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ORIGINAL ARTICLE

Fatigue in survivors of malignant melanoma and its determinants: a register-based cohort study

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Abstract

Purpose Fatigue has found increasing attention as a debilitating and lasting condition of cancer patients. However, it has remained unclear to what degree long-term survivors of malignant melanoma suffer from fatigue. Therefore, this study aimed to determine fatigue and its link with quality of life, aftercare behavior, and mental and physical symptoms among melanoma survivors.

Methods A register-based sample of 684 long-term survivors an average of 8.4 (*SD* = 1.72; range 5.67–12.17) years after diagnosis was compared to 2049 participants from a representative survey by the Multidimensional Fatigue Inventory. In a hierarchical linear regression, statistical predictors for fatigue were ascertained.

Results Overall fatigue was not increased in melanoma survivors except for younger melanoma survivors under 40 years. As in the general population, fatigue increased with age, and it was higher in women compared to men. Fatigue was associated with decreased quality of life, reduced functioning, and increased physical and mental symptoms. Substantial predictors (30% explained variance) were higher age, additional chronic illness, self-blame, detrimental interactions and lack of social support, and also fear of recurrence. There was neither an effect of medical parameters (clinical stage, time since diagnosis) nor of participation in follow-up care.

Conclusions Fatigue needs to be taken seriously in the aftercare of melanoma survivors as it is associated with multiple functional and quality of life impairments and heightened distress. Reduction of fatigue in melanoma patients should address younger survivors (under 40 years) and older survivors (over 60 years) with additional chronic illness and focus on illness coping and social support.

Keywords Cancer · Fatigue · Malignant melanoma · Mental health

Introduction

Malignant melanoma has become one of the most frequent forms of cancer [1]. We recently confirmed a high degree of distress in the acute treatment phase [2]. Detected at an early stage, however, the vast majority of cases are treated effectively and it has remained controversial to what extent long-term survivors' quality of life is compromised and whether they experience lasting psychological distress. In particular, they have to grapple with ongoing threats of recurrence and of UV exposure, continued self-examination, and dermatological controls [3].

In a previous study of the current sample with long-term survivors, we found slightly increased depression and anxiety (only women), but no impaired global quality of life compared to the general population [4]. Yet, survivors evidenced functional decline and more physical symptoms. Distress and

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symptoms were higher in women compared to men and in middle adulthood (vs. older patients). They were consistently predicted by lack of social support, fear of recurrence, pessimism, and self-blame. Distress was also increased by a family history of melanoma, and additional mental and somatic diseases.

Physical symptoms also comprise experiences of fatigue. Fatigue describes an individual's subjective experience of tiredness, exhaustion, and overall lack of energy. Fatigue is widespread, affecting about a third of the general population at least moderately (regarding the last 6 months), with a slight preponderance of women [5]. The reduction of fatigue has been listed among the aims the World Health Organization outlined in its International Classification of Functioning, Disability and Health (ICF) [6]. The perceived burden from fatigue can pertain to the physical and/or mental domain. As a nonspecific symptom, fatigue has been linked to previous stress [7], and to highly diverse medical conditions such as neurological disorders and cancer as well as mental illnesses [5, 8, 9], sharing commonalities with depression and somatoform disorder [10]. Unlike common tiredness, fatigue has no direct link to (mental or physical) exertion. Otherwise, adequate behavior such as resting or sleeping might not aid recuperation, and it is perceived as unpleasant. In fact, fatigue has been reported as one of the most debilitating symptoms of many illnesses significantly reducing patients' quality of life [11–13].

As fatigue is very common in cancer patients and increasing with multiple types of treatment (e.g., chemotherapy), the term "cancer-related fatigue" [8] has been coined. It has been recognized as one of the most widespread consequences of cancer, exceeding nausea and vomiting, both of which can nowadays be ameliorated by medication [14]. The prevalence of fatigue in cancer patients differs depending on tumor localization, being the highest in cancers of the lymphatic and hematopoietic system, followed by cancers of the female genital organs, skin, and respiratory organs [15]. In cancer patients, fatigue has been shown to be more pronounced and experienced as more distressing than in non-cancer control groups, as cancer patients related it to their ill health, feelings of threat, and sadness [16]. Fatigue impairs cancer patients' quality of life due to its interference with treatment compliance, activities of everyday life, and is associated with mental distress such as anxiety and depression [15, 17, 18]. A recent study [17] reported fatigue as the most prevalent contributor to psychological distress in cancer patients, affecting more than half of a large, heterogeneous patient sample.

After successful cancer treatment, fatigue often does not resolve [19, 20]. It is estimated that around a third of cancer survivors suffer from persisting fatigue [21]. The reasons for lasting or chronic fatigue are still debated. Most likely tumor-associated metabolic, circulatory, endocrinological disorders, bodily defenses against the tumor, and treatment side effects such as sleep disorders, immobility or pain interact with psychological distress. In melanoma patients who often receive adjuvant interferon-α treatment [22], incidence levels of fatigue have been reported to reach up to 90%. As [23] have shown, fatigue during acute cancer treatment is predictive of chronic or lasting fatigue.

The present study assessed dimensions of general, physical, and mental fatigue, reduced activity, and reduced motivation based on the Multidimensional Fatigue Inventory (MFI) [24], which has been widely used in cancer patients [25]. We wish to answer the following questions: (1) Are there differences between fatigue in melanoma survivors and in the general population? (2) What is the association of fatigue among melanoma survivors with mental health (depression, anxiety) and quality of life (EORTC-QLQ-C30)? (3) What are predictors of fatigue among melanoma survivors?

Methods

Samples

In the state of Rhineland-Palatinate, all cancer patients are registered by their physicians in the regional cancer registry. Data include re-identifiable personal data, and tumor diagnosis (ICD 10), location and morphology (ICD-O-3), staging (TNM), age, sex, and date of diagnosis. Estimated completeness of incident melanoma notifications in Rhineland-Palatinate is more than 95%. We included all registered former patients with a diagnosis of malignant melanoma (ICD-10: C43) registered by their dermatologist from 2000 to 2005 (a) who were still alive at the time of the study, (b) at least 14 years old at the date of diagnosis, and (c) who gave their written informed consent to participate in this study. Study information, informed consent, questionnaires, and the signed form letter of the physician were sent to the study participants by the study center. Patients who did not react to the letter of interest within 6 weeks got a reminder letter. Non-responders were not contacted further. For legal reasons and confidentiality, the cancer registry decoded the patients' names. Coded data were analyzed without reference to personal identification. The protocol was approved by the Ethics Committee of the Statutory Physician Board of the State of Rhineland Palatinate (Reference number 837.161.11.7703).

Out of 112 dermatologists who had registered 2112 patients between 2000 and 2005, 75 physicians participated (67%). Non-participating physicians ($n = 37$) reported no interest in studies, lack of time, no longer ongoing patient contact or cessation of medical practice. Participating physicians had registered 1701 (80.5%) of the total patients who were therefore considered contactable. Three hundred eighty-two patients could not be reached, because mail was not delivered (200/ 11.8%), or they had deceased (46/2.7%) or they were excluded by their physician because of dementia or other causes for being unable to take part in the study (136/ 8%). Overall, out of 1319 contacted patients, 689 (52.2%) replied and data was available for the analysis [26].

Melanoma survivors' fatigue was compared to fatigue scores of the general German population [27]. This sample had previously been recruited with the assistance of a demography consulting company (USUMA, Berlin) using a total of 216 sample points regions, covering rural and urban areas from all regions in Germany, were randomly drawn from the most recent political election register. Inclusion criteria were age above 13 years and German as a native language. Following a random-route procedure, 2050 of 3020 subjects agreed to be interviewed and completed several standardized psychological and sociological questionnaires. Thus, sampling was conducted using a threefold random selection procedure. The aim of the sampling procedure was to obtain a sample that was representative of the German population in terms of age, sex, and education. For the current study, a total N of 2049 questionnaires was valid. With respect to age, sex, and education, the sociodemographic characteristics of the collected sample closely matched those of the total population in Germany. The study adhered to ICH-GCP-guidelines as well as to the guidelines of the ICC/ESOMAR International Code of Marketing and Social Research Practice. All participants were informed of the study procedures, data collection and anonymization of all personal data. All participants provided verbal informed consent, which was documented by the trained interviewer before starting with the survey.

Measures

Fatigue The Multidimensional Fatigue Inventory (MFI) by [24] is an internationally validated self-report questionnaire of 20 items. Each subscale consists of four items with a 5-point Likert scale (1 = yes, that is true to 5 = no, that is not true), higher scores indicating increased fatigue. The MFI subscales have shown satisfying reliability and convergent validity with other fatigue scales. An investigation of the herein reported sample with malignant melanoma survivors showed in sum satisfying (.66) to good (.86) internal consistency (Cronbach's α [28]) for all subscales: general fatigue (.81), physical fatigue (.86), reduced activity (.84), reduced motivation (.66), and mental fatigue (.81). The patterns were similar to those of the German population [27].

Depression The German version of the Patient Health Questionnaire-9 (PHQ-9) assessed depression with 9 items [29]. Occurrence in the past 2 weeks was rated from 0 = not at all to 3 = nearly every day. Internal consistency was good $\alpha = .86$ in the current sample with melanoma patients.

Anxiety The Generalized Anxiety Disorder Questionnaire (GAD-7) assessed symptom severity in the past 2 weeks by 7 items. Internal consistency in our sample was good (Cronbach's $\alpha = .89$), response range was from 0 = not at all to 3 = nearly every day [30].

Quality of life We used the mean score of global health status and quality of life of the Quality of Life Core Questionnaire EORTC-QLQ-C30 [31] to measure global quality of life. Additional measures were the five functional scales (physical, role, emotional, cognitive, social), eight symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea), and the perceived financial impact of the disease, and a two-item global health/ QoL scale. The respective Likert scales range from 0 = not at all to 3 = very much. Higher functional and global health scores represent better functioning, whereas higher symptom scores reflect greater symptom distress.

Coping The Brief Cope (BC) is a short version of the COPE questionnaire [32, 33], which has proven useful in health-related research. It consists of 28 items using a Likert scale ranging from 1 = never to 4 = very often. Following Beutel et al. [4], the three subscales Seeking External Support ($\alpha = .75$), Denial/Self-blame ($\alpha = .74$), and Positive reappraisal/Active coping ($\alpha = .76$) showed satisfying internal consistency.

Social support We assessed social support and detrimental interactions with the Illness-specific Social Support Scale (ISSS), which was developed by Revenson and Schiaffino [34] and translated and modified to a German version by Ramm and Hasenbring [35]. In line with Beutel et al. [4], we used the two subscales Positive social support (15 items, $\alpha = .94$) and Detrimental interaction (9 items, $\alpha = .72$) with good to excellent internal consistencies. The subscale Positive social support represents emotional, informational and tangible support of significant others. Detrimental interactions consist of illness-specific dismissive attitude and less empathetic behavior of significant others, e.g., lack of compassion, playing down illness-specific sequelae, intrusive advices, exerting pressure, and expressing overwhelming fear, pessimism, or anger. All items were rated on a 5-point Likert scale ranging from 0 = never to 4 = always.

Statistical analysis

Descriptive analyses and subsequent univariate (ANOVA) and multivariate analyses of variance (MANOVA) were performed. Bivariate analyses were calculated by using Pearson product-moment correlation. Hierarchical multiple regression models using the enter method for each block were tested to investigate sociodemographic, somatic, and psychological predictors of fatigue and quality of life among melanoma survivors. The regression models were checked for multicollinearity using the variance inflation factor for each predictor indicating no multicollinearity (all < 2). Analyses were performed using SPSS 23. Effect sizes of correlation, analyses of variance, and regression coefficients are interpreted after Cohen [36].

Results

The mean age of patients with melanoma included in this study ($N = 689$) was 62 years ($M = 61.71$, SD = 14.57; range from 28 to 94). Men ($n = 335$) and women ($n = 354$) were almost equally represented. The average time since diagnosis was 8.41 years ($SD = 1.72$; range 5.67 to 12.17 years). According to the cancer registry, the tumor stage at diagnosis (UICC) was I in 53%, II in 4.9%, and III in 1.0%. A total of 41.1% of tumor stages were missing, however, as in many instances the dermatologist registered the case before the presence of metastases could be excluded by intensive diagnostic work-up. A total of 78% suffered from additional sleep disorder and chronic diseases (hypertension, thyroid disease, allergy, coronary heart disease, diabetes, other cancer). For the current study, the analysis sample consisted of $N = 684$ participants due to five incomplete data sets with regard to the main variable fatigue. Table 1 compares overall fatigue and the five subscales of fatigue between the survivors of malignant melanoma and the general population. The reference population consisted of $N = 2049$ individuals ($n = 1145$ female, $n = 904$ male), age 49.3 ± 17.24 years with a range from 14 to 92 years.

Mean sum scores and standard deviations are presented separately for men and for women and according to age groups (≤ 39, 40–59, ≥ 60 years). As determined by ANOVA, overall fatigue did not differ between melanoma survivors and the general population ($F(1, 2720) = 1.23$, $p =$ n.s., $\eta_p^2 = .00$). In both samples, fatigue increased with age with a moderate effect size ($F(2, 2720) = 79.92$, $p < .001$, $\eta_p^2 = .06$), and it was higher in women compared to men, but with a neglectable effect size ($F(1, 2720) = 6.10$; $p < .05$, $\eta_p^2 = .00$). Figure 1 illustrates the significant interaction between group and age: Younger melanoma survivors ≤ 39 years reported higher and older survivors (≥ 60 years) lower scores of overall fatigue than the general population ($F(2, 2720) = 8.80$, $p < .001$, $\eta_p^2 = .01$); the middle group showed no difference. There was no significant interaction between sex and age ($F(2, 2720) = 1.36$, $p =$ n.s., $\eta_p^2 = .00$) for overall fatigue. Also, no significant three-way interaction of group with sex and age was observed ($F(2, 2720) = 1.26$, $p =$ n.s., $\eta_p^2 = .00$).

Further analyses at subscale level were conducted by using MANOVAs since the MFI subscales correlated substantially with each other (range of $r = .59–.80$). In sum, MANOVA with all five fatigue subscales as dependent variables revealed

Table 1 Descriptive statistics (mean sum scores and standard deviation) and inference tests of fatigue dimensions based on the Multidimensional Fatigue Inventory (MFI) for the general population vs. survivors of malignant melanoma

	Values for the general population M (SD), N = 2049						Values for survivors of malignant melanoma M (SD), N = 684					
	Male ($n = 904$)			Female ($n = 1145$)			Male ($n = 335$)			Female ($n = 349$)		
	≤ 39 ($n = 284$)	40–59 ($n = 321$)	≥ 60 ($n = 299$)	≤ 39 ($n = 397$)	40–59 ($n = 373$)	≥ 60 ($n = 375$)	≤ 39 ($n = 19$)	40–59 ($n = 85$)	≥ 60 ($n = 231$)	≤ 39 (n = 34)	40–59 ($n = 163$)	≥ 60 ($n = 152$)
Overall Fatigue	6.31 (2.26)	7.55 (2.76)	9.61 (3.35)	7.05 (2.52)	8.19 (3.07)	10.26 (3.29)	7.70 (2.87)	8.18 (3.74)	8.90 (3.29)	8.08 (3.34)	7.81 (3.00)	9.56 (4.07)
General Fatigue	6.54 (2.68)	7.95 (3.17)	9.95 (3.75)	7.67 (3.18)	8.71 (3.53)	10.76 (3.68)	8.72 (4.07)	9.01 (4.42)	9.14 (3.99)	10.18 (4.03)	9.27 (3.89)	10.21 (4.67)
Physical Fatigue	6.08 (2.89)	7.56 (3.53)	10.26 (4.27)	6.76 (2.94)	8.20 (3.84)	11.04 (4.17)	6.78 (3.00)	8.16 (4.31)	9.42 (4.11)	7.79 (4.18)	7.44 (3.49)	10.32 (4.92)
Reduced Activity	6.41 (2.89)	7.54 (3.20)	10.22 (4.02)	7.08 (3.02)	8.23 (3.70)	10.44 (4.01)	7.41 (3.19)	7.90 (4.32)	9.58 (4.01)	7.43 (4.02)	7.22 (3.38)	9.52 (5.03)
Reduced Motivation	6.21 (2.43)	7.56 (2.93)	8.98 (3,28)	6.73 (2.73)	8.01 (3.13)	9.89 (3.48)	7.74 (3.31)	7.96 (3.70)	8.40 (3.21)	7.38 (3.87)	7.18 (3.10)	9.11 (4.07)
Mental Fatigue	6.39 (2.66)	7.12 (3.21)	8.64 (3.56)	7.02 (3.06)	7.79 (3.09)	9.18 (3.42)	7.83 (3.00)	7.71 (4.25)	8.08 (3.68)	7.62 (3.52)	7.96 (3.69)	8.84 (4.17)

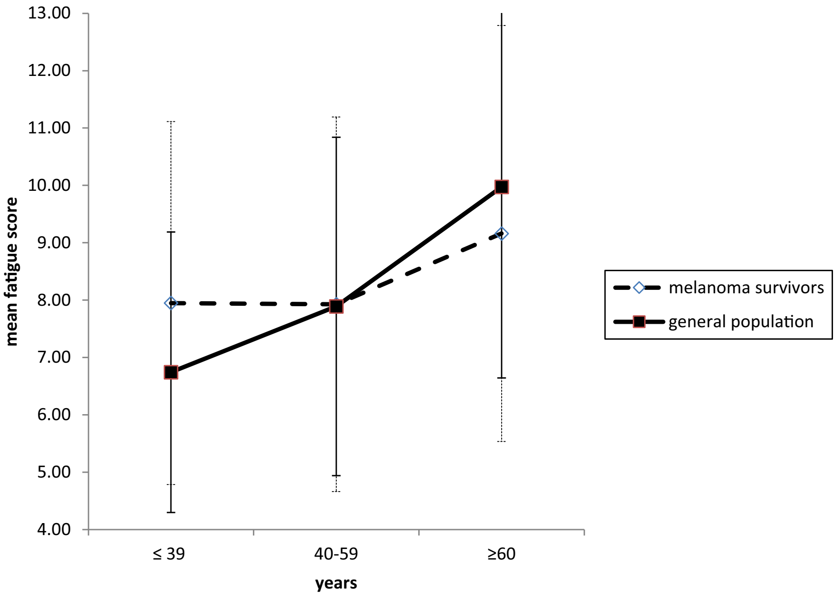

Fig. 1 Interaction of overall fatigue assessed with the MFI predicted by group (melanoma survivors vs. general population) × age (≤ 39, 40–59, ≥ 60 years). Note: Melanoma survivors N = 684, general population N = 2049. MFI = Multidimensional Fatigue Inventory

similar patterns, but with partly higher effect sizes compared to the ANOVA results. For instance, comparison of fatigue levels between melanoma survivors and the general population showed significant results with low effect size (Wilks' $\lambda = .98$, $F(5, 2713) = 9.22$, $p < .001$., $\eta_p^2 = .02$). Post hoc ANOVAs revealed that this effect is mainly based on the subscale general fatigue among melanoma survivors. An effect for age was found again with similar moderate effect size (Wilks' $\lambda = .91$, $F(10, 5426) = 9.22$, $p < .001$., $\eta_p^2 = .05$). The interaction of sample with age was also significant, but with very low effect size similar to analysis with the MFI total score (Wilks' $\lambda = .98$, $F(10, 5426) = 4.94$, $p < .001$., $\eta_p^2 = .01$). Again, general fatigue showed the strongest effect when comparing all subscales. The highest fatigue scores were reported by younger melanoma survivors. Sex was a significant predictor, but with very low effect size (Wilks' $\lambda = .99$, $F(5, 2713) = 6.01$, $p < .001$., $\eta_p^2 = .01$). Female melanoma survivors reported the highest fatigue scores, especially on the subscale general fatigue. The interaction between sex and age was significant, but with very low effect size, too (Wilks' $\lambda = .99$, $F(10, 5426) = 3.15$, $p < .001$., $\eta_p^2 = .01$). Three-way interactions showed no significant results.

Table 2 shows mean scores and SD of mental health and QoL scores in survivors of malignant melanoma and their correlation with the MFI and its subscales.

Consistently, the strongest negative correlations were found between overall fatigue and the subscales of functional and global health and positively with symptom scales of the EORTC QLQ-C30, and with its fatigue subscale. Somewhat smaller correlations were found with depression, anxiety and the functioning scales of the EORTC QLQ-C30. Some of the correlations were specific, e.g., physical fatigue correlated strongly with physical and mental fatigue with cognitive functioning. There were medium correlations of fatigue (overall and at subscale level) with pain, dyspnea, insomnia, and financial difficulties. Correlations with gastrointestinal complaint (constipation, appetite loss, diarrhea, nausea /vomiting) were comparatively small.

Table 3 shows results of a hierarchical multiple linear regression analysis predicting fatigue assessed by MFI. As Table 3 shows, in the first step, demographical and disease characteristics were entered. However, only age showed an association, but neither sex nor clinical stage or time since diagnosis. In step 2, the presence of other chronic illness was predictive of fatigue. In step 3, individual coping style and perceived social support were entered as predictors. Results show that self-blame as individual coping style and detrimental social interactions positively predicted fatigue. In contrast, perceived positive support is linked with decreased fatigue. Coping styles such as search for external support and reappraisal turned out to be not predictive. In step 4, fear of recurrence was an additional factor, but neither taking part in medical follow-up nor psychosocial care.

Discussion

Differences between fatigue in melanoma survivors and in the general population

Comparing fatigue among melanoma survivors and the general population, there was no overall increased fatigue in long-term melanoma survivors. Hence, this study provides evidence that fatigue might not be as prevalent among long-term melanoma survivors compared to other cancer survivors [17]. It was also markedly less pronounced than in melanoma

Table 2 Descriptive statistics (M, SD) of mental health and QoL in survivors of malignant melanoma and their correlation with fatigue

			Multidimensional Fatigue Inventory				
		Overall Fatigue	General Fatigue	Physical Fatigue	Reduced Activity	Reduced Motivation	Mental Fatigue
Mental health	M (SD)						
PHQ-9 Depression	3.90 (4.07)	.65	.67	.53	.52	.51	.60
GAD-7 Anxiety	3.36 (3.88)	.51	.53	.39	.35	.42	.53
EORTC QLQ-C30	M (SD) range 0–100						
Functional scales							
Physical	86.35 (19.48)	−.65	−.56	−.71	−.62	−.51	−.43
Role	83.78 (26.13)	−.62	−.54	−.67	−.58	−.47	−.41
Emotional	74.77 (24.80)	−.58	−.61	−.46	−.43	−.48	−.54
Cognitive	82.06 (22.44)	−.62	−.57	−.50	−.49	−.50	−.66
Social	86.15 (24.17)	−.63	−.56	−.60	−.54	−.51	−.49
Symptom scales							
Fatigue	26.21 (25.32)	.76	.77	.73	.64	.59	.57
Nausea/vomiting	3.18 (9.96)	.36	.36	.32	.29	.31	.28
Pain	22.87 (29.90)	.56	.51	.63	.51	.43	.37
Dyspnea	15.34 (26.68)	.48	.46	.52	.43	.36	.31
Insomnia	30.79 (32.69)	.45	.47	.42	.33	.35	.39
Appetite loss	4.99 (15.06)	.36	.34	.36	.31	.31	.24
Constipation	8.91 (21.78)	.31	.27	.27	.24	.27	.28
Diarrhea	8.90 (20.07)	.28	.26	.20	.24	.24	.28
Financial difficulties	9.40 (23.15)	.44	.41	.41	.36	.37	.35
Global Health	70.52 (21.79)	−.73	−.68	−.75	−.63	−.60	−.53

Note: $N = 684$. All results were statistically significant at $p \leq .0001$, two-tailed, based on Bonferroni correction calculation for multiple comparisons. *M* mean scores. *SD* standard deviations. *QoL* quality of life. *PHQ-9* Patient Health Questionnaire-9. *GAD-7* General Anxiety Disorder Questionnaire. *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-30

patients currently in treatment [22], and melanoma survivors with shorter times since diagnosis, e.g., treated in the context of specialized rehabilitation care settings [15]. Thus, register-based approaches imply a useful complement to previous research as their results also speak to those former patients' status who have been relatively unaffected by late effects and who are therefore less likely to frequent treatment facilities.

In both samples, slightly higher fatigue was reported by older and female participants. These findings are consistent with previous analyses in this patient population showing that distress was higher in older vs. younger survivors of malignant melanoma [4]. These results are also in line with a large German study involving cancer patients in a variety of care settings [17]. However, a small interaction effect indicated that overall or general fatigue was slightly higher among younger melanoma survivors under 40 years in comparison to the corresponding age group in the general population. The shorter time period since clinical diagnosis among younger melanoma survivors might have an impact on this effect indicating less time for processing and learning to deal with illness-related sequelae most likely shape the quality of life outcomes. This finding of a comparatively higher impairment among younger melanoma patients corresponds to the increased psychological impact of cancer diagnosis and treatment in younger individuals previously confirmed in large samples of (early) breast cancer survivors, highlighting individually different health-related needs and expectations [37, 38]. It has not been comprehensively established which role demographic factors play in cancer patients' and survivors' levels of fatigue [39]; however, researchers note that underlying factors might differ between younger and older patients. For instance, a large investigation of health-related quality of life in cancer patients which drew from 25 randomized controlled trials detected challenges specifically affecting different age groups [40]. Younger cancer patients' difficulties included financial worries as well as social and role functioning, whereas older patients were rather encumbered by appetite loss. Moreover, serious illness carries different meaning and relevance across the life span. As they often lack previous comparable

Table 3 Hierarchical regression of overall fatigue on medical and sociodemographic variables, habitual coping strategies, and illness-related items

	Fatigue (MFI)				
	ΔR^2	R^2	Final β	B	95% CI
Step 1 (model 1)	.06**	.06**			
Age			.24***	0.06	0.03/0.09
Sex			.04	0.23	− 0.48/0.95
Clinical stage			− .04	− 0.38	− 1.31/0.55
Time since diagnosis			− .04	− 0.09	− 0.29/0.11
Step 2 (model 2)	.03**	.09**			
Other chronical illness			.10	0.84	− 0.09/1.77
Step 3 (model 3)	.17***	.26***			
Brief COPE					
Seeking external support			− .02	− 0.09	− 0.84/0.66
Denial/self-blame			.15*	1.46	0.30/2.63
Positive reappraisal/active coping			− .02	− 0.13	− 0.88/0.61
ISSS					
Detrimental interactions			.20***	1.23	0.58/1.87
Positive social support			− .12*	− 0.46	− 0.91/−0.02
Step 4 (model 4)	.04**	.30**			
Illness-related items					
Fear of reoccurrence			.16**	0.35	0.10/0.61
Medical follow-up			.03	0.47	− 1.05/1.99
Psychosocial care			.09	0.78	− 0.15/1.72
Wish for any support			.08	0.64	− 0.16/1.45

Note: *N* = 684. * $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$. *ISSS* Illness-specific Social Support Scale. *CI* 95% confidence interval. Sex: 1 = male. 2 = female; other chronical illness: 0 = no. 1 = yes; fear of reoccurrence: 0 = not at all to 5 = very much; medical follow-up: 0 = no. 1 = yes; psychosocial care: 0 = no. 1 = yes; wish for any support: 0 = no. 1 = yes

In this hierarchical regression model, predictor sets were subsequently added to the initial model (model 1). Each step displays the additional inclusion of new predictors in the regression model. Model 4 includes all predictor variables listed in this table

experiences relating to their own and their social environment's medical history, especially physical limitations were perceived as more impeding among the young [41, 42].

In this sense, especially younger melanoma patients should be informed about the risk of increased fatigue symptoms compared to their peer group. In particular, those who used to be physically or socially active before undergoing treatment might benefit from allowing themselves time to adjust to the sequelae of melanoma cancer. No significant differences were found among older age groups.

Association of fatigue among melanoma survivors with mental health and quality of life

Based on the MFI, overall fatigue was strongly negatively associated with EORTC (physical, role, emotional, cognitive, social) functioning scales and global health, and positively with symptom scales, depression and anxiety and also with financial difficulties. Some scales were specifically related (e.g., physical fatigue to physical functioning, mental fatigue to cognitive functioning). As to be expected, the MFI score showed the highest correlations with the EORTC fatigue symptom scale. As correlations among the MFI subscales were very high and similar results were found using the overall score vs. all five MFI subscales, we mostly relied on the use of a single index of overall fatigue. On the whole, fatigue is associated with a wide range of indicators of impairment, reduced quality of life and distress.

Predictors of fatigue among melanoma survivors

As determined by multiple hierarchical regression analyses, fatigue was predicted to a substantial degree (30% variance) by higher age, additional chronic illness, self-blame, detrimental interactions, lack of social support, and fear of recurrence. Neither medical parameters (clinical stage, time since diagnosis) nor follow-up care had effects. Findings referring to main predictors of fatigue emphasize the relevance of encouraging positive social support on the one hand, and reduction of self-blame, fear of recurrence, disappointing, and rejecting interactions on the other hand.

Clinical implications

In addition to its previously established relevance for adherence and quality of life during treatment [22], fatigue needs to be assessed routinely in the aftercare of melanoma survivors as it is strongly associated with multiple functional and quality of life impairments and heightened distress [15]. In previous studies, fatigue was shown to be most predictive of other problems, and also identified as the single most debilitating somatic ailment of cancer survivors [17]. Counseling cancer survivors in structuring daily activities and performing moderate physical activity may be helpful [22]. As our data indicate, psycho-oncologic interventions should additionally focus on the reception of helpful support by training assertiveness for empowering melanoma survivors to articulate or object to non-supportive interactions.

Younger melanoma survivors showed increased fatigue scores in comparison to normal levels. Therefore, fatigue among younger patients should be monitored in order to prevent sequelae of fatigue-related impairments, e.g., with regard to activities of daily living and ability to work. The study indicated a number of variables to be taken into account in aftercare. Thus, reduction of fatigue in melanoma patients should also address older survivors with additional chronic illness and focus on illness coping and social support.

Study limitations

As in other European trials, recruitment of patients for the present study relied on a state-wide registry which included more than 95% of all melanoma patients. To protect participants' confidentiality, this procedure demands indirect recruitment (i.e., recruitment by reporting physicians rather than researchers involved with the project) which has contributed to lower participant rates. Other studies carried out in direct contract to former patients reported slightly lower rates of study participation than 48% as was the case in the present study [26]. Moreover, lower participant rates might in part be attributed to the many years elapsed before follow-up. Thus, it is possible that there was a bias towards more or less distressed melanoma survivors eventually taking part. Statistical comparisons were carried out with a large and representative survey of the general German population. Whereas this is a strong point of our study, the representative sample of the general German population may have also comprised an unknown and not controlled for proportion of individuals also afflicted by cancer, and other chronic health conditions. A further weakness pertains to missing information regarding tumor stage. In reference to the aforementioned long follow-up times, however, we do not expect a high prevalence of patients with progressed disease who may be expected to suffer from high rates of fatigue following alpha-interferon treatment in our sample [22]. As immune therapy has greatly increased the survival rates of melanoma patients with stage III and IV disease, future prospective studies are relevant to assess their levels of fatigue in the long run. Lastly, our analyses did not include treatment-related variables and thus did not test their effects.

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Compliance with ethical standards

The protocol was approved by the Ethics Committee of the Statutory Physician Board of the State of Rhineland Palatinate (Reference number 837.161.11.7703).

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

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