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ORIGINAL ARTICLE

Associations between cancer-related distress and fatigue in childhood cancer survivors: A longitudinal study

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Abstract

Background and Aims: A chronic feeling of fatigue occurs in up to 85% of childhood cancer survivors (CCS). This phenomenon has a detrimental effect on quality of life, reintegration in daily life activities and psychosocial functioning of the patient. Therefore, it is important to elucidate potential individual risk and protective factors.

Methods: CCS who were treated in the University Hospital of Leuven, completed two annual questionnaires on cancer-related distress (fear of cancer recurrence and post-traumatic stress, resilience and fatigue). Associations between distress and fatigue levels were examined by performing cross-lagged panel analyses. Resilience was included as a potential moderator. These models included all within-time associations, stability paths, and cross-lagged paths. Gender and time since diagnosis were included as covariates.

Results: In total, 110 CCS participated in this study, aged 14–25 years (average time since diagnosis 12.2 years; 41.8% boys; diagnosed with leukemia/lymphoma [49%], solid tumor [15%], brain tumor [16%] or other [20%]). Fear of cancer recurrence and post-traumatic stress at baseline positively predicted fatigue 1 year later. Cross-lagged panel analyses showed that resilience did not buffer the effect of fear of cancer recurrence on fatigue, in contrary to our expectations. Stability coefficients were high for all study variables.

Conclusion: This study indicates associations between cancer-related distress (fear of cancer recurrence and post-traumatic stress), resilience and cancer-related fatigue over time in CCS. Interventions to improve fatigue levels could be focusing on both tackling cancer-related distress, while improving resilience levels as well.

KEYWORDS
cancer, fatigue, longitudinal study, oncology, psycho-oncology, psychological distress, survivors of childhood cancer

1 | BACKGROUND

Over the past decades treatment for different types of pediatric cancer has improved tremendously, resulting in an increased survival rate estimated around 85% in 10-year survival.[1] Despite these increasing survival rates, the cancer and its treatment have an enduring impact later on in the child's life.[2] By the age of 26, 62% of childhood cancer survivors (CCS) experience at least one long term effect of the cancer and its treatment.[3] One of the most frequently reported late effects is a chronic feeling of fatigue. It occurs in up to 85% of children and adolescents after the completion of their cancer treatment.[4,5] Cancer-related fatigue is a type of chronic fatigue that is not proportional to recently performed activity and does not disappear with rest or sleep.[6] It has a detrimental effect on daily psychosocial functioning and quality of life of the patient.[7,8] The exact etiology of cancer-related fatigue is not yet known. It is hypothesized that cancer-related distress can sensitize the immune system, leading to elevated levels of low-grade chronic inflammation. Studies have shown that low-grade chronic inflammation lays at the base of "sickness behaviors" that can include cancer-related fatigue.[9] Fatigue is a subjective, dynamic and multifactorial symptom making it complicated to understand, monitor and predict.[10] Longitudinal studies are essential to acquire a better understanding of its risk factors and prevalence in survivorship. Studying risk and protective factors could help our understanding of why some survivors experience cancer-related fatigue, whereas others do not.

Factors that have been investigated in their association with cancer-related fatigue in CCS include demographic risk factors, treatment features and physical health features. Regarding treatment features, inconsistent results were found on whether the type of treatment (surgery, chemotherapy, radiotherapy or combination therapy) is associated with the severity and chronicity of fatigue in CCS. Multiple previous studies suggested that a history of chemotherapy or radiation therapy is related to more cancer-related fatigue,[11,12] but these findings were not consistently replicated.[13,14] Furthermore, higher levels of cancer-related fatigue were mainly found shortly after diagnosis.[15] Regarding demographic risk factors, the age of CCS seems to be associated with cancer-related fatigue as well. More specifically, adolescents and young adults show more severe cancer-related fatigue than older cancer survivors. The hypothesis is that these survivors are in a turbulent stage of their lives of finishing their studies, starting their first job, starting a relationship and possibly having children.[16] Regarding physical functioning, Kelada et al. (2019) and Rach et al. (2017) showed that decreased mobility, lower levels of physical activity, as well as pain, are associated with cancer-related fatigue.[17,18]

Besides the abovementioned treatment-related, physical, and demographic risk factors, we would expect that psychological risk factors also play an important role in cancer-related fatigue. Concerning mental health features associated with cancer-related fatigue, research today is increasing, but still scarce. Getting diagnosed with cancer is a major negative life event with an enormous impact. Hence, it is likely that the cancer diagnosis and its treatment are experienced by the patient as a traumatic event.[19] Besides post-traumatic stress that cancer survivors can experience after their cancer diagnosis and treatment, they also frequently report health- and cancer-related worries.[20] They can worry about developing other types of cancer or about cancer recurrence in the future.[21,22] This fear of cancer recurrence can have a substantial negative impact on psychological well-being and quality of life.[23,24] The post-traumatic stress can be interpreted as retrospective brooding about the past, while fear of recurrence can be interpreted as prospective worrying about the future. The impact of cancer-related distress (i.e. both post-traumatic stress and fear of cancer recurrence) can last for months or even years after treatment completion.[25] We investigated fatigue complaints in a longitudinal design, to determine to which extent fear of recurrence and post-traumatic stress predict these levels of fatigue.

We hypothesized a positive relation between cancer-related distress (post-traumatic stress and fear of cancer recurrence) and cancer-related fatigue. Furthermore, since it had been shown that cancer patients and survivors with higher resilience reported a better quality of life,[26] we wanted to examine the potential moderating role of resilience on the relationship between worrying behavior and cancer-related fatigue. Resilience can be conceptualized as a developmental process that encompasses an individual's capacity to adapt positively following significant adversity. It is a dynamic process that changes over time, influenced by neurobiological systems such as the hypothalamic–pituitary–adrenal axis and psychosocial systems,[27] and is known to have a positive effect on mental health, by reducing the risk of depression and anxiety in the general population.

2 | METHODS

2.1 | Design

The current study was part of a larger cohort study, the LInC-study: Longitudinal Identity study in CCS, approved by the Medical Ethics Committee of KU Leuven (Prikken et al. (2022)[28]).

After receiving a general information letter, CCS were contacted with the question whether they wanted to participate and receive the pen-and-paper questionnaires. They were asked to return the completed questionnaires and informed consent forms by post. For minors, parents were asked to give consent as well. Participants received the questionnaires at baseline (T0), 1 year later (T1) and 2 years later (T2) (up to March 2020). For this specific study, a fatigue questionnaire was added from the second assessment (T1) onwards.

2.2 | Participants

435 Dutch speaking CCS were invited to participate in this study, of whom 213 survivors agreed to participate. CCS who were diagnosed with any cancer type and treated during childhood (0–18) at the

University Hospital of Leuven in Belgium, aged 14–25, were included. Exclusion criteria included: mental retardation that hindered completion of the questionnaire bundle, being younger than 14 years and older than 25 years at the start of the study, being physically incapable to complete the questionnaire bundle and insufficient knowledge of Dutch language.

2.3 | Measures

Full details on all included questionnaires in the LInC-study were described previously (Prikken et al. (2022)[28]). To examine our objective, we focused on the assessment of fear of cancer recurrence, post-traumatic stress, resilience and fatigue at two timepoints with a 1-year interval (T1 and T2).

2.3.1 | Fear of cancer recurrence

The questionnaire, consisting of 4 items as described by Kypriotakis et al. (2016),[21] was used to measure fear of cancer recurrence in survivors at T1 and T2. Items were answered on a 5-point rating scale from 1 (Completely disagree) to 5 (Completely agree). Higher scores indicated more fear of cancer recurrence. Sum scores range between 4 and 20. Cronbach's α was 0.89 at T1 and T2.

2.3.2 | Post-traumatic stress

The Children's Revised Impact of Event Scale (CRIES-13) was used to estimate post-traumatic stress levels. This questionnaire consists of 13 items, as described by Perrin (2005),[29] measuring post-traumatic stress disorder symptoms in survivors. Items were answered on a 4-point rating scale from 1 (not at all) to 4 (often). Sum scores ranged between 0 and 65 with a cut-off score of 30. Cronbach's α were 0.88 at T1 and 0.89 at T2. Dutch version retrieved from http://www.childrenandwar.org/.

2.3.3 | Resilience

The Brief Resilience Scale was used to measure levels of resilience in survivors. This questionnaire consists of 6 items as described by Smith et al. (2008).[30] Items were answered on a 5-point rating scale from 1 (strongly disagree) to 5 (strongly agree). Sum scores ranged between 6 and 30. The total sum has to be divided by the total number of questions answered, with a score between 1.00 and 2.99 referring to low resilience, 3.00–4.30 average resilience and 4.31–5.00 high resilience. Our low resilience group contained 15 survivors, the average resilience group 66 survivors and the high resilience group 18 survivors. Cronbach's α were 0.88 at T1 and 0.92 at T2.

2.3.4 | Fatigue

Experiences of fatigue were explored by use of the Short Fatigue Form, a Dutch 4-item questionnaire as described by Alberts et al. (1997)[31]. Items were answered on a 7-point rating scale from 1 (no, that's not right) to 7 (yes, that's right). Sum scores ranged between 4 and 28. Higher scores reflect a higher level of fatigue. Cronbach's α was 0.87 at T1 and T2.

For each questionnaire (covering fear of cancer recurrence, resilience, post-traumatic stress and fatigue), sum scores were calculated at T1 and T2 as main variables of interest.

2.3.5 | Medical information

Information on cancer type and time since diagnosis was extracted from medical records.

2.4 | Statistical analysis

First, to prepare the data set, continuous variables were standardized and categorical variables were dummy-coded: gender (0 = male, 1 = female). Second, associations between study variables and background variables at T1 were explored in IBM SPSS Statistics v28, using Pearson correlations for continuous variables and MANOVAs for categorical variables. In survivors, associations were explored with gender and time since most recent diagnosis. Background variables that were significantly associated with study variables were included in further analysis. Third, to predict fatigue outcomes at T2 and correct for baseline features, cross-lagged analyses were performed. More specifically, the maximum likelihood estimation with robust Huber-White standard errors was applied. FIML was applied to account for missing data. The first model included fear of cancer recurrence (at T1 and T2), resilience (at T1 and T2), their interaction (a continuous interaction term at T1), and fatigue (at T1 and T2). The second model included post-traumatic stress (at T1 and T2), resilience (at T1 and T2), their interaction (a continuous interaction term at T1) and fatigue (at T1 and T2). Models included all within-time associations, stability paths, and cross-lagged paths. Demographic factors (i.e. gender and time since most recent diagnosis) which were significantly associated with study variables at baseline, were included as covariate in each model. The model fit was evaluated using the following indices: the χ^2 (i.e. as small as possible) yuan-bentler scaled, the Root Mean Square Error of Approximation (RMSEA) (i.e. RMSEA < 0.08), the Standardized Root Mean squared Residual (SRMR) (i.e. SRMR < 0.10), the Comparative Fit Index (CFI) (i.e. CFI > 0.90).[32] For the reviewer's interest, we do want to emphasize that cross-lagged models focus on rank-order changes (relative changes) instead of mean-level changes. The model corrected for baseline values of all included factors in the model. Simple slope analyses were performed in SPSS to investigate the differential

linear associations between cancer-related distress and fatigue for each resilience subgroup (i.e. low, moderate, high).

3 | RESULTS

3.1 | Sample characteristics

The longitudinal data of interest were available of 110 CCS (participation at T1 and/or T2). At T1, survivors' mean age was 20.77 (SD = 2.64). The average time since diagnosis was 12.15 years (minimum 3 years, maximum 23 years, SD = 5.38), 41.1% was male,. The survivors had been diagnosed with leukemia/lymphoma (49%), a solid tumor (15%), a brain tumor (16%) or another cancer type (20%).

The study variables and their correlations at T1 and T2 are summarized in Table 1, showing significant negative correlations between resilience and complaints of fatigue, fear of cancer recurrence and post-traumatic stress (T1/T2). No significant changes in complaints were detected between T1 and T2, using ANOVA for repeated measures.

Gender and time since most recent diagnosis were included in further analyses, as they were significantly associated with study variables. In survivors, gender was negatively correlated with time since most recent diagnosis ($r = -0.074$) and resilience ($r = -0.425$, $p < 0.01$). A MANOVA in SPSS showed significant differences between males and females on fear of cancer recurrence at T1 and T2 ($p = 0.003$ and $p = 0.023$), fatigue at T1 and T2 ($p = 0.021$ and $p = 0.004$) and resilience at T1 and T2 ($p < 0.001$ and $p = 0.002$). No significant differences were shown between males and females in post-traumatic stress at T1 and T2 ($p = 0.068$ and $p = 0.118$) and time since most recent diagnosis ($p = 0.528$). Females scored higher on fear of cancer recurrence (t [92] = −2.97, $p < 0.01$), fatigue (t [97] = −3.31, $p = 0.001$) and post-traumatic stress (t [96] = −2.04) than males, whereas males scored higher on resilience (t [96] = 4.59, $p < 0.001$) at T1. Time since most recent diagnosis was negatively correlated with gender at T1 ($r = -0.074$), fear of cancer recurrence at T1 ($r = -0.078$) and post-traumatic stress ($r = -0.061$) at T1. Correlations between study and background variables and t-test results for comparing study variables between males and females are shown in the supplementary materials (see Supplementary Tables S2–S4).

3.2 | Cross-lagged analysis

The cross-lagged models modeled both directions of effects: cancer-related distress at T1 predicting relative changes in fatigue at T2, and vice versa. The pathway from fatigue (T1) predicting relative changes in cancer-related distress (T2), however, was not significant.

3.2.1 | Fear of cancer recurrence, resilience and fatigue in survivors

The final cross-lagged model including fear of cancer recurrence, had a good fit (χ^2 [3] = 6.26, $p = 0.1$; RMSEA = 0.08; SRMR = 0.02; CFI = 0.99). Figure 1A shows high stability coefficients ($\beta = 0.77$, $p < 0.001$ for fear of cancer recurrence, $\beta = 0.82$, $p < 0.001$ for resilience). For fatigue the stability coefficient is moderately high ($\beta = 0.52$, $p < 0.001$). Baseline fear of cancer recurrence predicted relative increases in fatigue at T2, meaning that individuals with more fear of cancer recurrence at T1 experienced a larger increase in fatigue from T1 to T2 compared to individuals with lower fear at T1, while higher levels of baseline resilience predicted relative decreases in fatigue at T2. In Figure 1 only significant paths are shown. The interaction between fear of cancer recurrence and resilience was significant for the survivors ($\beta = 0.12$, $p = 0.03$). Simple slope analysis in SPSS confirmed a significant association between the fear of cancer recurrence and fatigue for average resilience ($\beta = 0.245$, $p = 0.017$) but not for low and high resilience (with $\beta = 0.939$, $p = 0.351$ and $\beta = 0.504$, $p = 0.170$ for the low and high resilience groups, respectively) (Figure 2A).

3.2.2 | Post-traumatic stress, resilience and fatigue in survivors

The final cross-lagged model including post-traumatic stress, had a good fit (χ^2 [3] = 2.33, $p = 0.507$; RMSEA = 0.00; SRMR = 0.03; CFI = 1.00). Figure 1B shows high stability coefficients ($\beta = 0.85$, $p < 0.001$ for post-traumatic stress, $\beta = 0.70$, $p < 0.001$ for resilience). For fatigue the stability coefficient is lower ($\beta = 0.49$, $p < 0.001$). Similar to the fear of cancer recurrence, baseline post-traumatic stress predicted relative increases in fatigue and

TABLE 1 Descriptive statistics and correlations within and between T1 and T2

	1	2	3	4	*M* (SD)	*r* (T1,T2)
1. Fear of cancer recurrence	1	0.607**/0.561**	−0.505**/−0.404**	0.427**/0.408**	2.18 (1.03)/2.21(1.08)	0.773**
2. Post−traumatic stress		1	−0.573**/−0.631**	0.494**/0.437**	0.90(0.62)/0.84(0.62)	0.864**
3. Resilience			1	−0.491**/−0.517**	3.45(0.84)/3.37(0.92)	0.810**
4. Fatigue				1	3.52(1.37)/3.64(1.43)	0.677**

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

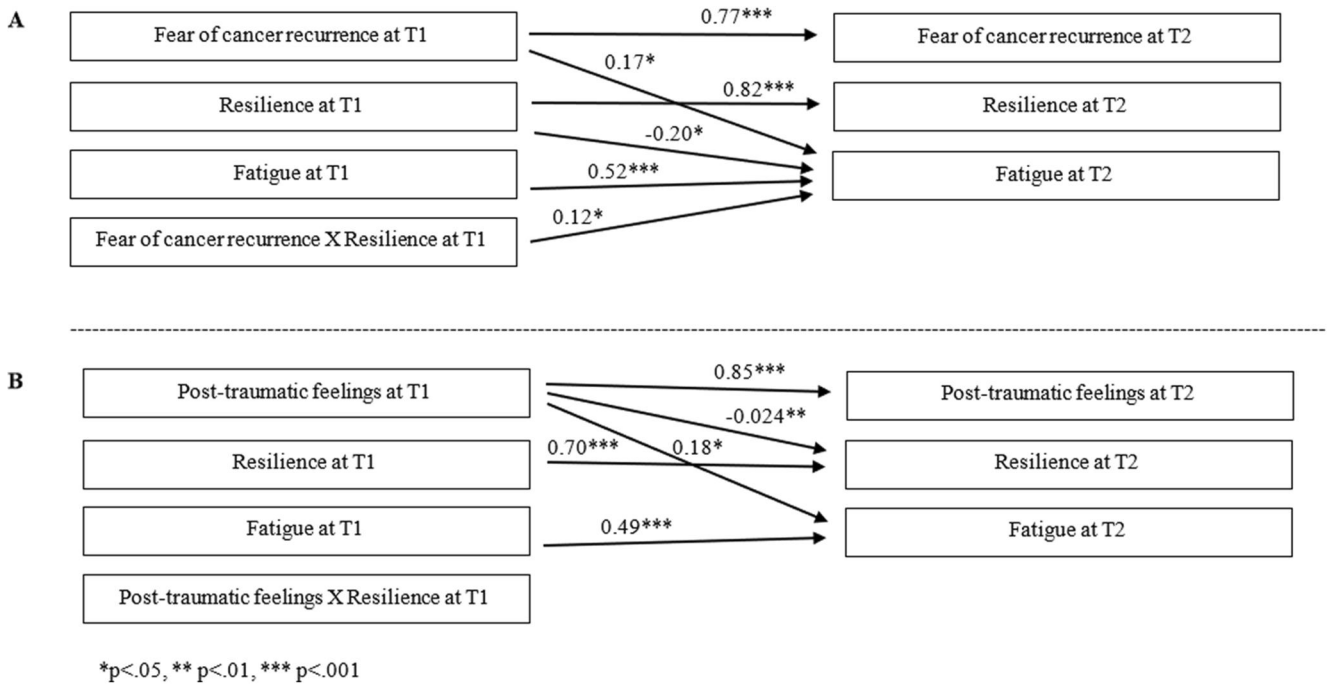

FIGURE 1 Cross-lagged models. (A) Cross-lagged model with fear of cancer recurrence. (B) Cross-lagged model with post-traumatic stress. Only significant cross-lagged paths are displayed. Covariates are not shown for reasons of clarity

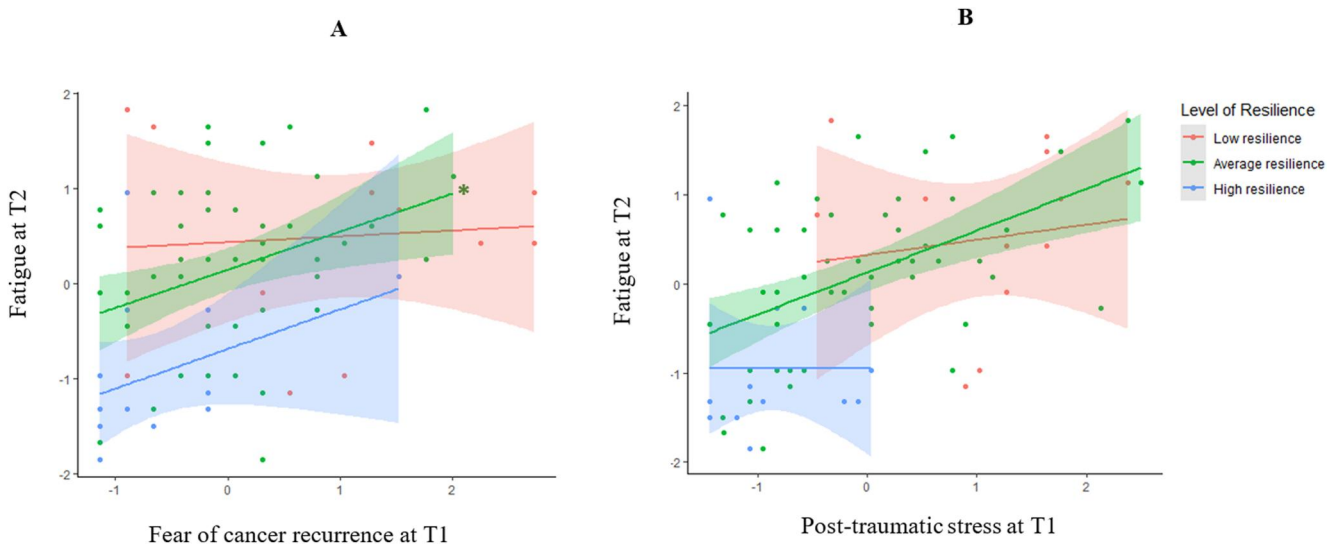

FIGURE 2 Interaction term effect. (A) Significant interaction between fear of cancer recurrence and fatigue with resilience as moderator. (B) No significant interaction between post-traumatic stress and fatigue with resilience as moderator. Standardized values. Low resilience (−1 SD), mean resilience, and high resilience (+1 SD). (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$)

resilience at T2. In Figure 1 only significant paths are shown. The interaction term between post-traumatic stress and resilience, however, was not significantly associated with fatigue levels. Simple slope analysis in SPSS confirmed no significant association between post-traumatic stress and fatigue for low resilience ($\beta = 0.222$, $p = 0.100$), average resilience ($\beta = 0.143$, $p = 0.132$) and high resilience ($\beta = 0.507$, $p = 0.202$) (Figure 2B).

4 | DISCUSSION

To our knowledge, this is the first longitudinal study examining the relationship between cancer-related distress (including fear of cancer recurrence and levels of post-traumatic stress), resilience and fatigue in CCS, and subsequently looking at resilience as a potential moderator in the relationship between cancer-related distress

(including fear of cancer recurrence and levels of post-traumatic stress) and fatigue.

The main findings in this cohort of CCS, showed that cancer-related distress predicted relative increases in fatigue over time, but fatigue did not predict relative changes in distress over time. Our findings support the earlier mentioned hypothesis about cancer-related distress causing low-grade chronic inflammation. However, this hypothesis requires more in-depth investigation. Higher levels of fear of cancer recurrence or post-traumatic stress at baseline both predicted relative increases in fatigue over time. These results are consistent with earlier findings of Öcalan et al. (2021)[33] in their recent cross-sectional study in adult cancer survivors. Any type of cancer diagnosis, seen as a major negative life event, can have an impact, resulting in high levels of rumination, which in turn can lead to fatigue. Furthermore, our results showed that CCS with higher levels of resilience reported lower levels of fatigue at the same timepoint and over time. These results are consistent with earlier findings of Zou et al. (2018)[34] in adult patients with gastric cancer.

Based on our main findings, we can conclude that interventions to reduce survivors' fear of cancer recurrence and post-traumatic stress and improve resilience, could directly help to reduce cancer-related fatigue. Screening for fear of cancer recurrence and post-traumatic stress during clinical follow-up, can make it possible to intervene early.[35] Concerning resilience, Shin et al. (2021) showed that courageous coping, spirituality, hope, family communication and social support were associated with higher levels of resilience among Korean adolescents and young adult survivors of childhood cancer.[36] Working on developing a strong social network, different coping strategies, communication and practicing meditation (mindfulness-based stress reduction) could be a first step in improving a patient's resilience.[37]

In addition to the associations our results showed between cancer-related distress and fatigue, we aimed to investigate whether cancer-related distress (fear of cancer recurrence and post-traumatic stress) differently affected CCS who showed higher or lower resilience levels compared to their peers. When looking at resilience as a possible moderator of the fear of cancer recurrence and post-traumatic stress on fatigue, our results showed a significant interaction between fear of cancer recurrence and resilience on fatigue. More specifically, our results showed a positive relation between fear of cancer recurrence and fatigue for survivors with average levels of resilience. For CCS with high or low resilience levels, our results did not show a prospective relation between the fear of cancer recurrence and fatigue (see Figure 2A).It seems that higher levels of resilience do not buffer the negative effect of the fear of cancer recurrence on fatigue, but they can have additive effects. A plausible explanation for the significant interaction effect, is that the interaction effect may be the consequence of a ceiling effect (as a statistical artefact) of the fatigue scores in our sample. More specifically: survivors with low levels of resilience already scored high on fatigue (see Figure 2A). Consequently, there was no margin left to score even worse, meaning that higher scores on the fatigue questionnaire simply did not occur in our sample.

Regarding demographic factors, females scored higher on the fear of cancer recurrence and post-traumatic stress, which might be the result of females being more prone to ruminative thinking in general.[38] Another possible explanation is that younger, female patients might experience more life challenges (i.e. sexuality, intimate relationships, job opportunities, household) years after their disease.[39] Furthermore, they also reported higher levels of fatigue. This can be explained by the positive relationships between more cancer-related distress (fear of cancer recurrence and post-traumatic stress) and cancer-related fatigue. We need to note that the distribution of males and females was unequal in our sample. Females were more motivated to participate in the study, possibly because females, experienced more long-term symptoms. In addition, males scored higher on resilience than females. Gender is not the only known factor contributing to a cancer patient's level of resilience. Other personal factors (i.e. age, family, employment status, household, income, education level, social support, religion and race), disease-related factors (i.e. stage, severity, treatment, comorbidity) and internal factors play an important role.[40] The exact interplay between these factors, however, remains to be elucidated.

4.1 | Study limitations

Several limitations have to be reported. First, this study only included Dutch speaking patients treated at the University Hospitals Leuven (Belgium). Hereby, the representativeness of the sample in terms of ethnic background may be impacted and participation bias cannot be excluded since the proportion of participating females was bigger than the proportion of participating males. It is also possible that only survivors experiencing more long-term effects than their average peer, participated. Second, the cross-lagged analyses' power may have been hampered by the relatively low response rate. Structural equation modeling in complex models (i.e. cross-lagged modeling) requires a sample size of >200.[32] Third, measurements were performed at two timepoints only, with an interval of 1 year. This allowed us to identify relatively long-term trends, but not daily variations. For future research we would recommend studying day-to-day fluctuations and inter-individual differentiation in these dynamics (i.e. using the experience sampling method). Fourth, future research should take other covariates into account as well, for example, age at diagnosis. Some survivors had cancer at a very young age (20% of survivors were diagnosed before the age of 3) and cannot remember their cancer diagnosis and treatment consciously, which can have a different effect on their worrying behavior later in life. Fifth, we only used self-report measures (questionnaires). Consequently, there could be a chance of recall bias and social desirability bias. In future research self-report measures should therefore be complemented by a wider set of multimodal measures (i.e. proxy-rated questionnaires, wearable devices, experience sampling method). Sixth, due to time restrictions the questionnaire to measure fatigue was the Short Fatigue Form, consisting of only four items. More extensive questionnaires (i.e. the PedsQL multidimensional fatigue scale) could provide insight into different more specific subdomains of fatigue (i.e. physical vs. mental fatigue).

4.2 | Future research and clinical implications

More research is needed to determine risk- and protective factors for cancer-related fatigue and map the dynamic evolution of cancer-related fatigue over time. In clinical practice, it is recommended to pay attention to CCS' cancer distress symptoms (fear of cancer recurrence and post-traumatic stress) and cancer-related fatigue. Focusing on improving survivors' resilience (developing a strong social network, working on different coping strategies, communication and practicing meditation), while keeping their cancer distress symptoms in mind on the one hand, and working on trauma and fear of cancer recurrence complaints, while keeping an eye on their resilience profile on the other hand, could contribute to reducing cancer-related fatigue.

5 | CONCLUSION

Our findings indicate association between cancer-related distress (fear of cancer recurrence and post-traumatic stress) as well as resilience and cancer-related fatigue over time in CCS. Higher levels of a survivor's resilience did not necessarily buffer the negative effects of fear of cancer recurrence and post-traumatic stress on fatigue. Consequently, interventions to improve fatigue levels could be focusing on both tackling cancer-related distress (fear of cancer recurrence and post-traumatic stress), while improving resilience levels as well. This information can help to tailor psychological counseling to individual risk profiles based on both factors.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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