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ORIGINAL ARTICLE

Age-specific health-related quality of life in long-term and very long-term colorectal cancer survivors versus population controls – a population-based study*

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ABSTRACT

Background: Previous research suggests an age differential in health-related quality of life (HRQOL) among long-term (5–10 years post-diagnosis, LTS) colorectal cancer (CRC) survivors. Few studies have specifically addressed the association of age differentials with HRQOL for very long-term CRC survivors (>10 years post-diagnosis, VLTS) and non-cancer population controls. We aimed to assess possible deficits in HRQOL of disease-free CRC-LTS and CRC-VLTS in comparison with non-cancer population controls, and whether the observed pattern varies by age and time since diagnosis.

Methods: We used data from the *CAncEr Survivorship - A multi-Regional* (CAESAR+) study in collaboration with five population-based German cancer registries. HRQOL from controls was accessed from the *L*ebensqualität *in DE*utschland (LinDE) study. All respondents completed the European Organization for Research and Treatment of Cancer Quality of Life Core-30 questionnaire. We calculated least square means of HRQOL scores. Analyses were adjusted for age, sex, and education, where appropriate.

Results: The sample included 862 CRC-LTS, 400 CRC-VLTS and 1689 controls. CRC survivors reported overall good HRQOL but significantly poorer social functioning and more problems with dyspnea, constipation, diarrhea and finances than controls. When stratified by age, deficits in functioning and global health, and more problems with symptoms and finances were noted mainly among younger CRC survivors. Further stratification by time since diagnosis showed that similar deficits in HRQOL and symptoms were noted mainly among the younger CRC-LTS group when compared with controls. Generally, CRC-VLTS reported comparable HRQOL to controls. An exception was noted for diarrhea, whereby CRC survivors, regardless of age and time since diagnosis, reported significantly more problems with this symptom than controls.

Conclusions: In comparison with non-cancer controls, disease-free CRC survivors reported overall good HRQOL but experience persistent specific detriments in HRQOL many years after diagnosis. In age stratified analyses, HRQOL deficits were noted mainly among younger CRC-LTS.

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Background

Earlier detection and improved treatments of colorectal cancer (CRC) have contributed significantly to the increasing number of individuals living >5 years after initial diagnosis. Approximately 59,000 individuals are expected to be newly diagnosed with CRC in Germany in 2018 of whom >50% are expected to be alive 5 years post-diagnosis [1]. Similarly in the US, approximately 60% of the 1.2 million individuals living with a CRC diagnosis in 2012 are long-term survivors

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Supplemental data for this article can be accessed here.

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German Society for Epidemiology Annual Meeting, Lübeck 2017.
International Association of Cancer Registries Meeting, Utrecht 2017.
DKFZ Conference on Preventive Oncology, Heidelberg 2018.
European Cancer Rehabilitation & Survivorship Symposium, Copenhagen 2018.

(≥5 years post-diagnosis), including 30% who survived ≥10 years (very long-term survivors) [2]. As CRC survivors are living longer and getting older, long-term or late effects of cancer treatment and comorbidity [3] can increase symptom burden and pose a challenge to functioning and health-related quality of life (HRQOL) [4].

The HRQOL of CRC survivors deteriorates during and shortly after end of treatment but does improve thereafter with time [5]. A systematic review reported that long-term CRC survivors have, in general, good overall HRQOL that is comparable to population norms [6]. However, on specific aspects of HRQOL, long-term CRC survivors have poorer physical functioning, higher symptom burden, and higher depression scores than population norms. Fewer studies have addressed the HRQOL of very long-term CRC survivors and results are mixed. For example, CRC survivors who had previously participated in clinical trials reported significantly better physical and mental HRQOL than non-cancer controls 5–19 years post-surgery [7]. Likewise, a Canadian population-based study of CRC survivors >15 years post-diagnosis reported that survivors had better social well-being and HRQOL than matched controls [8]. In a community-based study of adult onset cancer survivors including CRC, very long-term survivors had less cognitive difficulties and social concerns when compared with short and long-term survivors, although other aspects of HRQOL were similar among the three groups [9]. In contrast, a French population-based study of CRC survivors 5–15 years post-diagnosis, reported lower social functioning among long-term survivors and more problems with diarrhea among long- and very long-term survivors when compared with population controls [10]. However, none of these studies specifically addressed age-specific detriments in HRQOL. A recent study by our group indicated that detriments in HRQOL persist more than a decade in a sample of population-based cancer survivors and was more prominent among younger cancer survivors [11]. However this study included survivors of different cancer diagnoses and did not report specifically on CRC survivors.

Also, previously our research group found that among 1–10 year CRC survivors, younger CRC survivors reported poorer HRQOL and more symptom complaints than non-cancer controls throughout follow-up. On the other hand, older CRC survivors reported comparable or better HRQOL than controls in the short-term, but had poorer HRQOL in the 5–10 years follow-up [12]. A previous study of long-term CRC survivors found that older age was associated with poorer physical health [13]. We could not find published studies that have specifically addressed the association of age differentials on HRQOL for very long-term CRC survivors.

Therefore, the aims of our study are three-fold: (1) to compare the HRQOL of (very) long-term disease-free CRC survivors with a non-cancer population, (2) whether any deficits in HRQOL of CRC survivors observed 5–10 years past diagnosis persist beyond the 10th year after diagnosis, and (3) whether the observed pattern varies by age.

Methods

Setting and participants

CAESAR+ study

The population-based *CA*nc*E*r *S*urvivorship - *A* multi-*R*egional (CAESAR+) study aims to describe the long-term HRQOL of breast, prostate, and colorectal cancer survivors. The study was conducted by the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in collaboration with six epidemiologic cancer registries in Germany (Bremen, Hamburg, North Rhine-Westphalia, Rhineland-Palatinate, Schleswig-Holstein, and Saarland). This study used data from five cancer registries as no CRC survivors were recruited from Schleswig-Holstein due to logistic reasons. CRC survivors diagnosed between January 1994 and June 2004 as registered in the participating cancer registries, and aged between 20 and 75 years at diagnosis were eligible. Data collection was conducted between July 2009 and May 2011 by postal questionnaire. Depending on the cancer registry, the participants were contacted directly by the cancer registry (Hamburg, Saarland) or via the treating/study physician (Bremen, Rhineland-Palatinate, North Rhine-Westphalia). Details of the study design have been published elsewhere [11,14].

LinDE study (population controls)

Individual level HRQOL from a representative sample of German population was accessed from the *L*ebensqualität *in DE*utschland ('Quality of life in Germany', LinDE) study [11]. Eligible participants 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 controls received detailed study information and a questionnaire by mail. Non-respondents received two follow-up reminder mails and a telephone contact (or one mailed reminder or home visit, if necessary). Further details of sample selection are reported elsewhere [11].

Ethical approval

The study was approved by the ethics committee of the University of Heidelberg and the local ethics committees of the participating cancer registries. Written informed consent was obtained from all participants. All procedures involving human participants were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Data collection

HRQOL

HRQOL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Core-30 (EORTC-QLQ-C30) questionnaire [15]. This 30-item questionnaire consists of five functional scales (physical, role,

Table 1. Sociodemographic and clinical characteristics of colorectal cancer (CRC) survivors stratified by years since diagnosis, and population controls.

	CRC									
	LTS ($n = 862$)			VLTS ($n = 400$)			Controls ($n = 1689$)			
	n	% crude	MI[a] % adj[b]	*n*	% crude	MI[a] % adj[b]	*n*	% crude	MI[a] % adj[b]	*p*-value[c]
Sociodemographic										
Gender										1.00
Female	346	40	40	196	49	40	911	54	40	
Male	516	60	60	204	51	60	778	46	60	
Mean age at survey[c] ± SD	69.7 ± 8.3		69.7 ± 8.3	70.0 ± 8.3		70.0 ± 8.2	69.6 ± 8.8		69.6 ± 8.8	
Age at survey										1.00
<65 years	194	23	23	62	16	23	929	55	23	
65–69 years	155	18	18	69	17	18	177	10	18	
70–74 years	249	29	29	96	24	29	210	12	29	
75–79 years	183	21	21	79	20	21	122	7	21	
≥80 years	81	9	9	94	24	9	251	15	9	
In a partnered relationship										.015
Yes	660	77	77	266	67	72	1132	67	72	
No	200	23	23	132	33	28	541	32	28	
Missing	2	0.2	–	2	1	–	16	1	–	
Nationality										.38
German	823	95	99	377	94	98	1530	91	98	
Others	11	1	1	7	2	2	49	3	2	
Missing	28	3	–	16	4	–	110	7	–	
Education level										<.0001
<9 years	518	60	61	247	62	60	612	36	47	
10-11 years	164	19	20	67	18	19	457	27	22	
>12 years	159	18	18	72	18	21	566	34	30	
Missing	21	2	–	14	4	–	54	3	–	
Employment status										<.0001
Full/part-time	110	13	13	30	8	11	704	42	18	
(Early) retirement/unemployed	605	70	72	293	73	75	742	44	71	
Housewife/man	109	13	13	52	13	12	161	10	10	
Others	16	2	2	7	2	2	37	2	1	
Missing	22	3	–	18	5	–	45	3	–	
Monthly household income										.07
<1000 euros	66	8	12	25	6	12	145	9	9	
1000–3000 euros	468	54	69	184	46	67	977	58	66	
>3000 euros	128	15	19	49	12	20	521	31	25	
Missing	200	23	–	142	36	–	46	3	–	
Self-reported comorbidity[d]										.28
No comorbidity	597	69	69	265	66	69	1324	78	71	
1 comorbid condition	197	23	23	98	25	24	284	17	23	
≥2 comorbid conditions	67	8	8	31	8	7	63	4	6	
Missing	1	0.1	–	6	2	–	18	1	–	
Prevalence of comorbidity										
Stroke	46	5	5	20	5	4	61	4	5	.77
Myocardial infarction	50	6	6	25	6	7	61	4	5	.58
Heart failure	113	13	14	64	16	14	123	7	11	.23
Diabetes mellitus	137	16	16	57	14	15	176	10	16	.64
Clinical										
Mean since diagnosis[c] ± SD	7.0 ± 1.2		7.0 ± 1.2	11.6 ± 1.5		11.6 ± 1.5	–	–	–	
Type of cancer							–	–	–	.35
Colon	494	57	57	228	57	55				
Rectum	368	43	43	172	43	45				
Cancer stage at diagnosis (UICC)							–	–	–	.22
I	240	28	32	76	19	25				
II	263	31	36	121	30	40				
III	212	25	27	89	22	30				
IV	34	4	4	11	3	1				
Missing	113	13	–	103	26	–				
Received chemotherapy							–	–	–	.0001
Yes	341	40	41	171	43	51				
No	491	57	59	161	40	49				
Missing	30	3	–	68	17	–				
Received radiotherapy							–	–	–	<.0001
Yes	151	18	19	86	22	32				
No	658	76	81	208	52	68				
Missing	53	6	–	106	27	–				

(*continued*)

Table 1. Continued.

	CRC									
	LTS ($n = 862$)			VLTS ($n = 400$)			Controls ($n = 1689$)			
	n	% crude	MI[a] % adj[b]	*n*	% crude	MI[a] % adj[b]	*n*	% crude	MI[a] % adj[b]	*p*-value[c]
Permanent stoma							–	–	–	.48
Yes	95	11	11	46	12	12				
No	764	89	89	352	88	88				
Missing	3	0.35	–	2	1	–				

CRC-LTS: long-term survivors (5–9 years post-diagnosis); CRC-VLTS: very long-term survivors (≥10 years post-diagnosis). Percentages might not add up to 100% due to rounding up.
[a]MI: based on 25 imputations.
[b]Adjusted using weights derived from the age and sex distributions of CRC-LTS.
[c]*p*-values of categorical variables are corrected for age and/or sex using Cochrane-Mantel-Haenszel. Comparison on adjusted non-MI data (data not shown). Sociodemographic variables: comparison between CRC-LTS, CRC-VLTS, and LinDe; clinical variables: comparison between CRC-LTS and CRC-VLTS.
[d]Self-reported comorbid conditions include stroke, myocardial infarction, heart failure and diabetes mellitus.

Table 2. Least square mean EORTC-QLQ-C30 scores of disease-free colorectal cancer (CRC) survivors and population controls.

	Mean scores adjusted for sex, age, and education							Imputed mean scores adjusted for sex, age, and education						
	CRC Survivors		Controls		Difference CRC survivors and controls			CRC survivors		Controls		Difference CRC survivors and controls		
	Mean	SE	Mean	SE	Mean*	95%CL	95%CU	Mean	SE	Mean	SE	Mean*	95%CL	95%CU
Function scales														
Physical functioning	80.00	0.96	81.84	0.87	−1.85 [t]	−3.33	−0.37	81.77	0.66	84.05	0.48	−2.28 [t]	−3.82	−0.75
Role functioning	71.46	1.39	74.08	1.27	−2.61 [t]	−4.77	−0.45	74.89	0.99	78.44	0.72	−3.56 [t]	−5.86	−1.25
Emotional functioning	69.83	1.13	72.14	1.03	−2.32 [t]	−4.07	−0.56	70.24	0.86	72.79	0.62	−2.54 [t]	−4.53	−0.56
Cognitive functioning	79.52	1.07	80.85	0.98	−1.33	−3.00	0.35	80.61	0.78	82.47	0.57	−1.86 [t]	−3.68	−0.05
Social functioning	74.37	1.33	79.95	1.21	−5.58 [s]	−7.65	−3.51	76.55	0.97	83.27	0.70	−6.72 [s]	−8.98	−4.47
Global health/QOL	62.80	1.09	64.08	1.00	−1.28	−2.98	0.42	64.94	0.80	66.39	0.58	−1.45	−3.31	0.42
Symptom scales														
Sleep problems	31.01	1.54	30.81	1.40	0.19	−2.20	2.59	30.18	1.14	29.43	0.83	0.75	−1.90	3.40
Fatigue	34.20	1.19	31.85	1.09	2.35 [t]	0.49	4.20	32.79	0.89	30.06	0.65	2.73 [t]	0.67	4.80
Pain	27.23	1.44	31.79	1.35	−4.56 [t]	−6.80	−2.31	24.42	1.05	28.32	0.75	−3.90 [t]	−6.32	−1.49
Dyspnea	22.82	1.40	18.23	1.27	4.59 [s]	2.41	6.77	22.48	0.98	17.37	0.71	5.10 [s]	2.82	7.39
Constipation	17.95	1.16	9.10	1.06	8.85 [s]	7.07	10.64	16.22	0.83	7.28	0.60	8.94 [s]	7.02	10.85
Diarrhea	21.95	1.13	8.03	1.03	13.91 [m]	12.16	15.66	20.89	0.82	5.70	0.60	15.19 [m]	13.29	17.10
Appetite loss	11.41	0.95	9.26	0.87	2.16 [t]	0.68	3.64	10.15	0.70	7.83	0.51	2.32 [t]	0.70	3.94
Nausea and vomiting	5.45	0.54	4.11	0.50	1.34 [t]	0.49	2.19	4.40	0.39	2.90	0.28	1.50 [t]	0.61	2.40
Financial difficulties	17.13	1.23	12.77	1.12	4.37 [s]	2.45	6.28	15.32	0.89	10.26	0.65	5.06 [s]	3.00	7.13

EORTC-QLQ-C30: higher scores indicated better function or global health but more symptom complaints.
Imputed mean scores are based on 25 imputations.
*Based on published guidelines [17,18], mean differences represent: (t)rivial, (s)mall or (m)edium clinical relevance.
95CL/CU – 95% confidence level lower and upper limits.

cognitive, emotional, social), a global health/quality of life (QOL) scale, and nine items/scales on symptom and financial impact. Answers are ranged from 1 (not at all) to 4 (very much), and from 1 ('very poor') to 7 ('excellent') for items in the global health/QOL scale. All scales and single item measures were linearly transformed to a scale of 0–100 using standard procedures [16]. Higher functioning and global health/QOL scores indicated better function or health status; higher scores on symptom items/scales and financial impact indicated more symptom complaints and greater financial impact. Clinically meaningful differences in HRQOL scores were determined using published guidelines [17,18]. These guidelines are based on meta-analysis of reported mean differences and are subscale-specific. Differences in scores could be broadly grouped into trivial, small, medium, or large effects. Trivial effects can be considered negligible, with interest focused on larger differences [17]. Small differences range between >3 and 6 scale points, medium differences between >7 and 19 scale points, and large differences between >14 and 29 scale points (Supplementary Table 1).

Demographics and clinical data

The CAESAR + questionnaire also contained questions concerning clinical history and socio-demographic factors. Information on cancer treatment received and disease progression (recurrence, metastasis, new cancer) were self-reported. The date of diagnosis, cancer site, and the cancer stage were provided by the particular cancer registry. Cancer site (either colon or rectum) was classified according to the International Classification of Diseases-10 codes (C18-21).

Statistical analyses

As the sex and age distribution of the population controls reflected a stratified sampling scheme, we used direct standardization for these variables with weights derived from the CRC survivors' population. Differences in demographic and clinical characteristics among the groups were determined with analysis of variance (ANOVA) for continuous variables or Chi-square for categorical variables.

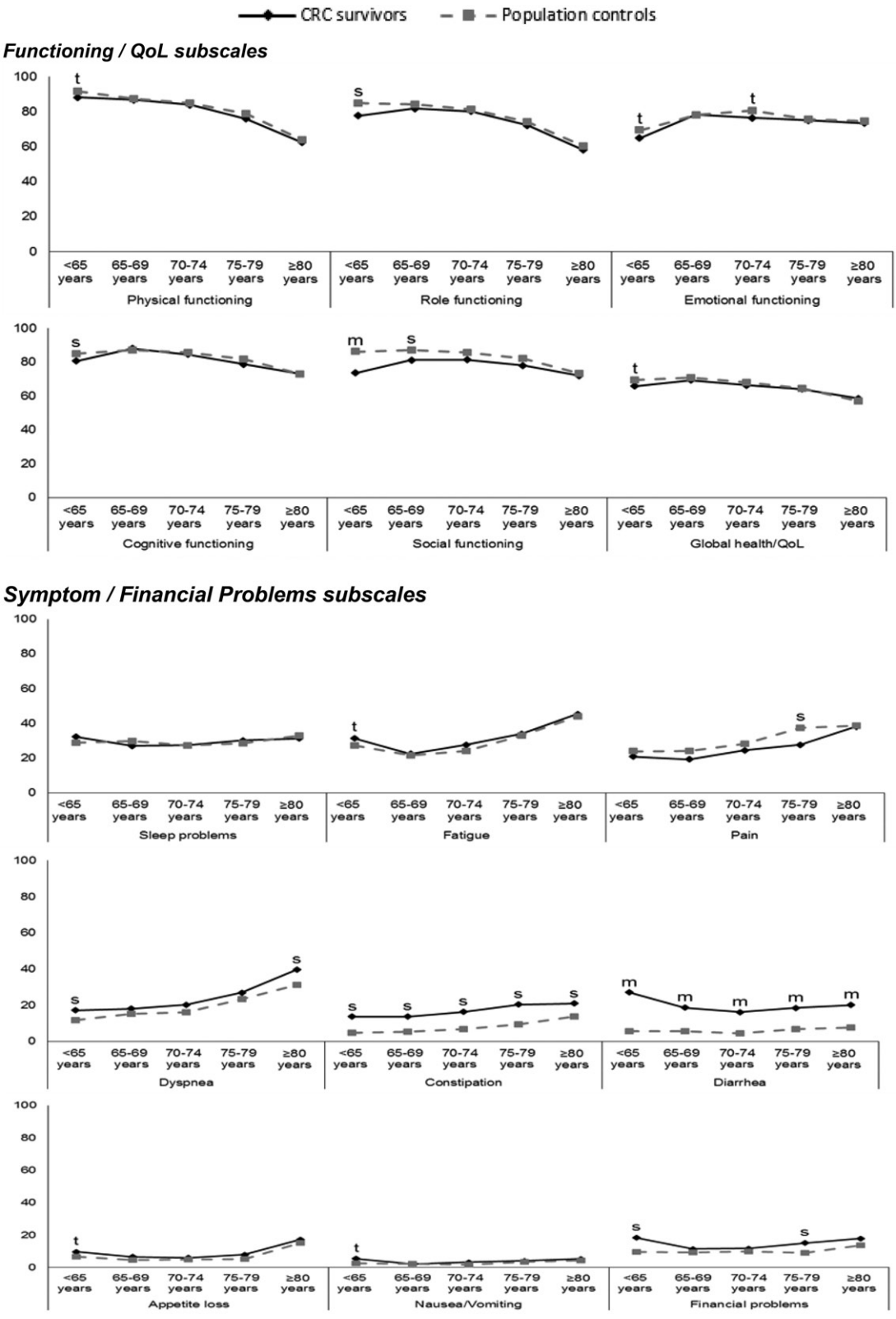

Figure 1. Least square mean EORTC-QLQ-C30 scale scores of colorectal cancer (CRC) survivors and population controls, stratified by age at survey (adjusted for sex and education). Results are based on 25 imputations. For age strata that showed a significant statistical difference in mean EORTC scores, clinical relevance was estimated based on published guidelines [17,18]: (t)rivial, (s)mall, or (m)edium difference.

Using multiple linear regression, least square means of HRQOL scores among CRC survivors and controls were adjusted for age, sex, and education, where appropriate. Although employment status, comorbidity, and body mass index also differed between CRC survivors and controls, these were not included for adjustment. As these characteristics reflected the situation at time of survey, some of these differences could be a consequence of the cancer among the CRC survivors and are therefore not considered confounders. The age of CRC survivors was categorized as follows: <65, 65–69,

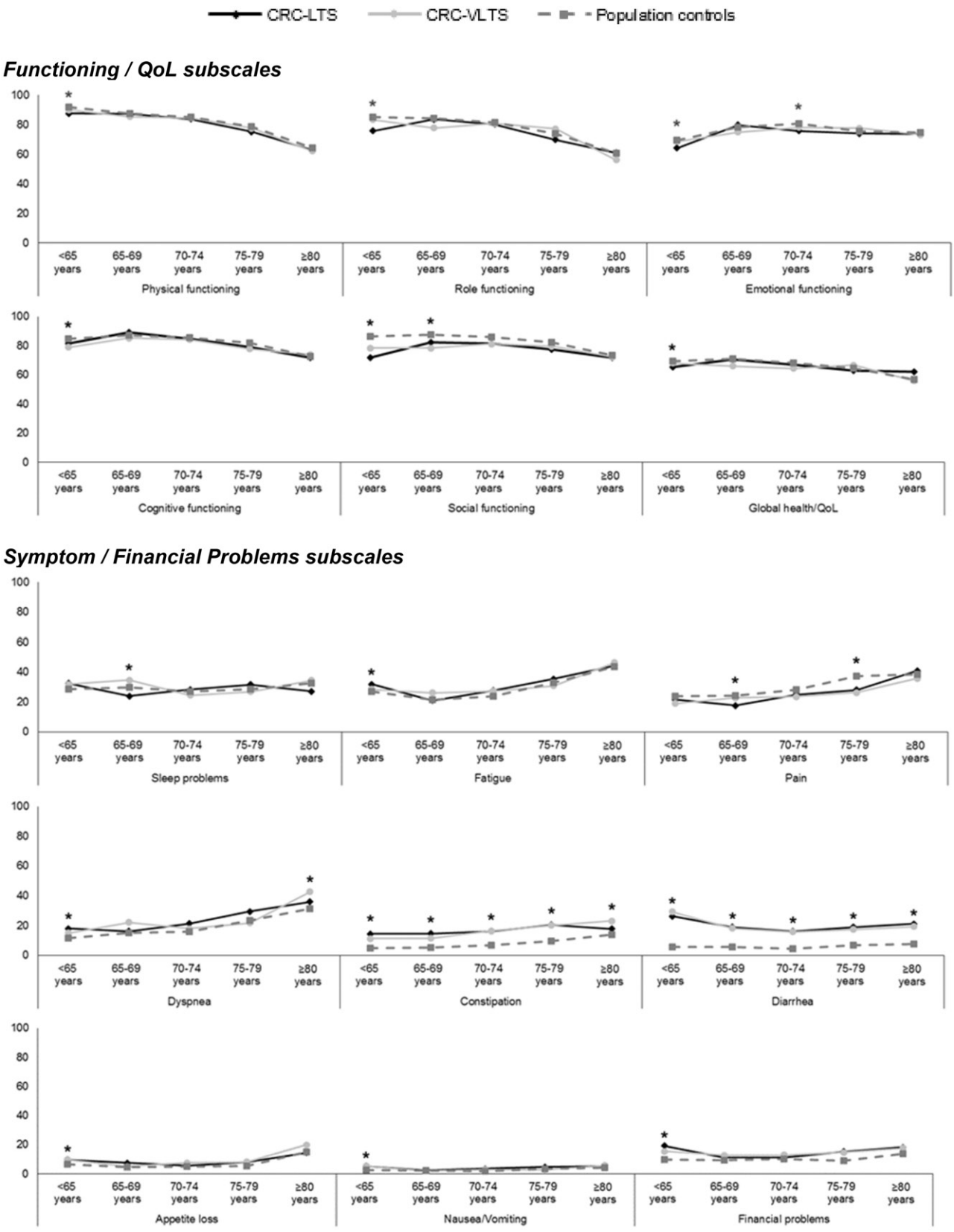

Figure 2. Least square mean EORTC-QLQ-C30 scale scores of term colorectal cancer (CRC) survivors and population controls, stratified by age at survey and time since diagnosis (adjusted for sex and education). CRC-LTS: long-term survivor; CRC-VLTS: very long-term survivor. Results are based on 25 imputations. *Indicates significance in paired comparisons. The difference in mean scores, 95% confidence intervals, and the clinical relevance of the difference in mean scores of the pair-wise comparisons are shown in Supplementary Table 2.

70–74, 75–79, ≥80 years. CRC survivors were further stratified by time since diagnosis: (1) 5–9 years post-diagnosis (long-term survivors, CRC-LTS) and (2) ≥10 years post-diagnosis (very long-term survivors, CRC-VLTS).

To address possible bias due to missing values (in general less than 10%), we conducted sensitivity analyses imputing the missing values with the Markov chain Monte Carlo method. All analyses were conducted with SAS (version 9.4 for Windows, SAS Institute Inc., Cary, NC). Statistical significance was determined at $p < .05$ (two-sided). The p-values were not adjusted for multiple testing, referring to the individual tests rather than a global test for differences.

Results

Study population characteristics

In total, 4029 CRC survivors were eligible for the study, of whom 1504 (37%) returned a completed questionnaire. Compared with non-respondents, respondents were more likely to be male (58% versus 52%, $p = .0002$) and were younger at diagnosis (62.1 ± 8.4 versus 63.6 ± 9.3, $p = .0001$) (data not shown). Cancer registry data on cancer location and cancer stage showed no difference between respondents and non-respondents. Of the respondents, 228 reported disease progression and 14 had missing data on time since diagnosis. These 242 respondents were excluded from further analyses, leaving a final CRC sample of 1262 respondents.

For the LinDE study, 2424 (29%) individuals completed the questionnaire. Of these respondents, 735 were excluded as 372 had a previous history of cancer and 363 were either younger or older than CRC survivors. A final sample of 1689 was used for analyses.

Among the CRC survivors, 68% were CRC-LTS and 32% were CRC-VLTS. When compared with CRC-LTS and CRC-VLTS, controls were more likely to be female, younger, better educated, and in full-/part-time employment (Table 1). CRC-LTS were more likely to be in a partnered relationship. There were no significant differences between CRC-LTS and CRC-VLTS on clinical factors except for treatment received (Table 1). CRC-VLTS were more likely to have been treated with chemotherapy or radiotherapy.

HRQOL of CRC survivors and population controls

CRC survivors reported lower scores on physical, role, emotional, and social functioning scales than population controls (Table 2). Although statistically significant, these differences were mainly of trivial clinical relevance, except for social functioning which had a difference of small clinical relevance. CRC survivors reported comparable global health/QOL scores to that of population controls.

On the symptom scales, significant differences were found on all scales except for sleep problems. In general, CRC survivors reported significantly higher symptom scores than controls. In contrast, population controls reported more pain than CRC survivors. The clinical relevance of differences in symptom scores were trivial (fatigue, pain, nausea/vomiting, appetite loss), small (dyspnea, constipation, financial difficulties) and medium (diarrhea).

Similar results on functioning, global health/QOL, and symptoms scales were found using imputed data (Table 2). As such, we report subsequent results using imputed data.

HRQOL of CRC survivors and population controls, stratified by age at survey

When stratified by age at survey, younger CRC survivors reported lower functioning and global health/QOL scores when compared with population controls (Figure 1, Supplementary Table 2). Differences in physical, role, cognitive functioning and global health/QOL between CRC survivors and population controls were found in the <65 years age group. These differences, while significant, were either of trivial or small clinical relevance. For social functioning, a significant difference of medium clinical relevance was found in the <65 years age group while differences of small clinical relevance were found in the 65–69 years age group.

Generally, younger CRC survivors reported higher levels of fatigue, appetite loss and nausea/vomiting when compared with population controls (Figure 1, Supplementary Table 2). These differences were of trivial clinical relevance. The youngest (<65 years) and oldest (≥80 years) CRC survivors reported experiencing more dyspnea, which were of small clinical significance. No age differences were observed for constipation and diarrhea; CRC survivors in all age groups reported significantly higher scores than population controls. These differences were of small clinical relevance for constipation, and of medium clinical relevance for diarrhea. Small clinically relevant differences were noted in the <65 and 75–79 years age groups on financial problems.

HRQOL of CRC survivors and population controls, stratified by age at survey and time since diagnosis

In general, deficits of trivial or small clinical relevance in functioning and global health/QOL were observed among the younger CRC-LTS groups (Figure 2, Supplementary Table 3) when compared with population controls or CRC-VLTS. An exception is social functioning, in which the lower score observed for CRC-LTS in the <65 years age group was of medium clinical relevance when compared with population controls.

The pattern in deficits observed for symptoms and financial problems scales were more varied when stratified by time since diagnosis. Deficits of trivial or small clinical relevance were observed mainly in the younger CRC-LTS groups when compared with population controls (Figure 2, Supplementary Table 3). Of note, both CRC-LTS and CRC-VLTS in the 75–79 years age group reported lower scores on pain when compared with population controls of the same age. These differences were of small clinical relevance. No age or time since diagnosis differentials were noted on diarrhea. CRC-LTS and CRC-VLTS in all age groups reported higher scores of medium clinical relevance on diarrhea when

compared with population controls. An almost similar pattern was noted for constipation in which CRC-LTS and CRC-VLTS in most age groups (except for the ≥80 years CRC-LTS and 65–69 CRC-VLTS groups) reported more problems with constipation than population controls. These deficits were of small clinical relevance.

Discussion

This population-based study showed that disease-free CRC-survivors 10–16 years past diagnosis reported comparable scores on most aspects of HRQOL to population controls. Detriments in HRQOL of modest clinical relevance, namely in social and role functioning, were mainly visible in younger CRC survivors 5–9 years past diagnosis. CRC survivors, regardless of age or time since diagnosis, reported being more burdened by diarrhea when compared with population controls.

CRC survivors in our study generally reported lower functioning and global health/QOL scores, albeit of small magnitude, when compared with population controls. Our results are in contrast with previous studies of CRC survivors with a comparable length of survivorship. In a US study, survivors rated their physical HRQOL and mental health significantly better than non-cancer controls [7]. Likewise in a Canadian study, CRC survivors reported having higher total HRQOL and social well-being than controls [8]. These differences in findings could be attributed to differences in the study samples. The US study sampled CRC survivors who had been treated within a clinical trial protocol. Moreover, that sample had higher levels of education when compared with our study sample. It has been previously shown that cancer survivors with higher education tend to report better HRQOL [19, 20]. The Canadian sample was older than our sample. As our results showed, younger CRC survivors were more likely to report lower HRQOL scores when compared with population controls in the same age group. On the other hand, a French study reported poorer social functioning among 5-year CRC survivors when compared with non-cancer controls [10]. In our study, both CRC-LTS and CRC-VLTS in the younger age groups reported clinically significant lower social functioning than population controls within the same age groups.

Regardless of age and time since diagnosis, CRC survivors reported having more problems with diarrhea and constipation than population controls. This finding is in line with previous studies which reported that CRC-LTS and CRC-VLTS experience persistent bowel dysfunction many years after diagnosis [8, 10]. Chronic diarrhea is associated with CRC treatments [21–23] and could be a hindrance to social functioning [24]. We found a significant albeit modest negative correlation between diarrhea with role functioning ($r = -0.18$) and with social functioning ($r = -0.25$) (data not shown). Also, younger CRC survivors (<65 years) reported clinically significantly lower role and social functioning scores than their age peers. These results are intuitive as fear of and embarrassment about leaking stools and fecal odor could increase restrictions on daily and social activities [25]. Although bowel dysfunction is a common side effect of CRC and its treatment, the scope of problem is unknown as embarrassment about diarrhea could also restrict survivors to seek help [26]. Clinical interventions for diarrhea are available, however the efficacy of these treatments still needs research [23, 27]. Nevertheless, CRC survivors could still benefit from a coordinated multidisciplinary approach by health care providers to help survivors better self-manage and limit the deleterious impact of diarrhea on their HRQOL [26]. These could include pro-active identification of CRC survivors at-risk of developing chronic bowel dysfunction, conducting appropriate physical examination (e.g. blood tests, biochemical tests), and having an established referral pathway to relevant specialists (e.g. gastroenterologist, dietician, medical psychologist, stoma nurse) [26].

It is noteworthy that CRC survivors, and in particular those in the 75–79 years age range, reported lower levels of pain when compared with population controls. This finding is in contrast with a study that compared pain among a heterogeneous group of cancer survivors including CRC of varying survivorship vintage, with controls [28]. In that study, cancer survivors were more likely to report experiencing pain when compared with age-matched controls. However, that study sample included a larger proportion of younger, short-term cancer survivors when compared with our study. Another possible explanation for our results could be due to response shift, in which survivors' perception of pain threshold is changed following cancer when compared with healthy age peers [29, 30].

A systematic review reported that cancer can have a negative financial impact that persists many years after treatment has ended [31]. Our study found that CRC survivors reported more financial difficulty when compared with population controls. In stratified analyses, CRC-LTS in the <65 year age group reported greater financial difficulties which were of small clinical relevance. This could be due to changes in employment as a study of middle-aged CRC survivors showed that reduced or ceased employment contributes to financial vulnerability within a year after diagnosis [32]. It is intriguing that we find CRC survivors report significant financial problems, albeit of small clinical relevance, as Germany has a universal access health care system. A study of Irish CRC survivors reported that survivors under <70 years or are working incurred significant out-of-pocket costs despite having universal access to health care [33].

In contrast with a previous study on CRC survivors, [12] our results in general, did not show significant age differences on HRQOL between CRC-LTS and CRC-VLTS. However, our observation is derived from a panel comparison which is prone to potential survival bias. For example, 24% of the CRC-VLTS were in the ≥80 year age group, in comparison with 9% in the CRC-LTS group. This suggests that the inclusion of the 'healthiest' CRC-VLTS could underestimate detriments in the long run as potential study participants who have died prior to the start of study were more likely to have poorer HRQOL and more symptoms than those surviving longer [34]. We are currently conducting a follow-up study of CAESAR + respondents and we aim to contribute

further the understanding of the late and long-term effects of cancer on the HRQOL of very long-term cancer survivors.

Our study has further limitations. Although we have a large population-based study sample, the response rate of 37% suggests there could be an issue of generalizability of results to the CRC population. We report on the HRQOL of CRC survivors diagnosed before 2005. Therefore, our results might not reflect the HRQOL of survivors diagnosed later where changes in CRC treatment regimens could influence HRQOL. Also, the proportion of elderly LTS and younger VLTS respondents were much smaller in relation to the total sample of CRC respondents (data not shown) which could have influenced the confidence intervals of the results. Although our models were adjusted for sociodemographic variables, we cannot rule out the possibility of residual confounding that could influence HRQOL. We used the EORTC QLQ-C30 assessment which might not capture all aspects of HRQOL relevant for (very) long-term cancer survivors. Future studies could use the EORTC QLQ-Cancer Survivorship questionnaire to better assess HRQOL of (very) long-term cancer survivors [35]. We also have to contend with the issue of missing data on relevant variables such as cancer stage because this variable had limited registration by the cancer registries in the period when the survivors were first diagnosed. We imputed the missing data and ran sensitivity analyses which showed that results derived from multiple imputations were similar to those from non-imputed data.

Nevertheless, strengths of our study include the large population-based sample of long- and very long-term disease-free CRC survivors. Furthermore, we could compare the HRQOL of CRC survivors with a non-cancer control group with same age range.

In conclusion, despite the observation that long-term disease-free CRC survivors report overall HRQOL comparable to population controls, the negative effects of CRC and its treatment can linger and still impact aspects of HRQOL of survivors up 5–16 years after diagnosis. In stratified analyses, these detriments are more evident in younger CRC-LTS survivors. However, it is heartening to note these detriments are often of trivial or small magnitude.

Disclosure statement

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