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ORIGINAL ARTICLE

Body image, sexual function and depression in Korean patients with breast cancer: modification by 5-HTT polymorphism

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Abstract
Background Nearly 50% of women with breast cancer show depressive symptoms after diagnosis and treatment. The purpose of this study was to clarify how psychosocial factors (body image, sexuality, and social relationships) and genetic factors (functional polymorphism of the serotonin transporter-linked promoter region) influence depression.
Methods The participants were categorized by DSM-IV diagnoses; scored according to their depressive symptoms, body image and social and sexual function (BIRS), self-esteem, and quality of life; and genotyped by functional polymorphism of the serotonin transporter promoter.
Results Patients with depressive symptoms showed low self-esteem, poor body image, relationship problems, and low quality of life. Genotype frequencies did not differ between two groups categorized by the presence or absence of depressive symptoms. However, the patients with the short allele of the 5-HTTLPR had significantly higher HAM-D scores (F=7.59, p=0.047).
Conclusion The results suggest that psychosocial factors related to breast cancer treatment such as body image, self-esteem, and interpersonal relationship influence the development of depressive symptoms. The 5-HTTLPR may be associated with the severity of depressive symptoms rather than susceptibility to the development of depressive symptoms.

Keywords Breast cancer · Depression · Body image · 5-HTTLPR

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Introduction

Breast cancer is the most common cancer in women worldwide regardless of the country's level of development [1]. In Korean women, breast cancer was the most common cancer after gastric cancer in 2001. However, in 2002, it became the most common cancer in Korean women and comprised 16.8% of all female cancers [2].

With advances in detection and treatment, the number of women who survive breast cancer has increased significantly in recent years. Five-year survival rates have increased to 96%, resulting in an estimated 2 million North American women living as survivors of breast cancer [3]. As survival times increase, important goals for breast cancer patients and survivors are to improve quality of life and reduce adverse effects of breast cancer and its treatment on long-term outcomes [4].

Of various complaints experienced by breast cancer patients, depression is conceivably the most significant and most investigated psychiatric problem. Reported rates of depression in women with breast cancer range from 1.5% to 50% depending on assessment time, sample, and, particularly, definition of depression and method of assessment

[5]. Although the prevalence of major depressive disorder may be considerably lower, the majority of studies reported that 20% to 30% of women experience depressive symptoms that cause significant impairment [6]. Depression has a negative effect on all aspects of quality of life in cancer patients and is associated with diminished medical adherence [7], lack of understanding of treatment recommendations, and concerns about adverse effects of treatment [8]. There is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients [9]. Therefore, identification of patients susceptible to depression is critical to providing qualified care.

Many factors can influence depression in breast cancer patients. Psychosocial factors may increase the risk of depressive symptoms in this population; these factors include history of depression, poor social function, and occurrence of other stressful life events. Somatic factors including pain, disability, and poor body image also show modest associations with depression [10]. In contrast, objective variables of cancer diagnosis and treatment are not consistently associated with depressive symptoms; these variables include stage of disease, type of treatment received and tamoxifen use [10]. These findings suggest that depression in breast cancer patients is more strongly influenced by psychosocial and physical factors than disease severity or treatment regimen.

Over the last two decades, the etiological research of depression and breast cancer has only focused on psychosocial, somatic, and demographic risk factors [11, 12]. However, the role of biological factors in the development of depression has not been considered. In recent years, the molecular genetic approach has been widely used to evaluate the biological mechanisms contributing to interindividual differences in susceptibility to depressive disorders. Therefore, it is increasingly believed that gene–environment interactions contribute to the etiology of mood disorders [13]. Although, the genetic hypothesis of depression secondary to medical conditions has not been scrutinized, we should consider the possibility of a genetic predisposition to depression in patients with breast cancer [14].

The most widely reported genetic abnormality in depressive disorder involves the serotonin system [15]. The serotonin transporter (5-HTT) is of particular interest because selective serotonin reuptake inhibitors, the standard treatment of depression, target the 5-HTT [16], and 5-HTT availability is critical to homeostasis of serotonin function [17]. In addition, 5-HTTLPR polymorphism has been shown to influence individual variations in the development of major depressive disorder in response to life stress [18, 19]. A 5-HTT dysfunction has been implicated in the etiology of psychiatric disorders such as mood disorders, obsessive–compulsive disorders, and substance-related disorders [20]. The short form of this variant, labeled as *s*, is associated with lower expression and induced transcriptional efficiency of the 5-HTT gene promoter, resulting in lower serotonin activity than that of the long form, labeled as *l* [21]. The previous study investigated the associations between 5-HTTLPR genotypes and behavioral variants; the authors reported that subjects with one or two copies of the *s* variant exhibited significantly higher levels of anxiety, hostility, and depression than those of subjects homozygous for the *l* genotype [17, 22].

Because breast cancer is a major life stress event and depressive disorder is associated with severe physical and psychosocial disruptions in breast cancer patients, the 5-HTTLPR may modulate depression in these patients. In this study, we investigated the depressive symptom profiles and psychosocial variables in association with the 5-HTTLPR genotypes in 186 breast cancer patients.

Methods

Participants

The subjects were consecutively recruited from out-patient populations of the Oncology Division of the Yonsei Cancer Center, Severance Hospital, in Korea during an 8-month period from May 2008 to January 2009. The inclusion criteria for the study were as follows: (1) histologically or cytologically confirmed breast cancer, (2) female, age 20 years or older, and (3) an estimated life expectancy exceeding 6 months (as assessed by the physician). The exclusion criteria were as follows: (1) cognitive impairment, (2) too ill to participate, or (3) under treatment for a current psychiatric disorder. Axis I and axis II diagnoses were made using the Structured Clinical Interviews for DSM-IV by a psychiatrist. The diagnosis of major depressive disorder was determined using the Structured Clinical Interview for DSM-IV and DSM-IV-TR diagnostic criteria.

This study was approved by the Institutional Review Board and the Ethics Committee of the Yonsei University Severance Hospital. Written informed consent was obtained from each subject prior to the start of this study.

Clinical measures

The Hospital Anxiety and Depression Scale (HADS) [23] is a widely used self-report instrument designed as a brief assessment of the levels of anxiety and depression. It is a 14-item questionnaire that consists of two subscales of seven items each, which determines levels of anxiety and depression. The ease, speed, and patient acceptability of the HADS has led to its use in a wide variety of clinical

populations where significant anxiety and depression may coexist with physical illness, and it has also been extensively used in clinical oncology as a screening and research tool [24]. The Body Image and Relationship Scale (BIRS) is a 32-item measure of experiences pertaining to appearance, health, physical strength, sexuality, relationships, and social functioning that are unique to women diagnosed with breast cancer. Higher scores on each subscale indicate greater impairment.

The patients' QOLs were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23. The QLQ-C30 is a 30-item self-report questionnaire on functional and symptom-related aspects of QOL in cancer patients [25]. The QLQ-BR23 is the breast cancer module and consists of 23 questions assessing disease symptoms, adverse treatment events, body image, sexuality, and future perspective [26]. A high score for a functional item represents a high level of functioning, and a high score for global health status and quality of life represents a high QOL. On the other hand, a high score for a symptom item represents a high level of symptomatology and problems. The validity and reliability of the Korean version of the EORTC QLQ-C30 and QLQ-BR23 have been confirmed [27, 28].

The severity of depression was assessed by the Hamilton Depression Rating Scale (HAM-D), and all ratings were performed at the time of inclusion in the study.

DNA genotyping of the 5-HTTLPR polymorphous locus

Venous blood samples were collected in EDTA vials from the study subjects, and the genomic DNA was extracted. The samples were stored at −20°C until analysis was carried out. The primers were 5′-GGC GTT GCC GCT CTG AAT GC-3′ (forward) and 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′ (reverse) [15]. Amplification of the polymorphic region was performed using a GeneAmp PCR system (Perkin-Elmer, Norwalk, CT), and the thermal program consisted of initial denaturation at 94°C for 5 min, 30 cycles of 94°C for 30 s, 61°C for 30 s, and 72°C for 60 s, and a final extension period at 72°C. In order to identify the alleles, the amplicons were separated by 2.5% agarose gel electrophoresis and stained with ethidium bromide. All laboratory procedures were performed blind to subject status.

Results

Subjects' characteristics

Of 200 consecutive patients with breast cancer, 186 who fulfilled the inclusion/exclusion criteria were genotyped. They were divided into two subgroups according to the presence or absence of depressive symptoms. Demographic and clinical characteristics of the participants are presented in Table 1. Depressed and nondepressed patients did not differ in age at evaluation, education, age at diagnosis, duration of illness, or disease stage. As expected, higher HAM-D scores were observed in depressed patients (t=28.753, p<0.001). Analysis of BIRS subscales showed depressed patients had greater impairments in strength and health, social barriers, appearance, and sexuality. In the quality of life assessment by QLQ-BR23, depressed patients reported worse body images (t=3.569, p<0.001) and future perceptions (t=4.247, p<0.001) than nondepressed patients. Moreover, other aspects of body symptoms were severer in depressed patients.

Genotype distribution in depressed and nondepressed groups

The genotype distribution and the allele frequency in the depressed and nondepressed groups are shown in Table 2. The genotypes of the nondepressed group were *s*/*s* (N=76, 55.5%), *s*/*l* (N=54, 39.4%), and *l*/*l* (N=7, 5.1%), and those of the depressed group were *s*/*s* (N=26, 53.1%), *s*/*l* (N=22, 44.9%), and *l*/*l* (N=1, 2%). The frequency of the 5-HTTLPR in the Korean population was comparative to that of previous reports. No significant differences were found in the allele frequencies between the depressed and nondepressed groups.

To determine whether this polymorphism was associated with differences in the symptoms typical of depression, clinical variables of the depressed patients were compared. In depressed patients, there was also no significant correlation between genotype and clinical variables.

A potential gene–environment interaction effect on the severity of depression was tested by a general linear model with depression severity (Hamilton Depression Scale score) as the dependent variable and 5-HTTLPR genotype, and body image and other psychosocial variables as independent variables. The overall model (F=1.084, p=0.03) and the interaction of genotype and BIRS scores (F=7.59, p=0.047) were significant (Fig. 1). The *s* allele was associated with more severe depression in the group with poorer body image and sexual function (high BIRS scores group).

Discussion

Consistent with previous research, depressive patients had reduced scores for several indicators of body image, sexual function, interpersonal problem, and quality of life. However, contrary to our expectations, no significant associations were found between 5-HTTLPR polymorphisms in

Table 1 Demographic and clinical characteristics of depressed and non depressed patients with breast cancer

Variable	Depressed(N=49)	Nondepressed (N=137)	t/χ^2	p
Age (years)	54.1±8.7	54.0±8.5	−0.95	0.924
Education (years)	11.4±3.5	8.3±3.3	0.934	0.352
Age at diagnosis (years)	47.1±8.4	46.0±8.4	−0.783	0.434
Duration of illness (years)	7.3±3.8	8.3±3.3	1.795	0.074
Stage				
I	8	18		
II	34	98	0.390	0.942
III	6	17		
IV	1	4		
HAM-D	21.9±4.5	4.6±3.2	−28.753	<0.001
HADS-A	6.8±4.1	4.9±2.9	−3.758	<0.001
HADS-D	7.4±3.5	4.3±2.6	−6.676	<0.001
BIRS				
Strength and health	34.3±8.7	27.9±7.4	−4.844	<0.001
Social barrier	23.7±8.7	18.3±7.7	−3.955	<0.001
Appearance and sexuality	35.4±8.26	31.3±7.4	−3.208	<0.001
Total	93.5±22.1	77.5±19.1	−4.691	<0.001
QLQ-BR23				
Functional scales				
Body image	50.2±29.8	65.8±23.6	3.569	<0.001
Sexual functioning	15.2±23.8	21.2±24.5	1.417	0.158
Sexual enjoyment	40.7±46.5	40.0±33.0	−0.057	0.955
Future perspective	39.3±30.4	59.2±26.0	4.247	<0.001
Symptom scales/items				
Systemic therapy side effect	35.6±17.7	22.7±16.1	−4.487	<0.001
Breast symptoms	45.1±27.7	36.3±21.8	−2.234	0.027
Arm symptoms	35.3±25.8	24.4±22.9	−2.657	0.009
Upset by hair loss	60.7±30.4	40.8±26.0	−4.247	<0.001

the *5-HTT* gene and scores of psychosocial and clinical variables. In our study, breast cancer patients with depression had worse body image, decreased sexual functioning, and relationship problems, and the short allele of the 5-HTTLPR correlated with the severity of depressive symptoms and also modulated the impact of body image and other psychosocial variables.

Table 2 Distribution of the 5-HTTLPR genotype and allele frequencies in the depressed patients and nondepressed patients

Variables	Depressed (N=49)	Nondepressed (N=137)	t/χ^2	p
Genotype				
SS	26 (53.1)	76 (55.5)		
LS	22 (44.9)	54 (39.4)	1.094	0.579
LL	1 (2.0)	7 (5.1)		
Allele frequencies				
S	74 (75.5)	206 (75.2)	1.086	0.579
L	24 (24.5)	68 (24.8)		

5-HTTLPR serotonin transporter-linked polymorphic region

Previous research on breast cancer has focused primarily on treatment outcomes such as rates of survival and recurrences; more recently, the long-term effects of breast cancer treatment on outcomes such as quality of life have been considered. However, research on psychosocial outcomes in breast cancer survivors has traditionally utilized broad measures of quality of life, which gauge nonspecific psychological and social functioning. However, the BIRS targets specific components of psychosocial adjustment and functioning in breast cancer survivors that are not represented by existing quality-of-life surveys. In this study, we used the BIRS to compare the profiles of patients who developed depressive symptoms with those of nondepressed patients.

About genetic polymorphism, the 5-HTTLPR *s/s* genotype occurred with a greater frequency in both the control subjects and depressed patients. The frequency of the 5-HTTLPR genotypes in this study is comparable with that of previous reports on the Asian population. Dysfunctional genes in the

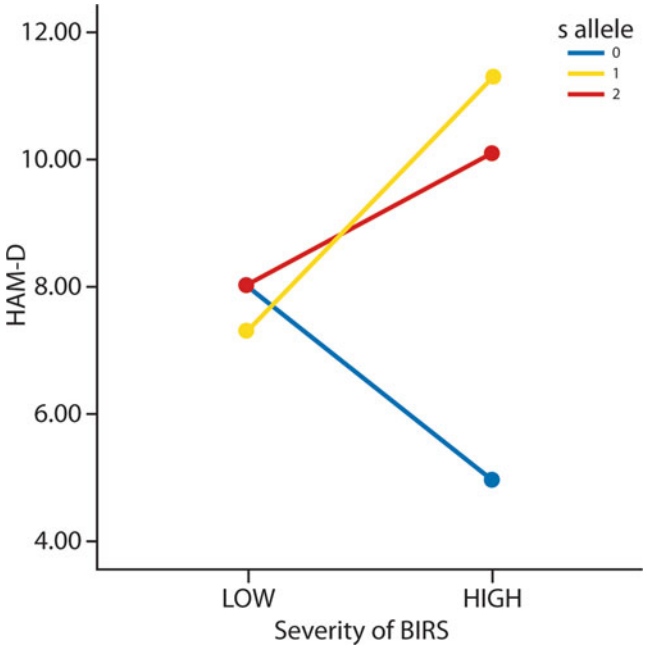

Fig. 1 Relationship of depression severity and BIRS scores by 5-HTTLPR genotype. Note: high and low BIRS scores were defined using a median split. *HAM-D* Hamilton Depression Rating Scale, *BIRS* Body Image Relationship Scale

serotonergic system are candidates for assessing susceptibility to major depressive disorder. The *s* allele is associated with lower levels of 5-HT and transcriptional efficiency of the 5-HTT gene promoter than those of the *l* allele. Therefore, we expected the *s* and *l* allele distribution to differ between the depressed and nondepressed patients.

In this study, there was no significant difference in the 5-HTTLPR genotype distribution and allele frequency between the depressed patients and controls. Despite ethnic variations, 5-HTTLPR polymorphism does not appear to be involved in a genetic predisposition to depression after breast cancer. Lack of an allelic association among depressed patients with breast cancer indicates that the pathophysiology of depression in women with breast cancer is more heterogeneous than in the general population. In other words, nongenetic factors including psychosocial and other biological factors may play a more important role in the development of depression. Another explanation for the lack of a strong association in our study is small sample size. The study by Collier et al. comprised about 2,000 subjects with affective disorders [29], so our results may be influenced by the smaller sample size. Other studies have reported that 5-HTT polymorphism may not independently influence development of depression but rather through interaction effects with other psychosocial variables. The influence of the 5-HTTLPR on 5-HTT transcription in the brain may be modified by nongenetic factors including stress. Furthermore, as with functional major depression, multiple genes and complex gene interactions might be associated with depressive disorder after breast cancer.

In our results, the *s* allele of the 5-HTTLPR was associated with the severity of depressive symptoms in patients with reduced body image and sexual function. These findings suggest that the BIRS score, which is an index of psychosocial impairment, is a relatively important indicator of depression in individuals with the *s* allele who are genetically predisposed to depression. Further studies, preferably using family-based associations and various ethnic groups, are required to clarify the influence of serotonergic genes on depressive disorders and other psychosocial effects of such disorders.

These findings suggest that depression in breast cancer is influenced by psychosocial aspects and other factors such as genetic polymorphism. Therefore, despite the presence of similar clinical and demographic variables, depressive symptoms differ among individuals, which can be explained by the gene–environment interaction hypothesis.

Our study has several limitations. First, the sample size may have been inadequate. With our study parameters, the power analysis showed that our sample size could detect a small to medium effect. Second, only one polymorphism of the *5-HTT* gene was investigated in this study. Additionally, there was no follow-up assessment of the breast cancer patients, and some patients in the nondepressed group may have developed depression at a later stage. Furthermore, this sample was drawn from an out-patient clinic and most patients were ambulatory and of relatively well functioning, which limits generalization.

Despite these limitations, this is the first report, to date and to our knowledge, suggesting that the 5-HTTLPR genotype may contribute to the severity of depressive disorder after diagnosis of breast cancer and that the *s* allele is a predictor of depression severity via a gene–body image interaction effect.

Conclusion

Depression in patients with breast cancer is heterogeneous in its etiology and presentation. This is the first report suggesting that psychosocial factors influence susceptibility to depressive disorder after diagnosis of breast cancer, and genotype independently predicts depression severity via a gene–body image interaction effect. Depression may contribute to an unfavorable outcome in breast cancer patients; therefore, the BIRS scores and 5-HTTLPR genotypes are potentially of diagnostic, therapeutic, and prognostic value for depression in breast cancer patients.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108
2. Shin HR, Jung KW, Won YJ, Park JG (2004) 139 KCCR-affiliated Hospitals. 2002 annual report of the Korea Central Cancer Registry: based on registered data from 139 hospitals. Cancer Res Treat 36:103–114
3. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A et al (2005) Cancer statistics, 2005. CA Cancer J Clin 55(1):10–30
4. Ganz PA (2003) Why and how to study the fate of cancer survivors: observations from the clinic and the research laboratory. Eur J Cancer 39(15):2136–2141
5. Massie MJ (2004) Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 32:57–71
6. Schou I, Ekeberg O, Ruland CM, Sandvik L, Karesen R (2004) Pessimism as a predictor of emotional morbidity one year following breast cancer surgery. Psychooncology 13(5):309–320
7. Ayres A, Hoon PW, Franzoni JB, Matheny KB, Cotanch PH, Takayanagi S (1994) Influence of mood and adjustment to cancer on compliance with chemotherapy among breast cancer patients. J Psychosom Res 38(5):393–402
8. Ell K, Sanchez K, Vourlekis B, Lee PJ, Dwight-Johnson M, Lagomasino I et al (2005) Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. J Clin Oncol 23(13):3052–3060
9. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T (2003) Depression as a prognostic factor for breast cancer mortality. Psychosomatics 44(1):24–30
10. Bardwell WA, Natarajan L, Dimsdale JE, Rock CL, Mortimer JE, Hollenbach K et al (2006) Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 24(16):2420–2427
11. Vahdaninia M, Omidvari S, Montazeri A (2010) What do predict anxiety and depression in breast cancer patients? A follow-up study. Soc Psychiatry Psychiat Epidemiol 45(3):355–361
12. Montazeri A (2008) Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 27:32
13. Malhi GS, Moore J, McGuffin P (2000) The genetics of major depressive disorder. Curr Psychiatry Rep 2(2):165–169
14. Morris PL, Robinson RG, Raphael B, Samuels J, Molloy P (1992) The relationship between risk factors for affective disorder and poststroke depression in hospitalised stroke patients. Aust N Z J Psychiatry 26(2):208–217
15. Owens MJ, Nemeroff CB (1994) Role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. Clin Chem 40(2):288–295
16. Pirker W, Asenbaum S, Kasper S, Walter H, Angelberger P, Koch G et al (1995) Beta-CIT SPECT demonstrates blockade of 5HT-uptake sites by citalopram in the human brain in vivo. J Neural Transm Gen Sect 100(3):247–256
17. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S et al (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274(5292):1527–1531
18. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H et al (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301(5631):386–389
19. Anguelova M, Benkelfat C, Turecki G (2003) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: Ii. Suicidal behavior. Mol Psychiatry 8(7):646–653
20. Serretti A, Calati R, Mandelli L, De Ronchi D (2006) Serotonin transporter gene variants and behavior: a comprehensive review. Curr Drug Targets 7(12):1659–1669
21. Greenberg BD, Tolliver TJ, Huang SJ, Li Q, Bengel D, Murphy DL (1999) Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. Am J Med Genet 88(1):83–87
22. Grassi L, Rossi E, Cobianchi M, Aguiari L, Capozzo M, Martinis E et al (2010) Depression and serotonin transporter (5-HTTLPR) polymorphism in breast cancer patients. J Affect Disord 124(3):346–350
23. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
24. Lloyd-Williams M, Friedman T, Rudd N (2001) An analysis of the validity of the Hospital Anxiety and Depression Scale as a screening tool in patients with advanced metastatic cancer. J Pain Symptom Manage 22(6):990–996
25. Aaronson NK, Ahmedzai S, Bergman B, Li Q, Bengel D, Murphy DL (1983) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85 (5):365–376
26. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M et al (1996) The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 14(10):2756–2768
27. Yun YH, Park YS, Lee ES, Bang SM, Heo DS, Park SY et al (2004) Validation of the Korean version of the EORTC-QLQ-C30. Qual Life Res 13(4):863–868
28. Yun YH, Bae SH, Kang IO, Shin KH, Lee R, Kwon SI et al (2004) Cross-cultural application of the korean version of the European Organization for Research and Treatment of Cancer (EORTC) Breast-Cancer-Specific Quality of Life Qquestionnaire (EORTC QLQ-C30). Support Care Cancer 12(6):441–445
29. Collier DA, Stöber G, Li T, Heils A, Catalano M, Di Bella D et al (1996) A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry 1(6):453–460