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ORIGINAL ARTICLE

Chronic fatigue and associated factors among long-term survivors of cancers in young adulthood

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ABSTRACT

Background: Chronic fatigue (CF) is scarcely explored among young adult cancer survivors (YACSs), and more knowledge is needed to develop targeted interventions for YACSs with CF. The present study aimed to investigate the prevalence of CF and associated factors in YACSs. Also, the change of fatigue with time was explored.

Material and methods: The present cross-sectional study is part of a nation-wide population based survey of Norwegian survivors of cancer in childhood, adolescence, and young adulthood (The NOR-CAYACS study).YACSs diagnosed at the age of 19–39 years with breast cancer stage ≤ III (BC), colorectal cancer (CRC), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia, or non-metastatic malignant melanoma (MM) were included 5–30 years after diagnosis. Survivors of MM treated with limited surgery were included as a reference group. CF was assessed by the Fatigue Questionnaire. Logistic regression analyses were performed to identify factors associated with CF.

Results: In total, 1488 survivors completed the questionnaire (a response rate of 42%), of which 1088 were eligible for the present study. Overall, 25% reported CF. CF was significantly more prevalent among survivors of BC (29%) ($p < .001$), CRC (29%) ($p = .001$) and NHL (27%) ($p = .003$) than among survivors of MM (15%). CF was associated with systemic treatment combined with surgery and/or radiotherapy ($p = .018$), comorbidity ($p = .038$), pain ($p = .002$), numbness in hands/feet ($p = .046$), and depressive symptoms ($p < .001$) in the multivariable model. Among survivors with CF, 60% reported that they had been tired since cancer treatment, and among these, 65% reported worsening or no change of fatigue with time.

Conclusion: One of four YACSs reported CF 15 years from diagnosis (mean). CF was associated with several possibly treatable factors. Health professionals involved in the follow-up of YACSs should have knowledge of CF and approaches to manage it.

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Introduction

Despite a low cancer incidence among young adults aged 19–39 years [1], the prevalence of young adult cancer survivors (YACSs) is steadily growing, and the 5-year overall survival rate in this population has now exceeded 80% [2]. Cancer during this age period might affect specific aspects related to young adulthood, such as education, work life, financial independence, and establishing a family. YACSs are, therefore, likely to experience survivorship challenges different from those described among older adult or childhood cancer survivors [2]. Still, limited knowledge exists about late effects following curative cancer treatment in YACSs [2,3].

Fatigue, a subjective and persistent sense of tiredness not proportional to recent activity and not relieved by rest, is a distressing late effect following cancer treatment with a highly negative impact on physical, psychological, and social functioning [4]. Fatigue is also a large burden for the family of those affected and the society as a whole in terms of reduced work ability and increased social security costs [5]. This might be particularly relevant for YACSs, as these cancer survivors typically have family responsibilities and many years of active work life ahead. Still, fatigue is rarely explored among YACSs. The few existing studies indicate that YACSs are more fatigued compared to survivors diagnosed with cancer further into adulthood, and healthy age-matched controls [3,6–9]. However, these studies did not use fatigue-specific instruments [6–8], and/or were conducted on small populations during or shortly after cancer treatment [3,9].

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Chronic fatigue (CF), defined as a substantially elevated level of fatigue lasting for 6 months or longer [10], affects up to 35% of long-term cancer survivors (5 years or more from diagnosis) diagnosed as older adults or children [11,12]. Among long-term survivors of lymphoma and testicular cancer, which are common cancer types in young adults, one out of four reports CF [13,14]. No previous population-based studies have explored CF exclusively among long-term YACS.

The exact underlying mechanisms of CF are multifactorial and not fully understood [4]. Associations with various somatic and psychological factors such as comorbidities, hormonal dysfunction, pain, and psychological distress are shown among both adult and childhood cancer survivors [4,11,15]. In addition, a recent meta-analysis found that the risk of fatigue increased with more advanced disease stages and more intense therapy among breast cancer survivors [16]. However, the relationship between fatigue and cancer treatment intensity is inconsistent [4,17], and scarcely explored among YACSs. In order to develop relevant and targeted interventions aimed at improving fatigue in YACSs, we consider knowledge of the socio-demographic and medical characteristics of those affected as necessary. To our best knowledge, the prevalence and associated factors of CF among long-term YACSs have not been assessed previously.

In 2015/2016, a population-based cross-sectional survey was conducted among Norwegian childhood, adolescent and young adult cancer survivors (The NOR-CAYACS study), to explore health care- and information needs in individuals who had received cancer treatment at a young age. The survey also aimed to collect information on a range of late effects, health, and lifestyle behavior. Using data from the NOR-CAYACS study the present study aimed to

1. Investigate the prevalence of CF and the level of fatigue among survivors diagnosed with breast cancer (BC) stages I–III, colorectal cancer (CRC), acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL) and malignant melanoma (MM) at age 19–39 years
2. Investigate the associations between CF and socio-demographic variables, cancer-related factors, somatic health/lifestyle characteristics, and psychological factors.
3. Describe if CF has changed with time, based on retrospective self-report.

Material and methods

Design and study population

The present study population was extracted from the NOR-CAYACS cross-sectional study, in which participants were identified by The Cancer Registry of Norway (CRN). In total, 3558 YACSs diagnosed with BC (stage $\leq$ III), CRC, NHL, ALL, or MM at the age of 19–39 years between 1985 and 2009 were invited to study-participation during September 2015 through January 2016. The survivors received an informed consent form, a questionnaire and a pre-addressed reply-paid envelope by mail. Non-responders received one reminder.

The specific cancer types were selected as they affect a high number of individuals at a young age, typically with good prognoses, but also with a high risk of late effects among those treated. One exception is the survivors of non-metastatic MM, who typically receive only surgical removal of a skin lesion as a curative cancer treatment, defined as limited surgery in the present study. To explore the relationship between treatment burden and CF, survivors of MM were thus included as a reference group. Survivors after testicular and gynecological cancers were not included because these survivors were involved in other research projects at our institution at the time of the survey. Eligibility criteria of the present study included YACSs without recurrence, distant metastases or new cancers since diagnosis, and absence of active cancer treatment. Respondents were only included if they provided treatment information in the questionnaire, and completed the Fatigue Questionnaire.

Ethical considerations

The Norwegian Data Protection Authority (15/00395-2/CGN), the Regional Committee for Medical Research Ethics (2015/232 REK s⊘r-⊘st B), the Data Protection Officer at Oslo University and the CRN approved the study. All participants signed an informed consent form.

Measurements and variables

The questionnaire included a total of 302 items, of which 100 were included in the present analyses.

CF was assessed by the Fatigue Questionnaire (FQ) [10]. FQ contains 11 items concerning physical (seven items) and mental (four items) fatigue during the past month, scored from zero to three (0,1,2,3). The total fatigue score ranges from zero to 33, with a higher score implying more fatigue. A dichotomized score (0,0,1,1) of the responses to each item is used for case definition of CF. An additional question assesses the duration of fatigue (less than 1 week/less than 3 months/3–6 months/6 months or more). CF is defined by a dichotomized sum score of four or more and duration for at least 6 months [10]. Missing items in FQ were substituted using the individual survivor's mean score of completed items within the mental and physical subscale, given a response of at least 50%. Internal consistency (Cronbach's alpha) for the population included in this analysis was .91 for the physical subscale, .84 for the mental subscale, and .92 for the whole scale. Fatigue duration categories of 6 months–1 year, 1–5 years, and 5 years or more were added for the present study.

Change of CF over time was assessed by asking the survivors whether they had been tired since cancer treatment (yes or no), and if yes, how the fatigue had changed with time (no change, improved with time or worse with time).

Socio-demographic and cancer-related variables

Information on gender, age at diagnosis and at survey was obtained from the CRN. Living as a couple (married or

cohabitant) (no versus yes), living with children ≤18 years (yes versus no), and years of education (≤13 years versus >13 years) were self-reported. Based on information on cancer type and stage obtained from the CRN and self-report on treatment, four treatment groups were identified: (1) limited surgery only (survivors after non-metastatic MM), (2) surgery and/or radiotherapy (local treatment), (3) systemic treatment only, and (4) systemic treatment combined with surgery and/or radiotherapy. Systemic treatment included chemotherapy, endocrine treatment, antibody treatment, and/or high-dose chemotherapy with stem cell support/bone marrow transplantation.

Somatic health, lifestyle, and psychological variables

Comorbidity was assessed by self-reported history of a number of comorbidities, including cardiovascular- and pulmonary diseases, diabetes, kidney disease, gastro-intestinal disease, rheumatic disease, arthrosis, muscle/joint pain, epilepsy, and thyroid diseases. An individual's number of comorbidities were added up and categorized into no comorbidity/1–2 comorbidities/>2 comorbidities.

Survivors with numbness in hands/feet were identified if responding 'Yes, have experienced it myself' to a question about this symptom.

Presence of pain interfering with normal work was assessed by the pain item from the 12-Item Short Form Survey (SF-12) [18]. Responses were dichotomized into not at all/a little bit/moderately (no) versus quite a bit/extremely (yes).

Trouble sleeping was assessed by questions modified from the Nord Trøndelag Health (HUNT) Study [19], and defined as experiencing one or more of the following several times a week; difficulties falling asleep at night, waking up repeatedly during the night and/or waking up too early without being able to go back to sleep.

Body mass index (BMI, kg/m^2) was calculated from self-reported height and body weight, and categorized into <30 and ≥30. Physically active survivors were those reporting to meet the public health exercise guidelines for weekly aerobic physical activity (i.e., ≥150 min of moderate or ≥75 min of high-intensity aerobic exercise, or an equivalent combination) [20], using a modified version of the Leisure Score Index from the Godin Leisure Time Exercise Questionnaire (GLTEQ) [21]. Questions modified from the HUNT study were used to assess alcohol consumption and smoking [19]. Binge drinking (defined as drinking ≥ five units of alcohol on the same occasion) was dichotomized into never/monthly (no) versus weekly/daily (yes). Smoking was dichotomized into never smoked/discontinued smoking (no) versus smoking now and then/daily smoking (yes).

Anxiety was assessed by the anxiety subscale of The Hospital Anxiety and Depression Scale (HADS-A) [22]. Each of the seven items has four response alternatives ranging from zero (not present) to three (highly present), with higher scores implying more anxiety. Cronbach's alpha for HADS-A in the present population was .83. Depressive symptoms were measured by a modified version of The Patient Health Questionnaire-9 (PHQ-9) [23]. The PHQ-9 contains nine items assessing the frequency of depressive symptoms the last 2 weeks with response categories ranging from zero (not at all) to three (nearly every day). To avoid overlap between some depressive symptoms and other measures, four items covering sleep problems, fatigue, weight/appetite change, and psychomotor retardation/agitation were excluded. The five remaining items (anhedonia, depressed mood, feelings of worthlessness/guilt, poor concentration, and thoughts of self-harm/suicidal ideations) provided a sum score ranging from zero to 15, with a higher score indicating a higher level of depressive symptoms. Cronbach's alpha for this modified version of PHQ-9 was .84 in the present sample.

Statistics

Descriptive statistics were performed, and group comparisons were carried out by Chi-square test, *t*-tests, and ANOVA with Tukey post hoc tests as appropriate. Basic de-identified information on non-responders from the CRN (including age, gender, diagnostic group, and age at diagnosis) was used to compare those who responded to the questionnaire with those who did not. Logistic regression analyses were performed with CF as the dependent variable. In multivariable analyses, the independent variables were included in separate blocks by the following order: socio-demographic variables, cancer-related variables, somatic health-/lifestyle variables, and finally psychological variables. A p value of less than .05 was considered statistically significant, and all tests were two-sided. Analyses were carried out using IBM SPSS Statistics version 21.0 (SPSS, Chicago, IL).

Results

Among the 3558 YACSs identified by CRN, 1488 (42%) consented and returned the questionnaire. Of these, 400 survivors were ineligible for the present study according to the exclusion criteria (Figure 1). Compared to non-responders, participants were slightly older at survey (mean age 49.1 versus 48.1 years, p = .001) and diagnosed a longer time ago (mean 15.2 versus 14.4 years, p = .003). Moreover, a higher proportion of females (74% versus 70%, p =.008) and BC survivors (40% versus 31%, p < .001), and a lower proportion of MM survivors (23% versus 31%, p < .001) responded compared to those who did not (data not shown).

Survivor characteristics

Of 1088 included YACSs, 440 were diagnosed with BC, 120 with CRC, 172 with NHL, 110 with ALL, and 246 with MM. In total, 74% of the participants were female (Table 1). Time since diagnosis was 5–9 years in 27%, 10–19 years in 43%, and 20–30 years in 30%. A total of 56% were physically active, 17% had a BMI ≥ 30 kg/m^2, 20% were smoking, and 7% reported weekly binge drinking. None of the participants reported daily binge drinking.

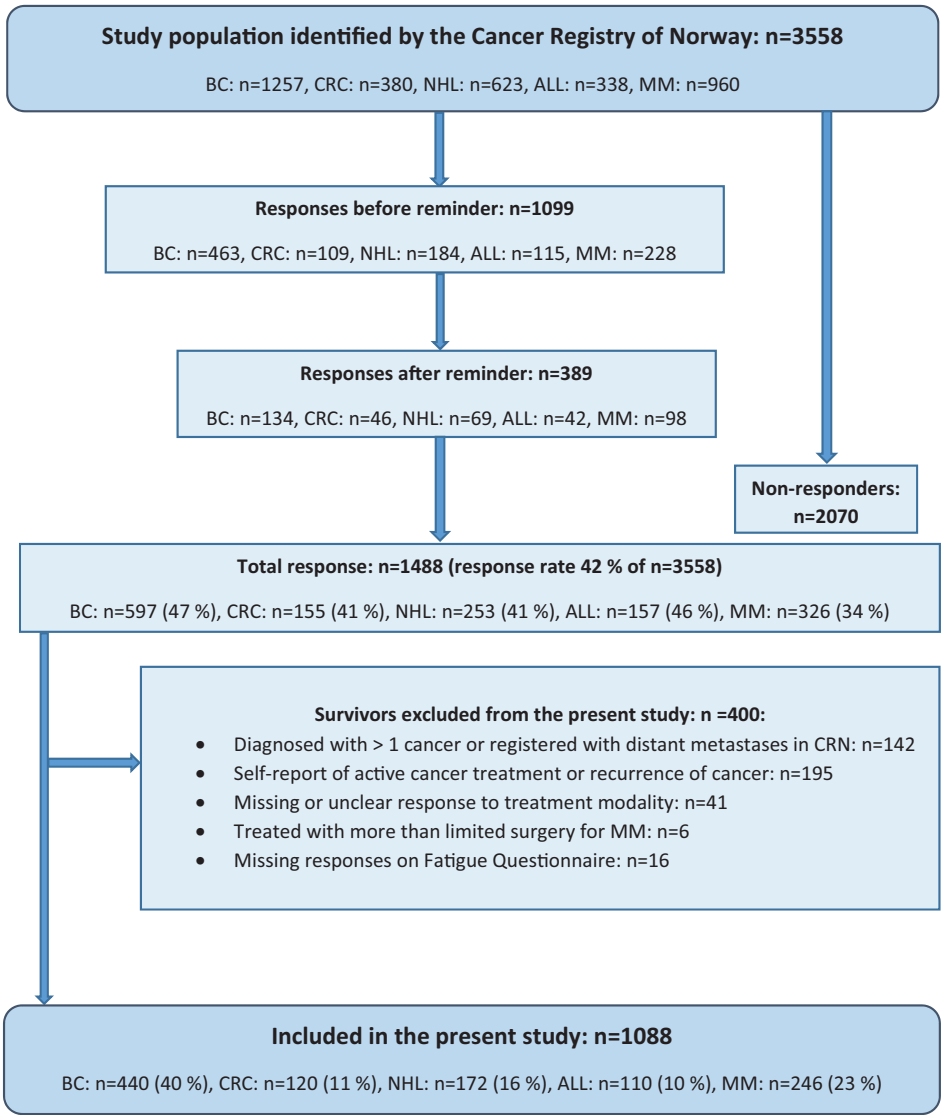

Figure 1. Flowchart of inclusion. BC: breast cancer; CRC: colorectal cancer; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; MM: malignant melanoma.

Prevalence of chronic fatigue and total fatigue score

Overall, 25% reported CF (Figure 2(a)). The prevalence of CF was significantly higher among survivors of BC (29%, $p < .001$), CRC (29%, $p = .001$), and NHL (27%, $p = .003$) compared to MM (15%). There was no statistically significant difference in the prevalence of CF between survivors of ALL (20%) and MM.

As shown in Figure 2(b), the mean FQ score was 13.2 (SD 5.1) for all survivors, with significantly higher scores among survivors of BC (13.8 (SD 5.2), $p < .001$) and NHL (13.5 (SD 5.0), $p = .036$) compared to MM survivors (12.1 (SD 4.1)). FQ total mean score was 19.9 (SD 4.5) among those with CF and 11.0 (SD 3.0) among those without CF ($p < .001$) (Table 2).

Factors associated with chronic fatigue

Unadjusted logistic regression analyses showed that survivors with younger age at survey ($p = .001$) and not living as a couple ($p = .015$) were more likely to report CF (Table 2). Shorter time since diagnosis ($p < .001$) and systemic treatment combined with surgery and/or radiotherapy ($p < .001$) (versus limited surgery for MM) were also associated with CF. In addition, having 1–2 ($p = .001$) or > 2 comorbidities ($p < .001$), pain ($p < .001$), trouble sleeping ($p < .001$), numbness in hands/feet ($p < .001$), and BMI $\geq 30\,kg/m^2$ ($p = .018$) increased the odds of CF. Finally, increasing HADS-A, PHQ-9, and FQ scores were associated with CF ($p < .001$), while being physically active decreased the odds of CF ($p < .001$) (Table 2).

In the final multivariable logistic regression analysis (block 1 + 2 + 3 + 4), the following variables remained statistically significant associated with CF: systemic treatment combined with surgery and/or radiotherapy (OR 1.88, 95% CI 1.11–3.18), 1–2 comorbidities (OR 1.63, 95% CI 1.03–2.60), pain (OR 2.39, 95% CI 1.36–4.19), numbness in hands/feet (OR 1.60, 95% CI 1.01–2.52), and increasing depressive symptoms (OR 1.46, 95% CI 1.32–1.61) (Table 3).

Table 1. Socio-demographic, cancer-related, health-/lifestyle, and psychological characteristics of survivors.

Variables	Total sample $n = 1088$	BC $n = 440$ (40%)	CRC $n = 120$ (11 %)	NHL $n = 172$ (16 %)	ALL $n = 110$ (10 %)	MM $n = 246$ (23 %)
Socio-demographic variables						
Sex, *n* (%)						
Female	807 (74)	440 (100)	62 (52)	81 (47)	51 (46)	173 (70)
Male	281 (26)	0	58 (48)	91 (53)	59 (54)	73 (30)
Age in years at survey						
Mean (SD)	49.1 (7.8)	49.4 (6.8)	48.9 (9.2)	48.3 (8.3)	47.0 (8.0)	50.1 (8.0)
Median (min.–max.)	48.6 (26.6–64.9)	48.8 (30–64.6)	48.7 (27.7–64.8)	47.7 (26.6–64)	46.6 (27.8–63.8)	49.6 (29.3–64.9)
Living as a couple, *n* (%)	866 (80)	349 (79)	93 (78)	137 (80)	87 (79)	200 (81)
Living with children < 18 years, *n* (%)	425 (39)	171 (39)	45 (38)	64 (37)	50 (46)	95 (39)
Education level > 13 years, *n* (%)	635 (59)	254 (58)	76 (64)	98 (57)	56 (51)	151 (62)
Cancer-related variables						
Age in years at diagnosis						
Mean (SD)	32.9 (5.4)	35.2 (3.5)	33.6 (5.2)	30.6 (5.7)	29.0 (5.9)	31.6 (5.8)
Median (min.–max.)	34 (19–39)	36 (21–39)	35 (20–39)	31 (19–39)	29 (19–39)	33 (19–39)
Time since diagnosis (years)						
Mean (SD)	15.2 (6.8)	13.1 (5.9)	14.3 (7.5)	16.7 (7.0)	17.0 (6.2)	17.5 (6.9)
Median (min.–max.)	14 (5–30)	12 (5–30)	12 (5–30)	17 (5–30)	17 (5–29)	18 (5–30)
Treatment modality, *n* (%)						
Limited surgery	246 (23)	0	0	0	0	246 (100)
Surgery and/or radiotherapy	171 (16)	71 (16)	81 (68)	20 (12)	0	0
Systemic treatment alone	151 (14)	0	0	49 (28)	102 (93)	0
Systemic treatment with surgery and/or radiotherapy	518 (48)	369 (84)	39 (33)	103 (60)	8 (7)	0
Somatic health–/lifestyle variables, n (%)						
Number of comorbidities						
No comorbidity	300 (28)	126 (29)	29 (24)	29 (17)	28 (25)	88 (36)
1–2 comorbidities	580 (53)	239 (54)	69 (58)	98 (57)	57 (52)	117 (48)
>2 comorbidities	204 (19)	72 (16)	21 (18)	45 (26)	25 (23)	41 (17)
Pain interfering with normal work	112 (10)	50 (11)	13 (11)	19 (11)	11 (10)	19 (8)
Trouble sleeping	487 (45)	223 (51)	58 (49)	80 (47)	33 (30)	93 (38)
Numbness in hands/feet	176 (17)	69 (17)	19 (18)	57 (33)	30 (27)	1 (<1)
Psychological variables, mean (SD)						
HADS-A score	4.7 (3.8)	5.0 (4.0)	4.3 (3.6)	5.1 (3.9)	4.6 (3.6)	4.1 (3.4)
PHQ-9 score[a]	2.4 (2.7)	2.8 (2.9)	2.5 (2.9)	2.6 (2.5)	2.3 (2.7)	1.8 (2.3)

Min.: minimum; Max.: maximum; SD: standard deviation; BMI: body mass index (kg/m^2); BC: breast cancer; CRC: colorectal cancer; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; MM: malignant melanoma; HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale; PHQ-9: the Patient Health Questionnaire-9.

[a]Somatic symptoms excluded, score from 0 to 15. Numbers may not add up to 1088 because of missing data. Percentages may not add up to 100% because of rounding.

Duration and development of chronic fatigue

Among survivors with CF ($n = 268$), duration of fatigue was 6 months 1 year in 14%, 1–5 years in 31%, and 5 years or more in 55% (Figure 3(a)). Sixty percent of survivors with CF reported that they had been tired since cancer treatment (Figure 3(b)).

Of the 160 survivors who had been tired since cancer treatment, 20% reported no change, 35% improvement, and 45% worsening of fatigue with time (Figure 3(c)).

Discussion

In this population-based cross-sectional study of YACSs, one-fourth reported CF at a median of 14 years (range 5–30 years) from diagnosis. CF was most prevalent among survivors of BC (29%), CRC (29%), and NHL (27%), while survivors of localized MM treated with limited surgery only had the lowest prevalence of CF (15%). Systemic treatment combined with surgery and/or radiotherapy, comorbidity, pain, numbness in hands/feet, and depressive symptoms were associated with CF. The majority of the survivors with CF had been tired since cancer treatment.

Our findings fit well with results from two prior studies assessing CF among survivors of cancers typically affecting young adults, reporting a prevalence of CF of 27% among survivors of testicular cancer and lymphoma [13,14]. As expected, the prevalence of CF is remarkably higher than that of 11% found in the Norwegian general population [24]. Recently, Poort et al. [9] demonstrated that 48% of YACSs had severe fatigue compared to 20% among population-based controls. However, that study included only 83 YACSs examined mean two years after diagnosis and is thus in line with prior research on fatigue in this group of cancer survivors; limited by small sample sizes, including individuals close to cancer treatment, not investigating duration of fatigue and using fatigue instruments different from the present study [3,6,7]. The majority of existing data regarding fatigue among YACSs is therefore not directly comparable with our study, which is the first to explore CF exclusively among a high number of long-term YACSs, and to compare the prevalence of CF and level of fatigue across survivors of different cancer diagnoses.

The prevalence of CF and fatigue levels found among survivors of BC and NHL in the present study are consistent with previous findings among survivors diagnosed with BC and NHL as older adults [12,25]. Among the CRC survivors, our result supports the finding of Thong and colleagues [26], who demonstrated a high prevalence of fatigue (35%) up to 10 years post-diagnosis in CRC survivors aged mean 70 years at the survey. However, as that study did not include information on the duration of fatigue, our study is to the best of

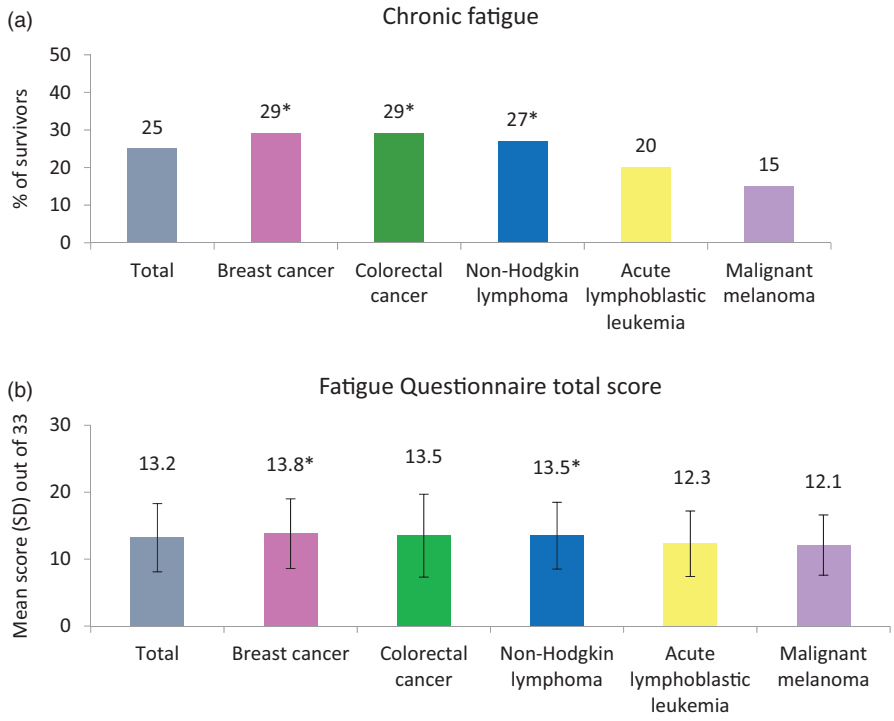

Figure 2. Prevalence of chronic fatigue (a) and fatigue questionnaire total score (b). (a) Prevalence of chronic fatigue. * = statistically significant higher prevalence of chronic fatigue (CF) compared to malignant melanoma. Survivors of breast cancer versus malignant melanoma: $p < .001$, colorectal cancer versus malignant melanoma: $p = .001$, non-Hodgkin lymphoma versus malignant melanoma: $p = .003$. p Values obtained by Chi-square test. (b) Mean total fatigue questionnaire (FQ) score. Range 0–33, higher score imply worse fatigue. * = statistically significant higher score than malignant melanoma. Survivors of breast cancer versus malignant melanoma: $p < .001$. Colorectal cancer versus malignant melanoma: $p = .072$. Non-Hodgkin-lymphoma versus malignant melanoma: $p = .036$. p Values obtained by one-way ANOVA with Tukey post hoc test. Error bars display standard deviation (SD).

our knowledge the first to estimate the prevalence of CF in CRC survivors in general. Our results are also consistent with prior findings of CF among survivors diagnosed with ALL and NHL in childhood; our group has previously reported CF in 22% of ALL and 30% of NHL survivors at median 20 years after diagnosis [11]. Another study in childhood ALL survivors found that 30% had a high level of fatigue, using a different questionnaire than the FQ [27].

Survivors of MM treated with limited surgery were included as a reference group to explore the association between treatment burden and CF. A 15% prevalence of CF among the survivors of MM is somewhat higher than reported in the general population [24], and one can, therefore, speculate that the burden of being diagnosed with cancer itself might lead to increased risk of CF. In addition, there was a high proportion of females (70%) within the MM group, which in the general population have a slightly higher prevalence of CF compared to men [24].

The range of associated factors of CF identified in the present study support the multifactorial etiology of CF [4]. Systemic treatment in combination with surgery and/or radiotherapy increased the risk of CF several years after completion of cancer treatment. This finding is in line with results from a recent systematic review conducted on 12,327 BC survivors up to 10 years after treatment, in which a higher risk of fatigue among those treated with chemotherapy alone or in combination with surgery and radiotherapy with or without hormone therapy, than among survivors treated with surgery with or without radiotherapy was reported [16]. Also in agreement with our results, Thong et al. [26] found that the combination of surgery, chemotherapy, and radiation was strongly associated with fatigue compared to surgery alone in CRC survivors at an older age than the CRC survivors in the present study. On the other hand, results from other studies indicate that fatigue is weakly related to the treatment [17]. In general, the relationship between treatment-related variables and fatigue is inconsistent, possibly due to the differences in treatment characteristics across studies [4].

Similar to other studies on cancer survivors diagnosed at older and younger ages, CF was associated with depressive symptoms [11–13,26], comorbidity [15], and pain [12,27]. These conditions might be possible to treat and prevent and should, therefore, be targeted when treating YACSs with CF. The association between CF and numbness in hands/feet could be an indication of neuropathy increasing the risk of CF, and is thus in line with Sprauten et al. [14], who found that testicular cancer survivors with high levels of neuropathy had three to four times higher risk of CF compared to those without neuropathy.

The present study indicates that fatigue among YACSs can be long-lasting; the mean time since diagnosis was almost 14 years among survivors with CF, and more than half of those with CF reported that they had been tired since cancer treatment. However, as almost 40% of the survivors with CF responded that they had not been tired since cancer treatment, CF among YACSs also might develop several years after completion of cancer treatment. This also corresponds to the findings of Sprauten et al. [14], who demonstrated that the prevalence of CF among testicular cancer survivors

Table 2. Prevalence of chronic fatigue and unadjusted associated factors.

	Chronic fatigue		Unadjusted analyses[a]		
	No	Yes	OR	95% CI	*p*
All ($n = 1088$)	820 (75)	268 (25)			
Sociodemographic variables					
Sex, *n* (%)					
Female (reference)	597 (74)	210 (26)	1.0		
Male	223 (79)	58 (21)	0.74	0.53–1.03	0.072
Age in years at survey, mean (SD)	49.6 (7.8)	47.7 (7.7)	0.97	0.95–0.99	0.001
Living as a couple, *n* (%)					
Yes (reference)	667 (77)	199 (23)	1.0		
No	152 (69)	68 (31)	1.50	1.08–2.08	0.015
Living with children <18 years, *n* (%)					
No (reference)	502 (76)	159 (24)	1.0		
Yes	317 (75)	108 (25)	1.08	0.81–1.43	0.612
Education level, *n* (%)					
≤13 years (reference)	328 (74)	118 (27)	1.0		
>13 years	486 (77)	149 (24)	0.85	0.65–1.13	0.262
Cancer-related variables					
Age at diagnosis, mean (SD)	32.9 (5.4)	32.8 (5.4)	1.0	0.97–1.02	0.898
Time since diagnosis (years), mean (SD)	15.6 (6.8)	13.8 (6.7)	0.96	0.94–0.98	<.001
Treatment modality, *n* (%)					
Limited surgery (reference)	209 (85)	37 (15)	1.0		
Surgery and/or radiotherapy	139 (81)	33 (19)	1.34	0.80–2.25	0.254
Systemic treatment alone	118 (78)	33 (22)	1.58	0.94–2.66	0.085
Systemic treatment with surgery and/or radiotherapy	354 (68)	165 (32)	2.63	1.77–3.91	<.001
Somatic health-/lifestyle variables, *n* (%)					
Number of comorbidities					
No comorbidity (reference)	254 (85)	46 (15)	1.0		
1–2 comorbidities	431 (74)	149 (26)	1.91	1.33–2.75	0.001
>2 comorbidities	131 (65)	73 (36)	3.08	2.01–4.71	<.001
Pain interfering with normal work					
No (reference)	767 (79)	200 (21)	1.0		
Yes	48 (43)	64 (57)	5.11	3.41–7.67	<.001
Trouble sleeping					
No (reference)	502 (84)	96 (16)	1.0		
Yes	315 (65)	172 (35)	2.86	2.14–3.80	<.001
Numbness in hands/feet					
No (reference)	651 (78)	181 (22)	1.0		
Yes	102 (58)	74 (42)	2.61	1.85–3.67	<.001
BMI					
<30 (reference)	684 (77)	205 (23)	1.0		
≥30	122 (69)	56 (32)	1.53	1.08–2.18	0.018
Physically active[c]					
No (reference)	321 (70)	140 (30)	1.0		
Yes	474 (80)	121 (20)	0.59	0.44–0.78	<.001
Binge drinking[d]					
No (reference)	746 (75)	249 (25)	1.0		
Yes	59 (78)	16 (21)	0.81	0.46–1.44	0.476
Smoking					
No (reference)	660 (76)	210 (24)	1.0		
Yes	157 (73)	58 (27)	1.16	0.83–1.63	0.388
Psychological variables, mean (SD)					
HADS–A score	4.0 (3.3)	6.9 (4.3)	1.23	1.18–1.28	<.001
PHQ-9 score[b]	1.7 (2.1)	4.7 (3.1)	1.55	1.45–1.65	<.001
Fatigue Questionnaire total score	11.0 (3.0)	19.9 (4.5)	1.95	1.79–2.12	<.001

[a]Univariable logistic regression analyses with chronic fatigue as the dependent variable.
[b]Somatic symptoms excluded, score from 0 to 15. Numbers may not add up to 1088 because of missing data. Percentages may not add up to 100% because of rounding.
OR: odds ratio; 95% CI: 95% confidence interval; SD: standard deviation; BMI: body mass index, kg/m^2; HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale. PHQ-9: The Patient Health Questionnaire.
[c]Physically active defined as performing at least 150 min moderate or 75 min high-intensity physical activity per week.
dBinge drinking defined as consuming five or more units of alcohol at the same occasion weekly.

increased from 15% 12 years after treatment to 27% seven years thereafter.

Our findings indicate a need for a close follow-up and evaluation of fatigue among young adults who have finalized cancer therapy. Considering the substantial proportion of survivors in our study experiencing worsening or no change of fatigue with time, health professionals caring for survivors with fatigue should ideally try to intervene as early as possible in order to limit the duration and negative impact of fatigue. As many of long-term YACSs will no longer have their follow-up in secondary care, general practitioners should also be attentive to CF among long-term YACSs. Clinicians should focus on targeting treatable associated factors of CF among YACSs with an individually directed approach as highlighted by the fatigue guidelines of the American Society of Clinical Oncology (ASCO) [28]. According

Table 3. Multivariable logistic regression model of factors associated with chronic fatigue.

	Model: block 1			Model: block 1 + 2			Model: block 1 + 2+3			Model: block 1 + 2+3 + 4		
Variables	OR	95 % CI	*p* Value	OR	95 % CI	*p* Value	OR	95 % CI	*p* Value	OR	95 % CI	*p* Value
Block 1: socio-demographic variables												
Sex												
Female (reference)	**1.0**			1.0			1.0			1.0		
Male	**0.71**	**0.51–0.99**	**0.042**	0.83	0.58–1.19	0.318	0.85	0.56–1.29	0.452	0.86	0.55–1.35	0.512
Age at survey	**0.96**	**0.95–0.98**	**<.001**	0.97	0.95–1.00	0.071	0.97	0.94–1.0	0.082	0.98	0.94–1.01	0.212
Living with partner												
Yes (reference)	**1.0**			**1.0**			**1.0**			1.0		
No	**1.60**	**1.14–2.24**	**0.006**	**1.58**	**1.12–2.22**	**0.009**	**1.66**	**1.12–2.47**	**0.012**	1.28	0.83–1.98	0.265
Living with children below 18 years												
No (reference)	1.0			1.0			1.0			1.0		
Yes	0.92	0.67–1.27	0.618	0.93	0.67–1.28	0.642	0.98	0.68–1.42	0.912	1.03	0.69–1.55	0.871
Education level												
≤13 years (reference)	1.0			1.0			1.0			1.0		
>13 years	0.80	0.60–1.06	0.120	0.82	0.62–1.10	0.188	0.98	0.70–1.37	0.906	0.98	0.68–1.43	0.929
Block 2: cancer-related variables												
Time since diagnosis				0.99	0.96–1.02	0.548	0.99	0.95–1.03	0.518	1.0	0.96–1.04	0.999
Treatment modality												
Limited surgery (reference)				1.0			1.0			1.0		
Surgery and/or radiotherapy				1.31	0.77–2.21	318	1.09	0.59–2.02	0.780	1.15	0.58–2.23	0.691
Systemic treatment alone				1.53	0.90–2.62	0.120	1.40	0.74–2.61	0.299	1.29	0.66–2.53	0.464
Systemic treatment with surgery and/or radiotherapy				**2.33**	**1.54–3.53**	**<.001**	**2.11**	**1.30–3.43**	**0.003**	**1.88**	**1.11–3.18**	**0.018**
Block 3: health-/lifestyle variables												
Comorbidity conditions												
No comorbidity (reference)							**1.0**			**1.0**		
1–2 comorbidities							**1.67**	**1.09–2.54**	**0.018**	**1.63**	**1.03–2.60**	**0.038**
>2 comorbidities							**2.06**	**1.19–3.56**	**0.010**	1.78	0.97–3.26	0.063
Trouble sleeping												
No (reference)							**1.0**			1.0		
Yes							**2.24**	**1.61–3.13**	**<.001**	1.36	0.93–1.98	0.110
Pain interfering with normal work												
No (reference)							**1.0**			**1.0**		
Yes							**3.22**	**1.95–5.33**	**<.001**	**2.39**	**1.36–4.19**	**0.002**
Numbness in hands or feet												
No (reference)							**1.0**			**1.0**		
Yes							**1.66**	**1.10–2.52**	**0.016**	**1.60**	**1.01–2.52**	**0.046**
BMI, n (%)												
<30 (reference)							1.0			1.0		
≥30							0.99	0.64–1.56	0.983	0.97	0.59–1.58	0.889
Physically active[a]												
No (reference)							**1.0**			1.0		
Yes							**0.68**	**0.49–0.94**	**0.020**	0.72	0.50–1.03	0.074
Binge drinking[b]												
No (reference)							**1.0**			1.0		
Yes							**0.86**	**0.43–1.72**	**0.673**	0.69	0.32–1.51	0.353
Smoking												
No (reference)							**1.0**			1.0		
Yes							**0.85**	**0.56–1.29**	**0.455**	0.86	0.55–1.35	0.503
Block 4: Psychological variables												
HADS-A score										0.99	0.93–1.06	0.797
PHQ-9score[c]										**1.46**	**1.32–1.61**	**<.001**

BMI: body mass index (kg/m^2); HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale; PHQ-9: The Patient Health Questionnaire-9.
[a]Physically active defined as performing at least 150 min moderate or 75 min high-intensity physical activity per week.
[b]Binge drinking defined as consuming five or more units of alcohol at the same occasion weekly.
[c]Somatic symptoms excluded, score from 0 to 15. Bold: *p*-value < .05.

to a recent meta-analysis, exercise (both aerobic- and strength training) and psychological interventions (such as cognitive behavioral therapy and psychoeducational methods) have equally moderate positive effects on fatigue symptoms during and after cancer treatment [29]. However, as there is a lack of studies on management of fatigue with CF as an inclusion criterion for study entry, evidence on how to manage CF is largely absent [29], and should be further explored in future studies.

Strengths of our study include the large population-based sample size and inclusion of a wide range of factors potentially associated with CF. A limitation of the present study is the cross-sectional design not allowing causal inferences. The trajectory of fatigue after different cancer treatment regimens in YACSs should, therefore, be further explored in prospective studies. Also, the response rate of 42% and an overrepresentation of BC survivors might yield response bias and limit the generalization of our results. Also, a higher proportion of survivors bothered by fatigue might have answered, which could have led to a prevalence of CF higher than reality. On the other hand, survivors bothered by severe fatigue might be too tired to answer, which

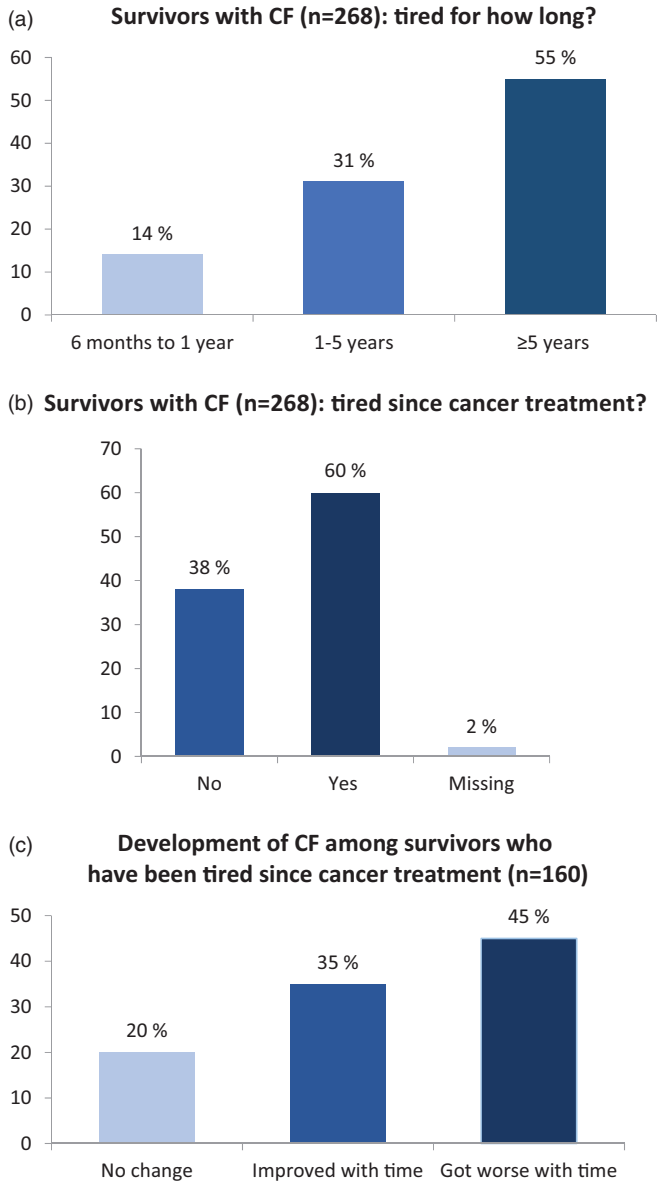

Figure 3. (a–c) Duration and development of chronic fatigue (CF).

could result in an underestimation of the prevalence of CF. Another limitation of our study is the use of self-reported data. Recall bias might have affected both self-reported treatment information and aspects of start, development, and duration of fatigue. Further, information on physical activity, alcohol consumption and smoking may be influenced by social desirability. Finally, our study is limited by lack of a control group from the general population, as it might be that the prevalence of CF is different now than in the national representative sample reported by Loge et al in 1998 [24]. However, we believe our findings of a higher prevalence of CF and level of fatigue among YACSs with a history of higher treatment burden compared to survivors of MM treated by limited surgery support the use of MM as a relevant reference group in our study.

In conclusion, health professionals should be aware of the high prevalence of CF in YACSs. It is not possible to provide specific treatment recommendations based on the present cross-sectional study; however, management of CF should involve targeting of modifiable associated factors, such as comorbidities, pain, and depressive symptoms, along with exercise and psychological interventions as appropriate.

Disclosure statement

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