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ORIGINAL ARTICLE

Examining the effect of 5-HTTLPR on depressive symptoms in postmenopausal women 1 year after initial breast cancer treatment

Justine S. Wang[1] · Yvette P. Conley[1] · Susan M. Sereika[1] · Catherine M. Bender[1] · Poorwa Godbole[1] · Susan W. Wesmiller[1]

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Abstract

Background Depression following the diagnosis of breast cancer has been well documented, and occurs in as many as 40% of women. The serotonin transporter gene SLC6A4 and its functional polymorphism 5-HTTLPR have been extensively studied as factors in the development of depression. Many research studies have demonstrated conflicting results, and the contribution of 5-HTTLPR to depression is unclear.

Purpose The purpose of this study was to compare the relationship between depressive symptoms and serotonin transporter gene polymorphisms between women with early-stage breast cancer 1 year following initial diagnosis and surgery and matched controls.

Methods Participants ($N = 125$), included postmenopausal women following breast cancer surgery ($n = 80$) and age-and education-matched healthy controls ($n = 45$). The genetic elements of interest were the long (LA) and short (S) alleles of 5-HTTLPR, as well as the single nucleotide polymorphism rs25531 A > G within the L-allele (LG). DNA was extracted from either blood or saliva and analyzed for the SLC6A4 polymorphisms. The outcome measures for this longitudinal study included Beck Depression Inventory scores and physical function domain scores from the Medical Outcome Study Short Form 36. Results: Women with breast cancer demonstrated greater depressive symptomatology and decreased physical function compared to healthy controls. The LA/LA genotype was associated with increased depressive symptomatology in the overall sample and within the controls. The LA/LA genotype appeared with greater frequency in the experimental group, but the relationship with increased depressive symptoms was not observed. Physical function was a significant ($p < 0.00$) predictor of depressive symptoms in both groups at 12 months.

Conclusion The relationship between 5-HTTLPR and depressive symptomatology in breast cancer patients remains unclear. A potential clinical application includes monitoring physical function and addressing increased depressive symptoms as physical function declines.

Keywords Breast cancer · 5-HTTLPR · Depressive symptoms · Physical function

Background

Depressive symptoms in breast cancer

Breast cancer is the most common cancer occurring in women [1]. In 2017, 252,710 women will be diagnosed with breast cancer in the USA. Women with breast cancer also comprise the largest group of cancer survivors, with over 3.1 million living in the USA today [1]. Depression following the diagnosis of breast cancer has been well documented, and occurs in as many as 40% of women [2]. Of those experiencing depressive episodes, it is estimated that up to 10–25% of this group experiences a major depressive episode—a rate exceeding that found in the general female population by 50% [3]. Women seem to be most vulnerable for depression early after the breast cancer diagnosis, with an incidence rate of 33% [4]. The rate then decreases to 25% in the 2–4 years following diagnosis and falls to 15% the fifth year after diagnosis [2, 3]. By the time women have completed therapy and are in remission, they report similar levels of depression found in

✉ Susan W. Wesmiller
swe100@pitt.edu

[1] School of Nursing, University of Pittsburgh, 440 Victoria Building, Pittsburgh, PA 15261, USA

the general female population [5, 6]. However, recurrence of the disease sharply increases the risk of new-onset or recurrent depression. [5].

Several factors increase the likelihood of women experiencing depressive symptoms after receiving a diagnosis of breast cancer, including a previous diagnosis of depression, younger age at diagnosis, greater disease severity, decreased physical function, poorer perception of body image, and greater number of disease- and treatment-related symptoms [2–5, 7]. In a study by Gonda et al., researchers found that there was a significant association between the 5-HTTLPR genotype and financial difficulties in the development of depressive symptoms [8]. In addition to these well-documented risk factors, there is evidence that genetic predispositions are important in the etiology of depressive symptoms precipitated by major life events (such as breast cancer diagnoses) acting as environmental risk factors [9, 10].

Physical function in breast cancer survivors

Deterioration in physical functioning, an important component of quality of life, has been well documented in women following treatment for breast cancer [7, 11]. Decreased physical function was noted in a recent study from the Women's Health Initiative [12], which found that physical function scores were significantly lower 1-year post-diagnosis when compared to pre-cancer scores. These data from women with breast cancer are not consistent with reports of healthy postmenopausal women who have stable physical function [12].

Depressive symptoms are related to poorer physical function in individuals with multiple chronic diseases, [13–15] including breast cancer [16–19]. In a recent study, severe depressive symptoms and physical disabilities were shown to increase the risk of suicidal ideation in breast cancer patients 1 week following breast cancer surgery [20]. Depressive symptoms and poorer physical function are predictors of poorer adherence to endocrine therapy in women with breast cancer [21] and may be related to reduced survival [22].

Physiologic mechanisms

Serotonin (5-HT) is a monoamine neurotransmitter that is considered to play a key role in depression [6]. The serotonin transporter gene *SLC6A4* located on chromosome 17q11.1-17q12 regulates the duration and intensity of 5-HT action on its target receptors through reuptake, which has made it the focus of many studies exploring the genetic contribution to depression [7–9, 23]. The area that has received the most attention is a 44 base-pair insertion/deletion functional polymorphism in the promoter region of *SLC6A4* known as the serotonin-transporter-linked polymorphic region (5-HTTLPR). Many antidepressant medications act directly on the serotonin transporter, which makes the 5-HTTLPR polymorphisms a logical target for research in current psychiatric genetics [24, 25]. However, the results of previous research have demonstrated an unclear and often confusing relationship between 5-HTTLPR and depression [26]. Caspi et al. found that individuals with decreased serotonin transporter expression are more susceptible to depressive symptomology after experiencing a stressful life event [27]. Studies have shown that the correlation between the serotonin transporter gene and depressive symptomology is maintained in adults with a history of childhood abuse [28] and adults who have been exposed to natural disasters [29]. A recent study found small, but not significant associations with depressive symptoms and genes of the serotonin pathway (including the serotonin transport gene) in obese patients [30]. Rao et al. determined that two missense mutations in the *SLC6A4* gene, L550 V and K605 N, could increase the genetic risk of developing major depressive disorder and suicide attempts in certain populations [23]. Furthermore, this study found that the variant rs6354 of the *SLC6A4* gene might also be linked to major depressive disorder and increased suicide attempts [23].

In humans, there are two common, functional versions of the 5-HTTLPR: a "long" (L) allele and a "short" (S) allele, based on the presence or absence of the insertion [10, 25]. Results of in vitro studies have shown that the LL genotype is associated with higher serotonin mRNA transcription expression and increased serotonin reuptake [31]. Individuals who have the S-allele have decreased transcriptional efficiency, resulting in decreased serotonin transporter expression and serotonin uptake [10]. In addition, *SLC6A4* also displays a single nucleotide polymorphism (SNP, rs25531 A > G) in the same region that is found exclusively with the L-allele [10, 11]. This G for A substitution results in the L_G-allele functioning more like the S-allele than the original L_A-allele in terms of transcription efficacy [32].

An early clinical study found that depression in the presence of adverse life events was significantly increased in patients who carried at least one S-allele [27]. However, subsequent studies have produced inconsistent and sometimes even controversial results [32, 33]. For example, a study of women in the early postoperative period after breast cancer surgery found that those with the L/L genotype were at greater risk for depressive symptoms and a sense of hopelessness [10]. Because allelic variations with both the L-allele and the S-allele have been implicated in increased depressive symptoms, some researchers believe that significant perturbation of serotonin transport activity in either direction increases the patient's risk for depressive symptoms [15].

Several genetic studies have focused specifically on women with breast cancer and depressive symptoms but, as in the general depression studies, these results are also inconsistent. Grassi and colleagues did not find differences in depression between the L/L and S/S groups in their study of 145 women with breast cancer. Similar results were also reported by Kim

and colleagues, who studied 186 Korean women with breast cancer [34].

However, none of the studies that focused on women with breast cancer evaluated the potentially moderating effect of the rs25531 A > G polymorphism on depressive symptoms. In addition, no other study has focused on the relationship of depressive symptoms and 5-HTTLPR in women with early breast cancer as compared to healthy controls, and no studies have evaluated the influence of functional ability on these relationships. The purpose of this study was to compare the relationship between depressive symptoms and serotonin transporter gene polymorphisms between women with early-stage breast cancer1 year following initial diagnosis and surgery and matched controls. A secondary purpose was to determine the potential moderating effect of physical function on the relationship between depressive symptoms and the promoter region functional polymorphism HTTLPR controlling for breast cancer status.

Methods

Study design

This study used longitudinal phenotype data from a prospective cohort study examining the long-term effects of adjuvant therapy on cognitive function in postmenopausal women with early-stage breast cancer (Stage I, II, IIIA) [21]. In this study, depressive symptoms and physical function were measured every 6 months, with the baseline assessment completed after the breast cancer diagnosis and primary surgery but before the initiation of systemic adjuvant therapy (chemotherapy and/or anastrozole therapy) for breast cancer participants and at comparable time points in a matched healthy control group. Data were collected at baseline, 6 months, and 12 months post-baseline. This study added data collection for genetic variability in *SLC6A4* using DNA collected as part of an ancillary study.

Study participants

Data from 125 participants who provided samples for genomic evaluation were included in this analysis. The postmenopausal women ($n = 80$) with early-stage breast cancer were recruited from the Comprehensive Breast Care Program of the University of Pittsburgh Cancer Institute and the University of Pittsburgh Medical Center Cancer Centers. Control group participants ($n = 45$) were healthy postmenopausal women, who were matched with breast cancer participants on age and years of education. Women in the control group were recruited from the University Center for Social and Urban Research via random digit dialing, responses to a local ad, or referrals of friends by breast cancer participants.

All participants were between the ages of 18 and 75 years, could speak and read English, and had a minimum of 8 years of education. Exclusion criteria included hospitalization for psychiatric illness within 2 years of study enrollment or a history of neurologic disease or cancer. Noteworthy for this study, participants with premorbid depression were not eliminated from analyses. The study was approved by the University of Pittsburgh Institutional Review Board and informed consent was obtained from all study participants.

Phenotype data collection

Demographic information, including age and years of education, was collected by self-report; information related to disease characteristics was collected from the medical record. Depressive symptoms, the main dependent variable of interest for this study, was measured using the second edition of the Beck Depression Inventory (BDI-II). The BDI-II is a 21-item self-report measure in which participants rate depressive symptoms and attitudes on a scale from 0 (absence of symptom) to 3 (persistent expression of symptom in the past 2 weeks). The overall score is a measure of the severity of depressive symptoms, with a score of 14–28 indicating mild to moderate depression and a score of 29–63 indicating severe depression [24, 26]. The BDI-II has been found to have high internal consistency ranging from $\alpha = 0.88$ to $\alpha = 0.94$ [24].

Physical function was measured, using the Medical Outcome Study Short Form 36 (MOS SF-36) Health Survey. This questionnaire contains 36 items that can be grouped into eight health-related aspects of the patient's life [35, 36]. Scores on the subscales are standardized, ranging from 0 to 100, with higher scores indicating better function. Participants were directed to respond based on activity level for the past week. Internal consistency of the subscales ranged from 0.62 to 0.96; test-retest reliability ranged from 0.60 to 0.81 with a median of 0.76 after 2 weeks in patients with diabetes [35, 36]. The MOS SF-36 has been shown to be sensitive to changes in functional ability associated with cancer and cancer treatment [35, 36].

Genetic data collection

DNA was extracted from either blood or saliva using standard techniques and then analyzed for the *SLC6A4* polymorphisms. The two polymorphisms of interest, HTTLPR and rs25531, were genotyped using a polymerase chain reaction (PCR) restriction fragment length polymorphism assay as follows: initial denaturation 94 °C for 4 min, 35 cycles consisting of 94 °C for 30 s, 69 °C for 1 min and 30 s, 72 °C for 1 min, and final extension step on 72 °C for 10 min. The PCR products were then analyzed for size in 7% polyacrylamide gels stained with ethidium bromide to genotype HTTLPR. To genotype rs25531, the PCR products were digested with 3 U of MspI (Fermentas, Canada) according to manufacturer's

recommendations and resolved in 7% polyacrylamide gels. All genotypes were double called by individuals blinded to the phenotype data, and discrepancies were addressed by evaluating the raw data or recollecting the genotype data.

Statistical analysis

Appropriate descriptive statistics, including frequencies and percentages for categorical variables and means and standard deviations for continuous type variables, were used to characterize the total sample and by key grouping variables. Allele frequencies were calculated for all 125 participants. Genotypes were grouped based on predicted serotonin activity, with those participants who carried two L_A alleles (high serotonin activity) compared to all other combinations. Contingency table analysis with odds ratios (OR) and 95% confidence intervals (CI) were computed to summarize the association between genotypes and breast cancer status (breast cancer vs. healthy control). Linear mixed modeling was used to determine within-group changes across time points and to determine possible relationships with the key grouping variables of breast cancer status and predicted serotonin activity based on genotype (L_A/L_A vs. All other) on depressive symptoms and physical function. Linear mixed modeling was also used to consider physical function as a possible moderator. All data analyses were performed using IBM® SPSS® Statistics (Version 24, IBM Corp., Armonk, NY). The level of statistical significance was set at .05 for two-sided hypothesis testing.

Results

A summary of baseline characteristics for all participants is presented in Table 1. The sample consisted of 125 women, 80 (64.0%) of whom had early-stage breast cancer and 45 (36.0%) of whom were healthy controls. The mean age for all women in the study was 59.29 years (SD = 6.20). Among the women with breast cancer, the majority (67.9%) were diagnosed with Stage I disease.

We first compared depressive symptoms and physical function between the women with breast cancer and the healthy controls over time, independent of genotype grouping. In these analyses, there was a significant group (breast cancer versus healthy controls) by time interaction for depressive symptom ($p = 0.038$). Specifically, there was not a significant difference in depressive symptoms at baseline between the two groups ($p = 0.707$); however, there were significant differences at 6 months ($p = 0.041$) and 12 months ($p = 0.026$), with women with breast cancer reporting more depressive symptoms at these time points. Healthy control women demonstrated a significant decrease in depressive symptoms from baseline to 12 months (mean change = − 1.313, SE = 0.524; $p = 0.016$), but not at 6 months (mean change = 0.466, SE = 0.513; $p = 0.367$). In contrast, breast cancer survivors showed a significant increase in depressive symptoms from baseline to 6 months of adjuvant therapy (mean change = 1.20, SE = 0.524; $p = 0.024$), but not at 12 months (mean change = 0.573, SE = 0.639; $p = 0.373$). For physical function, there was also a significant group by time interaction ($p = 0.040$). At baseline, women with breast cancer had significantly poorer physical function compared to the healthy controls ($p = 0.005$), and that difference persisted significantly across time ($p < 0.001$ at 6 months, $p < 0.001$ at 12 months). Women with breast cancer showed significant declines in physical function at 6 months (mean change = − 6.496, SE = 2.069; $p = 0.002$) and 12 months (mean change = − 6.558, SE = 2.069; $p = 0.003$) relative to baseline, while no significant changes were observed for healthy controls over the 12-month period ($p \geq .05$).The genotype frequencies for the HTTLPR polymorphism are presented in Table 2. Although women with breast cancer had a slightly higher frequency ($n = 27$, 33.8%) of the L_A/L_A genotype when compared to the healthy controls ($n = 9$, 20.0%), this difference was not statistically significant ($p = 0.103$; OR = 2.04, 95%CI = [0.86, 4.84]). No significant main effects for the L_A/L_A genotype (no, yes) and time (baseline, 6 months, 12 months) or their two-way interactions were found for depressive symptoms ($p \geq 0.05$). Only small differences were found at baseline, where the L_A/L_A genotype was associated with higher BDI-II scores for the overall sample (mean difference = 2.265, SE = 1.0890; $p = 0.039$), and a slight increase from baseline to 6 months for the not LALA group (mean change = 1.040, SE = 0.458; $p = 0.024$). When we explored the relationship between L_A/L_A genotype and depressive

Table 1 Participant characteristics at baseline

Characteristic	Women with breast cancer ($n = 80$)	Healthy controls ($n = 45$)	Total ($n = 125$)	p value
Age (years)	59.8 ± 5.8	58.5 ± 6.9	59.3 ± 6.2	0.270
Education (years)	15.3 ± 2.9	15.1 ± 3.4	15.1 ± 3.2	0.559
Depressive symptoms (BDI-II score)	5.4 ± 5.5	5.1 ± 5.8	5.3 ± 5.6	0.424
Physical function (SF36 physical function domain score)	75.6 ± 19.4	86.3 ± 18.0	79.9 ± 19.5	0.004

Table 2 5-HTTLPR allele distribution in the study sample

HTLPPR alleles	Women with breast cancer ($n = 80$)	Healthy controls ($n = 45$)	Total sample ($n = 125$)
S/S	17 (21.3)	8 (17.8)	25 (20.0)
S/L_G	3 (3.8)	3 (6.7)	6 (4.8)
S/L_A	25 (31.3)	20 (44.4)	45 (36.0)
L_A/L_G	8 (10.0)	5 (11.1)	13 (10.4)
L_A/L_A	27 (33.8)	9 (20.0)	36 (28.8)
Serotonin activity: high vs. low			
L_A/L_A	27 (33.8)	9 (20.0)	36 (28.8)
All other groups	53 (66.3)	36 (80.0)	89 (71.2)

symptoms exclusively in the women with breast cancer, no significant main or interaction effects were observed and the difference between L_A/L_A genotype groups was no longer significant at baseline, yet the increase in depressive symptoms from baseline to 6 months in the not LALA group remained (mean difference = − 1.962, SE = 0.634; p = 0.002). When focusing in the healthy controls, only an overall main effect for the L_A/L_A genotype was found (F = 5.06, p = 0.030). In general, women with the L_A/L_A genotype reported higher depressive symptoms than those without the L_A/L_A genotype (mean difference = 3.661, SE = 1.628); specifically, a significant difference was found at 12 months ($p = 0.025$) and trends at baseline ($p = 0.058$) and 6 months ($p = 0.052$) (see Table 3).

Regarding physical function based on the SF36 physical function domain score, only significant time effects were found (F = 6.04, $p = 0.003$), where significant decreases from baseline were observed at 6 months (mean change = − 4.723, SE = 1.662; $p = 0.005$) and 12 months (mean change = − 5.3502, SE = 1.714; $p = 0.002$). Women who inherited the L_A/L_A genotype were not significantly different in level of physical function when compared to women with all other genotypes (with at least one S or G allele) in general (F = 2.13, $p = 0.147$) or over time ($F = 0.44$, $p = 0.645$). Within the healthy control group, no significant main effects for L_A/L_A genotype ($F = 1.85$, $p = 0.203$) and time ($F = 0.98$, $p = 0.401$) or L_A/L_A genotype by time interactions ($F = 1.06$, 0.375) were observed; however, significant time effects were found in women with breast cancer ($F = 6.48$, $p = 0.002$), with significant declines from baseline observed at 6 months ($p = 0.002$) and 12 months ($p = 0.004$).

At baseline, physical function was a significant predictor of depressive symptoms in the total sample ($b = -0.063$, SE = 0.025; $p = 0.012$) in healthy women ($b = -0.120$, SE = 0.043; $p = 0.008$), but not the breast cancer group (b = − 0.036, SE = 0.032; $p = 0.266$). At 12 months, physical function was a significant predictor for depressive symptoms in the total sample ($b = -0.088$, SE = 0.020; $p < 0.001$) and in both groups (healthy controls: b = − 0.091, SE = 0.026; $p = 0.001$; breast cancer: $b = -0.081$, SE = 0.030; $p = 0.009$). When we examined the influence of time on the serotonin transport gene and physical function (SF36) as predictors for depressive symptoms using a linear mixed modeling approach, we did not find a significant interaction in the breast cancer group at 1 year.

Table 3 Physical function and depressive symptoms by genotype stratified by breast cancer status at baseline, 6 and 12 months

Outcome	Breast cancer survivors ($n = 80$) Means ± SE			Healthy controls ($n = 45$) Means ± SE		
	L_A/L_A	All others	p value	L_A/L_A	All others	p value
Depressive symptoms baseline	6.44 ± 1.12	4.92 ± 0.80	0.270	8.33 ± 1.87	4.25 ± 0.94	0.058
Depressive symptoms 6 months	6.15 ± 1.12	6.89 ± 0.80	0.591	7.56 ± 1.65	3.89 ± 0.81	0.052
Depressive symptoms 12 months	6.27 ± 1.14	5.90 ± 0.81	0.790	6.40 ± 1.25	3.17 ± 0.62	*0.025*
Physical function baseline	76.30 ± 4.25	75.31 ± 3.03	0.851	77.78 ± 7.43	88.71 ± 3.10	0.194
Physical function 6 months	67.33 ± 4.29	70.05 ± 3.04	0.606	83.14 ± 8.07	87.91 ± 3.11	0.588
Physical function 12 months	68.90 ± 4.38	69.16 ± 3.22	0.962	73.90 ± 8.38	87.75 ± 3.13	0.140

Value in italics is significant at $p < 0.05$

SE standard error

Discussion

The primary aim of this project was to compare the relationship between depressive symptoms and serotonin transporter gene polymorphisms in postmenopausal women with early-stage breast cancer following surgery and initial diagnosis and matched healthy controls from baseline (pre-adjuvant therapy) and through 1 year post-baseline. We also sought to investigate the relationship between the serotonin transporter gene, depressive symptoms, and physical function, and how that relationship differed between women with breast cancer in the first year after surgery and healthy women.

By incorporating matched controls into this observational study, we were able to detect differences in depressive symptoms and genotype frequencies between the healthy and breast cancer groups. Within the healthy control group, we found that women with the L_A/L_A genotype had significantly higher scores on the BDI-II and increased depressive symptomology than women with the other genotypes. At baseline, the difference in depressive symptoms for the healthy control group between the L_A/L_A and other genotypes was trending significant ($p = 0.058$), but at 6 and 12 months, the difference was significant ($p = 0.038$ and $p = 0.021$). However, within the breast cancer group, we did not find a significant difference in depressive symptoms between women with the L_A/L_A genotype and women with all other genotypes. Of interest is the fact that the L_A/L_A genotype appeared with greater frequency in women with breast cancer.

To better understand this finding, we found evidence that demonstrated an association between serotonin and breast cancer. Studies have shown a positive correlation between plasma serotonin levels and progression of breast cancer, with significantly higher serotonin levels in patients with advanced disease than in patients with localized disease [37]. Furthermore, in the human breast cancer cell line MCF-7, which fully expresses the 5-HT2A receptor subtype, serotonin promotes cancer cell growth [38]. This may help to explain why women with breast cancer exhibited a higher frequency of the LA/LA genotype, but did not display the same correlation between the LA/LA variant and increased depressive symptoms shown in the healthy control group.

Our data regarding the change in physical function over time was consistent with previous research that showed reduced physical function1 year after cancer diagnosis compared to function before the disease [12]. In our study, there was a decrease in physical function across all genotypes in the breast cancer group in the first 6 months post-baseline that was not observed in the healthy controls. However, there was little change in physical function in the breast cancer group between 6 and 12 months following baseline.

Our data regarding depression and physical function also agreed with previous research demonstrating that depressive symptoms are related to poorer physical function including in individuals with breast cancer [16–19]. We observed that physical function was a significant predictor for depressive symptoms in both the breast cancer and control groups at 12 months. It was interesting to find that decreased physical function was not associated with depression in women recently diagnosed with breast cancer at baseline and 6 months post-baseline. Perhaps at the time of diagnosis, women are not focused on their physical function but, at a year after their diagnosis, they believe that they should be back to their "normal" selves, and their inability to be active becomes a source of depressive symptoms.

A limitation of this study was the relatively small sample size of 125 subjects, with 80 women with breast cancer and 45 controls. Future studies with increased sample sizes are necessary. In addition, because we did not remove participants with premorbid depressive symptoms, we were not able to focus solely on depressive symptoms within the context of breast cancer. However, matching breast cancer participants with healthy controls based on characteristics may have mitigated the effects of including premorbid depression.

Our results for the overall sample and for healthy women are consistent with the mixed results found in the literature. Although our data did not reveal a relationship between the serotonin transporter gene and depressive symptomology in women with breast cancer, we do show that physical functioning is an important correlate to depressive symptoms in the 1-year breast cancer survivor and warrants further study.

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Compliance with ethical standards

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

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