Received: 29 June 2022 | Revised: 3 November 2022 | Accepted: 19 November 2022

DOI: 10.1111/aogs.14490

ORIGINAL RESEARCH ARTICLE

A study of modifiable factors associated with health-related quality of life in long-term cervical cancer survivors

Alv A. Dahl[1] | Anne Gry Bentzen[2] | Sophie D. Fossa[1,3] | Siri Lothe Hess[1] | Cecilie E. Kiserud[1]

[1]National Advisory Unit for Late Effects After Cancer Treatment, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway

[2]Department of Oncology, University Hospital of Northern Norway, Tromsø, Norway

[3]Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence
Alv A. Dahl, National Advisory Unit for Late Effects After Cancer, Oslo University Hospital, The Norwegian Radium Hospital, P.O. Box 4953, Nydalen, 0424 Oslo, Norway.
Email: alvdah@ous-hf.no

Funding information
Kreftforeningen, Grant/Award Number: 45980; Norwegian Cancer Society

Abstract

Introduction: Health-related quality of life (HR-QoL) in cancer survivors is relevant for symptom relief and optimal care. The aim of this cross-sectional study of long-term cervical cancer survivors was two-fold: (a) To compare HR-QoL in long-term cervical cancer survivors with reference data; and (b) to identify modifiable factors significantly associated with low levels of generic cancer HR-QoL in long-term cervical cancer survivors using high HR-QoL as reference.

Material and methods: Women treated for cervical cancer from 2000 through 2007 who were cancer-free and alive in 2013 received a mailed questionnaire including scales for anxiety, depression, and HR-QoL. To obtain a homogeneous sample only women with FIGO stages 1 and 2 were included. The questionnaire included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.C-30 (EORTC QLQ C-30) for generic HR-QoL. Groups with high and low HR-QoL were defined by the median score on the general HR-QoL item. Between-group differences were examined with descriptive statistics. Logistic regression analyses examined independent variables associated with low generic HR-QoL.

Results: Complete C-30 scores were delivered by 472 long-term cervical cancer survivors. Median age at survey was 53 (interquartile range 14.9) years, and median time since diagnosis was 11 (interquartile range 3.9) years. The proportion of survivors with stage 1 disease was 83% and stage 2 was 17%. Mean generic HR-QoL scores showed minor differences between long-term cervical cancer survivors and reference data. In the multivariable analysis, only modifiable variables remained significantly associated with low generic HR-QoL namely self-rated health, probable depression, fatigue, and pain. In bivariate analyses other modifiable variables also showed significant associations with low generic HR-QoL like probable anxiety disorder, obesity, smoking, sleep disturbances, and bowel symptoms.

Abbreviations: CC, cervical cancer; CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; FIGO, International Federation of Gynecology and Obstetrics; HADS, Hospital Anxiety and Depression Scale; HR-QoL, health-related quality of life; IQR, interquartile range; LTCCSs, long-term cervical cancer survivors; PHQ-9, Patient Health Questionnaire-9; QLQ, Quality of Life Questionnaire.

Conclusions: Clinicians should be aware that generic HR-QoL in long-term cervical cancer survivors eventually may be improved by identification and treatment of modifiable factors through the whole follow-up period.

KEYWORDS
cervical cancer, EORTC QLQ C-30, health-related quality-of-life, long-term survivors, reference data

1 | INTRODUCTION

Health-related quality of life (HR-QoL) has been defined as "the extent to which one's usual or expected physical, emotional or social well-being is affected by a medical condition or its treatment."[1] Studies of HR-QoL in cancer patients are important as a guide for symptom relief, optimal care, and rehabilitation of patients. Long-term survivors after curative treatment for cancer may have health problems affecting their HR-QoL long after their treatment has been completed.[2] Improving HR-QoL is an important task for health care providers of cancer survivors, and identification of modifiable factors associated with poor HR-QoL is relevant for that task.

To examine HR-QoL in cancer patients, the European Organization for Research and Treatment of Cancer (EORTC) has developed a core instrument (the Quality of Life Questionnaire [QLQ]-C30) designed to cover generic HR-QoL issues relevant for a broad spectrum of cancer patients.[3,4] In addition to the C-30, we also included scales for anxiety and depression in the present study.

Cervical cancer (CC) typically affects young adult women with a long-life expectancy, and in Norway their five-year relative survival is 82%.[5] Therefore, the generic HR-QoL of long-term (≥5 years since diagnosis) CC survivors (LTCCSs) is of significant clinical relevance. In 2006 our research group published a review of HR-QoL studies of CC patients,[6] but only five of 23 studies concerned LTCCSs. We have identified five subsequent studies of HR-QoL in LTCCSs of which one compared treatment modalities,[7] one compared invasive vs noninvasive CC,[8] two dealt with survivors vs controls,[9,10] and one was designed according to length of the follow-up period.[11] All these designs have their merits, but they do not aim specifically to identify modifiable factors that eventually could be treated and thereby improve the generic HR-QoL of LTCCSs.

To identify such factors in LTCCSs we used a cross-sectional design comparing LTCCSs with low and high generic HR-QoL dichotomized based on the QLQ-C30 quality of life item scores. Since we also had access to QLQ-C30 reference data for Norwegian women, we explored the following two research questions: (a) Are there significant between-group differences on the QLQ-C30 dimensions between LTCCSs and controls? (b) What are the significant modifiable independent variables significantly associated with low generic HR-QoL as dependent variable using high HR-QoL on the C-30 as references?

Key message

Health-related quality of life might eventually be improved by identification and treatment of mental distress, pain and, fatigue in long-term survivors of cervical cancer.

2 | MATERIAL AND METHODS

2.1 | Patient sampling

The study received ethical approval in March 2013, and the Cancer Registry of Norway then identified all women with CC diagnosed between January 1, 2000, and December 31, 2007, and treated at hospitals located in the Health Regions of South-Eastern Norway (2.8 million inhabitants) and of Northern Norway (0.5 million inhabitants). Women with a history of previous or new primary cancers were excluded by the Cancer Registry of Norway. The design of the present study is described elsewhere.[12]

LTCCSs who were alive by December 31, 2012, were included if they were aged ≤75 years and had no recorded history of second cancer. The gynecologists responsible for their management at the relevant hospitals were then contacted to confirm that their patients were considered tumor-free, not on any current cancer treatment, and that their health conditions made them fit for study participation. After their approval, 974 LTCCSs were eligible for the study ($n = 822$ region South-East and $n = 152$ region North).

Eligible LTCCSs were sent a questionnaire by mail in the beginning of 2015, and 555 responded (57% response rate). We omitted 55 respondents who had not completed the functional subscale items of the C-30, and 28 respondents with missing, stage 3 or 4 FIGO staging.[13] Our analyses thus concerned 472 LTCCSs with FIGO stages 1 and 2. Information about FIGO stages and treatment modalities were retrieved from the medical records.

2.2 | Treatment for CC

Treatment for CC was principally based on the patient's FIGO stage[13] and included surgery, radiation and chemotherapy or combinations of these modalities. We defined four treatment groups: (a) Removal of a large conus for FIGO stage 1a malignancy (conization group).

(b) Radical hysterectomy with pelvic lymph node dissection with or without bilateral salpingo-oophorectomy for FIGO stages 1a-1b and 2a malignancies (major surgery group). (c) The chemo-radiation group concerned FIGO stages 1b-2b malignancies. (d) The surgery + chemo-radiation group also concerned FIGO stages 1b to 2b and had either received neoadjuvant chemotherapy (5-fluorouracil, etoposide, and cisplatin), followed by standard major surgery, or combinations of surgery and external beam pelvic radiation along with chemotherapy. The correlation between treatment modalities and the dichotomized FIGO stages (1A1, 1A2, 1B1, 1B2 vs 2A and 2 B) was 0.63.

2.3 | Generic HR-QoL

The QLQ C-30 questionnaire version 3 consists of 30 items covering six function subscales, three symptom scales, and six single symptom items.[3,4] All scores are transformed to 0–100 scales, where higher function scores indicate better function, and lower symptom scores indicate less symptom load. Internal consistency measured by the Cronbach coefficient alpha was 0.61 for cognitive function and between 0.83 and 0.94 for the five other function subscales.

QLQ C-30 item no. 30 "How would you rate your overall quality of life during the past week?" was used to dichotomize generic HR-QoL in our sample. The response is scored on 7-point Likert scale from 1 ("Very poor") to 7 ("Excellent"). When converted to 0–100, these scorings are: 0, 16.7, 33.4, 50.0, 67.7, 83.3, and 100. Based on the sample's median score of 83, the sample was dichotomized into the low (0 to 68) and the high (83 to 100) generic HR-QoL groups with 222 and 250 LTCCSs, respectively.

2.4 | Reference data

As reference data for the QLQ C-30 we used data previously published by our research group. An age-representative sample of 3500 women aged 19 to 79 was identified from the general adult Norwegian population with planned oversampling of the oldest age groups. Due to requirements for anonymity, no reminder was sent to nonresponders. Among those invited, 1370 women delivered a completed C-30 form (36% response rate). Their mean age was 53 years with standard deviation of 15.6 years, and the age range was 19–79 years.[14]

2.5 | Scales

The Hospital Anxiety and Depression Scale (HADS) comprised seven items each on the anxiety and depression subscales rated for the last week. The item scores ranged from 0 ("Not present") to 3 ("Highly present"), providing a 0 to 21 severity score. Only the anxiety subscale (HADS-A) was adopted, and alpha was 0.66 in our sample. A probable anxiety disorder had a HADS-A sum score ≥8.[15]

The Patient Health Questionnaire-9 (PHQ-9) contained nine items covering depression for the last 2 weeks, and each item was scored from 0 ("Not at all") to 3 ("Nearly every day"), providing a sum-score of 0 to 27. A probable major depressive episode was defined by a PHQ-9 sum score ≥ 10. Alpha was 0.87 in our sample.[16]

2.6 | Other variables

Self-reported variables were operationalized as follows: Paired relationship was dichotomized as married or living together (paired) vs nonpaired being never married, divorced, or widowed (nonpaired). Level of education was dichotomized into short (≤12 years) and long (>12 years). Income status was classified as paid work, disability pension, retirement pension, and other statuses. Somatic comorbidity concerned heart diseases, stroke, hypertension, kidney diseases, asthma and chronic obstructive lung disease, diabetes, gastric ulcers, thyroid diseases, rheumatic arthritis, osteoporosis, fibromyalgia, arthrosis, and other skeletal or muscular diseases of long duration. The total number of comorbid somatic diseases reported was classified as zero, one, or ≥ two. Self-rated health was dichotomized according to response alternatives into "Excellent to Good" ("Excellent"/ "Very good"/"Good") and "Fair to Poor" ("Fair"/"Poor"). Daily smoking concerned any number of cigarettes. Body mass index was calculated as kg/meter,[2] and obesity was defined as body mass index ≥30. In addition, menopausal status, and current use of hormone replacement therapy were registered.

2.7 | Statistical analyses

Sample and group characteristics were given by descriptive statistics. Between-group comparisons of continuous data were made by *t*-tests, and effect sizes were calculated as Cohen's coefficient *d*. An effect size of Cohen's *d* 0.50–0.79 was considered of moderate clinical significance.[17] Between-group comparisons of categorical variables were calculated with Pearson's chi-square tests. The internal consistencies of scales were examined with Cronbach's coefficient alpha. Bivariate and multivariable logistic regression analyses examined the relation between independent variables and low generic HR-QoL as dependent variable (high HR-QoL as reference). All symptom scales and items of the C-30 were tested against the generic HR-QoL dichotomy, and the Pearson's correlation coefficients varied from 0.21 to 0.64, so they were all included in the bivariate analyses. Due to 222 LTCCSs in the low HR-QoL group, we only applied 15 independent variables in the multivariable analysis selected by their clinical relevance. The strength of association was expressed as odds ratios (ORs) with 95% confidence intervals (95%CI). The *p*-value was set as <0.05, and all tests were two-sided. The statistical software applied was SPSS version 25 for PC (IBM Corporation, Armonk, New York, USA).

2.8 | Ethics statement

The Regional Committees for Medicine and Health Research Ethics of South-Eastern Norway approved the study on March 6, 2013, with reference number 2012/2018. All patients included gave written informed consent when returning their questionnaires.

3 | RESULTS

3.1 | Characteristics of the LTCCSs sample

The median age at diagnosis was 42 years (interquartile range [IQR] 15.2), median age at survey 53 years (IQR 14.9), and median time from diagnosis to survey 11 years (IQR 3.9). Concerning treatment

TABLE 1 Characteristics of long-term cervical cancer survivors with high and low generic health-related quality of life (HR-QoL)

Variables	High HR-QoL (*N* = 250)	Low HR-QoL (*N* = 222)	*p*-value	Total sample (*N* = 472)
Age at diagnosis (years), median (IQR)	41 (15.4)	43 (14.5)	**0.007**	42 (15.2)
Age at survey (years), median (IQR)	50 (15.0)	54 (14.9)	0.080	53 (14.9)
Time from diagnosis to survey, median (IQR)	11 (4.0)	11 (3.7)	**0.034**	11 (3.9)
Treatment modalities, *n* (%)			**<0.001**	
Conization	60 (24)	27 (12)		87 (18)
Major surgery	130 (52)	106 (48)		236 (50)
Chemo-radiation	27 (11)	51 (23)		78 (17)
Major surgery + chemo−/radiation	33 (13)	38 (17)		71 (15)
FIGO disease stages, *n* (%)			**<0.001**	
Stage 1A1, 1A2, 1B1, 1B2	223 (87)	169 (76)		392 (83)
Stage 2A, 2B	27 (11)	53 (24)		80 (17)
Menopausal status, *n* (%)			**0.026**	
Premenopausal	47 (19)	25 (11)		72 (15)
Postmenopausal	201 (82)	193 (89)		394 (85)
Current use of HRT, *n* (%)	46 (18)	58 (26)	**0.043**	104 (22)
Level of education, *n* (%)			**0.017**	
≤12 years	122 (49)	132 (60)		254 (54)
>12 years	127 (51)	88 (40)		215 (46)
Partner status, *n* (%)			0.146	
Married, living together	181 (73)	147 (67)		328 (70)
Never married, widow, divorced	68 (27)	74 (33)		142 (30)
Income status at survey, *n* (%)			**<0.001**	
Paid work	200 (78)	124 (51)		324 (65)
Disability pension	11 (4)	59 (25)		70 (14)
Retirement pension	30 (12)	39 (16)		69 (14)
Other statuses	15 (6)	20 (8)		35 (7)
Somatic comorbidity, *n* (%)			**<0.001**	
None	185 (74)	114 (51)		299 (63)
One	53 (21)	76 (34)		129 (28)
Two or more	12 (5)	32 (15)		44 (9)
Current self-rated health, *n* (%)			**<0.001**	
Excellent to good	243 (98)	116 (52)		359 (76)
Moderate to poor	6 (2)	106 (48)		112 (24)
Obesity, *n* (%)	28 (11)	45 (21)	**0.006**	73 (16)
Daily smoking, *n* (%)	43 (17)	50 (23)	0.13	93 (20)
HADS-anxiety sum-score ≥8, *n* (%)	57 (23)	122 (55)	**<0.001**	179 (38)
PHQ-9 depression sum-score ≥ 10, *n* (%)	6 (2)	85 (38)	**<0.001**	91 (19)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRT, hormone replacement therapy; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9.

TABLE 2 Generic HR-QoL in the high and low HR-QoL groups and in a normative sample (NORMs)

	Generic (C-30) HR-QoL			Normative (C-30) HR-QoL		
Variables	High HR-QoL (*N* = 250)	Low HR-QoL (*N* = 222)	Total HR-QoL (*N* = 472)	NORMs (*N* = 1,370)	*p*-value	Effect size
Function scales, mean (SD)						
Physical function	94.5 (9.2)	73.3 (21.3)	84.5 (19.3)	86.6 (19.4)	**0.042**	0.11
Role Function	95.6 (12.8)	64.0 (31.9)	80.8 (28.5)	81.1 (21.1)	0.868	0.01
Emotional function	90.7 (14.2)	66.6 (23.8)	79.4 (22.8)	85.4 (17.7)	**<0.001**	**0.31**
Cognitive function	90.5 (14.4)	67.3 (27.2)	78.6 (24.3)	82.1 (26.1)	**0.011**	0.14
Social function	92.3 (14.7)	59.7 (28.1)	76.9 (27.4)	85.2 (23.2)	**<0.001**	**0.34**
Global quality of life	88.9 (9.8)	49.7 (17.7)	70.4 (24.1)	72.4 (23.6)	0.115	0.08
Symptom scales and items, mean (SD)						
Fatigue	15.8 (16.2)	50.8 (24.7)	32.3 (27.0)	29.6 (24.4)	**0.044**	0.11
Nausea and vomiting	1.5 (6.4)	10.3 (18.9)	5.6 (14,.4)	3.8 (10.9)	**0.005**	0.15
Pain	10.2 (16.0)	44.1 (33.9)	26.1 (31.0)	21.7 (27.0)	**0.003**	0.16
Shortness of breath	6.3 (14.7)	26.6 (31.4)	15.8 (26.1)	15.7 (24.8)	0.940	0.00
Sleep disturbance	21.5 (25.1)	49.2 (31.7)	34.4 (31.5)	23.7 (29.6)	**<0.001**	**0.36**
Lack of appetite	3.7 (12.1)	19.8 (27.5)	11.3 (22.3)	6.4 (17.4)	**<0.001**	**0.26**
Constipation	9.4 (26.2)	21.0 (29.0)	14.8 (28.1)	13.7 (23.3)	0.413	0.04
Diarrhea	11.6 (24.2)	31.2 (33.5)	20.8 (30.5)	10.8 (20.2)	**<0.001**	**0.43**
Financial problems	4.6 (13.6)	22.5 (30.2)	13.0 (24.6)	7.3 (21.1)	**<0.001**	**0.26**

18% had undergone conization, 50% major surgery only, 17% chemo-radiation, and 15% major surgery + chemo−/radiation (Table 1).

Postmenopausal status was reported by 85% of LTCCSs, and 22% currently used hormone replacement therapy. Living with a partner was stated by 70%, and 65% was in paid work. Somatic co-morbidity was found in 37%, and 76% indicated good to excellent self-rated health. Probable anxiety disorder was present in 38%, and probable depression in 19%.

The proportions of high and low HR-QoL did not differ significantly between the two health regions (data not shown).

3.2 | Comparisons with the reference group

We also compared The LTCCSs mean scores on the QLQ C-30 dimensions and symptoms with the mean scores of the reference group, but none of the between-group differences reached moderate clinical significance ($d \geq 0.50$), and the means on the global quality of life was quite similar in these groups.

3.3 | Comparisons of the high and low generic HR-QoL groups

All generic HR-QoL functions and symptoms were significantly worse in the low HR-QoL group as expected from our dichotomized definition of these groups (Table 2). The group with low HR-QoL had significantly higher median age at diagnosis and shorter follow-up time than the high HR-QoL group. Stage 2 CC was significantly more common in the low HR-QoL group which thereby also had significantly higher frequencies of more intensive treatments. Significantly more LTCCSs used hormone replacement therapy in the low HR-QoL group. A significantly lower proportion in that group had long education and held paid work, and a higher proportion had somatic comorbidity, moderate to poor self-rated health, and obesity compared to the high HR-QoL group. The low HR-QoL group also had significantly more cases of probable anxiety disorder and probable major depression (Table 1).

3.4 | Logistic regression analyses findings

The bivariate analyses (Table 3) confirmed the significant cancer-related, sociodemographic, mental, lifestyle, and HR-QoL-related between-group differences shown in Tables 1 and 2. In the multivariable analysis poor to moderate self-rated health, probable depression and increased levels of fatigue and pain remained significantly associated with low generic HR-QoL (Table 3).

4 | DISCUSSION

The generic HR-QoL mean score on the QLQ C-30 showed no clinically significant differences between LTCCSs and controls. In

TABLE 3 Logistic regression analyses of independent variables and low HR-QoL ($N = 222$) and high HR-QoL ($N = 250$) (reference) at survey

	Bivariate analyses			Multivariable analysis		
Variables	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age at diagnosis (years)	1.02	1.00–1.04	**0.015**	1.02	0.98–1.06	0.306
Age at survey (years)	1.00	1.00–1.04	0.056	–	–	–
Time from diagnosis to survey	0.91	0.85–0.99	**0.025**	–	–	–
Treatment modalities			**<0.001**			0.848
Conisation (reference)	1.00	–	–	1.00	–	–
Major surgery	1.81	1.08–3.05	**0.026**	1.22	0.55–2.72	0.620
Chemo-radiation	4.20	2.19–8.05	**<0.001**	1.24	0.64–2.40	0.526
Major surgery + chemo-/radiation	2.56	1.34–4.91	**0.001**	0.87	0.30–2.55	0.796
FIGO disease stages				MC		
Stage 1A1, 1A2, 1B1, 1B2 (ref)	1.00	–	–			
Stage 2A, 2B	2.59	1.56–4.29	**<0.001**			
Menopausal status				–		
Postmenopausal (premenopausal reference)	1.81	1.07–3.05	**0.027**			
Current use of HRT	1.57	1.01–2.43	**0.044**	1.24	0.64–2.40	0.526
Level of education						
≤12 years (>12 years, reference)	1.56	1.08–2.25	**0.017**	1.10	0.61–1.99	0.759
Partner status						
Never married, widow, divorced (married, living together reference)	1.34	0.90–1.99	0.146	–	–	–
Work status at survey						
Not in paid work (in paid work (reference)	1.19	1.12–1.28	**<0.001**	0.96	0.84–1.10	0.574
Somatic comorbidity			**<0.001**			0.349
None (reference)	1.00	–	–	1.00	–	–
One	1.93	1.27–2.94	**0.002**	1.35	0.70–2.60	0.372
Two or more	4.73	2.26–9.94	**<0.001**	2.06	0.70–6.06	0.187
Current self-rated health						
Moderate to poor (excellent to good reference)	14.16	7.50–26.75	**<0.001**	5.62	1.98–15.94	**0.001**
Obesity	2.35	1.38–3.97	**0.002**	1.03	0.44–2.38	0.949
Daily smoking	2.03	1.27–3.24	**0.003**	–	–	–
HADS-Anxiety sum-score ≥ 8	4.05	2.72–6.04	**<0.001**	MC		
PHQ-9 Depression sum-score ≥ 10	9.62	5.07–18.26	**<0.001**	6.74	2.36–19.30	**<0.001**
EORTC QLQ C-30, Symptom scales						
Fatigue	1.09	1.07–1.10	**<0.001**	1.06	1.04–1.08	**<0.001**
Nausea and vomiting	1.05	1.05–1.10	**<0.001**	–	–	–
Pain	1.04	1.04–1.06	**<0.001**	1.02	1.00–1.03	**0.041**
Shortness of breath	1.04	1.03-1.05	**<0.001**	–	–	–
Sleep disturbance	1.03	1.02–1.04	**<0.001**	1.00	0.99–1.01	0.805
Lack of appetite	1.04	1.03 -1.06	**<0.001**	–	–	–
Constipation	1.02	1.01–1.03	**<0.001**	1.00	0.99–1.01	0.997
Diarrhea	1.02	1.01–1.03	**<0.001**	1.01	0.99–1.02	0.328
Financial problems	1.04	1.03–1.05	**<0.001**	–	–	–

Note: MC: Excluded from multivariable analyses due to multicollinearity: stages vs treatment modalities, and anxiety vs depression.

Abbreviations: HRT, hormone replacement therapy; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9; EORTC QLQ C-30, European Organization for Research and Treatment of Cancer quality of life questionnaire.

our analyses of LTCCSs with low and high generic HR-QoL, we included both unmodifiable variables (such as age, and treatments) and modifiable ones (such as depression and pain). We observed that low generic HR-QoL was significantly associated with both modifiable and nonmodifiable variables in bivariate regression analyses. However, in the multivariable analysis only modifiable ones remained significantly associated with low generic HR-QoL, namely poor to moderate self-rated health, probable major depression, and increased levels of fatigue and pain. Probable anxiety disorder should be added here since that variable was omitted from the multivariable analysis due to high correlation with probable major depression. However, in bivariate analyses other modifiable variables such as obesity, smoking, sleep disturbances, and bowel symptoms also showed significant associations with low generic HR-QoL. To sum up, low generic HR-QoL in LTCCSs is significantly associated with many factors and not only related to CC-factors.

The factors significantly associated with low generic HR-QoL could have their onset at variable time points related to the cancer trajectories of the LTCCSs. Education most likely was finished before diagnosis, while staging was done at diagnosis and was followed by treatments. As to somatic comorbidities, obesity, or probable major depression for example, we cannot identify their onset due to our single survey cross-sectional design. In a repeated measurement longitudinal design, we could have identified predictors significantly associated with low generic HR-QoL. In our design, we can only call associated factors potential predictors of HR-QoL, but in general such predictors are lacking concerning LTCCSs.

We therefore checked if the factors identified by us have been identified in survivors of other types of cancer. A systematic review of HR-QoL identified mostly the same factors in survivors of breast cancer[18] and colorectal cancer[19] as found in our LTCCSs sample. We therefore suggest that the identified modifiable and nonmodifiable factors significantly associated with low generic HR-QoL in LTCCSs probably are potential predictors.

Since we had easy access to reference data on the QLQ C-30 instrument, we observed the findings in LTCCSs only showed small effect sizes of the mean score differences between the groups. The reference data were collected in 2004 and the LTCCSs data in 2015, but the reference data collected in 1996 and 2004 hardly differed.[14] Therefore, we do not consider the differences in sampling time to be of much relevance. However, the 36% response rate of the normative study, could be of relevance, though most nonresponders belonged to the age groups <50 years. Mostly nonsignificant differences between LTCCSs and normative controls were also reported in two other studies.[9,10] We consider this a positive outcome worth communicating to CC patients at diagnosis and treatment planning instigation hope although on a group level.

As to clinical implications we identified several modifiable factors related to low generic HR-QoL in LTCCSs. Major depression, anxiety disorder, pain, obesity, and smoking are obvious targets for clinical and lifestyle interventions by LTCCSs health care providers. Low self-rated health and elevated levels of fatigue could have multiple explanations, requiring more detailed inquiries of LTCCSs by their medical caretakers at regular intervals. We, therefore, suggest that examinations for these potential predictors of low generic HR-QoL are considered from the start of follow-up examinations of LTCCSs.

An advantage of our study is the considerable sample size giving enough statistical power to the analyses. We also included multiple cancer-related, demographic, health and lifestyle, and mental factors including both modifiable and nonmodifiable ones, relevant for a broad approach to HR-QoL in LTCCSs. Another strength is our use of well-established self-rating instruments with documented psychometric properties. Our response rate of 57% at a median of 11 years after diagnosis we consider as acceptable. However, our lack of data for an attrition analysis trying to characterize the nonrespondents further, is a weakness. This raises the issue of the representativity of our sample, which also could be raised concerning the normative data set we used for comparison.[14] Since we only have cross-sectional data, we present significant associations between variables, rather than causal findings. We have only made one cross-sectional survey giving long-term data, and a stronger design for identification of changes over time, had been post-treatment surveys at regular time intervals. We also had data on the CC-specific European Organization for Research and Treatment of Cancer CX24,[20] but since we did not have normative data on this scale or any natural division between high and low HR-QoL, we omitted these data from our presentation.

5 | CONCLUSION

In a considerable sample of LTCCSs we have shown that these survivors have generic HR-QoL comparable to Norwegian reference data. Low generic HR-QoL in LTCCSs was positively associated with modifiable clinical factors. Evaluation and treatment of these factors by LTCCSs health care providers, could improve their generic HR-QoL and should be examined for during the whole follow-up period.

AUTHOR CONTRIBUTIONS

AAD performed the statistical analyses and wrote up the drafts of the manuscript; AGB collected data in Region North and gave feedback to the drafts of the manuscript; SDF gave feedback to the drafts of the manuscript; SLH performed the quality assurance of the dataset and gave feedback to the drafts of the manuscript, CEK applied for grants to the study protocol and gave feedback to the drafts of the manuscript. All authors agreed on the final version of the manuscript.

ACKNOWLEDGMENTS

Rita Steen, MD, PhD for collection of data in Region South-East.

FUNDING INFORMATION

This study was financially supported by a grant (no. 45980) from the Norwegian Cancer Society.

ORCID

Alv A. Dahl https://orcid.org/0000-0002-6849-2756

REFERENCES

1. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. *Oncology (Willston Park)*. 1995;9(Suppl 11):47-60.
2. Haraldstad K, Wahl A, Andenæs R, et al. A systematic review of quality of life research in medicine and health sciences. *Qual Life Res*. 2019;28:2641-2650.
3. Aaronson NK, Ahmedzai S, Bergman B, et al. 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 Nat Cancer Inst*. 1993;85:365-376.
4. Sprangers MA, Cull A, Bjordal K, et al. The European Organization for Research and Treatment of cancer approach to quality of life assessment: guidelines for developing questionnaire modules. *Qual Life Res*. 1993;2:287-295.
5. Cancer Registry of Norway. *Cancer in Norway 2019*. Kreftregisteret; 2007.
6. Vistad I, Fosså SD, Dahl AA. A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. *Gynecol Oncol*. 2006;102:563-572.
7. Frumowitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. *J Clin Oncol*. 2005;23:7428-7436.
8. Bartoces MG, Severson RK, Rusin BA, Schwartz KL, Ruterbusch JJ, Neale AV. Quality of life and self-esteem of long-term survivors of invasive and noninvasive cervical cancer. *J Womens Health*. 2009;18:655-661.
9. Khalil J, Bellefqih S, Afif M, et al. Impact of cervical cancer on quality of life beyond the short term (Results from a single institution). *Gynecol Oncol Res Pract*. 2015;2:7.
10. Le Borgne G, Mercier M, Woronoff A-S, et al. Quality of life in long-term cervical cancer survivors: a population-based study. *Gynecol Oncol*. 2013;129:222-228.
11. Korfage IJ, Essink-Bot M-L, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. *Int J Rad Oncol Biol Physics*. 2009;73:1501-1509.
12. Steen R, Dahl AA, Lothe Hess S, Kiserud CE. A study of chronic fatigue in Norwegian cervical cancer survivors. *Gynecol Oncol*. 2017;146:630-635.
13. Sobin L, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 6th ed. UICC International Union against Cancer; 2002:155-157.
14. Fosså SD, Lothe Hess S, Dahl AA, Hjermstad MJ, Veenstra M. Stability of health-related quality of life in the Norwegian generic population and impact of chronic morbidity in individuals with and without cancer. *Acta Oncol*. 2007;46:452-461.
15. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res*. 2002;52:69-77.
16. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Int Med*. 2001;16:606-613.
17. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol*. 2013;4:863.
18. Syrowatka A, Motulsky A, Kurteva S, et al. Predictors of distress in female breast cancer survivors: a systematic review. *Breast Cancer Res Treat*. 2017;165:229-245.
19. Martijn JL, Bours MJL, Bernadette WA, et al. Candidate predictors of health-related quality of life of colorectal cancer survivors: a systematic review. *Oncologist*. 2016;21:433-452.
20. Greimel ER, Vlasic KK, Duric VM, et al. The European Organization for Research and Treatment of cancer (EORTC) quality-of-life questionnaire cervical cancer module. *Cancer*. 2006;107:1812-1822.

How to cite this article: Dahl AA, Bentzen AG, Fosså SD, Hess SL, Kiserud CE. A study of modifiable factors associated with health-related quality of life in long-term cervical cancer survivors. *Acta Obstet Gynecol Scand*. 2023;102:218-225. doi:10.1111/aogs.14490