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Self-perceived cognitive functioning and quality of life among cancer survivors: results from the PROFILES registry

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Abstract

Purpose The aim was to investigate the level of self-perceived cognitive functioning and its associated factors among a large population-based cohort of cancer survivors and their matched controls.

Methods Data were obtained from population-based PROFILES registry cohorts, including colon, rectum, prostate or thyroid cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia, multiple myeloma (MM), melanoma, or basal cell carcinoma (BCC)/squamous cell carcinoma (SCC). All patients completed the EORTC QLQ-C30 from which self-perceived cognitive functioning, fatigue, functioning, and global health status/quality of life (GHS/QoL) were used. The PROFILES registry data were linked with the Netherlands Cancer Registry to obtain sociodemographic and clinical data.

Results Six thousand seven hundred eighty-six survivors were included (response rate=76%). Survivors, except for melanoma and BCC/SCC, reported on average lower self-perceived cognitive functioning scores compared to their matched controls (all p's<0.01). Largest differences with the norm were observed in thyroid cancer, HL, NHL and MM, and younger survivors (<50 years). Survivors with lower emotional functioning and more fatigue were more likely to report impaired self-perceived cognitive functioning.

Conclusion Self-perceived impaired cognitive functioning is prevalent among a wide range of cancer survivors, especially among survivors <50 years. Approaches targeting cognitive problems including attention for co-occurring symptoms such as fatigue and emotional impairments are needed to improve care for these patients.

Implications for Cancer Survivors Cancer survivors and clinicians should be aware that impaired self-perceived cognitive functioning is a frequently reported consequence of cancer and its treatment among survivors of various cancer types. Clinicians can redirect survivors to a relevant healthcare provider or program to target cognitive problems.

Keywords Cancer survivors · Cognitive functioning · Quality of life · Fatigue · Anxiety · Normative population

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Introduction

Cancer-related cognitive problems are prevalent among cancer survivors and include impairments in memory, attention, executive functioning, and information processing [1]. The impact of cognitive impairment on everyday life and quality of life (QoL) can be considerable [2–5], and survivors who report cognitive impairment are often significantly bothered by them [6].

The perspective of a patient on their cognitive functioning is an important facet of cancer-related cognitive functioning and is called self-perceived cognitive functioning [7]. Patient reported outcomes (PROs) can be used to assess self-perceived cognitive functioning for example during the last week. PROs can therefore capture symptoms that may not occur at time of neuropsychological testing [7]. Although the correlation between subjectively assessed self-perceived cognitive impairments and objectively determined cognitive functioning is modest to low [8, 9], both measurement types are responsive in measuring improvements of cognitive functioning after a cognitive rehabilitation intervention [10, 11].

Research showed that between 15 and 70% of cancer survivors report self-perceived impaired cognitive functioning [12, 13]. This range can be explained by the type of treatment patients received, such as chemotherapy, but also by varying study designs and definitions of self-perceived impaired cognitive functioning [14, 15]. The performed studies were predominantly in patients with brain tumors or among breast cancer survivors and seldom used a population-based design or normative population [12]. Comparisons to normative populations are valuable in evaluating the specific impact of cancer and its treatment beyond the natural aging process and the impact of comorbidities and can be used to study age-related differences [16]. Little is known about these age-related differences in (self-perceived) impaired cognitive functioning. Since younger survivors are generally faced with higher work-related and social demands than older cancer survivors, the impact of self-perceived impaired cognitive functioning on everyday life can be even bigger among the younger. Besides age, sex, and education, other factors can influence self-perceived cognitive functioning, including treatment, comorbidities, and factors as fatigue and impaired emotional functioning [17–19].

The aim of the present study is to [1] investigate the level of self-perceived cognitive functioning among a large population-based cohort of cancer survivors and compare it with an age- and sex-matched normative population, with subgroup analyses per cancer type, age, educational level, and survival time; [2] identify factors (sociodemographic, clinical, fatigue, and emotional functioning) that are associated with self-perceived impaired cognitive functioning; and [3] investigate the impact of self-perceived impaired cognitive functioning on role and social functioning and global health status/QoL (GHS/QoL).

Methods

Study design and setting

Data from the PROFILES ("Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship") registry were used for secondary analyses. The PROFILES registry (www.profilesregistry.nl) is an ongoing data collection of PROs within the sampling frame of the Netherlands Cancer Registry (NCR) and can be linked with clinical data of all individuals newly diagnosed with cancer in the Netherlands [20]. PROFILES comprises data of several cohorts of cancer survivors and data collection of the first cohort started in 2008.

Study population

The current study encompassed several population-based cohorts from the PROFILES registry: survivors of colon, rectum, prostate or thyroid cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), melanoma, or basal cell carcinoma (BCC)/squamous cell carcinoma (SCC). Participants were included if they were older than 18 years at diagnosis and excluded if they were not able to complete a Dutch questionnaire, or according to their specialist had severe psychopathology and dementia or were in transition to terminal care. The inclusion period differed per cohort, and survivors were included between May 2009 and October 2015 and were diagnosed between 4 months and 20 years ago at time of study inclusion. Ethical approval was locally obtained for all study samples separately.

Data collection

A detailed description of the data collection method has been reported previously [20]. In brief, in each cohort, cancer survivors were informed about the study via a letter by their (ex-)attending specialist. This letter contained either an informed consent form and a paper questionnaire, or a secured link to a web-based informed consent form and questionnaire. In the cohorts where the secured link was provided, the patient could return a postcard to request a paper-and-pencil questionnaire, if preferred.

Measures

Sociodemographic data

Age and sex were obtained from the NCR. Age at time of questionnaire completion was categorized in 18–35, 36–49, 50–64, 65–74, and ≥75 years. Patients' marital status (partner yes/no) and educational level (low (i.e., no/primary school), medium (i.e., lower general secondary education/vocational training), high (i.e., pre-university education/high vocational training/university) were assessed in the questionnaire.

Clinical data

Clinical data (cancer type, stage, primary treatments received, and date of diagnosis) were obtained from the NCR. Cancer type was classified according to the third International Classification of Diseases for Oncology (ICDO-3) [21], and stage was classified according to TNM [22] or Ann Arbor Code for HL and NHL. TNM 5, 6 and 7 were used for patients diagnosed from 2002–2003, 2003–2010, and 2010 respectively. Primary treatments received were classified into surgery, systemic therapy (chemotherapy, targeted therapy, immune therapy, hormone therapy), radiation therapy (including brachytherapy), and active surveillance/no treatment. For BCC/SCC treatment was not registered. Survivors were categorized according to time since diagnosis into short (<2 years), mid (2–5 years), long (5–10 years), and very long-term (>10 years) survivors.

Comorbidity at the time of questionnaire completion was assessed with an adapted version of the Self-Administered Comorbidity Questionnaire [23] and was categorized in no, one, or two and more comorbidities.

Self-perceived cognitive functioning

Self-perceived cognitive functioning was measured with the cognitive functioning scale of the Dutch validated version of the EORTC QLQ-C30 [24] (version 3.0). This scale consists of two items assessing difficulty concentrating and memory problems. Answer categories are one (not at all), two (a bit), three (quite a bit), and four (very much). The scores were reversed, and after linear transformation, the scale ranges from 0 to 100, whereby a higher score implies better cognitive functioning. Self-perceived impaired cognitive functioning was defined using the EORTC cognitive functioning scale threshold for clinical importance, whereby a score of ≤ 75 is considered impaired [25].

Fatigue, functioning, and GHS/QoL

Fatigue, functioning, and GHS/QoL were also measured with the EORTC QLQ-C30 [24]. Fatigue and emotional functioning were included as they have shown to have a large impact on cognitive functioning [19]. The fatigue scale consists of 3 items and the emotional functioning scale of 4 items.

Role functioning (ability to work/perform daily activities and ability to perform hobby's), social functioning (ability to carry out family life and social activities), and GHS/QoL (overall health and quality of life) were included to study the impact on daily functioning and GHS/QoL.

After linear transformation, the scales range from 0 to 100, whereby a higher score implies better functioning, QoL, and more fatigue.

Normative populations

Age- and sex-matched normative populations were selected from a reference cohort of 2040 individuals from the general Dutch population (CentER panel) [26]. The set of questionnaires completed by the reference cohort in November 2011 included the EORTC QLQ-C30, SCQ, and sociodemographics. This cohort is considered representative for the Dutch-speaking population in the Netherlands [26].

To ensure a similar age and sex distribution for survivors and the normative population, the reference cohort was matched to the survivors on age and sex. For matching, strata were formed using sex and age in order to make the most optimal selection. Within each stratum, a maximum number of persons from the reference cohort was randomly matched according to the "strata frequency distribution" of the cancer survivors.

In addition, matches were made for each cancer type (10 matches), age group (5 matches), educational level (3 matches), and time since diagnosis group (4 matches) separately.

Statistical analyses

Chi-square and *t*-tests were used to test the differences between survivors and the normative population on sociodemographics and comorbidities.

The mean self-perceived cognitive functioning scores from survivors in total, per cancer type, age group, educational level, and time since diagnosis group were compared with the mean scores of the age- and sex-matched controls using ANCOVA with educational level as covariate.

Multivariable logistic regression analyses were performed to investigate the independent association between sociodemographic variables (i.e., sex, age, having a partner, educational level), clinical variables (i.e. cancer type, stage, primary treatment, years since diagnosis, and comorbidity),

fatigue, and emotional functioning with self-perceived impaired cognitive functioning. Variables were included into the model in separate steps and were a priori determined. Patients with BCC/SCC were not included in the model as no information on treatment was available.

To study differences in role and social functioning and GHS/QoL mean scores between survivors with no versus impaired self-perceived impaired cognitive functioning, ANCOVA was performed, with sex, age, having a partner, educational level, cancer type, and comorbid conditions as covariates.

Comparisons resulting in a p-value of <0.05 were considered statistically significant. Clinically relevant differences on self-perceived cognitive functioning were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups [27], whereby the effect size is divided into large >14 points, medium 9–14 points, small 3–9 points, and trivial 0–3 points. These guidelines were also used for clinically relevant differences with respect to role and social functioning and GHS/QoL. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, 1999).

Results

Study sample and normative population

Of the 10,280 survivors who were sent a questionnaire, 1035 (10%) had an unverifiable address and 6996 survivors responded (response rate=76%). In total, 210 (3%) survivors had a missing value on self-perceived cognitive functioning; hence this resulted in a sample of 6786 cancer survivors included in the main analyses. Non-respondents were less frequently treated (13% versus 9%; p<0.01), somewhat older (68.8 versus 67.0 years; p<0.01)), and on average diagnosed more recently (3.6 versus 4.2 years; p<0.01) compared to respondents.

Mean age of survivors at time of survey was 67 years and 62% were male (Table 1). Most survivors were diagnosed with colon cancer (23%), prostate cancer (17%), or NHL (17%). More than half of survivors underwent surgery, and almost one-third underwent systemic therapy as their primary treatment, whether or not part of combination therapy. About two-third of survivors reported comorbidities, the most common being high blood pressure, arthritis, and heart condition.

In the age- and sex-matched normative population, mean age of survey was 66 years and 63% was male. Similar to cancer survivors, almost two-third of the normative population reported comorbid conditions, the most common being high blood pressure, arthritis, and heart condition. Both 78% of survivors and the normative population had a partner. Cancer survivors were somewhat lower educated than the normative population (p<0.01; Table 1).

Self-perceived cognitive functioning of survivors versus normative population

The mean cognitive functioning score was 84.7 (SD=21), and survivors of all cancer types, except for melanoma and BCC/SCC, reported on average lower self-perceived cognitive functioning scores compared to their cancer type specific age- and sex-matched normative population. These differences were the largest, for survivors of thyroid cancer, HL, NHL, and MM (p<0.01; Fig. 1) and defined as of medium clinical relevance.

Age-related differences

Mean scores of self-perceived cognitive functioning were similar when comparing the five age groups (Fig. 2). Compared to their age- and sex-matched normative population, survivors aged younger than 35 years or between 36 and 49 years showed the largest differences, whereby these differences were of medium clinical relevance. The differences for survivors aged 50–64, 65–74, or older than 75 years compared to their age- and sex-matched normative population were of small or trivial clinical relevance.

Educational level related differences

Survivors with a low, middle, and high educational level reported mean self-perceived cognitive functioning scores that were statistically lower than the mean score of their age- and sex- and educational level-matched normative populations. These differences where of small clinical relevance for all three groups.

Time since diagnosis-related differences

Both short, mid, long, and very long-term survivors reported mean self-perceived cognitive functioning scores that were statistically and clinically relevantly lower than the mean score of the age- and sex-matched normative population (all p<0.05 and small clinical relevance).

Factors associated with self-perceived impaired cognitive functioning

Twenty-three percent (N=1586) was categorized with self-perceived impaired cognitive functioning according to the threshold for clinical importance of the EORTC QLQ-C30 [25]. Multivariable logistic analyses were performed to assess associations with impairment status. In block 1, sociodemographic characteristics were entered into the model,

Table 1 Sociodemographic and clinical characteristics of survivors (*N*=6786) and respondents of an age- and sex-matched normative population (*N*=457)

	N (%) Cancer survivors *N*=6786	*N* (%) Age- and sex-matched normative population *N*=407	*p*-value
Age at time of survey: mean (SD)/ range	67.0 (12.0)/18–97	66.1 (12.4)/18–90	0.99
≤35	141 (2)	9 (2)	
36–49	491 (7)	28 (7)	
50–64	1876 (28)	114 (28)	
65–74	2413 (36)	144 (35)	
≥75	1865 (27)	112 (28)	
Sex, *N* (%)			0.88
Male	4226 (62)	255 (63)	
Female	2560 (38)	152 (37)	
Cancer type, *N* (%)		NA	
Colon	1563 (23)	–	
Rectum	995 (15)	–	
Melanoma	228 (3)	–	
Basal/squamous cell carcinoma	677 (10)	–	
Prostate	1146 (17)	–	
Thyroid	302 (4)	–	
Hodgkin lymphoma	210 (3)	–	
Non-Hodgkin lymphoma	1122 (17)	–	
Chronic lymphocytic leukemia	285 (4)	–	
Multiple myeloma	256 (4)	–	
Stage at diagnosis, *N* (%)		NA	
I	1607 (24)	–	
II	2032 (30)	–	
III	1295 (19)	–	
IV	617 (10)	–	
Not available[a]	1235 (18)	–	
Primary treatment, *N* (% yes, whether or not part of combination therapy)		NA	
Surgery	3520 (52)	–	
Systemic therapy (chemo, immune, targeted and hormonal)	2426 (36)	–	
Radiotherapy	1863 (27)	–	
Active surveillance/no therapy	621 (9)	–	
Years since diagnosis: mean (SD)/median	4.2 (3.0)/3.3	NA	
<2 years	1612 (24)		
2–5 years	3013 (44)		
5–10 years	1848 (27)		
>10 years	313 (5)	–	
Self-reported comorbidity, *N* (%)			0.18
No comorbid condition	2016 (31)	145 (36)	
1 comorbid condition	2127 (33)	125 (31)	
2 or more comorbid conditions	2310 (36)	137 (34)	
Most frequently reported comorbid conditions			
High blood pressure	1975 (33)	135 (33)	
Arthritis	1658 (28)	106 (26)	
Heart condition	1213 (20)	70 (17)	
Diabetes	760 (13)	51 (13)	

Table 1 (continued)

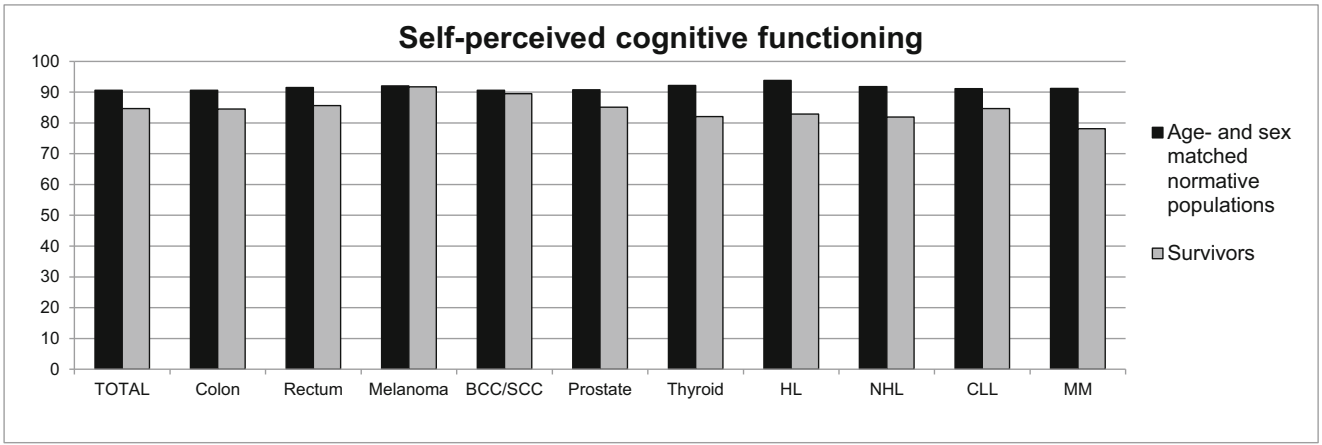
	N (%) Cancer survivors *N*=6786	*N* (%) Age- and sex-matched normative population *N*=407	*p*-value
Asthma, chronic bronchitis, COPD	697 (12)	38 (9)	
Partner			0.88
Yes	5250 (78)	317 (78)	
No	1465 (22)	121 (22)	
Educational level[$]			<0.01
Low	1159 (17)	25 (6)	
Medium	4083 (61)	210 (52)	
High	1457 (22)	172 (42)	

NA not applicable

[a] Not available: no stage was determined for patients with CLL, MM, and low-grade NHL

[$] Educational levels included low, no/primary school; medium, lower general secondary education/vocational training; or high, pre-university education/high vocational training/university

and survivors who did not have a partner were more likely to report impaired cognitive functioning. Those with a higher educational level were less likely to report impaired cognitive functioning (Table 2). In block 2, sociodemographic and clinical characteristics were entered into the model, and the same associations as appeared from block 1 remained present. In addition, survivors of several cancer types, those who underwent systemic therapy and those who self-reported comorbidities, were more likely to report impaired cognitive functioning. In block 3, besides sociodemographic and clinical characteristics, also emotional functioning and fatigue were entered into the model. Now only emotional functioning,



	Cancer survivors			Age and sex matched normative populations					
	N	mean	SD	N	mean	SD	p-value	Difference	Clinal relevance
Total	6786	84.7	20.9	469	90.6	15.3	<0.001	5.9	Small
Colon	1563	84.5	20.7	293	90.6	14.7	<0.001	6.1	Small
Rectum	995	85.6	19.9	443	91.5	14.2	<0.001	5.9	Small
Melanoma	228	91.7	15.8	590	92.0	13.8	0.68	0.3	Trivial
BCC/SCC	677	89.5	17.9	308	90.6	14.9	0.16	1.1	Trivial
Prostate	1146	85.1	20.3	249	90.8	13.5	<0.001	5.7	Small
Thyroid	302	82.1	22.8	506	92.2	14.0	<0.001	10.1	Medium
HL	210	82.9	21.8	349	93.8	13.5	<0.001	10.9	Medium
NHL	1122	81.9	22.9	473	91.8	14.2	<0.001	9.9	Medium
CLL	287	84.7	21.6	424	91.1	13.3	<0.001	6.4	Small
MM	256	78.1	22.9	490	91.2	14.8	<0.001	13.1	Medium

Fig. 1 Differences in EORTC QLQ-C30 cognitive functioning mean scores for the group in total and per cancer type compared with age- and sex-matched normative populations. BCC, basal cell carcinoma; SCC, squamous cell carcinoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma

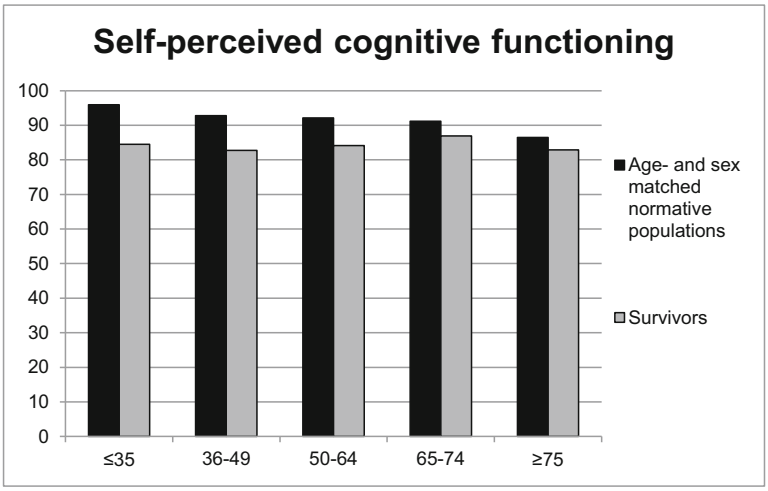


Fig. 2 Differences in EORTC QLQ-C30 cognitive functioning mean scores between total group of cancer survivors and their age- and sex-matched normative population stratified per age category. EORTC QLQ-C30, European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30

Age group	Cancer survivors			Norm population					
	N	mean	SD	N	mean	SD	p-value	Difference	Clinal relevance
≤35	141	84.5	23.2	74	95.9	9.1	<.0001	11.4	Medium
36-49	504	82.7	22.9	232	92.8	15.5	<.0001	10.1	Medium
50-64	1876	84.1	21.9	343	92.1	15.9	<.0001	8.0	Small
65-74	2413	86.9	19.2	195	91.2	14.9	<.0001	4.3	Small
≥75	1865	82.9	21.1	121	86.5	15.7	<.0001	3.6	Trivial

fatigue, and high education were independently associated with self-perceived impaired cognitive functioning. Survivors who scored lower on emotional functioning (indicative of more distress) and higher on fatigue symptoms were more likely to report impaired self-perceived cognitive functioning, and patients with a high education (compared to a middle education) were less likely to report impaired self-perceived cognitive functioning. The totally explained variance of model 3 was R^2= 0.37.

Association impaired self-perceived cognitive functioning and functioning and GHS/QoL

Survivors without self-perceived impaired cognitive functioning had statistically and large clinically relevantly better role and social functioning and better GHS/QoL compared to survivors who reported self-perceived impaired cognitive functioning (Fig. 3).

Discussion

Our results show that survivors of all cancer types that we included, except for melanoma and BCC/SCC, both short- and long-term survivors and of all educational levels, on average report lower self-perceived cognitive functioning scores compared to their cancer type specific age- and sex-matched normative population. These differences were the largest, and of medium clinical relevance, for survivors of thyroid cancer, HL, NHL, and MM. Our findings are in line with others who demonstrated lower self-perceived cognitive functioning compared to a normative population after cancer diagnosis [28–32]. However, a direct comparison between several cancer types and a specific age- and sex-matched normative population, as described in this paper has never been made. Furthermore, survivors aged younger than 50 years showed the largest differences compared to their age- and sex-matched controls. This might be explained by the fact that younger survivors are faced with higher work-related and social demands and have often more competing responsibilities compared to older cancer survivors. Other studies also observed that deficits in QoL, including cognitive functioning, were more prominent among younger age groups when comparing to a normative population [28, 33, 34].

The independent association of more self-perceived cognitive impairment by survivors who underwent systemic therapy disappeared after adding fatigue and emotional functioning to the model, as was observed by another study [31]. In contrast, most research among for example breast and colorectal cancer survivors has observed an association with chemotherapy and self-perceived cognitive impairment even after controlling for anxiety and depressive symptoms [17, 32–35].

Fatigue and emotional functioning were the largest factors associated with impaired self-perceived cognitive functioning. Increased baseline levels of anxiety and depressive symptoms were observed to be predictive of perceived cognitive impairment in a large longitudinal study among breast cancer survivors [31], and also posttraumatic stress symptoms have recently been linked to perceived cognitive impairment [17]. Managing anxiety and depressive feelings, commonly

Table 2 Odds ratios with confidence intervals (CI) of the multivariable logistic regression model evaluating independent variables for impaired self-perceived cognitive functioning among cancer survivors

	Clinical important self-perceived cognitive impairment (yes) Block 1 Odds (95% CI)	Clinical important self-perceived cognitive impairment (yes) Block 1+2 Odds (95% CI)	Clinical important self-perceived cognitive impairment (yes) Block 1+2+3 Odds (95% CI)
Sociodemographic characteristics			
Sex (male=ref)	1.03 (0.92–1.16)	1.01 (0.89–1.15)	0.87 (0.75–1.02)
Age at time of questionnaire	0.99 (0.98–0.99)	0.99 (0.89–0.99)	0.99 (0.99–1.01)
Partner (no=ref)	0.71 (0.62–0.81)	0.74 (0.64–0.84)	0.88 (0.74–1.03)
Education (middle=ref)			
Low	1.06 (0.91–1.23)	1.06 (0.90–1.24)	0.88 (0.73–1.07)
High	0.70 (0.60–0.81)	0.72 (0.62–0.84)	0.82 (0.68–0.98)
Clinical characteristics			
Cancer type (basal/squamous cell carcinoma=ref)			
Colon		1.74 (1.28–2.35)	1.24 (0.87–1.75)
Rectum		1.67 (1.21–2.31)	1.13 (0.78–1.65)
Melanoma		1.05 (0.65–1.70)	0.90 (0.52–1.54)
Prostate		1.62 (1.18–2.23)	1.04 (0.72–1.50)
Thyroid		2.37 (1.57–3.58)	1.37 (0.85–2.21)
Hodgkin lymphoma		1.81 (1.15–2.85)	1.09 (0.64–1.88)
Non-Hodgkin lymphoma		1.99 (1.47–2.71)	1.14 (0.80–1.63)
Chronic lymphocytic leukemia		1.56 (1.02–2.39)	0.82 (0.49–1.35)
Multiple myeloma		2.76 (1.87–4.06)	1.13 (0.72–1.78)
Primary treatment			
Surgery alone (no=ref)		0.97 (0.77–1.23)	0.99 (0.76–1.31)
Systemic (chemo immune targeted and hormonal therapy (no=ref)		1.31 (1.07–1.60)	1.19 (0.94–1.51)
Radiotherapy alone (no=ref)		1.08 (0.89–1.31)	1.11 (0.88–1.38)
Active surveillance (no=ref)		1.07 (0.79–1.46)	1.10 (0.77–1.58)
Years since diagnosis		0.97 (0.95–0.99)	0.99 (0.96–1.01)
Self-reported comorbidity (no=ref)			
1 comorbid condition		1.53 (1.30–1.80)	1.14 (0.95–1.37)
2 or more comorbid conditions		2.51 (2.15–2.94)	1.11 (0.92–1.34)
Emotional functioning			0.965 (0.961–0.969)
Fatigue			1.032 (1.029–1.036)
R^2 (Nagelkerke)	0.01	0.07	0.37

Clinical important self-perceived cognitive impairment was based on the threshold of clinical importance of ≤75 [25] (*N*=1.586)

experienced by cancer survivors during diagnosis and treatment, but also during follow-up, may therefore also reduce self-perceived cognitive impairment. Co-occurring symptoms such as anxiety and depressive feelings are not present in *every* patient, and research has shown that symptoms of anxiety do not entirely explain self-perceived impaired cognitive functioning [36]. The influence of other co-occurring symptoms on self-perceived cognitive impairment does warrants attention [37], but these symptoms cannot be per definition seen as the cause.

In our sample, cancer survivors were in general lower educated compared to the normative population; this may have resulted in an overestimation of the difference between survivors and their controls. Though we observed that compared to their educational level specific norm, survivors of all educational levels reported worse cognitive functioning. While it is well known that education impacts performance on cognitive tests, it seems that self-perceived cognitive functioning is less differentially affected by educational levels; another study focusing on self-perceived cognitive functioning did not observe a significant effect of education either [31].

Survivors reporting substantial self-perceived impaired cognitive functioning had clinically relevant worse role and social functioning and lower GHS/QoL compared to survivors

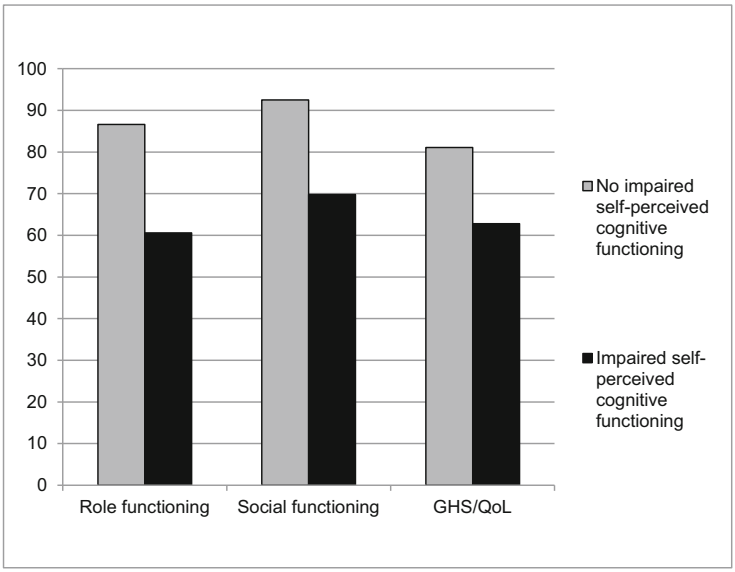


Fig. 3 Differences in EORTC QLQ-C30 role functioning, social functioning, and GHS/QoL mean scores between survivors scoring under and above the threshold for clinical relevant impaired self-perceived cognitive functioning. EORTC QLQ-C30, European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL, Global Health Status/Quality of Life. Asterisk indicates that confounding background variables for adjustment were determined a priori and chosen to be sex, age, educational level, partner, cancer type, years since diagnosis, and comorbid conditions

	No self-perceived CF problems		Self-perceived CF problems			
	N=5131		N=1637			
EORTC QLQ-C30	Mean	SD	Mean	SD	P-value*	Clinical relevance
Role functioning	86.6	22.5	60.6	32.1	<.001	Large
Social functioning	92.5	16.0	69.8	29.0	<.001	Large
GHS/QoL	81.1	16.5	62.8	20.9	<.001	Large

with no/little self-perceived impaired cognitive functioning, showing the large impact of cognitive functioning problems on the daily life of survivors, as also observed by others [38]. With the continuously growing group of cancer survivors who need to deal with the daily impact of cognitive problems, identifying patients with self-perceived cognitive functioning is necessary to ensure adequate supportive care is provided to those who need it. As suggested by Mayo et al. [39] the first step is routine symptom screening including symptoms of cognitive functioning. In daily clinical practice, the Distress Thermometer and Problem list [40, 41], the EORTC QLQ-C30 [24], and FACT-COG [42] are being used more frequently to assess and screen for symptoms, all containing cognitive functioning. For the QLQ-C30, thresholds of clinical importance have been developed for use in clinical practice recently [25], with a threshold of 75 for the cognitive functioning scale. If the threshold is met, further examination including objective measures of cognitive impairments may be indicated to initiate supportive strategies. Different approaches, including pharmacological, exercise interventions and cognitive rehabilitation, tailored to the situation of a patient can be employed when targeting self-perceived cognitive impairments [11, 19, 39, 43, 44].

This study has some limitations. First, the cross-sectional design limits the determination of changes over time in survivors' self-perceived cognitive functioning. Longitudinal studies are needed to assess within-person changes to identify risk groups for persistent self-perceived cognitive impairment for whom interventions are most needed. Second, detailed follow-up treatment and relapse data was lacking because the NCR registered only primary treatment at that time. Lastly, the use of only the EORTC cognitive functioning scale may result in an underestimation of a patients' cognitive symptom as it only focuses on concentration and memory [12]. Although specifically these two questions are meaningful to clinicians and feasible to use in daily clinical practice as screening tool. Strengths of this study are that we included a large and heterogeneous population-based sample of cancer survivors, including different primary cancer sites among which are not the most commonly studied in the field of cognitive functioning, with a high response rate (76%). In addition, through linkage with NCR, we had access to comprehensive data on sociodemographic and clinical characteristics, for respondents and non-respondents.

In conclusion, our findings show that self-perceived cognitive impairment is prevalent among a wide range of cancer survivors. Those reporting self-perceived cognitive impairment have clinically relevant lower daily functioning and QoL. Younger survivors showed the largest differences compared to their controls, and the influence of co-occurring symptoms such as fatigue, anxiety, and depressive feelings warrants attention. Identifying patients with self-perceived cognitive functioning by routine symptom screening is crucial to ensure adequate supportive care.

Author contribution SO: conceptualization, data curation, formal analysis, investigation, methodology, and writing original draft
SBS: conceptualization, methodology, and writing-review and editing
CH: conceptualization, methodology, and writing-review and editing
OH: conceptualization, investigation, methodology, and writing-review and editing
DS: conceptualization, methodology, and writing-review and editing
LvdP: funding acquisition, conceptualization, investigation, methodology, and writing-review and editing

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Availability of data and material Since 2011, PROFILES registry data is freely available according to the FAIR (Findable, Accessible, Interoperable, Reusable) data principles for non-commercial (international) scientific research, subject only to privacy and confidentiality restrictions. Data is made available through Questacy (DDI 3.x XML) and can be accessed by our website (www.profilesregistry.nl). In order to arrange optimal long-term data warehousing and dissemination, we follow the quality guidelines that are formulated in the "Data Seal of Approval" (www.datasealofapproval.org) document, developed by Data Archiving and Networked Services (DANS).

Code availability Not applicable

Declarations

Ethics approval Ethical approval for the questionnaire and methodology was locally obtained for all study samples separately.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable (consent statement regarding publishing an individual's data or image)

Conflict of interest The authors declare no competing interests.

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