Supportive Care in Cancer (2019) 27:351–371
https://doi.org/10.1007/s00520-018-4508-3

REVIEW ARTICLE

Systematic review of genetic polymorphisms associated with psychoneurological symptoms in breast cancer survivors

Gee Su Yang[1] · Sreelakshmy Kumar[1] · Susan G. Dorsey[2] · Angela R. Starkweather[3] · Debra Lynch Kelly[1] · Debra E. Lyon[1]

Received: 27 April 2018 / Accepted: 9 October 2018 / Published online: 20 October 2018

Abstract

Purpose Psychoneurological (PN) symptoms, such as anxiety, cognitive impairment, depression, fatigue, sleep disturbances, and pain, are highly prevalent in breast cancer patients undergoing cancer treatment. Emerging evidence suggests that genetic polymorphisms may contribute to differential symptom susceptibility. We aimed to systematically review associations between genetic polymorphisms and PN symptoms during or after cancer treatment for early-stage breast cancer.

Methods Twenty-six eligible articles published until October 2017 were identified in PubMed, PsycINFO, Web of Science, and additional records. Information on study characteristics, genetic polymorphisms, and PN symptoms was extracted. Study quality was evaluated by the *STrengthening the REporting of Genetic Association* (STREGA) guideline. Genes included in the analysis were categorized by biological pathways based on the *Reactome* database.

Results A total of 54 single nucleotide polymorphisms and haplotypes that are significantly associated with PN symptoms were identified; half of them were associated with increased severity of PN symptoms, while the other half contributed to the decrease of PN symptoms. Pain has the known highest number of associated genetic polymorphisms reported, followed by fatigue, cognitive impairment, depressive symptoms, sleep disturbances, and anxiety. The majority of genetic polymorphisms were involved in immune system and neuronal system pathways. Most studies were unsuccessful in meeting the STREGA guideline, which requires transparent reporting of methods and results.

Conclusions This review provides comprehensive evidence of genetic polymorphisms underlying PN symptoms, which may pave the way for the development of personalized therapeutics targeting these symptoms. More well-designed genome-wide association studies are required to validate and replicate these findings.

Keywords Breast cancer · Psychoneurological symptoms · Genetic polymorphism · Single nucleotide polymorphism · Systematic review

Introduction

Breast cancer remains the second leading cause of cancer deaths among women, and it has a higher diagnosis rate at a younger age than other common cancers in the USA [36]. While the overall rate of breast cancer survivorship has improved in the past decades due to early detection and advanced treatment [3], some breast cancer patients experience distressing symptoms that may have a negative impact on quality of life and functional status, partially due to cancer treatment [11]. Breast cancer patients during or after cancer treatment often report multiple symptoms, such as anxiety, cognitive impairment, depressive symptoms, fatigue, sleep disturbances, and/or pain, collectively described as "psychoneurological (PN) symptoms." Highly prevalent in breast cancer patients, PN symptoms refer to a set of behavioral and emotional symptoms that are relevant to psychological and neurological dysfunction [20, 26, 48]. Fatigue is one of the most frequently observed and severe symptoms [16,

✉ Gee Su Yang
gyang1@ufl.edu

[1] Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, 1225 Center Drive, Gainesville, FL 32610, USA

[2] Department of Pain and Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, MD, USA

[3] School of Nursing, University of Connecticut, Storrs, CT, USA

26], and sleep disturbances, pain, depressive symptoms, and cognitive dysfunction (e.g., problems with memory, psychomotor speed, reaction time, complex attention, and/or cognitive flexibility) are also commonly experienced in 56–73% of breast cancer patients [5, 26].

A previous review found that each PN symptom may share common biological signaling pathways, such as pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA)-axis system alterations, and monoamine neurotransmission (e.g., 5-HT system and noradrenergic system) [20]. For example, HPA-axis functioning alterations may cause depressive symptoms, fatigue, and sleep disturbances, and monoamine neurotransmitter system changes are associated with depressive symptoms, cognitive impairment, fatigue, and sleep disturbances. However, it should be noted that these findings were derived from patients with either a heterogeneous group of cancers or non-cancer populations and not patients with breast cancer [20]. Emerging evidence suggests that genetic factors may make certain individuals more susceptible to PN symptoms [4, 45]; thus, understanding genetic components, such as single nucleotide polymorphisms (SNPs) that are single-base variations in DNA structure, can provide greater insight into PN symptoms in breast cancer patients receiving treatment. SNPs have been studied in order to identify associations with symptom phenotypes. By comparing the frequencies of rare alleles among patients with the symptom phenotype to patients without the symptom phenotype or healthy controls, the proportion of the phenotypic variance that is explained by the genetic variation can be determined [51]. The identification of genetic polymorphisms associated with PN symptoms may lead to a deeper understanding of the underlying molecular pathways and thereby pave the way for the development of novel therapies targeting these symptoms.

Genetic polymorphisms specific to PN symptoms in breast cancer have been studied over the past several years. However, to our knowledge, there have been no systematic reviews comprehensively evaluating the association between genetic polymorphisms and PN symptoms in breast cancer patients. In this review, we aimed to analyze the literature and provide evidence of genetic polymorphisms associated with anxiety, cognitive impairment, depressive symptoms, fatigue, pain, and sleep disturbances during or after cancer treatment for women with early-stage breast cancer. Findings may reveal the genetic markers that can be used to develop personalized therapeutics for addressing PN symptoms in breast cancer patients.

Methods

Search strategy

This systematic review was performed based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guideline [27]. Records that were published until October 2017 were retrieved from the PubMed, PsycINFO, and Web of Science databases. Additional sources were also identified through a manual search of citations in original publications and Google Scholar. The keywords "Genes," "Genetic variant," "Genetic variation," "Single nucleotide polymorphism," "SNP," and "Genetic polymorphism" were combined with "Psychoneurological symptoms," "Pain," "Discomfort," "Fatigue," "Lethargy," "Exhaust," "Weakness," "Frailty," "Tiredness," "Depression," "Distress," "Sadness," "Mood disturbance," "Depressive symptoms," "Emotional distress," "Psychosocial stress," "Anxiety," "Fear," "Sleep disturbance," "Sleep," "Memory," "Cognitive dysfunction," "Neurocognition," "Cognitive impairment," and "Cognitive dysfunction," as well as "Breast cancer," "Breast neoplasm," and "Breast tumor" for the search. Two authors (G.Y. and S.K.) independently screened records, compared the results, and discussed discrepancies to obtain consensus at each step based on the criteria of study selection. Eligible studies were sorted depending on types of PN symptoms: anxiety, cognitive impairment, depressive symptoms, fatigue, pain, and sleep disturbances (Fig. 1).

Inclusion and exclusion criteria of study selection

Breast cancer patients who underwent (adjuvant) chemotherapy, radiation therapy, and/or surgery (e.g., mastectomy, lumpectomy) were included, whereas women with metastatic breast cancer, Alzheimer's disease, dementia, psychosis, and/or peripheral neurotoxicity were excluded. Any comparator such as baseline, healthy group, or control group who reported none or less PN symptoms was included. The outcomes of interest were genetic polymorphisms associated with PN symptoms in breast cancer patients receiving treatment. Only significant genetic polymorphisms that were statistically associated with PN symptoms were included in the analysis because most studies tested a large number of candidate genetic polymorphisms. Studies were included if they (1) reported frequencies of genotypes and alleles; (2) were designed as cohort, case-control, or cross-sectional trials; and (3) were published in peer-reviewed journals in the English language. Case reports, conference/dissertation abstracts, qualitative studies, systematic literature reviews, meta-analyses, animal model studies, and in vitro experiments were excluded. Publication dates were not limited.

Data extraction

The information for evaluating study characteristics included author, year, study design, research question/aim, location where the study was conducted, sample size for genotyping, age, duration of follow-up, focused cancer treatment, gene of interest, associated symptoms, symptom assessment tool,

genotyping methods/platform, and biological specimens used (e.g., blood, saliva). To collect genetic polymorphism information, gene, reference SNP cluster ID (SNP rsID), nucleotide change (i.e., replacement with another nucleotide, a single DNA building block, such as adenine, guanine, cytosine, and thymine, in a particular stretch of DNA), functional consequence, associations with symptom phenotypes, and pathways were considered.

Assessment of methodological quality

To assess study design, methods, and reporting results of genetic association studies, the methodological quality of each study was evaluated based on the *STrengthening the REporting of Genetic Association* (STREGA) guideline [29]. It consists of five main categories (i.e., genotyping methods and errors, population stratification, haplotype variation, Hardy-Weinberg equilibrium, replication), and the first category includes five items (i.e., genotyping platform, error and call rates, genotyping in batches, centers/laboratories of genotyping, the numbers of individuals of successful genotyping). Therefore, a total of nine items were evaluated. Two reviewers independently assessed the study quality and discussed results to reach the consensus (G.Y. and S.K.). To compare the study quality, a total score was calculated by assigning one point to each item, with the higher score indicating the better genetic study quality (range 0–9).

Categorization of genes per biological pathway

Genes included in the analysis were divided into seven main biological pathway categories based on the *Reactome* database (www.reactome.org), which provides peer-reviewed interpretation and analysis of pathway knowledge to genome analysis and basic research. The pathway categorization of genes was visually depicted as a Venn diagram in Fig. 2.

Results

Literature search

The systematic search yielded a total of 493 titles from databases and additional sources and 58 potential studies after an

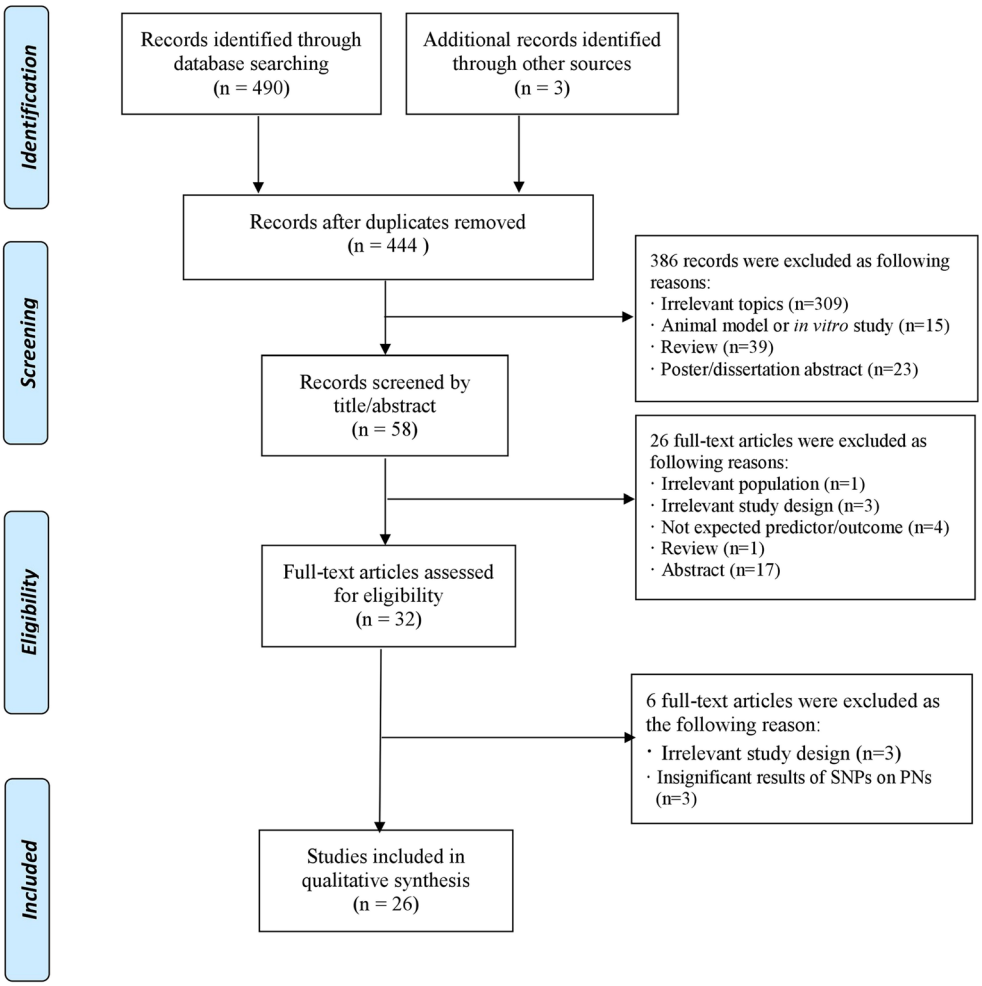

Fig. 1 PRISMA flow diagram of selecting studies that examine associations between genetic polymorphisms and psychoneurological symptoms in breast cancer patients undergoing cancer treatment

abstract and title review. Finally, 26 studies were obtained by excluding studies of irrelevant populations and study designs, unexpected predictors and outcomes, and review papers and abstracts (Fig. 1).

Study characteristics

Breast cancer patients undergoing cancer treatment were assessed to identify genetic polymorphisms that may predispose patients to develop PN symptoms, including anxiety, cognitive impairment, depressive symptoms, fatigue, pain, and sleep disturbances (Table 1). In a total of 26 studies, 17 were cohort study designs and nine were cross-sectional study designs. Thirteen cohort studies completed follow-ups of candidate SNP genotypes and PN symptoms at 6 months after initiating cancer treatment. Studies were conducted in a variety of geographical locations, including the USA, Italy, China, South Korea, Singapore, Finland, Spain, and Belgium. The average age of participants ranged from 48 to 64 years. Approximately 83% of patients who completed questionnaires of symptoms at baseline also accepted genotyping at follow-up. In each study, clinical outcome measures of PN symptoms were assessed by self-reported questionnaires that had high reliability and validity (detailed information in Table 1). Blood and saliva samples were collected from participants for extracting DNA, and genotyping was carried out through various methods and platforms, such as hybridization (e.g., Sanger sequencing), primer extension-ligation (e.g., Golden Gate, improved multiplex ligase detection reaction (iMLDR)), primer extension (e.g., iPLEX, MassARRAY), polymerase chain reaction (PCR) (e.g., TaqMan, capillary electrophoresis, KASPar), and restriction fragment length polymorphism assays.

Study quality assessment

Most of the selected studies met five of the nine items of the STREGA guideline. No one study reported on all nine items; however, Kober et al. [23] reported seven items except for descriptions of where the genotyping was done and whether the assays were conducted simultaneously or in batch. On the contrary, Bower et al. [4] stated only two items, including genotyping methods/platform and statement of whether Hardy-Weinberg equilibrium was considered. Only one study provided information on whether genotyping was conducted simultaneously or in smaller batches [12]. The majority of the studies reported genotyping methods and platform, modeling haplotype variation, and Hardy-Weinberg equilibrium (Table 2).

Genetic polymorphisms underlying psychoneurological symptoms

Genetic polymorphisms that were significantly associated with PN symptoms are described below. Detailed information on SNP rsID, nucleotide change, functional consequence,

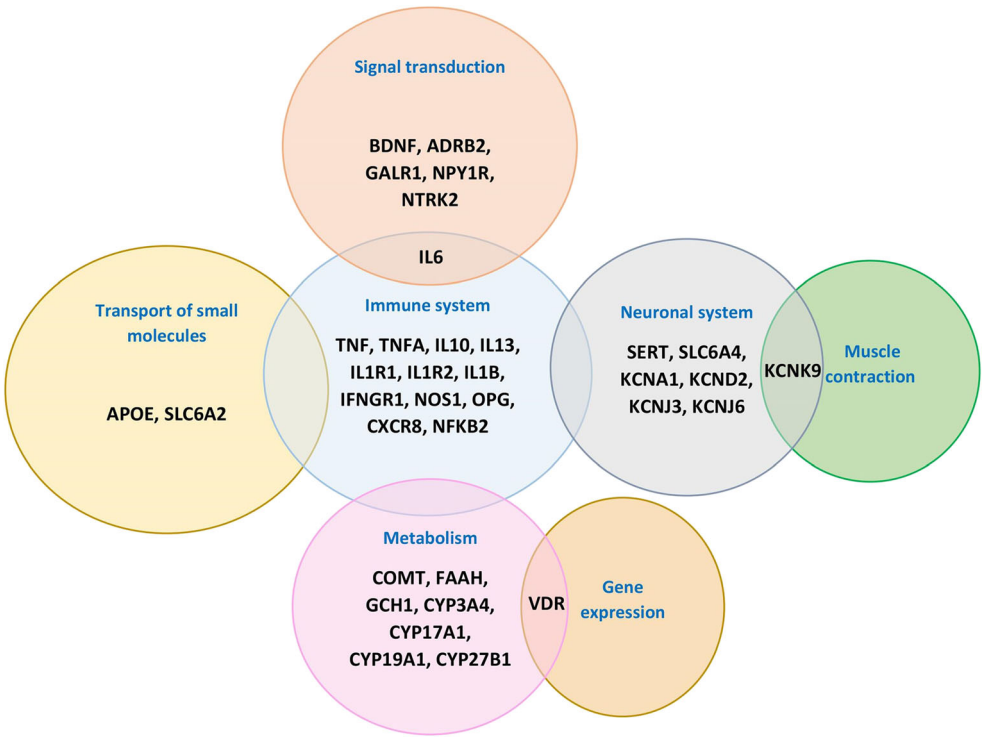

Fig. 2 Biological pathways of genes that are significantly associated with psychoneurological symptoms in breast cancer patients. Gene pathways are categorized into signal transduction, transport of small molecules, immune system, neuronal system, metabolism, gene expression, and muscle contraction based on Reactome database (www.reactome.org)

Table 1 Study characteristics

Symptom	First author, year	Study design	Location	Successfully genotyped/total sample size	Age (mean + SD, years)	Follow-up	Gene	Assessment tool	Samples; genotyping methods/platforms
Anxiety	Miaskowski et al., 2016 [34]	Cohort	USA	310/398 (77.9%)	- Lower anxiety class ($n = 147$), 57.5 ± 11.5 - Higher anxiety class ($n = 251$), 53.4 ± 11.3	6 months	*TNFA*	Spielberger state-trait anxiety inventories	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Anxiety	Schillani et al., 2012 [44]	Cohort	Italy	48 (T1), 35 (T2)/ 48 (enrollment) (72.9%)	60.2 ± 1.3 (SE)	1 (T1) and 3 (T2) months	*SERT* (5-HTTLPR)	Mini mental adjustment to cancer scale Hospital anxiety and depression scale	Blood and buccal cells; PCR and gel-based electrophoresis
Cognitive impairment	Cheng et al., 2016 [7]	Cross-sectional	China	245/245 (100%)	- TNBC ($n = 80$), 48.48 ± 10.57 - NTNBC ($n = 165$), 49.39 ± 10.61	N/A	*COMT*	Neuropsychological background test Retrospective memory and prospective memory	Blood; improved multiplex ligase detection reaction (iMLDR)
Cognitive impairment	Koleck et al., 2014 [24]	Cohort	USA	128/128 (100%)	59.31 ± 5.70	6 and 12 months	*APOE*	Neuropsychological tests	Blood and saliva; PCR-based TaqMan® SNP genotyping assay and i-PLEX® MassARRAY® multiplex assay
Cognitive impairment	Merriman et al., 2014 [31]	Cohort	USA	302/397 (76.1%)	- High attentional function, 56.7 ± 11.2 - Moderate attentional function, 55.2 ± 10.3 - Low-moderate attentional function, 52.6 ± 12.6	6 months	*IL1R1*	Attentional function index	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Cognitive impairment	Ng et al., 2016 [39]	Cohort	Singapore	145/145 (100%)	50.8 ± 8.8	6 weeks, 3 months	*BDNF*	Functional assessment of cancer therapy-cognitive function	Blood; PCR-based Sanger sequencing
Perceived cognitive function	Myers et al. 2017 [37]	Cross-sectional	USA	99/143 (69.2%)	54.86 ± 10.78	N/A	*IL1R1*	Functional assessment of cancer therapy-cognition version scale for perceived cognitive impairment	Saliva; Sequenom iPLEX MassARRAY
Cognitive performance	Small et al., 2011 [47]	Cross-sectional	USA	334/334 (100%)	- Healthy control ($n = 204$), 57.07 ± 9.52 - Radiotherapy group ($n = 58$), 56.93 ± 9.01	6 months	*COMT*	Neuropsychological tests	Saliva; TaqMan gene expression assays

Table 1 (continued)

Symptom	First author, year	Study design	Location	Successfully genotyped/total sample size	Age (mean + SD, years)	Follow-up	Gene	Assessment tool	Samples; genotyping methods/platforms
					- Chemotherapy group ($n = 72$), 51.22 ± 8.63				
Depression	Dooley et al., 2016 [12]	Cross-sectional	USA	112/112 (100%)	- Val/Val genotype ($n = 75$), 51.4 ± 8.9 - Met/Met and Met/Val genotypes ($n = 37$), 51.2 ± 7.0	N/A (focusing on data from the baseline visit)	*BDNF*	Beck Depression Inventory	Blood; PCR-based TaqMan SNP genotyping assay
Depression	Kim et al., 2012 [21]	Cohort	South Korea	244 (1 year)/ 309 (baseline) (79%)	50.8 ± 9.7 (baseline)	1 week, 1 year	*BDNF*	Mini-international neuropsychiatric interview for DSM-IV	Blood; restriction fragment length polymorphism assays
Depression	Kim et al., 2013 [22]	Cohort	South Korea	244 (1 year)/ 309 (baseline) (79%)	Baseline: - No depression ($n = 235$), 50.6 ± 9.9 - Prevalent depression ($n = 74$), 51.5 ± 8.7	1 week, 1 year	*IL1B*	Mini-international neuropsychiatric interview for DSM-IV	Blood; PCR-based restriction fragment length polymorphism assays
Depression	Saad et al., 2014 [43]	Cohort	USA	302/398 (75.9%)	- Resilient class ($n = 155$), 57.3 ± 11.0 - Subsyndromal class ($n = 180$), 53.0 ± 11.9	6 months	*IFNGR1*, *IL6*, *TNFA*	Center for Epidemiologic Studies Depression Scale	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Fatigue	Collado-Hidalgo et al., 2008 [9]	Cross-sectional	USA	47/47 (100%)	- Fatigued group ($n = 33$), 54.1 ± 8.3 - Non-fatigued group ($n = 14$), 61.1 ± 8.5	N/A	*IL1B*	Multidimensional Fatigue Symptom Inventory	Blood; PCR-based restriction fragment length polymorphism assay
Fatigue and energy	Eshragh et al., 2017 [14]	Cohort	USA	310/398 (77.9%)	- Lower-fatigue class ($n = 153$), 57.8 ± 11.9 - Higher-fatigue class ($n = 244$), 53.1 ± 11.0	6 months	*ADRB2*, *COMT*, *BDNF*, *CYP3A4*, *GALR1*, *GCH1*, *NPY1R*, *NOS1*, *SLC6A2*, *SLC6A4*	Lee Fatigue Scale	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Fatigue and energy	Kober et al., 2016 [23]	Cohort	USA	310/398 (77.9%)	- Lower-fatigue class ($n = 153$), 57.8 ± 11.9 - Higher-fatigue class ($n = 244$), 53.1 ± 11.0	6 months	*IL1B*, *IL10*, *IL6*, *TNF*, *COMT*, *NTRK2*	Lee Fatigue Scale	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)

Table 1 (continued)

Symptom	First author, year	Study design	Location	Successfully genotyped/total sample size	Age (mean + SD, years)	Follow-up	Gene	Assessment tool	Samples; genotyping methods/platforms
Pain	Cajanus et al., 2016 [6]	Cross-sectional	Finland	926/1000 (92.6%)	57.0	N/A	*FAAH*	Numerical Rating Scale, \experimental pain (cold pain sensitivity, cold pain, heat pain)	Blood; MassARRAY system and iPLEX Gold Single Base Extension chemistry
Pain (arthralgia)	Garcia-Giralt et al., 2013 [17]	Cohort	Spain	334 (3 months), 321 (12 months)/ 343 (baseline) (93.6%)	61.96 ± 8.71	3 and 12 months	*CYP17A1*, *CYP19-A1*, *VDR*, *CYP27B1*	Visual analogic scale	Blood; KASPar v4.0 genotyping systems and Kraken allele-calling algorithm
Pain	Kambur et al., 2013 [19]	Cross-sectional	Finland	900/1000 (90%)	57.0 ± 9.3	N/A	*COMT*	Numerical Rating Scale, experimental pain (heat pain and cold pain)	Blood; MassARRAY system and iPLEX Gold Single Base Extension chemistry
Breast pain	Langford et al., 2015 [25]	Cohort	USA	302/398 (75.9%)	- No pain group (n = 126), 58.6 ± 11.4 - Mild pain group (n = 173), 53.4 ± 11.5	6 months	*KCNA1*, *KCND2*, *KCNJ3*, *KCNJ6*, *KCNK9*	Numerical Rating Scale, Breast Symptoms Questionnaire, Postsurgical Pain Questionnaire	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Musculoskeletal pain	Lintermans et al., 2016 [28]	Cohort	Belgium	254/254 (100%)	- AI group (n = 159), 63 - Tamoxifen (n = 95), 64	3, 6, and 12 months	*OPG*	Visual analogue score	Blood; Sequenom MassARRAY®
Breast pain	Stephens et al., 2014 [49]	Cohort	USA	310/398 (77.9%)	- No pain group (n = 126), 58.6 ± 11.4 - Severe pain (n = 46), 52.4 ± 9.4	6 months	*IL1R2*, *IL10*	Breast Symptom Questionnaire, Postsurgical Pain Questionnaire	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Breast pain	Stephens et al., 2017 [50]	Cohort	USA	310/398 (77.9%)	- No pain group (n = 126), 58.6 ± 11.4 - Mild pain (n = 173): 53.4 ± 11.5	6 months	*IL6*, *CXCL8*, *TNF*	Breast Symptom Questionnaire, Postsurgical Pain Questionnaire	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Sleep disturbances	Alfaro et al., 2014 [1]	Cohort	USA	310/398 (77.9%)	- Low sustained sleep disturbance class (n = 158), 57.7 ± 12.1 - High sustained sleep disturbance class (n = 219), 53.0 ± 10.9	6 months	*IL1R2*, *IL13*, *NFKB2*	General Sleep Disturbance Scale	Blood; hybridization to array matrix and BeadChip (GoldenGate® assay)
Fatigue, depressive symptoms,	Bower et al., 2013 [4]	Cross-sectional	USA	171/190 (90%)	51.5 (range 31–66)	N/A	*IL6*, *TNF*	Multidimensional Fatigue Symptom Inventory-Short	Blood; PCR-based TaqMan genotyping assay

Table 1 (continued)

Symptom	First author, year	Study design	Location	Successfully genotyped/total sample size	Age (mean + SD, years)	Follow-up	Gene	Assessment tool	Samples; genotyping methods/platforms
memory complaints								Form, Beck Depression Inventory, Squire Memory Questionnaire	
Fatigue, pain	Fernandez-de-las-Peñas et al., 2012 [15]	Cross-sectional	Spain	128/128 (100%)	49 ± 9	N/A	*COMT*	Piper Fatigue Scale, visual analogic scale, experimental pain (pressure pain thresholds)	Saliva; PCR-based TaqMan® drug metabolism genotyping assays
Anxiety, pain, sleep disturbances, fatigue	Young et al., 2017 [52]	Cohort	USA	51/60 (85%)	51.9 ± 11.4	Pretreatment (T1), at 7–8 weeks after initiation of chemo (T2), 1 week following completion of chemo (T3)	*NTRK2*, *COMT*	Hospital Anxiety and Depression Scale, Brief Pain Inventory-Short Form, General Sleep Disturbance Scale, Brief Fatigue Inventory	Blood; PCR-based direct sequencing

5-HTTLPR, 5-hydroxytryptamine transporter gene-linked polymorphic region; *ADRB2*, adrenoceptor beta 2; *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyl transferase; *CXCL8*, C-X-C motif chemokine ligand 8; *CYP3A4*, cytochrome P450 family 3 subfamily A member 4; *CYP17A1*, cytochrome P450 family 17 subfamily A member 1; *CYP27B1*, cytochrome P450 family 27 subfamily B member 1; *DSM-IV*, Diagnostic and Statistical Manual of Mental Disorders; *FAAH*, fatty acid amide hydrolase; *GALR1*, galanin receptor 1; *GCH1*, GTP cyclohydrolase 1; *IFNGR1*, interferon-gamma receptor 1; *IL1B*, interleukin-1 beta; *IL1R1*, interleukin-1 receptor 1; *IL6*, interleukin-6; *KCNA1*, potassium voltage-gated channel subfamily A member 1; *KCND2*, potassium voltage-gated channel subfamily D member 2; *KCNJ3*, potassium voltage-gated channel subfamily J member 3; *KCNJ6*, potassium voltage-gated channel subfamily J members 6; *KCNK9*, potassium voltage-gated channel subfamily K member 9; *NFKB*, nuclear factor kappa beta; *NOS1*, nitric oxide synthase 1; *NPY1R*, neuropeptide Y receptor Y1; *NTNBC*, non-triple-negative breast cancer; *NTRK2*, neurotrophic tyrosine kinase receptor 2; *OPG*, osteoprotegerin; *PCR*, polymerase chain reaction; *SD*, standard deviation; *SERT (5-HTT)*, serotonin transporter; *SLC6A2*, solute carrier family 6 member 2; *SLC6A4*, solute carrier family 6 member 4; *SNP*, single nucleotide polymorphism; *TNBC*, triple-negative breast cancer; *TNFA*, tumor necrosis factor-alpha; *VDR*, vitamin D_3 receptor

Table 2 The quality of reporting using the STrengthening the REporting of Genetic Association (STREGA) guideline ($N = 26$)

Study (first author, year)	Description of genotyping methods and errors					Description of modeling population stratification	Description of modeling haplotype variation	Statement of whether Hardy-Weinberg equilibrium was considered	Statement of whether the study is the first report of a genetic association, a replication effort, or both	Total score
	Genotyping methods and platforms	Error rates and call rates	Laboratory/ center where the genotyping was done	Conducting genotypes simultaneously or in smaller batches	The numbers of individuals for whom genotyping was attempted and successful					
Miaskowski et al., 2016 [34]	√	√				√	√	√	√	6
Schillani et al., 2012 [44]	√					√	√	√		4
Cheng et al., 2016 [7]	√	√					√	√		4
Koleck et al., 2014 [24]	√				√	√	√		√	5
Merriman et al., 2014 [31]	√	√				√	√	√	√	6
Ng et al., 2016 [39]	√						√	√	√	4
Myers et al., 2017 [37]	√	√					√	√		4
Small et al., 2011 [47]	√		√			√	√	√		5
Dooley et al., 2016 [12]	√			√		√	√	√		5
Kim et al., 2012 [21]	√					√	√	√	√	5
Kim et al., 2013 [22]	√						√	√	√	4
Saad et al., 2014 [43]	√	√				√	√	√	√	6
Collado-Hidalgo et al., 2008 [9]	√								√	2
Eshragh et al., 2017 [14]	√	√				√	√	√		5
Kober et al., 2016 [23]	√	√			√	√	√	√	√	7
Cajanus et al., 2016 [6]	√		√		√		√	√	√	6
Garcia-Giralt et al., 2013 [17]	√		√				√	√		4
Kambur et al., 2013 [19]	√				√		√	√	√	5
Langford et al., 2015 [25]	√	√				√	√	√	√	6
Lintermans et al., 2016 [28]	√		√		√		√	√	√	6
Stephens et al., 2014 [49]	√	√				√	√	√	√	6
Stephens et al., 2017 [50]	√	√				√	√	√	√	6
Alfaro et al., 2014 [1]	√	√				√	√	√	√	6
Bower et al., 2013 [4]	√							√		2
Fernandez-de-las-Peñas et al., 2012 [15]	√						√		√	3
Young et al., 2017 [52]	√	√			√		√	√	√	6

associations with symptom phenotypes, cancer treatment type, biological pathway, and the references are shown in Table 3.

Anxiety

Two studies evaluated genetic associations underlying anxiety [34, 44]. The majority of participants underwent tumor surgery. The polymorphism in tumor necrosis factor-α (*TNFA*) (rs1799964) showed a decreased chance of higher anxiety, whereas another polymorphism in *TNFA* (rs3093662) was associated with an increased risk of higher anxiety [34]. Given that the functional activity of the 5-hydroxytryptaimine transporter gene-linked polymorphic region (*5-HTTLPR*) differs depending on the combination of short (S) and long (L) alleles, women carrying S/L or L/L alleles in *5-HTTLPR* exhibited decreased levels of anxiety compared to women with S/S alleles [44].

Cognitive impairment

Six studies investigated genetic polymorphisms that may predict cognitive impairment [7, 24, 31, 37, 39, 47]. The majority of patients received adjuvant chemotherapy or conventional chemotherapy, and some patients underwent tumor surgery in one study conducted by Merriman et al. [31]. Findings indicated that the catechol-*O*-methyltransferase (*COMT*), apolipoprotein E (*APOE*), interleukin-1 receptor 1 (*IL1R1*), and brain-derived neurotrophic factor (*BDNF*) genes were significantly associated with cognitive function. Cheng et al. [7] found that *COMT* polymorphism (rs165599) was correlated with impaired retrospective memory in patients receiving doxorubicin, paclitaxel, cyclophosphamide, or fluorouracil. On the contrary, Small et al. [47] reported that the *COMT* polymorphism (rs4680 [Val158Met]) improved cognitive function; Val carriers exhibited worse cognitive performance in aspects of attention, verbal fluency, and motor speed compared to Val/Met or Met/Met carriers. In the study of Koleck et al. [24], functional polymorphisms in *APOE* (rs429358, rs7412) may contribute to poorer performance on tasks of executive function, attention, verbal learning and memory, and visual learning and memory following chemotherapy and/or hormonal therapy (e.g., anastrozole). In addition, polymorphisms in *IL1R1* were associated with altered cognitive function. Patients homozygous or heterozygous for the rare A allele (*IL1R1* rs949963 [G>A]) were more likely to be detrimental to attentional function, while those possessing one or more rare A alleles in *IL1R1* (rs2287047 [G>A]) showed better perceived cognitive function [31, 37]. In another study investigating the role of *BDNF* polymorphism (rs6265 [Val66Met]) in breast cancer patients receiving anthracycline- or taxane-based regimens, the Met/Met genotype showed significantly lower odds of developing cognitive impairment, and patients with the Met/Met or Met/Val genotypes performed better in verbal fluency and multitasking ability compared to those with the Val/Val genotype [39].

Depressive symptoms

Four studies examined genetic associations underlying depressive symptoms [12, 21, 22, 43]. The majority of participants who underwent breast cancer surgery reported depressive symptoms. Polymorphisms in *BDNF* (rs6265 [Val66Met]) and several inflammatory cytokine genes were found to influence the development and severity of depressive symptoms. The *BDNF* Met/Met genotype showed apparent depressive symptoms compared to the Val/Val genotype [12, 21]. Saad et al. [43] concluded that polymorphisms in *IL6* (rs2069840) and interferon-gamma receptor 1 (*INFGR1*) (rs9376268) increased the possibility of having depressive symptoms; possession of one or two rare alleles was associated with a 3.06- and 1.87-fold increase in the odds of belonging to the subsyndromal group rather than the resilient group, respectively. On the contrary, the polymorphism in *TNFA* (rs1799964) decreased the chance of depressive symptoms; carrying two rare alleles was associated with an 87% decrease in the odds of belonging to the subsyndromal group rather than the resilient group [43]. In addition, the polymorphism in *IL1B* -511 (rs16944) was significantly associated with a 9.5-fold increase in the odds of persistent depression [22].

Fatigue

Six studies examined the role of genetic polymorphisms underlying fatigue [4, 9, 14, 15, 23, 52]. In the study of Collado-Hidalgo et al. [9], the C/C or C/T genotypes for *IL1B* -511 (rs16944) were substantially greater among fatigued participants than among non-fatigued, and the C/C (rare allele) or G/G (common allele) genotypes for *IL6* -174 (rs1800795) were approximately twofold greater representation in the fatigued breast cancer participants compared to the non-fatigued controls. Kober et al. [23] found that patients with the polymorphism in *IL1B* -511 (rs16944) were approximately three times more likely to experience higher fatigue, while patients with the polymorphism in *IL10* (rs3024496) were 34% less likely to experience higher fatigue. Furthermore, polymorphisms in *IL6* -174 (rs1800795) and *TNF* -308 (rs1800629) were linked to decreased fatigue, such that women homozygous for common alleles of *IL6* -174 and *TNF* -308 reported significant elevated fatigue [4]. Eshragh et al. [14] identified that patients carrying at least one rare allele for beta-2-adrenergic receptor (*ADRB2*) (rs1042718), *COMT* (rs9332377), *BDNF* (rs6265), *CYP3A4* (rs4646437), GTP cyclohydrolase 1 (*GCH1*) (rs3783642), nitric oxide synthase 1 (*NOS1*) (rs9658498), and *5-HTTLPR* plus polymorphism in soluble-like carrier family 6 member 4-GABA transporter (*SLC6A4*) (rs25531)

Table 3 Genetic polymorphisms underlying psychoneurological symptoms

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
Anxiety	*TNFA*	rs1799964	T>C	Downstream variant 500B, upstream variant 2KB	Patients homozygous for rare C allele showed an 88% decreased chance of belonging to higher anxiety class compared to lower anxiety class	Surgery	Immune system	Miaskowski et al., 2016 [34]
		rs3093662	A>G	Intron variant	Patients homozygous or heterozygous for rare G allele were 4 times as likely to belong to higher anxiety class compared to lower anxiety class			
Anxiety	*SERT* (5-HTTL-PR)			Promoter region variant	The decrease of anxious preoccupation with time was less pronounced in women carrying 1 or 2 short (S) alleles compared to the patients who are carriers of the long (L)/L genetic variant	Surgery, radiation therapy, hormonal therapy	Neuronal system	Schillani et al., 2012 [44]
Cognitive impairment	*COMT*	rs165599	G>A	Downstream variant 500B, intron variant, UTR variant 3′	Chemotherapy-induced cognitive impairment was seen in triple-negative breast cancer survivors that were also carriers of the A allele, especially with respect to retrospective and prospective memory compared to non-triple-negative breast cancer survivors	Chemotherapy	Metabolism	Cheng et al., 2016 [7]
Cognitive impairment	*APOE*	rs429358, rs7412 (comprising the ε2, ε3, and ε4 alleles)	T>C C>T	Missense	Possession of 1 or more ε4 (C/C) alleles contributed to poorer verbal learning and memory performance following cancer treatment and anastrozole treatment and possession of 1 or more ε4 alleles were negatively correlated to executive function performance	Chemotherapy ± adjuvant therapy (anastrozole)	Transport of small molecules	Koleck et al., 2014 [24]
Cognitive impairment	*IL1R1*	rs949963	G>A	Intron variant, upstream variant 2KB	Patients homozygous or heterozygous for rare A allele were 2 times as likely to belong to a lower attentional function class	Surgery	Immune system	Merriman et al., 2014 [31]
Cognitive impairment	*BDNF*	rs6265	C>T (Val66Met)	Missense	Patients carrying the Met/Met genotype exhibited significantly lower odds of developing cognitive impairment. The Met carriers were less likely to experience impairment in the domains of verbal fluency and multitasking ability compared with the Val homozygote carriers	Chemotherapy	Signal transduction	Ng et al., 2016 [39]
Cognitive impairment	*IL1R1*	rs2287047	G>A	Intron variant	The A/A+A/G polymorphism was shown to be associated with higher perceived cognitive function. The polymorphism affects the normal activation of nuclear factor kappa B involved in synaptic plasticity and memory	Chemotherapy	Immune system	Myers et al., 2017 [37]
Cognitive impairment	*COMT*	rs4680	G>A (Val158-Met)	Missense	Val carriers performed worse than Met homozygote carriers on tests of attention, verbal fluency, and motor speed; Met carriers treated with chemotherapy alone performed better than Val carriers treated with chemotherapy alone and Met carriers treated with radiation on tests of attention.	Chemotherapy, radiation therapy	Metabolism	Small et al., 2011 [47]
Depressive symptoms	*BDNF*	rs6265	C>T (Val66Met)	Missense	The polymorphism was significantly interacted with CRP, and higher CRP was related to more cognitive depressive symptoms among Met allele carriers, but not among Val/Val homozygotes	Surgery ± chemotherapy, ± radiation therapy	Signal transduction	Dooley et al., 2016 [12]

Table 3 (continued)

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
Depressive symptoms	*BDNF*	rs6265	C>T (Val66Met)	Missense	The Met/Met genotype showed prevalent (OR = 2.63) and persistent (OR = 8.07) depression	Surgery	Signal transduction	Kim et al., 2012 [21]
Depressive symptoms	*IL1B -511*	rs16944	C>T	Upstream variant 2KB	Patients with the T/T genotype were more susceptible to depression 1 week after surgery and persistent depression 1 year later	Surgery	Immune system	Kim et al., 2013 [22]
Depressive symptoms	*TNFA*	rs1799964	T>C	Downstream variant 500B, upstream variant 2KB	Patients homozygous for the rare C allele had an 87% decrease in the odds of belonging to the subsyndromal class (versus the resilient class)	Surgery	Immune system	Saad et al., 2014 [43]
	IFNGR1	rs9376268	G>A	Intron variant	Patients homozygous or heterozygous for the rare A allele was associated with a 1.9-fold increase in the odds of belonging to the subsyndromal class (versus the resilient class)		Immune system	
	IL6	rs2069840	C>G	Intron variant, upstream variant 2KB	Patients homozygous for the rare G allele had a 3.6-fold increase in the odds of belonging to the subsyndromal class		Immune system, signal transduction	
Fatigue	*IL1B* -511	rs16944	C>T	Promoter region variant	*IL1B* -511 polymorphism revealed a substantial over-representation of C/C alleles among fatigued survivors, and a substantial under-representation of T/T alleles	All cancer treatment	Immune system	Collado-Hidalgo et al., 2008 [9]
	IL6 -174	rs1800795	G>C	Promoter region variant	Fatigued breast cancer survivors showed an elevated occurrence of homozygosity for both the variant C allele and the wild-type G allele of the IL6 -174 (G/C) polymorphism, with approximately 2-fold greater representation of both G/G and C/C alleles in the fatigued group compared to non-fatigued controls			
Fatigue	*ADRB2*	rs1042718	C>A	Synonymous codon	The polymorphisms lead to patients homozygous for the A allele (silent mutation) having an 87% less chance of belonging to the higher-fatigue class	Surgery	Signal transduction	Eshragh et al., 2017 [14]
	COMT	rs9332377	T>C	Intron variant	Patients heterozygous or homozygous for the rare C allele had a 52% lower chance of belonging to the higher-fatigue class via the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system		Metabolism	
	BDNF	rs6265	G>A (Val66Met)	Missense	Patients either heterozygous or homozygous for the rare A allele had a 50% decreased chance of belonging to the higher-fatigue class		Signal transduction	
	CYP3A4	rs4646437	C>T	Intron variant	Women with the rare T allele had higher expression and activity of the *CYP3A4* enzyme and therefore showed a 52% less chance of belonging to the higher-fatigue class		Metabolism	
	GALR1	rs949060	G>C		Patients homozygous for the rare C allele had a 2.46-fold higher chance of being in the higher-fatigue class		Signal transduction	
	GCH1	rs3783642	T>C	Intron variant	Being heterozygous or homozygous for the rare C allele was associated with a 53% less chance of being in the higher-fatigue class		Metabolism	

Table 3 (continued)

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
	NPY1R haplotype A04	rs9764; rs7687423	T>C; G>A	Intron variant 3′ UTR Intronic region	Each additional dose of *NPY1R* HapA04 showed a 1.77-fold higher chance of being in the higher-fatigue class		Signal transduction	
	NOS1	rs9658498	T>C	Intron variant	Patients homozygous for C allele had a 55% lower chance of being in the higher-fatigue class		Immune system	
		rs2293052	C>T	Intron variant	Patients homozygous for the rare T alleles had a 4.58-fold higher chance of being in the higher-fatigue class			
	SLC6A2	rs17841327	G>A	Intron variant	Patients homozygous for A allele had a 10.31-fold higher chance of being in the higher-fatigue group		Transport of small molecules	
	SLC6A4	5-HTTLPR + rs25531			Carrying at least 1 L_A allele was associated with a 47% lower odds of belonging to the higher-fatigue class		Neuronal system	
Fatigue	*IL1B* -511	rs16944	G>A	Upstream variant 2KB	Patients homozygous or heterozygous for the rare A allele were 2.98 times more likely to be in the higher-fatigue class	Surgery	Immune system	Kober et al., 2016 [23]
	IL10	rs3024496	T>C	UTR variant 3′	Patients carrying the rare C allele were less likely to be in the higher-fatigue class (OR = 0.66)		Immune system	
Fatigue	*IL6* -174	rs1800795	G>C	Intron variant, upstream variant 2KB	Fatigue was elevated in the G/G genotype relative to G/C or C/C genotype	Radiation therapy, chemotherapy	Immune system, signal transduction	Bower et al., 2013 [4]
	TNF -308	rs1800629	G>A	Upstream variant 2KB	Self-reported fatigue severity was approximately twice as high in the G/G genotype than G/A and 12 times higher in G/G than A/A		Immune system	
Fatigue	*COMT*	rs4680	G>A (Val158-Met)	Missense	The patients with the Met/Met or Val/Met genotype exhibited higher-fatigue score compared to those with the Val/Val genotype.	Surgery	Metabolism	Fernandez-de-las-Peñas et al., 2012 [15]
Fatigue	*NTRK2*	rs1212171	C>T	Upstream variant 2KB	Patients homozygous for the T allele reported significantly more fatigue-related interference in their daily functioning	Surgery, chemotherapy	Signal transduction	Young et al., 2017 [52]
Pain	*FAAH*	rs324420	C>A (germline) (Pro129T-hr)	Missense	Decreased FAAH protein expression via a posttranslational mechanism has been shown to be associated with increased cold pain sensitivity and required less postoperative analgesia	Surgery	Metabolism	Cajanus et al., 2016 [6]
Pain	*CYP17A1*	rs6163	C>A	Synonymous codon	The polymorphism was significantly associated with worsening pain at 3 months (OR = 0.61) and 12 months (OR = 0.70)	Adjuvant chemotherapy	Metabolism	Garcia-Giralt et al., 2013 [17]
	CYP19A1	rs4775936	C>T	Promoter region variant	The polymorphism was associated with worsening pain at 3 months (OR = 1.62)		Metabolism	
	VDR	rs11568820	G>A	Promoter region variant	The combination of rs6163 (*CYP17A1*) and rs1568820 (*VDR*) incremented pain at 12 months after therapy initiation. The polymorphism alters transcriptional activity, affecting musculoskeletal pain intensity.		Metabolism, gene expression (transcription)	
	CYP27B1	rs4646536	T>C	Intron variant	The unfavorable alleles for rs4646536 (*CYP27B1*) and rs6163 (*CYP17A1*) had an average increase of 2 points in pain score compared to those with only 1 unfavorable allele. Polymorphisms decrease the efficiency of the		Metabolism	

Table 3 (continued)

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
					hydroxylation of 25(OH)D to 1,25(OH)2D resulting in suboptimal concentrations of the active ligand			
Pain	*COMT*	rs887200	C>T	Intron variant	Homozygous minor allele (C/C) carriers were less sensitive to pain than other genotypes, and C/C carriers also tolerated cold stimulation longer as compared with non-carriers. The polymorphism showed strong evidence of increased cold pain intensity	Surgery	Metabolism	Kambur et al., 2013 [19]
	COMT	rs165774	G>A	Intron variant	Subjects carrying the A allele showed lower pain intensity than homozygous G carriers		Metabolism	
Pain	*KCNA1*	rs4766311	C>T	UTR variant 3′	Each additional copy of the rare T allele was associated with a 40% reduction in the odds of belonging to the mild pain compared with the no pain class	Surgery	Neuronal system	Langford et al., 2015 [25]
	KCND2	rs1072198	A>G	Intron variant	Patients who were heterozygous or homozygous for the rare G allele had a 2.3-fold increase in the odds of belonging to the mild pain class compared with the no pain class		Neuronal system	
		rs17376373	A>G	Intron variant	Patients who were heterozygous or homozygous for the rare G allele had an 88% reduction in the odds of belonging to the severe pain class			
	KCNJ3	rs12995382	T>C	Intron variant	Patients who were heterozygous or homozygous for the rare C allele had a 68% decrease in the odds of belonging to the mild pain class compared with the no pain class		Neuronal system	
		rs17641121	T>C	Intron variant	Patients who were homozygous for the rare C allele had an 8.5-fold increase in the odds of belonging to the mild pain class compared with the no pain class			
	KCNJ3 haplotype A2	rs3111020; rs11895478	A>G; G>A	Intron variant	Each dose of the haplotype A2 was associated with an 89% decrease in the odds of belonging to the severe pain class		Neuronal system	
	KCNJ6	rs858003	C>T	Intron variant	Patients who were homozygous for the rare T allele had a 10.0-fold increase in the odds of belonging to the mild pain class (rather than the no pain class)		Neuronal system	
		rs2835925	A>G	Intron variant	Each additional copy of the rare G allele was associated with 19.3-fold higher odds of belonging to the severe pain class			
	KCNK9	rs2542424	A>G	Intron variant	Patients who were heterozygous or homozygous for the rare G allele had a 56% decrease in the odds of belonging to the mild pain class (rather than the no pain class)		Neuronal system, muscle contraction	
		rs2545457	C>T	Intron variant	Patients who were heterozygous or homozygous for the rare C allele had a 2.2-fold increase in the odds of belonging to the mild pain class compared with the no pain class			
		rs2014712	C>T	Intron variant	Patients who were homozygous for the rare T allele had a 9.9-fold increase in the odds of belonging to the severe pain class			

Table 3 (continued)

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
Pain	*OPG*	rs2073618	G>C	Missense, upstream variant 2KB	Patients carrying the G allele experienced significantly more AI-associated pain compared to wild-type allele. The use of aromatase inhibitors has been associated with musculoskeletal symptoms, and decreased OPG expression leads to increased RANKL expression, leading to net bone resorption	Adjuvant chemotherapy (aromatase inhibitors or tamoxifen)	Immune system	Lintermans et al., 2016 [28]
Pain	*IL1R2*	rs11674595	T>C	Intron variant	C allele increases a risk (36-fold) of developing severe persistent breast pain. IL1R2 encodes for IL1 type II receptor that inhibits inflammatory signaling by preventing IL1β from binding to IL1R1	Surgery	Immune system	Stephens et al., 2014 [49]
	IL10 haplotype A8	rs3024505, rs3024498, rs3024496, rs1878672, rs1518111, rs1518110, rs3024491	T>C A>G T>C A>G G>A A>T A>T		Each dose of this haplotype decreased the odds of belonging to the severe breast pain class by 79%		Immune system	
Pain	*IL6*	rs2069840	C>G	Intron variant, upstream variant 2KB	Patients homozygous for the rare G allele were 79% less likely to be in the mild breast pain class compared with the no pain class	Surgery	Immune system, signal transduction	Stephens et al., 2017 [50]
	CXCL8	rs4073	A>T	Upstream variant 2KB	The T allele is associated with the development of mild persistent breast pain following surgery. Patients homozygous for the rare A allele were 60% less likely to be in the mild breast pain class compared with the no pain class		Immune system	
	TNF	rs1800610	C>T	Intron variant	Patients who were heterozygous or homozygous for the rare T allele were 63% less likely to be in the mild breast pain class		Immune system	
Pain	*COMT*	rs4680	G>A (germline) (Val158-Met)	Missense	Met/Met genotype has been shown to have greater neck pain and pressure pain hypersensitivity in the neck-shoulder area (e.g., C5–C6 zygapophyseal joints, deltoid muscles). The rare A allele associated with lower pain threshold, enhanced stress vulnerability, and lowered *COMT* enzymatic activity, all of which have been shown to be associated with higher levels of pain interference during breast cancer treatment	Surgery	Metabolism	Fernandez-de-las-Peñas et al., 2012 [15]
Pain	*COMT*	rs4818	C>G	Synonymous codon	The G/G genotype reported significantly reduced pain severity and interference following the completion of surgery and chemotherapy treatment	Surgery, chemotherapy	Metabolism	Young et al., 2017 [52]
		rs4680	G>A (germline) (Val158-Met)	Missense	Patients homozygous for the A allele reported significantly more pain-related interference in normal function during cancer treatment			
Sleep disturbances	*NFKB2*	rs1056890	C>T	Downstream variant 500B, non-coding	Women with 1 or 2 rare alleles had a 47% decreased chance of belonging to the high sustained sleep disturbance class,	Surgery	Immune system	Alfaro et al., 2014 [1]

Table 3 (continued)

Symptom	Parent gene	SNP rsID	Nucleotide change	Functional consequence	Associations with symptom phenotypes	Cancer treatment type	Pathway	Reference
				transcript variant, UTR variant 3′	and carriers of the rare allele were less likely to be classified in the higher sleep disturbance class			
	IL13	rs1800925	C>T	Upstream variant 2KB	Carrying 1 or 2 rare alleles was associated with a 2.21-fold increase in the odds of belonging to the high sustained sleep disturbance class		Immune system	
	IL1R2 haplotype A2	rs11674595, rs7570441	T>C G>A	Intron variant	Each additional dose of IL1R2 HapA2 was associated with a 2.08 increase in the odds of belonging to the high sustained sleep disturbance class		Immune system	
Sleep disturbances	*NTRK2*	rs1212171	C>T	Upstream variant 2KB	Patients carrying the T allele showed an increase in sleep disturbance, with the C/T genotype carriers reporting moderate sleep disturbance and the T/T genotype carriers reporting the highest levels of sleep disturbance compared to the C/C carriers	Surgery, chemotherapy	Signal transduction	Young et al., 2017 [52]

5-HTTLPR, 5-hydroxyptryptamine transporter gene-linked polymorphic region; *ADRB2*, adrenoceptor beta 2; *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyltransferase; *CRP*, C-reactive protein; *CYP3A4*, cytochrome P450 family 3 subfamily A member 4; *CXCL8*, C-X-C motif chemokine ligand; *CYP17A1*, cytochrome P450 family 17 subfamily A member 1; *CYP27B1*, cytochrome P450 family 27 subfamily B member 1; *FAAH*, fatty acid amide hydrolase; *GALR1*, galanin receptor 1; *GCH1*, GTP cyclohydrolase 1; *IFNGR1*, interferon-gamma receptor 1; *IL1B*, interleukin-1 beta; *IL1R1*, interleukin-1 receptor type 1; *IL6*, interleukin-6; *KCNA1*, potassium voltage-gated channel subfamily A member 1; *KCND2*, potassium voltage-gated channel subfamily D member 2; *KCNJ3*, potassium voltage-gated channel subfamily J member 3; *KCNJ6*, potassium voltage-gated channel subfamily J member 6; *KCNK9*, potassium voltage-gated channel subfamily K member 9; *NFKB*, nuclear factor kappa B; *NOS1*, nitric oxide synthase 1; *NPY1R*, neuropeptide Y receptor Y1; *NTRK2*, neurotrophic receptor tyrosine kinase 2; *OPG*, osteoprotegerin; *OR*, odds ratio; *SERT*, serotonin transporter; *SLC6A2*, solute carrier family 6 member 2; *SLC6A4*, solute carrier family 6 member 4; *TNFA*, tumor necrosis factor-alpha; *UTR*, untranslated region; *VDR*, vitamin D receptor

exhibited significantly lower odds of presenting higher fatigue. On the contrary, polymorphisms in galanin receptor 1 (*GALR1*) (rs949060), *NOS1* (rs2293052), and *SLC6A2* (rs17841327) showed 2.46-, 4.58-, and 10.31-fold higher odds of presenting higher fatigue, respectively [14]. Patients carrying polymorphisms in neuropeptide Y receptor Y1 (*NPY1R*) haplotype A04 (rs9764, rs7687423) exhibited a 1.77-fold higher likelihood of reporting higher fatigue per each additional dose of the haplotype [14]. A SNP in *COMT* (rs4680) was positively correlated with fatigue; patients with the Met/Met or Val/Met genotypes reported higher fatigue scores compared to those with the Val/Val genotype [15]. In addition, the possession of two rare alleles of *NTRK2* (rs1212171) was significantly associated with greater fatigue-related interference in their daily functioning [52].

Pain

Nine studies examined genetic polymorphisms associated with pain [6, 15, 17, 19, 25, 28, 49, 50, 52]. The majority of participants underwent tumor surgery, and some participants received adjuvant chemotherapy (e.g., aromatase inhibitors) in two studies [17, 28]. Three studies investigated the role of *COMT* polymorphisms, which diminish *COMT* activity and increase sensitivity to pain [19, 30]. Patients with the Met/Val or Met/Met genotypes in *COMT* (rs4680) reported greater intensity of neck pain than those with Val/Val genotype, and patients carrying the Met/Met genotype in *COMT* (rs4680) showed greater pressure pain hypersensitivity in the C5-C6 zygapophyseal joint and deltoid muscle compared to those carrying the Val/Met or Val/Val genotypes [15]. Similarly, patients homozygous for the rare allele in *COMT* (rs4680) experienced more pain-related interference in functioning during cancer treatment, and those homozygous for the rare allele in *COMT* (rs4818) were also associated with greater pain interference and perceived severity after surgery and chemotherapy [52]. On the contrary, two SNPs in *COMT* (rs887200, rs165774) decreased pain sensitivity; homozygous rare alleles for *COMT* were significantly associated with less heat pain intensity (rs165774) and less cold pain intensity (rs887200) [19]. The polymorphism in fatty acid amide hydrolase (*FAAH*) (rs324420), which regulates endocannabinoid degradation, also contributed to the decrease in experimental cold pain and postoperative pain [6]. For polymorphisms in potassium voltage-gated channel subfamily A member 1 (*KCNA1*) (rs4766311), potassium voltage-gated channel subfamily J member 3 (*KCNJ3*) (rs12995382), *KCNJ3* haplotype A2 (rs3111020, rs11895478), and potassium voltage-gated channel subfamily K member 9 (*KCNK9*) (rs2545424), patients who were homozygous or heterozygous for the rare alleles exhibited decreased odds of belonging to the mild pain or severe pain group rather than the no pain group. On the contrary, for polymorphisms in *KCND2* (rs1072198), *KCNJ3* (rs17641121), *KCNJ6* (rs858003, rs2835925), and *KCNK9* (rs2545457, rs2014712), patients homozygous or heterozygous for the rare allele had an increased likelihood of belonging to the mild pain or severe pain group rather than the no pain group [25]. Notably, cytokine gene polymorphisms also contributed to the development of persistent pain. Patients homozygous for the rare allele in the *IL1R2* (rs11674594) showed a 36.1-fold increased chance to develop severe breast pain [49], while patients homozygous or heterozygous for the rare allele in *IL10* haplotype A8, *IL6* (rs2069840), C-X-C motif chemokine ligand 8 (*CXCL8*) (rs4073), and *TNF* (rs1800610) decreased the odds of belonging to the pain group by 79%, 79%, 60%, and 63%, respectively [50]. Lastly, polymorphisms in cytochrome P450 family 17 subfamily A polypeptide 1 (*CYP17A1*), *CYP19A1*, *CYP27B1*, vitamin D receptor (*VDR*), and osteoprotegerin (*OPG*) genes were significantly associated with worsening pain or incremented pain sensitivity [17, 28].

Sleep disturbances

Two studies investigated genetic polymorphisms underlying sleep disturbances in breast cancer patients [1, 52]. Polymorphisms in *IL13* (rs1800925) and *IL1R2* Hap A2 (rs1167595, rs7570441) increased sleep disturbances, whereas the polymorphism in *NFKB2* (rs1056890) decreased the possibility of the disorder [1]. Patients who possess at least one rare allele for *IL1R2* Hap A2 or *IL13* (rs1800925) were 2.08 or 2.21 times more likely to experience high sustained sleep disturbances; however, those who carry one or two of the rare alleles for *NFKB2* (rs1056890) were 0.47 times less likely to experience sleep disturbances. In addition, individuals with the heterozygous rare allele in neurotrophic receptor tyrosine kinase 2 (*NTRK2*) (rs1212171) reported moderate sleep disturbances, and patients with the homozygous rare allele presented the highest level of sleep disturbances following surgery and chemotherapy [52].

Biological pathways of genes associated with PN symptoms

The majority of genes were included in the immune system, metabolism, signal transduction, and neuronal system pathways. Inflammatory pathway genes were frequently investigated for identifying SNPs in all types of symptoms. The signal transduction pathway genes (e.g., *BDNF*, *ADRB*, *GALR1*, *NPY1R*, and *NTRK2*) were found to have associations with fatigue. In particular, *BDNF* polymorphisms were tested for various PN symptoms [12, 14, 21, 39]. The metabolism pathway genes (e.g., *COMT*, *GCH1*, *FAAH*, *VDR*, *CYP3A4*, *CYP17A1*, *CYP19A1*, and *CYP27B1*) turned out to be associated with fatigue and pain. *COMT* polymorphisms were most frequently analyzed across seven studies to explore

its association with fatigue, pain, and cognitive impairment. The neuronal system pathway genes (e.g., *SERT*, *SLC6A4*, KC*N*A1, *KCND2*, *KCNJ3*, and *KCNJ6*) were associated with anxiety or pain.

Discussion

This review was the first to synthesize studies examining associations between genetic polymorphisms and PN symptoms in breast cancer patients receiving cancer treatment. In addition, we evaluated the quality and rigor of each study by checking whether key information that should be included in the reporting of genetic association studies was provided. A total of 54 SNPs and haplotypes that are significantly associated with PN symptoms were identified. Half of them were associated with increased severity of PN symptoms, and the others contributed to the decrease of PN symptoms, with the lowest odds ratio (OR) being 0.11 (*KCNJ3* haplotype A2) and the highest OR being 36.07 (*IL1R2* rs11674595) for pain. Notably, pain has the known highest number of associated genetic polymorphisms reported, followed by fatigue, cognitive impairment, depressive symptoms, sleep disturbances, and anxiety. The majority of genetic polymorphisms included were involved in immune system and neuronal system pathways. A few polymorphisms in *BDNF*, *COMT*, and *IL6* genes were frequently tested in multiple studies, and some studies explored the role of novel genetic polymorphisms (e.g., *FAAH*) in relation to PN symptoms.

Polymorphisms in inflammatory cytokine genes were most frequently studied across all PN symptoms, and findings indicated that inflammatory pathway genes may play a major role in the development of PN symptoms in breast cancer patients receiving cancer treatment. Gilbertson-White et al. [18] suggested that the cytokine-induced sickness behavior model may explain the effect of cytokine genes on distressing symptoms in cancer patients. Due to an infection or administration of chemotherapy agents triggering an inflammatory response, individuals experience physiologic changes and the associated cluster of distressing symptoms, called sickness behavior [10, 13]. Most common symptoms reported by cancer patients are known to result from changes in levels of pro- and anti-inflammatory cytokines [32, 46]. Reyes-Gibby et al. [42] found that immune-response genes, such as *ENOS*, *IL1B*, and *TNFR2*, were predictive for the symptom cluster of pain, depressed mood, and fatigue in lung cancer patients. Recently, Miaskowski et al. [33] demonstrated that the severity of mood-cognitive symptom cluster was associated with polymorphisms in *CXCL8*, *IL13*, and *NFKB2*, and the severity of the treatment-related symptom cluster was associated with *IL1R1*, *IL6*, and *NFKB1*, indicating that the most common symptom clusters in oncology patients are correlated with polymorphisms in genes involved in inflammatory processes. Following inflammatory pathway genes, metabolism pathway genes, such as *COMT*, *FAAH*, *GCH1*, *CYP3A4*, *CYP17A1*, *CYP19A1*, and *CYP27B1*, are mainly responsible for the development and severity of PN symptoms, specifically pain. These genes are known to regulate pain sensitivity and nociception as well as opioid metabolism [2, 38, 40]. More studies are required to investigate whether these genes have potential roles as prognostic biomarkers of pain in patients with breast cancer treatment and whether other metabolism pathway genes may have similar actions on pain.

In genetic association studies, the reporting of methods and results is important to assess internal and external validity of study design because genotyping errors can frequently occur while sample processing and analysis are carried out. Poor equipment precision or failure, human error in sample handling and conduct of the array or handling the data obtained from the array, or biochemical artifacts may lead to biased genotyping results [41]. In this review, only four studies reported the place where the genotyping was complete, which may be related to human and equipment errors, and one study described whether genotyping occurred simultaneously or in smaller batches. The STREGA guideline underscores the description of whether genotypes are assigned using all of the data simultaneously or in smaller batches because genotyping in batches may introduce an undesirable batch effect into an analysis (e.g., differences in DNA storage, collection, or processing protocols) [8, 35].

In this analysis, the majority of studies were sufficiently powered to detect associations. The average sample size in 22 studies was above 300, and approximately 87% of patients consented to genotyping. It is considered adequate to generalize results of the association between SNPs and PN symptoms. However, results of four studies that examined genotyping with less than 100 participants should be interpreted cautiously [9, 37, 44, 52]. In particular, rare genotypes, such as *NTRK2*, in a small group may not have validated inferences about associations with symptom outcomes [52]. The conclusions derived may require confirmation by larger studies.

Although the meta-analysis result was not reported as main findings, the overall pooled OR of 46 SNPs that are associated with the development of PN symptoms was not significant (OR = 0.964, 95% CI = 0.731–1.272, $P = .798$) in 14 studies, indicating there was no tendency of decreasing or increasing the presence or severity of PN symptoms. Twenty-two SNPs may be associated with lower severity or absence of PN symptoms, while another 24 SNPs may be associated with higher severity or presence of PN symptoms after cancer treatment. In addition, no significant differences were observed across the subgroups of PN symptoms (OR = 0.982, 95% CI = 0.739–1.304, $P = .898$), and the overall OR of biological pathways was not significant as well (OR = 0.981, 95% CI = 0.888–1.085, $P = .711$).

In our analysis, SNPs shown to have no significant associations with some specific PN symptoms were excluded

because a large number of potential SNPs were tested in each study. Thus, we were not able check possible relationships of the SNPs with other PN symptoms in women with breast cancer. Furthermore, nine out of 26 studies were conducted and reported by Miaskowski and colleagues using the same breast cancer patient cohort who had undergone breast tumor surgery [1, 14, 23, 25, 31, 34, 43, 49, 50]. This may lead to a bias of our findings by decreasing the heterogeneity of study population.

In conclusion, this systematic review evaluated the findings of studies investigating the association between genetic polymorphisms and PN symptoms following breast cancer treatment. Current evidence suggested that genetic polymorphisms play a role as potential biological mechanisms of PN symptoms in breast cancer patients. Particularly, immune system and metabolism pathway genes seem to be critical to the development of PN symptoms. However, more well-designed genome-wide association studies are still required to validate these findings. This review may provide comprehensive evidence for the future development of personalized therapeutics for addressing distressing PN symptoms in breast cancer patients.

Acknowledgements We would like to thank Ms. Debra McDonald for proofreading.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Alfaro E, Dhruva A, Langford DJ, Koetters T, Merriman JD, West C, Dunn LB, Paul SM, Cooper B, Cataldo J, Hamolsky D, Elboim C, Kober K, Aouizerat BE, Miaskowski C (2014) Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery. Eur J Oncol Nurs 18:85–93. https://doi.org/10.1016/j.ejon.2013.08.004
2. Belfer I, Segall S (2011) COMT genetic variants and pain. Drugs Today (Barc) 47:457–467. https://doi.org/10.1358/dot.2011.47.6.1611895
3. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792
4. Bower JE, Ganz PA, Irwin MR, Castellon S, Arevalo J, Cole SW (2013) Cytokine genetic variations and fatigue among patients with breast cancer. J Clin Oncol 31:1656–1661. https://doi.org/10.1200/jco.2012.46.2143
5. Buchanan ND, Dasari S, Rodriguez JL, Lee Smith J, Hodgson ME, Weinberg CR, Sandler DP (2015) Post-treatment neurocognition and psychosocial care among breast cancer survivors. Am J Prev Med 49:S498–S508. https://doi.org/10.1016/j.amepre.2015.08.013
6. Cajanus K, Holmstrom EJ, Wessman M, Anttila V, Kaunisto MA, Kalso E (2016) Effect of endocannabinoid degradation on pain: role of FAAH polymorphisms in experimental and postoperative pain in women treated for breast cancer. Pain 157:361–369. https://doi.org/10.1097/j.pain.0000000000000398
7. Cheng H, Li W, Gan C, Zhang B, Jia Q, Wang K (2016) The COMT (rs165599) gene polymorphism contributes to chemotherapy-induced cognitive impairment in breast cancer patients. Am J Transl Res 8:5087–5097
8. Clayton DG, Walker NM, Smyth DJ, Pask R, Cooper JD, Maier LM, Smink LJ, Lam AC, Ovington NR, Stevens HE, Nutland S, Howson JM, Faham M, Moorhead M, Jones HB, Falkowski M, Hardenbol P, Willis TD, Todd JA (2005) Population structure, differential bias and genomic control in a large-scale, case-control association study. Nat Genet 37:1243–1246
9. Collado-Hidalgo A, Bower JE, Ganz PA, Irwin MR, Cole SW (2008) Cytokine gene polymorphisms and fatigue in breast cancer survivors: early findings. Brain Behav Immun 22:1197–1200. https://doi.org/10.1016/j.bbi.2008.05.009
10. Dantzer R, Kelley KW (2007) Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 21:153–160
11. Dodd MJ, Cho MH, Cooper BA, Miaskowski C (2010) The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs 14:101–110. https://doi.org/10.1016/j.ejon.2009.09.005
12. Dooley LN, Ganz PA, Cole SW, Crespi CM, Bower JE (2016) Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer. J Affect Disord 197:43–50. https://doi.org/10.1016/j.jad.2016.02.059
13. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR (2010) Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry 68:748–754. https://doi.org/10.1016/j.biopsych.2010.06.010
14. Eshragh J, Dhruva A, Paul SM, Cooper BA, Mastick J, Hamolsky D, Levine JD, Miaskowski C, Kober KM (2017) Associations between neurotransmitter genes and fatigue and energy levels in women after breast cancer surgery. J Pain Symptom Manag 53:67–84 e67. https://doi.org/10.1016/j.jpainsymman.2016.08.004
15. Fernandez-de-las-Peñas C, Fernandez-Lao C, Cantarero-Villanueva I, Ambite-Quesada S, Rivas-Martinez I, del Moral-Avila R, Arroyo-Morales M (2012) Catechol-O-methyltransferase genotype (Val158met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. Breast Cancer Res Treat 133:405–412. https://doi.org/10.1007/s10549-011-1757-y
16. Fu OS, Crew KD, Jacobson JS, Greenlee H, Yu G, Campbell J, Ortiz Y, Hershman DL (2009) Ethnicity and persistent symptom burden in breast cancer survivors. J Cancer Surviv 3:241–250. https://doi.org/10.1007/s11764-009-0100-7
17. Garcia-Giralt N, Rodriguez-Sanz M, Prieto-Alhambra D, Servitja S, Torres-Del Pliego E, Balcells S, Albanell J, Grinberg D, Diez-Perez A, Tusquets I, Nogues X (2013) Genetic determinants of aromatase inhibitor-related arthralgia: the B-ABLE cohort study. Breast Cancer Res Treat 140:385–395. https://doi.org/10.1007/s10549-013-2638-3
18. Gilbertson-White S, Aouizerat BE, Miaskowski C (2011) Methodologic issues in the measurement of cytokines to elucidate the biological basis for cancer symptoms. Biol Res Nurs 13:15–24. https://doi.org/10.1177/1099800410379497
19. Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA (2013) Effect of catechol-o-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. Anesthesiology 119:1422–1433. https://doi.org/10.1097/aln.0000000000000013
20. Kim HJ, Barsevick AM, Fang CY, Miaskowski C (2012) Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nurs 35:E1–E20. https://doi.org/10.1097/ncc.0b013e318233a811

21. Kim JM, Kim SW, Stewart R, Kim SY, Shin IS, Park MH, Yoon JH, Lee JS, Park SW, Kim YH, Yoon JS (2012) Serotonergic and BDNF genes associated with depression 1 week and 1 year after mastectomy for breast cancer. Psychosom Med 74:8–15. https://doi.org/10.1097/psy.0b013e318241530c
22. Kim JM, Stewart R, Kim SY, Kang HJ, Jang JE, Kim SW, Shin IS, Park MH, Yoon JH, Park SW, Kim YH, Yoon JS (2013) A one year longitudinal study of cytokine genes and depression in breast cancer. J Affect Disord 148:57–65. https://doi.org/10.1016/j.jad.2012.11.048
23. Kober KM, Smoot B, Paul SM, Cooper BA, Levine JD, Miaskowski C (2016) Polymorphisms in cytokine genes are associated with higher levels of fatigue and lower levels of energy in women after breast cancer surgery. J Pain Symptom Manag 52:695–708 e694. https://doi.org/10.1016/j.jpainsymman.2016.04.014
24. Koleck TA, Bender CM, Sereika SM, Ahrendt G, Jankowitz RC, McGuire KP, Ryan CM, Conley YP (2014) Apolipoprotein E genotype and cognitive function in postmenopausal women with early-stage breast cancer. Oncol Nurs Forum 41:E313–E325. https://doi.org/10.1188/14.onf.e313-e325
25. Langford DJ, Paul SM, West CM, Dunn LB, Levine JD, Kober KM, Dodd MJ, Miaskowski C, Aouizerat BE (2015) Variations in potassium channel genes are associated with distinct trajectories of persistent breast pain after breast cancer surgery. Pain 156:371–380. https://doi.org/10.1097/01.j.pain.0000460319.87643.11
26. Lengacher CA, Reich RR, Post-White J, Moscoso M, Shelton MM, Barta M, Le N, Budhrani P (2012) Mindfulness based stress reduction in post-treatment breast cancer patients: an examination of symptoms and symptom clusters. J Behav Med 35:86–94. https://doi.org/10.1007/s10865-011-9346-4
27. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62:e1–e34. https://doi.org/10.7326/0003-4819-151-4-200908180-00136
28. Lintermans A, Van Asten K, Jongen L, Van Brussel T, Laenen A, Verhaeghe J, Vanderschueren D, Lambrechts D, Neven P (2016) Genetic variant in the osteoprotegerin gene is associated with aromatase inhibitor-related musculoskeletal toxicity in breast cancer patients. Eur J Cancer 56:31–36. https://doi.org/10.1016/j.ejca.2015.12.013
29. 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 AF, Birkett N (2009) Strengthening the Reporting of Genetic Association Studies (STREGA): an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. J Clin Epidemiol 62:597–608 e594. https://doi.org/10.1016/j.jclinepi.2008.12.004
30. Mannisto PT, Kaakkola S (1999) Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev 51:593–628
31. Merriman JD, Aouizerat BE, Cataldo JK, Dunn L, Cooper BA, West C, Paul SM, Baggott CR, Dhruva A, Kober K, Langford DJ, Leutwyler H, Ritchie CS, Abrams G, Dodd M, Elboim C, Hamolsky D, Melisko M, Miaskowski C (2014) Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. Cytokine 65:192–201. https://doi.org/10.1016/j.cyto.2013.11.003
32. Miaskowski C, Aouizerat BE (2012) Biomarkers: symptoms, survivorship, and quality of life. Semin Oncol Nurs 28:129–138. https://doi.org/10.1016/j.soncn.2012.03.008
33. Miaskowski C, Conley YP, Mastick J, Paul SM, Cooper BA, Levine JD, Knisely M, Kober KM (2017) Cytokine gene polymorphisms associated with symptom clusters in oncology patients undergoing radiation therapy. J Pain Symptom Manag 54:305–316 e303. https://doi.org/10.1016/j.jpainsymman.2017.05.007
34. Miaskowski C, Elboim C, Paul SM, Mastick J, Cooper BA, Levine JD, Aouizerat BE (2016) Polymorphisms in tumor necrosis factor-alpha are associated with higher anxiety levels in women after breast cancer surgery. Clin Breast Cancer 16:63–71 e63. https://doi.org/10.1016/j.clbc.2014.12.001
35. Miclaus K, Wolfinger R, Vega S, Chierici M, Furlanello C, Lambert C, Hong H, Zhang L, Yin S, Goodsaid F (2010) Batch effects in the BRLMM genotype calling algorithm influence GWAS results for the Affymetrix 500K array. Pharmacogenomics J 10:336–346. https://doi.org/10.1038/tpj.2010.36
36. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A (2016) Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 66:271–289
37. Myers JS, Koleck TA, Sereika SM, Conley YP, Bender CM (2017) Perceived cognitive function for breast cancer survivors: association of genetic and behaviorally related variables for inflammation. Support Care Cancer 25:2475–2484. https://doi.org/10.1007/s00520-017-3654-3
38. Nasirinezhad F, Jergova S, Pearson JP, Sagen J (2015) Attenuation of persistent pain-related behavior by fatty acid amide hydrolase (FAAH) inhibitors in a rat model of HIV sensory neuropathy. Neuropharmacology 95:100–109. https://doi.org/10.1016/j.neuropharm.2014.11.024
39. Ng T, Teo SM, Yeo HL, Shwe M, Gan YX, Cheung YT, Foo KM, Cham MT, Lee JA, Tan YP, Fan G, Yong WS, Preetha M, Loh WJ, Koo SL, Jain A, Lee GE, Wong M, Dent R, Yap YS, Ng R, Khor CC, Ho HK, Chan A (2016) Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. Neuro-Oncology 18:244–251. https://doi.org/10.1093/neuonc/nov162
40. Overholser BR, Foster DR (2011) Opioid pharmacokinetic drug-drug interactions. Am J Manag Care 17(Suppl 11):S276–S287
41. Pompanon F, Bonin A, Bellemain E, Taberlet P (2005) Genotyping errors: causes, consequences and solutions. Nat Rev Genet 6:847–859. https://doi.org/10.1038/nrg1707
42. Reyes-Gibby CC, Swartz MD, Yu X, Wu X, Yennurajalingam S, Anderson KO, Spitz MR, Shete S (2013) Symptom clusters of pain, depressed mood, and fatigue in lung cancer: assessing the role of cytokine genes. Support Care Cancer 21:3117–3125. https://doi.org/10.1007/s00520-013-1885-5
43. Saad S, Dunn LB, Koetters T, Dhruva A, Langford DJ, Merriman JD, West C, Paul SM, Cooper B, Cataldo J, Hamolsky D, Elboim C, Aouizerat BE, Miaskowski C (2014) Cytokine gene variations associated with subsyndromal depressive symptoms in patients with breast cancer. Eur J Oncol Nurs 18:397–404. https://doi.org/10.1016/j.ejon.2014.03.009
44. Schillani G, Era D, Cristante T, Mustacchi G, Richiardi M, Grassi L, Giraldi T (2012) 5-HTTLPR polymorphism and anxious preoccupation in early breast cancer patients. Radiol Oncol 46:321–327. https://doi.org/10.2478/v10019-012-0024-0
45. Schreiber KL, Kehlet H, Belfer I, Edwards RR (2014) Predicting, preventing and managing persistent pain after breast cancer surgery: the importance of psychosocial factors. Pain Manag 4:445–459. https://doi.org/10.2217/pmt.14.33
46. Seruga B, Zhang H, Bernstein LJ, Tannock IF (2008) Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 8:887–899. https://doi.org/10.1038/nrc2507
47. Small BJ, Rawson KS, Walsh E, Jim HS, Hughes TF, Iser L, Andrykowski MA, Jacobsen PB (2011) Catechol-O-methyltransferase genotype modulates cancer treatment-related

cognitive deficits in breast cancer survivors. Cancer 117:1369–1376. https://doi.org/10.1002/cncr.25685

48. Starkweather AR, Lyon DE, Elswick RK Jr, Montpetit AJ, Conley Y, McCain NL (2013) A conceptual model of psychoneurological symptom cluster variation in women with breast cancer: bringing nursing research to personalized medicine. Curr Pharmacogenomics Person Med 11:224–230. https://doi.org/10.2174/18756921113119990004
49. Stephens K, Cooper BA, West C, Paul SM, Baggott CR, Merriman JD, Dhruva A, Kober KM, Langford DJ, Leutwyler H, Luce JA, Schmidt BL, Abrams GM, Elboim C, Hamolsky D, Levine JD, Miaskowski C, Aouizerat BE (2014) Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. J Pain 15:169–180. https://doi.org/10.1016/j.jpain.2013.09.015
50. Stephens KE, Levine JD, Aouizerat BE, Paul SM, Abrams G, Conley YP, Miaskowski C (2017) Associations between genetic and epigenetic variations in cytokine genes and mild persistent breast pain in women following breast cancer surgery. Cytokine 99:203–213. https://doi.org/10.1016/j.cyto.2017.07.006
51. Syvanen AC (2001) Accessing genetic variation: genotyping single nucleotide polymorphisms. Nat Rev Genet 2:930–942
52. Young EE, Kelly DL, Shim I, Baumbauer KM, Starkweather A, Lyon DE (2017) Variations in COMT and NTRK2 influence symptom burden in women undergoing breast cancer treatment. Biol Res Nurs 19:318–328. https://doi.org/10.1177/1099800417692877