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Research Article

Brain-Derived Neurotrophic Factor (BDNF) VAL66MET Polymorphism and Symptoms in Breast Cancer Survivors

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Abstract

The relationship between occurrence and severity of cancer-related symptoms in breast cancer survivors following treatment and the presence or absence of the Brain-Derived Neurotrophic Factor (BDNF) Val66Met polymorphism was examined in this study. Individuals with the BDNF polymorphism were predicted to be more prone to persistent cancer-related symptoms following treatment. Breast cancer survivors post-treament (6 months to 6 years; majority: 3 years or more) completed an on-line version of the Therapy-Related Symptom Checklist (TRSC). A subpopulation of participants was genotyped to determine the presence or absence of the BDNF polymorphism. The results indicated BDNF genotype did not have a significant effect on total TRSC scores (OR = 0.27; 95% CI, [0.036, 1.98]; p = 0.196); the sample size was small (weak statistical power). But, the odds of having higher TRSC scores (OR=29.29; 95% CI [2.81, 305.10], p=.005) were found in subjects who had experienced chemotherapy treatment. Also, higher percent occurrence of 7 symptoms were reported by breast cancer survivors with absent BDNF SNP. It can be concluded that chemotherapy effects (symptom occurrence and severity) are long lasting; and (b) a larger study on BDNF is needed.

Keywords: BDNF: Brain-Derived Neurotrophic Factor; Breast Cancer Survivors; Symptoms; Therapy Related Symptom Checklist, (TRSC); VAL66MET Polymorphism

Advances in detection and treatment of breast cancer have increased the survival rate for women. Many of these survivors continue to suffer from physiological and psychological symptoms after completion of their treatment. Occurrence and severity of these symptoms may have serious consequences on survivors' quality of life (QOL) as well as their morbidity and mortality. Finding a common biological mechanism contributing to symptoms could provide a means of identifying at-risk patients for breast cancer and a basis for developing interventions to improve QOL.

Description of the Problem

Although no single explanation accounts for symptoms that persist after successful completion of cancer treatment, evidence from a number of sources suggests that chronic inflammation may be a common etiological factor for a number of symptoms. Chronic inflammation is a complex interaction between the central nervous system, the neuroendocrine system, and the immune system and all three are thought to play a major role [individually or in combination(s) with

each other] in many pathophysiological and psychological disorders.

Dysregulation of the Hypothalamic-pituitary-adrenal (HPA) axis has been linked with cancer-related fatigue (CRF) in breast cancer survivors and changes in the cortisol awakening response and diurnal cortisol slope have been associated with poor prognosis [1] and survival rates [2] in cancer patients. High levels of cortisol have been shown to reduce hippocampal volume in patients suffering from chronic depression and other behavioral disorders [3].

Decreased volumes of the hippocampus and prefrontal cortex (PFC) have been correlated with low levels of BDNF [4]. BDNF is the most abundant neurotrophin found in the brain and functions in promoting neurogenesis, neuronal protection, and neural plasticity. Most of the evidence connecting altered glucocorticoids and/or glucocorticoid receptors (GRs) to reduced BDNF levels in the brain comes from the use of mouse models of depression [5,6]. However, evidence of the involvement of reduced BDNF in human pathophysiology is growing. This model of neurotrophic depression is supported by evidence indicating that many antidepressants may function by increasing BDNF expression [7].

A single nucleotide polymorphism (SNP) in the BDNF gene has been described valine (Val) to methionine (Met) substitution at position 66 of the prodomain was identified. The SNP is found only in humans and has been shown to be related to reduced hippocampal volume and poor hippocampus-mediated memory performance. This SNP has been utilized as a tool to determine the contributions of BDNF to the symptoms of various psychiatric disorders including bipolar disorder [8]. In healthy individuals with the Met allele, Alexander et al. [9] reported an attenuated HPA axis response compared to subjects with the Val/Val genotype. In addition, Shalev et al. [10] reported a gender-dependent effect for the Met allele, with a reduced cortisol response in male subjects to a psychological stressor. From this evidence, individuals with the Met66 allele may be less able to adapt to a stressful life experience, making them more vulnerable to behavioral disorders [11].

Considering the role of BDNF in neuronal protection and neural plasticity, as well as the association of the BDNF Val66Met polymorphism with other behavioral disorders, cancer patients with BDNF polymorphism may be more vulnerable to the physiological and psychological stressors associated with cancer treatment, resulting in symptoms that persist beyond the cessation or completion of their treatment. Therefore, the primary purpose of this study was to examine whether a relationship exists between the occurrence and severity of ongoing symptoms, and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors who have completed their treatments for 6 months or longer.

Materials and Methods

This study used a cross-sectional design with two phases: Phase 1, an electronic survey to collect data on symptom occurrence and severity, daily activities, and quality of life; and Phase 2, the collection of saliva samples for genotyping. In Phase 1, a convenience sample of volunteer participants (n = 195) was recruited from the database of a statewide breast cancer coalition of a single Mid-Atlantic state. Since a maximum number of participants were desirable in Phase 1, the only exclusions from the original registry data base were (a) all males, (b) females under 18 years of age, and (c) breast cancer patients at less than six months post treatment completion. In Phase 2, an enriched subset of Phase 1 participants included the top and bottom scorers on the Therapy-Related Symptom Checklist (TRSC). The top scorers (n = 25) were defined as having TRSC scores ranging from 23-54; the bottom scorers (n = 26) consisted of scores ranging from 0-14.

The study was approved by the University of Kansas Cancer Center Protocol Review and Monitoring Committee (PRMC) and the KUMC Human Subjects Committee (HSC) before recruitment began. The url link to the electronic survey was sent via email to all potential participants listed in the coalition data base, inviting them to involve themselves in the research. The Phase 1 survey instruments included the TRSC and the Demographic and Health Form. The Demographic and Health Form included factors such as age, education, and ethnicity, in addition to type of treatments received and the length of time since completion of treatment. Additional questions related to any "current illnesses" and "medicines currently taken" in order to evaluate the possible impact of current illness or medication on the study variables.

Instruments

Therapy-Related Symptom Checklist:

The first instrument was the Therapy-Related Symptom Checklist (TRSC). The total score on the TRSC indicated the occurrence and severity of symptoms as reported by the participants in the study. In this study, the TRSC Cronbach's-α was 0.91. The TRSC has demonstrated good psychometric properties, including internal consistency reliability as well as concurrent, discriminant, and construct validity in a number of studies conducted in the U.S. and internationally [12-20].

The study participants indicated the occurrence of symptoms experienced by first checking whether a symptom was present and then rating the severity of that symptom on a 5-point scale, from 0 (none) to 4 (very severe) on the TRSC. Additional space was provided to write in and rate other symptoms that were not listed. The 25 listed items were summed (possible range 0 – 100), where higher scores on the TRSC indicated greater fre-

quency (occurrence) and severity of symptoms reported. The TRSC has fourteen symptom subscales developed for use by a principal components analysis [14,15].

Demographic and Health Form:

Subject characteristics and health information were obtained via electronic survey. Data collected for Phase 1 included the respondent's age and ethnicity and self-reported medical information (medications, co-morbid conditions, and treatment modality). Demographic information requested on the electronic survey was adapted from items used in previous studies [13,16-20], based on the selections available in the electronic format template as well as the most common responses given on the 2010 census by residents of the state from which the majority of respondents were drawn. Subject characteristics were chosen as variables for the study because they have been shown to impact symptoms in breast cancer patients in previous studies [21,22].

Procedures

In Phase 2, a purposive, subsample of the Phase 1 respondents was selected. Respondents willing to participate in Phase 2 were screened, from which 51 individuals were selected for two groups based on their TRSC scores. The first group consisted of 26 individuals who had the highest total TRSC scores (ranging from 23 to 54), indicating a high occurrence and severity of symptoms. The second group of 25 participants had the lowest total TRSC scores (0 to 14), indicating low or minimal occurrence and/or severity of symptoms. This procedure was followed in order to maximize variability. Saliva samples for BDNF genotyping were collected from the consenting participants at convenient times and locations in face-to-face meetings. Data reliability was safeguarded using a number of measures; including a single researcher who collected data with an approach that carefully maintained consistency from subject to subject. Personal or situational factors were controlled or described to avoid measurement error.

Saliva collection and BDNF Val66Met Genotyping. All saliva samples were collected using the Oragene self-collection device (DNA Genotek, Kanata, Canada), following the manufacturer's recommended instructions. The device contains a DNA stabilizing buffer to ensure sample integrity during storage and during shipping to the Institute of Genomic Medicine (IGM) at the University of Medicine and Dentistry of New Jersey (UMDNJ) for genotyping. Samples were labeled only with subject codes and remaining samples were destroyed on site.

Results

Sample Characteristics

The data analysis was completed using Statistical Package for the Social Sciences (SPSS). Table 1 shows the sample characteristics of Phase 1 and Phase 2 subjects. The majority of the 175 Phase 1 participants who provided demographic and health information were Caucasian (92.6%), although the population of the state in which most of the study participants resided was only 69% Caucasian, according to the U.S. census data (U.S. Census Bureau, 2010). Nearly all of the study participants had surgery as part of their treatment (92.1%). Almost three fourths of the subjects (72.6%) were over 50 years old. The respondents were highly educated; 58.9% held a bachelor's degree or higher, and an additional 17.1% had vocational training or an associate's degree. The majority of participants (73.1%) were three or more years post-treatment, and had no other conditions that they felt contributed to symptoms (60.9%). No selection biases were found regarding age, ethnicity, or education as profile of the Phase 2 purposive subsample of 51 participants did not vary from the Phase 1 sample, as shown in Table 1.

Thirty-six percent (9 out of 25) of the Phase 2 subjects with a low TRSC score had the Val66Met SNP, which is similar to the frequency (33%) expected in a healthy control sample. In contrast, only 7.7% (2 out of 26) of the subjects with high TRSC scores had the Val66Met SNP. In the overall Phase 2 sample, before adjusting for potential confounders, the presence of the BDNF Val66 Met SNP variant was significantly associated with low TRSC scores (odds ratio, OR = 0.148; 95% confidence interval (CI [0.028, 0.78]; Fisher's p = 0.019). This means the odds that a subject with the variant has a high TRSC score was 85% lower than the odds for a subject without the variant, ([0.148-1] x 100 = -85%). Although the lower TRSC scores were related to the presence of the BDNF Val66Met SNP or variant, and higher scores were related to the absence of the variant, the association between them was in the opposite direction of what was originally expected based on the literature. However, the effect size was small, and once adjustment was made for confounding variables, the results were no longer significant.
Table 2 shows the results of the logistic regression analysis that was conducted to investigate the association between the BDNF Val66Met SNP variant and TRSC scores. To control for potential confounders, a stepwise selection procedure was used to build a logistic regression model of high TRSC scores. The variable BDNF was forced to remain in the model during the selection procedure regardless of its degree of statistical significance. The potential independent variables investigated were age, education, type of treatment, and time since treatment completion. Ethnicity was not included since the sample contained only one nonwhite subject (1 out of 51). Only two variables were significantly associated with high TRSC scores: treatment type (defined as chemotherapy versus no chemotherapy) and education (defined as high level – bachelor's degree or higher, versus low level – less than a bachelor's degree).

Table 1. Sample Characteristics: Phase1 and Phase 2.

Variables	Categories	Phase 1 Subjects (n = 175) * (#, %)	Phase 2 Subjects High TRSC (n = 26; #,%)	Phase 2 Subjects Low TRSC (n = 25; #, %)
Age Groups				
	≤50 years	48 (27.4)	9 (36.4)	4 (16.0)
	51-60 years	68 (38.9)	10(38.5)	12 (48.0)
	≥61 years	59 (33.7)	7 (26.9)	9 (36.0)
Ethnic Background				
	White	162 (92.6)	25 (96.2)	25(100.0)
	African American/Black	6 (3.4)	1 (3.8)	0 (0.0)
	Asian	2 (1.1)	0 (0.0)	0 (0.0)
	Hispanic	3 (1.7)	0 (0.0)	0 (0.0)
	Other	2 (1.1)	0 (0.0)	0 (0.0)
Years of Education				
	High School	42 (24.0)	9 (34.6)	2 (8.0)
	Vocational/Associate's Degree	30 (17.1)	6 (23.1)	2 (8.0)
	Bachelor's Degree	49 (28.0)	7 (26.9)	11 (44.0)
	Master's/Graduate Degree	54 (30.9)	4 (15.4)	10 (40.0)
Treatment				
	Surgery Only	24 (13.7)	0 (0.0)	5 (20.0)
	Radiation Only	5 (2.9)	0 (0.0)	1 (4.0)
	Surgery/Chemotherapy	38 (21.7)	7 (26.9)	7 (28.0)
	Surgery/Radiation	27 (15.4)	1 (3.8)	8 (32.0)
	Surgery/Chemo/Radiation	81 (46.3)	18 (69.2)	4 (16.0)
Completed Treatment				
	≤ 2 years	42 (26.9)	6 (23.1)	6 (24.0)
	3-4 Years	59 (33.7)	10 (38.5)	8 (32.0)
	≥5 years	69 (39.4)	9 (34.6)	11 (44.0)
	Missing	0 (0.0)	1 (3.8)	0 (0.0)
Primary Caregiver				
	Self	71 (40.6)	10 (38.5)	12 (48.0)
	Spouse	36 (20.6)	9 (34.6)	4 (16.0)
	Other	4 (2.3)	0 (0.0)	1 (4.0)
	Self/Spouse	40 (22.9)	2 (7.7)	4 (16.0)
	Self/Other	9 (5.1)	2 (7.7)	3 (12.0)
	Spouse/Other	4 (2.3)	1 (3.8)	1 (4.0)
	Self/Spouse/Other	11 (6.3)	2 (7.7)	0 (0.0)

Children Living at Home				
	No Children	120 (69.4)	18 (69.2)	20(80.0)
	<6 years	6 (3.5)	1 (3.8)	2 (8.0)
	7-17 Years	20 (11.6)	1 (3.8)	2 (8.0)
	18-26 Years	15 (8.7)	2 (7.7)	1 (4.0)
	>26 years	4 (2.3)	1 (3.8)	0 (0.0)
	<6 and 7-17 years	3 (1.7)	2 (7.7)	0 (0.0)
	7-17 and 18-26 years	3 (1.7)	1 (3.8)	0 (0.0)
	7-17 and >26 years	1 (0.6)	0 (0.0)	0 (0.0)
	18-26 and >26 years	1 (0.6)	0 (0.0)	0 (0.0)
Other Conditions				
	If Yes, Please Specify	0 (0.0)	0 (0.0)	8 (32.0)
	Yes	68 (39.1)	6 (23.1)	0 (0.0)
	No	106 (60.9)	20 (76.9)	17(68.0)
Taking Medications (OTC,				
Herbals, Prescriptions, Etc.)	If Yes, Please Specify	0 (0.0)	21(80.8)	19 (76.0)
	Yes	147 (84.5)	2 (7.7)	1 (4.0)
	No	27 (15.5)	2 (7.7)	5 (20.0)

After adjusting for treatment type and education, the BDNF genotype did not have a significant effect on high TRSC scores (OR = 0.27; 95% CI, [0.036, 1.98]; p = 0.196). However, the odds for a subject with the variant and who had a high TRSC score was 73% lower than the odds for a subject without the variant after adjusting for confounders ([0.27-1] x 100 = -73%). This reduction in the odds was not statistically significant.

Table 2 also shows the sizes of the effects (odds ratios) of treatment type and education on the odds of having a high TRSC score. After adjusting for education and BDNF genotype, the odds of having a high TRSC score were significantly and substantially increased (almost by 3000%) if the type of treatment included chemotherapy (OR = 29.29, p = 0.005). Also, after adjusting for treatment type and BDNF genotype, the odds of having a high TRSC score were 86% lower in subjects with a high education level (OR = 0.14, p = 0 .027).

Table 2

Logistic Regression Model of High TRSC Scores

Variable	Odds Ratios	CI* Lower	CI* Upper	*p* Value
Val66Met SNP Present	0.27	0.036	1.981	0.196
Chemotherapy Included as Part of Treatment	29.29	2.812	305.096	0.005
High Level of Education (Bachelor's Degree and Higher)	0.14	0.025	0.798	0.027

Note. Hosmer-Lemeshow Goodness of Fit Test Chi-square = 2.4, $p = .662$ indicating that the model fit well.

*95% Confidence interval (CI).

Table 3

TRSC Scores: Present Versus Absent BDNF SNP and Percent Distributions on Symptom Severity* and on Symptom Occurrence

	Met/Met (BDNF SNP **absent**) (n = 39)							Val/Met or Val/Val **present** (n = 10)						
TRSC Symptoms	0	1	2	3	4	Mean	%	0	1	2	3	4	Mean	%
By subscales						Severity	Occur						Severity	Occur
1. Fatigue														
Feeling Sluggish	15.4	28.2	35.9	15.4	5.1	1.67	84.6	30.0	50.0	0.0	20.0	0.0	1.10	70.0
Depression	28.2	35.9	28.2	5.1	2.6	1.18	71.8	50.0	30.0	20.0	0.0	0.0	0.70	50.0
Difficulty Concentrating	12.8	43.6	30.8	10.3	2.6	1.46	87.2	30.0	40.0	30.0	0.0	0.0	1.00	70.0
Difficulty Sleeping	30.8	15.4	41.0	5.1	7.7	1.44	69.2	30.0	20.0	40.0	10.0	0.0	1.30	70.0
2. Eating														
Taste Change	44.4	19.4	22.2	8.3	5.6	1.11	55.6	77.8	0.0	11.1	11.1	0.0	0.56	22.2
Loss of Appetite	47.2	27.8	22.2	2.8	0.0	0.81	52.8	77.8	0.0	11.1	11.1	0.0	0.56	22.2
Weight Loss	77.2	19.4	8.3	0.0	0.0	0.36	27.8	66.7	33.3	0.0	0.0	0.0	0.33	33.3
Difficulty Swallowing	79.5	12.8	5.1	2.6	0.0	0.31	20.5	100.0	0.0	0.0	0.0	0.0	0.00	0.0
3. Oropharyngeal														
Sore Mouth	74.4	12.8	10.3	2.6	0.0	0.41	25.6	80.0	20.0	0.0	0.0	0.0	0.20	20.0
Sore Throat	87.2	10.3	0.0	2.6	0.0	0.18	12.8	80.0	20.0	0.0	0.0	0.0	0.20	20.0
Jaw Pain	87.2	10.3	2.6	0.0	0.0	0.15	12.8	90.0	0.0	10.0	0.0	0.0	0.20	10.0
4. Nausea														
Nausea	44.4	25.0	22.2	8.3	0.0	0.94	55.6	77.8	11.1	11.1	0.0	0.0	0.33	22.2
Vomiting	72.2	13.9	11.1	2.8	0.0	0.44	27.8	77.8	11.1	11.1	0.0	0.0	0.33	22.2
5. Fever														
Fever	79.5	17.9	2.6	0.0	0.0	0.23	20.5	100.0	0.0	0.0	0.0	0.0	0.00	0.0
Bruising	84.6	15.4	0.0	0.0	0.0	0.15	15.4	90.0	0.0	10.0	0.0	0.0	0.20	10.0
6. Respiratory														
Cough	82.1	17.9	0.0	0.0	0.0	0.18	17.9	90.0	10.0	0.0	0.0	0.0	0.10	10.0
Shortness of Breath	61.5	30.8	7.7	0.0	0.0	0.46	38.5	70.0	30.0	0.0	0.0	0.0	0.30	30.0
7. Pain	38.5	20.5	38.5	2.6	0.0	1.05	61.5	40.0	30.0	20.0	10.0	0.0	1.00	60.0
8. Numbness in														
Fingers and/or Toes	48.7	17.9	23.1	10.3	0.0	0.95	51.3	50.0	20.0	10.0	10.0	10.0	1.10	50.0
9. Bleeding	84.6	15.4	0.0	0.0	0.0	0.15	15.4	90.0	10.0	0.0	0.0	0.0	0.10	10.0
10. Hair Loss	28.2	17.9	2.6	17.9	33.3	2.10	71.8	80.0	0.0	0.0	0.0	20.0	0.80	20.0
11. Skin Changes	30.8	38.5	30.8	0.0	0.0	1.00	69.2	70.0	20.0	10.0	0.0	0.0	0.40	30.0
12. Constipation	48.7	15.4	23.1	10.3	2.6	1.03	51.3	60.0	20.0	20.0	0.0	0.0	0.60	40.0
13. Soreness in Vein	74.4	17.9	2.6	5.1	0.0	0.38	25.6	90.0	0.0	10.0	0.0	0.0	0.20	10.0
14. Decreased Interest														
in Sexual Activity	17.9	25.6	20.5	25.6	10.3	1.85	82.1	40.0	20.0	20.0	10.0	10.0	1.30	60.0

*TRSC severity scale: "0" none; no symptom; "1" mild; "2" moderate; "3" severe; "4" very severe

Descriptive data in Table 3 show the percent symptom occurrence and percent distribution of symptom severity scores on all 25 items of the TRSC as reported by Phase 2 participants, grouped into those with present vs. absent Val66Met SNP. Although the sample size was small, a pattern emerged, which, when compared to the "present" group that reported low symptom occurrence and severity to the "absent" BDNFSNP group, which reported a 50% or higher (51.3% to 87.2%) occurrence, 12 particular symptoms were identified from the data on the TRSC. The data included all four symptoms on the Fatigue subscale, two symptoms on the Eating subscale, one on the Nausea-Vomiting subscale, and the single-item subscales of Pain, Numbness of Fingers and/or Toes, Hair Loss, Skin Changes, Decreased Interest in Sexual Activity, and Constipation.

Discussion

The primary aim of this study was to examine the relationship between self-reported symptom occurrence and severity measured by the total scores from the Therapy-Related Symptom Checklist (TRSC), and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors. While the expected result was that higher symptom occurrence and severity scores would align with the presence of the variant, the findings revealed that those subjects with the variant absent had higher scores on the TRSC.

The literature indicates that the evidence is mixed regarding the relationship between the presence or absence of the BDNF Val66Met SNP and symptom occurrence and severity. A group of studies have linked Val66Met polymorphism with various behavioral and metabolic disorders. However, other studies have also reported that under some circumstances the Met66 allele may offer a biological advantage [23-25] which stated that these reports reinforce the idea that, for the Met66 allele to be sustained through evolution in 30% of the population, some biological advantage might be associated with this genotype.

The present study focused on the relationship between the presence or absence of the BDNF Val66Met SNP and symptom occurrence and severity experienced by breast cancer survivors six or more months after cessation or completion of treatment. Findings show that the "absence" of the BDNF SNP seems to be associated with more symptom occurrence and severity, as compared to the "present" BDNF SNP group. The odds of having higher TRSC scores (OR=29.29; 95% CI [2.81, 305.10], p=.005) also were found in subjects who had chemotherapy. Moreover, higher percent occurrence of the symptoms feeling sluggish, depression, difficulty concentrating, nausea, taste change, appetite loss, skin changes. were reported by breast cancer survivors with absent BDNF SNP. More research with higher power is needed to clarify the relationships found in this study, and determine the implications.

The effect of chemotherapy. Studies during outpatient cancer treatments in the US and internationally have reported the occurrence of 12 or more symptoms by the majority of the samples used [12,13,17-19]. That is, the symptoms top-ranked by presence and severity included: Feeling sluggish, difficulty sleeping, taste change, constipation, numbness of fingers/toes, pain, nausea, loss of appetite, decreased interest in sexual activity, weight loss, shortness of breath, and difficulty concentrating. In the present study and although the subjects a have completed their treatments for 6 months or longer, the findings were similar to those conducted with patients undergoing active treatment and those that had chemotherapy in their treatment regime had more symptoms.

Common drugs that are given in various combinations and schedules to treat breast cancer include cytotoxic, methotrexate, doxorubicin, and fluorouracil. In addition, women may be on long term therapy with an oral anti-estrogen drug, depending on the biology of their tumors. Chemotherapy and hormonal therapy for breast cancer has been shown to have a number of late effects particularly cognitive function or "chemo-brain". The effect of education. Another study finding was that symptom occurrence and severity (i.e., the total score on the TRSC) was inversely associated with the subject's level of education. That is, higher TRSC scores were significantly related to lower education levels. More specifically, after adjusting for treatment type and BDNF genotype, the odds of having a high TRSC score were 86% lower in subjects with a high education level (OR = 0.14, p = 0 .027).

Individuals with higher levels of education tend to be healthier, and that both education and health are secondarily associated with socioeconomic status [26]. Education is associated with greater cognitive reserve which may be related to morphological and biochemical changes in the brain [27].

Study limitations may be related to the use of a computer survey. Access to a computer may have been related to socioeconomic status, ethnicity, and/or educational level, resulting in a more homogeneous sample. The instrument has not been used in electronic surveys; therefore, continued use is recommended. Since all of the data were self-reported and no medical records review was conducted there could be concerns about making assumptions from the data. Also, since the medical records were not accessed, including information on specific targeted therapies (e.g, endocrine therapy and anti-HER2 therapy), no correlations with TRSC scores could be done. Future studies may focus on this issue.

The impact of other physiological biomarkers were not measured only the genotyping of one SNP. Further investigations related to the role of inflammatory cytokines and neuroendocrine biomarkers may provide additional information regarding the role of BDNF in the occurrence and severity of cancer-related symptoms in breast cancer survivors.

Patient care availability after treatments was not studied in this online survey. Moreover, only breast cancer survivors were studied. This recommends to focus on BDNF Val66Met polymorphism in other cancers (as related to post-treatment symptom occurrence and severity, reported on the TRSC) be studied also.

Conclusions

The original prediction was that carriers of the Met66 allele would be more vulnerable to the psychological and physiological stress of cancer and cancer treatment, and that these indi-

viduals would be more likely to continue to experience symptoms even after the completion of treatments (i.e., the cancer survivorship period). Instead, the Met66 allele tended to provide a biological advantage and was associated with fewer and less severe symptoms. Other studies have reported stronger evidence that the BDNF polymorphism plays a protective role. The findings in the current study, although not statistically significant, did suggest that the effects of treatment type (chemotherapy) and educational level likely had an impact on symptom occurrence and severity as measured on a checklist (the TRSC). More research with larger samples is needed to determine more definitively the impact of the Val66Met BDNF polymorphism on the occurrence and severity of symptoms among breast cancer survivors who have completed their treatments.

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Special Note

This article from dissertation research: Heinze, S. (2012). Relationships among symptoms, brain-derived neurotrophic factor (BDNF), daily activities, self-care, and quality of life in breast cancer survivors. (Doctoral dissertation). Available at http://kuscholarworks.ku.edu/dspace/handle/1808/11445

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