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Health-related quality of life among women with breast cancer – a population-based study

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Abstract

Background. High incidence rates of breast cancer emphasize the importance of increased knowledge about the health-related quality of life (HRQoL) in this patient group. The aim of the present study was to describe and compare HRQoL among breast cancer patients shortly after diagnosis with normative data from the general population, and to investigate how clinical, demographic, and socio-economic factors and social support are associated with HRQoL. *Material and methods.* Participants were identified in a population-based Breast Cancer Quality Register in central Sweden. Of 1573 women newly diagnosed with breast cancer during a one-year period (2007–2008), 69% (n = 1086) completed a questionnaire including the EORTC QLQ-C30, BR23 and the HADS. *Results.* Compared to age-adjusted normative data, breast cancer patients (mean age 62 years, range 25–94), especially younger women (<50 years), experienced clinically meaningful poorer HRQoL. Clinically significant levels of anxiety and depressive symptoms were found among 14% and 6% of the patients, respectively. Factors associated with more problems/symptoms among study participants included chemotherapy, lack of social support, sick leave and a poor financial situation. Adding socio-economic factors diminished the association between age and HRQoL ($p > 0.05$). *Conclusion.* Recently diagnosed breast cancer patients reported poorer HRQoL in several dimensions compared to normative data. In addition to clinical and demographic factors, an unfavorable socio-economic standing was associated with more problems/symptoms. The present findings emphasize the importance of taking a variety of factors into account when assessing HRQoL in the clinical setting.

Sweden has one of the highest incidence rates of breast cancer in Europe [1], with more than 7000 incident cases recorded in 2008 [2]. Improvements in the diagnosis and treatment have led to increased survival rates among breast cancer patients [3], emphasizing the importance of use of short- and long-term patient-reported outcomes as clinical and decision-making endpoints in cancer care [4,5]. Patient-reported outcomes constitute direct, subjective provision of information on different elements of health [6], with health-related quality of life (HRQoL) being acknowledged as an important patient-reported outcome in cancer care frequently used as a supplement to physiological and biological measures of health [7].

Shortly after diagnosis, breast cancer patients have been reported to experience poorer HRQoL compared to women in the general population with regard to, for example role, social and emotional functioning as well as fatigue and pain [8–10]. In addition, anxiety and depressive symptoms are common problems

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related to a breast cancer diagnosis affecting between 20% and 30% of women with breast cancer [11].

Young age [8,11,12–14], lack of social support [11,14,15] and type of adjuvant therapy, in particular chemotherapy [7,8,13,15], have been reported to negatively affect HRQoL among women with breast cancer, whereas the potential influence of demographic and socio-economic factors on HRQoL has not been clarified [8,12–15]. In a recent Swedish study by Eaker et al. [16], breast cancer management was associated with aspects of socio-economic standing, why a potential role of these factors on HRQoL also must be considered. Furthermore, little is known to what extent age and established clinical factors are affected by sequential inclusion of demographic and socio-economic factors. In a clinical setting, an improved understanding of the role of these factors could help identify vulnerable breast cancer patients.

Many previous studies have failed to simultaneously control for various factors of potential importance when assessing HRQoL [8,12,14,15]. Furthermore, many studies have neglected the importance of assessing the clinical meaningfulness of statistically significant findings [12,15], and have been limited to subgroups of women with breast cancer, for example early stage breast cancer [12,13] or excluded the oldest women [12,14,15].

The aim of the present study was twofold. Firstly, to describe and compare patient-reported HRQoL in a large Swedish population-based cohort of breast cancer patients shortly after diagnosis with normative data from the general population. Secondly, to investigate how clinical, demographic and socio-economic factors and social support are associated with HRQoL.

Material and methods

Study design

The present study was conducted as a questionnaire study based on patients residing in central Sweden identified in a Breast Cancer Quality Register and is the first part of a longitudinal project. The study was approved by the Ethical Review Board in Uppsala, Sweden.

Study population

Incident cases of breast cancer in Sweden are registered in the National Breast Cancer Quality Register administered by six Regional Oncologic Centres. For the purpose of the present study, eligible patients were identified in the Breast Cancer Quality Register of the Uppsala/Örebro Region in central Sweden, administered by the Oncologic Centre in Uppsala. The regional register was established in 1992 and has been estimated to include 98–100% of all incident cases of breast cancer in the region [17].

All women registered with a primary breast cancer diagnosis between March 1, 2007 and July 31, 2008 constituted the potentially eligible sample. Women reported to the register later than August 31, 2008 (n = 568) and one woman misclassified in the register were excluded. Of 1573 eligible women with breast cancer approached regarding study participation, 1108 women agreed to participate in the study (70%). In total, 22 women were excluded from the analyses because of: response provided by next of kin (n = 2); response later than eight months post-diagnosis (n = 5); and missing identification numbers (n = 15). In the final analysis, 1086 women were included, constituting 69% of the approached sample.

Procedure

During the inclusion period, a monthly search in the Quality Register was carried out to identify newly reported cases. Following verification in the Swedish National Population Register, all women still alive received a letter explaining the purpose of the study, an inquiry about participation and a postal questionnaire. Women were requested to return the completed questionnaire to the Regional Oncologic Centre in a pre-stamped envelope which was regarded as providing informed consent. A maximum of two reminders were sent out within two months of the first inquiry.

Measures

HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [18] and the Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) [19]. In the present study sample, Cronbach's α values for all scales varied between 0.66 and 0.92, with the exception of the subscale nausea and vomiting (Cronbach's α 0.49). Clinically meaningful medium differences between groups were assessed based on the guidelines for subscales of the EORTC QLQ-C30 recommended by Cocks et al. [20]. For the BR23 and the QLQ-C30 emotional functioning subscale clinical meaningfulness was based on previous guidelines by Osoba et al. [21].

Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS), which was developed to be applied in somatic health care [22]. Validated cut-off scores were used to categorize anxiety and depressive symptoms (<8 = *non-cases*, 8–10 = *doubtful cases, >10 = clinically significant cases*) [22]. In the present study sample, the internal consistency was high for both anxiety and depressive symptoms (Cronbach's α 0.89 and 0.84, respectively).

Based on research by Puhan et al. [23], clinically meaningful between-group differences were calculated as a difference of ≥ 20% in mean values of anxiety and depressive symptoms, only including women comprised in the specified analyses.

Normative data from a random sample of the general Swedish female population were used for comparisons of the EORTC QLQ-C30 [24]. Data were collected in the late 1990s (not specified). The response rate was 80% and the sample included 1619 women aged 18–79 years (mean age 51.2 for both genders). For the HADS, comparisons were made using normative data from a random sample of the general female population in northwestern Sweden, including 357 women aged 30–59 years (mean age 44 for both genders) [25]. Year of data collection was 1993, and the response rate for both genders was 48%.

Additional variables in the questionnaire included study-specific items regarding demographic factors, social support and socio-economic factors. Demographic factors included marital status (single/living-apart or married/cohabiting) and children (yes or no). Social support was assessed within (yes or no) and outside the family (yes or no). Socio-economic factors included education (university level or other), financial situation (11-point numerical scale: 0 = worst imaginable, 10 = best imaginable) and main occupation (retirement pension, employed/student, sick leave, other). The category other occupation included disability pension, home-making and not working (unspecified). Self-reported comorbidity (no, 1 or ≥ 2 comorbidities) was assessed by asking participants to report whether they during the past year had received treatment for any one of 21 listed common conditions (e.g. high blood pressure, thyroid dysfunction and joint problems).

Clinical background data and age at diagnosis were obtained from the records of the Regional Breast Cancer Quality Register of the Uppsala/Örebro Region. In the analyses, age was used as a continuous variable as well as dichotomized (<50 or ≥50) based on previous research [8]. Time since diagnosis (date of histopathology report) was based on the date of return of the questionnaire assessed as a continuous variable and dichotomized based on the mean value (≤4 or >4 months). Disease- and treatment-specific variables included data on previous breast cancer diagnosis (yes or no), laterality (uni- or bilateral), invasiveness (invasive or in situ cancer), tumor size (in situ cancer/invasive cancer ≤20 mm or invasive cancer ≥21 mm), lymph node involvement (≥1 metastases or in situ/no surgery/no metastases), distant metastases (yes or no), surgery (no surgery/partial mastectomy or mastectomy), radiation therapy (yes or no), chemotherapy (yes or no), endocrine therapy (yes or no) and antibody therapy (yes or no).

Statistical analysis

Differences in clinical characteristics between the study sample and eligible women excluded from the analyses were assessed with independent sample's t-test for continuous variables, and χ^2 for categorical variables.

Missing values within a subscale for the EORTC QLQ-C30 + BR23 and the HADS were substituted with the mean of the patient's responses, provided that at least half of the subscale items had been completed [26].

Comparisons with normative data were performed calculating expected mean values adjusting for age, according to Hjermstad et al. [27]. One-sample t-tests were carried out to test for statistically significant differences between expected and observed mean values for the total study population (total scores) as well as stratified by age (<50, ≥50 years). Normative data were available only for women aged ≤79 years and 30–59 years for the EORTC QLQ-C30 [24] and the HADS [25], respectively, why comparative analyses were limited to study participants within these age groups.

Sequential multivariable linear regression analyses were performed to study how clinical, demographic, and socio-economic factors and social support were associated with HRQoL. Outcome measures included nine subscales of the EORTC QLQ-C30, BR23 and the HADS selected based on values indicating problems in descriptive and/or comparative analyses; global health status/QoL, role and social functioning, fatigue and insomnia were selected based on values indicating problems in descriptive and comparative analyses; sexual functioning and systemic therapy side effects were selected solely based on descriptive analyses; and HADS-anxiety and -depression were selected based on comparative analyses and previous research [11]. Explanatory variables were transformed into dummy variables, except age, time since diagnosis and financial situation, which were kept as continuous variables. In order to assess clinically meaningful mean group differences, dichotomizations were performed for age (<50 or ≥50 years), time since diagnosis (1–4 or 5–8 months) and financial situation (0–4 or 5–10). In the regression analyses, all explanatory variables were entered in the following sequence: Step 1) age and clinical factors, Step 2) demographic factors and social support, and Step 3) socio-economic factors. Variables and the sequential order were chosen to study the potential contribution of factors entered in Step 2 and 3. Inclusion of selected variables in Step 2 and 3 statistically significantly improved the models (F-changes = $p < 0.001$), and all models were statistically significant (F-tests = $p < 0.001$). Associations were reported as unstandardized B-coefficients with 95% confidence intervals, and the level of

multicollinearity was acceptable for all the analyses (Variance Inflation Factor ≤ 3.05). Separately, simple linear regression analyses were performed to investigate whether outcome measures differed by time since diagnosis not controlling for other explanatory variables.

Throughout the results section, statistically significant mean group differences were interpreted for clinical meaningfulness. The level of statistical significance was set to $p < 0.05$ and all tests were two-sided. Data were analyzed using PASW Statistics version 18.0.

Results

Characteristics of the study sample

Table I presents the clinical characteristics of the study sample (n = 1086). The participating women completed the questionnaire with a mean time of four months post-diagnosis (range 1–8 months; SD 1.57; 1–4 months 66%; 5–8 months 34%). Thirty-four percent (n = 369) had ≥ 2 comorbidities, 30% (n = 321) had 1 comorbidity and the remaining 36% (n = 396) had no comorbidities. The majority of the participants were married/co-habiting (n = 722, 66%), had children (n = 951, 88%), experienced social support within (n = 949, 87%) and outside the family (n = 951, 88%), and did not have university education (n = 767, 71%). Forty-three percent (n = 467) were on retirement pension, 25% (n = 274) were on sick leave, 20% (n = 215) were employed or studying and 11% (n = 123) reported other occupations. The mean value of self-assessed financial situation was 6.1 (range 0–10; SD 2.4; 0–4 21%, 5–10 69%).

In comparison with the study sample (n = 1086), non-approached women (n = 568) and approached women excluded from the analyses (n = 487) were significantly older, and fewer had undergone surgery or received oncological treatment, in particular radiation and chemotherapy (Table I). In addition, compared to the study sample, a larger proportion of non-approached women had distant metastases and

Table I. Clinical characteristics among breast cancer patients in Sweden: the study sample vs. non-approached eligible patients (n = 568) and approached eligible patients not included in the analyses (n = 487[a]).

	Study sample (n = 1086)	Non-approached eligible patients (n = 568)		Approached non-included eligible patients (n = 487)	
	n (%)	n (%)	p	n (%)	p
Age (mean;range;SD)	61.8;25–94;12.6	64.4;24–97;14.4	***	67.9;30–99;14.8	***
Previous breast cancer					
Yes	50 (4.6)	31 (5.5)	NS	24 (4.9)	NS
No	1036 (95.4)	537 (94.5)		463 (95.1)	
Laterality					
Unilateral	1060 (97.6)	555 (97.7)	NS	472 (96.9)	NS
Bilateral	26 (2.4)	13 (2.3)		15 (3.1)	
Invasiveness					
In situ cancer	101 (9.3)	66 (11.6)	NS	53 (10.1)	NS
Invasive cancer	984 (90.6)	495 (87.1)		430 (88.3)	
Tumor size					
In situ cancer/invasive cancer ≤ 20mm	710 (65.4)	360 (63.4)	NS	290 (59.5)	NS
Invasive cancer ≥ 21mm	368 (33.9)	167 (29.4)		180 (37.0)	
Lymph node involvement					
In situ/no axillary surgery/0 metastases	738 (68.0)	404 (71.1)	NS	334 (68.6)	NS
≥ 1 lymph node metastases	346 (31.9)	156 (27.5)		148 (30.4)	
Distant metastases					
Yes	15 (1.4)	29 (5.1)	***	13 (2.7)	NS
No/assessment not possible	1068 (98.3)	537 (94.5)		472 (96.9)	
Surgery					
No surgery	10 (0.9)	74 (13.0)	***	39 (8.0)	***
Partial mastectomy	618 (56.9)	289 (50.9)		229 (47.0)	
Mastectomy	458 (42.2)	204 (35.9)		219 (45.0)	
Oncological treatment					
No treatment	99 (9.1)	92 (16.2)	***	65 (13.3)	*
Radiation therapy	731 (67.3)	321 (56.5)	***	260 (53.4)	***
Chemotherapy	389 (35.8)	157 (27.6)	**	116 (23.8)	***
Endocrine therapy	736 (67.8)	362 (63.7)	NS	316 (64.9)	NS
Antibody therapy	83 (7.6)	42 (7.4)	NS	31 (6.4)	NS

Abbreviation: NS, no significance.

[a]One patient excluded due to misclassification in the register.

*p < 0.05, **p < 0.01, ***p < 0.001

fewer approached women excluded from analyses had undergone partial mastectomy than mastectomy.

HRQoL descriptives

Including all participants (age 25–94), lowest mean scores for EORTC QLQ-C30 global and functioning scales (range 0–100), indicating poorer HRQoL, were reported for global health status/QoL (mean 65.1; SD 23.1), role (mean 68.1; SD 32.0) and social functioning (mean 76.2; SD 26.6). In addition, highest mean scores for symptom scales (range 0–100), indicating more symptoms, were reported for fatigue (mean 36.5; SD 26.0) and insomnia (mean 32.7; SD, 31.8). For the BR23, lowest scores on functioning scales (range 0–100) were reported for sexual functioning (mean 17.1; SD 21.9) and sexual enjoyment (mean 55.4; SD 25.0). Symptom scales with highest scores included upset by hair loss (mean 53.6; SD 36.6) and systemic therapy side effects (mean 24.8; SD 20.0) (data not shown).

The mean score for HADS-anxiety was 5.36 (range 0–21; SD 4.43) and for HADS-depression 3.95 (range 0–21; SD 3.60). Clinically significant levels of anxiety and depressive symptoms were found in 14% and 6% of the breast cancer patients, respectively.

Comparisons with normative data

Table II presents comparative analyses based on data provided by participants aged $\leq$ 79 years and 30–59 years according to the normative data available for the EORTC QLQ-C30 and the HADS, respectively. Compared to the normative data, study participants reported clinically meaningfully poorer global health status/QoL, social functioning as well as higher levels of fatigue and anxiety. Young breast cancer patients ($<$50 years) also reported poorer role, emotional and cognitive functioning as well as more nausea and vomiting, dyspnea, insomnia, appetite loss, diarrhea, financial difficulties and depressive symptoms compared to normative data.

Factors associated with HRQoL

Tables III, IV and V summarize the fully adjusted regression models of selected HRQoL subscales. The explained variances varied between 13% and 45%. Consistently, in the first two steps (before inclusion of socio-economic factors), younger age was statistically significantly ($p < 0.01$) associated with poorer HRQoL on all subscales except sexual functioning, for which a reverse association was found. The associations for age were clinically meaningful for social and sexual functioning, anxiety and depressive symptoms (data not shown). In the fully adjusted models, chemotherapy, lack of social support within and outside the family, being on sick leave and experiencing a poor financial situation were clinically meaningfully associated with poorer HRQoL on four or more of the subscales. Younger age, previous breast cancer diagnosis, invasive breast cancer, $\geq$ 1 lymph node metastases, $\geq$ 2 comorbidities and other occupation (disability pension, home-making and not working (unspecified)) were clinically meaningfully associated with poorer HRQoL on between one and three of the subscales. Time since diagnosis was not clinically meaningfully associated with HRQoL neither in univariate analyses (data not shown) nor in multivariate analyses.

Discussion

In the present study, the breast cancer patients reported poorer HRQoL in several dimensions shortly after diagnosis compared to normative data. In addition to age and clinical factors, social support and socio-economic factors were found to be associated with HRQoL. The effect of age on HRQoL was reduced when taking socio-economic factors into account.

In agreement with previous studies [8–10], the breast cancer patients, especially young women ($<$ 50 years), experienced poorer HRQoL compared to age-adjusted normative data. EORTC QLQ-C30 and BR23 subscales with values demonstrating poor functioning or high symptom burden included global health status/QoL, role and social functioning, fatigue, insomnia, sexual functioning and enjoyment, upset by hair loss and systemic therapy side effects. Supported by previous studies [10,11,13] these subscales may be of particular concern in the clinical setting. In addition, poor emotional functioning and high levels of anxiety and depressive symptoms were more pronounced among young breast cancer patients compared to normative data, corroborating findings in a study by Disipio et al. [8].

The proportion of breast cancer patients classified as suffering from clinically significant anxiety and depressive symptoms was substantially lower than in previous studies [11]. Because the HADS has been reported to be a valid and reliable instrument [28], these findings may be explained by satisfactory care and/or study-specific differences in methods used and in patient characteristics. To exemplify, the articles reviewed by Knobf [11] included breast cancer patients with a lower mean age compared to the present study sample. Older breast cancer patients in general are more prone to suffer from age-related physical changes rather than emotional distress [11], why smaller proportions classified as cases of anxiety and depressive symptoms in the present study sample might be explained by the population-based nature of the study.

Table II. Comparisons between the study sample of breast cancer patients in Sweden and normative data from the general Swedish female population adjusting for age (EORTC QLQ-C30: ≤ 79 years; HADS: 30–59 years).

	Normative data (expected mean)	Observed mean	Mean difference	95% CI
EORTC QLQ-C30[a]				
Global health status/QoL[b]				
Total (n = 974)	75.7	65.0	**−10.7**	−12.1–−9.2
<50 yrs (n = 190)	75.3	59.6	**−15.7**	−18.9–−12.5
≥50 yrs (n = 784)	75.8	66.3	−9.5	−11.1–−7.9
Physical functioning[b]				
Total (n = 982)	86.1	82.3	−3.8	−5.0–−2.6
<50 yrs (n = 194)	92.5	83.6	−9.0	−11.4–−6.5
≥50 yrs (n = 788)	84.5	82.0	−2.5	−3.8–−1.2
Role functioning[b]				
Total (n = 982)	85.4	67.7	−17.7	−19.7–−15.7
<50 yrs (n = 194)	87.4	59.2	**−28.2**	−32.9–−23.5
≥50 yrs (n = 788)	84.9	69.8	−15.1	−17.3–−12.9
Emotional functioning[b]				
Total (n = 975)	80.6	72.3	−8.3	−9.7–−6.8
<50 yrs (n = 190)	75.6	65.0	**−10.6**	−14.0–−7.1
≥50 yrs (n = 785)	81.8	74.1	−7.7	−9.3–−6.1
Cognitive functioning[b]				
Total (n = 975)	88.7	80.6	−8.1	−9.5–−6.6
<50 yrs (n = 190)	88.6	73.0	**−15.6**	−19.4–−11.9
≥50 yrs (n = 785)	88.8	82.5	−6.2	−7.7–−4.7
Social functioning[b]				
Total (n = 973)	90.2	75.2	**−15.1**	−16.8–−13.4
<50 yrs (n = 190)	88.5	64.8	**−23.7**	−27.7–−19.7
≥50 yrs (n = 783)	90.7	77.7	**−13.0**	−14.8–−11.2
Fatigue[c]				
Total (n = 985)	22.2	36.4	**14.1**	12.5–15.7
<50 yrs (n = 194)	22.9	44.7	**21.7**	17.8–25.6
≥50 yrs (n = 791)	22.1	34.3	12.2	10.5–14.0
Nausea and vomiting[c]				
Total (n = 986)	3.2	9.5	6.2	5.2–7.3
<50 yrs (n = 194)	3.7	13.3	**9.7**	7.0–12.3
≥50 yrs (n = 792)	3.1	8.5	5.4	4.3–6.5
Pain[c]				
Total (n = 985)	21.7	20.9	−0.8	−2.3–0.8
<50 yrs (n = 194)	20.2	21.6	1.4	−2.1–5.0
≥50 yrs (n = 791)	22.0	20.7	−1.3	−3.0–0.4
Dyspnoea[c]				
Total (n = 978)	15.6	22.9	7.3	5.6–9.1
<50 yrs (n = 192)	14.5	26.0	**11.5**	7.5–15.5
≥50 yrs (n = 786)	15.9	22.2	6.3	4.4–8.2
Insomnia[c]				
Total (n = 982)	21.4	33.3	11.9	9.9–13.9
<50 yrs (n = 194)	18.5	38.1	**19.6**	14.8–24.4
≥50 yrs (n = 788)	22.1	32.1	10.0	7.8–12.2
Appetite loss[c]				
Total (n = 984)	4.5	14.5	10.0	8.5–11.6
<50 yrs (n = 194)	4.5	19.4	**14.9**	11.0–18.8
≥50 yrs (n = 790)	4.4	13.3	8.9	7.1–10.6
Constipation[c]				
Total (n = 984)	7.5	13.1	5.6	4.1–7.1
<50 yrs (n = 194)	6.4	14.4	8.0	4.4–11.6
≥50 yrs (n = 790)	7.7	12.7	5.0	3.4–6.7
Diarrhoea[c]				
Total (n = 971)	4.8	10.8	6.0	4.7–7.4
<50 yrs (n = 189)	5.6	13.6	**8.0**	4.5–11.5
≥50 yrs (n = 782)	4.6	10.1	5.6	4.1–7.0
Financial difficulties[c]				
Total (n = 969)	8.0	16.4	8.4	6.7–10.1
<50 yrs (n = 189)	7.3	30.5	**23.2**	18.6–27.8
≥50 yrs (n = 780)	8.2	12.9	4.8	3.1–6.5

(*Continued*)

Table II. *(Continued)*

	Normative data (expected mean)	Observed mean	Mean difference	95% CI
HADS[d]				
Anxiety[e]				
Total (n = 449)	4.76	6.17	**1.41**	0.99–1.83
<50 yrs (n = 191)	4.81	6.57	**1.76**	1.12–2.40
≥50 yrs (n = 258)	4.72	5.87	1.15	0.59–1.72
Depression[f]				
Total (n = 449)	4.09	4.30	0.21	−0.14–0.56
<50 yrs (n = 191)	3.60	4.63	**1.03**	0.49–1.58
≥50 yrs (n = 258)	4.45	4.06	−0.39	−0.85–0.06

Abbreviations: CI, confidence interval.
[a]Only clinically meaningful mean group differences are in bold.
[b]Scores 0–100. Higher scores indicate better function.
[c]Scores 0–100. Higher scores indicate more symptoms/problems.
[d]Scores 0–21. Higher scores indicate more symptoms.
[e]Clinically meaningful mean group differences ≥ 1.23 are in bold.
[f]Clinically meaningful mean group differences ≥ 0.86 are in bold.

In accordance with previous research, young age [8,11,12–14], chemotherapy [7,8,13,15] and lack of social support [11,14,15] were associated with HRQoL in the first two steps of the regression analyses. Associations with other clinical factors were found to be less pronounced suggesting age and chemotherapy to be of particular importance. In the final models including socio-economic factors, associations with chemotherapy and social support remained for a majority of HRQoL dimensions, whereas clinically meaningful associations with age remained only for anxiety, social and sexual functioning. These results indicate that it is not young age per se that determines low levels of several HRQoL dimensions. More specifically, being on sick leave and having a poor financial situation diminish the effect of young age on HRQoL. Corroborating results from previous research [16], the present findings point towards an unfavorable influence of socio-economic factors on HRQoL, which should be interpreted within the context of the Swedish society with a tax funded National Health Care System. Even though the patient's own direct costs for health care are relatively low, treatment-related sick leave in general reduces income by about 20%. The majority of Swedish women of working age have paid work and young women often have financial responsibilities for family and children. Therefore, it is reasonable to expect that cancer treatment to a higher degree has financial implications for younger breast cancer patients than older patients. Hence, even though socio-economic factors diminished the influence of age on several HRQoL dimensions in the present study, the importance of age should not be neglected.

The explained variances of the selected outcome measures varied from 13% to 45%, highlighting the multidimensionality of HRQoL and indicating that HRQoL is a complex patient-reported outcome. Even though the study design enabled inclusion of many potential explanatory variables, other factors such as personality traits [29] and patient satisfaction [30] have been suggested to contribute substantially to variations in HRQoL, and thus these factors should be included in future studies. Also previous research has observed ethnic differences in HRQoL among breast cancer patients [31], but the possible influence of ethnicity on HRQoL among Swedish breast cancer patients remains unclear. Regarding the variable financial situation, the relatively large proportion of missing values in the present study introduces a risk of selection bias. In future studies, alternative methods of data collection regarding socio-economic variables should be sought in order to reduce this risk. Furthermore, the cross-sectional design of the present study limits conclusions regarding temporal relationships between patient-reported explanatory variables and HRQoL. Thus, longitudinal studies are needed in order to be able to identify such associations.

One of the main strengths of the present study is the population-based nature of the study sample. The study was based on a regional Breast Cancer Quality Register with almost complete coverage of all new incident cases of breast cancer, resulting in a generalizable sample. However, 1055 eligible women were not included in the present analyses due to delay in registration, non-response and internal exclusion criteria. Women not included in the analyses were significantly older and received less treatment than participants, indicating some selection bias. Despite controlling for these variables in the regression analyses, it cannot be excluded that selection bias may have had some influence on the generalizability of the present results. Another possible limitation is the

Table III. Clinically meaningful mean group differences based on fully adjusted[a] regression models of EORTC functioning scales (study sample: breast cancer patients in Sweden).

	Global health status/QoL (n = 910)[b]		Role functioning (n = 915)[b]		Social functioning (n = 909)[b]		Sexual functioning (n = 889)[b]	
	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]
Age and clinical factors								
Age[e]	NS		NS		0.3 (0.9–0.5)**	**−13.5**	−0.5 (−0.7–−0.3)***	**10.8**
Time since diagnosis[f]	−1.1 (−2.0–−0.3)**	4.2	NS		−1.1 (−2.1–−0.1)*	5.1	NS	
Invasiveness								
In situ cancer (ref.)	–		–		–		–	
Invasive cancer	−6.8 (−12.1–−1.4)*	**−13.4**	−11.4 (−18.9–−3.9)**	−18.1	NS		NS	
Chemotherapy								
No (ref.)	–		–		–		–	
Yes	−9.3 (−13.1–−5.5)***	**−14.7**	−13.2 (−18.6–−7.8)***	**−23.0**	−13.2 (−17.7–−8.6)***	**−18.9**	NS	
Comorbidity								
No comorbidity (ref.)	–		–		–		–	
1 comorbidity	−5.8 (−9.1–−2.5)**	−0.2	NS		NS		−3.8 (−7.2–−0.3)*	−3.1
≥ 2 comorbidities	−11.3 (−14.6–−8.0)***	−9.3	−9.5 (−14.2–−4.9)***	−8.1	−7.3 (−11.3–−3.4)***	−4.6	−4.3 (−7.8–−0.8)*	−6.5
Demographic factors and social support								
Support within the family								
Yes (ref.)	–		–		–		–	
No	−7.4 (−12.0–−2.7)**	**−12.9**	−7.8 (−14.4–−1.3)*	−11.7	−13.4 (−18.9–−7.8)***	**−16.9**	−6.8 (−11.8–−1.9)**	−9.6
Support outside the family								
Yes (ref.)	–		–		–		–	
No	−7.3 (−12.1–−2.6)**	**−11.4**	NS		−6.2 (−11.9–−0.4)*	−9.1	NS	
Socio-economic factors								
Education								
University level (ref.)	–		–		–		–	
Other	NS		NS		NS		−5.7 (−8.7–−2.7)***	−9.3
Occupation								
Retirement pension (ref.)	–		–		–		–	
Employed/student	NS		NS		NS		NS	
Sick leave	−12.1 (−17.1–−7.2)***	**−12.8**	−25.3 (−32.3–−18.4)***	**−25.8**	−6.8 (−12.6–−0.9)*	**−14.8**	NS	
Other occupation	−9.1 (−14.1–−4.2)***	−8.8	−14.2 (−21.1–−7.3)***	−7.8	−7.5 (−13.4–−1.7)*	−9.6	NS	
Financial situation[g]	2.2 (1.6–2.8)***	**−15.0**	2.2 (1.4–3.0)***	−15.0	2.0 (1.3–2.7)***	**−11.7**	0.8 (0.2–1.4)**	−7.1

Abbreviations: B, unstandardized coefficient; CI, confidence interval; Mean diff., mean difference between explanatory variables; NS, no significance.

[a]Adjusted for previous breast cancer diagnosis, laterality, tumor size, lymph node involvement, type of surgery and oncological treatment, marital status and children.

[b]Scores 0–100. Higher scores indicate better function.

[c]Mean differences were only calculated for associations with statistical significance.

[d]Associations with clinically meaningful mean group differences are in bold.

[e]Categorized when assessing clinically meaningful mean group differences (<50, ≥50 (ref.) years).

[f]Categorized when assessing clinically meaningful mean group differences (1–4 months, 5–8 months (ref.)).

[g]Categorized when assessing clinically meaningful mean group differences (0–4 = poor, 5–10 = good (ref.)).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table IV. Clinically meaningful mean group differences based on fully adjusted[a] regression models of EORTC symptom scales (study sample: breast cancer patients in Sweden).

	Fatigue (n = 916)[b]		Insomnia (n = 914)[b]		Systemic therapy side effects (n = 911)[b]	
	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]
Age and clinical factors						
Age[e]	NS		−0.4 (−0.6–−0.1)**	7.3	NS	
Time since diagnosis[f]	1.3 (0.3–2.2)*	−5.7	NS		1.2 (0.5–1.8)***	−5.8
Previous breast cancer diagnosis						
No (ref.)	–		–		–	
Yes	NS		12.1 (3.1–21.0)**	9.0	NS	
Invasiveness						
Insitu cancer (ref.)	–		–		–	
Invasive cancer	11.1 (4.9–17.2)***	**16.7**	NS		6.7 (2.6–10.8)**	**15.7**
Lymph node involvement (N)						
In situ, invasive no surgery/N (ref.)	–		–		–	
≥ 1 lymph node metastases	5.4 (1.4–9.4)**	**13.1**	NS		NS	
Chemotherapy						
No (ref.)	–		–		–	
Yes	8.8 (4.4–13.2)***	**17.0**	6.1 (0.4–11.9)*	12.0	22.1 (19.1–25.0)***	**24.7**
Endocrine therapy						
No (ref.)	–		–		–	
Yes	−4.4 (−8.0–−0.8)*	0.3	NS		NS	
Comorbidity						
No comorbidity (ref.)	–		–		–	
1 comorbidity	NS		NS		3.5 (1.0–6.0)**	0.7
≥ 2 comorbidities	10.7 (6.9–14.5)***	9.7	6.7 (1.7–11.7)**	6.7	6.7 (4.2–9.2)***	3.8
Demographic factors and social support						
Support within the family						
Yes (ref.)	–		–		–	
No	7.9 (2.6–13.2)**	12.6	9.9 (2.9–16.9)**	**15.8**	6.1 (2.5–9.6)**	7.4
Support outside the family						
Yes (ref.)	–		–		–	
No	NS		11.5 (4.3–18.6)**	**14.4**	NS	
Socio-economic factors						
Occupation						
Retirement pension (ref.)	–		–		–	
Employed/student	NS		NS		NS	
Sick leave	10.3 (4.6–16.0)***	**15.0**	7.8 (0.3–15.2)*	12.4	4.5 (0.7–8.3)*	**13.1**
Other occupation	7.8 (2.2–13.5)**	9.7	11.8 (4.4–19.3)**	**14.3**	6.8 (3.0–10.5)***	7.5
Financial situation[g]	−2.0 (−2.7–−1.3)***	**13.9**	−1.3 (−2.1–−0.4)**	12.1	−1.3 (−1.8–−0.9)***	8.8

Abbreviations: B, unstandardized coefficient; CI, confidence interval; Mean diff., mean difference between explanatory variables; NS, no significance.

[a]Adjusted for laterality, tumor size, type of surgery and oncological treatment, marital status, children and education.

[b]Scores 0–100. Higher scores indicate more symptoms/problems.

[c]Mean differences were only calculated for associations with statistical significance.

[d]Associations with clinically meaningful mean group differences are in bold.

[e]Categorized when assessing clinically meaningful mean group differences (< 50, ≥ 50 (ref.) years).

[f]Categorized when assessing clinically meaningful mean group differences (1–4 months, 5–8 months (ref.)).

[g]Categorized when assessing clinically meaningful mean group differences (0–4 = poor, 5–10 = good (ref.)).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

validity of the information regarding the type of oncological treatment that the study participants actually received, because records in the register refer to planned treatment. Also we were not able to specify during which phase of the treatment process the women completed the questionnaires. Instead we used time since diagnosis as an alternative measure, which was not found to be clinically meaningfully associated with HRQoL.

The fact that the present results are not limited to statistical significance should be regarded as a methodological strength. Hence, the results do not reflect small statistically significant differences in mean scores owing to a large sample size or a large amount of statistical analyses. In addition, the assessment of clinically meaningful mean group differences of the EORTC QLQ-C30 was based on evidence-based guidelines for specific subscales [20], while

Table V. Clinically meaningful mean group differences based on fully adjusted[a] regression models of the HADS (study sample: breast cancer patients in Sweden).

	Anxiety (n = 914)[b]		Depression (n = 914)[b]	
	B (95% CI)	Mean diff.[cd]	B (95% CI)	Mean diff.[cd]
Age and clinical factors				
Age[e]	−0.1 (−0.1–−0.0)**	**1.4**	NS	
Previous breast cancer diagnosis				
No (ref.)	–		–	
Yes	1.8 (0.6–3.0)**	**1.1**	NS	
Chemotherapy				
No (ref.)	–		–	
Yes	NS		0.8 (0.2–1.4)*	**1.5**
Comorbidity				
No comorbidity (ref.)	–		–	
1 comorbidity	0.7 (0.0–1.3)*	−0.4	0.7 (0.2–1.3)**	0.1
≥2 comorbidities	1.6 (0.9–2.3)***	**1.4**	1.2 (0.6–1.7)***	**1.1**
Demographic factors and social support				
Support within the family				
Yes (ref.)	–		–	
No	2.1 (1.1–3.0)***	**3.2**	2.1 (1.3–2.8)***	**3.0**
Support outside the family				
Yes (ref.)	–		–	
No	1.4 (0.5–2.4)**	**2.2**	1.5 (0.7–2.2)***	**2.3**
Socio-economic factors				
Occupation				
Retirement pension (ref.)	–		–	
Employed/student	NS		NS	
Sick leave	NS		NS	
Other occupation	NS		1.2 (0.4–1.9)**	**1.6**
Financial situation[f]	−0.4 (−0.5–−0.3)***	**2.8**	−0.3 (−0.4–−0.2)***	**2.3**

Abbreviations: B, unstandardized coefficient; CI, confidence interval; Mean diff., mean difference between explanatory variables; NS, no significance.

[a]Adjusted for time since diagnosis, laterality, invasiveness, tumor size, lymph node involvement, type of surgery and oncological treatment, marital status, children and education.

[b]Scores 0–21. Higher scores indicate higher levels of symptoms.

[c]Mean differences were only calculated for associations with statistical significance.

[d]Associations with clinically meaningful mean group differences of ≥ 1.1 for anxiety and ≥ 0.8 for depression are in bold.

[e]Categorized when assessing clinically meaningful mean group differences (< 50, ≥ 50 (ref.) years).

[f]Categorized when assessing clinically meaningful mean group differences (0–4 = poor, 5–10 = good (ref.)).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

future studies should seek to establish the validity of current guidelines for the BR23 and the QLQ-C30 emotional functioning subscale [21]. Regarding the HADS, further research is needed among breast cancer patients to establish whether 20% of the mean value is a valid proportion when assessing clinical meaningfulness.

With regard to comparisons with normative data, some caution must be taken regarding the interpretation of the present results, as comparisons included only study participants within age groups for whom normative data were available, i.e., 25–79 years for the EORTC QLQ-C30 [24] and 30–59 years for the HADS [25]. This implies that the results can only be generalized to breast cancer patients within these age groups. Regarding the HADS, normative data were based on responses from 357 women from the general female population. When stratifying by age (<50, ≥50 years), breast cancer patients ≥50 years were compared with relatively few observations from the normative data, which should be considered when interpreting the results. Furthermore, the normative data used in the present study were obtained in the 1990s. While overall public health in Sweden has improved during the past decades, there is evidence of an unfavorable development regarding mental health issues among young women in particular [32]. Thus, the group differences observed in the present study may entail potential underestimation of problems among women with breast cancer regarding some general health issues, and potential overestimation of mental health problems among young breast cancer patients. Updated reference values for the general population are needed to increase validity of results.

Conclusion

Corroborating findings from previous studies, recently diagnosed breast cancer patients, in particular young women, reported poorer HRQoL in several dimensions compared to normative data. Factors associated with more problems/symptoms among study participants included chemotherapy, lack of social support, sick leave and a poor financial situation. An association between age and HRQoL became less pronounced following adjustment for socio-economic factors. The present findings emphasize the importance of taking a variety of factors into account when assessing HRQoL in the clinical setting. In Sweden, it has recently been proposed that measures of HRQoL should be incorporated as standard items in the National Quality Registers on cancer [5]. The present results will be of importance when deciding on relevant variables for inclusion in Quality Registers on cancer in Sweden.

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