrates that the 105Val variant carrier is correlated with more thermolabile and altered catalytic activity compared with those having 105Ile, and concludes that the homozygous isoleucine carrier is associated with the highest GSTP1 activity, with that activity decreasing as more valine was substituted. The reduced GSTP1 activity was also associated with increased toxicity from chemotherapy. As the chemotherapy mechanism needs to be activated by GST and other hepatic enzymes, the decreased GSTP1 activity may suggest an inefficient metabolism and less active metabolite concentration in such patients' bodies.[60]

Another study conducted by Romero et al[59] suggested that breast cancer patients treated with doxorubicin and carrying homologous G alleles in *GSTP1* had a lower risk of chemoresistance, shown with polymorphism *GSTP1* c.313A>G as a main cause, but no association was found between any *GST* genotype and the response outcome in patients treated with docetaxel. The different responses might suggest that there is specialization within GSTs activity in catalyzing the conjugation of reduced glutathione. This activity is related to how doxorubicin acts in cancer cells, where it can generate superoxide as a reactive oxygen species (ROS) when the semiquinolone in doxorubicin's active metabolite is converted into quinine. The ROS then forms propenal, which can be detoxified by GSTP1.[59]

In contrary to those findings, Yao et al[26] suggested that there were no associations between polymorphism in *GSTP1* genes and treatment outcomes in a patient who received cyclophosphamide. This may strengthen the hypothesis that the relation between polymorphism of *GSTP1* genes and breast cancer therapy is drug specific and may vary in terms of affinity and activity for different drugs.

In cyclophosphamide metabolism, GSTs had a role as inactivator. 4-hydroxy-cyclophosphamide are metabolized through Phase II metabolism to be conjugated with thiol or sulfate by GSTT. Gor et al[50] conducted a study to measure chemoresistance relationship with polymorphism of *GSTT1* and found that those with null genotype of *GSTT1* have significantly better DFS and OS compared with those

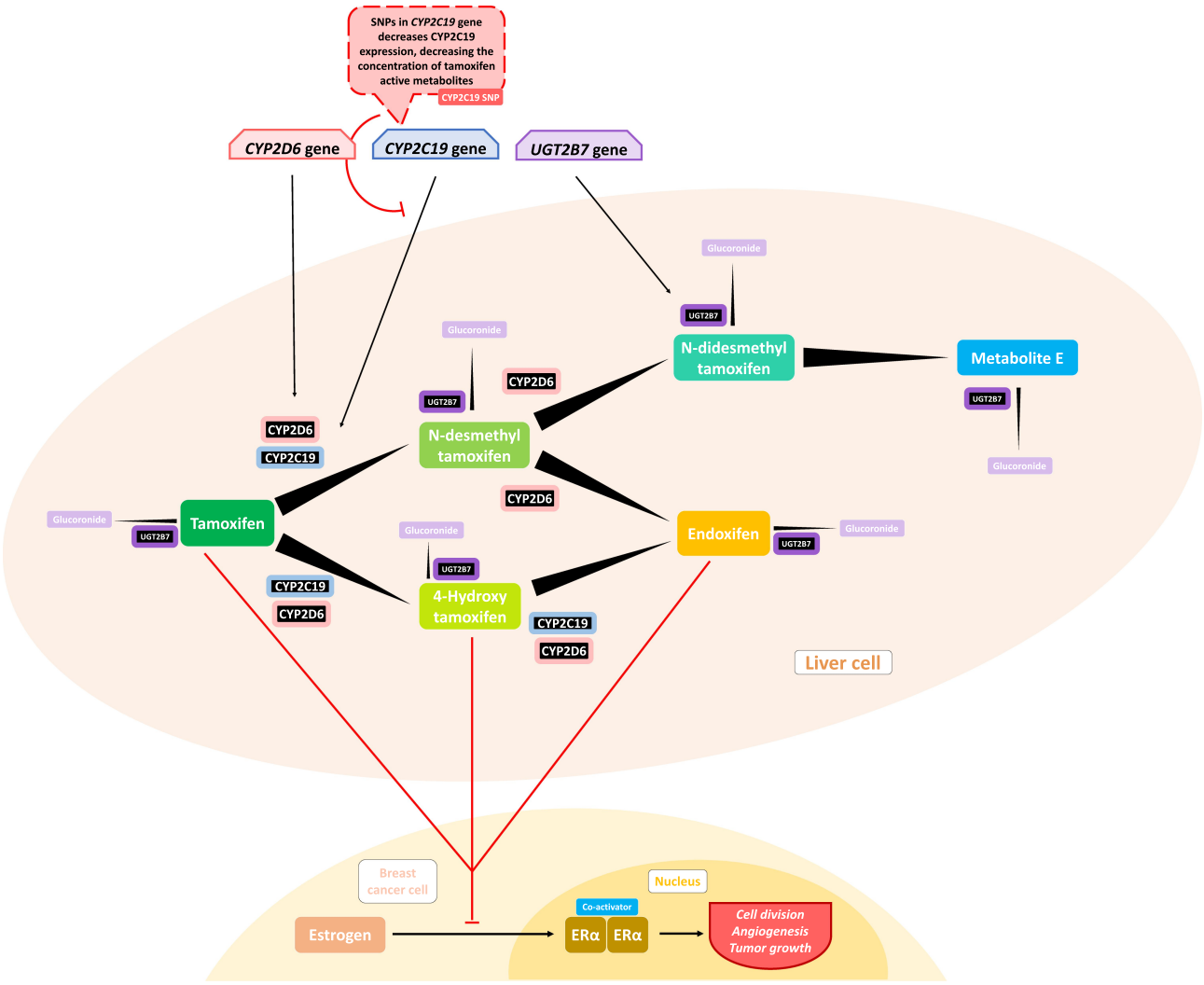

Figure 3 Possible mechanism of polymorphism influences related with MAPK and PI3K/AKT cell signaling. Drug resistance from some of the genes are resolved around MAPK and PI3K/AKT cell signaling. Polymorphisms in some genes mentioned may induce chemoresistance by disrupting the normal cell proliferation signaling and increase the aggressiveness of the tumor. The MAPK pathway are activated after Ras was phosphorylated and may induce cell proliferation, angiogenesis, and tumor growth. Ras may also activate PI3K, which further phosphorylating AKT that leads to activation of various signaling pathway leading to increase tumor growth rate. Genes that are hypothesized to disrupt these signaling are *HER2, HER3, VEGFR2*, and *FGFR4*. Polymorphism of *HER2* and *HER3* may increase receptor expression and this upregulation may further leads to increased MAPK/AKT signaling. In *HER3* rs2229046 carrier, Src expression is increased and leads to increase MAPK/AKT signaling, and those with rs77123 had heightened concentration of GSK-3β, that may inhibit c-myc as tumor growth suppressor and is suggested as chemoresistance mechanism. In *FGFR4* arg388 carrier, uPAR expression is increased and further inhibits TRAIL-induced apoptosis that leads to tumor cells resisting the induction of apoptosis.
Notes: ↑ Indicates phosphorylation process. T Activates/transactivates/upregulates/expresses. ⊣ Inhibits/downregulates.

without due to having higher concentration of circulating active drug. Kong et al[51] also found similar results in *GSTM1* null genotype for patients using anthracycline-based therapy in his meta-analysis, strengthening the association between polymorphism of GST and chemoresistance.

HER2 and HER3

Human epidermal growth factor receptor 2 (HER2), also known as erb-B2 receptor tyrosine kinase 2 (ERBB2), is one of the 20 known tyrosine kinase receptor families that are well known to be mutated in diseases that involve uncontrolled proliferation. It is also known to be an oncogenic driver.[110] The *HER2* gene is located at chromosome region 17q21 and can encode transmembrane tyrosine kinase GFR. It is usually expressed in the epithelial cells of breast tissue.[111] HER2 may interact with tyrosine kinase binding partners even while not having any ligand. This is of concern, as when HER2 is overexpressed, it exists in open conformation that can interact freely with any available tyrosine kinase, and leads to dimerization and promotes neoplastic transformation of cells.[110]

About one in five breast cancer patients have an overexpression of HER2, and it is also associated with worse disease prognosis. A monoclonal antibody, like trastuzumab, is used to directly target HER2 specifically. In 2015, Falchook et al[27] reported that with trastuzumab–lapatinib–bevacizumab combination therapy there are no associations between six SNPs in *HER2* (rs1810132 STR C>T, −1985 G>T, −3444C>T, P1170A C>G, rs1810132 STR C>T, I655A A>G) and stable disease (SD) ≥6 months/partial response (PR)/complete response (CR) rate, nor with TTF. This result contradicts previous findings that *HER2* SNPs had an association with the risk of developing breast cancer.[112] Falchook et al[27] also found that an escalated concentration of circulating HER2 extracellular domain (ECD) in plasma was significantly associated with SD ≥6 months/PR rate and TTF, consistent with previous studies.[113]

These results contradict a study conducted by Han et al[114] that found a resistance to trastuzumab accompanying Ile655Val *HER2* polymorphism, where HER2-positive patients with the Val/Ile and Val/Val genotype had a significantly worse DFS score compared with those with the Ile/Ile genotype. This may be caused by a decrease in tyrosine kinase activity when Val is substituted into Ile at codon 655,[115] and the combination showed a lower apoptosis rate and higher growth capacity in an in vitro study.[116]

Recently, data suggested that SNPs in epidermal growth factor genes may affect relapse-free survival or OS; this includes the *HER3* gene. Previous studies had shown that mutation in HER-family genes may activate the PI3K/AKT signaling pathway, and monoclonal antibody-based drugs are made to inhibit this activation by stopping downstream signaling of HER2 activation.[110]

Coté et al[18] found that patients who are treated with TCH and who have the minor allele of the *HER3* SNPs (rs2229046 and rs77123) had a higher risk of worse relapse-free survival compared with patients not using TCH. The data suggested that patients with SNP in rs2229046 had a heightened concentration of Src kinase, while those with rs77123 have significantly elevated glycogen synthase kinase-3 beta (GSK-3β) phosphorylation (Figure 3). The increase in PI3K/AKT signaling may potentially indicate unresponsiveness of the TCH-based regimen in selected patients. Despite not having a mechanism specific to cancer susceptibility, both of the SNPs have been related with alternative splicing, and there are not enough data to determine their specific action on signaling.[23]

IL12B

Interleukin 12 (IL12) is an immune modulator that has characteristics as a connector between acquired and innate immune response. Produced by macrophages, dendritics and monocytes, IL-12 consists of two polypeptide chains that bind to disulfide p35 or p40 to encode the *IL12A* and *IL12B* genes, respectively. *IL12A* is located on chromosome 3p12-q13.2 and *IL12B* is located on chromosome 5q31-33.[117] IL12 is known to have antitumor activity because it can induce cytotoxic T cell (CTL) activation, NK cell activation and differentiation of naïve cluster of differentiation 4 (CD4+) cells into T helper 1 (Th1) cells so that it can increase cytotoxic T lymphocyte response.-[118,119] This is supported by a study where the systemic administration of IL12 can prevent tumor growth in transgenic HER2/neu oncogene mice.[120] Therefore, giving IL12 could have potential in the treatment of breast cancer in humans. However, giving IL12 can also form autoimmunity. One example, excess production of IL12 is found in autoimmune diseases such as rheumatoid arthritis and type 1 diabetes mellitus.[121,122]

IL12B encodes IL12 p40 which is a subunit of the IL12 and IL23 heterodimeric structures that have an important role in immune cytokines in cell-mediated immunity. IL12 and IL 23 have a mechanism to convert naïve T cells into Th1 and T-helper 17 (Th17) and maintain a balance between Treg cells and Th17 cells in maintaining a normal immune response.[123] IL12B plays a major role in the initiation of the IL-12 activation signaling cascade.[124] Polymorphisms that occur in the *IL12A* and *IL12B* genes are known to play a role in cancer development. Polymorphisms will change the expression of the *IL12* gene and reduce IL12 protein synthesis so that it can lead to immune system dysfunction and the development of malignant tumors.[125]

ER-negative breast cancer patients have a high number of lymphocytes infiltrating the tumor. Tumor infiltration by immune cells, such as Treg cells and myeloid-derived suppressor cells (MDSCs) is involved in the prognosis of cancer patients after chemotherapy. The presence of polymorphisms in genes involved in the immunosuppressive pathway is known to modulate the response to given therapy.[123] One of them is evidenced by studies that reported IL12B SNPs have a relationship with OS in ER-Negative breast cancer patients after chemotherapy. There are two results obtained, namely *IL12B* rs2546892 (G> A) had a significant association with poorer OS (HR 1.50 (95% CI 1.21 to 1.86), P = 1.81 × 10−4) and *IL12B* rs2853694 (A> C) had a significant association with improved OS (HR 0.73 (95% CI 0.61 to 0.87), P = 3.67 × 10−4).[53]

KDR/VEGFR2

Kinase insert domain receptor (KDR), also referred as vascular endothelial protein receptor 2 (VEGFR2), is a tyrosine kinase receptor that regulates growth, survival, and endothelial cell movement through paracrine signaling by producing autocrine signal and can be expressed in tumor cells.[126,127] It is located at chromosome region 4q11–q12.[128] Studies about KDR expression with prognostic implication in carcinoma demonstrated that SNPs on the receptor genes may affect the VEGF signaling, which in turn influences the carcinoma prognosis and the treatment response. However, this information remains controversial.[129–133]

In 2018, Babyshkina et al[30] reported that the −604T>C (rs2071559) mutation may be a functional polymorphism within the *KDR* gene promoter region and may be able to change potential transcription of KDR, leading to reduced expression of KDR.[128] The value of pCR was higher in patients using the cyclophosphamide–doxorubicin–capecitabine (CAX) regimen than in those who used the fluorouracil–doxorubicin–cyclophosphamide (FAC) chemotherapy regimen. Therapy for those younger than 50 years carrying the −604TT genotype of rs2071559 gave results significantly correlated with pCR within the CAX-treated patients. However, there was no clear confirmation that the pCR rate correlates with *KDR* rs2305948 within the two treatment groups. KDR expression and polymorphism of *KDR* gene usually act as additional predictive markers of pCR in breast cancer patients.

Allegrini et al[29] suggested that *KDR* gene interacts with the *IL-8* gene and may affect the efficacy of bevacizumab therapy. In tumor progression, KDR has a significant role in promoting tumor angiogenesis.[134,135] The phosphorylation of KDR may be transactivated by IL-8 due to physical interactions between KDR and the IL-8 receptors, and it has been shown that this activity may occur in the presence of VEGF such as CBO-P-11 at the site (Figure 3). These findings may explain the failure of tumor angiogenesis inhibition when treating with drugs such as bevacizumab, as the overexpression of IL-8 in the presence of the SNP would lead to more transactivation of KDR. Added to the mutation of *KDR*, the upregulation of the receptor supports the angiogenic process. These findings were determined in a case-control study comparing patients treated with and without bevacizumab as a first-line chemotherapy; the study revealed decreased values of progression-free survival and OS in patients carrying SNP *KDR* rs11133360 and *IL-8* rs4073, suggesting a resistance to bevacizumab therapy.

MDM2

The mouse double minute-2 (MDM2) homolog is a promoter that suppresses p53 transcriptional activity[136] through direct binding, ubiquitination, and degradation.[137] In previous studies, overexpression of MDM2 has been studied as another mechanism for suppressing protein p53 (Figure 3), and MDM2 protein levels in the body may also be interpreted as prognostic biomarker of human breast cancer.[52,138]

Overexpression of MDM2 was suggested to be related to drug resistance in targeted cancer therapy, such as in chemotherapy and radiotherapy through the MDM2–p53 loop dependent pathway and epithelial–mesenchymal transition (EMT) pathway. In the EMT pathway, MDM2 overexpression induces the EMT process in tumor cells, resulting in resistance to the chemotherapeutic drug.[139] MDM2 overexpression was reported to inhibit the sensitivity to cisplatin, with potential for leading to cisplatin-based therapy resistance.[140] Also, overexpression of MDM2 was associated with resistance in trastuzumab regimens in HER2-positive breast cancer.[141]

The *MDM2* SNPs at T309G may decrease the activity of protein wild-type p53 and thus increase the chance of developing cancer cells. In a recent study, polymorphism in *MDM2* (SNP309T>G, rs2279744) was associated with increased risk of various cancer development through its association with an increased MDM2 mRNA level.[142,143] The effect of SNP 309G aligns with the mechanism of MDM2 that suppresses p53 protein activity.[142,144,145] Polymorphism in the 309G allele enhances MDM2 activity, so it may substitute for *TP53* mutation in similar patient cohorts, yet the importance of SNP309 in familial breast cancer remains unclear.[146] In a study conducted by Chrisanthar et al,[35] genotype differences of *MDM2* showed no association with treatment response to epirubicin or paclitaxel, and there was no effect on relapse-free survival value. In multivariate analysis, SNP309 TG/GG persisted as a poor prognostic factor by excluding ER status from the analysis.

MEG3

The maternally expressed 3 (*MEG3*) gene is located at chromosome region 14q32.3 in humans[147] and is involved in growth and development of cell. Reexpression of MEG3 suppressed proliferation of tumor cells in vitro (Figure 3)[148–151] and reduced the growth of gliomas, tumor volume, and the expression of Ki67.[152]

Cao et al[153] reported that SNP in *MEG3* can increase cancer development risk and toxicity of chemotherapy in other type of cancers.[154] Peng et al[155] reported that in ER-positive breast cancer, MEG3 was downregulated, which in turn inhibited cell growth and thus induced apoptosis through ER stress activation, nuclear factor κB (NF-κB), and p53 pathways.[156]

Polymorphism in *MEG3* was associated with regulation of cells in breast cancer. In 2019, Bayarmaa et al[31] showed that SNP in *MEG3* rs10132552 was significantly associated with response to cisplatin-containing chemotherapy in breast cancer patients, such that a patient carrying the rs10132552 TT genotype had significantly worse DFS, and there was a higher level of Ki67 in patients who had the T-allele in the rs10132552 phenotype.

SLC

When chronically exposed to selective chemotherapy, cancer cells often regulate drug efflux transporters that may result in development of drug resistance. The change of transporter may be initiated when cancer cells demand more nutrients to support their rapid growth and gather these nutrients via plasma membrane transporters.[157] The solute carrier (*SLC*) genes were classified into 65 subfamilies. The main function of *SLC* genes is to encode the transporters of endogenous and exogenous compounds.[158–160] Most SLC transporters are equilibrative. This trait is beneficial in facilitating substrate uptake into the cell by regulating the electrochemical and concentration gradients. Polymorphisms in *SLC* genes have been affiliated with efficacy and toxicity outcomes of drugs.[157]

A recent study conducted by Okazaki et al[161] reported that *SLC28A3* rs7867504 polymorphism was significantly associated with toxicity in pancreatic cancer patients who received gemcitabine. SNPs in *SLC28A3* (rs7867504) and *SLC29A1* with the GA haplotype were associated with OS in metastatic breast cancer patients receiving a paclitaxel–gemcitabine combination. *SLC29A1* (rs747199 and rs760370) with the GA haplotype resulted in a significantly shorter OS, while *SLC28A3* (rs7867504) with the CC and CT genotypes was associated with a longer OS compared with the TT genotype. These findings suggested that the efficacy of paclitaxel–gemcitabine treatment may be influenced by the transport of gemcitabine.[32] Also, these results fall in line with earlier pharmacogenetic studies in other type of cancers that received gemcitabine as chemotherapy. SNPs in *SLC29A1, SLC28A1*, and *SLC28A3* (rs7867504) were associated with gemcitabine metabolite clearance in solid tumors.[162]

The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene has a common polymorphism as *SLCO1B1*5* at rs4149056. Patients carrying this SNP had higher estrogen levels prior to treatment with AI[163] and showed a higher exemestane level during treatment.[164] *SLCO1B1* SNP rs10841753 carriers are also known to have decreased estrogens prior to AI treatment, as they increased expression of the organic anion-transporting polypeptide 1B1 (OATP1B1) transporter.[163] A study conducted by Dempsey et al[33] showed that patients carrying the *SLCO1B1*5* allele (rs4149056) may have had worse outcomes when receiving AI treatment because they were at higher risk for having a higher concentration of detectable estrone, yet patients with SNP rs10841753 had a lower concentration of estrone during the first 3 months from the initiation of AI treatment. Those who had *SLCO1B1*5* rs4149056 SNP were associated with increased levels of estrone sulfate during pretreatment of AI chemotherapy, while rs10841753 carriers were associated with lower levels instead. However, there is no direct evidence associating suppression in estrogen with treatment effectiveness. Estrone is the most abundant estrogen in postmenopausal women.[165] The lack of association of *SLCO1B1*5* or rs10841753 polymorphism with risk of breast cancer development in a large genome-wide association study suggested that estrone and estrone sulfate levels do not have any clinical consequence in predicting the effectiveness of breast cancer therapy.[166]

TGFBR2

Transforming growth factor beta receptor II (TGFBR2) is an important cytokine in the tumor microenvironment and included as a ligand binding receptor for the TGF β family (TGF-1, −2, −3), this gene is located on chromosome 3 locus 3p22.[167] *TGFBR2* encodes the TGF-β receptor II which is the transmembrane serine/threonine protein kinase receptor in the TGF-β signaling pathway.[168] After binding to the ligand, TGFBR2 will induce phosphorylation of solvated metal atom dispersion (SMAD) 2/3 through activation of TGFBR1. This SMAD 2/3 induction will form hetero-oligomers with SMAD 4 and accumulate in the nucleus. In addition, TGFBR2 can induce intracellular pathways with non-SMAD signaling pathways via Src, PI3K/AKT, p42/44 and p38 MAPK.[169,170] TGFβ is known to have two roles depending upon the cellular context, namely as tumor suppression at the initial stage and invasion and metastatic tumors in later stage cancers, specifically TGFβ as a stimulator in Treg cell proliferation and immune prevention.[171]

The presence of overexpression of TGFBR2 in ER-negative breast cancer can be a poor prognostic indicator of patient survival.[172] Excessive TGFBR2 expression is associated with an overactive PI3K/AKT signaling pathway. AKT activation will mediate FAF1 phosphorylation and activate pro-metastatic function in cancer cells because it increases the stability of TGFBR2 on the cell surface.[170] This is proven by the association of TGFβ on lung metastases in patients with ER-negative breast cancer.[173] *TGFBR2* gene polymorphisms may be a prognostic indicator and predictor of breast cancer therapy by looking inhibition of TGFβ signaling. This is shown by a study that found SNPs *TGFBR2* rs1367610 (G> C) had a significant association with poorer OS in ER-negative patients who received chemotherapy (P = 3.08 × 10−4).[53] In addition, another study showed a low number of *TGFBR2* expression in ER-positive patients on tamoxifen therapy to have a significant association with shortened recurrence-free survival (RFS) (HR: 0.312, 95% CI, 0.131–0.742; P = 0.008).[174]

TP53 and CHEK2

The tumor protein (*TP53*) gene is the most common mutated gene in human cancer. Its presence in more than 50% of the whole cancer patient cohort implies that the *TP53* gene has some action related to the formation of cancer.[175] p53 is involved in processes such as growth, DNA repair, and apoptosis of cells.[176] In DNA repair activity, p53 gave signals to halt the cell cycle and gave the cell time to repair, resulting in revived genome stability. Additionally, p53 is directly involved in the activity of various DNA repair systems.[177]

The most common mutations in *TP53* are of the missense type, leading to diverse changes in amino acid positions.[178] Most of the time, mutations occurred more often in higher stages of cancers or in aggressive behavior subtypes such as triple-negative or HER2-related.[179–181] In patients with the wild-type of *TP53*, several tumors were confirmed to exhibit chemoresistance. Findings to date suggest that tumors may accommodate mutations in the checkpoint kinase 2 (*CHEK2*) gene, which expresses the Chk2 protein that phosphorylates p53.[137]

The *CHEK2* gene is located at chromosome region 22q12.1 and can be activated by Thr68 phosphorylation via ataxia-telangiectasia mutated. CHEK2 has a role in regulating the cell cycle. Mutation in the *CHEK2* gene will affect the function and expression of the Chk2 protein.[182] In addition, mutation in the *CHEK2* gene can influence the activity of p53,[35] as this may be phosphorylated by various type of kinases, including Chk2. This process is important in the mechanism of antitumor agents when responding to DNA damage in breast cancer.[183] The nonfunctional Chk2 protein can affect drug sensitivity by altering the p53 activation process.[184] When mutations in *CHEK2* and *TP53* genes are compared, the role of Chk2 can be indirectly identified in chemoresistance (Figure 3).[185]

Previous studies reported that mutations within the *TP53* gene are related to resistance to anthracycline therapy in carcinoma patients.[184,186,187] In vitro studies showed that taxane sensitivity is related to p53 function.[188,189] However, a clinical study has shown that there is no correlation between *TP53* status and paclitaxel sensitivity.[187]

Chrisanthar et al[184] found that *TP53* and *CHEK2* mutations may predict resistance to paclitaxel treatment, but not in patients receiving epirubicin as first-line therapy. Mutations of *TP53* are related to poor prognosis in carcinoma patients who are not using any adjuvant therapy.[190] These effects probably are due to the inclusion of patients with paclitaxel as a second-line treatment. *CHEK2* nonsense mutations were previously shown to affect Chk2 activity and may be used to predict resistance to anthracycline treatment.[184]

UGT

The uridine 5′diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, *UGT*) gene in mammals is known to have four families: *UGT1, UGT2, UGT3*, and *UGT8*.[61] This superfamily usually encodes enzymes that can place glycosyl groups on a lipophilic substrate.[191] The *UGT1* gene is located at chromosome region 2q37.[192] It is known to encode nine types of enzymes related with glucuronidation process. *UGT2* genes are classified further into two subfamilies, *UGT2A* and *UGT2B*. The latter are encoded by different genes such as *UGT2B4, UGT2B7, UGT2B10, UGT2B11, UGT2B15*, and *UGT2B17*.[193]

Various *UGT* gene isoforms exhibited different selectivity and sensitivity roles in every process of drug glucuronidation. Many types of drugs are metabolized by the *UGT* gene. Epirubicin is an anticancer drug in the anthracycline group. Like other anthracyclines, epirubicin undergoes metabolism in the liver by interacting with aldo-ketoreductase to form epirubicinol[194] or undergoes glucuronidation to form EPI-glucuronide.[195] Epirubicinol and EPI-glucuronide are inactive forms of epirubicin, and EPI-glucuronide had a faster excretion rate than epirubicinol and was noncardiotoxic.[196] The epirubicin glucuronidation process is carried out by UGT, specifically UGT2B7 in the liver.[195] *UGT2B7* gene is located at chromosome region 4q13.2.[197] The presence of polymorphisms in the *UGT2B7* gene may disrupt the inactivation process for

epirubicin. One study showed that breast cancer patients which carry the G-allele homozygous *UGT2B7* gene on rs3924194 experienced a worse recurrence-free interval (RFI) when treated with the fluorouracil, epirubicin, cyclophosphamide (FEC) based regimen.[25]

In addition to epirubicin, tamoxifen is also often used in breast cancer therapy as a selective ER modulator and goes through a metabolic process catalyzed by UGTs.[34] Tamoxifen that had passed through the metabolism stage, which is catalyzed by UGTs, was found to add glucuronide groups and to produce 4-HT and endoxifen, which may deactivate antiestrogenic effects (Figure 2).[198] Variants in the *UGT2B15, UGT2B7*, and *UGT1A8* genes are not correlated with breast cancer recurrence in tamoxifen treatment.[34] Dezentjé et al[40] found a contradictory result, reporting that *UGT2B15*2* may be associated with worse DFS in his exploratory study, but this result requires further investigation.

Conclusion and Future Prospects

After exploring through studies related with breast cancer chemoresistance caused by gene polymorphisms, we have reached a conclusion that some of the molecular changes that are caused by upregulation or downregulation due to different genetic activity, and some may lead to increase efficacy of the drug while the other halts the drug activity. Genes that suggesting chemoresistance due to having significant association with decreased drug efficacy and may be studied further to determine its exact mechanism are *ABCB1* rs1045642, *BARD1* rs2070096, *CYBA* rs4673 CT, *CYP19A1* rs4646, *CYP2C9* rs1057910, *CYP2D6* poor metabolizers, *CYP3A4* *1B*/*1A, *FCGR3A* 158V/V, *GSTP1* 105Val/Val genotype, *GSTM null* genotype, *HER3* rs2229046 and rs77123, *KDR* rs11133360 (T>C) for patients carrying SNP IL-8 rs4073, *IL12B* rs2546892 (G>A), *MEG3* rs10132552 TT genotype, *SLC* rs4149056, *TGFBR2* rs1367610 (G>C), *TP53, UGT2B15* *2, and *UGT2B7* rs3924194. While some studies, which are included in the study or not, may have conflicting results caused by different clinical setting or chemotherapy used and other factors, these studies strengthen the importance of exploring polymorphism and its impact on genes related with breast cancer.

Genetic polymorphisms in patients with breast cancer are related to variation in therapeutic responses in patients using the same drug. This review examines the relationship between genetic polymorphisms and breast cancer therapy resistance. There are several gene polymorphisms that produce differences in results in terms of OS, relapse-free survival, pathological CR, DFS, and other parameters. Moreover, many studies suggest that polymorphism in genes may be assessed as a predictive and prognostic biomarker for identifying breast cancer. Although conflicting results remain to be understood, in the future these polymorphisms may become considerations in developing personalized medicines that yield better results for each individual and in predicting the clinical outcome of breast cancer therapies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work

Disclosure

All authors report no conflicts of interest in this work.

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