MINIMAL DEPRESSIVE SYMPTOMS WERE ASSOCIATED WITH IMPAIRED HEALTH UTILITY VALUE AMONG BREAST CANCER PATIENTS: A PROSPECTIVE LONGITUDINAL STUDY

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INTRODUCTION

Depressive symptoms are frequently found in cancer patients, and these symptoms significantly deteriorate health-related quality of life (HRQOL). This is especially true in female cancer patients, as emotional distress, including depression or anxiety, occurs more frequently than in male patients. In particular, it has been found that women with breast cancer have higher levels of emotional distress because those experience not only pain from the disease state itself but also experience adverse effects from cancer treatment.

In outpatient cancer clinics, the depressive symptoms of patients are underestimated or even neglected. This is because breast cancer patients who are receiving adjuvant endocrine therapies (AET), include tamoxifen and aromatase inhibitors (AIs) such as letrozole and anastrozole, may experience several physical side effects including hot flushes, sweating, and joint pain. Oncologists are likely to perceive that relieving physical symptoms is much more important for improving the quality of life than managing depressive symptoms.

However, depressive symptoms in breast cancer patients have been associated with negative outcomes, such as more rapidly progressing symptoms, higher medication non-adherence, and poorer HRQOL. The health utility value (HUV), which is a component of the quality-adjusted life year (QALY) calculation, can be a good single indicator of a cancer patient's HRQOL status and an important element in healthcare policy decisions and cancer-based clinical studies.

There is growing evidence of depressive symptoms in breast cancer patients undergoing AET, but mostly limited to cross-sectional studies. Given this background, the aim of this study was to estimate patients' changes in relative utility value and depressive symptoms over a year period after having started AET according to AET types, and to predict the impact of depressive symptoms on HUVs between a year.

METHODS

Study design and population. Between 2018 and 2021, outpatients with breast cancer were recruited from the National Cancer Center. Of the 740 individuals enrolled, 638 breast cancer patients who completed the informed consent and questionnaires were eligible for the study and were included in the analysis (NCC2018-0151).

Measurements. The Patient Health Questionnaire-9 (PHQ-9) was used to assess the depressive symptoms in breast cancer patients. Higher scores of depressive symptoms indicated greater severity. HUV was measured using the 3-level version of the EuroQoL 5-dimension descriptive system (EQ-5D-3L; −1 [significant problems for all items] to 1 [no problems for all items]) and the EuroQoL visual analog scale (EQ-VAS; 0 [worst imaginable health state] to 100 [best imaginable health state]).

Statistical analysis. The association between AET types (AIs including anastrozole and letrozole vs. tamoxifen) and depressive symptoms was analyzed using the analysis of variance. Multivariable linear regression was used to predict the impact of depressive symptoms on HUVs between a year. Reported *p* values < 0.05 were considered significant.

RESULTS

The subjects' characteristics, stratified by the types of AET, are shown in Table 1. Among 638 patients with breast cancer, including 427 (66.9%) who received tamoxifen, HUV was significantly improved after a year ($p < 0.0001$ for the EQ-5D-3L and EQ-VAS, Table 2).

In Table 3, those with a PHQ-9 score of 5 or more at baseline had significantly improved depressive symptoms after a year ($p < 0.0001$), whereas those with minimal depressive symptoms (PHQ-9 score < 5) at baseline had significantly worse ($p < 0.0001$). The deterioration of PHQ-9 score among patients with minimal depressive symptoms was significant regardless of AET types ($p < 0.0001$ in AIs and tamoxifen group). However, the AIs group showed a more significant increase in PHQ-9 score ($p = 0.0141$).

The shrunk model after backward variable elimination with a cut-off *p*-value of 0.5 was summarized in Table 4. In patients with minimal depressive symptoms at baseline, the PHQ-9 score was significantly associated with a decrease in HUV ($p < 0.0001$ for the EQ-5D-3L and EQ-VAS). This association was also significant in analysis according to AET types ($p < 0.0001$ and $p = 0.035$ for the EQ-5D-3L and EQ-VAS in AIs group; $p < 0.0001$ and $p = 0.004$ for the EQ-5D-3L and EQ-VAS in tamoxifen group, respectively).

Table 2. Comparison of HUVs according to the AET types at baseline and after a year

Variables	Total (n = 638)			AIs (n = 211)			Tamoxifen (n = 427)		
	Baseline	After a year	*p* value[a]	Baseline	After a year	*p* value[a]	Baseline	After a year	*p* value[a]
EQ-5D-3L	0.872 ± 0.126	0.888 ± 0.133	0.0144	0.857 ± 0.128	0.846 ± 0.158	0.4227	0.880 ± 0.124	0.908 ± 0.113	<0.0001
EQ-VAS	66.58 ± 18.21	70.59 ± 17.37	<0.0001	66.57 ± 17.80	69.78 ± 18.29	0.0249	66.58 ± 18.43	70.99 ± 16.91	<0.0001

[a] Paired t-tests were conducted to compare the means between baseline and one-year follow-up.

Table 3. Comparison of PHQ-9 total score according to depressive symptoms at baseline by AET types at baseline and after a year

Variables	Total (n = 638)			AIs (n = 211)			Tamoxifen (n = 427)		
	Baseline	After a year	*p* value[a]	Baseline	After a year	*p* value[a]	Baseline	After a year	*p* value[a]
PHQ-9 total score 0–4 at baseline[b]	1.743 ± 1.453	3.792 ± 3.623	<0.0001	1.839 ± 1.430	4.580 ± 3.748	<0.0001	1.697 ± 1.464	3.415 ± 3.508	<0.0001
PHQ-9 total score ≥ 5 at baseline[b]	9.192 ± 4.525	6.572 ± 5.357	<0.0001	8.859 ± 3.799	6.818 ± 4.875	0.0003	9.363 ± 4.856	6.446 ± 5.597	<0.0001

[a] Paired t-tests were conducted to compare the means between baseline and one-year follow-up.
[b] Depressive symptoms were measured using the PHQ-9: minimal (scores 0 to 4) and mild–severe depressive symptoms (scores 5 to 27).

Table 1. Characteristics of the study subjects according to the AET types

Variables	Total (n = 638)	AIs (n = 211)	Tamoxifen (n = 427)	*p* value[a]
Age, mean ± SD (years)	50.3 ± 8.4	58.2 ± 5.2	46.4 ± 6.8	<0.0001
≤ 44; n (%)	154 (24.1)	2 (1.0)	152 (35.6)	<0.0001
45–54	284 (44.5)	49 (23.2)	235 (55.0)	
55–64	168 (26.3)	135 (64.0)	33 (7.7)	
≥ 65	32 (5.0)	25 (11.8)	7 (1.7)	
Marital status, n (%)				
Married	528 (82.8)	168 (79.6)	360 (84.3)	0.140
Single, widowed, or divorced	110 (17.2)	43 (20.4)	67 (15.7)	
Education status, n (%)				
High school or less	332 (52.1)	153 (72.9)	179 (41.9)	<0.0001
College or above	305 (47.9)	57 (27.1)	248 (58.1)	
Adjusted household income ($)[b], n (%)				
< $3,500	367 (57.5)	140 (66.3)	227 (53.2)	0.002
≥ $3,500	271 (42.5)	71 (33.6)	200 (46.8)	
Menopausal status, n (%)				
Pre-menopausal	350 (54.9)	2 (1.0)	348 (81.5)	<0.0001
Post-menopausal	288 (45.1)	209 (99.0)	79 (18.5)	
Childbirth experience, n (%)				
No	87 (13.6)	22 (10.4)	65 (15.2)	0.097
Yes	551 (86.4)	189 (89.6)	362 (84.8)	
Cancer stage, n (%)				
I or II	576 (90.3)	187 (88.6)	389 (91.1)	0.321
III or IV	62 (9.7)	24 (11.4)	38 (8.9)	
Radiation, n (%)				
No	56 (8.8)	13 (6.2)	43 (10.1)	0.101
Yes	582 (91.2)	198 (93.8)	384 (89.9)	
Comorbid illness, n (%)				
No	377 (59.1)	86 (40.8)	291 (68.1)	<0.0001
Yes	261 (40.9)	125 (59.2)	136 (31.9)	

[a] Chi-squared and t-tests were used to assess the significance of differences for categorical and continuous variables.
[b] KRW were converted into USD ($1 = 1,200 KRW).

Table 4. The multivariable analysis of the impact of paired PHQ-9 score on HUVs according to depressive symptoms at baseline

Variables	Total (n = 638)					
	EQ-5D-3L			EQ-VAS		
	β	95% CI	*p* value	β	95% CI	*p* value
PHQ-9 total score 0-4 at baseline[a]						
(Constant)	–0.007	–0.105 to 0.901	0.887	2.264	–5.345 to 9.873	0.559
Age	0.001	–0.001 to 0.002	0.406			
Marital status						
Single, widowed, or divorced	–0.027	–0.067 to 0.013	0.178	6.431	1.413 to 11.45	0.012
Education status						
College or above				–4.365	–8.522 to –0.209	0.040
Menopausal status						
Post-menopausal				2.534	–1.721 to 6.790	0.242
Childbirth experience						
Yes	–0.021	–0.066 to 0.024	0.361			
Cancer stage						
III or IV	–0.025	–0.074 to 0.023	0.311	–4.656	–11.39 to 2.082	0.175
Radiation						
Yes	–0.030	–0.080 to 0.021	0.248	–6.843	–13.79 to 0.107	0.054
Comorbid illness						
Yes				–5.619	–9.913 to –1.324	0.011
Paired PHQ-9 total score[b]	–0.012	–0.016 to –0.008	<0.0001	–0.994	–1.535 to –0.454	<0.0001

[a] Depressive symptoms were measured using the PHQ-9: minimal (scores 0 to 4) and mild–severe depressive symptoms (scores 5 to 27).
[b] To calculate the paired PHQ-9 total score, the PHQ-9 total score at baseline was subtracted from that at after a year.

DISCUSSION

In the present study, we report that depressive symptoms are one of the important determinants of HUV in breast cancer patients who received AET. While depressive symptoms score improved over time in patients with mild to severe depressive symptoms at baseline, those with minimal depressive symptoms at baseline had an increased depressive symptoms score, which was associated with impaired HUV. The results indicate that proper management even minimal depressive symptoms is important for improving the overall health status of breast cancer patients.

There are several limitations to the present study. First, the results of this study have limited generalizability to all breast cancer patients because a nonrandomized sample was recruited from a single center. Second, the follow-up period for assessing HUV and depressive symptoms was limited to a year after starting AET. A longer follow-up time may have revealed further or different changes. Finally, it is possible that uncaptured confounders may influence HUV.

The findings of this study suggest that even minimal depressive symptoms are independently associated with the decrease in overall health status, represented by HUV, in breast cancer patients who received AET. Thus, healthcare providers should screen breast cancer patients with depressive symptoms before initiating AET and make an effort to implement customized emotional interventions for each AET treatment period because depressive symptoms may change over time. Therefore, future studies with long-term multicenter follow-up are required to find the changes and associations between depressive symptoms and HUV.

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