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EPIDEMIOLOGY

Health-related quality of life in long-term disease-free breast cancer survivors versus female population controls in Germany

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Abstract

Purpose Little is known about breast cancer (BC) survivors' health-related quality of life (HRQoL) > 5 or even > 10 years past diagnosis. It is of interest whether, in the long run, survivors' HRQoL aligns with that of the general population. Study objectives were to (1) compare disease-free BC survivors' HRQoL to that of non-cancer controls, and (2) compare long-term survivors (LTS, 5–9 years post-diagnosis), very long-term survivors (VLTS, ≥ 10 years post-diagnosis), and controls with respect to their HRQoL.

Methods The samples of 2647 disease-free BC survivors (5–16 years post-diagnosis) and 1005 population controls were recruited in German multi-regional population-based studies. HRQoL was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (EORTC QLQ-C30). Differences in HRQoL were assessed with multiple regression, controlling for age and education.

Results Disease-free BC survivors < 80 years (at survey) reported overall global health status/quality of life comparable to controls, but statistically significant lower physical, role, emotional, social, and cognitive functioning. They also indicated more fatigue, insomnia, dyspnoea, and financial difficulties. However, differences were only of trivial or small clinical relevance. At age 80–89, no differences between BC survivors and controls were observed. Deficits in emotional and cognitive functioning and some symptoms (e.g. insomnia and fatigue) persist, as both LTS and VLTS reported more detriments than controls.

Conclusions In view of the persistent, small but significant detriments in disease-free BC survivors' cognitive and emotional functioning and higher symptom burden, possibilities to prevent detriments from becoming chronic should be explored.

Keywords Health-related quality of life · Breast cancer survivors · Very long-term · Population-based · Age effects

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Background

Breast cancer (BC) in women is one of the most common cancers, with more than 70,000 new diagnoses per year in Germany [1] and almost 2.1 million worldwide [2]. Due to improving prognosis and demographic ageing, the number of long-term cancer survivors is increasing [1]. Cancer is now considered a chronic disease that can affect survivors' life even years after treatment cessation [3–5]. As symptoms and functioning impairments can be transient, persisting or even progressive in the long run [6], looking into health-related quality of life (HRQoL) and well-being of long-term survivors (LTS, ≥ 5 years post-diagnosis) or very long-term survivors (VLTS, ≥ 10 years post-diagnosis) is of growing importance [7].

During or shortly after BC treatment, pain, fatigue, arm morbidity, and postmenopausal symptoms are among the most frequently reported symptoms [8]. Approximately one-third of BC survivors experience these symptoms after treatment cessation [9]. Symptom burden, like fatigue, sleep problems, depression, and pain, may have a considerable negative impact on HRQoL [6, 9].

Few studies have compared the HRQoL of long-term BC survivors to that of the general population and results are mixed [9, 10]. Most studies reported comparable overall quality of life in LTS compared to control groups, but survivors were more likely to report specific problems like a thick and painful arm [11], sexual difficulties [10], subjective cognitive deficits [12], higher levels of fatigue and dyspnoea [13], more financial burden [12], or lower physical [13, 14], role, and social functioning [13].

Previous studies have shown age differences in HRQoL of BC survivors. For example, older BC survivors (1 year post-diagnosis) reported a better role, emotional, cognitive, and social functioning than younger survivors, while in the general population all functioning scores tended to decrease with age [15]. Long-term BC survivors with higher age at therapy (> 65 years compared to ≤ 65 years) reported lower physical functioning and more pain, but less financial impact [16]. Studies also showed that younger BC survivors suffered from more HRQoL restrictions than older BC survivors [6, 9, 17]. As such, studies should address age-specific patterns, so that possible late effects of the cancer or its treatment can be distinguished from normative ageing effects [16]. Time since diagnosis as well as tumour characteristics, sociodemographic background, or depression can also be associated with HRQoL [9, 10, 16, 18] and therefore be considered as potential effect modifiers.

This study aimed to compare the HRQoL of disease-free, (very) long-term BC survivors with that of female population controls taking into account the potential moderating effects of age and time since diagnosis.

Methods

Setting and participants

The study population was derived from two German population-based studies, *CAESAR+* ("Cancer Survivorship—A multi-regional population-based study") and *LINDE* ("Lebensqualität in Deutschland"—Quality of life in Germany).

CAESAR+ (BC survivors)

The CAESAR+ study included long-term cancer survivors diagnosed between 1994 and 2004, reported to one of six participating German cancer registries (Bremen, Hamburg, North Rhine-Westphalia, Rhineland-Palatinate, Saarland, and Schleswig-Holstein). Inclusion criteria were age at diagnosis 20–75 years and a histological confirmation of breast, colorectal, or prostate cancer. Details of the study have been published elsewhere [19, 20]. Briefly, data collection was conducted between March 2008 and May 2011 by postal questionnaire. Non-respondents received up to two follow-up reminder letters and a telephone contact. Out of 6553 BC participants chosen for participation, 3045 completed the full-length questionnaire (response rate: 46.5%). Respondents who did not indicate date of diagnosis and who did not consent to linkage of clinical information from the cancer registry ($n = 7$) were excluded. We further excluded participants with self-reported recurrence or metastasis ($n = 319$) or another primary cancer after their breast cancer ($n = 72$), leading to a final sample of 2647 disease-free BC survivors (Online Resource 1).

LINDE (population controls)

The LINDE study aimed to assess individual HRQoL from a representative sample of the German population. A total of 10,580 men and women, aged 18 and above, stratified by age and sex, were randomly selected from the general German population via regional municipal offices. Data collection was conducted between 2013 and 2014. Potential participants received detailed study information and a postal questionnaire. Non-respondents received two follow-up reminder mails and a telephone contact (or one mailed reminder and a home visit, if necessary). Further study details have been reported elsewhere [11]. In total, 2849 individuals participated (response rate: 29%). As a comparison group for BC survivors, we only included females ($n = 1523$). We excluded women who completed a short questionnaire ($n = 131$) or a telephone interview ($n = 86$) only, as only the full-length questionnaire included information about comorbidities, including cancer. Participants with self-reported history of cancer ($n = 165$) and who were younger (< 30 years,

$n = 124$) or older than the BC sample (> 89 years, n = 12) were excluded. Finally, 1005 LINDE participants remained in the sample.

Measurements

HRQoL

HRQoL was assessed with the internationally validated *European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30* questionnaire. This 30-item questionnaire consists of five functional scales (physical, role, emotional, cognitive, social), a global health/quality of life (QoL) scale, and nine items/scales on symptoms and financial difficulties. Answers range from 1 ('very poor') to 7 ('excellent') for items in the global health/QoL scale and from 1 ('not at all') to 4 ('very much') for all other scales. Linear transformation of raw scores to a scale of 0–100 was performed according to the EORTC scoring manual [21]. High scores on the functioning scales and global health/QoL indicate better functioning. On the symptom and financial difficulty scales, a high score represents a greater burden. Differences in mean scores were classified as trivial, small, medium, and large according to published guidelines [22, 23]. The classification proposed by Cocks et al. [22] is based on meta-analyses of reported mean differences and thus is subscale-specific. Small differences start with > 3 to > 6 scale points, medium differences with > 7 to > 19 scale points, and large differences with > 14 to > 29 scale points (Online Resource 2). Trivial differences can be considered negligible, with interest focused on larger differences, indicating more clinical relevance [23].

Sociodemographic and clinical data

In both studies, the questionnaires included sociodemographic and clinical information such as marital status, education, income, and comorbidities. Information on treatment and disease progression since initial diagnosis (recurrence, metastasis, new cancer) was also assessed via self-report. The particular cancer registries provided additional clinical information on cancer survivors such as year of diagnosis and cancer stage.

Statistical analyses

Sociodemographic differences between BC survivors and population controls were determined with Cochran–Mantel–Haenszel tests (CMH). The age distribution of population controls reflected a stratified sampling scheme but was still significantly different from that of BC survivors. Therefore, we used direct standardisation to compare further sample characteristics, using the age distribution of BC survivors as standard.

Least square means of HRQoL scores were adjusted for age and education using multiple linear regression. Employment status and comorbidity also differed between BC survivors and controls. These variables, however, were not included for adjustment, as they reflect the situation at the time of the survey and potential differences could also be a consequence of the cancer among the BC survivors. Age at the survey was categorised as follows: 30–49, 50–59, 60–69, 70–79, and 80–89 years. BC survivors were further stratified by time since diagnosis: 5–9 years post-diagnosis (long-term survivors, LTS) and ≥ 10 years post-diagnosis (very long-term survivors, VLTS).

We employed multiple imputation, based on the Markov Chain Monte Carlo method with 25 repetitions to reduce possible bias due to missing values (in general less than 10%). All analyses were conducted with SAS (version 9.4 for Windows; SAS Institute Inc., Cary, NC). A p value < 0.05 (two-sided) was considered statistically significant. The p values were not adjusted for multiple testing, referring to the individual tests rather than a global test for differences.

Results

Non-respondent analysis

Based on cancer registry data, we compared respondents and non-respondents of *CAESAR* + to check representativeness of the BC survivor sample. Overall, the two groups appeared to be comparable on most variables, except for some differences that were small, but statistically significant ($p < 0.05$). Respondents were slightly younger at diagnosis (57.1 vs. 57.6 years) and at the time of the survey (65.3 vs. 66.2 years), they had a shorter time since diagnosis (8.2 vs. 8.6 years) and they were less likely to have distal extension/stage IV disease (1.2% vs. 2.0%). However, the distribution of local and regional tumour extension and of stage I–III did not differ significantly between respondents and non-respondents (Online Resource 3).

Study population characteristics

As controls were younger than BC survivors at time of survey (mean age 58.7 vs. 65.4 years), the age distribution of controls was adjusted to that of BC survivors to further compare the characteristics of the two samples (Table 1). Even after age standardisation, BC survivors reported lower education (≤ 9 years of education: 54.4% vs. 43.7%), were less likely to work full-time (7.7% vs. 13.4%), and were more often retired at time of the survey (50.3% vs. 44.0%) in comparison to controls. BC survivors reported higher rates of

Table 1 Description of study population (breast cancer (BC) survivors versus female population controls), after multiple imputation of missing values

	BC survivors		Population controls			Difference[b]			
						Crude		Adj.[a]	
	n	% crude	*n*	% crude	%adj.[a]	abs. %	*p*	abs. %	*p*
Total	2647	100.0	1005	100.0					
Mean age (SD)	65.4	(9.4)	58.7	(14.3)					
Age at survey									
30–49	171	6.5	309	30.7	6.5	24.2	**< 0.0001**	–	–
50–59	533	20.1	222	22.1	20.1	2.0	0.19	–	–
60–69	965	36.5	209	20.8	36.5	−15.7	**< 0.0001**	–	–
70–79	842	31.8	160	15.9	31.8	−15.9	**< 0.0001**	–	–
80–89	136	5.1	105	10.4	5.1	5.3	**< 0.0001**	–	–
German nationality	2606	98.5	973	96.9	97.8	−1.6	**0.0020**	−0.7	0.24
Education									
≤ 9 years	1441	54.4	346	34.5	43.7	−19.9	**< 0.0001**	−10.7	**< 0.0001**
10 years	748	28.3	339	33.7	31.2	5.4	**0.0013**	2.9	0.14
≥ 12 years	458	17.3	320	31.8	25.1	14.5	**< 0.0001**	7.8	**< 0.0001**
Employment									
Full-time	204	7.7	207	20.6	13.4	12.9	**< 0.0001**	5.7	**< 0.0001**
Part-time	388	14.7	259	25.8	16.8	11.1	**< 0.0001**	2.1	0.10
Unemployed	42	1.6	29	2.8	2.5	1.2	**0.0146**	0.9	0.14
Housewife	606	22.9	180	17.9	20.1	−5.0	**0.0011**	−2.8	0.11
(Early) retirement	1331	50.3	287	28.6	44.0	−21.7	**< 0.0001**	−6.3	**0.0011**
Other	75	2.8	43	4.3	3.2	1.5	**0.0292**	0.4	0.62
Having a partner	1894	71.5	726	72.2	71.0	0.7	0.69	−0.5	0.77
Having children	2244	84.8	833	82.9	85.6	−1.9	0.16	0.8	0.59
Current household size									
1 person	686	25.9	238	23.6	26.6	−2.3	0.16	0.7	0.72
2 persons	1558	58.9	458	45.6	57.7	−13.3	**< 0.0001**	−1.2	0.57
≥ 3 persons	403	15.2	309	30.8	15.8	15.6	**< 0.0001**	0.6	0.67
Comorbidities (self-report)									
Stroke	67	2.5	22	2.2	2.7	−0.3	0.56	0.2	0.80
Myocardial infarction	52	2.0	11	1.1	1.5	−0.9	0.09	−0.5	0.45
Heart failure	246	9.3	58	5.7	6.6	−3.6	**0.0005**	−2.7	**0.0239**
Diabetes mellitus	276	10.4	89	8.9	11.1	−1.5	0.16	0.7	0.63
Depression (ever before)	598	22.6	207	20.6	19.0	−2.0	0.19	−3.6	**0.0394**

A bold *p*-value indicates that the difference was considered statistically significant ($p < 0.05$)

All results based on 25 imputations

SD Standard deviation

[a]Adj: adjusted to age distribution of BC survivors cohort

[b]Absolute difference (abs. %) in proportions of controls minus BC survivors

heart failure (9.3% vs. 6.6%) and ever having had depression (22.6% vs. 19.0%). There were no differences in nationality (which was German for the vast majority of both BC survivors and controls), household size, and having a partner or children (Table 1).

LTS and VLTS, after age standardisation, did not differ with respect to nationality, education, marital status, partnership, or comorbidity (data not shown). Regarding clinical variables, LTS compared to VLTS were more often diagnosed at stage II (50.3% vs. 44.4%), had undergone more often axilla dissection (96.6% vs. 94.0%), and treated less often with radiotherapy (78.1% vs. 84.8%). There was no significant difference in proportion of survivors having undergone breast-conserving surgery, chemo- or hormone therapy, and no difference in extension of disease (Table 2).

Table 2 Characteristics of breast cancer (BC) survivors by time since diagnosis at recruitment, after multiple imputation of missing values

	All cancer survivors		Survivors 5–9 years past diagnosis (LTS)			Survivors ≥ 10 years past diagnosis (VLTS)			Diff. VLTS–LTS, age-adjusted[b]	
	n	% crude	*n*	% crude	% adj.[a]	*n*	% crude	% adj.[a]	abs. %	*p*
Total	2647	100.0	2081	100.0		566	100.0			
Mean age (SD)	65.4	(9.4)	64.9	(9.2)		67.3	(9.8)			
Age at survey										
30–49	171	6.5	147	7.1	6.5	24	4.2	6.5	–	–
50–59	533	20.1	428	20.6	20.1	105	18.6	20.1	–	–
60–69	965	36.5	776	37.3	36.5	189	33.4	36.5	–	–
70–79	842	31.8	659	31.7	31.8	183	32.3	31.8	–	–
80–89	136	5.1	71	3.4	5.1	65	11.5	5.1	–	–
Extension of disease[c]										
Local	1754	66.3	1374	66.0	66.8	380	67.1	66.2	0.6	0.73
Regional	868	32.8	688	33.1	32.2	181	31.9	32.9	−0.7	0.72
Distant	25	0.9	19	0.9	1.0	5	1.0	0.9	0.1	0.84
Stage										
I	1197	45.2	953	45.8	42.0	244	43.0	45.9	−3.9	0.11
II	1204	45.5	926	44.5	50.3	278	49.1	44.4	5.9	**0.0171**
III	220	8.3	182	8.8	6.6	38	6.7	8.7	−2.1	0.11
IV	26	1.0	20	0.9	1.1	6	1.1	0.9	0.2	0.73
Treatment										
Organ-preserving[d]	2066	78.0	1645	79.0	76.2	421	74.4	78.7	−2.5	0.26
Axilla dissection	2501	94.5	1957	94.1	96.9	544	96.1	94.0	2.9	**0.0015**
Radiotherapy	2208	83.4	1770	85.0	78.1	438	77.4	84.8	−6.7	**0.0007**
Chemotherapy	1558	58.9	1263	60.7	55.6	295	52.1	59.7	−4.1	0.08
Hormone therapy	1321	49.9	1040	50.0	49.7	281	49.6	49.8	−0.1	0.72

A bold *p*-value indicates that the difference was considered statistically significant ($p < 0.05$)

All results based on 25 imputations

SD standard deviation

[a]Adj.: Adjusted to age distribution of total BC survivors cohort

[b]Absolute difference (abs. %) in proportions of very long-term minus long-term BC survivors

[c]Extension at time of diagnosis according to the SEER staging scheme (local: primary tumour, regional: regional nodes, distant: metastases). Survivors with metastases at time of diagnosis but no further progression up to the survey were included in the sample

[d]Breast-preserving therapy or mastectomy with reconstruction

HRQoL of BC survivors and population controls

Disease-free BC survivors and population controls reported comparable global health status/overall QoL (Table 3). On all five functioning scales, BC survivors reported lower scores than controls. Although these differences were statistically significant, the clinical relevance was trivial (physical, role, emotional, and social functioning) or small (cognitive functioning). Insomnia, fatigue, pain, and dyspnoea were the most prevalent symptoms in both groups. For all symptoms except pain, and for financial difficulties, BC survivors reported significantly higher burden than controls. These differences were of trivial or small clinical relevance.

HRQoL of BC survivors and population controls, stratified by age at survey

In age-stratified analyses, BC survivors and controls showed comparable global health status/overall QoL in most age groups (Fig. 1). Only BC survivors 60–69 years reported significantly lower scores than controls (trivial clinical relevance). On the functioning scales, BC survivors in most age groups < 80 years scored significantly lower than controls; however, these differences were of trivial or small clinical relevance. At age 80–89 years, BC survivors reported higher scores than controls in global health status/overall QoL, cognitive, physical, and social functioning; however, the differences were not significant.

Table 3 Health-related quality of life (HRQoL) in breast cancer (BC) survivors and population controls, after multiple imputation of missing values

	Mean scores adjusted for age									Mean scores adjusted for age and education								
	BC survivors		Controls		Difference survivors—controls					BC survivors		Controls		Difference survivors—controls				
	Mean	SE	Mean	SE	Mean	95CL	95CU	*p* (glm)	CR	Mean	SE	Mean	SE	Mean	95CL	95CU	*p* (glm)	CR
Functioning scales																		
Physical functioning	75.0	0.5	79.2	0.7	−4.2	−5.6	−2.8	**<0.0001**	t	76.4	0.5	80.0	0.7	−3.6	−5.0	−2.2	**<0.0001**	t
Role functioning	68.5	0.8	75.1	1.0	−6.7	−8.8	−4.5	**<0.0001**	s	70.0	0.8	76.0	1.0	−6.0	−8.1	−3.8	**<0.0001**	t
Emotional functioning	67.2	0.7	72.3	1.0	−5.1	−7.2	−3.1	**<0.0001**	s	68.3	0.8	72.9	1.0	−4.7	−6.7	−2.6	**<0.0001**	t
Cognitive functioning	77.3	0.6	82.4	0.9	−5.2	−7.0	−3.3	**<0.0001**	s	78.4	0.7	83.0	0.9	−4.7	−6.5	−2.9	**<0.0001**	s
Social functioning	77.5	0.7	83.1	1.0	−5.6	−7.6	−3.5	**<0.0001**	s	79.0	0.8	83.9	1.0	−4.9	−6.9	−2.9	**<0.0001**	t
Global health status/QoL	62.1	0.6	64.3	0.8	−2.3	−4.0	−0.5	**0.0103**	t	63.9	0.6	65.3	0.8	−1.5	−3.2	0.3	0.09	
Symptom scales																		
Fatigue	38.3	0.7	33.4	1.0	4.9	2.9	6.9	**<0.0001**	t	37.5	0.7	33.0	1.0	4.5	2.5	6.6	**<0.0001**	t
Nausea and vomiting	5.3	0.3	4.0	0.5	1.3	0.4	2.3	**0.0067**	t	4.8	0.4	3.7	0.5	1.1	0.1	2.0	**0.0251**	t
Pain	36.2	0.8	34.4	1.1	1.8	−0.6	4.2	0.14		33.9	0.9	33.1	1.1	0.7	−1.6	3.1	0.54	
Dyspnoea	28.1	0.8	21.0	1.1	7.1	4.9	9.3	**<0.0001**	s	26.3	0.8	20.0	1.1	6.3	4.1	8.5	**<0.0001**	s
Insomnia	42.6	0.9	35.1	1.3	7.5	4.9	10.2	**<0.0001**	s	40.9	1.0	34.1	1.3	6.8	4.1	9.4	**<0.0001**	s
Appetite loss	11.1	0.5	9.3	0.7	1.9	0.4	3.4	**0.0142**	t	10.4	0.6	8.9	0.7	1.5	0.1	3.0	**0.0436**	t
Constipation	15.0	0.7	10.6	0.9	4.4	2.5	6.3	**<0.0001**	t	13.9	0.7	10.0	0.9	3.9	2.0	5.8	**<0.0001**	t
Diarrhoea	10.0	0.6	6.7	0.8	3.3	1.7	4.9	**<0.0001**	s	9.8	0.6	6.6	0.8	3.2	1.6	4.8	**<0.0001**	s
Financial difficulties	16.3	0.7	10.2	0.9	6.1	4.1	8.1	**<0.0001**	s	14.5	0.7	9.2	0.9	5.3	3.3	7.3	**<0.0001**	s

A bold *p*-value indicates that the difference was considered statistically significant ($p < 0.05$)

All results based on 25 imputations

SE standard error of mean, *95CL* 95% confidence interval (lower limit), *95CU* 95% confidence interval (upper limit), *p p* value referring to null hypothesis, *HRQoL cancer survivors* HRQoL population controls, *CR* Scale-specific clinical relevance of statistical significant subgroup differences ($p < 0.05$), *t* trivial, *s* small, *QoL* quality of life

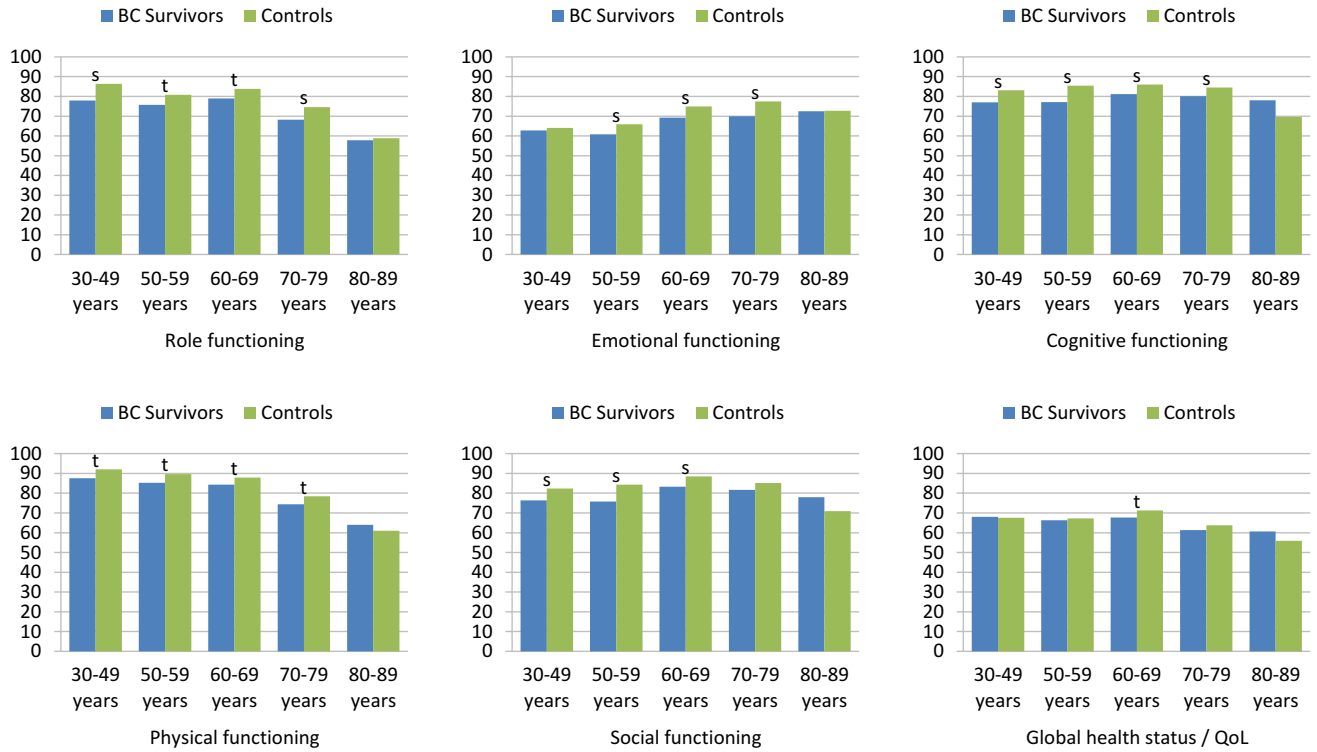

Fig. 1 Functioning and quality of life (QoL) of breast cancer (BC) survivors and population controls: stratified by age, adjusted for age and education. Scale-specific clinical relevance of statistical significant subgroup differences ($p < 0.05$) marked as *t* trivial or *s* small. Results are based on 25 imputations of missing values

Regarding symptoms, no clear pattern of differences between BC survivors and controls emerged (Fig. 2). Statistically significant differences in favour of controls that were of small clinical relevance could be found for fatigue (60–79 years), insomnia (50–79 years), dyspnoea (30–79 years), constipation (70–79 years), diarrhoea (50–59 and 70–79 years), and financial difficulties (30–59 years).

HRQoL of BC survivors and population controls, stratified by age at survey and time since diagnosis

An additional stratification of BC survivors by time since diagnosis revealed no significant differences between LTS and VLTS in functioning (Fig. 3, Online Resource 4). LTS reported significantly lower physical, role, and social functioning than controls in most age groups (trivial to small clinical relevance), while this could not be found for VLTS when compared to controls. However, in cognitive functioning (30–79 years), emotional functioning (60–79 years), and role functioning (70–79 years), VLTS also scored significantly lower than controls (small or medium clinical relevance). In age group 80–89 years, VLTS reported significantly higher cognitive functioning and a higher global health status/overall QoL than controls (medium clinical relevance).

Concerning symptoms, no clear pattern emerged (Fig. 4, Online Resource 5). Both LTS and VLTS differed significantly from controls on several items/scales and in certain age groups. Significant differences of small or medium clinical relevance were observed between VLTS and controls for dyspnoea and insomnia (70–79 years), and for financial difficulties (30–49 years).

Discussion

The number of women surviving breast cancer (BC) is increasing and it is important to learn more about long-term BC survivors' HRQoL to identify potential needs of this group.

We found that disease-free BC survivors had comparable global health status/overall QoL, but lower social, role, emotional, cognitive, and physical functioning, and more symptoms such as insomnia, fatigue, dyspnoea, constipation, diarrhoea, and more financial difficulties than controls. Previous studies reported comparable results regarding a good overall HRQoL, along with specific detriments [10]. Most of the differences we found between disease-free BC survivors and controls were of trivial or small clinical relevance. This suggests that BC survivors without disease progression in

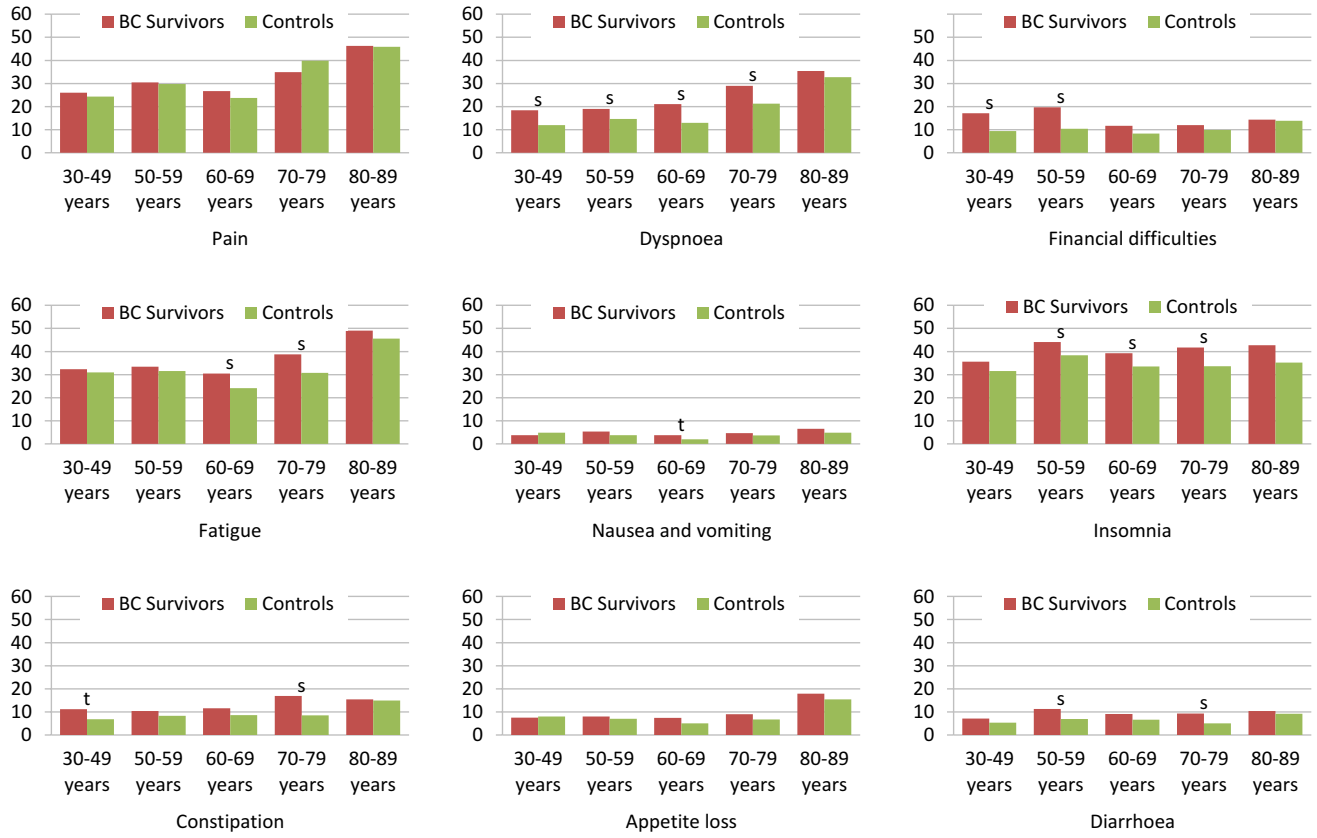

Fig. 2 Symptoms of breast cancer (BC) survivors and population controls: stratified by age, adjusted for age and education. Scale-specific clinical relevance of statistical significant subgroup differences ($p < 0.05$) marked as *t* trivial or *s* small. Results are based on 25 imputations of missing values

general have good chances to achieve HRQoL comparable to the general population in the long run.

Stratification by age revealed that some detriments in BC survivors compared to controls were observed only in certain age groups. This underlines the importance of stratification by age when assessing cancer survivors' HRQoL. For example, financial difficulties were found to be most relevant for BC survivors < 60 years and could therefore be a result of a limited ability to work due to late effects of the cancer or its treatment. In our sample, BC survivors were less likely to be in full-time employment and more likely to have (early) retirement when compared with controls. Loss of work could also contribute to detriments in social functioning that we found in BC survivors < 70 years compared to controls.

With increasing age, both BC survivors and controls tended to have lower physical and role functioning and higher symptom burden (e.g. fatigue, pain, dyspnoea), but better emotional functioning. A French population-based study also found significantly lower HRQoL in long-term BC survivors 65–85 years compared to younger survivors [24]. In the oldest age cohort in our study, 80–89 years, both BC survivors and controls reported lower HRQoL in many domains. This suggests that detriments at higher age could be a consequence of the normal ageing process rather than of the cancer and its treatment.

After additional stratification by time since diagnosis, we found that some detriments seem to diminish with increasing time since diagnosis, e.g. physical and social functioning, where only LTS but not VLTS differed significantly from controls. This is in line with other studies [25, 26]. Some detriments were evident both in LTS and VLTS compared to controls, especially in cognitive functioning. Poor cognitive functioning could also be explained by fatigue or poorer sleep, as both showed a significant negative correlation with cognitive functioning in BC survivors ($r = -0.52$ for fatigue, $r = -0.36$ for insomnia, both $p < 0.0001$, data not shown), whereby the causality remains unclear. Further differences in HRQoL between LTS and controls in certain age groups that were still evident between VLTS and controls included, e.g. emotional functioning, fatigue, insomnia, and dyspnoea. The finding that not all HRQoL aspects improve with increasing time since diagnosis is in line with longitudinal studies that found general HRQoL improvements in long-term BC survivors over time, but remaining deficits in self-reported cognitive functioning and financial impact [12] or in cognitive function and sleep [13, 27]. Early intervention seems to be

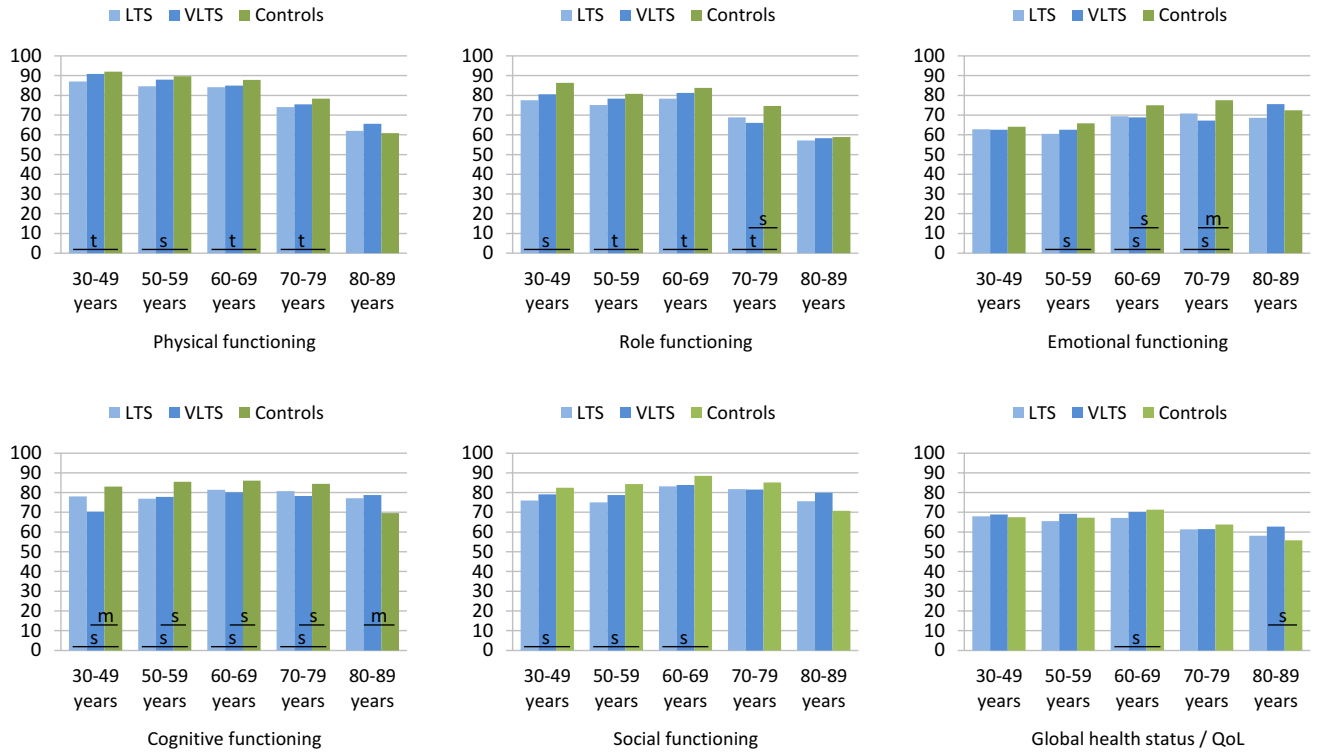

Fig. 3 Functioning and quality of life (QoL) of long-term breast cancer survivors (LTS), very long-term breast cancer survivors (VLTS), and population controls: stratified by age, adjusted for age and education. Scale-specific clinical relevance of statistical significant subgroup differences ($p < 0.05$) marked as *t* trivial, *s* small, *m* medium. The spans of the lines indicate which subgroups differ significantly in pairwise comparison (e.g. in physical functioning, age 30–49 years, LTS and controls differ significantly, while VLTS do not differ from any other group). Results are based on 25 imputations of missing values

important to prevent deficits from becoming chronic. Sleep and fatigue can be improved with cognitive-behavioural psychotherapy, e.g. improving sleep hygiene, addressing faulty beliefs concerning sleep and sleep loss [28], or relaxation training [29]. Physical exercise has positive effects on chronic fatigue [30] and on overall HRQoL [31, 32].

VLTS aged 80–89 years even scored higher than controls in cognitive functioning and global health status/overall QoL. This could reflect a normalisation process, which can be seen as a core process of cancer recovery [33]. BC survivors of higher age and with longer time since diagnosis would have had a longer time to perceive strains as "normal" part of their life course and to develop resources for responding to them [34].

Some limitations have to be considered when interpreting the results found in this study. Although the response rate of 46.5% for BC survivors is relatively good, there is a possibility of healthy survivor bias as elderly survivors and those with certain medical conditions, with a longer time period since diagnosis, or poorer health are in general less likely to participate in cancer survivorship studies [19]. This non-response pattern might result in an overestimation of the observed HRQoL in participating survivors, which in turn corresponds to an underestimation of the true difference between survivors and controls. Likewise, non-participation among non-cancer controls, where the response rate was 29%, might also introduce bias [19]. Due to a lack of baseline data, we were not able to adjust for baseline HRQoL of BC survivors. Moreover, differences according to age and time since diagnosis were based on cross-sectional analysis rather than on longitudinal development of individuals. Thus, the relationships between age, cancer, and HRQoL cannot be interpreted causally. Besides, in cross-sectional data, age and birth cohort cannot be disentangled. Participants of each age cohort also belong to the same birth cohort that shares specific experiences, e.g. regarding social milieu or medical care [35]. It has been shown for well-being that controlling for birth cohort can reverse putative age effects [35, 36]. Similarly, in our study, potential HRQoL differences according to birth cohorts could have led to an overestimation of HRQoL differences according to age. In contrast, selective survival could have biased the comparison between LTS and VLTS. Furthermore, we had missing data on relevant variables such as cancer stage because this variable was not fully reported to the cancer registries in the period when the survivors were first diagnosed. We imputed

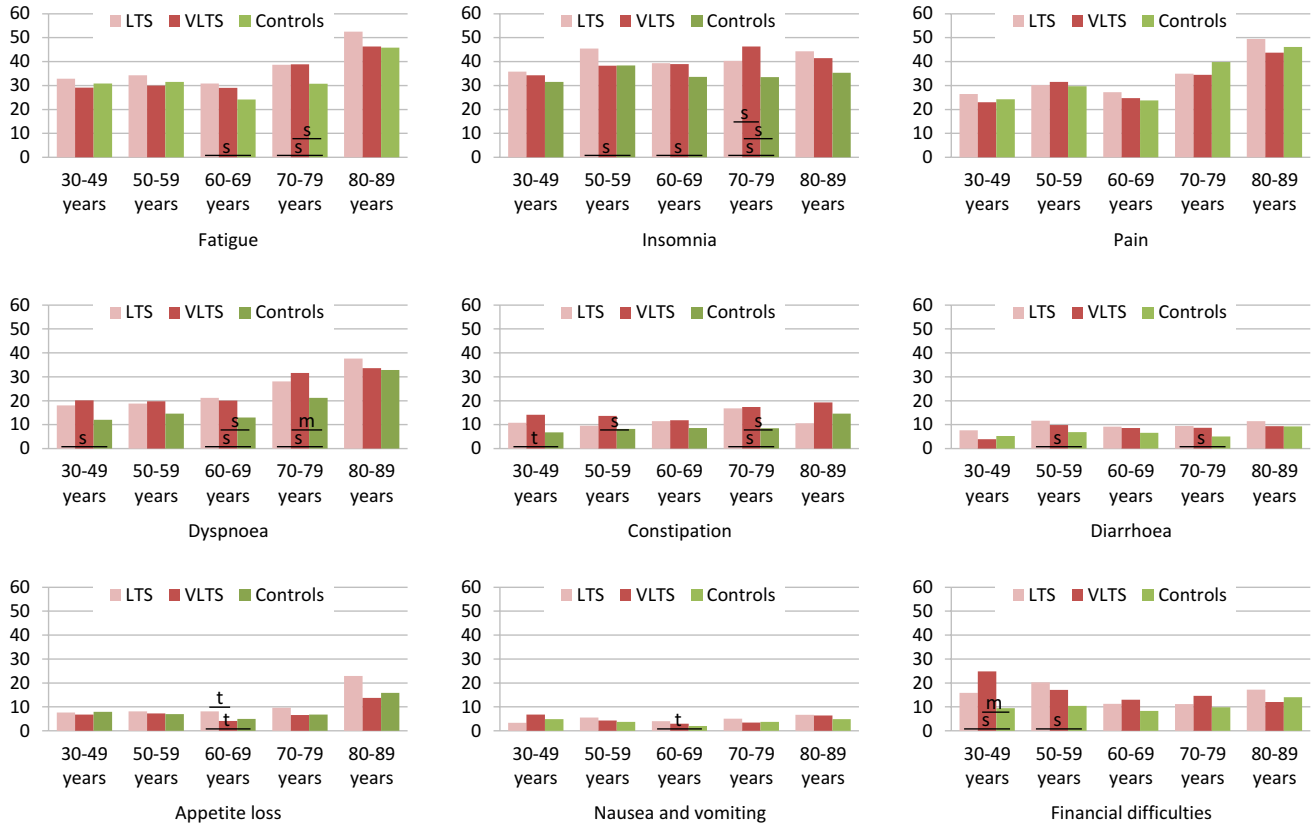

Fig. 4 Symptoms of long-term breast cancer survivors (LTS), very long-term breast cancer survivors (VLTS), and population controls: stratified by age, adjusted for age and education. Scale-specific clinical relevance of statistical significant subgroup differences ($p < 0.05$) marked as *t* trivial, *s* small, *m* medium. The spans of the lines indicate which subgroups differ significantly in pairwise comparison (e.g. in fatigue, age 70–79 years, LTS and controls differ significantly, VLTS and controls differ significantly, but LTS and VLTS do not differ). Results are based on 25 imputations of missing values

missing data and ran sensitivity analyses which showed that results derived from multiple imputations were similar to those from non-imputed data.

Strengths of this study include the population-based recruitment of both the BC survivors and the non-cancer control group with comparable data collection mode, which resulted in diverse cohorts with respect to sociodemographics, treatments, and stages. The large sample size allowed for stratification by age and by time since diagnosis, leading to a more diverse picture of HRQoL aspects in the analysed subgroups.

The long-term, disease-free BC survivors included in this study reported a good global health status/overall QoL, which was comparable to that of the general population. Although we found statistically significant detriments on almost all functioning and symptom scales, these differences were of trivial or small clinical relevance and were observed only in certain age groups. Nevertheless, BC survivors and health-care providers should be aware of possible late effects and chronic sequelae. Considering that these can be age-specific, long-term BC survivors' needs can be very different depending on their current situation. With increasing time since diagnosis, levels of some HRQoL aspects approached that of non-cancer population, but not all, e.g. cognitive functioning. Possibilities of early prevention to cope with possible detriments before they become chronic should be explored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures involving human participants were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Both studies (CAESAR+ and LINDE) were approved by the ethics committee of the medical faculty of the University of Heidelberg and by all local ethics committees accountable for the participating cancer registries.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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