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

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Kyung Ran Kim

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

<ABSTRACT>

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

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Nearly half of the women with breast cancer show depressive symptoms after diagnosis and treatment. The purpose of the present study was to clarify how psychosocial factors and genetic factors influence depression of women with breast cancer. As we expected, patients with depressive symptoms showed low self esteem, bad body image, more relationship problems, and low quality of life. Genotype and allele frequencies were did not differ between two groups divided by presence of depressive symptoms. However, we found that patients with the short allele of the 5HTTLPR had significantly higher scores on the HAM-D scores. The result suggests that the psychological problems related breast cancer treatment such as body image, self esteem, relationship problems affect on the depressive symptoms. 5HTTLPR associated polymorphism may be related to the severity of depressive symptoms rather than to the vulnerability to development of depressive symptoms.

Key words: Breast cancer, Depression, Body image, 5-HTTLPR

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1. INTRODUCTION

Breast cancer is the most common cancer in women worldwide regardless of the countries' level of development.[1] Among Korean women, breast cancer was the second most common cancer following gastric cancer in year 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 climbed to 96%, resulting in an estimated 2 million North American women living as survivors of breast cancer.[3] As survival times increase, an important goal for breast cancer patients and survivors is to improve their quality of life and reduce the adverse effect and impact of breast cancer and its treatment on long-term outcomes.[4]

Of various disturbances experienced by patients with breast cancer, depression is perhaps the most significant and best studied psychiatric problem. Reported rates of depression among women with breast cancer range from 1.5% to 50% depending on the assessment time, sample and particularly the 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 some depressive symptoms which cause significant impairment .[6] As might be expected, depression has a negative effect on all aspects of quality of life in cancer patients and is associated with poorer medical adherence [7], lack of understanding of treatment recommendations, worries about treatment adverse effects.[8] There is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients.[9] Thus, identification of patients likely to experience depression is critical to providing qualified care.

There are a number of factors that can influence depression in breast cancer patients. Psychosocial factors seem to be the well known risk factors of depressive symptoms in this population, including history of depression, poor social function, and occurrence of other stressful life events. Somatic factors, including pain, disability, and injured 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, including stage of disease, type of treatment received, and tamoxifen use.[10] These findings suggest that the occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen.

Over the last two decades, the etiological research in depression and breast cancer has only focused on the assessment of psychosocial, somatic and demographic risk factors. Whereas, role of biological factors as determinants of development of depression has been unconcerned. In recent years, the molecular genetic approach has been widely used to address the biological mechanisms contributing to inter-individual differences in susceptibility to depressive disorders. Therefore, it is increasingly believed that gene/environment interactions contribute to the etiology of mood disorders.[11] Although, the genetic hypothesis of depression secondary to medical condition has not been clearly examined to date, we should investigate the possibility of genetic

predisposition to depression in patients with breast cancer.[12]

The most widely reported genetic abnormality in depressive disorder involves serotonin system.[13] Serotonin transporter (5-HTT) is of particular interest because selective serotonin reuptake inhibitors, mainstream of treatment of depression, target the 5-HTT[14] and 5-HTT availability is critical in maintaining the homeostasis of serotonin function.[15] Also, 5-HTTLPR polymorphism has shown to influence the individual variation in the development of major depressive disorder in response to life stress.[16,17] A dysfunction of 5-HTT has been implicated in the etiology of psychiatric disorders such as mood disorders, obsessive-compulsive disorders, and substance related disorders.[18] The short form of this variant, labeled as s. is associated with lower basal and induced transcriptional efficiency of the 5-HTT gene promoter, resulting in lower serotonin uptake activity, compared with long form labeled as l.[19] The previous study related 5-HTTLPR genotypes and behavioral variants, the authors reported that subjects with 1or 2 copies of the s variant exhibit significantly greater levels of anxiety, hostility, depression than subjects with homozygous for the l genotype.[15]

Since breast cancer is a major life stress event and depressive disorder is associated with severe physical and psychosocial consequences in patients with breast cancer, it is possible that 5-HTTLPR may play a role in depression in patients with breast cancer. In the current study we investigated the depressive symptom profiles and other psychosocial variables in a sample of 186 patients with breast cancer in relationship to the 5-HTTLPR genotype.

II. METHODS

1. Participants

The subjects were consecutively recruited from out-patient populations of the Oncology Division of the Yonsei Cancer Center, Severance Hospital in Korea during 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, (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; (3) being treated for current psychiatric disorder. Axis I and axis II diagnoses were made using the Structured Clinical Interviews for DSM-IV by psychiatrist. The diagnosis of major depressive disorder was determined by using the Structured Clinical Interview for DSN-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 before the start of this study.

2. Clinical Measures

The Hospital Anxiety and Depression Scale (HADS) [20] is a widely used self-report instrument designed as a brief assessment tool of the distinct dimensions of anxiety and depression. It is a 14-item questionnaire that consists of two sub-scales of seven items designed to measure levels both of anxiety and depression. The ease, speed and patient acceptability of the HADS has led to it being applied to a wide variety of clinical populations where significant anxiety and depression may co-exist with the manifestation of physical illness and has also been used widely in the clinical oncology setting as a screening and research tool.[21] Body image and relationship scale (BIRS) is 32-item measures that captures experiences related to appearance, health, physical strength, sexuality, relationships, and social functioning that are unique to women diagnosed with breast cancer. Higher scores on each subscale indicated greater impairment.

Patients' QOL was 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 covering functional and

symptom-related aspects of QOL for cancer patients.[22] 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.[23] A high score for a functional scale 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 scale or 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.[24, 25] Depression severity was rated on Hamilton Depression Rating Scale (HAM-D) and all ratings were performed at the time of inclusion of the study.

3. DNA genotyping for the 5-HTTLPR polymorphous locus

Venous blood samples were obtained from the study subjects in EDTA vials, and the genomic DNA was isolated. The samples were stored at −20◦C until analysis was required. The applied 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 over 30 cycles (94◦C for 30 seconds, 61◦C for 30 seconds, 72◦C for 60 seconds) of reactions, an initial denaturation at 94◦C for 5 minutes, and a final extension period at 72◦C using a GeneAmp PCR system (Perkin-Elmer, Norwalk, CT). In order to distinguish the alleles, all the amplicons were separated by 2.5% agarose gel electrophoresis and stained with ethidium bromide. All laboratory procedures were performed blind to subject status.

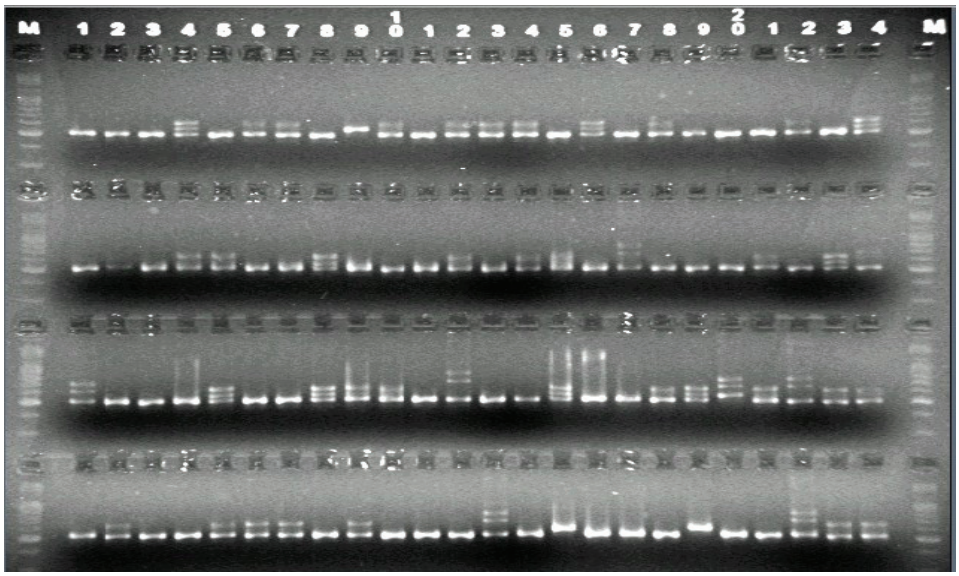


Figure 1. Agarose gel electrophoresis photograph of amplified genomic DNA

III. RESULTS

1. Subjects' characteristics

Among 200 consecutive patients with breast cancer, 186 fulfilled 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 Table 1. Depressed patients and non-depressed patients did not differ for age at evaluation, education, age at diagnosis, duration of illness, disease stage. As expected, a higher HAM-D score was observed in depressed patients ($t=-28.753$, $p<0.001$). The analysis of BIRS subscales showed depressed patients had greater impairments in strength and health, social barriers, appearance and sexuality. Quality of life assessment by QLQ-BR23 showed depressed patients reported poor body image ($t=3.569$, $p<0.001$) and worse future perspectives ($t=4.247$, $p<0.001$). Moreover, other items of body symptoms were severe in depressed patients.

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

Variable	Depressed (N= 49)	Non-depressed (N=137)	t/ χ^2	p
Age (y)	54.1±8.7	54.0±8.5	-0.95	0.924
Education (y)	11.4±3.5	8.3±3.3	0.934	0.352
Age at diagnosis (y)	47.1±8.4	46.0±8.4	-0.783	0.434
Duration of illness (y)	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 & 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

Note: HAM-D: Hamilton Depression Rating Scale; HADS-A: Hospital Anxiety Depression Scale-Anxiety; HADS-D: Hospital Anxiety Depression Scale-Depression; BIRS: Body Image and Relationship Scale; QLQ-BR23: Quality of Life Questionnaire Breast Cancer Module

2. Genotype distribution in depressed and non-depressed groups

The genotype distribution and the allele frequency in the depressed and non-depressed groups are shown Table 2. The genotype of non-depressed group was *s/s* (N=76, 55, 5%), *s/l* (N=54, 39.4%), *l/l* (N=7, 5.1%). Those of depressed groups was *s/s* (N=26, 53.1%), *s/l* (N=22, 44.9%), *l/l* (N=1, 2%). The frequency of 5-HTTLPR in the Korean population was in line with other previous reports. No significant differences were found in the 5-HTTLPR genotype and allele frequencies between the depressed and non-depressed group.

Table 2. Distribution of the 5-HTTLPR Genotype and allele frequencies in the depressed patients and non-depressed patients

Variables	Depressed (N= 49)	Non-depressed (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)		

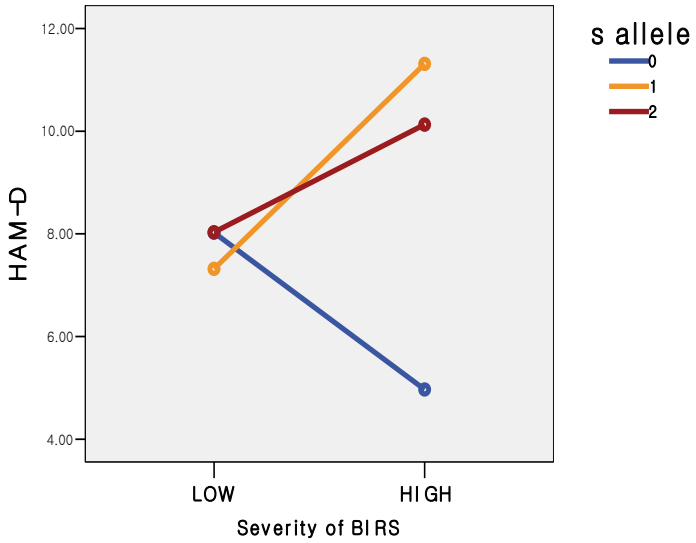
Note: 5-HTTLPR (serotonin-transporter-linked polymorphic region)

In order to determine whether the function of this polymorphism could be subtly different in the symptomatology of depression, clinical variables of the depressed patients were compared. In depressed patients, there was also no significant correlation between the genotype and the clinical variables.

A potential gene / environment interaction effect on severity of depression was tested by a general linear model with depression severity (Hamilton

depression scale score) as the dependent variables and 5-HTTLPR genotype and body image and other psychosocial variables as independent variables. The overall model was significant (F=1.084, p=0.03), and the interaction of genotype and BIRS scores (F=7.59, p=0.047). The s allele was associated with more severe depression in worse body image and sexual function groups (high BIRS scores group).

Figure 2. 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

IV. DISCUSSION

Consistent with the previous researches, depressive patients reported impaired scores on several measures of body image, sexual function, relational

problem, quality of life. However, contrary to our expectations, no significant relationships were found between the 5-HTTLPR polymorphisms in the 5-HTT gene and scores on various measures of psychosocial and clinical variables. In current results, breast cancer patients with depression put up with worse body image, lower sexual functioning and relationship problems. And short allele of 5-HTTLPR was related with severity of depressive symptoms and also and modulates the impact of body image and other psychosocial variables.

Previous research on breast cancer has focused primarily on treatment outcomes, such as rates of survival and recurrences; more recently, research has included the study of long-term effects of breast cancer treatment on outcomes such as quality of life. However, research on psychosocial outcomes in breast cancer survivors has traditionally utilized broad measures of quality of life, which generally suggests nonspecific psychological and social functioning. Specifically, BIRS targets specific components of psychosocial adjustment and function for breast cancer survivors that have not been captured by existing quality of life instruments. In this study, we compared those profiles to determine the effect of on the development of depressive symptoms by BIRS.

With regards to genetic polymorphism, the 5-HTTLPR allele s/s genotype occurred with a greater frequency in the control subjects and depressed patients. The frequency of the 5-HTTLPR genotype in this study is comparable with previous reports on the Asian population. Dysfunctional genes in the serotonergic system are plausible candidates for mediating the susceptibility to major depressive disorder. Among them, the presence of the s allele is associated with a lower level of both 5-HT uptake and transcriptional efficiency of the 5-HTT gene promoter than the l allele. Therefore, it was expected that there would be a different *s* and *l* allele distribution between the depressed patients and the controls.

In our investigations, there was no significant difference in the 5-HTTLPR genotype and allele frequency distribution between the patients and

controls. Despite ethnic variations, a 5-HTTLPR polymorphism does not appear to be involved in a genetic predisposition to depression after breast cancer. Lack of an allelic association among patients with breast cancer may indicate that the patho-physiology of depression in women with breast cancer is more heterogeneous than in general population. In other words, non-genetic factors, including psychosocial and other biological factors, may have a more important role in development of depression. Another explanation for the lack of a strong association in our study is related to small sample size. The study of Collier et al. examined about 2,000 subjects of affective disorders, so our results may reflect a smaller sample size. Other studies 5-HTT polymorphism itself may not mediate susceptibility to development of depression, but rather exert its effect through another interaction effect with other psychosocial variables. The expression of 5-HTTLPR on 5-HTT transcription in the brain may be modified by nongenetic factors, including stress. Furthermore, similar to functional major depression, it is possible that multiple genes and complex gene interactions might be associated with depressive disorder after breast cancer.

In our results, s allele of 5-HTTLPR was related with severity of depressive symptoms in worse body image and sexual function. These findings suggest that BIRS, which is an index of psychosocial impairments, may mediate a relatively large effect on depression in individuals with the s allele who are genetically predisposed to depression. Further studies, preferably using family based association approaches and on different ethnic groups, are required to clarify the influence of serotonergic genes on depressive disorder and other psychosocial correlates of such disorders.

These findings collectively suggest that depression in breast cancer is influenced not only by psychosocial factors but also other factors such as the genetic polymorphism. Therefore, despite the presence of similar clinical and demographic variables, the depressive symptoms differ from one individual to another, and this can be understood on the basis of gene-environment

interaction hypothesis.

Our study has several limitations. First, the sample size of this might not be enough. With our study parameters, the power analysis showed that our sample size had a power to detect a small to medium effect size. Second, only 1 polymorphism of 5–HTT gene was investigated in this association study. Additionally, we did not involve consecutive assessment of breast cancer patients, and some cases included in the non-depressed group may ultimately develop depression at a later stage. Furthermore, this sample was drawn from an outpatient clinic and the majority was ambulatory and relatively well functioning, which limits generalization.

Despite these limitations, this is the first report, to data and to our knowledge, suggesting that the genotype of 5-HTTLPR may contribute to the severity to depressive disorder after diagnosis of breast cancer and genotype predicts severity via a genotype or s-allele by body image interaction effect on depression severity.

V. CONCLUSION

Depression in patients with breast cancer is heterogeneous in its etiology and presentation. This is the first report suggesting that the integrative psychosocial factors may contribute to the susceptibility to depressive disorder after diagnosis of breast cancer and genotype independently predicts severity via a genotype or s-allele by body image interaction effect on depression severity. Since depression may be associated with a poor outcome of breast cancer patients, the BIRS scores and 5-HTTLPR might be diagnostic and potentially also of the therapeutic and prognostic value for depression in patients with breast cancer.

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<ABSTRACT (IN KOREAN)>

한국인 유방암 환자에서 우울증과 신체상, 성기능의 관계 및 5-HTT 유전자 다형성이 이에 미치는 영향

<지도교수: 남궁 기 교수>

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김 경 란

반 수 이상의 유방암 환자들이 진단 및 치료 이후 우울증상을 호소한다. 본 연구의 목적은 심리사회적 변인과 유전적 변인이 유방암 환자의 우울증에 어떻게 영향을 미치는지 알아보았다. 가설과 같이 우울 증상을 호소하는 환자들은 낮은 자존감, 손상된 신체 이미지, 대인 관계 문제, 낮은 삶의 질을 호소하였다. 유전자형과 대립유전자형의 빈도는 우울증의 유무에 따라 집단을 나누었을 때 차이를 보이지 않았다. 세로토닌 수송체 유전자 전사조절부위 (5-HTTLPR)의 S 대립유전자형은 높은 HAM-D 점수와 관련을 보였다.

본 연구 결과는 신체상, 자존감, 대인 관계 문제와 같은 유방암 치료와 관련된 심리적 문제들이 우울 증상에 영향을 준다는 것을 시사하며, 5-HTTLPR과 관련된 유전자 다형성은 우울 증상의 발생에 대한 취약성 보다는 우울 증상의 심각도와 관련

있다고 볼 수 있다.

핵심 되는 말: 유방암, 우울증, 신체상, 5-HTTLPR