Biomedical Research 2018; 29 (6): 1164-1175 *ISSN 0970-938X*
www.biomedres.info

Genetic polymorphisms associated with common symptoms experienced by breast cancer patients.

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Abstract

The recent advances have led to a considerable increase in the proportion of breast cancer survivors, however, majority of them experience symptoms such as fatigue, pain, depression and sleep disturbances that impair their Quality of Life (QOL) significantly. In addition, a significant inter-individual variability in QOL of breast cancer patients exists which has been partly attributed to genetic variations. However, details of how these variations are influenced by genetic factors remain largely unknown. Therefore, detecting patients with greater susceptibility to reduced QOL using genetic markers may help in designing intervention strategies for personalized medicine. Although limited number of studies have reported on the associations between genetic polymorphisms and QOL, cytokine gene polymorphisms has consistently been linked to increased susceptibility to the development of common symptoms (fatigue, pain, depression and sleep disturbances) in breast cancer patients. More interestingly, these symptoms share some common molecular pathways making it possible to consider them as symptom cluster. In this review, the relationship between genetic variation and common symptoms among breast cancer patients is discussed. In order for genetic factors to be integrated into clinical practice and nursing care of breast cancer patients with impaired QOL, additional studies are encouraged to understand the underlying molecular mechanisms involved in the development of these symptoms and their impact on QOL for identification of patients based on the presence of a symptom cluster using genetic biomarkers.

Keywords: Breast cancer, Genetic polymorphisms, Quality of life, Fatigue, Depression, Pain, Sleep disturbances.

Accepted on December 18, 2017

Introduction

Overall, breast cancer is the second most common cancer and by far the most frequent cancer in women with an estimated 1.7 million cases reported in 2012. However, in terms of mortality, it ranks 5th as a result of fairly favourable prognosis [1]. The recent advances in early diagnosis and treatment of breast cancer have led to a significant increase in the number of survivors with a five year survival rate climbing to 90% [2]. Nevertheless, currently, a significant proportion of breast cancer survivors suffer lot of consequences that considerably impair their quality of life (QOL) among which include psychological distress [3,4], fatigue and sleep disturbances [5], as well as pain [6]. These symptoms are believed to be related to one another with a recent data suggesting that they can manifest as a symptom cluster [7-9] that can cause significantly impaired QOL among cancer patients [10-12].

With regards to management of breast cancer related symptoms, most attention in the past has been focused on individual symptoms or more recently on symptom cluster; nevertheless QOL assessment has recently been recognized as an important patient-reported outcome in breast cancer and other oncology patients [13-16]. To date, the reported inter-individual variability in QOL of breast cancer patients [17,18] has not been fully explained by the socio-demographic factors or biological characteristics of the disease and/or its treatment [19-23]. There exist a number of reports to support the fact that an individual's intrinsic factors including genetic factors may play a role in the inter-individual differences in QOL [24-26].

A number of studies have reported a significant impairment of QOL that is associated with fatigue, pain, depression and sleep disturbance among cancer patients which constitute their major complaints [3,27-30]. In view of the fact that these symptoms are the most common domains considered in assessing QOL, understanding their association with genetic variation and its impact on inter-individual differences in QOL through high quality studies was recently advocated [31]. Although some

studies have recently reported on the association between cytokine gene polymorphisms and QOL in lung cancer patients [32,33] as well as patients with cancers of the breast, prostate, lung and brain and their family caregivers [34], at the time of this review, no study has specifically reported on the impact of genetic polymorphisms on QOL in breast cancer patients. A closely related study has revealed an association between nuclear factor kappa beta 2 (*NFKB2*) gene and three (physical, social and spiritual) of the four QOL domains in oncology patients and their family caregivers [35], thus further corroborating the potential role of gene polymorphisms in inter-individual differences in QOL.

In this article, the impacts of genetic variation on the major symptoms commonly experienced by breast cancer patients and are believed to significantly influence the QOL of patients are reviewed with a view to providing insight on possible identification of patients with higher risk of QOL impairment using genetic markers.

Fatigue and Energy Levels

Pro-inflammatory cytokines have been suggested to play a role in activating the central and autonomic nervous systems to trigger fatigue and other behavioural symptoms in both cancer-related fatigue as well as in inflammatory diseases-related fatigue [36,37]. A larger body of literature also suggests that there is an association between fatigue and inflammatory markers among breast cancer patients and survivors [38-43]. A number of Single Nucleotide Polymorphisms (SNPs) in pro-inflammatory cytokines have been reported to be linked with breast cancer susceptibility and prognosis [44-48] as well as the development of treatment-related adverse effects [49,50]. Some evidences have emerged from recent literatures that the energy level in an individual may be considered as a distinct but related symptom to fatigue [51-54]. Therefore, owing to the relationship between fatigue and energy level, it is hypothesized that a significant number of cytokines and neurotransmitters [55-58] could play a vital role in the development of these related symptoms.

Cytokine genes and fatigue and energy

An earlier finding in a small cohort of breast cancer survivors suggested that patients harbouring the heterozygous or homozygous rare T variant allele of *IL1B*-511 C>T (rs16944) had higher odds of not having fatigue while those carrying the homozygous G/G or C/C variants of *IL6*-174 G>C (rs1800795) are more likely to suffer from fatigue [59]. The study reported that *IL1B*-511 appeared to be a more reliable marker of fatigue than *IL6*-174 because it remained significant even after controlling for demographic and clinical confounders which was not the case with the other SNP (*IL6*-174) that was confounded by age and some clinical variables. Nevertheless, the results of this study were not strongly conclusive due to the 1) relatively small sample size used and 2) lack of a control group of women without breast cancer which would have provided more information on whether the association between cytokines SNPs fatigue was specific to breast cancer patients and/or treatment of the disease. Consequently, to address this limitation, Reinertsen et al. conducted a similar study in a larger cohort of breast cancer survivors in two parts with the second part categorising the patients in to persistent- and never-fatigued subjects [60]. Their study did not find any significant association between fatigue and the above SNPs (rs16944 and rs1800795) as previously reported by Collado-Hidalgo et al. [59]. Several reasons could contribute to the disparity seen i.e. the 1) relatively small sample size used by Collado-Hidalgo et al., 2) use of different fatigue measures, 3) differences in the types of subjects used; where the breast cancer women recruited by Collado-Hidalgo et al. consisted of those diagnosed with early-stage breast cancer stages 0-II [59], Reinertsen et al. included stages II and III breast cancer subjects [60]. Furthermore, the depression scores in Collado-Hidalgo et al. were significantly higher among the fatigued subjects. After correcting for depression, although the relationship between fatigue and rs16944 in the *IL1B*-511 became near-significant (p=0.052) it continued to show significance after controlling for other variables; and after adjusting for age and several treatment-related factors, the relation between fatigue and rs1800795 in the *IL6*-174 became insignificant [59]. Therefore, at this stage, the roles of rs16944 and rs1800795 as predictors of fatigue in breast cancer patients can be considered as inconclusive especially due to the disagreement between the two studies above and the fact that only a limited number of pro-inflammatory SNPs were investigated, leaving room for the possibility of identification of novel SNPs in the inflammatory pathways in future.

To further clarify the above contradictions, Bower et al. examined *TNF*-308 G>A (rs1800629) together with *IL1B*-511 C>T and *IL6*-174 G>C discussed above among women with early-stage breast cancer [61]. Their results demonstrated that fatigue was significantly associated with both *TNF*-308 and *IL6*-174 but was not associated with *IL1B*-511 C>T. The addition of *TNF*-308 previously established to be associated with fatigue among oncology patients undergoing treatment [62] might have enhanced the sensitivity of Bower et al. study to detect SNPs association with fatigue. Although this recent study [61] suggests that breast cancer patients harbouring certain variants of cytokines genes may be at higher risk of developing fatigue, it still cannot be concluded at this point if genetic variants of pro-inflammatory cytokines could serve as clinical genetic biomarkers to predict breast cancer patients who have higher risk of having fatigue. Indeed, more studies involving additional genetic variants especially in a larger cohort of different ethnicities are needed.

A more comprehensive study examining the impact of genetic variation in cytokines and their receptors on fatigue and lack of energy was recently conducted in breast cancer patients before and after breast cancer surgeries [54]. It was observed that patients carrying the homozygous rare variants of *IL1B* (rs16944) and *IL10* (rs3024496) had increased and decreased odds of belonging to the higher fatigue class respectively. Furthermore, patients heterozygous or homozygous for *IL1R1* (rs2110726) rare variants had decreased odds of belonging to the "lower energy" group. To this point, the results of the

association between *IL1B* (rs16944) and the development of fatigue remain contradictory where a study [54] reported increased while the other [59] reported decreased likelihood of belonging to the fatigued group in patients carrying the rare variant allele while two other studies reported no significant association [60,61].

Neurotransmitter genes and fatigue and energy

An earlier study [63] has revealed an association between catechol-O-methyltransferase (*COMT*) gene and the risk for having fatigue in breast cancer patients following breast surgery. Patients with homozygous (Met/Met) or heterozygous (Val/Met) for *COMT* allele variant (rs4680) had higher fatigue scores when compared with those carrying the wild type (Val/Val). Although there are many SNPs in the *COMT* that are worth investigating, this study provides a preliminary data supporting the potential role of genetic variation affecting neurotransmission in predicting fatigue among breast cancer patients.

To further explore the influence of neurotransmitter gene polymorphisms on fatigue and another important symptom (i.e. energy) among breast cancer patients, Eshragh et al. [53] conducted a more comprehensive study to examine some candidate genes involved in the metabolism of many anti-cancer drugs, neurotransmission and transport of molecules through cell membranes. It was observed that the presence of the following genotypes was associated with lower odds of having more fatigue: homozygous AA for *ADRB2* (rs1042718), heterozygous (G/A) or homozygous (A/A) for *BDNF* (rs6265), heterozygous (T/C) or homozygous (C/C) for *COMT* (rs9332377), heterozygous (C/T) or homozygous (T/T) for *CYP3A4* (rs4646437), heterozygous (T/C) or homozygous C/C for *GCH1* (rs3783642), homozygous (C/C) for *NOS1* (rs9658498), and heterozygous LA or homozygous LA for *5HTTLPR* (rs25531). On the other hand, the presence of the following genotypes was associated with higher odds of being classified in the high fatigue group: homozygous (C/C) for *GALR1* (rs949060), homozygous (T/T) for *NOS1* (rs2293052), *NPY1R HapA04* (rs9764, rs7687423, and homozygous (A/A) for *SLC6A2* (rs17841327). Similarly, for the energy level, the presence of the following genotypes was associated with lower odds of being classified in the lower energy group of patients: homozygous (T/T) for *NOS1* (rs471871), *SLC6A1 HapD01* (rs10514669, rs297138 and rs1062246), heterozygous (A/G) for *SLC6A2* (rs36027), and homozygous (A/A) for *SLC6A4* (rs2020942). On the other hand, the presence of the following genotypes was associated with higher odds of belonging to the lower energy class: heterozygous (T/C) or homozygous (C/C) for *SLC6A1* (rs2675163), homozygous (A/A) for *SLC6A3* (rs37022) and homozygous (G/G) for *TAC1* (rs2072100). In another previous study [58] a significant difference was observed in gene expression between breast cancer patients who had low and high fatigue levels. It is plausible that polymorphisms may affect the gene expression regulating the neurotransmitter system, inflammatory pathways and energy metabolism leading to increased susceptibility to fatigue and low energy levels.

The findings in the above study are very interesting because they have uncovered a significant number of neurotransmitter genes, a gene encoding for the drug metabolizing enzyme (*CYP3A4*) as well as genes regulating the transport of molecules across cell membrane that could serve as genetic markers of increased susceptibility to high fatigue and low energy in breast cancer patients after surgery. While polymorphisms in *COMT* and *SLC6A4* have been previously linked with fatigue [63,64], other SNPs and/or haplotypes in *ADRB2, BDNF, CYP3A4, GALR1, GCH1, NPY1R HapA04, SLC6A1, SLC6A2, SLC6A3, NOS1* and *TAC1* are being linked to fatigue or energy or both for the first time in breast cancer patients [53]. Of note is the presence of the three genes (*NOS1, SLC6A2* and *SLC6A4*) that were associated with both fatigue and energy, thus further strengthening the hypothesis that fatigue and energy level though commonly grouped together are distinct symptoms. Additional studies are needed to confirm the reproducibility of the role of these SNPs as potential genetic markers of increased susceptibility to fatigue and low energy in breast cancer patients as well as other cancer types.

Psychological Distress

Mood disturbances are common side effects related to breast cancer diagnosis and treatment and since they may sometimes persist for years after treatment [3], they significantly affect the QOL of breast cancer patients. Recent studies have suggested that inflammatory pathways are involved in a variety of depressive disorders [65-70].

A recent report suggested an association between depression and cytokines gene polymorphisms in breast cancer patients [71]. In particular, patients homozygous for *IL1B*-511 T/T had increased risk for depression both at baseline and after one year follow up. This observation is in agreement with two previous studies also conducted in patients with chronic diseases such as Alzheimer's disease [72] and schizophrenia [73], though a contrary report also exists with regards to the association between *IL1B*-511 C/T genetic polymorphism and risk of Alzheimer's disease [74].

The roles of pro-inflammatory cytokines genetic polymorphisms in developing breast cancer-associated depression was further provided by Bower et al. who established that breast cancer patients with heterozygous GG genotype of *IL6*-174 SNP experienced higher depressive symptoms when compared with those carrying the GC and CC genotypes [61]. Another similar study [75] reported that breast cancer patients who were homozygous for a rare allele variant of *TNF-α* (rs1799964) had lower odds of developing subsyndromal depression. The study also demonstrated that SNPs in Interferon Gamma Receptor 1 (*IFNGR1*, rs9376268) and *IL6* (rs2069840) were associated with the development of subsyndromal depressive symptoms. Nevertheless, in contrast to the findings by Kim et al. [71] which demonstrated a significant association between *IL1B* and depression, similar findings could not be confirmed by Saad et al. [75]. Furthermore, the associations between SNPs in cytokines and

depression appeared to vary depending on the cancer type; for instance, Duun et al. [76] reported an association between two *TNF-α* SNPs (rs2229074, rs1800629) and depression in patients with various types of cancer (breast, prostate, lung and brain) and their family care givers. On the contrary, similar association was not demonstrable in a cohort of breast cancer patients [71,75]. Owing to the complex nature of cancer related depression with multiple genetic factors implicated, additional larger multi-centre studies involving different ethnicities and targeting multiple SNPs may reveal the actual combined effects of the genes [71].

Recent data also suggest that an individual's genetics play an important role in the development of anxiety disorders [77-80]. Additionally, the link between the development of anxiety and inflammatory signalling pathways has also been established [69,81].

Consistent with the findings of Saad et al. on the association between *TNF-α* (rs1799964) and the development of subsyndromal depression [75], a corresponding decreased odds of higher anxiety class was also observed with the SNP (rs1799964) among breast cancer patients undergoing breast surgery [82]. On the other hand, this study also observed that *TNF-α* (rs3093662) was associated with higher odds of developing anxiety therefore suggesting that *TNF-α* SNPs may serve as important predictive marker of increased susceptibility to psychological distress among breast cancer patients.

Memory and Cognitive Function

Memory impairment is one of the main complaints by patients with breast cancer [83-85] and has been linked to inflammatory processes [86,87]. It was demonstrated that breast cancer patients harbouring the *IL6*-174 GG and TNF-308 GG genotypes had near significant worse memory complaints [61]. This study therefore suggests that genetic polymorphisms in inflammatory cytokines may contribute to memory impairment among breast cancer patients. However, further studies are required to establish the role of cytokine genes in behavioural changes at both initial stages of breast cancer diagnosis and along the course of treatment; since inflammatory cytokines may also be influenced by surgery, chemotherapy and radiotherapy.

It is well established that breast cancer survivors experience impaired cognitive function which is often associated with cancer treatment [88-90]. The effect of genetic variation on cognitive function of breast cancer survivors was earlier reported by Ahles et al. [91]. The study revealed that breast cancer and lymphoma patients (treated with chemotherapy) who carry at least one allele for apolipoprotein E ε4 (*APOE ε4*) gene were more likely to have deficits in cognitive function compared to those who do not harbour the allele. Although the sample size in this study was relatively small (breast cancer (n=51), lymphoma (n=29), Hodgkin's (n=10) and non-Hodgkin's lymphomas (n=19)) and included patients with lymphomas, it supports the hypothesis that genetic factors could predispose cancer patients to a diminished cognitive function. Subsequently, a more comprehensive study was carried out by Small et al. [92] to examine the impact of *COMT* polymorphisms on the cognitive function of breast cancer patients. They reported that patients treated with chemotherapy and carry the *COMT*-Met (Met/Met) genotype were more likely to have a better cognitive function compared to those carrying the Val/Met or Val/Val genotypes. These findings and those of Ahles et al. on *APOE ε4* [91] could potentially contribute in future personalized therapy of deficits in cognitive function that are associated with breast cancer chemotherapy.

Sleep Disturbance

Sleep disturbance is a common but often an unidentified complaint in patients with a variety of cancer diseases [93-95] and particularly among breast cancer women [27,96-98] which can adversely affect patients' QOL [99,100]. Recent studies have suggested an association between cytokine genes and sleep disturbance in oncology patients with several types of cancer (such as breast, prostate, lung or brain) and their family caregivers [62,101,102]. However, these findings could not be replicated in a later report which evaluated the association among breast cancer patients only [61]. In contrast, a subsequent similar study on breast cancer patients by Miaskowski et al. [103] demonstrated that *NFKB2* (rs1056890) carriers had decreased odds of being classified in the high sustained sleep disturbance class, while carriers of the *IL13* (rs1800925) SNP *IL1R2* HapA2 haplotype (rs11674595, rs7570441) had increased odds of having a high sustained sleep disturbance. The fact that no association could be established between *IL13* and sleep disturbance among oncology patients and their family care givers [102] warrants additional multi-centre studies to delineate the specific role of cytokines in predicting sleep disturbance among cancer patients including breast cancer.

Pain

Acute and chronic pains constitute a major complaint associated with breast cancer and its treatment [104-107]. A number of factors may be responsible for breast pain in breast cancer patients. Prior to surgery, breast pain may result from the release of pain mediators by the tumour or inflammatory changes in the breast tissue (following tissue biopsy) which is mainly mediated by pro-inflammatory cytokines [108-111]. On the other hand, post-operative pain in breast cancer patients may arise from or be associated with nerve injury that may occur during surgery or following radiotherapy [104,112,113]. Persistent pain is associated with significant impairment of quality of life [28,114-116].

Cytokine genes and pain

McCann et al. [117] documented for the first time that cytokine genes are associated with the development of breast pain prior to surgery (preoperatively). They reported that carriers of *IL1R1* (rs2110726) had reduced odds of having breast pain before surgery while carriers of *IL13* (rs1295686) had higher

odds of having breast pain prior to surgery. A similar study conducted among breast cancer women following surgery (postoperatively) [118] demonstrated that carriers of *IL1R2* (rs11674595) had higher odds of developing a severe persistent breast pain while those harbouring the *IL10* haplotype A8 (made up of seven SNPs i.e. rs3024505, rs3024498, rs3024496, rs1878672, rs1518111, rs1518110, rs3024491) had decreased odds of having severe persistent breast pain. Nevertheless, the role of *IL10* haplotype A8 requires further validation since contradictory findings have been reported in terms of its functional significance in other disease conditions [119-122].

Potassium channel genes and pain

The role of potassium channel genes in predicting the occurrence of both pre- and postoperative breast pain has recently been investigated. In the preoperative pain assessment, it was reported that four potassium channel genes (*KCNS1* (rs4499491), *KCNJ3* (rs7574878), *KCNJ6* (rs2835914, rs8129919, rs2836050) and *KCNK9* (rs3780039, rs11166921)) were associated with the occurrence of breast pain prior to breast cancer surgery [123], thus suggesting that variation in potassium channel genes potentially contribute to inter-individual variability in developing preoperative breast pain. To further explore the contribution of genetic variation in potassium channel genes on the development of persistent breast pain, Langford et al. [124] also examined the association between potassium channel genes and the development of persistent breast pain in a similar cohort of women with breast cancer following surgery. They reported that *KCNA1* (rs4766311), *KCND2* (rs1072198), *KCNJ3* (rs12995382 and rs17641121), *KCNJ6* (rs858003) and *KCNK9* (rs2542424 and rs2545457) were associated with persistent breast pain postoperatively. Overall, the findings in breast cancer patients both before and after surgery strongly suggest that potassium channel genes may serve as potential therapeutic targets in the management of persistent pain associated with breast cancer. However, further investigations are warranted in larger samples which should also include functional studies involving the target genes.

Neurotransmitter genes and pain

At the time of this review, only a single study [63] reported on the influence of neurotransmitter gene polymorphisms on pain in breast cancer patients where patients harbouring the Met/Met or Val/Met genotypes for *COMT* (rs4680) were more likely to experience greater sensitivity to pain as compared to those carrying the Val/Val genotype. Additional studies are suggested to explore the roles of as many SNPs as possible in the *COMT* gene as predictors of higher sensitivity to pain in breast cancer patients and other cancer types.

The influence of genetic variation on various symptoms is summarized in Table 1.

Table 1. *Summary of SNPs and the affected symptoms.*

Gene/allele/SNP	Symptoms assessed	Major findings	References
IL1B C>T (rs16944)	Fatigue	Increased odds of belonging to non-fatigued group among T/T or C/T carriers	[59]
IL6 G>C (rs1800795)	Fatigue	Increased odds of belonging to the fatigued group among GG or C/C carriers	
TNF G>A (rs1800629)	Fatigue	G/G carriers had higher fatigue scores	[61]
IL6 G>C (rs1800795)	Fatigue	Higher fatigue scores in G/G carriers	
IL1B G>A (rs16944)	Fatigue	Increased odds of being classified in the higher fatigue group among A/A carriers	[54]
IL10 T>C (rs3024496)	Fatigue	Decreased odds of being classified in the higher fatigue group among C/C carriers	
IL1R1 C>T (rs2110726)	Energy levels	Decreased odds of being classified in the lower energy class among C/T or T/T carriers	
COMT G>A (rs4680)	Fatigue	higher fatigue scores in Met/Met or Val/Met carriers	[63]
ADRB2 C>A (rs1042718)	Fatigue	Decreased odds of belonging to higher fatigue class in A/A carriers	[53]
BDNF G>A (rs6265)	Fatigue	Decreased odds of belonging to higher fatigue class in G/A or A/A carriers	
COMT T>C (rs9332377)	Fatigue	Decreased odds of belonging to higher fatigue class in T/C or C/C carriers	
CYP3A4 C>T (rs4646437)	Fatigue	Decreased odds of belonging to higher fatigue class in C/T or T/T carriers	
GCH1 T>C (rs3783642)	Fatigue	Decreased odds of belonging to higher fatigue class in T/C or C/C carriers	
NOS1 T>C (rs9658498)	Fatigue	Decreased odds of belonging to higher fatigue class C/C carriers	
5HTTLPR+rs25531	Fatigue	Decreased odds of belonging to higher fatigue class in heterozygous or homozygous LA carriers	

GALR1 G>C (rs949060)	Fatigue	Increased odds of belonging to higher fatigue class in C/C carriers	
NOS1 C>T (rs2293052)	Fatigue	Increased odds of belonging to higher fatigue class in T/T carriers	
NPY1R HapA04 (rs9764, rs7687423)	Fatigue	Increased odds of belonging to higher fatigue class	
SLC6A2 C>A (rs17841327)	Fatigue	Increased odds of belonging to higher fatigue class in A/A carriers	
NOS1 A>T (rs471871)	Energy levels	Decreased odds of being classified in the lower energy group among T/T carriers	
SLC6A1 HapD01 (rs10514669, rs297138 and rs1062246)	Energy levels	Decreased odds of being classified in the lower energy group	
SLC6A2 A>G (rs36027)	Energy levels	Decreased odds of being classified in the lower energy group among A/G carriers	
SLC6A4 G>A (rs2020942)	Energy levels	Decreased odds of being classified in the lower energy group among A/G carriers	
SLC6A1 T>C (rs2675163)	Energy levels	Increased odds of being classified in the lower energy group among T/C or C/C carriers	
SLC6A3 T>A (rs37022)	Energy levels	Increased odds of being classified in the lower energy group among A/A carriers	
TAC1 A>G (rs2072100)	Energy levels	Increased odds of being classified in the lower energy group among G/G carriers	
IL1B-511 C>T (rs16944)	Depression	Increased odds of having depression in T/T carriers	[71]
IL6-174 G>C (rs1800795)	Depression	Higher depressive symptoms in G/G carriers	[61]
TNF-α T>C (rs1799964)	Depression	Decreased odds of belonging to subsyndromal depression in C/C carriers	[75]
IFNGR1 G>A (rs9376268)	Depression	Increased odds of belonging to subsyndromal depression in G/A or A/A carriers	
IL6 C>G (rs2069840)	Depression	Increased odds of belonging to subsyndromal depression in G/G carriers	
TNF-α T>C (rs1799964)	Anxiety	Decreased odds of belonging to high anxiety class in C/C carriers	[82]
TNF-α A>G (rs3093662)	Anxiety	Increased odds of belonging to high anxiety class in A/G or G/G carriers	
NFKB2 C>T (rs1056890)	Sleep disturbance	Decreased odds of being classified in the high sustained sleep disturbance class among C/T or T/T carriers	[103]
IL13 C>T (rs1800925)	Sleep disturbance	Increased odds of being classified in the high sustained sleep disturbance class among C/T or T/T carriers	
IL1R2 HapA2 (rs11674595, rs7570441)	Sleep disturbance	Increased odds of being classified in the high sustained sleep disturbance class	
IL1R1 C>T (rs2110726)	Pain	Decreased odds of reporting breast pain in C/T and T/T carriers	[117]
IL13 G>A (rs1295686)	Pain	Increased odds of reporting breast pain in G/A or A/A carriers	
IL1R2 T>C (rs11674595)	Pain	Increased odds of being classified in the severe pain class in C/C carriers	[118]
IL10 haplotype A8	Pain	Decreased odds of being classified in the severe pain class in C/C carriers	
KCNS1 C>A (rs4499491)	Pain	Increased odds of reporting preoperative breast pain in A/A carriers	[123]
KCNJ3 T>G (rs7574878)	Pain	Decreased odds of reporting preoperative breast pain in T/G or G/G carriers	
KCNJ6 G>C (rs2835914)	Pain	Decreased odds of reporting preoperative breast pain in G/C or C/C carriers	
KCNJ6 G>A (rs8129919)	Pain	Increased odds of reporting preoperative breast pain in patient carrying each dose of the rare A allele	
KCNJ6 C>T (rs2836050)	Pain	Increased odds of reporting preoperative breast pain in T/T carriers	
KCNK9 T>G (rs3780039)	Pain	Increased odds of reporting preoperative breast pain in T/G or G/G carriers	
KCNK9 C>A (rs11166921)	Pain	Increased odds of reporting preoperative breast pain in A/A carriers	

KCNA1 C>T (rs4766311)	Pain	Decreased odds of belonging to the mild pain class in patients carrying each dose of T allele	[124]
KCND2 A>G (rs1072198)	Pain	Increased odds of belonging to the mild pain class in A/G or G/G carriers	
KCNJ3 T>C (rs12995382)	Pain	Decreased odds of belonging to the mild pain class in T/C or C/C carriers	
KCNJ3 T>C (rs17641121)	Pain	Increased odds of belonging to the mild pain class in C/C carriers	
KCNJ6 C>T (rs858003)	Pain	Increased odds of belonging to the mild pain class in T/T carriers	
KCNK9 A>G (rs2542424)	Pain	Decreased odds of belonging to the mild pain class in A/G or G/G carriers	
KCNK9 T>C (rs2545457)	Pain	Increased odds of belonging to the mild pain class in T/C or C/C carriers	
COMT G>A (rs4680)	Pain	Increased odds of pain sensitivity in Met/Met or Val/Met carriers	[63]
APOE ε4	Cognitive function	Increased likelihood of having impaired cognitive function in carriers of at least one *APOE ε4* allele	[91]
COMT G>A (rs4680)	Cognitive function	Increased likelihood of having better cognitive function in carriers of Met/Met genotype	[92]

Genetic Polymorphisms and Symptom Cluster

It could be deduced from the above discussion that genetic variations in the cytokine genes influence a number of commonly encountered symptoms in breast cancer patients which include fatigue, psychological distress (depression and anxiety), pain, sleep disturbance and memory impairment all of which are associated with inflammatory cytokines. In the era of personalized medicine, identification of molecular markers that can predict patients at risk of developing these debilitating complaints in the form of symptom cluster is important. Recent evidences support the fact that fatigue, depression, pain and sleep disturbances share some common pathways that make them a symptom cluster [7,125,126].

The findings from two recent studies which evaluated the influence of genetic variation on symptoms cluster in oncology patients and their family care givers [127]; specifically among breast cancer patients [128] have revealed promising results that could pave way for establishing the link between genetic markers and symptom cluster. In a later study [128], it was demonstrated that breast cancer patients who were homozygous for the rare allele (G/G) of *IL6* (rs2069845), heterozygous (G/A) or homozygous (A/A) for *IL13* (rs1295686) as well as heterozygous (C/T) or homozygous (T/T) for *TNF-α* (rs1800610) had higher odds of being categorized in the all high symptom class (i.e. those who reported high levels of fatigue, pain, depression and sleep disturbances).

Although the *IL6* (rs2069845) is reported to be associated with the symptom cluster for the first time in this study, other SNPs in the *IL6* have been previously reported to be associated with fatigue [61] and depression [61,75]. For the *IL13* (rs1295686), contradictory results exist in a different cohort of oncology patients and their family caregivers [127] where no association was established with the symptom cluster. Notwithstanding, the *IL13* (rs1295686) was reported to be associated with breast pain before surgery [117]. For the *TNF-α* (rs1800610), no study has previously reported its association with any of these symptoms, although another SNP in the *TNF-α* (rs1800629) was shown to be associated with fatigue in breast cancer patients (61) and depression in oncology patients and their family caregivers [76]. The association of this SNP with depression was however not reproducible in breast cancer patients [71,75]. The inconsistency may warrant further investigations to define common molecular pathways underlining the symptom cluster of fatigue, pain, depression and sleep disturbance which in turn can be used for the development of targeted interventions for symptom cluster based on genetic markers.

Nevertheless, sine the majority of the studies were conducted in a homogenous breast cancer cohort at different clinical stages, it will be interesting to determine if these findings can be replicated in women diagnosed with breast cancer from various racial, ethnic and socio-economic status. It is also important to conduct larger multicentre studies that consider a control group (where applicable) of women without prior history of breast cancer so as to determine whether the SNPs are primarily specific to breast cancer or they also play a similar role in apparently healthy population.

Conclusions

The impact of genetic polymorphism on patient-reported symptoms that are associated with QOL impairment vary depending on the cancer types. Certain gene polymorphisms exert an opposing influence with respect to the risk of some breast cancer symptoms. For instance *COMT* (Met/Met) genotype was associated with better cognitive function in one study while in another study; it was associated with higher fatigue and pain scores in breast cancer patients. Consequently, when evaluating patients for personalized treatment in future, this variation may be important in ensuring maximum benefit for patients.

Although the vast majority of the SNPs reported in the reviewed literature are yet to be fully validated for integration in to clinical practice or clinical drug development, the SNPs in

the cytokines genes appear to be promising. Additional functional studies are therefore needed to establish whether the presence of polymorphisms is associated with correspondingly altered functions based on the different alleles. A thorough understanding of the underlying molecular mechanisms mediating the development of the various symptoms might help in detection of at-risk patients and designing of novel therapeutic interventions. When validated, the different genotypes could serve as genetic predictors of poor QOL and may also be useful in the development of targeted therapy and designing of non-pharmacologic interventions to ameliorate the debilitating impairment of QOL in breast cancer patients.

Acknowledgements

This work was supported by grant No. 1001/PPSP/853005 from Universiti Sains Malaysia (USM). The authors wish to acknowledge the Tertiary Education Trust Fund (TETFund) awarded to the first author.

Conflicts of Interest

The authors declare no conflicts of interest.

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