





Health-related quality of life in long-term early-stage breast cancer survivors compared to general population in Korea

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Abstract

Purpose This study assessed health-related quality of life (HRQoL) of long-term breast cancer (BC) survivors diagnosed at early stages and compare with cancer-free, age-matched women.

Methods The study population included BC survivors diagnosed with ductal carcinoma in situ (DCIS) or breast cancer stages I-II, who had undergone lumpectomy/mastectomy, with time since diagnosis ranging from 9 to 16 years. Survey was conducted at two tertiary hospitals in 2020. Data for cancer-free female controls was randomly drawn from a population-based survey and age-, education-matched with 1 case: 3 controls ratio. Self-reported HRQoL was assessed using EQ-5D with five dimensions. EQ-5D utility index score was calculated. Difference in EQ-5D score was evaluated using the Tobit regression model with adjustment for other covariates.

Results Of 273 survivors, 88% and 12% underwent mastectomy and lumpectomy, respectively. The mean (standard deviation, SD) age at survey was 57.3 (8.5) years old. BC survivors reported significantly more problems performing daily activities (11% vs. 5%, $p < 0.001$), pain/discomfort (46% vs. 23%, $p < 0.001$), and anxious/depressed feelings (44% vs. 8%, $p < 0.001$) relative to the controls. Difference in EQ-5D score between BC survivors and the general population was higher in older age groups. The overall EQ-5D score of BC survivors was statistically lower than that of the control subjects (adjusted $\beta = 0.117$, $p < 0.001$).

Conclusion Long-term BC survivors who survived beyond ten years post-diagnosis experience more pain, anxiety, and distress, leading to an overall poorer HRQoL.

Implications for Cancer Survivors This study suggest the importance of follow-up care, particularly focusing on pain, anxiety, and distress management to enhance the HRQoL of long-term BC survivors.

Keywords Health-related quality of life · Breast cancer survivor · Anxiety · Depression · Pain

Introduction

With more than 2.3 million cases diagnosed in 2020 and 7.8 million survivors by the end of 2020, breast cancer (BC) has become the most prevalent cancer worldwide [1]. The implementation of national BC screening and enhancement in treatments has improved BC patients' five-year and ten-year survival rates to 90.1% and 84.6% [2], respectively.

Thus, more than two hundred thousand BC survivors were reported in South Korea [3]. In general, BC survivors might experience a wide range of adverse effects stemming from treatment [4]. Some of these effects last for a short period and have little impact on BC patients' health-related quality of life (HRQoL); however, some patients suffer from long-term complications that affect their HRQoL.

Due to the increase in the BC survivor population, there has been considerable interest in their HRQoL several years after treatment, especially in those who had undergone surgery for breast cancer. Most previous studies on BC survivors' HRQoL focused on the immediate period following primary treatment until five years post-diagnosis [5–7]. Few studies have assessed BC survivors' status beyond ten years post-diagnosis [8–10]. Previous studies suggest that BC

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survivors' HRQoL improves after treatment, allowing them to return to work and their daily routines [8, 11]. However, it is unclear if survivors' HRQoL is comparable to that of the general population.

Recent cancer statistics have reported that the median age of onset of BC among Korean women is around ten years earlier [12] than that among women in other countries, including China [13] and the US [14]. Thus, long-term Korean BC survivors might have different characteristics from BC survivors in other countries due to the age gap at the onset of the disease. Meanwhile, the majority of breast cancer patients undergo either breast-conserving therapy or mastectomy as one of the treatment modalities. Despite the previous literature on the impact on HRQoL in the early years post-operative, knowledge regarding the long-term impact of breast surgery on HRQoL has remained limited. To better understand the status of long-term BC survivors, this study investigated the HRQoL of long-term survivors and the difference in HRQoL reported by the cancer-free general population.

Materials and methods

Participants and procedures

Two data sources were utilized in this study. The first data source consisted of information on 333 BC survivors who had been diagnosed with *ductal carcinoma* in situ or invasive breast cancer stages I to II between 2004 to 2011 at two tertiary hospitals in Korea, namely the National

Cancer Center and Samsung Medical Center. These patients had been previously recruited for participation in cohort studies, and details regarding the initial recruitment process can be found elsewhere [15–18]. In 2020, the survivors were contacted and invited to take part in a long-term follow-up assessment in order to evaluate their status as long-term survivors. The mean (standard deviation, SD) time since cancer diagnosis to the long-term FU survey was 11.6 (2.7) and the median was 10 years (interquartile range 10–14 years). Participants who had been diagnosed at advanced stages or had a history of recurrence were excluded from the analysis. The final number of long-term BC survivors was 273 participants (Fig. 1).

In order to compare HRQoL of BC survivors, the control subjects were randomly selected from the Korea National Health and Nutrition Examination Survey (KNHANES) [19]. The KNHANES is a cross-sectional, nationally representative survey conducted by the Korean Center for Disease Control and Prevention to assess the Korean general population's health and nutritional status. We used KNHANES data collected between 2015 to 2019. Women with a history of any cancer type and missing HRQoL measure were excluded. As previously documented in other studies [20, 21], both age and education level have been demonstrated to be associated with HRQoL, rendering them significant potential confounding factors affecting individuals' HRQoL. Given the discrepancy in age and education level distribution between the long-term breast cancer (BC) survivors and KNHANES data, we employed a frequency matching process to ensure

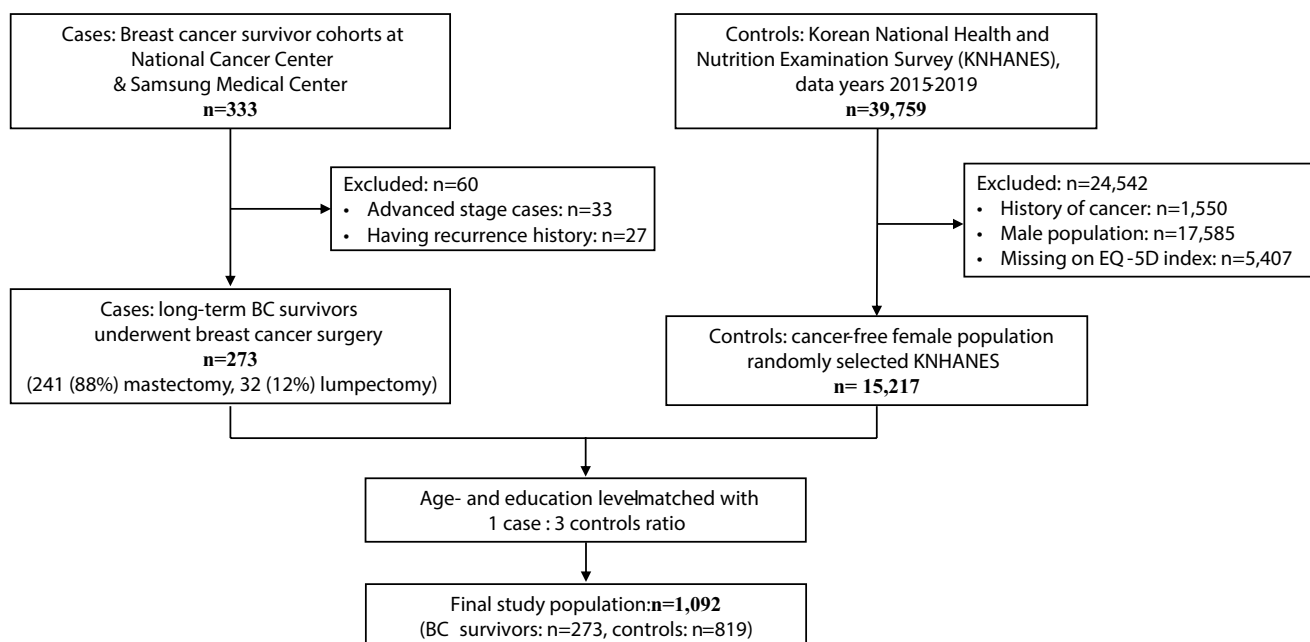


Fig. 1 Flow diagram of the selection of the study population

that controls were matched to BC survivor cases based on both age and education level with a ratio of one case to three controls.

This study was approved by the National Cancer Center's institutional review board (IRB approval number: NCC2019-0281). For breast cancer survivors, we obtained written informed consent forms directly from all participants in our study. The KNHANES data are de-identified and publicly available for research. We used a de-identified public version of the KHANES data provided by the Korean CDC.

Outcome measurement

Health-related Quality of Life. HRQoL was measured using the EuroQol 5-Dimension Questionnaire (EQ-5D). The Korean version of the EQ-5D has been cross-cultural adapted and validated in a previous study [22]. The five dimensions of EQ-5D corresponding to five items include mobility, self-care, daily activities, pain/discomfort, and depression/anxiety. Participants respond to the EQ-5D items in three levels: "no problems," "moderate problems," and "severe problems." In this study, we categorized these responses into two groups: "non-problematic" and "problematic" (presenting either moderate or severe problems). To calculate EQ-5D utility index score, we applied the weighted quality values for the Korean population [23]. EQ-5D score ranges from -0.17 to 1, with a higher value indicating better HRQoL status [24]. For the EQ-5D index, a difference of 0.07 or higher is considered a meaningful minimal clinical difference [25, 26].

Covariate measurement

The socio-demographic factors assessed include age, marital status, household income, education level, and employment status. Health-related factors include comorbidity status, menopausal status, age at menopause, pregnancy history, and BMI. Marital status has two values, "married and living with spouse" and "other" (e.g., single, widowed). Education was categorized into no education or primary school, middle school graduate, high school graduate, university graduate, and graduate/post-graduate degree.

Statistical analysis

The statistical significance of differences in demographic characteristics was tested using Fisher's exact test or a *t-test* where appropriate. We assessed differences between BC survivors and the general population in the following outcomes: reporting problems in the five EQ-5D dimensions and overall QoL measured by EQ-5D index. Due to the ceiling effect of the EQ-5D index, we implemented Tobit regression [27], considering the right censor of the scores and adjusted for other covariates in the model. The Tobit regression is a

regression model utilized when there is censored data [27], and has been applied in previous studies [28–30]. The difference in EQ-5D index thus was modeled using the univariable and multivariable Tobit regression model. The factors adjusted in the multivariate model include education level, marital status, employment status, menopausal status, pregnancy history, obesity status, and comorbidity status.

In addition, we conducted further sensitivity analyses using two different matching approaches: age-matching only and selecting controls without any matching variables (random sample). More details regarding the sensitivity analysis can be found in the supplemental materials. All analyses were conducted using SAS software, version 9.4 (SAS Institute). Figures were plotted using R software version 3.6.1 (R Foundation for Statistical Computing). All analyses were conducted with a two-sided type I error and an alpha of 0.05.

Results

Of 273 BC survivors and 819 cancer-free control subjects, the mean (SD) age was 57.3 (8.5) and 57.2 (8.6) years old, respectively, and more than 70% were less than 65 years old (Table 1). Among BC survivors, the proportion of married and living with spouse women was significantly lower than that among non-cancer controls (71.8% vs. 79.7%, $p=0.003$).

In terms of health-related characteristics, long-term BC survivors had a significantly higher proportion of menopausal women (83.2% vs. 73.6%, $p<0.001$), younger age menopause (48.9 vs. 50.0 years old, $p<0.001$), and later age at first birth (27.1 vs. 26.0 years old, $p<0.001$). Further, the two groups had a similar proportion of common comorbidities, including hypertension, arthritis, diabetes, thyroid, depression, cataract, and allergic rhinitis.

Among the EQ-5D dimensions, the two groups reported less problems in mobility, self-care, and usual activities dimensions in general. (Fig. 2) The long-term BC survivor group reported significantly fewer mobility problems (4% vs. 10%, $p<0.001$) compared to the general population. However, BC survivors reported significantly more problems in daily activities (11% vs. 5%, $p<0.001$), pain/discomfort (46% vs. 23%, $p<0.001$), and anxiety/depression dimensions (44% vs. 8%, $p<0.001$).

A significant difference in EQ-5D index scores between the two groups was observed across various demographic groups, and EQ-5D index scores of the BC survivors were lower than that of the general population. (Table 2) The difference in EQ-5D index score was higher in younger age groups: 0.015 in the age group ≥ 65 ($p=0.001$), 0.044 in the age group 50 to <65 ($p<0.001$), and 0.049 in ≤ 50 age group ($p<0.001$). Among participants with high school and

Table 1 Demographic and health-related characteristics of BC survivors compared with the general population

Characteristics	BC survivors		General population		<i>p</i> -value [†]
	<i>n</i> =273	%	<i>n</i> =819	%	
Age, years (mean, SD)	57.3	8.5	57.2	8.6	0.797
Age group					
≤ 50 years	50	18.3	151	18.4	0.907
50 to < 65 years	162	59.3	475	58.0	
≥ 65 years	61	22.3	193	23.6	
Education level:					
Primary school or lower	12	4.4	36	4.4	1.000
Middle school	27	9.9	81	9.9	
High School	119	43.6	357	43.6	
University or higher	115	42.1	345	42.1	
Marital status:					
Married & living with spouse	196	71.8	653	79.7	0.006
Other	77	28.2	166	20.3	
Employment status					
Housewife/unemployed	148	54.2	320	44.8	0.008
Employed	125	45.8	394	55.2	
Menopausal status					
Yes	227	83.2	603	73.6	0.001
No	46	16.9	216	26.4	
Age at menopause, years	48.9	5.4	50.0	4.2	<0.001
Pregnancy history, have given birth	246	90.4	787	98.5	<0.001
Age at first birth, years (mean, SD)	27.1	3.7	26.0	3.5	<0.001
BMI (mean, SD)	23.1	3.1	23.5	3.1	0.052
Weight status					
Underweight (BMI < 18.5)	12	4.4	28	3.4	0.072
Normal (18.5 ≤ BMI < 23)	133	48.9	372	45.5	
Overweight (23 ≤ BMI < 25)	71	26.1	184	22.5	
Obese (BMI ≥ 25)	56	20.6	233	28.5	
Obesity (BMI ≥ 25)					
No	216	79.4	584	71.5	0.010
Yes	56	20.6	233	28.5	
Comorbidity status	159	58.2	470	57.4	0.804
Comorbidities by type					
Hypertension	65	23.8	177	21.6	0.449
Arthritis	48	17.6	144	17.6	1.000
Diabetes	28	9.9	56	7.0	0.064
Thyroid	24	8.8	67	8.2	0.752
Depression	19	6.9	46	5.6	0.417
Cataract	20	7.3	62	9.9	0.222
Allergic rhinitis	34	12.5	116	14.2	0.477

BC breast cancer, SD Standard deviation, BMI body mass index

[†] *p*-values were obtained from t-test and Chi-squared tests

university/post-graduate education levels, the EQ-5D index reported by long-term BC survivors was significantly lower than that reported by the non-cancer control group (difference 0.069, $p < 0.001$).

In the regression model, after adjusting for other covariates, long-term BC survivors had significantly

lower EQ-5D scores than the general population with $\beta = -0.117$ ($p < 0.001$). (Table 3), Consistently, the sensitivity analyses yielded a significantly lower EQ-5D score in the long-term BC survivors compared with that of the general population. For more details, see Supplemental Table 1. BC survivors who exhibited arthritis (0.061, $p < 0.001$)

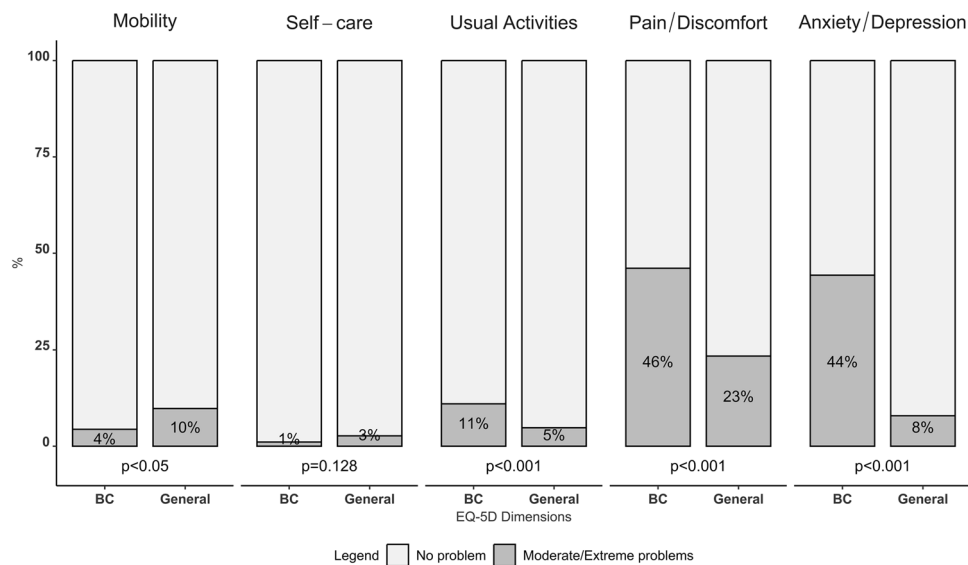


Fig. 2 Differences in EQ-5D dimensions between long-term breast cancer survivors and the general population. *P*-values were obtained from Chi-squared test. The numbers of participants among breast cancer survivors who reported problem in five dimensions are as follows: mobility 12/273; self-care 3/273; usual activities 30/273; pain/discomfort 126/273; and anxiety/depression 121/273. The numbers of

participants among general population who reported problem in five dimensions are as follows: mobility 80/819; self-care 22/819; usual activities 39/819; pain/discomfort 192/819; and anxiety/depression 65/819. BC, breast cancer long-term survivors; General: age- and education-matched general population

and depression (0.094, $p < 0.001$) reported a lower EQ-5D score than individuals exhibiting no comorbidities.

Discussion

Although the negative effects of cancer persist long after treatment completion and have a detrimental impact on the HRQoL of cancer survivors, there is a lack of focus on the HRQoL of long-term survivors, especially those who have surpassed the ten-year mark since diagnosis. This study population possesses unique characteristics. First, it targeted early-stage BC survivors with long-term survival periods, ranging from 9 to 16 years since diagnosis. Moreover, considering the earlier age at which Korean women develop BC [12], the study focused on individuals diagnosed at a young age, with an average of 45 years. The extended survival time and early age at diagnosis of our long-term BC survivors distinguish our findings from previous studies and enhance the value to this research. Given the increasing number of long-term BC survivors and the scarcity of information regarding their HRQoL in comparison to the general population, our findings can help identify the extent to which the HRQoL of long-term BC survivors differs from that of age-matched women without a cancer history. Overall, our findings indicated that long-term survivors are more likely to experience pain, discomfort, anxiety and depression compared to their cancer-free counterparts. Additionally, they

face greater difficulties in performing daily activities, such as work, housework, and family activities. Consequently, their overall quality of life (QoL) appears to be poorer than that of the general population, with a notable difference of 0.09 in the EQ-5D index. This evidence can be valuable in addressing the challenges faced by long-term BC survivors and providing essential information for the development of support programs tailored to this specific population.

We observed that long-term BC survivors have a significantly lower overall HRQoL compared to age-matched controls, with an effect size of 0.117. This difference, as found in our study, is both statistically significant and clinically meaningful, surpassing the minimal clinical difference of 0.07 for EQ-5D index [25, 26]. Consistent with previous research, our findings align with the notion that BC cancer survivors generally report poorer overall health status than the general population [31, 32]. For instance, a study focusing on long-term cancer survivors, more than five years post-diagnosis, discovered that these survivors experienced worse physical function, role, and emotional well-being compared to the general population [32]. However, it is worth noting that some studies have reported no significant disparities in overall HRQoL when comparing BC survivors with the general population [8, 9, 33].

Roughly half of the participants in our study reported experiencing moderate to severe pain and discomfort, which was 2.5 times higher than what was reported by women in the control group. Chronic pain, characterized as pain

Table 2 EQ-5D index by demographic and health characteristics of long-term BC survivors and non-cancer controls

Characteristics	BC survivors		Controls		Diff	<i>p</i> -value [†]
	Mean	SD	Mean	SD		
Total	0.919	0.082	0.957	0.085	0.038	<0.001
Age group						
≤ 50 years	0.923	0.066	0.972	0.082	0.049	<0.001
50 to < 65 years	0.922	0.081	0.966	0.066	0.044	<0.001
≥ 65 years	0.907	0.094	0.923	0.115	0.015	0.001
Education level:						
University or higher	0.846	0.138	0.915	0.095	0.069	0.018
High School	0.926	0.069	0.916	0.130	-0.010	0.097
Middle school	0.920	0.079	0.957	0.090	0.037	<0.001
Primary school or lower	0.924	0.076	0.970	0.056	0.047	<0.001
Marital status:						
Other	0.919	0.082	0.961	0.075	0.042	<0.001
Married, living with spouse	0.919	0.082	0.941	0.115	0.023	<0.001
Employment status						
Housewife/unemployed	0.924	0.079	0.965	0.067	0.041	<0.001
Employed	0.912	0.084	0.945	0.102	0.033	<0.001
Menopausal status						
Yes	0.916	0.085	0.953	0.086	0.037	<0.001
No	0.934	0.063	0.967	0.080	0.033	<0.001
Pregnancy history						
No	0.921	0.087	0.962	0.075	0.041	<0.001
Yes	0.919	0.081	0.956	0.086	0.038	<0.001
Weight status						
Underweight (BMI < 18.5)	0.899	0.070	0.962	0.055	0.063	0.178
Normal (18.5 ≤ BMI < 23)	0.926	0.076	0.964	0.086	0.038	<0.001
Overweight (23 ≤ BMI < 25)	0.929	0.070	0.955	0.081	0.027	<0.001
Obese (BMI ≥ 25)	0.893	0.104	0.945	0.088	0.053	<0.001
Obesity						
No	0.926	0.074	0.961	0.083	0.036	<0.001
Yes	0.893	0.104	0.945	0.088	0.053	<0.001
Comorbidity status						
No	0.931	0.076	0.974	0.059	0.043	<0.001
Yes	0.910	0.085	0.944	0.098	0.034	<0.001
Comorbidities by type						
Hypertension	0.899	0.096	0.961	0.081	0.062	0.064
Arthritis	0.886	0.102	0.911	0.118	0.025	0.020
Diabetes	0.904	0.086	0.934	0.108	0.030	0.695
Thyroid	0.906	0.131	0.940	0.121	0.034	<0.001
Depression	0.874	0.073	0.909	0.146	0.035	<0.001
Cataract	0.899	0.100	0.930	0.111	0.031	0.103
Allergic rhinitis	0.902	0.088	0.955	0.084	0.053	<0.001

BC breast cancer, SD Standard deviation, BMI body mass index

[†] *p*-value was obtained from Wilcoxon's signed-rank test

occurring on most days or every day over the past six months [34], is a prevalent long-term consequence of cancer treatment and has been linked to a decline in QoL [35]. Recent studies have indicated that 10% to 30% of cancer survivors suffer from chronic pain [34, 36]. Persistent pain among BC

survivors can impede their ability to carry out daily activities, necessitating effective management strategies. Earlier research has also highlighted that BC survivors experience higher levels of pain intensity and unpleasantness compared to women in the general population. These factors

Table 3 Univariable and multivariable Tobit regression model for EQ5D utility index

Characteristics	Univariable model			Multivariable model [†]		
	β	SE	<i>p</i> -value	β	SE	<i>p</i> -value
Controls	Ref			Ref		
BC survivors	-0.110	0.014	<0.001	-0.117	0.014	<0.001
Age	-0.004	0.001	<0.001	-0.001	0.001	0.521
Education level:						
University or higher	Ref			Ref		
High School	-0.023	0.001	0.099	0.008	0.023	0.610
Middle school	-0.076	0.020	0.005	-0.038	0.031	0.102
No education/Primary school	-0.125	0.025	<0.001	-0.073	0.012	0.020
Marital status:						
Others	Ref			Ref		
Married & living with spouse	0.036	0.015	<0.001	0.024	0.017	0.141
Employment status						
Employed	Ref			Ref		
Housewife/unemployed	0.032	0.014	0.001	0.030	0.014	0.032
Menopausal status (Ref.: yes)	-0.049	0.016	<0.001	0.020	0.021	0.335
Pregnancy history (Ref.: yes)	-0.038	0.034	0.268	0.008	0.032	0.805
Obesity (Ref.: yes)	0.036	0.012	0.015	0.033	0.016	0.033
Comorbidity status: (Ref.: yes)	0.071	0.014	<0.001	0.017	0.019	0.393
Comorbidities by type: (Ref.: yes)						
Hypertension	0.044	0.015	0.003	-0.009	0.019	0.634
Arthritis	0.107	0.016	<0.001	0.061	0.018	<0.001
Diabetes	0.056	0.015	<0.001	-0.006	0.025	0.791
Thyroid	0.033	0.023	0.149	0.032	0.023	0.170
Depression	0.112	0.025	<0.001	0.094	0.027	<0.001
Cataract	0.055	0.023	0.016	0.015	0.024	0.522
Allergic rhinitis	0.015	0.019	0.412	-0.002	0.021	0.938

BC breast cancer, SE standard error; Ref., reference group; β , beta coefficient

[†] Multivariable model was adjusted for age, education, marital status, employment status, menopausal status, obesity status, comorbidity status and other disease status

are significantly associated with depressive symptoms, pain-related worry, and interference with daily functioning [37]. The observed disparities in pain experiences between BC survivors and women without a history of BC underscore the critical importance of proper chronic pain management in the survivorship phase.

In this study, long-term BC survivors reported a higher prevalence of depression and anxiety-related problems. This finding aligns with a previous study conducted on Korean BC survivors, which also reported higher levels of anxiety and depression compared to women without BC [38]. However, contrasting results were found in a recent cross-sectional study on Korean cancer survivors, where community-dwelling cancer survivors exhibited low depression scores, suggesting that depression is uncommon in this population [33]. Consequently, the evidence regarding depression among cancer survivors in comparison to the general population remains inconclusive. Furthermore, it is important to consider that self-reported depressive symptom may vary

and should be understood within the appropriate context, which can differ based on ethnic and cultural factors.

Several limitations should be acknowledged in our study. Firstly, the HRQoL of BC survivors was assessed using the EQ-5D questionnaire. Although EQ-5D is widely used to measure HRQoL [19], concerns have been raised about its ceiling effects when employed in the general population [39, 40]. This issue was also evident in the KNHANES data, where 60.5% of participants reported a perfect EQ-5D score [41]. Therefore, caution should be exercised in interpreting the EQ-5D utility index scores in this study due to the potential ceiling effects. Secondly, the relatively small sample size prevented us from conducting further stratified analyses based on cancer stage or age at diagnosis. Thus, our results should be interpreted with caution, particularly because 90% of the study participants were BC stage 0 to II, indicating that they would generally have better HRQoL compared to patients with advanced-stage BC. However, despite the limited number of participants, our control group

was representative due to the nationwide distribution of the KNHANES data, while the long-term BC survivor data were collected from two tertiary hospitals in Korea.

In conclusion, our findings offer valuable insights into the HRQoL reported by long-term BC survivors. We identified a significant disparity in pain and anxiety levels among long-term BC survivors, which adversely affected their overall HRQoL when compared to the general population. These findings have important implications for clinicians and healthcare providers in developing targeted long-term follow-up care for cancer survivors. Furthermore, the effective management of pain and psychological concerns should be a key focus in the design and implementation of survivorship programs for long-term BC survivors. By addressing these specific areas, we can strive to enhance the well-being and overall quality of life of individuals who have completed their BC treatment.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11764-023-01482-2>.

Author contributions Thi Xuan Mai Tran: Conceptualization, data curation, methodology, formal analysis, writing—original draft; So-Youn Jung: Conceptualization, data curation, supervision, writing—review and editing; Eun-Gyeong Lee: Conceptualization, data curation, and writing—review and editing; Heeyoun Cho: Project administration, writing—review and editing; Na Yeon Kim: Conceptualization, project administration, writing—review and editing; Sungkeun Shim: data curation, writing—review and editing; Ho Young Kim: data curation, writing—review and editing; Danbee Kang: Conceptualization, data curation, writing—review and editing; Juhee Cho: Conceptualization, supervision, methodology and writing—review and editing; Eunsook Lee: Conceptualization, supervision and writing—review and editing; Yoonjung Chang: Conceptualization, funding acquisition, methodology, supervision and writing—review and editing; Hyunsoon Cho: Conceptualization, methodology, formal analysis, supervision, writing—original draft.

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Data Availability The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval This study was approved by the National Cancer Center's institutional review board (IRB approval number: NCC2019-0281). The written informed consent forms were obtained.

Competing interests The authors declare no competing interests.

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