CANCER GENOMICS & PROTEOMICS *21*: 421-438 (2024)
doi:10.21873/cgp.20461

Review

Pharmacogenetics of Toxicities Related to Endocrine Treatment in Breast Cancer: A Systematic Review and Meta-analysis

KINAN MOKBEL[1], MICHAEL WEEDON[2], VICTORIA MOYE[2] and LEIGH JACKSON[2]

[1]*Health and Care Profession Department, Faculty of Health and Life Sciences, University of Exeter Medical School, Exeter, U.K.;*
[2]*Clinical and Biomedical Sciences, Faculty of Health and Life Sciences, University of Exeter Medical School, Exeter, U.K.*

Abstract. *Background/Aim: Endocrine therapy is the standard treatment for hormone receptor-positive (HR+) breast cancer (BC). Yet, it is accompanied by treatment-related toxicities, leading to poor treatment adherence, high relapse, and low rates of survival. While pharmacogenomic variants have the potential to guide personalized treatment, their predictive value is inconsistent across published studies. Materials and Methods: To systematically assess the literature's current landscape of pharmacogenomics of endocrine therapy-related adverse drug effects, systematic searches in MEDLINE, Embase, Cochrane CENTRAL, Google Scholar and PharmGKB databases were conducted. Results: We identified 87 articles. Substantial heterogeneity and variability in pharmacogenomic effects were evident across studies, with many using data from the same cohorts and predominantly focusing on the Caucasian population and postmenopausal women. Meta-analyses revealed Factor V Leiden mutation as a predictor of thromboembolic events in tamoxifen-treated women (p<0.0001). Meta-analyses also found that rs7984870 and rs2234693 were associated with musculoskeletal toxicities in postmenopausal women receiving aromatase inhibitors (p<0.0001 and p<0.0001, respectively). Conclusion: Overall, the current body of evidence regarding the potential role of pharmacogenomics in endocrine therapy-related toxicity in BC remains largely inconclusive. Key concerns include the heterogeneity in toxicity definitions, lack of consideration for genotype-treatment interactions, and the failure to account for multiple testing. The review underscores the necessity for larger and well-designed studies, particularly with the inclusion of premenopausal women and non-Caucasian populations.*

Correspondence to: Kinan Mokbel, Health and Care Profession Department, Faculty of Health and Life Sciences, University of Exeter Medical School, RILD Building, Royal Devon and Exeter Hospital, Barrack Road, Exeter, EX2 5DW, U.K. Tel: +44 01392408223, e-mail: k.a.mokbel@exeter.ac.uk

Key Words: Systematic review, meta-analysis, adverse drug reactions, side effects, drug safety, toxicity, breast cancer, endocrine therapy, tamoxifen, aromatase inhibitors, pharmacogenomics, pharmacogenetics, personalized medicine, review.

Breast cancer (BC) is the most commonly diagnosed cancer globally (1). Seventy to eighty per cent of BC cases are hormone receptor-positive (HR+) cases, for which endocrine therapy, including tamoxifen and aromatase inhibitors (AIs), plays a pivotal role in preventing recurrence and improving survival. While AIs are preferred for postmenopausal women with HR+ early BC, both treatments significantly reduce relapse rates and increase survival rates when administered for 5-10 years (2). Despite advances, BC remains the leading cause of cancer-related death in women, largely due to recurrence and metastasis (3). Adverse drug effects (ADEs) related to endocrine therapy are key predictors of poor adherence and persistence, affecting 30%-70% of patients (4).

Efforts to enhance BC survivorship including interventions to mitigate endocrine therapy-related ADEs have been made. Emerging evidence suggests that specific genomic variations may impact the clinical toxicity outcomes of patients with BC undergoing endocrine therapy. Previous reviews on the pharmacogenomics of toxicities related to endocrine therapy have almost exclusively been narrative in nature, concentrating on individual genes or specific toxicities for a given endocrine agent. Identifying variants that predispose individuals to a wider range of toxicity outcomes from various endocrine drugs would be more clinically useful as it gives patients more options for

Table I. *The inclusion and exclusion criteria in this study.*

Inclusion criteria	Exclusion criteria
English-language publications	Non-human studies
Articles in journals	Case reports
Theses and dissertations	Editorials
Toxicity outcome of any grade	Publications without full texts
Toxicity-related biomarker changes	Abstracts only/conference proceedings
Toxicity-related quality of life (HRQL)	Non-cancerous disease
Toxicity-related discontinuation	Adverse events due to reduced effectiveness
Female patients	Studies of overall response, recurrence, survival
Breast cancer disease	
Endocrine agents: Tamoxifen, Anastrozole, Letrozole or Exemestane	
Genomic variants (*e.g.*, SNVs, frame-shift mutations, repeats, deletions, duplications, diplotypes, haplotypes)	
Phenotypes or activity scores derived from genotypes	

SNVs: Single-nucleotide variants.

alternating between agents. Therefore, a comprehensive systematic assessment of pharmacogenomics of endocrine therapy-related toxicities is crucial to improve the existing evidence base for both researchers and clinicians. Herein, we conducted a systematic review to provide a comprehensive analysis of the current landscape and critically evaluate the methodological quality of the studies identified.

Materials and Methods

Data sources and search strategy. We systematically searched MEDLINE, Embase and Cochrane CENTRAL databases to identify pharmacogenomic studies investigating toxicities or ADEs related to endocrine therapy in BC. We also searched Google Scholar to capture reports from journals not indexed in these databases. Our database-specific search strategies are detailed in Tables S1-S3. To ensure comprehensive coverage, we examined clinical annotations and phenotypes in PharmGKB concerning toxicities and ADEs associated with endocrine treatment (5).

In addition to peer-reviewed articles, efforts were made to include unpublished data and non-peer-reviewed studies to minimize publication bias. This involved searching for dissertations, theses and subsequent or follow-up reports from conference abstracts. In cases of missing information or the need for clarification, we reached out to original investigators and sought any subsequent unpublished results. To ensure comprehensiveness, we performed retrospective reference harvesting of influential studies. To identify studies with potentially relevant data, we reviewed the study methodology in full-text articles.

Eligibility criteria. Eligibility criteria for study inclusion were defined a priori based on the PICO framework (Population, Intervention, Comparison, Outcome), to ensure transparency in the selection process. Refer to Table I for details.

Study selection. The search outcomes from different databases were extracted and compiled using Mendeley. Duplicates were manually eliminated. Abstract and title screening was independently performed by two reviewers (KM, LJ), and irrelevant items were excluded. Relevant records underwent a full-text examination according to our pre-determined criteria for inclusion. Consensus decisions were made and articles not deemed relevant were excluded.

Data extraction. Key study characteristics, including sample size, year of publication, population description, study authors, study design, interventions(s), gene, genomic variant(s), toxicity outcomes and menopausal status were extracted and documented. Data for meta-analysis were collected from eligible studies.

Quality assessment. The methodological rigor of the studies was assessed using a validated 15-item checklist designed specifically for genetic research, which incorporates crucial methodological aspects vital to genetic studies (6). This checklist was adapted from the STrengthening the REporting of Genetic Association Studies (STREGA), an extension of the Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) Statement (7). To assess the overall quality of the studies included in this review, summary scores were computed.

Quantitative data synthesis and statistical analysis. Quantitative data from eligible studies were combined *via* meta-analysis. Consideration was given to both clinical and statistical aspects to determine appropriateness. A meta-analysis was conducted by combining studies that examined the same treatments and variants with similar measures of related toxicity outcomes and excluding those with different or tangentially related outcomes. Due to their diverse definitions, we did not meta-analyze studies on CYP2D6 genotype-predicted metabolizer phenotypes or activity scores. We discussed their findings descriptively instead. In cases where multiple studies used data from the same cohort, only the study with the largest analysis and/or longest follow-up period was included to prevent overrepresenting patient data in the meta-analysis. When necessary, effect sizes were transformed into a uniform metric for meta-analysis after being calculated using standard procedures. We employed random-effects models to address the anticipated heterogeneity resulting from the broad range of study characteristics that satisfied our eligibility

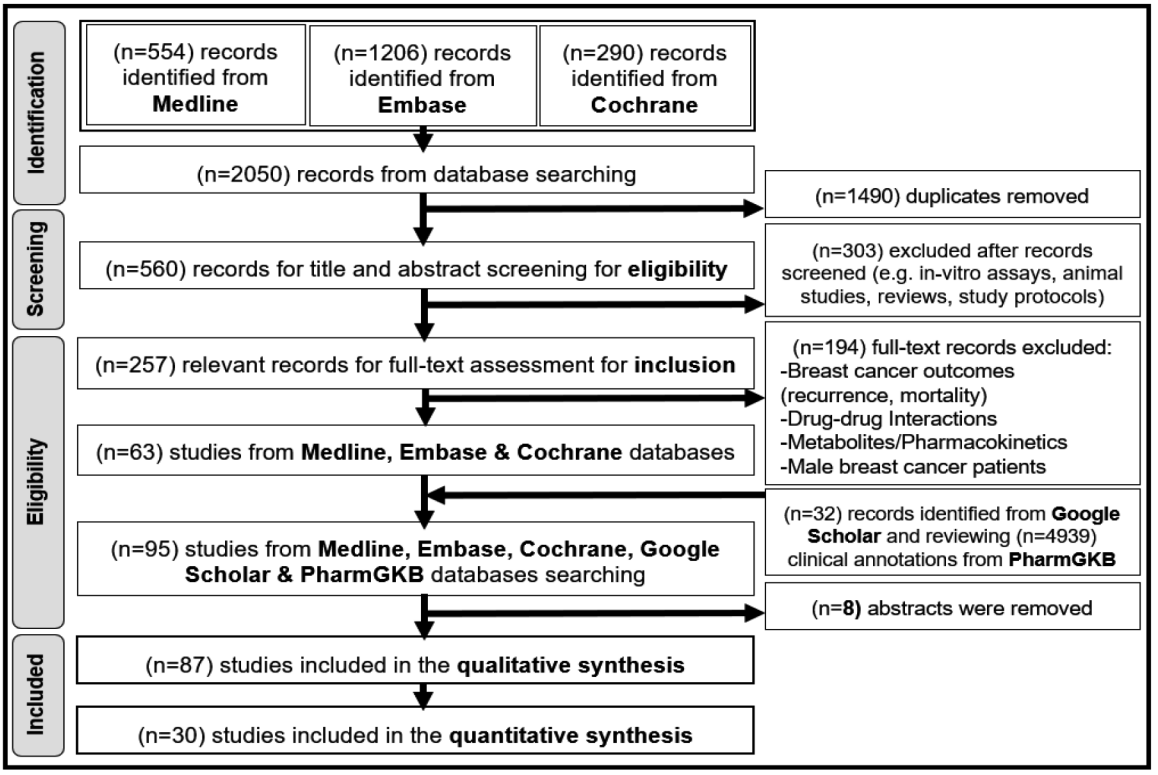

Figure 1. *The PRISMA flow chart of systematic literature search and selection process. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram demonstrating the screening and selection stages of pharmacogenetic studies of adverse drug effects related to endocrine therapy in breast cancer.*

criteria. The Bonferroni correction was applied to the *p*-values to account for multiple hypothesis testing. Forest plots were generated to visualize overall patterns. Stata/SE version 16.0 (StataCorp, College Station, TX, USA) was used for the statistical analyses. Both I2 and *p*-values for Q-statistic are displayed in forest plots.

Results

Eighty-seven studies fulfilled our inclusion criteria. Having screened 2,050 publications from various databases, 63 studies met the inclusion criteria. An additional 32 records were identified from PharmGKB and Google Scholar searches. Having excluded abstracts with insufficient data, 87 studies (encompassing 45,630 patients) were included with sample sizes ranging from 24 to 4,580 (8-94). The PRISMA flow chart of the systematic literature search and the selection process of studies are depicted in Figure 1.

Aromatase inhibitors and musculoskeletal adverse effects were the most examined. Third-generation AIs were the most studied treatment modality, representing 87% of total associations (Figure S1). Musculoskeletal and vasomotor ADEs (MS-ADEs and VM-ADEs) were the most examined among the 87 studies. Forty-seven studies examined MS-ADEs (12, 14, 33-37, 39-41, 47, 48, 16, 49-52, 55, 56, 58, 60, 65, 67, 18, 69-71, 73, 76-78, 80-82, 19, 83-85, 89-92, 21, 27-29, 32), while 32 investigated VM-ADEs (8, 11, 29-31, 36, 38, 44-46, 53, 55, 13, 58, 59, 62-64, 66, 68, 72, 76, 80, 15, 87, 94, 18-20, 22, 24, 25) (Figure S2). Yet, MS-ADEs accounted for 48.4% of all associations, followed by overall toxicities, which were examined by ten studies and comprised 34.4% of the total associations (Figure S3).

Heterogeneity in definitions and measures of toxicity outcomes. It should be noted that there was considerable heterogeneity in the definitions and measures of toxicity outcomes, ranging from specific toxicity endpoints to general ADEs. Toxicity outcomes measurement methods varied widely across studies including biomarker changes, time to onset of toxicity, and treatment discontinuation due to ADEs (21, 34, 35, 61, 73, 79, 82, 85, 91). Some studies used composite outcomes or analyzed declined health-related quality-of-life and/or their impact on treatment discontinuation (18, 58, 61, 74).

Premenopausal women and non-Caucasian populations were underrepresented. Early-stage BC was the most examined, though some studies did not specify the BC stage and few

analyzed data from patients with advanced or metastatic BC (10, 33, 87). Premenopausal women and non-Caucasian populations were notably underrepresented in the studies. Most associations, 89%, were in postmenopausal women, with just 0.9% in premenopausal women (Figure S4). The majority of studies (86.6%) were conducted in high-income countries, mainly in the USA and Europe, and predominantly Caucasian cohorts (Figure S5).

Most research focused on candidate gene studies. The majority of studies were candidate gene studies, with only three genome-wide association studies identified (16, 40, 91) all investigating MS-ADEs associated with AIs, with two of them using data from the same MA.27 trial (16, 40). Almost all included studies were retrospective with only one randomized genotype-guided study identified (87).

ESR1 and CYP19A1 were the most investigated. The included studies explored variants from 58 genes, with *ESR1* and *CYP19A1* being the most studied, representing 23% and 19% of total associations, respectively (Figure S6). Most investigations focused on single nucleotide variants (SNVs) and genotype-predicted metabolizer phenotypes, with a few examining haplotypes (11, 19, 37, 45, 51, 52, 67, 81), and deletions namely the *UGT2B17* deletion (61, 70, 74, 78, 80).

Across all identified studies, most studies used germline DNA, seven studies utilized DNA samples extracted from FFPE BC tissues (10, 20, 26, 41, 45, 47, 50), and three did not explicitly specify the source of their DNA samples (11, 48, 73).

The overwhelming majority of associations were not statistically significant. Among the 87 studies, there were various toxicity outcomes, genomic variants, and genetic models, resulting in a total of 4,423 associations, the vast majority of which (94.3%) were non-significant. Approximately 10% of studies solely reported positive results, while 22 studies did not report any significant results (8, 10, 24, 30, 31, 33, 38, 40, 42, 53, 59, 61, 12, 63, 64, 69, 70, 72, 76-78, 84, 87, 14, 90, 92, 16-18, 20, 22, 23) (Figure S7). Amongst the individual endocrine agents examined, more significant associations were found for tamoxifen (43%). However, aromatase inhibitors collectively showed more significant associations (55.5%) compared to selective estrogen receptor modulators (SERMs) such as tamoxifen (Figure S1).

Notably, the majority of studies in this review overlooked potential interactions. Out of 87 studies, only 13 included genotype-treatment interactions in their analyses. Additionally, while most studies adjusted their analyses for patient risk factors, inconsistencies existed regarding which covariates to adjust for (Figure S8).

Data duplication was evident across studies. It is noteworthy that most studies were small, with 37 publications (42.5%) using data from the same clinical trial(s) or cohort(s). For instance, six studies drew data from the ELPh trial (34, 49, 57, 73, 78, 91), six studies used data from the TAM trial (13, 14, 27, 36, 86, 94), four studies used data from the MAP.3 trial (61, 70, 74, 80), three studies used data from the BIG 1-98 trial (26, 47, 50), three studies used data from the MA.27 study (16, 40, 71), three studies used data from the B-ABLE cohort (35, 51, 67), two studies used data from the TEAM trial (41, 45), two studies used data from IBIS-I trial (8, 24) and two publications used data from the same longitudinal study (32, 54). Moreover, two studies were performed in the same cohort (81, 90), and one study (58) expanded on a previous pilot study (18) for statistical power.

Key characteristics of studies with significant findings are summarized in Table II.

The included studies had overall high-quality scores. The studies generally scored high in quality with an average score of 88.24% on the STREGA and STROBE checklists. It should be noted that discrepancies were observed in reporting biases, adherence to Hardy-Weinberg equilibrium and ethnic classification across studies. Only 56 studies met bias reporting criteria, 47 reported Hardy-Weinberg equilibrium, and only 21 of the 45 studies addressing mixed ethnicities met this criterion (Table S4).

Only three meta-analyses showed a significant summary effect size. We conducted 44 meta-analyses involving 30 studies. Only three meta-analyses yielded significant results, detailed in Table III, with corresponding forest plots in (Figure 2, Figure 3 and Figure 4). Meta-analysis of four studies (8, 15, 46, 53) showed that the Factor V Leiden (FVL) mutation significantly increased the risk of thromboembolic events in tamoxifen-treated women OR=3.47 (1.95, 6.17), $p<0.0001$. Even when one study using a broader definition for thromboembolic events was excluded (15), the association persisted between the FVL mutation and venous thromboembolism in tamoxifen-treated patients OR=2.55 (1.13, 5.75), $p=0.024$ (Figure 5). Furthermore, *ESR1* PvuII (rs2234693) and *RANKL* rs7984870 were significantly associated with MS-ADEs in postmenopausal women treated with AIs, OR=1.64 (1.25, 2.14), $p<0.0001$ and OR=1.45 (1.18, 1.79), $p<0.0001$, respectively. Due to the small number of studies in each meta-analysis (<10), funnel plots were not created, and asymmetry tests were not performed. Pooled estimates for all meta-analyses performed are provided in Table S5.

The complete list of associations between genomic variants and endocrine therapy-related ADEs is provided in (Table S6). Variants associated with ADEs were annotated with font colors: black for increased risk, green for decreased risk, and red for no significant association.

Table II. *Characteristics of studies which reported statistically significant findings*.

Study (author, year of publication)	Drug(s)	Gene	Genomic variant(s)	Toxicity outcomes	Study size	Demographics/ Population description	Menopausal status	Study type	Ref.
Al-Mamun 2017	Tam	*CYP2D6, UGT2B7, SULT1A1*	*CYP2D6*10, UGT2B7*2, SULT1A1*2*	Decreased libido, Depression, Vaginal dryness, HF	388	Bangladesh	Pre-, Peri-, Post-	Cohort	(62)
Basmadjian 2019	Exe	*UGT2B17*	*UGT2B17* deletion	Decline in physical HRQL	3345	Canada, USA, Spain, France	Post-	*Post-hoc* analysis of RCT	(74)
Argalacsova 2017	Tam	*ABCB1*	rs1045642, rs2032582	Time to ADEs, EH, Endometrial cancer, HF	258	Czech Republic	Pre-, Post-	Cohort	(66)
Baatjes 2020	Anas; Exe; Letr	*CYP19A1*	rs10046	BMD [LS, hip]	72	South Africa	Post-	Prospective cohort	(83)
Baxter 2014	Tam	*CYP2D6, CYP3A4*	*CYP2D6* IM *vs*. EM, CYP3A4*22	HF severity	132	Canada	Pre-, Post-	Prospective cohort	(44)
Borrie 2020	Anas; Letr	*ESR1, CYP19A1*	rs2234693, rs4775936, rs9322336, rs9340799	Arthralgia, Arthralgia-related treatment discontinuation	196	Canada	Post-,	Prospective cohort	(85)
Chu 2007	Tam	*CYP3A4*	CYP3A4*1B	Endometrial cancer	63 cases/ 63 controls	Canada	Pre-, Post-	Case/control	(75)
Dempsey 2018	Exe; Letr	*RANKL*	rs7984870	Time to MS-ADEs discontinuation	500	(89%) Caucasian, remaining African or Asian	Post-	Prospective cohort	(73)
Dezentje 2014	Tam	*ESR1*	XbaI/PvuII diplotype (rs9340799/ rs2234693)	HF	742	Netherlands	Post-	*Post-hoc* cohort of randomized trial	(45)
Dieudonné 2014	Tam	*CYP2D6*	rs1800716	ET	184	Belgium	Post-	Retrospective cohort	(43)
Fontein 2014	Exe	*CYP19A1*	rs16964189, rs7176005, rs934635	VM-ADEs, MS-ADEs	737	Netherlands	Post-	*Post-hoc* of randomized open-label trial	(41)
Garber 2010	Tam	*F5*	Factor V Leiden mutation	Thrombo-embolic events	124 cases/ 248 controls	USA	Pre-, Peri-, Post- [Most were Post-]	Case/control	(15)
Garcia-Giralt 2013	Anas; Exe; Letr	*CYP17A1*, *VDR*	rs10786712, rs11568820, rs3781287, rs4775936 rs4919683, rs4919687, rs6163, rs743572	Arthralgia	343	Spain	Post-	Prospective observational cohort	(35)
Gervasini 2017	Anas	*CYP19A1*, *ABCB1*	rs1008805, rs1045642	Arthralgia	110	Spain	Post-	Retrospective cohort	(65)
Günaldı 2014	Tam	*CYP2D6*	*CYP2D6* UM EM IM PM groups	TC, TG, ET	92	Turkey	Pre-, Post- [Most were Pre-]	Cohort	(39)
Hartmaier 2012	Tam	*NCOA1*	rs1804645	BMD [LS]	111	USA	Pre-, Post-	Cohort from prospective observational study	(27)
He 2020	Tam	*CYP2D6*	*CYP2D6* UM *vs*. NM	Treatment discontinuation	1309	Sweden	Pre-, Post-	Data from case-only cohort and cohort studies	(79)

Table II. *Continued*

Table II. *Continued*

Study (author, year of publication)	Drug(s)	Gene	Genomic variant(s)	Toxicity outcomes	Study size	Demographics/ Population description	Menopausal status	Study type	Ref.
Henry 2009	Tamo	*CYP2D6*	*CYP2D6* IMs *vs*. EMs or PMs	HF	297	USA	Pre-, Peri, Post-	Prospective cohort	(13)
Henry 2013	Exe	*ESR1*	rs9322336	MS-ADEs discontinuation	432	USA	Post-	Data from prospective randomized trial	(34)
Hertz 2016	Tam	*CYP2D6*	*CYP2D6* UM, EM, IM, PM	Distractedness, Irritability, Mood swings, Vomiting, Night sweats, HF, Breast tenderness, Vaginal problems, Dyspareunia, incontinence, Arm Problems	480 [353 were available for follow-up analysis]	USA	Pre-, Peri-, Post-	Secondary analysis of prospective genotype-guided study	(58)
Hertz 2021	Anas; Exe; Letr	*OPG*	rs2073618	MS-ADEs	143	USA	Post-	Secondary analysis of prospective observational cohort	(89)
Hertz 2022	Exe; Letr	*TCL1A, ESR1, SUPT20H, CCDC148, RANKL, PPP1R14*C	rs11849538, rs1324052, rs2347868, rs2369049, rs74418677, rs79048288, rs7984879, rs912571, rs9322336	MS-ADEs discontinuation	400	USA	Post-	GWAS of prospective, open-label study	(91)
Ho 2020	Exe	*UGT2B17*	*UGT2B17* deletion	Severe fatigue	1752	Canada, USA, Spain, France	Post-	*Post-hoc* of RCT	(80)
Jin 2008	Tam	*ESR2*	ESR2–02 (rs4986938)	HF	297	USA	Pre-, Peri-, Post-	Open-label prospective observational trial	(94)
Johansson 2016	Exe; Tam	*CYP19A1*	rs10046	HF, Sweating	1967	International	Pre- (+OFS)	Retrospective analysis of RCT	(56)
Kiyotani 2012	Tam	*CYP2D6*	*CYP2D6* [*10,*41] or [*5,*21,*36-*36] *vs*. *1/*1	Hyperhidrosis	98	Japan	Pre-, Post-	Cohort	(25)
Koukouras 2012	Anas; Exe; Letr	ESR1	PuvII (rs2234693), XbaI (rs9340799)	LDL, TG, ET	87 cases/ 80 control	Greece	Post-	Prospective case-control study	(28)
Kovac 2015	Tam	F5	Factor V Leiden and Factor II mutations	VTE	150	Serbia	Pre-, Post-	Prospective case control study	(46)
Leyland-Jones 2015 [1]	Tam; Letr	*CYP19A1*	rs10046, rs700518, rs936308, rs4646	Fractures, Osteoporosis, MS-ADEs	4580	Denmark, France, Switzerland	Post-	Substudy of RCT	(47)

Table II. *Continued*

Table II. *Continued*

Study (author, year of publication)	Drug(s)	Gene	Genomic variant(s)	Toxicity outcomes	Study size	Demographics/ Population description	Menopausal status	Study type	Ref.
Leyland-Jones 2015 [2]	Tam; Letr	*ESR2*, *ESR1*	ESR2–02 (rs4986938), XbaI (rs9340799), rs2077647	HF, Night sweats, Fractures, Osteoporosis	3,401	Denmark, France, Switzerland	Post-	Sub-study of RCT	(50)
Lintermans 2016	Anas; Exe; Letr	*OPG*	rs2073618	MS-ADEs	159	Belgium	Post-	Analysis of prospective observational cohort study	(55)
Mao 2011	Anas; Exe; Letr	*CYP19A1*	rs60271534 (TTTAn) At least one 8-repeats	Arthralgia, MS-ADEs	390	USA	Post-	Cross-sectional study	(21)
Mazzuca 2016	Anas; Letr	*CYP19A1*	rs4646	Bone loss [osteoporosis]	45	Italy	Post-	A retrospective cohort	(60)
Miranda 2021	Tam	*ESR1* *CYP3A5* *SULT1A1*	rs121913044, CYP3A5*3, SULT1A1*2	Vaginal bleeding, EH	162	Chile	Pre-, Post-	Retrospective case-control study	(88)
Napoli 2013	Anas; Exe; Letr	*CYP19A1*	rs700518	BMD [LS]	97	USA	Post-	Longitudinal prospective observational study	(32)
Napoli 2015	Anas; Exe; Letr	*CYP19A1*	rs700518	Truncal fat and fat-free mass indexes	82	USA	Post-	Longitudinal prospective study	(54)
Niravath 2018	Anas; Exe	*VDR*	rs2228570	Arthralgia	72 cases/ 144 controls	USA, Canada	Post-	Nested case-control study	(71)
Ntukidem 2008	Tam	*ESR2, ESR1*	ESR2–02 (rs4986938), XbaI (rs9340799)	TG, HDL, TC	134	USA	Post-	Cohort from a prospective observational open-label clinical study	(86)
Oesterreich 2015	Anas; Exe; Letr	*ESR2, ESR1, HTR2A, CYP19A1*	rs10140457, rs2813543, rs3742278, rs4870061, rs6493497, rs9322335	BMD and T score [LS, hip], Bone loss [urinary NTx, serum BAP]	503	USA	Post-	PGx analysis of randomized study	(49)
Ohnishi 2005	Tam	*CYP17A1*	rs743572	Hepatic steatosis	180	Japan	Pre-, Post-	Cohort	(9)
Onitilo 2009	Tam	*ESR1*	XbaI/PvuII diplotype, rs9340799 (XbaI)	VTE [PE or DVT]	219	USA	Pre-, Peri-, Post-	Population-based cohort study	(11)
Park 2011	Letr	*CYP19A1*	Haplotype M_5_3	Arthralgia, HF	109	Korea	Pre-, Post-	Cohort	(19)
Pineda-Moncusi 2017	Anas; Exe; Letr	*CYP11A1*	D15S520 [pentanucleotide [TTTTA] n repeat, Haplotypes: GATGAAA 17.3; GATGACA 17.4; CAT 11.2	BMD [FN], Arthralgia	391	Spain	Post-	Cohort	(67)
Regan 2012	Tam	*CYP2D6*	CYP2D6 IM *vs*. EM, CYP2D6 PM vs. EM	HF, Night sweats	4,393	Denmark, France, Switzerland	Post-	*Post-hoc* of randomized, phase III double-blind study	(26)

Table II. *Continued*

Table II. *Continued*

Study (author, year of publication)	Drug(s)	Gene	Genomic variant(s)	Toxicity outcomes	Study size	Demographics/ Population description	Menopausal status	Study type	Ref.
Rodríguez-Sanz 2015	Anas; Exe; Letr	*CYP11A1*	SNPs and haplotypes for (rs11632698, rs4077581, rs900798)	BMD [FN]	391	Spain	Post-	Prospective, observational, clinical cohort study	(51)
Rolla 2012	Tam	*CYP2D6*	CYP2D6 UM *vs*. EM-IM-PM	ADEs [HF, headache, muscle cramps, weight gain, depression, vaginal symptoms, ET]	61	Italy	Pre-, Post-	Cohort	(29)
Romero 2020	Anas; Exe; Letr	*HSD17B2*	rs11648233	Arthralgia	1,049	USA (White)	Post-	Cross-sectional study	(82)
Santa-Maria 2016	Letr	*CYP19A1*	rs1062033, rs749292, rs10046, rs1008805, rs2289105, rs3759811, rs4646, rs4775936 rs700518	HDL, TG	303	USA	Post-	Subset analysis of prospective randomized open-label trial	(57)
Servitja 2015	Anas; Exe; Letr	*CYP27B1*, *CYP17A1*	rs4646536, rs6163	MS-ADEs	687	Spain	Post-	Cohort	(48)
Umama-heswaran 2020	Letr	*CYP19A1*	rs10459592, rs4775936, rs700518, rs700519. Haplotypes: H11; H5; H6; H10; H3	MS-ADEs, VM-ADEs	198	India	Post-	Cohort	(81)
Wang 2013	Anas; Letr	ESR1	rs2234693 and rs9340799	MS-ADEs	206 cases/ 230 controls	China [East Asian]	Post-	Case/control study	(37)
Wang 2015	Anas; Letr	*RANKL*, *OPG*	SNPs and haplotypes for rs7984870, rs2073618	MS-ADEs, Bone turnover [CTX, PINP], BMD and T-score [LS]	208 cases/ 212 controls	China [East Asian]	Post-	Case/control study	(52)
Weng 2013	Tam	PTCSC2, E2F7, SLC22A23, PLEKHA5	rs10983920, rs10983932, rs10984098, rs310786, rs4959825, rs9862879	BMD [hip, LS], HF	245	USA	Pre-, Peri-, Post-	Sub-study of open-label, prospective observational trial	(36)
Wickramage 2017	Tam	*CYP2D6*	CYP2D6*41	Fatty liver	24	Sri Lanka	Pre-, Post-	Retrospective cohort	(68)
Zhou 2022	Tam	*CYP2D6*	CYP2D6 EM	GGT, Liver dysfunction, DET, Gynecological ADEs, Dyslipidemia events (TG, abnormality in LP(a), TC)	192	China	Pre-, Post-	Propensity-score matched cohort study	(93)

LS: Lumbar spine; NTx: type I cross-linked N telopeptides; BAP: bone alkaline phosphatase; OFS: ovarian function suppression; AIs: aromatase inhibitors; RCT: randomized control Trial; HF: Hot Flushes; TC: total cholesterol; TG: Triglycerides; HDL: High-Density Lipoprotein; ADEs: adverse drug effects; EH: endometrial hyperplasia; VTE: venous Thromboembolic events; PE: pulmonary embolism; DVT: Deep Vein Thrombosis; MS-ADEs: musculoskeletal adverse effects [Muscle pain or Arthralgia]; VM-ADEs: vasomotor adverse Effects; FFPE: formalin-fixed paraffin-embedded tumor; HRQL: physical health-related quality of life; CTX: carboxy terminal telopeptide; PINP: procollagen type I N-terminal propeptide; GGT: Gamma-glutamyl transferase; ET: endometrial thickness; DET: double endometrial thickness; EH: endometrial hyperplasia; FM: femoral neck; LP(a): lysophosphatidic acid; BMD: bone mineral density; EM: extensive metabolizer; IM: intermediate metaboliser; PM: poor metabolizer; UM: ultrarapid metabolizer; Tam: tamoxifen; Anas: Anastrozole; Exe: Exemestane; Letr: Letrozole; Pre-: premenopausal; Peri-: peri-menopausal; Post: postmenopausal.

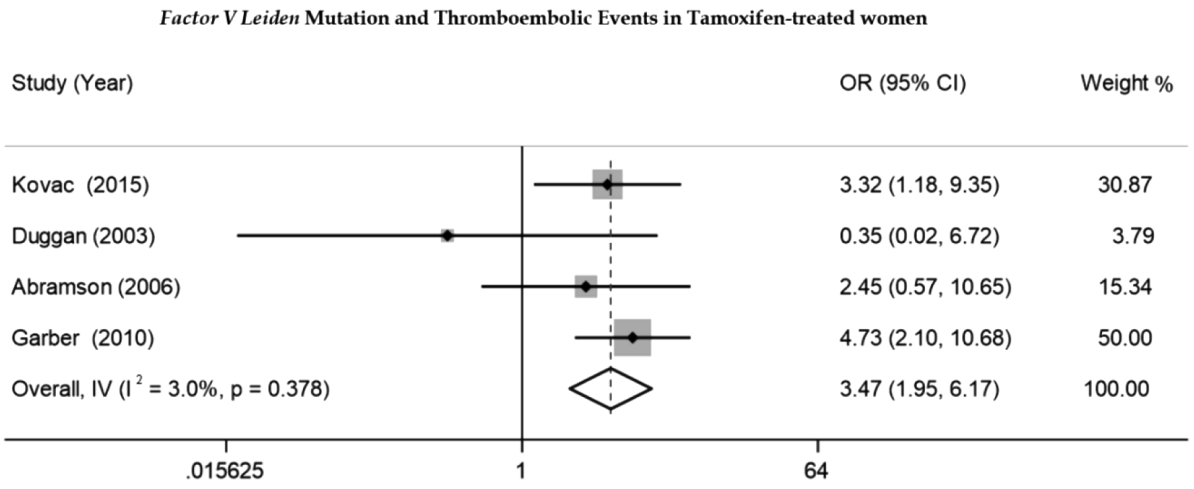

Figure 2. *Meta-analysis of Factor V Leiden mutation and thromboembolic events in tamoxifen-treated patients. Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of four studies examined Factor V Leiden mutation (rs6025) and thromboembolic events in patients taking tamoxifen. Individual and pooled odds ratios from studies are reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.*

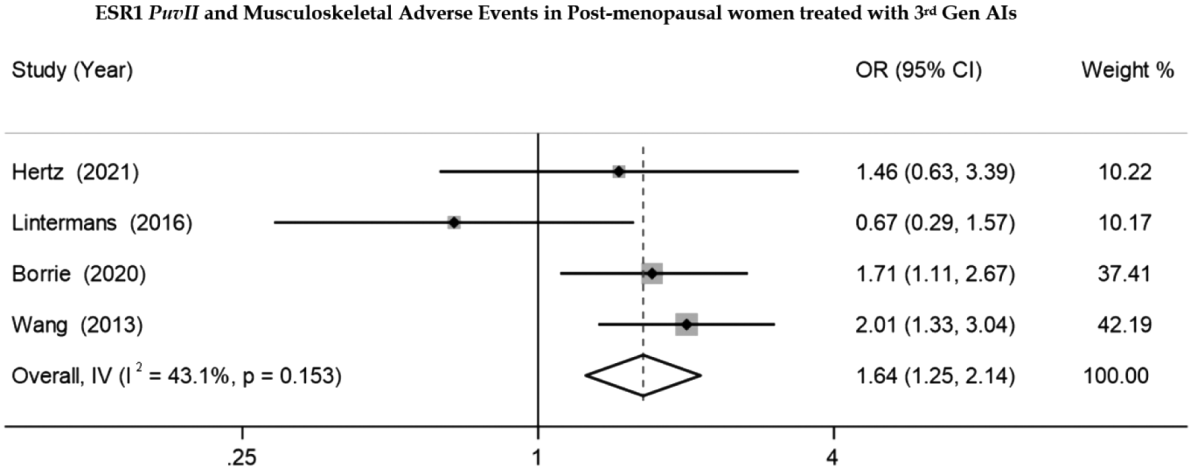

Figure 3. *Meta-analysis of ESR1 PuvII and musculoskeletal adverse effects in postmenopausal women treated with third-generation aromatase inhibitors. Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined ESR1 PuvII (rs2234693) and musculoskeletal adverse effects in postmenopausal women taking third-generation aromatase inhibitors. Individual and pooled odds ratios from studies are reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.*

Discussion

Interventions to reduce ADEs associated with endocrine therapy are an integral part of the effort to improve BC survivorship. Research indicates that certain genetic variants can modulate the toxicity outcomes associated with endocrine therapy in patients with BC. Using a comprehensive search strategy and large-scale meta-analyses, this review provides an extensive analysis of the available evidence regarding the pharmacogenomics of endocrine therapy-related toxicities, advancing our understanding of pharmacogenomics research overall.

While the majority of identified associations were statistically non-significant, three meta-analyses yielded significant results. The FVL mutation can serve as a

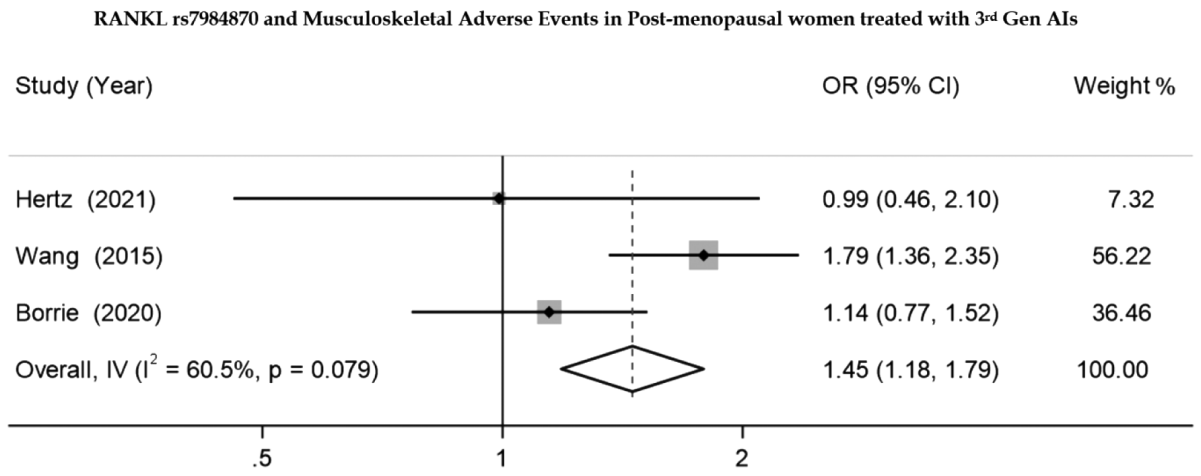

Figure 4. *Meta-analysis of RANKL rs7984870 and musculoskeletal adverse effects in postmenopausal women treated with third-generation aromatase inhibitors. Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined RANKL rs7984870 and musculoskeletal adverse effects in postmenopausal women taking third-generation aromatase inhibitors. Individual and pooled odds ratios from studies are reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.*

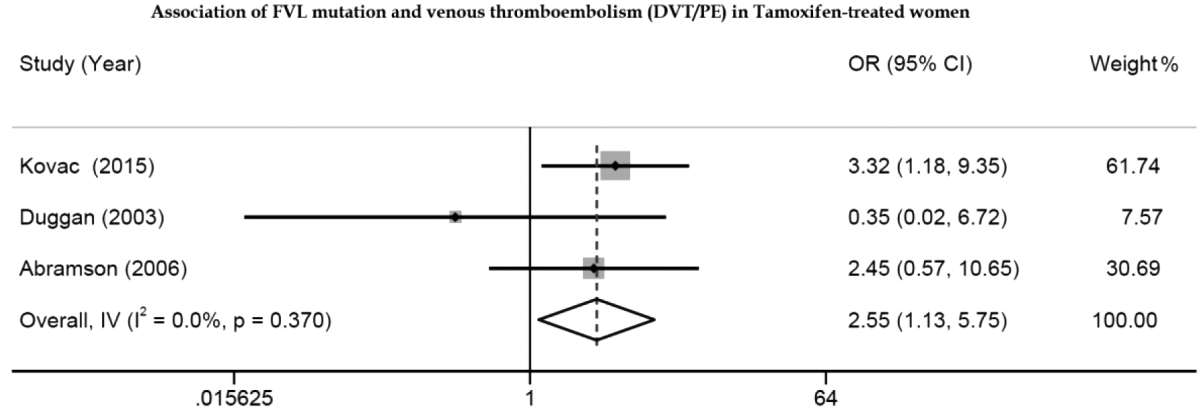

Figure 5. *Meta-analysis of Factor V Leiden mutation and venous thromboembolism in tamoxifen-treated patients. Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined Factor V Leiden mutation (rs6025) and venous thromboembolism in patients taking tamoxifen. Individual and pooled odds ratios from studies are reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.*

predictive genetic marker of thromboembolic events in patients with BC on tamoxifen, who can be switched to alternative endocrine agents or potentially targeted for monitoring to improve adherence and consequently overall survival rates. While meta-analyses showed that *PuvII* (rs2234693) is associated with MS-ADEs in postmenopausal women who had received AI treatment, no significant associations were observed in other studies with either MS-ADEs-related discontinuation of Exemestane and/or Letrozole under any genetic model (34) or with MS-ADEs in patients taking endocrine agents (56). Similarly, while meta-analyses demonstrated that postmenopausal women carrying *RANKL* rs7984870 who received AIs had an increased risk of MS-ADEs, another study did not find significant alterations in the MS-ADEs symptom cluster (73). The evidence for these two variants with regard to MS-

Table III. *Meta-analyses with a statistically significant summary effect size.*

Toxicity outcomes	Drug(s)	Genomic variant	Risk allele	Pooled effect estimate (95%Cl)	I^2 (%), *p*-value (Cochran's Q)	Ref.
Thromboembolic events	Tam	*Factor V Leiden* (rs6025)	A	OR=3.474 (1.955, 6.174), $p<0.0001$	(3.0%), 0.378	(8, 15, 46, 53)
MS-ADEs	Anas; Exe; Letr	*PuvII* (rs2234693)	C	OR=1.636 (1.250, 2.141), $p<0.0001$	(43.1%), 0.153	(52, 55, 85, 89)
MS-ADEs	Anas; Exe; Letr	rs7984870	C	OR=1.455 (1.184, 1.786), $p<0.0001$	(60.5%), 0.079	(52, 85, 89)

Tam: Tamoxifen; Anas: Anastrozole; Exe: Exemestane; Letr: Letrozole.

ADEs is therefore inconsistent and larger studies are needed to provide more robust findings.

Almost all included studies were retrospective with only one randomized genotype-guided study identified (87), in which the study's authors concluded that ADEs did not vary significantly between increased dose and regular dose arms. It is noteworthy that the study focused on common ADEs related to tamoxifen and safety was not the primary endpoint. The majority of studies were candidate gene studies, with only three genome-wide association studies. Larger GWAS studies are necessary, given the small sample sizes in the three GWAS studies included in this review compared to typical GWAS on polygenic traits.

The majority of the studies were small, with approximately half of the publications utilizing data from the same cohort(s) or clinical trial(s). The substantial overlap in participants from the same trial or cohort across studies, especially the ones that yielded statistically significant results, can introduce biases and result in overestimation of pharmacogenomic effect estimates (95). The dependence occurs when the same participant samples are used in individual studies to estimate multiple effect sizes for the same or interrelated toxicity outcomes, leading to dependent sampling errors (96).

The broad range of characteristics among the eligible studies resulted in significant heterogeneity in both methodological and clinical aspects. The substantial heterogeneity in the definitions and measures of toxicity outcomes observed across studies emphasizes the need for using standardized toxicity-related symptom measurements and definitions of toxicity outcomes. This enables accurate interpretation and facilitates the pooling of effect estimates *via* meta-analysis.

Overall, the studies included in this review scored high in quality. Yet, it is vital to emphasize the need for greater attention to reporting biases and Hardy-Weinberg equilibrium across studies as well as addressing mixed ethnicities when applicable. Some investigators potentially introduce outcome reporting bias by grouping heterogeneous ADEs with varying degrees of seriousness and severity together. The selective reporting of findings observed, with some studies only reporting positive results, and the incomplete outcome reporting by some authors (14, 57, 82, 86) suggest outcome reporting bias and potentially exacerbate publication bias (97, 98). Additionally, while most studies adjusted their analyses for patient risk factors, inconsistencies existed regarding which covariates to adjust for, raising concerns about the robustness of the analyses. Hence, efforts should be made to improve data dissemination, transparency, and complete reporting among investigators to facilitate further statistical analyses (99).

Furthermore, the authors of most studies have not explored the potential genotype-treatment interactions in regression analyses, which is recommended in best practice guidelines (100, 101). The adverse implications of disregarding interaction effects or effect modifications in statistical analyses are well-documented in the literature (102). Thus, caution is required when interpreting the findings from associations reported across those studies that have not incorporated interaction terms in their statistical model.

Only a small fraction, less than 1%, of the associations investigated in the studies focused on premenopausal women. However, this proportion does not correspond with the incidence of BC cases in premenopausal compared to postmenopausal women (30.9% *vs*. 69.1%) (103). Due to the abrupt disruption in estrogen levels associated with systemic endocrine treatment, premenopausal women with ER-positive BC are more susceptible to endocrine therapy-related ADEs (104) and thereby more likely to discontinue their endocrine therapy regimen (105). Furthermore, the dense tissue of the breasts in premenopausal women makes it more challenging for clinicians to detect issues from mammography and so BC in premenopausal women is most frequently diagnosed at a later stage with more aggressive disease (106). Thus, this population faces more intensive therapy and lower survival rates compared to postmenopausal women, underscoring the necessity for further pharmacogenomics research in this population (104). It is noteworthy that premenopausal BC in less developed countries constitutes a significantly larger proportion of all incident BC cases and deaths compared with higher-income countries (103).

Most studies were performed in high-income countries or in cohorts of predominantly Caucasian or white people. Although BC incidence is notably lower in less developed countries compared to more developed ones (107), BC remains the most common cause of cancer-related death especially in middle and low-income countries. While this is largely attributed to recurrence and metastasis, early diagnosis and access to treatment continue to be significant challenges in low-income and middle-income countries (103). Furthermore, although black female patients have a lower incidence of BC compared to white or Caucasian women, their BC-related mortality rate is 40% higher. Moreover, in contrast to White and Asian patients, Black patients exhibit a higher prevalence of overweight or obesity and are more frequently receiving chemotherapy agents such as taxanes (108). Women who reported lower adherence to treatment behaviors were also more likely to be Black (as opposed to White) and had a higher medication-related ADE burden (109). In order to improve the generalizability of findings to other under-represented ethnic groups and decrease racial disparities and health inequalities, more inclusive research using larger cohorts with more diverse ethnic populations is required (110). To address the deficiency in pharmacogenetic data among African populations, initiatives such as the African Pharmacogenomics Network (APN) are essential (111). These efforts are crucial for advancing comprehensive pharmacogenetic studies to identify variants in pharmacogenes, which could be leveraged to reduce ADEs and enhance therapeutic efficacy (112).

Finally, given that multiple factors, such as ethnicity, age, and BMI can influence inter-individual variability (113), incorporating both genetic and non-genetic determinants of ADEs associated with endocrine agents has the potential to improve the precision of predicting individual responses to these agents (114).

This review has a few limitations. First, the retrospective nature of the vast majority of included studies and relying largely on published data may introduce bias despite our comprehensive searches. Although some studies were post-hoc analyses of randomized control trials, ADEs were rarely the primary endpoints and were often analyzed retrospectively. This could have resulted in false positives and an overestimation of effect estimates. Second, limiting the search to English-only publications may introduce language bias, potentially leading to an over-representation of studies from Western countries and patients of Caucasian backgrounds in the data. Third, the meta-analyses included a small number of studies with a limited number of patients and therefore heterogeneity among the studies cannot be eliminated. Finally, the inclusion of four dissertations and theses (61, 62, 70, 74) may raise concerns due to their perceived variability in their design quality compared to journal articles. Although it has been perceived that these non-traditional sources are not generally subject to the same peer-review procedures (115), this view has been challenged (116). Dissertations and theses usually undergo rigorous appraisal, and they scored high as per our quality assessment criteria. Moreover, the inclusion of non-traditional sources helps reduce publication bias and enhances the representation of relevant research particularly in rapidly evolving fields such as pharmaco-genomics.

Conclusion

The existing evidence on pharmacogenomics in breast cancer endocrine therapy-related toxicity is largely inconclusive and should move beyond small-scale studies and post-hoc analyses of clinical trials. To improve the evidence in this context, it is crucial to conduct carefully designed research and larger cohort studies, particularly involving premenopausal women and non-Caucasian populations. This study further underscores the imperative of incorporating both hypothesis-free and expanded candidate gene approaches in future research efforts.

Data Availability

All data relevant to the present study are included in the article or uploaded as supplementary information.

Supplementary Material

To access the supplementary materials, visit: https://doi.org/10.6084/m9.figshare.25872487.v3

Conflicts of Interest

The Authors declare that they have no conflicts of interest that are directly relevant to the content of this study.

Authors' Contributions

KM, MW, VM and LJ conceptualized the study and designed the research. KM and LJ conducted the research and graphical overviews. MW performed the statistical analysis and generated the graphs.

Acknowledgements

This study received support from the University of Exeter Sanctuary Scholarship. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) license to any Author Accepted Manuscript version arising from this submission.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/CAAC.21660

2 Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, Poole CJ, Bates T, Chetiyawardana S, Dewar JA, Fernando IN, Grieve R, Nicoll J, Rayter Z, Robinson A, Salman A, Yarnold J, Bathers S, Marshall A, Lee M, on behalf of the aTTom Collaborative Group: aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years *versus* stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 31(18_suppl): 5-5, 2013. DOI: 10.1200/JCO.2013.31.18_SUPPL.5

3 Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J: Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo – Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast 26: 106-114, 2016. DOI: 10.1016/J.BREAST.2016.01.006

4 Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW: Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat 134(2): 459-478, 2012. DOI: 10.1007/s10549-012-2114-5

5 Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE: Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 92(4): 414-417, 2012. DOI: 10.1038/clpt.2012.96

6 Haynes R: Clinical epidemiology: how to do clinical practice research. Lippincott Williams & Wilkins, 2012.

7 Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N: STrengthening the REporting of Genetic Association Studies (STREGA)—an extension of the STROBE statement. Genet Epidemiol 33(7): 581-598, 2009. DOI: 10.1002/GEPI.20410

8 Duggan C, Marriott K, Edwards R, Cuzick J: Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. J Clin Oncol 21(19): 3588-3593, 2003. DOI: 10.1200/JCO.2003.10.111

9 Ohnishi T, Ogawa Y, Saibara T, Nishioka A, Kariya S, Fukumoto M, Onishi S, Yoshida S: CYP17 polymorphism and tamoxifen-induced hepatic steatosis. Hepatol Res 33(2): 178-180, 2005. DOI: 10.1016/J.HEPRES.2005.09.030

10 Colomer R, Monzo M, Tusquets I, Rifa J, Baena JM, Barnadas A, Calvo L, Carabantes F, Crespo C, Muñoz M, Llombart A, Plazaola A, Artells R, Gilabert M, Lloveras B, Alba E: A single-nucleotide polymorphism in the aromatase gene is associated with the efficacy of the aromatase inhibitor letrozole in advanced breast carcinoma. Clin Cancer Res 14(3): 811-816, 2008. DOI: 10.1158/1078-0432.CCR-07-1923

11 Onitilo AA, McCarty CA, Wilke RA, Glurich I, Engel JM, Flockhart DA, Nguyen A, Li L, Mi D, Skaar TC, Jin Y: Estrogen receptor genotype is associated with risk of venous thromboembolism during tamoxifen therapy. Breast Cancer Res Treat 115(3): 643-650, 2009. DOI: 10.1007/S10549-008-0264-2

12 Okishiro M, Taguchi T, Jin Kim S, Shimazu K, Tamaki Y, Noguchi S: Genetic polymorphisms of CYP2D6*10 and CYP2C19*2,*3 are not associated with prognosis, endometrial thickness, or bone mineral density in Japanese breast cancer patients treated with adjuvant tamoxifen. Cancer 115(5): 952-961, 2009. DOI: 10.1002/CNCR.24111

13 Henry NL, Rae JM, Li L, Azzouz F, Skaar TC, Desta Z, Sikora MJ, Philips S, Nguyen AT, Storniolo AM, Hayes DF, Flockhart DA, Stearns V, Consortium on Breast Cancer Pharmacogenomics Investigators: Association between CYP2D6 genotype and tamoxifen-induced hot flashes in a prospective cohort. Breast Cancer Res Treat 117(3): 571-575, 2009. DOI: 10.1007/s10549-009-0309-1

14 Henry NL, Nguyen A, Azzouz F, Li L, Robarge J, Philips S, Cao D, Skaar TC, Rae JM, Storniolo AM, Flockhart DA, Hayes DF, Stearns V: Lack of association between oestrogen receptor polymorphisms and change in bone mineral density with tamoxifen therapy. Br J Cancer 102(2): 294-300, 2010. DOI: 10.1038/sj.bjc.6605460

15 Garber JE, Halabi S, Tolaney SM, Kaplan E, Archer L, Atkins JN, Edge S, Shapiro CL, Dressler L, Paskett ED, Kimmick G, Orcutt J, Scalzo A, Winer E, Levine E, Shahab N, Berliner N, Cancer and Leukemia Group B: Factor V Leiden mutation and thromboembolism risk in women receiving adjuvant tamoxifen for breast cancer. J Natl Cancer Inst 102(13): 942-949, 2010. DOI: 10.1093/jnci/djq211

16 Ingle JN, Schaid DJ, Goss PE, Liu M, Mushiroda T, Chapman JA, Kubo M, Jenkins GD, Batzler A, Shepherd L, Pater J, Wang L, Ellis MJ, Stearns V, Rohrer DC, Goetz MP, Pritchard KI, Flockhart DA, Nakamura Y, Weinshilboum RM: Genome-wide associations and functional genomic studies of musculoskeletal adverse events in women receiving aromatase inhibitors. J Clin Oncol 28(31): 4674-4682, 2010. DOI: 10.1200/JCO.2010.28.5064

17 Ramón y Cajal T, Altés A, Paré L, del Rio E, Alonso C, Barnadas A, Baiget M: Impact of CYP2D6 polymorphisms in tamoxifen adjuvant breast cancer treatment. Breast Cancer Res Treat 119(1): 33-38, 2010. DOI: 10.1007/s10549-009-0328-y

18 Irvin WJ Jr, Walko CM, Weck KE, Ibrahim JG, Chiu WK, Dees EC, Moore SG, Olajide OA, Graham ML, Canale ST, Raab RE, Corso SW, Peppercorn JM, Anderson SM, Friedman KJ, Ogburn ET, Desta Z, Flockhart DA, McLeod HL, Evans JP, Carey LA: Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 29(24): 3232-3239, 2011. DOI: 10.1200/JCO.2010.31.4427

19 Park IH, Lee YS, Lee KS, Kim SY, Hong SH, Jeong J, Lee H, Ro J, Nam BH: Single nucleotide polymorphisms of CYP19A1 predict clinical outcomes and adverse events associated with letrozole in patients with metastatic breast cancer. Cancer Chemother Pharmacol 68: 1263–1271, 2011. DOI: 10.1007/s00280-011-1615-y

20 Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, Reynolds C, Couch FJ, Lingle WL, Flockhart DA, Desta Z, Perez EA, Ingle JN: Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 23(36): 9312-9318, 2005. DOI: 10.1200/JCO.2005.03.3266

21 Mao JJ, Su HI, Feng R, Donelson ML, Aplenc R, Rebbeck TR, Stanczyk F, DeMichele A: Association of functional polymorphisms in CYP19A1 with aromatase inhibitor associated arthralgia in breast cancer survivors. Breast Cancer Res 13(1): R8, 2011. DOI: 10.1186/bcr2813

22 Damodaran SE, Pradhan SC, Umamaheswaran G, Kadambari D, Reddy KS, Adithan C: Genetic polymorphisms of CYP2D6 increase the risk for recurrence of breast cancer in patients receiving tamoxifen as an adjuvant therapy. Cancer Chemother Pharmacol 70(1): 75-81, 2012. DOI: 10.1007/S00280-012-1891-1

23 Lorizio W, Wu AH, Beattie MS, Rugo H, Tchu S, Kerlikowske K, Ziv E: Clinical and biomarker predictors of side effects from tamoxifen. Breast Cancer Res Treat 132(3): 1107-1118, 2012. DOI: 10.1007/s10549-011-1893-4

24 Sestak I, Kealy R, Nikoloff M, Fontecha M, Forbes JF, Howell A, Cuzick J: Relationships between CYP2D6 phenotype, breast cancer and hot flushes in women at high risk of breast cancer receiving prophylactic tamoxifen: results from the IBIS-I trial. Br J Cancer 107(2): 230-233, 2012. DOI: 10.1038/bjc.2012.278

25 Kiyotani K, Mushiroda T, Imamura CK, Tanigawara Y, Hosono N, Kubo M, Sasa M, Nakamura Y, Zembutsu H: Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients. Breast Cancer Res Treat 131(1): 137-145, 2012. DOI: 10.1007/s10549-011-1777-7

26 Regan MM, Leyland-Jones B, Bouzyk M, Pagani O, Tang W, Kammler R, Dell'orto P, Biasi MO, Thürlimann B, Lyng MB, Ditzel HJ, Neven P, Debled M, Maibach R, Price KN, Gelber RD, Coates AS, Goldhirsch A, Rae JM, Viale G, Breast International Group (BIG) 1-98 Collaborative Group: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst 104(6): 441-451, 2012. DOI: 10.1093/jnci/djs125

27 Hartmaier RJ, Richter AS, Gillihan RM, Sallit JZ, McGuire SE, Wang J, Lee AV, Osborne CK, O'Malley BW, Brown PH, Xu J, Skaar TC, Philips S, Rae JM, Azzouz F, Li L, Hayden J, Henry NL, Nguyen AT, Stearns V, Hayes DF, Flockhart DA, Oesterreich S: A SNP in steroid receptor coactivator-1 disrupts a GSK3β phosphorylation site and is associated with altered tamoxifen response in bone. Mol Endocrinol 26(2): 220-227, 2012. DOI: 10.1210/me.2011-1032

28 Koukouras D, Marioli DJ, Papadopoulos K, Adonakis GL, Armeni AK, Georgopoulos NA, Decavalas G: Association of estrogen receptor alpha (ERα) gene polymorphisms with endometrial thickness and lipid profile in women with breast cancer treated with aromatase inhibitors. Gynecol Endocrinol 28(11): 859-862, 2012. DOI: 10.3109/09513590.2012.671393

29 Rolla R, Vidali M, Meola S, Pollarolo P, Fanello MR, Nicolotti C, Saggia C, Forti L, Agostino FD, Rossi V, Borra G, Stratica F, Alabiso O, Bellomo G: Side effects associated with ultrarapid cytochrome P450 2D6 genotype among women with early stage breast cancer treated with tamoxifen. Clin Lab 58: 1211–1218, 2012. DOI: 10.7754/Clin.Lab.2012.120114

30 Ruddy KJ, Desantis SD, Gelman RS, Wu AH, Punglia RS, Mayer EL, Tolaney SM, Winer EP, Partridge AH, Burstein HJ: Personalized medicine in breast cancer: tamoxifen, endoxifen, and CYP2D6 in clinical practice. Breast Cancer Res Treat 141(3): 421-427, 2013. DOI: 10.1007/S10549-013-2700-1

31 Tucker AN, Tkaczuk KA, Lewis LM, Tomic D, Lim CK, Flaws JA: Polymorphisms in cytochrome P4503A5 (CYP3A5) may be associated with race and tumor characteristics, but not metabolism and side effects of tamoxifen in breast cancer patients. Cancer Lett 217: 61-72, 2005. DOI: 10.1016/j.canlet.2004.08.027

32 Napoli N, Rastelli A, Ma C, Yarramaneni J, Vattikutti S, Moskowitz G, Giri T, Mueller C, Kulkarny V, Qualls C, Ellis M, Armamento-Villareal R: Genetic polymorphism at Val80 (rs700518) of the CYP19A1 gene is associated with aromatase inhibitor associated bone loss in women with ER + breast cancer. Bone 55(2): 309-314, 2013. DOI: 10.1016/j.bone.2013.04.021

33 Liu L, Bai YX, Zhou JH, Sun XW, Sui H, Zhang WJ, Yuan HH, Xie R, Wei XL, Zhang TT, Huang P, Li YJ, Wang JX, Zhao S, Zhang QY: A polymorphism at the 3'-UTR region of the aromatase gene is associated with the efficacy of the aromatase inhibitor, anastrozole, in metastatic breast carcinoma. Int J Mol Sci 14(9): 18973-18988, 2013. DOI: 10.3390/ijms140918973

34 Henry NL, Skaar TC, Dantzer J, Li L, Kidwell K, Gersch C, Nguyen AT, Rae JM, Desta Z, Oesterreich S, Philips S, Carpenter JS, Storniolo AM, Stearns V, Hayes DF, Flockhart DA: Genetic associations with toxicity-related discontinuation of aromatase inhibitor therapy for breast cancer. Breast Cancer Res Treat 138(3): 807-816, 2013. DOI: 10.1007/s10549-013-2504-3

35 Garcia-Giralt N, Rodríguez-Sanz M, Prieto-Alhambra D, Servitja S, Torres-Del Pliego E, Balcells S, Albanell J, Grinberg D, Diez-Perez A, Tusquets I, Nogués X: Genetic determinants of aromatase inhibitor-related arthralgia: the B-ABLE cohort study. Breast Cancer Res Treat 140(2): 385-395, 2013. DOI: 10.1007/S10549-013-2638-3

36 Weng L, Ziliak D, Im HK, Gamazon ER, Philips S, Nguyen AT, Desta Z, Skaar TC, Flockhart DA, Huang RS, Consortium on Breast Cancer Pharmacogenomics (COBRA): Genome-wide discovery of genetic variants affecting tamoxifen sensitivity and their clinical and functional validation. Ann Oncol 24(7): 1867-1873, 2013. DOI: 10.1093/annonc/mdt125

37 Wang J, Lu K, Song Y, Xie L, Zhao S, Wang Y, Sun W, Liu L, Zhao H, Tang D, Ma W, Pan B, Xuan Q, Liu H, Zhang Q: Indications of clinical and genetic predictors for aromatase inhibitors related musculoskeletal adverse events in Chinese Han women with breast cancer. PLoS One 8(7): e68798, 2013. DOI: 10.1371/journal.pone.0068798

38 Jager NG, Koornstra RH, Vincent AD, van Schaik RH, Huitema AD, Korse TM, Schellens JH, Linn SC, Beijnen JH: Hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites. BMC Cancer 13: 612, 2013. DOI: 10.1186/1471-2407-13-612

39 Günaldı M, Erkisi M, Afşar CU, Erçolak V, Paydas S, Kara IO, Sahin B, Gulec UK, Secilmis A: Evaluation of endometrial thickness and bone mineral density based on CYP2D6 polymorphisms in Turkish breast cancer patients receiving tamoxifen treatment. Pharmacology 94(3-4): 183-189, 2014. DOI: 10.1159/000363304

40 Liu M, Goss PE, Ingle JN, Kubo M, Furukawa Y, Batzler A, Jenkins GD, Carlson EE, Nakamura Y, Schaid DJ, Chapman JA, Shepherd LE, Ellis MJ, Khosla S, Wang L, Weinshilboum RM: Aromatase inhibitor-associated bone fractures: a case-cohort GWAS and functional genomics. Mol Endocrinol 28(10): 1740-1751, 2014. DOI: 10.1210/me.2014-1147

41 Fontein DB, Houtsma D, Nortier JW, Baak-Pablo RF, Kranenbarg EM, van der Straaten TR, Putter H, Seynaeve C, Gelderblom H, van de Velde CJ, Guchelaar HJ: Germline variants in the CYP19A1 gene are related to specific adverse events in aromatase inhibitor users: a substudy of Dutch patients in the TEAM trial. Breast Cancer Res Treat 144(3): 599-606, 2014. DOI: 10.1007/s10549-014-2873-2

42 Georgopoulos NA, Adonakis GL, Fotopoulos A, Koika V, Spinos N, Saltamavros A, Keramopoulos A, Koukouras D, Decavalas G, Kourounis GS: Estrogen receptor polymorphisms in tamoxifen-treated women with breast cancer. Gynecol Endocrinol 22(4): 185-189, 2006. DOI: 10.1080/09513590600645767

43 Dieudonné AS, Lambrechts D, Smeets D, Belmans A, Wildiers H, Paridaens R, Hyonil C, Timmerman D, Christiaens MR, Vergote I, Neven P: The rs1800716 variant in CYP2D6 is associated with an increased double endometrial thickness in postmenopausal women on tamoxifen. Ann Oncol Off J Eur Soc Med Oncol 25(1): 90-95, 2014. DOI: 10.1093/ANNONC/MDT399

44 Baxter SD, Teft WA, Choi Y, Winquist E, Kim RB: Tamoxifen-associated hot flash severity is inversely correlated with endoxifen concentration and CYP3A4*22. Breast Cancer Res Treat 145(2): 419-428, 2014. DOI: 10.1007/s10549-014-2963-1

45 Dezentjé VO, Gelderblom H, Van Schaik RH, Vletter-Bogaartz JM, Van der Straaten T, Wessels JA, Kranenbarg EM, Berns EM, Seynaeve C, Putter H, Van de Velde CJ, Nortier JW, Guchelaar HJ: CYP2D6 genotype in relation to hot flashes as tamoxifen side effect in a Dutch cohort of the tamoxifen exemestane adjuvant multinational (TEAM) trial. Breast Cancer Res Treat 143: 1-9, 2014. DOI: 10.1007/s10549-013-2777-6

46 Kovac M, Kovac Z, Tomasevic Z, Vucicevic S, Djordjevic V, Pruner I, Radojkovic D: Factor V Leiden mutation and high FVIII are associated with an increased risk of VTE in women with breast cancer during adjuvant tamoxifen — Results from a prospective, single center, case control study. Eur J Intern Med 26(1): 63-67, 2015. DOI: 10.1016/J.EJIM.2014.12.015

47 Leyland-Jones B, Gray KP, Abramovitz M, Bouzyk M, Young B, Long B, Kammler R, Dell'Orto P, Biasi MO, Thürlimann B, Lyng MB, Ditzel HJ, Harvey VJ, Neven P, Treilleux I, Rasmussen BB, Maibach R, Price KN, Coates AS, Goldhirsch A, Pagani O, Viale G, Rae JM, Regan MM: CYP19A1 polymorphisms and clinical outcomes in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial. Breast Cancer Res Treat 151(2): 373-384, 2015. DOI: 10.1007/s10549-015-3378-3

48 Servitja S, Martos T, Rodriguez Sanz M, Garcia-Giralt N, Prieto-Alhambra D, Garrigos L, Nogues X, Tusquets I: Skeletal adverse effects with aromatase inhibitors in early breast cancer: evidence to date and clinical guidance. Ther Adv Med Oncol 7(5): 291-296, 2015. DOI: 10.1177/1758834015598536

49 Oesterreich S, Henry NL, Kidwell KM, Van Poznak CH, Skaar TC, Dantzer J, Li L, Hangartner TN, Peacock M, Nguyen AT, Rae JM, Desta Z, Philips S, Storniolo AM, Stearns V, Hayes DF, Flockhart DA: Associations between genetic variants and the effect of letrozole and exemestane on bone mass and bone turnover. Breast Cancer Res Treat 154(2): 263-273, 2015. DOI: 10.1007/s10549-015-3608-8

50 Leyland-Jones B, Gray KP, Abramovitz M, Bouzyk M, Young B, Long B, Kammler R, Dell'Orto P, Biasi MO, Thürlimann B, Harvey V, Neven P, Arnould L, Maibach R, Price KN, Coates AS, Goldhirsch A, Gelber RD, Pagani O, Viale G, Rae JM, Regan MM, BIG 1-98 Collaborative Group: ESR1 and ESR2 polymorphisms in the BIG 1-98 trial comparing adjuvant letrozole versus tamoxifen or their sequence for early breast cancer. Breast Cancer Res Treat 154(3): 543-555, 2015. DOI: 10.1007/s10549-015-3634-6

51 Rodríguez-Sanz M, García-Giralt N, Prieto-Alhambra D, Servitja S, Balcells S, Pecorelli R, Díez-Pérez A, Grinberg D, Tusquets I, Nogués X: CYP11A1 expression in bone is associated with aromatase inhibitor-related bone loss. J Mol Endocrinol 55: 69-79, 2015. DOI: 10.1530/JME-15-0079

52 Wang J, Lu K, Song Y, Zhao S, Ma W, Xuan Q, Tang D, Zhao H, Liu L, Zhang Q: RANKL and OPG polymorphisms are associated with aromatase inhibitor-related musculoskeletal adverse events in Chinese Han breast cancer patients. PLoS One 10(7): e0133964, 2015. DOI: 10.1371/journal.pone.0133964

53 Abramson N, Costantino JP, Garber JE, Berliner N, Wickerham DL, Wolmark N: Effect of Factor V Leiden and prothrombin G20210→a mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. JNCI J Natl Cancer Inst 98(13): 904-910, 2006. DOI: 10.1093/JNCI/DJJ262

54 Napoli N, Rastelli A, Ma C, Colleluori G, Vattikuti S, Armamento-Villareal R: Genetic polymorphism at Val80 (rs700518) of the CYP19A1 gene is associated with body composition changes in women on aromatase inhibitors for ER (+) breast cancer. Pharmacogenet Genomics 25(8): 377-381, 2015. DOI: 10.1097/FPC.0000000000000146

55 Lintermans A, Van Asten K, Jongen L, Van Brussel T, Laenen A, Verhaeghe J, Vanderschueren D, Lambrechts D, Neven P: Genetic variant in the osteoprotegerin gene is associated with aromatase inhibitor-related musculoskeletal toxicity in breast cancer patients. Eur J Cancer 56: 31-36, 2016. DOI: 10.1016/J.EJCA.2015.12.013

56 Johansson H, Gray KP, Pagani O, Regan MM, Viale G, Aristarco V, Macis D, Puccio A, Roux S, Maibach R, Colleoni M, Rabaglio M, Price KN, Coates AS, Gelber RD, Goldhirsch A, Kammler R, Bonanni B, Walley BA, the TEXT principal investigators: Impact of CYP19A1 and ESR1 variants on early-onset side effects during combined endocrine therapy in the TEXT trial. Breast Cancer Res 18(1): 110, 2016. DOI: 10.1186/s13058-016-0771-8

57 Santa-Maria CA, Blackford A, Nguyen AT, Skaar TC, Philips S, Oesterreich S, Rae JM, Desta Z, Robarge J, Henry NL, Storniolo AM, Hayes DF, Blumenthal RS, Ouyang P, Post WS, Flockhart DA, Stearns V, Consortium on Breast Cancer Pharmacogenomics (COBRA): Association of variants in candidate genes with lipid profiles in women with early breast cancer on adjuvant aromatase inhibitor therapy. Clin Cancer Res 22(6): 1395-1402, 2016. DOI: 10.1158/1078-0432.CCR-15-1213

58 Hertz DL, Deal A, Ibrahim JG, Walko CM, Weck KE, Anderson S, Magrinat G, Olajide O, Moore S, Raab R, Carrizosa DR, Corso S, Schwartz G, Graham M, Peppercorn JM, Jones DR, Desta Z, Flockhart DA, Evans JP, McLeod HL, Carey LA, Irvin WJ Jr: Tamoxifen dose escalation in patients with diminished CYP2D6 activity normalizes endoxifen concentrations without increasing toxicity. Oncologist 21(7): 795-803, 2016. DOI: 10.1634/theoncologist.2015-0480

59 Fox P, Balleine RL, Lee C, Gao B, Balakrishnar B, Menzies AM, Yeap SH, Ali SS, Gebski V, Provan P, Coulter S, Liddle C, Hui R, Kefford R, Lynch J, Wong M, Wilcken N, Gurney H: Dose escalation of tamoxifen in patients with low endoxifen level: evidence for therapeutic drug monitoring—the TADE study. Clin Cancer Res 22(13): 3164-3171, 2016. DOI: 10.1158/1078-0432.CCR-15-1470

60 Mazzuca F, Botticelli A, Mazzotti E, La Torre M, Borro M, Marchetti L, Maddalena C, Gentile G, Simmaco M, Marchetti P: CYP19A1 genetic polymorphisms rs4646 and osteoporosis in patients treated with aromatase inhibitor-based adjuvant therapy. Eurasian J Med 48(1): 10-14, 2016. DOI: 10.5152/eurasianjmed.2015.008

61 Knight B: The Association between the UGT2B17 gene deletion and menopause-related quality of life in postmenopausal women in the CCTG MAP.3 Breast Cancer Chemoprevention Trial, 2017.

62 Al-Mamun MA: Effect of SULT1A1, UGT2B7, CYP3A5 and CYP2D6 polymorphisms on tamoxifen response in breast cancer patients of Bangladesh. Poster presentation in 2nd International South Asian Biotechnology Conference, 2016 held in Dhaka, Bangladesh.

63 Zembutsu H, Nakamura S, Akashi-tanaka S, Kuwayama T, Watanabe C, Takamaru T, Takei H, Ishikawa T, Miyahara K, Matsumoto H, Hasegawa Y, Kutomi G, Shima H, Satomi F, Okazaki M, Zaha H, Onomura M, Matsukata A, Sagara Y, Baba S, Yamada A, Shimada K, Shimizu D, Tsugawa K, Shimo A, Tan EY, Hartman M, Chan C, Lee SC, Nakamura Y: Significant effect of polymorphisms in*CYP2D6* on response to tamoxifen therapy for breast cancer: a prospective multicenter study. Clin Cancer Res 23(8): 2019-2026, 2017. DOI: 10.1158/1078-0432.CCR-16-1779

64 Bonanni B, Macis D, Maisonneuve P, Johansson HA, Gucciardo G, Oliviero P, Travaglini R, Muraca MG, Rotmensz N, Veronesi U, Decensi AU: Polymorphism in the *CYP2D6* tamoxifen-metabolizing gene influences clinical effect but not hot flashes: data from the Italian tamoxifen trial. J Clin Oncol 24(22): 3708-3709, 2006. DOI: 10.1200/JCO.2006.06.8072

65 Gervasini G, Jara C, Olier C, Romero N, Martínez R, Carrillo JA: Polymorphisms in ABCB1 and CYP19A1 genes affect anastrozole plasma concentrations and clinical outcomes in postmenopausal breast cancer patients. Br J Clin Pharmacol 83(3): 562-571, 2017. DOI: 10.1111/bcp.13130

66 Argalacsova S, Slanar O, Bakhouche H, Pertuzelka L: Impact of ABCB1 and CYP2D6 polymorphisms on tamoxifen treatment outcomes and adverse events in breast cancer patients. J BUON 22: 1217-1226, 2017.

67 Pineda-Moncusí M, Rodríguez-Sanz M, Díez-Pérez A, Aymar P, Martos T, Servitja S, Tusquets I, García-Giralt N, Nogués X: Genetic analysis of steroid pathway enzymes associated with adverse musculoskeletal effects of aromatase inhibitors. Rev Osteoporos y Metab Miner 9: 72-81, 2017. DOI: 10.4321/S1889-836X2017000200004

68 Wickramage I, Tennekoon KH, Ariyaratne MA, Hewage AS, Sundralingam T: CYP2D6 polymorphisms may predict occurrence of adverse effects to tamoxifen: a preliminary retrospective study. Breast Cancer (Dove Med Press) 9: 111-120, 2017. DOI: 10.2147/BCTT.S126557

69 Borrie AE, Rose RV, Choi Y, Perera FE, Read N, Sexton T, Lock M, Vandenberg TA, Hahn K, Dinniwell R, Younus J, Logan D, Potvin K, Yaremko B, Yu E, Lenehan J, Welch S, Tyndale RF, Teft WA, Kim RB: Letrozole concentration is associated with CYP2A6 variation but not with arthralgia in patients with breast cancer. Breast Cancer Res Treat 172(2): 371-379, 2018. DOI: 10.1007/S10549-018-4910-Z

70 Bai S: Influence of the UGT2B17 gene on the relationship between exemestane and bone mineral density in postmenopausal women. Queen's University (Canada) ProQuest Dissertations & Theses, 2018. Available at: https://www.proquest.com/docview/2054013386?pq-origsite=gscholar&fromopenview=true&sourcetype=Dissertations%20&%20Theses [Last accessed on June 18, 2024]

71 Niravath P, Chen B, Chapman JW, Agarwal SK, Welschhans RL, Bongartz T, Kalari KR, Shepherd LE, Bartlett J, Pritchard K, Gelmon K, Hilsenbeck SG, Rimawi MF, Osborne CK, Goss PE, Ingle JN: Vitamin D levels, Vitamin D receptor polymorphisms, and inflammatory cytokines in aromatase inhibitor-induced arthralgias: an analysis of CCTG MA.27. Clin Breast Cancer 18(1): 78-87, 2018. DOI: 10.1016/j.clbc.2017.10.009

72 Jansen LE, Teft WA, Rose RV, Lizotte DJ, Kim RB: CYP2D6 genotype and endoxifen plasma concentration do not predict hot flash severity during tamoxifen therapy. Breast Cancer Res Treat 171(3): 701-708, 2018. DOI: 10.1007/s10549-018-4876-x

73 Dempsey JM, Xi J, Henry NL, Rae JM, Hertz DL: Attempted replication of SNPs in RANKL and OPG with musculoskeletal adverse events during aromatase inhibitor treatment for breast cancer. Physiol Genomics 50(2): 98-99, 2018. DOI: 10.1152/physiolgenomics.00085.2017

74 Basmadjian R: UGT2B17, exemestane metabolism, and their association with physical health-related quality of life in Caucasian postmenopausal women participating in the Mammary Prevention.3 Trial. Queen's Graduate Theses and Dissertations, 2019. Available at: https://qspace.library.queensu.ca/items/d35cbe40-8feb-443a-a1eb-8ee4b7893a44 [Last accessed on June 18, 2024]

75 Chu W, Fyles A, Sellers EM, McCready DR, Murphy J, Pal T, Narod SA: Association between CYP3A4 genotype and risk of endometrial cancer following tamoxifen use. Carcinogenesis 28(10): 2139-2142, 2007. DOI: 10.1093/CARCIN/BGM087

76 Rangel-Méndez JA, Rubi-Castellanos R, Sánchez-Cruz JF, Moo-Puc RE: Tamoxifen side effects: pharmacogenetic and clinical approach in Mexican mestizos. Transl Cancer Res 8(1): 23-34, 2019. DOI: 10.21037/tcr.2018.12.27

77 Abubakar MB, Lin Tan H, Murali Krishna Bhavaraju V, Hua Gan S: Impact of CYP3A4 and CYP3A5 single nucleotide polymorphisms on anastrozole-associated adverse events among Malaysian breast cancer patients. AsPac J Mol Biol Biotechnol 27: 33-42, 2019. DOI: 10.35118/apjmbb.2019.027.1.04

78 Kamdem LK, Xi J, Clark BL, Gregory BJ, Kidwell KM, Storniolo AM, Stearns V, Hayes DF, Gersch CL, Rae JM, Henry NL, Hertz DL: Exemestane may be less detrimental than letrozole to bone health in women homozygous for the UGT2B17*2 gene deletion. Breast Cancer Res Treat 175(2): 297-303, 2019. DOI: 10.1007/s10549-019-05158-3

79 He W, Grassmann F, Eriksson M, Eliasson E, Margolin S, Thorén L, Hall P, Czene K: CYP2D6 genotype predicts tamoxifen discontinuation and prognosis in patients with breast cancer. J Clin Oncol 38(6): 548-557, 2020. DOI: 10.1200/JCO.19.01535

80 Ho V, Pasquet R, Luo S, Chen G, Goss P, Tu D, Lazarus P, Richardson H, MAP3 Investigators: Variation in the UGT2B17 genotype, exemestane metabolism and menopause-related toxicities in the CCTG MAP.3 trial. Breast Cancer Res Treat 183(3): 705-716, 2020. DOI: 10.1007/s10549-020-05812-1

81 Umamaheswaran G, Kadambari D, Muthuvel SK, Kalaivani S, Devi J, Damodaran SE, Pradhan SC, Dubashi B, Dkhar SA, Adithan C: Association of CYP19A1 gene variations with adjuvant letrozole-induced adverse events in South Indian postmenopausal breast cancer cohort expressing hormone-receptor positivity. Breast Cancer Res Treat 182(1): 147-158, 2020. DOI: 10.1007/s10549-020-05656-9

82 Romero SAD, Su HI, Satagopan J, Li QS, Seluzicki CM, Dries A, DeMichele AM, Mao JJ: Clinical and genetic risk factors for aromatase inhibitor-associated arthralgia in breast cancer survivors. Breast 49: 48-54, 2020. DOI: 10.1016/j.breast.2019.10.008

83 Baatjes K, Peeters A, McCaul M, Conradie MM, Apffelstaedt J, Conradie M, Kotze MJ: CYP19A1 rs10046 pharmacogenetics in postmenopausal breast cancer patients treated with aromatase

inhibitors: one-year follow-up. Curr Pharm Des 26(46): 6007-6012, 2020. DOI: 10.2174/1381612826666200908141858

84 Bojanic K, Kuna L, Bilic Curcic I, Wagner J, Smolic R, Kralik K, Kizivat T, Ivanac G, Vcev A, Wu GY, Smolic M: Representation of CYP3A4, CYP3A5 and UGT1A4 polymorphisms within Croatian breast cancer patients' population. Int J Environ Res Public Health 17(10): 3692, 2020. DOI: 10.3390/ijerph17103692

85 Borrie AE, Rose FA, Choi Y, Perera FE, Read N, Sexton T, Lock M, Vandenberg TA, Hahn K, Younus J, Logan D, Potvin K, Yaremko B, Yu E, Lenehan J, Welch S, Teft WA, Kim RB: Genetic and clinical predictors of arthralgia during letrozole or anastrozole therapy in breast cancer patients. Breast Cancer Res Treat 183(2): 365-372, 2020. DOI: 10.1007/s10549-020-05777-1

86 Ntukidem NI, Nguyen AT, Stearns V, Rehman M, Schott A, Skaar T, Jin Y, Blanche P, Li L, Lemler S, Hayden J, Krauss RM, Desta Z, Flockhart DA, Hayes DF, Consortium on Breast Cancer Pharmacogenomics: Estrogen receptor genotypes, menopausal status, and the lipid effects of tamoxifen. Clin Pharmacol Ther 83(5): 702-710, 2008. DOI: 10.1038/sj.clpt.6100343

87 Tamura K, Imamura CK, Takano T, Saji S, Yamanaka T, Yonemori K, Takahashi M, Tsurutani J, Nishimura R, Sato K, Kitani A, Ueno NT, Mushiroda T, Kubo M, Fujiwara Y, Tanigawara Y: CYP2D6 genotype-guided tamoxifen dosing in hormone receptor-positive metastatic breast cancer (TARGET-1): a randomized, open-label, phase II study. J Clin Oncol 38(6): 558-566, 2020. DOI: 10.1200/JCO.19.01412

88 Miranda C, Galleguillos M, Torres R, Tardón K, Cáceres DD, Lee K, Redal MA, Varela NM, Quiñones LA: Preliminary pharmacogenomic-based predictive models of tamoxifen response in hormone-dependent Chilean breast cancer patients. Front Pharmacol 12: 661443, 2021. DOI: 10.3389/fphar.2021.661443

89 Hertz DL, Smith KL, Zong Y, Gersch CL, Pesch AM, Lehman J, Blackford AL, Henry NL, Kidwell KM, Rae JM, Stearns V: Further evidence that OPG rs2073618 is associated with increased risk of musculoskeletal symptoms in patients receiving aromatase inhibitors for early breast cancer. Front Genet 12: 662734, 2021. DOI: 10.3389/fgene.2021.662734

90 Umamaheswaran G, Kadambari D, Muthuvel SK, Kumar NAN, Dubashi B, Aibor Dkhar S, Adithan C: Polymorphisms of T- cell leukemia 1A gene loci are not related to the development of adjuvant letrozole-induced adverse events in breast cancer. PLoS One 16(3): e0247989, 2021. DOI: 10.1371/journal.pone.0247989

91 Hertz DL, Douglas JA, Miller RM, Kidwell KM, Gersch CL, Desta Z, Storniolo AM, Stearns V, Skaar TC, Hayes DF, Henry NL, Rae JM: Genome-wide association study of aromatase inhibitor discontinuation due to musculoskeletal symptoms. Support Care Cancer, 2022. DOI: 10.21203/rs.3.rs-1315678/v1

92 Abed SN, Sahib AS, Kadum MAA: Genetic polymorphic impact of metabolizing enzyme (CYP3A4 and UGT1A4 genes) on anastrazole response in Iraqi breast cancer women. Ann Clin Med Case Rep 8: 1-6, 2022. DOI: 10.47829/ACMCR.2022.8701

93 Zhou W, Jiang Y, Xu Y, Wang Y, Ma X, Zhou L, Lin Y, Wang Y, Wu Z, Li M, Yin W, Lu J: Comparison of adverse drug reactions between tamoxifen and toremifene in breast cancer patients with different CYP2D6 genotypes: A propensity-score matched cohort study. Int J cancer 150(10): 1664-1676, 2022. DOI: 10.1002/ijc.33919

94 Jin Y, Hayes DF, Li L, Robarge JD, Skaar TC, Philips S, Nguyen A, Schott A, Hayden J, Lemler S, Storniolo AM, Flockhart DA, Stearns V: Estrogen receptor genotypes influence hot flash prevalence and composite score before and after tamoxifen therapy. J Clin Oncol 26(36): 5849-5854, 2008. DOI: 10.1200/JCO.2008.16.8377

95 Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 87: 1277-1289, 1997. DOI: 10.1097/00000542-199712000-00004

96 Tanner-Smith EE, Tipton E, Polanin JR: Handling complex meta-analytic data structures using robust variance estimates: a tutorial in R. J Dev Life-Course Criminol 2(1): 85-112, 2016. DOI: 10.1007/S40865-016-0026-5

97 Hutton JL, Williamson PR: Bias in meta-analysis due to outcome variable selection within studies. J R Stat Soc Ser C (Applied Stat) 49(3): 359-370, 2000. DOI: 10.1111/1467-9876.00197

98 Pocock SJ, Hughes MD, Lee RJ: Statistical problems in the reporting of clinical trials. N Engl J Med 317(7): 426-432, 1987. DOI: 10.1056/NEJM198708133170706

99 McKenzie JE, Brennan SE: Synthesizing and presenting findings using other methods. Cochrane Handbook for Systematic Reviews of Interventions: 321-347, 2019. DOI: 10.1002/9781119536604.CH12

100 Allison PD: Testing for interaction in multiple regression. Am J Sociol 83(1): 144-153, 1977. DOI: 10.1086/226510

101 Hosmer DW Jr, Sturdivant RX, Lemeshow S: Applied logistic regression, 3rd edition, 2013.

102 Vatcheva KP, Lee M, McCormick JB, Rahbar MH: The effect of ignoring statistical interactions in regression analyses conducted in epidemiologic studies: an example with survival analysis using cox proportional hazards regression model. Epidemiology (Sunnyvale) 6(1): 216, 2015. DOI: 10.4172/2161-1165.1000216

103 Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM: Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study. Lancet Glob Heal 8(8): e1027-e1037, 2020. DOI: 10.1016/S2214-109X(20)30215-1

104 Vaz-Luis I, Francis PA, Di Meglio A, Stearns V: Challenges in adjuvant therapy for premenopausal women diagnosed with luminal breast cancers. Am Soc Clin Oncol Educ Book (41): e47-e61, 2021. DOI: 10.1200/edbk_320595

105 Huiart L, Bouhnik AD, Rey D, Tarpin C, Cluze C, Bendiane MK, Viens P, Giorgi R: Early discontinuation of tamoxifen intake in younger women with breast cancer: Is it time to rethink the way it is prescribed? Eur J Cancer 48(13): 1939-1946, 2012. DOI: 10.1016/J.EJCA.2012.03.004

106 Nazari SS, Mukherjee P: An overview of mammographic density and its association with breast cancer. Breast Cancer 25(3): 259-267, 2018. DOI: 10.1007/s12282-018-0857-5

107 Ghiasvand R, Adami HO, Harirchi I, Akrami R, Zendehdel K: Higher incidence of premenopausal breast cancer in less developed countries; myth or truth? BMC Cancer 14: 343, 2014. DOI: 10.1186/1471-2407-14-343

108 Stearns V, Jegede OA, Chang VT, Skaar TC, Berenberg JL, Nand R, Shafqat A, Jacobs NL, Luginbuhl W, Gilman P, Benson AB, Goodman JR, Buchschacher GL, Henry NL,

Loprinzi CL, Flynn PJ, Mitchell EP, Fisch MJ, Sparano JA, Wagner LI: A cohort study to evaluate genetic predictors of aromatase inhibitor musculoskeletal symptoms: results from ECOG-ACRIN E1Z11. Clin Cancer Res, 2024. DOI: 10.1158/1078-0432.CCR-23-2137

109 Sheppard VB, Sutton AL, Hurtado-de-Mendoza A, He J, Dahman B, Edmonds MC, Hackney MH, Tadesse MG: Race and patient-reported symptoms in adherence to adjuvant endocrine therapy: a report from the Women's Hormonal Initiation and Persistence Study. Cancer Epidemiol Biomarkers Prev 30(4): 699-709, 2021. DOI: 10.1158/1055-9965.EPI-20-0604

110 Siegel RL, Miller KD, Wagle NS, Jemal A: Cancer statistics, 2023. CA Cancer J Clin 73: 17-48, 2023. DOI: 10.3322/CAAC.21763

111 Home | African Pharmacogenomics Network. Available at: http://aphgn.org/ [Last accessed on June 17, 2024]

112 Kruger B, Shamley D, Soko ND, Dandara C: Pharmacogenetics of tamoxifen in breast cancer patients of African descent: Lack of data. Clin Transl Sci 17(3): e13761, 2024. DOI: 10.1111/cts.13761

113 Sidibe M, Tazzite A, Jouhadi H, Dehbi H: Impact of *CYP2D6, CYP2C9/19, CYP3A4, UGT*, and *SULT* variability on tamoxifen metabolism in breast cancer treatment. J Curr Oncol, 2024. DOI: 10.1177/25898892231223300

114 Golubenko EO, Savelyeva MI, Sozaeva ZA, Korennaya VV, Poddubnaya IV, Valiev TT, Kondratenko SN, Ilyin MV: Predictive modeling of adverse drug reactions to tamoxifen therapy for breast cancer on base of pharmacogenomic testing. Drug Metab Pers Ther 38(4): 339-347, 2024. DOI: 10.1515/DMPT-2023-0027

115 Rothstein HR, Hopewell S: Grey literature. In: The handbook of research synthesis and meta-analysis, 2nd ed. New York, NY, USA, Russell Sage Foundation, pp. 103-125, 2009.

116 Begg CB, Berlin JA: Publication bias: A problem in interpreting medical data. J R Stat Soc Ser A Statistics Soc 151(3): 419-445, 1988. DOI: 10.2307/2982993

Received May 21, 2024
Revised June 17, 2024
Accepted June 18, 2024