Serotonergic and BDNF Genes Associated With Depression 1 Week and 1 Year After Mastectomy for Breast Cancer

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Objective: Polymorphisms of serotonin transporter (5-HTT) and brain-derived neurotrophic factor (BDNF) genes have been investigated as candidate genes for depression occurring in medical disorders. The serotonin 2a receptor (5-HTR2a) genes have been investigated as risk factors for depression but rarely in combination with medical conditions. This study aimed to investigate whether polymorphisms of interest in 5-HTT, 5-HTR2a, and BDNF genes are associated with depression after mastectomy for breast cancer.

Methods: A total of 309 patients with breast cancer were evaluated 1 week after mastectomy, and 244 patients (79%) were followed up 1 year later. Depression (major and minor depressive disorders) was diagnosed according to DSM-IV criteria using the Mini-International Neuropsychiatric Interview and was classified into prevalent, persistent, and incident depression. Individual associations with 5-HTT gene–linked promoter region, serotonin transporter intron 2 variable number tandem repeat, 5-HTR2a 1438A/G, 5-HTR2a 102T/C, and BDNF Val66Met polymorphisms were estimated using logistic regression models, and gene-gene interactions were investigated using the generalized multifactorial dimensionality reduction method. Results: At baseline, 74 patients (24%) were classified with prevalent depression, and at follow-up, 19 patients (8%) and 25 patients (10%) were classified with persistent and incident depression, respectively. The BDNF Met/Met genotype was independently associated with prevalent (odds ratio = 2.63, 95% confidence interval = 1.12–6.14) and persistent (odds ratio = 8.07, 95% confidence interval = 1.26–51.6) depression. No associations with 5-HTT and 5-HTR2a genes (all p values > .21) were found, and no significant gene-gene interactions were identified (all p values > .36).

Conclusions: Our findings support a role of BDNF, not serotonin, in the etiology of depression occurring in women with breast cancer who received a mastectomy. Key words: breast cancer, depression, genetic association study, serotonin transporter, serotonin receptor, brain-derived neurotrophic factor.

INTRODUCTION

Breast cancer is the most prevalent cancer in women and the second most prevalent cancer in both sexes with an estimated 1.38 million new cases worldwide in 2008 (1). Despite the increasing 5-year survival rate now up to 89% (2), survivors remain at high risk of developing psychological problems (3). Depression is particularly common (4) and substantially impairs quality of life (5), as well as being associated with cancer progression or survival (6). Both psychosocial and biologic factors are important potential underlying factors (7,8).

There has been emerging evidence that genetic predispositions are important in the etiology of depression precipitated by medical conditions acting as environmental risk factors (9). The serotonin transporter (5-HTT) gene, located on chromosome 17q11.1 to 17q12, has received attention, particularly a biallelic polymorphism in the 5-HTT gene–linked promoter region (5-HTTLPR) with short (s) and long (l) alleles. The s allele has specifically been associated with depression occurring in combination with medical diseases including Parkinson disease (10), hip fracture (11), coronary disease (12), stroke (13), and multisystem chronic ill health (14). Another common variant is a triallelic polymorphism located in intron 2 with variable tandem repeat units (serotonin transporter intron 2 variable number tandem repeat [STI2 VNTR]), of which the 9- and 12-repeat alleles (STI2.9 and STI2.12, respectively) compared with the 10-repeat allele (STI2.10) have been found to be associated with depression comorbid with irritable bowel syndrome and stroke (13,15). The serotonin 2a receptor (5-HTR2a) gene, located on chromosome 13q14 to 13q21, is also a potential candidate. Two polymorphisms have been reported within this gene: a 1438A/G polymorphism in the promoter region and an MspI polymorphic site at position 1027C. The 5-HTR2a 1438A/G A allele and the 5-HTR2a 1027C C allele have been found to be associated with depressive disorders (16–19) but neither in the context of depression related to physical disorders. Another more recent candidate is the brain-derived neurotrophic factor (BDNF) gene, located on chromosome 11p14.1. These include...
BDNF GENE FOR DEPRESSION IN BREAST CANCER

the single-nucleotide polymorphism (SNP) at nucleotide 196G/A, which results in an amino acid substitution (valine to methionine) at codon 66 (Val66Met) of the proBDNF molecule, and the Met allele has been associated with depression after stroke (20) and coronary artery disease (21).

Although depression is common in people with cancer, there has been very little research into the role of these candidate polymorphisms. The 5-HTTLPR s allele was found to be associated with depression in 34 people with head and neck cancers (22) but not associated with depression in 145 women with breast cancer (23). To our knowledge, there have been no investigations into the role of other specific gene polymorphisms with respect to depression in people with cancer. This study aimed to investigate whether the 5-HTT, 5-HTR2a, and BDNF genes are associated with depression 1 week and 1 year after mastectomy in a cohort of Korean women with breast cancer. Taken together with previous research, the 5-HTTLPR s, STin2.9 and STin2.12, 5-HTR2a 1438A and 102C, and BDNF Met were considered as risk alleles for depression.

METHODS

Study Overview

This analysis was carried out as a component of a larger parent study, which seeks to investigate mental disorders in patients with breast cancer using a naturalistic prospective design. Participants were consecutively recruited from all women with breast cancer undergoing mastectomy within the Breast and Endocrine Tumor Clinic of Chonnam National University Hwasun Hospital, Hwasun, South Korea. Assessments are made 1 week and 1 year after the mastectomy to investigate both acute and chronic outcomes. The recruitment period for the initial baseline assessment was from March 2008 to May 2009, and for the follow-up evaluation, it was 1 year thereafter.

Participants

All women with breast cancer undergoing mastectomy at the study site were approached regarding participation. Inclusion criteria were as follows: a) confirmed breast cancer by histological examination, b) ability to complete the necessary investigations and questionnaires, and c) capacity to understand the objective of the study and provide informed consent. Exclusion criteria were as follows: a) secondary breast cancer, b) benign breast tumor, and c) male sex. This study was approved by the Chonnam National University Hwasun Hospital institutional review board. All participants gave written informed consent.

Measurements

Demographic and Clinical Characteristics

Data on age, year of education, marital status, cohabiting status, religious affiliation, current occupation, and personal and family histories of depression were obtained. The Social and Occupational Functioning Assessment Scale (SOFAS) (24) was administered to evaluate functioning levels over the past 1 month (a scale-based instrument with lower scores indicating lower functioning). Time since tumor detection, tumor recurrence state, and method of surgery (quadrantectomy or mastectomy) were recorded. Tumor size was measured as the longest diameter (in millimeters) at histological laboratory examination after mastectomy. Breast cancer staging was performed after surgery by an endocrine surgeon using the American Joint Committee on Cancer staging system for breast cancer (25).

Depression

Depression diagnoses were ascertained 1 week and 1 year after mastectomy, using the Mini-International Neuropsychiatric Interview, a structured diagnostic psychiatric interview for DSM-IV giving rise to major or minor depression categories (26). Cases of major depression were too rare in this sample to analyze separately and therefore were combined with minor depression into a single category. The Mini-International Neuropsychiatric Interview has been formally translated and standardized in Korean (27).

Genotyping

Blood samples for genotyping were obtained in a subsample who agreed to this. Deoxyribonucleic acid was extracted from venous blood using standard procedures. Polymerase chain reaction (PCR) and PCR-based restriction fragment length polymorphism assays were performed. Amplification of the 5-HTTLPR polymorphism gave five alleles differing by 44 base pairs (bp) (14, 16, 18, 20, and 22 copies of a repetitive sequence). The 14-copy allele identified the s allele; and all others, the l allele; and the genotypes were categorized as “s/s,” “s/l,” and “l/l.” Amplification of the STin2 VNTR polymorphism gave five alleles differing by 17 bp (9, 10, and 12 copies of a repetitive sequence). The 9 allele was not found, and the 10/10 genotype was extremely rare (present in only four participants), and therefore, the genotypes were categorized as “10 or 12/10” and “12/12.” For the 5-HTR2a 1438A/G polymorphism, the PCR products gave the 1438G (232- and 120-bp fragments) and 1438A (352-bp fragment) alleles with the corresponding restriction enzyme (MspI), and the genotypes were categorized as “G/G,” “G/A,” and “A/A.” For the 5-HTR2a 102T/C polymorphism, the PCR products gave the 102C (216- and 126-bp fragments) and 102T (342-bp fragment) alleles with the corresponding restriction enzyme (HpaII), and the genotypes were categorized as “C/C,” “C/T,” and “T/T.” For the BDNF Val66Met polymorphism, the PCR products gave the 66Val (490- and 208-bp fragments) and 66Met (698-bp fragment) alleles with the corresponding restriction enzyme (BbvI), and the genotypes were categorized as “Val/Val,” “Val/Met,” and “Met/Met.”

Statistical Analyses

We defined three dependent variables for the analyses: prevalent, persistent, and incident depression. Prevalent depression designated depression at baseline, persistent depression designated depression both at baseline and at follow-up, and incident depression designated depression not at baseline but at follow-up. Demographic and clinical characteristics were compared according to prevalent depression status for all those present at baseline using t tests, χ2 tests, or Fisher exact tests as appropriate. They were compared again, between patients with “no depression both at baseline and at follow-up” and those with persistent and incident depression. Genotype distributions and allele frequencies for the five polymorphisms were compared in a similar fashion using χ2 tests or Fisher exact tests as appropriate. Calculations for deviation from Hardy-Weinberg equilibrium were made using χ2 tests. Odds ratios for prevalent, persistent, and incident depression outcomes by genotype were estimated using logistic regression models after adjustment for those baseline demographic and clinical characteristics that were associated with depression status. Finally, gene-gene interactions were investigated using generalized multifactor dimensionality reduction (GMDR) methods; these have been described in detail previously (28), but in summary, the n-dimensional space formed by a given set of SNPs is reduced to a single dimension to analyze n-way interactions; score-based statistics are then calculated using maximum likelihood estimates to classify multifactor cells into two different groups (either high or low risk). This was carried out for all possible two- to five-locus SNP combinations, and the combination with the lowest misclassification error was selected. Permutation testing obtains empirical p values of prediction accuracy as a benchmark based on 1000 shuffles. Baseline characteristics associated with depression status were included in the gene-gene interaction analyses. Statistical analyses were carried out using SPSS 13.0 (SPSS Inc., Chicago, IL) and GMDR (Ref Nr 28) software. All p values were calculated using two-sided tests.

RESULTS

Recruitment

Recruitment at baseline and sample follow-up are described in Figure 1. Having applied inclusion and exclusion criteria, of 366 potentially eligible and consecutively enrolled women with breast cancer undergoing mastectomy, 336 (92%) consented to participate in the study. Of these, 309 (92%) agreed

to provide blood samples for genotyping and formed the baseline sample. There were no significant differences between participants and nonparticipants with respect to any demographic and clinical characteristics (all p values > .20). The mean (standard deviation [SD]) interview time point from mastectomy was 4.5 (1.2) days. Of the 309 participants, 74 (23.9%) were evaluated as having depression (11 with major depression and 63 with minor depression). At 1-year follow-up, 244 patients (79%) were reexamined. Those present or not at follow-up have no significant difference at baseline with respect to any demographic and clinical characteristic (all p values > .05). Depression was present in 44 (18.0%) of all 244 followed up participants (5 with major depression and 39 with minor depression). Persistence of depression (i.e., presence at both baseline and follow-up) was defined in 19 patients; incidence (i.e., presence at follow-up but not at baseline), in 25 patients; and recovery (i.e., presence at baseline but not at follow-up), in 36 patients.

Demographic and Clinical Characteristics by Depression Status

In the baseline sample of 309 participants, the mean (SD, range) age was 50.8 (9.7, 25–80) years, and the mean (SD) duration of education was 10.4 (3.9) years. Of those, 250 (80.9%) were married, 25 (8.1%) were living alone, 240 (77.7%) reported a religious affiliation, and 89 (28.8%) were currently employed. Previous depression was reported in 24 patients (7.8%); and a family history of depression, in 4 (1.3%) participants. The mean (SD, median, range) SOFAS score was 57.5 (5.2, 58, 40–86). Breast cancer was present for the first time in 301 participants (97.4%), and the mean (SD) duration of time since tumor detection was 2.5 (7.7) months. With respect to surgery method, 201 participants (65.0%) received quadrantectomy. The mean (SD) tumor size was 19.0 (12.0) mm. Tumor stage was 0 in 29 participants (9.4%), I in 105 (34.0%), II in 122 (39.5), III in 43 (13.9%), and IV in 10 (3.2%). These characteristics are compared by prevalent, persistent, and incident depression status. Participants with prevalent depression at baseline were more likely to have previous (p = .034) and family (p = .044) histories of depression and had lower mean SOFAS scores (p < .001) compared with those without depression at baseline. Compared with those without depression at baseline or follow-up, participants with persistent depression were more likely to have a previous (p = .017) and family (p = .029) histories of depression, had lower SOFAS score at baseline (p < .001), and had a larger tumor size (p = .027). The incident depression group did not differ significantly in any characteristics when evaluated against the same comparison group.

Genotype Distributions and Allele Frequencies by Depression Status

No deviation from the Hardy-Weinberg equilibrium was observed for any genotype (all p values > .05). Power estimates of allelic tests for the five SNPs were as follows: 5-HTTLPR, 60%; STin2 VNTR, 48%; 5-HTR2a 1438A/G, 54%; 5-HTR2a 102T/C, 57%; and BDNF Val66Met, 63%. Genotype distributions and allele frequencies are compared by depression status in Table 1. Patients with prevalent depression at baseline had significantly higher frequency of the BDNF Met allele compared with those with no depression at baseline. The persistent depression group had also significantly higher frequency of the BDNF Met allele compared with those without depression at baseline or follow-up. There were no significant differences in genotype distributions and allele frequencies between patients with incident depression and those without depression at baseline or follow-up.

Adjusted Associations Between Genotypes and Depression Status

Independent associations between genotypes and depression status adjusted for baseline demographic and clinical characteristics associated with each depression outcome are summarized in Table 2. BDNF Met/Met genotype remained significantly associated with both prevalent depression at baseline and persistent depression at follow-up. Repeated analyses excluding eight patients with a recurrent tumor did not alter the findings meaningfully (data not shown). No independent associations were found for any other genotypes and depression status. The impact of combinations of the five genotypes on depression status was explored through the GMDR analyses for two- to five-locus models adjusted for baseline characteristics not equally distributed. There were no models indicating significant interactions...
## TABLE 1. Genotype Distributions and Allele Frequencies by Depression Status

<table>
<thead>
<tr>
<th>Genotype Distribution</th>
<th>Baseline Analysis</th>
<th>Follow-Up Analysis</th>
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<tbody>
<tr>
<td></td>
<td>No Depression</td>
<td>Prevalent Depression</td>
</tr>
<tr>
<td></td>
<td>n = 235</td>
<td>n = 74</td>
</tr>
<tr>
<td>5-HTTLPR l/l</td>
<td>22 (9.4)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>l/s</td>
<td>76 (32.3)</td>
<td>31 (41.9)</td>
</tr>
<tr>
<td>s/s</td>
<td>137 (58.3)</td>
<td>38 (51.4)</td>
</tr>
<tr>
<td>l allele</td>
<td>120 (25.5)</td>
<td>41 (27.7)</td>
</tr>
<tr>
<td>s allele</td>
<td>350 (74.5)</td>
<td>107 (72.3)</td>
</tr>
<tr>
<td>STin2 VNTR 10 or 12/10</td>
<td>30 (12.8)</td>
<td>15 (20.3)</td>
</tr>
<tr>
<td></td>
<td>12/12</td>
<td>205 (87.2)</td>
</tr>
<tr>
<td>5-HTR2a 1438A/G</td>
<td>G/G</td>
<td>72 (30.6)</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>109 (46.4)</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>54 (23.0)</td>
</tr>
<tr>
<td>G allele</td>
<td>253 (53.8)</td>
<td>81 (54.7)</td>
</tr>
<tr>
<td>A allele</td>
<td>217 (46.2)</td>
<td>67 (45.3)</td>
</tr>
<tr>
<td>5-HTR2a 102T/C</td>
<td>T/T</td>
<td>61 (26.0)</td>
</tr>
<tr>
<td></td>
<td>T/C</td>
<td>109 (46.4)</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>65 (27.7)</td>
</tr>
<tr>
<td>T allele</td>
<td>231 (49.1)</td>
<td>69 (46.6)</td>
</tr>
<tr>
<td>C allele</td>
<td>239 (50.9)</td>
<td>79 (53.4)</td>
</tr>
<tr>
<td>BDNF Val66Met</td>
<td>Val/Val</td>
<td>59 (25.1)</td>
</tr>
<tr>
<td></td>
<td>Val/Met</td>
<td>135 (57.4)</td>
</tr>
<tr>
<td></td>
<td>Met/Met</td>
<td>41 (17.4)</td>
</tr>
<tr>
<td>Val allele</td>
<td>253 (53.8)</td>
<td>62 (41.9)</td>
</tr>
<tr>
<td>Met allele</td>
<td>217 (46.2)</td>
<td>86 (58.1)</td>
</tr>
</tbody>
</table>

Data are represented as n (%) unless otherwise indicated.

5-HTTLPR = serotonin transporter gene-linked promoter region; STin2 VNTR = serotonin transporter intron 2 variable number tandem repeat; 5-HTR2a = serotonin 2a receptor; BDNF = brain-derived neurotrophic factor.

5-HTTLPR s, STin2 12, 5-HTR2a 1438A and 102C, and BDNF Met were considered as risk alleles for depression.

All p values are empirical.

a p Value for no depression versus prevalent depression using χ² test, or Fisher’s Exact test as appropriate.

b p Value for no depression versus persistent depression using χ² test, or Fisher’s Exact test as appropriate.

c p Value for no depression versus incident depression using χ² test or Fisher exact test as appropriate.
for any combinations of genotypes (all \( p \) values > .36). Again, repeated analyses excluding eight patients with recurrent tumor did not alter the findings.

**DISCUSSION**

The principal finding in this prospective study of women with breast cancer was that the *BDNF Met/Met* genotype was significantly associated with depression 1 week after mastectomy and with persistent depression 1 year after mastectomy. This association was independent of potential covariates such as previous or family histories of depression, functioning level, and/or tumor size. This is the first report, to our knowledge, of such an association not only for breast cancer but also for any other cancer population.

Several explanations for this significant association are possible. The *BDNF Met* allele is associated with reduced activity-dependent secretion of BDNF (29). Because BDNF is the most abundant neurotrophin in the brain and has antidepressant neuroprotective effects (30), functional deficiency might increase depressogenic effects of biologic insults and/or psychological stresses. Tumor growth can increase the production of prooxidant compounds and change the antioxidant enzyme activities in extratumor tissues of the host (31,32). The expression of BDNF in the hippocampus has been found to be significantly decreased as an effect of those compounds and depressive behavior induced in tumor-bearing mice (33). The significant association between tumor size and persistent depression in this study supported these results in part. On the other hand, the *BDNF Met* allele has been found to be associated with depression after stressful life events (34,35) and depression after medical diseases such as stroke (20) and coronary artery syndrome (21), which are all potential life stresses, as, of course, are receiving a breast cancer diagnosis and undergoing a mastectomy. Of potential relevance, *BDNF Met* allele carriers under greater stress exposure were found to have smaller hippocampal and amygdalar volumes and heart rate elevations, which were associated with arousal pathways to syndromal depression (36). Finally, with respect to the allele frequency, our sample had higher *Met* allele (49%) frequency compared with reports from Western populations (approximately 17%–32%) (21,34), whereas the findings are similar to the reports from other Asian populations (37). The higher frequency of this risk allele might have increased the statistical power to detect associations.

It is noteworthy that the *BDNF Met* allele was associated with prevalent and persistent depression but not with incident depression in this sample. This finding supports a commonsense assumption that the etiology of depression may differ between early and late stages after mastectomy. For example, a recent review suggested that risk factors for depression may change from generic effects of the disease or its treatment in the acute phase to more individual-level vulnerability in the chronic phase (8). In this study, women with persistent depression shared risk factors such as previous and family histories of depression and lower baseline functioning levels with those with prevalent depression. However, incident depression was not associated with any characteristics investigated at

<table>
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<th>TABLE 2. Adjusted Associations of Genotypes With Depression Status</th>
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<tr>
<td><strong>Prevalent Depression</strong></td>
</tr>
<tr>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td>5-HTTLPR</td>
</tr>
<tr>
<td>l/l</td>
</tr>
<tr>
<td>l/s</td>
</tr>
<tr>
<td>s/s</td>
</tr>
<tr>
<td>STin2 VNTR</td>
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<tr>
<td>10 or 12/10</td>
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\( \text{OR} = \text{odds ratio; CI = confidence interval; } 5\text{-HTTLPR = serotonin transporter gene–linked promoter region; STin2 VNTR = serotonin transporter intron 2 variable number tandem repeat; } 5\text{-HTR2a = serotonin 2a receptor; } BDNF = \) brain-derived neurotrophic factor.

\( p \) Values for logistic regression likelihood ratio test. 5-HTTLPR s, STin2 VNTR, 5-HTR2a 1438A/G and 102C, and BDNF Met were considered as risk alleles for depression. All \( p \) values are empirical.

\( ^a \) Adjusted for previous and family histories of depression and Social and Occupational Functioning Assessment Scale (SOFAS) score.

\( ^b \) Adjusted for previous and family histories of depression, SOFAS score, and tumor size.
baseline in the analyses. New onset of depression after the acute phase might therefore be associated with other factors in the disease course. Overall, our results suggest that the role of the BDNF Met allele on depression in patients with breast cancer is particularly important at the acute phase of mastectomy and in those susceptible to persistent depression.

To date, the most widely studied factor with respect to gene-environment interactions in depression is the 5-HTTLPR s/l polymorphism (9). Specifically, the 5-HTTLPR s allele has been found to promote depression associated with stressful life events in various age groups (35,38,39) and has also been linked to depression occurring in a range of medical diseases (11–14,22). However, there have also been important negative findings for stressful life events as an exposure (40–42) and in medical diseases (43). To our knowledge, there has been only one previous study investigating the association between 5-HTTLPR gene polymorphism and depression in women with breast cancer (23) that, like ours (although with lower risk allele frequency), found no association. Furthermore, investigating another candidate 5-HTT gene, we also found no significant association between STin2 VNTR polymorphism and depression. The serotonergic receptor system has also been implicated in the pathophysiology of mood disorders and in the action of antidepressants. 5-HTR2a polymorphisms have received particular attention, in that the 5-HTR2a 1438A/G A allele has been found to be associated with mood disorders, seasonal affective disorder, and depressive mood (16,17,44) and that the 5-HTR2a 102T/C C allele was associated with particular traits related to depression such as suicidal ideation (18,19) and treatment responses (45,46).

To our knowledge, these polymorphisms have not been investigated in psycho-oncology. However, no associations were found between the two 5-HTR2a gene polymorphisms and depression in women with breast cancer in the present study. Linkage disequilibrium has been found between 5-HTTLPR and STin2 VNTR (47) and between 5-HTR2a 1438A/G and 102T/C polymorphisms (48), and there is evidence that serotonin and BDNF systems may be linked at multiple intracellular and intercellular levels (49). Therefore, we investigated potential gene-gene interactions using the GMDR method, but we did not identify any significant interactions.

Overall, our findings did not suggest a substantial etiologic role for 5-HTT and 5-HTR2a gene polymorphisms in depression related to breast cancer. However, there are some considerations before drawing conclusions. 5-HTTLPR s allele carriers have been suggested to be more vulnerable to major than minor depression in response to stressors (12,39), and the low frequencies of major depression (3.6% and 2.0% 1 week and 1 year after mastectomy, respectively) in this sample might have limited the extent to which effects could be detected. However, it was consistent with the results of a nationwide Korean epidemiologic study (reporting a 2.5% 1-month prevalence of major depression (50)) and the reports that prevalence of major depressive disorder was considerably low (1.5%) with a structured diagnostic interview (4). On the other hand, our East Asian sample had higher 5-HTTLPR s allele, 74% compared with approximately 43% to 46% (13,23); STin2 VNTR 12 allele, 92% compared with 67% (13); and 5-HTR2a 1438A/G A allele, 46% compared with approximately 38% to 41% (16,17). Taken together, potential risk alleles in the serotonergic genes of interest for depression (5-HTTLPR s, STin2 VNTR 12, and 5-HTR2a 1438A/G A) were relatively common in our sample, which increased power to detect associations. In this respect, it is also noteworthy that the risk allele identified BDNF Met was relatively frequent in our sample compared with Western populations, to an extent consistent with reports from other East Asian samples (37). Finally, it should be borne in mind that “persistent” depression was inferred because of information at two time points without knowledge of mood state in the intervening period (e.g., it may include some cases with an intervening remission followed by relapse).

Our study has several strengths. To our knowledge, we report the largest and the first prospective study to date on genes associated with depression related to cancer, as well as being the first to report associations with STin2 VNTR, 5-HTR2a, and BDNF polymorphisms, generating what we believe is a novel but plausible finding on the association between BDNF Met allele and depression in breast cancer. Other strengths were the high follow-up rate, and the facts that depression was formally ascertained using a structured diagnostic interview and that depression and other variables were assessed at a similar time point (1 week and 1 year after mastectomy) in all participants and at a similar time since diagnosis in most participants. It has been reported that the etiology of depression may differ according to the time elapsed after breast cancer (8). Therefore, the particular study design reduced the risk of error arising from heterogeneous examination times. A further advantage was that participants were consecutively enrolled from all patients with a diagnosis of breast cancer undergoing mastectomy at the study hospital, which reduced the likelihood of selection bias and increases the potential generalizability. It is important to bear in mind that the sample size, as indicated previously, had limited power for detecting associations. However, as stated, we believe that this is one of the first and the largest genetic association study in this important area of psycho-oncology and therefore provides an important basis for further more extensive research.

In conclusion, patients with breast cancer with BDNF Met/Met genotype were more susceptible to depression 1 week after mastectomy and persistent depression 1 year later. Considering the higher morbidity associated with depression in breast cancer, it is possible that more careful evaluation and management are indicated for those with increased genetic vulnerability. However, further research is required to evaluate whether genetic testing in clinical environments would be a helpful step, and it would also be necessary to demonstrate that early intervention in vulnerable groups (e.g., proactive screening programs and/or psychological/pharmacological intervention for subcase symptoms) resulted in demonstrable improvements. In this respect, the known high prevalence rate of the BDNF Met allele in East Asian populations (37) may potentially have clinical relevance, and future research should focus on these high-risk populations.
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