Health-Related Quality of Life and Sociodemographic Characteristics as Prognostic Indicators of Long-term Survival in Disease-Free Cervical Cancer Survivors

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Objectives: Health-related quality-of-life (HRQOL) issues of cancer patients are considered an important clinical outcome. We aimed to investigate the prognostic value of HRQOL on long-term survival outcomes in disease-free cervical cancer survivors (CCSs).
Methods: The study sample consisted of 860 disease-free CCSs from 6 Korean cancer hospitals recruited for HRQOL survey during 2005 (median time from diagnosis, 5.9 years). Health-related quality-of-life measures included the European Organization for Research and Treatment of Cancer QLQ-C30 and its Cervical Cancer Module (CX24). Survival data were retrieved from the Korean Statistical Office after 6 years from the survey. Health-related quality-of-life domains along with sociodemographic and clinicopathologic variables were analyzed as prognostic factors for survival from the date of survey.
Results: During the median follow-up period of 6.3 years after the survey, 30 (3.5%) patients died from all causes. Age, time since diagnosis, and physical activity were independent prognostic factors, which constituted the baseline model along with cancer stage. When HRQOL domains were tested separately against the baseline model, functional scales (physical, role, social, and emotional functioning), global health status, symptom scales (pain and appetite loss), and cervical cancer module items (body image, sexual inactivity, and sexual worry) were significantly associated with survival ($P < 0.05$).
Conclusions: These findings suggest that, in addition to well-known prognostic factors, including age, time since diagnosis, and physical activity, HRQOL scores obtained from disease-free CCSs are associated with survival.

Key Words: Cervical cancer, Cancer survivorship, Health-related quality of life, Prognostic factors

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Cervical cancer is the third most commonly diagnosed cancer in women worldwide according to statistics in 2008.[1] Because of the widespread implementation of screening programs and advances in treatment, the survival rate of cervical cancer has markedly increased and the 5-year survival rate for early-stage cervical cancer has exceeded 90%.[2] In Korea, where nationwide cancer screening has been performed since 1999, the 10-year relative survival of cervical cancer is estimated to be 77.7% and the proportion of long-term survivors (>5 years after diagnosis) among the total cervical cancer patient population is more than 60%.[3]

Along with the increased number of long-term cancer survivors, health-related quality-of-life (HRQOL) issues have been considered an important clinical outcome. Cancer survivors who have overcome the immediate effects of cancer and cancer treatment need a more comprehensive follow-up program that includes monitoring of multidimensional health problems, such as physical, psychological, social, and spiritual health issues. In this respect, HRQOL data or patient-reported outcomes (PROs), which can be used as measures of the overall well-being and functioning of patients, may be used as complementary monitoring tools in routine follow-up practice for cancer survivors. Routine assessment of HRQOL in oncology practice was shown to positively impact physician-patient communication and to improve HRQOL and emotional functioning in some patients.[4]

In addition to their utility in assessing patient well-being and facilitating clinical decision making, recent studies have suggested that HRQOL data can also provide distinct prognostic information.[5,6] Global quality of life, functioning domains, and symptom scores were shown to be predictive of survival duration in various cancers, including breast cancer, lung cancer, and head and neck cancer.[7–9] However, most of these studies were done during the treatment phase, and these results might not be applied directly to long-term cancer survivors. In cervical cancer, research on the relationship between HRQOL and survival is at an early stage. Most of the studies investigating HRQOL among cervical cancer survivors (CCSs) were either descriptive of long-term physical and psychosocial sequelae in comparison with the general population or performed at baseline during clinical trials.[10–13] There has been only 1 study on the association between HRQOL and survival among multiethnic CCSs.[14]

In 2005, we performed a multicenter survey on disease-free CCSs to evaluate HRQOL and sexual function and demonstrated that CCSs had worse HRQOL problems than did the general population and that the type of treatment, presence of comorbidities, and unemployment status affected HRQOL.[15–17] If HRQOL is predictive of survival among long-term CCSs, self-reported HRQOL measures may be practical and reliable monitoring tools for disease-free CCS. Therefore, based on the previous survey data of HRQOL scores among CCSs, the present study aimed to investigate the potential impact of HRQOL and explore its prognostic value along with sociodemographic and clinical variables on long-term survival outcomes of CCSs.

MATERIALS AND METHODS

Study Design and Participants

This study was conducted using data from the previous cross-sectional survey study of disease-free CCSs which was surveyed in 2005.[15] For this study, women who had undergone treatments for cervical cancer between 1983 and 2004 were screened from 6 Korean hospital–based cervical cancer registries. The inclusion criteria were as follows: (1) stage I to IVa cervical cancer, (2) on no current cancer therapy, (3) currently free of the disease, and (4) no other history of cancer.

Of the 5943 cervical cancer patients contacted from the registries, 3127 (52.6%) patients were unable to be reached. Among the remaining 2814 patients, 1887 patients agreed to participate in the study and we sent them a questionnaire with a postage-paid return envelope. However, of those, only 898 (47.6%) women returned the survey questionnaire. After excluding 38 patients whose cancer had recurred or who were receiving cancer therapy, 860 survivors remained for the study analysis. The study was approved by the institutional review board of each hospital. Detailed procedures for the enrollment of survivors were described in previous studies.[15]

Measures

During the survey, sociodemographic variables (age, marital status, income, physical activity, smoking and alcohol history, comorbidities) were inquired through systematically organized questionnaire items. Regular physical activity was defined as at least 30 minutes of moderate-to-vigorous physical activity 5 or more days per week (eg, ≥12.5 MET/week). In addition, clinicopathologic data (stage, treatment modalities, treatment compliance, and regular check-ups) were collected from medical charts and hospital-based cancer registries.

Health-Related Quality of Life

The HRQOL measurements used in the study include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) and its cervical cancer module (QLQ-CX24).

The EORTC QLQ-C30 is a 30-item cancer-specific questionnaire for measuring the general HRQOL of cancer patients. It incorporates 5 functioning domains (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), global health, and overall QOL scales and 6 single items that assess additional symptoms commonly reported by cancer patients

744

(dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) along with perceived financial difficulties.

The EORTC QLQ-CX24 incorporates 3 multi-item scales (symptom experience scale, body image scale, and sexual/vaginal functioning scale) and 6 single-item scales. All scores on the EORTC QLQ-C30 and QLQ-CX24 were transformed to a 0- to 100-scale according to the EORTC QLQ scoring manual.[18] For all missing data (one or more missing answers to items within the questionnaire), we used methods of missing imputations introduced in the manual. Higher scores represent better levels of functioning or worse levels of symptoms. The internal consistency of the HRQOL was assessed among the subjects in this study with Cronbach α, which was 0.921 for all variables.

Survival Data

We retrieved mortality data from the National Statistical Office. *Overall survival* was defined as the time elapsed from the date of survey to the date of death from any causes or to the date of the last contact. Survival status was censored up to December 31, 2011. During the study process of linkage with survival data, 4 CCS patients whose survival status was not matched were excluded from the study analysis.

Statistical Analysis

First, we performed univariate analysis on the aforementioned sociodemographic and clinicopathologic variables. Variables that were significant in univariate analysis were included in multivariate regression analysis using backward selection to identify the independent prognostic indicators of survival, which formed the baseline prognostic model.

Next, because of the statistical problem of high collinearity among the HRQOL variables, each HRQOL variable was tested separately in the Cox proportional hazard model, which incorporates the baseline prognostic model to identify independent HRQOL prognostic indicators for long-term survival. For the statistical analysis, we dichotomized each scale of EORTC QLQ-C30 and QLQ-CX24 based on QOL scores into problematic and nonproblematic. The *problematic group* was defined as one with a global HRQOL or functioning score of 33 or less or with a symptom score of more than 66.[19,20]

For each HRQOL item, adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were computed. A value of $P < 0.05$ was considered to indicate statistical significance. The statistical analysis was performed using SPSS for Windows (version 19.0; SPSS Inc, Chicago, Ill).

RESULTS

The mean age of the final 856 CCSs at the time of the original HRQOL study was 55 years. The median time interval between cancer diagnosis and survey was 5.9 years (range, 1.0–23.1 years). At the time of the present survival analysis study, the median time since cancer diagnosis was 12.1 years (range, 2.6–29.4 years). The sociodemographic and clinical characteristics of the study population are summarized in Tables 1 and 2.

TABLE 1. Clinical characteristics of 856 CCSs

Variables	No. (%) Patients
Mean age at survey (range), y	55.1 (30–87)
Mean age at diagnosis (range), y	48.6 (26–83)
Stage	
IA1-IB1	572 (66.8)
IB2-IVA	266 (31.1)
Unknown	18 (2.1)
Treatment	
Surgery only	503 (58.8)
Surgery + chemotherapy	118 (13.8)
Surgery + radiotherapy	50 (5.8)
Surgery + chemotherapy + radiotherapy	51 (6.0)
Radiotherapy only	59 (6.9)
Chemotherapy + radiotherapy	75 (8.8)
Median time since diagnosis to survey, mo	71.3 ± 47.7
Median follow-up time since survey, mo	75.1 ± 7.7

During the median follow-up period of 6.3 years after the survey (range, 1.1–75.1 months), 30 CCSs (3.5%) were deceased from all causes. Among the sociodemographic and clinical variables, age, stage, time since diagnosis, marital status, income level, employment status, support from private insurance, and regular physical activity were significantly associated with survival based on univariate analyses (Table 2). The baseline multivariate model was created using the aforementioned sociodemographic and clinical variables without HRQOL outcomes. Factors included in the baseline model were age, time since diagnosis, and regular physical activity (Table 3). Stage, which lost its statistical significance on multivariate analysis in the present study, was also included in the baseline model because it has conventionally been considered the most important prognostic factor and was also reported to be significantly associated with survival among CSSs in another study.[14]

When HRQOL domains were individually added to the baseline model, physical, emotional, role and social functioning, global health status, and 2 of the symptom scales, including pain and appetite loss, showed independently significant associations with survival outcomes (Table 3). In addition, lowered body image, sexual inactivity, and sexual worry, which were cervical cancer module items, also influenced survival significantly. Among the HRQOL domains showing prognostic significance, physical (aHR, 4.25; 95% CI, 1.79–10.06; $P = 0.001$) and role functioning (aHR, 4.82; 95% CI, 2.00–11.58; $P < 0.001$) were the most predictive of survival duration (Fig. 1).

DISCUSSION

This study demonstrates that HRQOL outcomes, in particular, physical and role functioning levels, were significantly associated with survival in disease-free CCS. Health-related

TABLE 2. Univariate Cox regression analyses of survival for sociodemographic and clinical variables

Variables	n (%)	HR	95% CI	*P*
Age in decades		3.65	2.50–5.32	<0.001
Time since diagnosis				
≥3 y	649 (75.8)	1		0.021
<3 y	187 (21.8)	2.37	1.14–4.92	
Currently married				
Yes	658 (76.9)	1		0.01
No	198 (23.1)	2.57	1.25–5.30	
Education				
≥High school	413 (48.2)	1		0.587
<High school	442 (51.6)	1.22	0.59–2.52	
Monthly income, USD				
≥2000	384 (44.9)	1		0.019
<2000	467 (54.6)	2.75	1.18–6.40	
Currently employed				
Yes	233 (27.2)	1		0.043
No	621 (72.5)	3.42	1.04–11.29	
Support from private insurance				
Yes	286 (33.4)	1		0.026
No	569 (66.5)	3.3	1.15–9.46	
Smoking status				
Nonsmoker or past smoker	812 (94.9)	1		0.694
Current smoker	44 (5.1)	1.33	0.32–5.6	
Drinking status				
Nondrinker or past drinker	691 (80.7)	1		0.207
Current drinker	164 (19.2)	0.46	0.14–1.53	
Regular physical activity				
Yes	444 (51.9)	1		0.001
No	412 (48.1)	4.39	1.79–10.73	
Comorbidities				
No	364 (42.5)	1		0.156
Yes	488 (57.0)	1.76	0.81–3.84	
Stage				
IA1-IB1	572 (66.8)	1		0.012
IB2-IVA	266 (31.1)	2.50	1.22–5.13	
Compliance to radiotherapy				
Yes	334 (39.0)	1		0.474
No	20 (2.3)	1.7	0.40–7.24	
Compliance to chemotherapy				
Yes	308 (36.0)	1		0.632
No	25 (2.9)	1.43	0.33–6.16	
Regular check-up				
Yes	705 (82.4)	1		
No	151 (17.6)	1.17	0.48–2.87	0.727

quality-of-life measures along with sociodemographic characteristics seem to be more relevant and sensitive prognostic factors for long-term CCSs than are conventional clinicopathologic factors, such as stage, which might be more applicable to cancer patients immediately after cancer diagnosis and treatment. These findings support recent studies suggesting that PROs,

TABLE 3. Multivariate Cox regression analyses of survival for sociodemographic and clinical variables (baseline model) and for each individual HRQOL scale after adjusting for covariates included in the baseline model

Variables	aHR	95% CI	P
Baseline model			
Age (in decades)	3.18	2.19–4.62	<0.001
Stage (≥IB2)	1.50	0.71–3.15	0.286
Time since diagnosis (≥3 y)	2.41	1.13–5.10	0.022
Regular physical activity	2.68	1.09–6.62	0.033
EORTC QLQ-C30			
Physical functioning	4.25	1.79–10.06	0.001
Role functioning	4.82	2.00–11.58	<0.001
Emotional functioning	4.72	1.52–14.66	0.007
Social functioning	3.04	1.22–7.56	0.017
General health status	2.48	1.09–5.65	0.031
Pain	2.82	1.25–6.37	0.013
Appetite loss	2.93	1.33–6.42	0.007
EORTC QLQ-CX24			
Body image	3.20	1.42–7.18	0.005
Sexual activity	5.75	1.55–21.35	0.009
Sexual worry	4.93	1.75–13.91	0.003

aHR, adjusted hazard ratio; CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-CX24, Quality of Life Questionnaire cervical cancer module.

particularly HRQOL, provide more relevant prognostic information for cancer survival than do standard clinical measures.[5]

Baseline HRQOL has been shown to be a prognostic indicator of survival in various cancers, including lung, head and neck, breast, and ovarian cancer.[7–9,21] In a meta-analysis of patient data from EORTC clinical trials, HRQOL scales of physical functioning, pain, and appetite loss provided prognostic information in addition to the conventional sociodemographic and clinical variables.[22] Moreover, in locally advanced non-small-cell lung cancer, a baseline QOL score superseded traditional prognostic factors.[8] From these studies, *QOL screening* has been suggested to identify patients at high risk for poor survival who may need more intense follow-up monitoring.[7] Gotay et al[5] suggested several possible explanations for the association between PROs/HRQOL and survival outcomes, including that (1) PROs may reflect different biological parameters; (2) PROs may pick up prognostically relevant information earlier than other measures; (3) higher PROs may be linked with more positive patient behaviors; and (4) PRO scores may reflect individual characteristics that affect the disease process.

In addition to the importance of baseline HRQOL measures before and during cancer treatments, HRQOL assessment may be useful in monitoring long-term disease-free cancer survivors who mostly recovered from the effects of cancer diagnosis and treatments and for whom more comprehensive health management strategies are required. Although there have not been many studies on prognostic factors for long-term survival among disease-free cancer survivors, a few epidemiological studies have demonstrated that the causes of death among cancer survivors included, but were not limited to, noncancerous diseases, such as cardiovascular
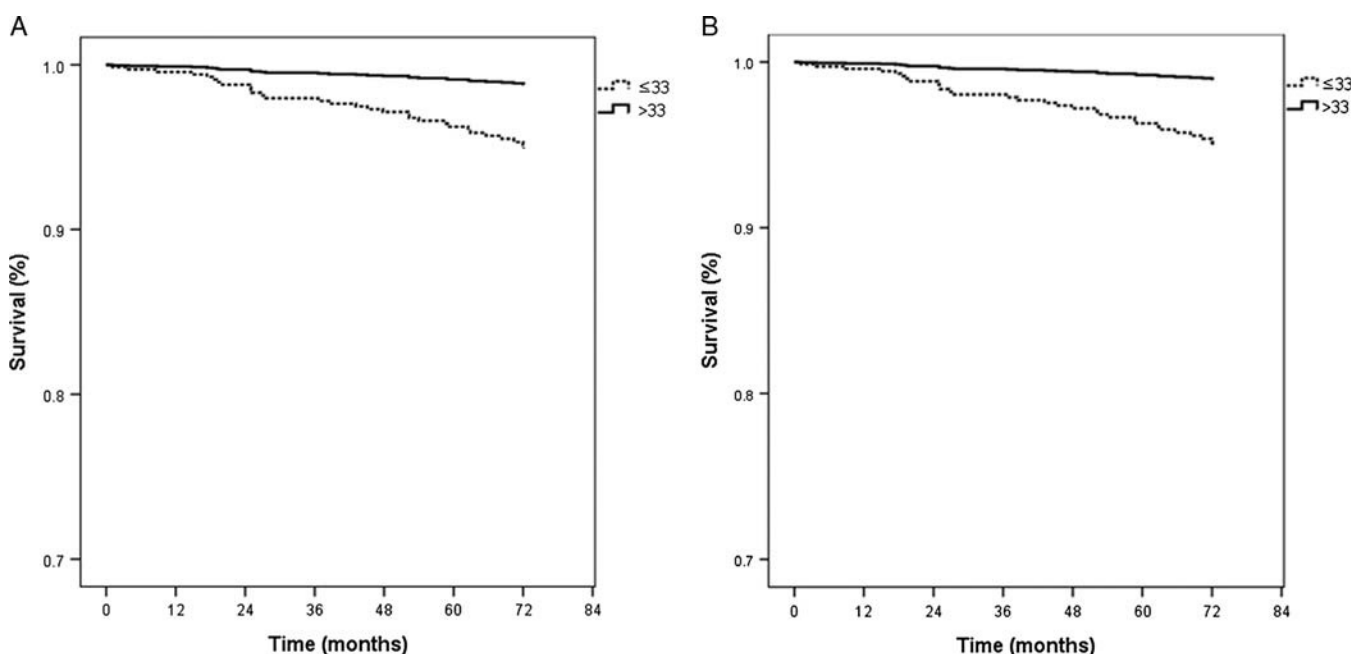
FIGURE 1. Overall survival curves by (A) physical functioning score (≤33 vs >33) and (B) role functioning score (≤33 vs >33) adjusted for age, stage, time since diagnosis, and regular physical activity.

disease and second primary cancers.[23] Similarly, a long-term follow-up study of cervical cancer patients reported that noncancerous disease was the main cause of death in addition to cancer itself.[24] The current study on disease-free CCSs also shows that cancer stage has little prognostic value compared with sociodemographic and HRQOL factors.

In this regard, HRQOL domains measuring patients' overall well-being and functioning may be eligible components of a comprehensive monitoring program for CCSs in addition to regular follow-up for noncancerous diseases.

Among HRQOL measures, physical and role functioning levels, which are closely related to the performance of the activities of daily living, are found to be especially important in this study ($P = 0.001$ and $P < 0.001$). This finding generally agreed with a former HRQOL study on CCSs demonstrating that subscales relating to functional well-being and cervical cancer concerns were associated with survival, although different assessment tools were used in the former and in our study.[14] In addition, appetite loss was shown to be a significant prognosticator ($P = 0.007$), which was consistent with a meta-analysis of EORTC clinical trials.[22]

Among cervical cancer module domains, body image, sexual activity, and sexual worry were also significantly associated with survival. Sexual problems have been shown to be increased in advanced-stage cervical cancer patients who received radiotherapy with or without surgery.[15,25] However, even after controlling for the stage, sexuality items were significantly associated with survival in this study, suggesting their value as independent prognosticators. There may be a few explanations for this finding. First, sexual problems might influence survival through their relationship with other health issues, such as late morbidities, presence of comorbidities, or possibly health behaviors. Comorbidities, especially heart and gastrointestinal disease, were demonstrated to affect these sexuality-related scales among CCSs,[16] and these chronic diseases might, in turn, have compromised the survival outcomes. Second, although the biological mechanisms are not clear, lowered HRQOL, presumably expressed in the form of sexual problems, might influence survival. This relationship is partly supported by a previous finding that sexual problems, which were more prevalent among CCSs than the general population, were highly associated with HRQOL, including global health status and functional scales.[15] Further studies are needed to clarify this issue.

In addition to HRQOL, sociodemographic variables, such as age, time since diagnosis, and regular physical activity, have also been shown to be independent prognostic factors. Although age is a well-known prognostic factor, time since diagnosis and physical activity were found to influence survival significantly even after controlling for age and stage. In particular, physical activity, which can be a modifiable factor, needs further consideration in terms of maintaining functional status. Recent studies on breast and colorectal cancer survivors demonstrated that physical inactivity was associated with cancer-specific and all-cause mortality.[26,27] In particular, postdiagnosis leisure time physical inactivity and more TV watching significantly increased mortality risk in colorectal cancer survivors, emphasizing the importance of promoting physical activity regardless of previous behaviors.[27]

Based on these findings, the effect of physical activity on survival outcomes among CCSs needs further investigation.

Although the present study was performed on a relatively large number of disease-free CCSs with a long survival follow-up period, there were several limitations in this study. First, the study lacked repeated HRQOL evaluations across time. Because HRQOL scores are dynamic in nature, analyzing the association of changes in HRQOL with survival outcomes would provide additional information on the prognostic value of HRQOL measures. Future studies assessing HRQOL periodically may enable us to understand the clinical significance of HRQOL in follow-up practice for CCSs more comprehensively.

Second, although EORTC questionnaires have been most widely used in HRQOL research, EORTC assessment tools originally designed to assess the effects of cancer and its treatment-related issues might not be able to pick up QOL problems of CCSs appropriately. There is a need to develop a comprehensive questionnaire specific to CCSs.[28]

In addition, the fact that participants were predominantly early-stage CCSs might lessen the prognostic significance of HRQOL because these long-term disease-free CCSs were highly unlikely to relapse. Although long-term disease-free cancer survivors were composed of early-stage patients by nature of the disease, it would be valuable to conduct further studies in a more advanced group of CCSs.

Despite these limitations, the current study highlighted the clinical importance of HRQOL assessment and of taking patients' sociodemographic factors into consideration during routine follow-up practice for CCSs. Through these comprehensive appraisals of HRQOL and health behaviors of CCSs, the survivorship program can be further improved to provide CCS-specific health promotion and, if possible, to extend the survival duration of CCSs.

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