A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands

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ABSTRACT

The course of fatigue and quality of life in survivors of non-Hodgkin's lymphoma is unknown. The aims of this study were, therefore, to assess fatigue and quality of life in patients with non-Hodgkin's lymphoma following primary treatment, compare fatigue and quality of life in these patients with those of an age- and sex matched normative population to assess the severity of concerns and identify associations with fatigue of survivors who remained fatigued. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with non-Hodgkin's lymphoma from 1999-2009. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the Fatigue Assessment Scale were completed once by 824 survivors of non-Hodgkin's lymphoma (80% response rate); 434 survivors completed these questionnaires again 1 year later. Survivors of non-Hodgkin's lymphoma reported more clinically relevant fatigue up till 10 years post-diagnosis compared to a normative population ($P<0.001$). Mean fatigue scores remained fairly stable over time (T1: $\bar{x}=28$, SD=26; T2: $\bar{x}=30$, SD=27, $P=0.14$): 22-28% of survivors reported deterioration, 19-23% reported improvement and 44-54% reported constant fatigue. Survivors who reported constant fatigue were more often diagnosed with stage IV disease and had more comorbid diseases. They were additionally more often female and divorced. Having comorbidities and being without a partner were also associated with constant fatigue in the normative population. In conclusion, six out of every ten responding non-Hodgkin's lymphoma survivors reported a high level of fatigue up till 10 years after diagnosis. Mean fatigue scores remained stable over time and survivors reporting constant fatigue more often had stage IV disease at diagnosis and comorbidities.

Introduction

As a result of new therapies, the survival of patients with non-Hodgkin's lymphoma (NHL) has improved considerably. Although the statistics vary, depending on the type of NHL, stage of disease at diagnosis, treatment, and age of the patient, the overall 5-year relative survival rate for all types of NHL (2001-2007) is 50-62%.[1] A person diagnosed with cancer is defined as a survivor from the moment of diagnosis through the rest of his or her life.[2] The number of NHL survivors in the USA increased from approximately 347,000 in 2001 to approximately 454,000 in 2008.[1] In the Netherlands there were approximately 19,600 NHL survivors at the end of 2008.[3,4]

As many cancer survivors live longer, they are at risk of adverse physical and psychosocial long-term effects, secondary tumors, and recurrence as a result of their cancer and/or of their medical treatments.[5-7] These long-term effects, such as fatigue, depression, marital disruption, and problems with infertility, can have a negative influence on survivors' health-related quality of life (HRQOL).[8-12]

In the last decades, more attention is being paid to HRQOL after cancer diagnosis. Some studies have investigated HRQOL and fatigue in NHL survivors,[13-21] but almost all used a cross-sectional approach (only one measurement at a defined time).[13,17-21] However, the longitudinal course of fatigue and HRQOL in patients with NHL and their return to normal life remains largely unknown. The aims of the present study were, therefore, to: (i) assess fatigue and HRQOL twice following primary treatment, (ii) compare fatigue and HRQOL with an age- and sex matched normative population to assess the severity of the concerns, and (iii) identify associations with fatigue in survivors who remained fatigued.

Design and Methods

Setting and population

This study is part of a dynamic, longitudinal, population-based survey among NHL survivors registered with the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South (CCCS).

The ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and two large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with NHL between January 1st, 1999 and July 1st, 2009. We included all patients with indolent (including chronic lymphocytic leukemia) and aggressive B-cell NHL as defined by the International Classification of Diseases for Oncology-3 (ICD-O-3) codes.[22]

Participants aged ≥85 years at time of the first measurement were excluded, because they would likely have had difficulty in completing self-administered questionnaires without assistance. To exclude patients who had died, our database was linked on every measurement with the database of the Central Bureau for Genealogy, which collects data on all deaths of Dutch citizens through the civil municipal registries. Ethical approval for the study was obtained from a local, certified Medical Ethics Committee.

Study measures

We used the Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) to assess HRQOL and fatigue. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scales implies a better HRQOL, whereas for symptoms a higher score refers to more symptoms.[23]

Fatigue was also assessed with the Fatigue Assessment Scale (FAS), a questionnaire consisting of ten items: five questions exploring physical fatigue and five questions exploring mental fatigue. The response scale is a 5-point scale (1 never to 5 always) and scores can range from 10 to 50. A score >21 indicates substantial fatigue. The psychometric properties are good.[24,25]

Comorbidity at the time of the survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ).[26] Survivors' marital status and educational level were also assessed in the questionnaire. Clinical information was available from the ECR which routinely collects data on tumor characteristics, including date of diagnosis, tumor grade, histology, Ann Arbor stage,[27] primary treatment, and patients' background characteristics, including gender and date of birth.

Data collection

Data were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the ECR. Details of the data collection method have been described previously.[28]

From May until November 2009, patients diagnosed between 6 months and 10 years previously received the baseline questionnaire (T1). A year later, patients who were willing to participate again received a 1-year follow-up questionnaire (T2).

EORTC QLQ-C30, SCQ, marital status and educational level data were also collected from an age-and sex-matched normative population[29] for comparison with the NHL survivors.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows; SAS Institute Inc., Cary, NC, USA). *P* values <0.05 were considered statistically significant. Clinically relevant differences were determined using evidence-based guidelines for the interpretation of EORTC QLQ-C30 scores between groups[30] and changes in scores[31] and Norman's 'rule of thumb' was used for the FAS whereby a ± 0.5 SD difference indicates a threshold of discriminating change in HRQOL scores.[32]

Differences in socio-demographic and clinical characteristics between respondents and non-respondents or patients with unverifiable addresses and patients who completed one or two questionnaires were compared with a chi-square or t-tests, where appropriate. The mean EORTC QLQ-C30 scores among the NHL survivors were compared with those from an age- and sex-matched Dutch normative population using independent sample t-tests. Paired sample t-tests were performed to compare the mean EORTC QLQ-C30 (both NHL survivors and the normative population) and FAS (only NHL survivors) Fatigue scale scores on T1 and T2.

Multivariate logistic regression analyses were carried out to investigate the independent association between the socio-demographic and clinical variables and constant fatigue (*versus* not constant fatigue). The "constant fatigue group" was defined by survivors/respondents of the normative population who had a Fatigue score >22 on both T1 and T2 for the EORTC QLQ-C30 (i.e. at least a small, clinically relevant higher score than that of the normative population[30]) *versus* the group who did not have a fatigue score >22 on both T1 and T2. With respect to the FAS, the "constant fatigue group" was defined by survivors who had a Fatigue score >21 on both T1 and T2 (i.e. indication of substantial fatigue[25]) *versus* the group who did not have a fatigue score >21 on both T1 and T2.

Results

Characteristics of the patients and normative population

Eight hundred and twenty-four NHL survivors completed the first questionnaire (80% response rate). Subsequently, 434 (53%) survivors completed this questionnaire again 1 year later, which represents 36% of the total group of NHL survivors. Of the 1731 respondents of the normative population who completed the EORTC QLQ-C30, 602 could be age- and sex-matched with the NHL survivors. Of those 602, 515 (86%) respondents completed the questionnaire again 1 year later.

Survivors with unverifiable addresses were more often female and younger compared to respondents, and non-respondents were more often diagnosed with indolent NHL and less often diagnosed with stage I disease (Table 1).

The mean age at completion of the baseline survey was 63.5 years with a mean time since diagnosis of 4.2 years. Chemotherapy was the most frequent primary treatment (42%; Table 1). Two-thirds of survivors reported one or more comorbid conditions, the most common being arthritis, back pain and hypertension (Table 2). In the age- and sex-matched normative population, the mean age at completion of the baseline survey was 63.5 years. Almost two thirds (65%) of respondents reported one or more comorbid conditions, the most common again being hypertension, back pain and arthritis (Table 2).

A comparison between survivors who completed one or both questionnaires indicated that those who completed both questionnaires had a significantly longer mean time since diagnosis at time of first enrollment (4.2 *versus* 5.1 years, *P*<0.001) and more often had a high educational

Table 1. Socio-demographic and clinical characteristics of questionnaire respondents, non-respondents, and patients with unverifiable addresses.

	Respondents N=824	N(%) Non-respondents N=212	Patients with unverifiable addresses N=184	P value
Sex				0.02[1]
Male	509 (62)	128 (61)	94 (51)	
Female	315 (38)	84 (39)	90 (49)	
Age at time of survey: mean (SD)	63.5 (12.4)	62.4 (14.0)	60.3 (14.8)	0.02[1]
<55 years	189 (23)	58 (27)	62 (34)	
55-69 years	336 (41)	75 (35)	59 (32)	
70+ years	299 (36)	79 (37)	63 (34)	
Years since diagnosis: mean (SD)	4.2 (2.7)	4.3 (2.9)	5.1 (2.9)	0.12
0-1 years	168 (20)	64 (30)	32 (17)	
2-4 years	316 (38)	70 (33)	65 (35)	
5-7 years	210 (25)	44 (21)	50 (27)	
8-10 years	130 (16)	34 (16)	37 (20)	
Stage at diagnosis				0.01[2]
I	202 (25)	41 (19)	48 (26)	
II	127 (15)	33 (16)	20 (11)	
III	116 (14)	23 (11)	19 (10)	
IV	202 (25)	44 (21)	51 (28)	
Unknown#	177 (21)	71 (33)	46 (25)	
Grade				0.04[2]
Indolent	443 (54)	134 (63)	106 (56)	
Aggressive	381 (46)	78 (37)	78 (44)	
Primary treatment				0.05
Radiotherapy	75 (9)	21 (10)	21 (11)	
Chemotherapy	345 (42)	65 (31)	63 (34)	
RT+CH*	99 (12)	29 (14)	21 (11)	
Active surveillance+	224 (27)	76 (36)	63 (34)	
CH±RT+Transplant*	11 (1)	6 (3)	0 (0)	
S±RT±CH*	70 (9)	14 (7)	16 (9)	

[1]P value reflects differences between respondents and patients with unverifiable addresses. [2]P value reflects differences between respondents and non-respondents. #Tumor stage could not be determined in some subtypes of indolent non-Hodgkin's lymphoma. *RT: radiotherapy, CH: chemotherapy, Transplant: autologous stem cell or bone marrow transplantation, S: surgery ±: with or without. +Patients under active surveillance but not receiving therapy.

Table 2. Socio-demographic characteristics of NHL survivors (n=824), and respondents of an age- and sex-matched normative population (n=602).

	N. (%) NHL survivors N=824	N. (%) Norm population N=602
Sex		
Male	509 (62)	400 (66)
Female	315 (38)	202 (34)
Age at time of survey: mean (SD)	63.5 (12.4)	63.5 (13.2)
<55 years	189 (23)	144 (24)
55-69 years	336 (41)	242 (40)
70+ years	299 (36)	216 (36)
Self-reported comorbidity		
No comorbid condition	215 (26)	214 (36)
1 comorbid condition	245 (30)	166 (28)
2 comorbid conditions	155 (19)	112 (19)
> 2 comorbid conditions	148 (18)	108 (18)
Most frequent comorbid conditions		
Arthritis	183 (22)	125 (21)
Back pain	177 (21)	178 (30)
Hypertension	164 (20)	173 (29)
Marital status		
Partner	646 (78)	460 (76)
Alone	41 (5)	142 (24)
Divorced	41 (5)	Unknown
Widowed	80 (10)	Unknown
Education level§		
Low	139 (17)	36 (6)
Medium	485 (59)	338 (56)
High	179 (22)	224 (37)

§Education levels were low = none/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/ high level vocational training/university.

level (19% versus 25%, P=0.013). No differences were observed between these groups for EORTC QLQ-C30 Fatigue ($\bar{x}$ =28.6 versus $\bar{x}$ =28.3, P=0.88) or FAS Fatigue scores ($\bar{x}$ =21.9 versus $\bar{x}$ =21.4, P=0.33).

Health-related quality of life and fatigue among survivors of non-Hodgkin's lymphoma and the normative population

Compared to an age- and sex-matched normative population, responding NHL survivors had, on average, worse scores for the EORTC QLQ-C30 Physical, Role, Cognitive and Social Functioning domains. NHL survivors also reported more Fatigue, Dyspnea, Sleeping Problems, Appetite Loss, Diarrhea and Financial Problems (all P≤0.001 and clinically relevant; Figure 1A and 1B). Scores between survivors of indolent and aggressive NHL were not significantly different. No clinically significant differences were found in EORTC QLQ-C30 mean fatigue scores depending on years since diagnosis (Figure 2).

Thirty-nine percent (n=321) of the NHL survivors did not have clinically relevant worse scores, i.e. they had a ≤5

point difference, for the EORTC QLQ-C30 Fatigue scale than the normative population. The other 61% did have clinically relevant worse scores for Fatigue, with the difference being small (>5 to 13 point difference) in 17% (n=140) of survivors; medium (>13 to 19 point difference) in 15% (n=124) and large (>13 point difference) in 29% (n=239).

Fatigue over time

The 1-year follow-up questionnaire was completed by 434 NHL survivors and 514 respondents of the normative population. With respect to FAS Fatigue (NHL survivors only), mean scores remained significantly stable over time (T1: $\bar{x}$ =21; T2: $\bar{x}$ =22, Table 3). However, 22% reported deteriorated fatigue scores with a mean difference of 6.4 and 19% reported improved scores with a mean difference of 5.9. With respect to the EORTC QLQ-C30 Fatigue, mean scores also remained significantly stable over time (T1: $\bar{x}$ =28; T2: $\bar{x}$ =29, Table 3), 32% reported deteriorated scores with a mean difference of 21 points, and 31% showed improved scores with a mean difference of 19 points. Similar mean scores and percentages of deterioration and improvement were observed when focusing on diffuse large B-cell lymphoma or follicular lymphoma only (Table 3). Mean scores of the normative population changed slightly over time (T1: $\bar{x}$ =17; T2: $\bar{x}$ =18, P<0.04; Table 2) with 31% reporting deteriorated and 24% report-

ing improved EORTC QLQ-C30 Fatigue scores.

Of NHL survivors, 54% reported constant EORTC QLQ-C30 Fatigue, i.e. had a Fatigue score above 22 for both T1 and T2. Of respondents of the normative population, 30% reported constant EORTC QLQ-C30 Fatigue. With respect to FAS Fatigue, 40% of NHL survivors reported constant fatigue i.e. had a Fatigue score above 21 on both T1 and T2.

Associations with fatigue

Multivariate logistic regression analyses showed that NHL survivors who reported constant fatigue (on both EORTC QLQ-C30 and FAS) were more often diagnosed with stage IV disease and more often reported comorbid diseases. They were additionally more often female and divorced (Table 4). Survivors who remained fatigued (however only on FAS fatigue) were also more often diagnosed longer ago, were under active surveillance and had a lower educational level.

With respect to survivors of diffuse large B-cell and follicular lymphoma, survivors who reported constant fatigue (on both the EORTC QLQ-C30 and FAS) reported comorbid diseases more often. Survivors of follicular lymphoma who reported constant fatigue were also more often females; however, this was only found on the FAS (Table 4).

Respondents of the normative population who reported constant fatigue also reported comorbid diseases more often and more often had no partner (Table 4).

Discussion

The majority of NHL survivors showed a constant, high level of fatigue in this population-based study up to 10 years after diagnosis. Six out of 10 survivors reported clinically relevant worse fatigue scores compared to the normative population. HRQOL was also worse to a clinically relevant degree among survivors. Mean fatigue scores remained significantly stable over time; 22-28% reported clinically relevant deterioration, whereas 19-23% reported clinically relevant improvement; 44-54% reported constant fatigue. No clinically significant differences in EORTC QLQ-C30 mean fatigue scores were observed in relation to years since diagnosis.

Changes over time in NHL survivors have so far been investigated in three small studies, only including short-term survivors for a maximum of 18 months after primary treatment. One prospective study found no clinically significant change in mean EORTC QLQ-C30 Fatigue scores[16]. One Dutch study and another Norwegian study showed mean deteriorations in EORTC QLQ-C30 Fatigue scores of 14 and 10 points when comparing start of treatment scores with those at 18 months and 1 year of follow up, respectively.[14,15] A limitation of these studies is that they all focused on mean differences. Mean scores do not reflect individual changes. Given the large standard deviations, there must be high degrees of variations within these groups. A better way is, therefore, to make a distinction between patients who improved and patients who deteriorated.

The present study showed that survivors with stage IV disease and comorbid conditions more often reported constant fatigue. Females and divorced survivors were also more likely to remain fatigued. In the normative population, we also observed a relation between comorbidity and having a partner and fatigue. This relation is not, therefore, specific to NHL survivors but is probably applicable to people in general. Type of NHL (aggressive or
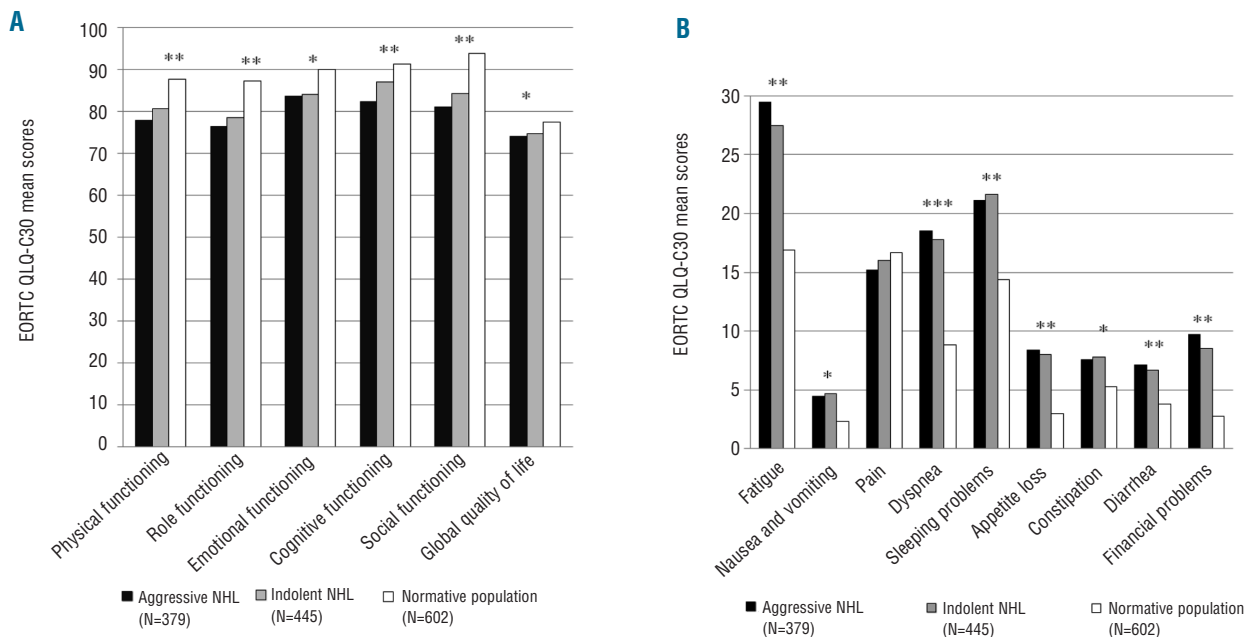

Figure 1. (A) Differences in EORTC QLQ-C30 mean functioning and global quality of life scores between survivors of aggressive NHL (n=379), indolent NHL survivors (n=445) and an age- and sex-matched normative population (n=602) *P<0.001**P<0.001 and small clinically important differences.[30] A higher score implies a better HRQOL. **(B)** Differences in EORTC QLQ-C30 mean symptom scores between survivors of aggressive NHL (n=379), indolent NHL (n=445) and an age- and sex-matched normative population (n=602)*P<0.001; **P<0.001 and small clinically important differences;[30] ***P<0.001 and medium clinically important differences.[30] A higher score indicates to more symptoms.

Table 3. Mean fatigue scores (SD) at baseline (T1) and follow-up (T2) among NHL survivors and respondents of the normative population who completed two questionnaires (NHL survivors; n=434; normative population, n=515), and percentages of patients/respondents who deteriorated/improved between these time points (mean difference and SD).

	Baseline (T1) Mean (SD)	Follow-up (T2) Mean (SD)	P	%	Deteriorated Mean difference (SD)	%	Improved Mean difference (SD)
FAS Fatigue NHL survivors in total (n=434)	21 (7.6)	22 (7.6)	0.18	22%	6.4 (2.7)	19%	5.9 (2.3)
FAS Fatigue Large B-cell NHL survivors (n=132)	22 (7.2)	22 (7.6)	0.93	19%	7.0 (3.6)	22%	5.8 (1.6)
FAS Fatigue Follicular NHL survivors (n=82)	22 (8.2)	22 (7.6)	0.50	22%	6.4 (2.7)	17%	6.7 (4.3)
EORTC Fatigue NHL survivors in total (n=434)	28 (26)	29 (26)	0.42	32%	21 (13)	31%	19 (11)
EORTC Fatigue Large B-cell NHL survivors (n=132)	29 (26)	28 (25)	0.81	33%	21 (13)	13%	22 (13)
EORTC Fatigue Follicular NHL survivors (n=82)	28 (25)	27 (24)	0.79	32%	19 (9.3)	35%	18 (8.1)
EORTC Fatigue Normative population	17 (19)	18 (21)	0.04	31%	20 (12)	24%	19 (10)

Deterioration and improvement determined using the guideline of at least a clinically small difference with respect to the EORTC[30](deterioration >5 point difference; improvement >4 point difference) and Norman's rule of thumb for the FAS[32] (half SD, i.e.3.8 for both deterioration and improvement).

indolent), treatment, and survival time since diagnosis were not associated, or only associated with one measure of fatigue in NHL survivors. The ECR collects data on primary treatment only. More detailed treatment information, longitudinally assessed, will enable us to study the relation between initial treatment and HRQOL and fatigue in more detail. Furthermore, detailed information about disease progression could also contribute to unraveling the course of HRQOL and fatigue and will help health care providers to give their patients better information about their expected HRQOL. As our HRQOL study is embedded in PHAROS (Population based HAematological Registry for Observational Studies) in which more detailed disease and treatment information is collected, as well as long-term side effects, we will be able to determine this relation better in the near future.

NHL survivors reported worse HRQOL compared to that of an age- and sex-matched normative population. Clinically relevant worse scores for survivors were observed for fatigue, appetite loss, diarrhea, dyspnea and all function scales including financial problems. One prospective and three cross-sectional studies also observed clinically worse scores for HRQOL domains for NHL survivors compared with those of a normative population.[13,15,17,20]

Numerous patients in our study showed large improvements (19-23%) or deteriorations (22-28%) within 1 year, which both indicate a clinically relevant change.[31] However, it is too soon to determine whether this can be defined as an actual change, due to regression to the mean. A longer follow-up time is needed to identify whether these differences can be considered as real changes or fluctuations over time.

Significant differences were not observed between patients with indolent or aggressive NHL, recapitulating findings in an American cross-sectional study,[33] nor between short- or long-term survivors, confirming results of a cross-sectional study among 761 NHL survivors.[20] This suggests that there is no improvement in time, which
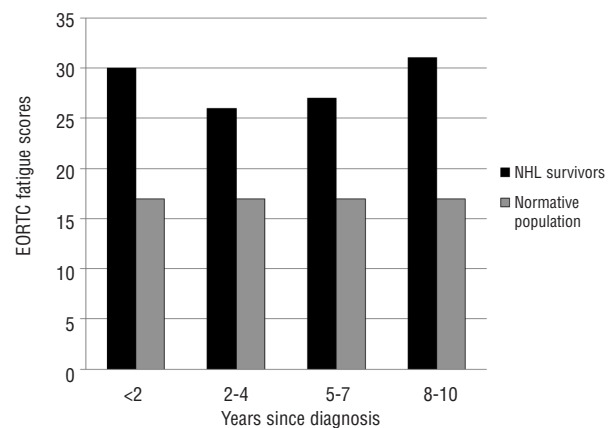

Figure 2. Differences between EORTC QLQ-C30 fatigue scores of all NHL survivors (n=824) according to years survived since diagnosis and an age- and sex-matched normative population (N=602). All *P*<0.001 and small or medium clinically important differences.[30] A higher score indicates more fatigue.

is also shown by our 1-year follow-up results.

Prevalence rates for cancer-related fatigue vary widely. Percentages between 32% and 60% have been reported[34-36] and in a recently published study an overall prevalence of 48% was found.[37] The observed percentage of 61% in this study is somewhat higher. In our study, 29% of survivors reported large, clinically important fatigue, whereas 15% reported medium clinically important fatigue, making a total of 44%. Adding the survivors with small, clinically important fatigue produced the observed total of 61% of patients with cancer-related fatigue. Besides differences between types of cancer, the use of different cut-off scores and fatigue assessment instruments contribute to the differences in reported prevalences.[38-40]

The underlying mechanisms that cause constant cancer-

Table 4. Odds ratios with confidence intervals (CI) of the multivariate logistic regression model evaluating independent variables for EORTC QLQ-C30 and FAS Fatigue scores for patients (n=434) and respondents of the normative population (n=515) who completed two questionnaires and remained fatigued.

| Independent variable | FAS Fatigue | | | EORTC Fatigue | | | |
	All NHL survivors Odds ratio (CI)	Large B-cell NHL Odds ratio (CI)	Follicular NHL Odds ratio (CI)	All NHL survivors Odds ratio (CI)	Large B-cell NHL Odds ratio (CI)	Follicular NHL Odds ratio (CI)	Normative population Odds ratio (CI)
Age (time of questionnaire)	ns	ns	ns	ns	ns	ns	ns
Sex (women)	1.6 (1.0-2.5)*	ns	3.4 (1.3-8.7)*	1.6 (1.0-2.5)*	ns	ns	ns
Time since diagnosis	1.1 (1.0-1.2)*	ns	ns	ns	ns	ns	NA
Tumor stage							NA
Stage 1 (reference)	-	-	-	-	-	-	NA
Stage 2	ns	ns	ns	ns	ns	ns	NA
Stage 3	ns	ns	ns	ns	ns	ns	NA
Stage 4	2.3 (1.0-5.2)*	ns	ns	2.7 (1.2-5.8)*	ns	ns	NA
Aggressive tumor grade	ns	NA	NA	ns	NA	NA	NA
Radiotherapy (yes)	ns	ns	ns	ns	ns	ns	NA
Chemotherapy (yes)	ns	ns	ns	ns	ns	ns	NA
Active surveillance (yes)	2.9 (1.0-8.1)*	ns	ns	ns	ns	ns	NA
Comorbidities							
None (reference)	-	-	-	-	-	-	-
1	2.7 (1.4-5.1)*	ns	ns	1.8 (1.0-3.2)*	2.9 (1.1-8.0)*	ns	2.0 (1.1-3.7)*
2	3.9 (1.9-8.3)*	ns	10.2 (2.2-47.1)*	ns	ns	6.5 (1.3-33.9)*	4.3 (2.2-8.2)*
>2	7.2 (3.3-15.7)*	6.3 (1.7-23.8)*	26.8 (5.3-135.7)*	4.7 (2.2-10.1)*	7.2 (1.9-27.6)*	13.9 (2.3-82.9)*	16.1 (7.9-32.9)*
Marital status							
Partner (reference)	-	-	-	-	-		NA
Divorced	6.0 (1.9-18.7)*	ns	ns	3.5 (1.1-11.1)*	ns	ns	NA
Widowed	ns	ns	ns	ns	ns	ns	NA
Alone	ns	ns	ns	ns	ns	ns	NA
Marital status							
Partner (reference)	-	-	-	-	-	-	-
No partner	ns	ns	ns	ns	ns	ns	2.7 (1.6-4.6)*
Education level							
Low	2.2 (1.1-4.5)*	ns	ns	ns	ns	ns	ns
Middle (reference)	-	-	-	-	-	-	-
High	ns	ns	ns	ns	ns	ns	ns

*Note. *P<0.05; ns: not significant, NA: not applicable.*

related fatigue are not yet clear.[41] Many factors are associated with the development of fatigue, such as type of treatment, the disease itself, medication-related adverse events, biological modifiers (such as interferon), depression, physical inactivity, anxiety, pain and sleep disturbances.[42-46] Although the cause of fatigue is not completely clear, results of a recently published review[47] show that patients with fatigue may benefit from pharmacological and/or non-pharmacological treatments, such as cognitive-behavioral interventions and exercise.[48] Further research is necessary to determine whether an early intervention for fatigue can reduce this long-term complication and whether patients can benefit from late intervention.

The present study had the following limitations: although information was available concerning socio-demographic and clinical characteristics of the non-respondents and patients with unverifiable addresses, it remains unknown whether non-respondents declined to participate in the study because of poor health or the absence of symptoms. Comparing patients who completed one questionnaire with patients who completed two questionnaires only indicated differences in mean time since diagnosis and educational level. This perhaps result-

ed in a small selection bias. In addition, there is always an uncertainty with the reproducibility of self-reported questionnaires. Some of the changes might be ascribed to that arbitrariness.

The strengths of our study are the population-based sampling frame instead of a hospital-based sampling frame. Furthermore, the large range in elapsed time since diagnosis facilitates extrapolation of the results to a broad range of NHL survivors in the population. In addition, the longitudinal design provides important information about development over time.

In conclusion, six out of every ten NHL survivors reported a high level of fatigue up until 10 years after diagnosis. HRQOL and fatigue scores of survivors were clinically relevant and worse than those of an age- and sex-matched normative population. Fatigue mean scores remained significantly stable over time and 44-54% of survivors reported constant fatigue. Survivors with stage IV disease, comorbid conditions as well as females and divorced survivors were more likely to remain fatigued. Having comorbidities and being without a partner were also associated with continuous fatigue in the normative population. As research on the underlying determinants of

fatigue proceeds, health care providers should continue to screen patients on their level of fatigue and inform them about possible rehabilitation programs.

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