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Symptom Clusters in 1330 Survivors of 7 Cancer Types From the PROFILES Registry: A Network Analysis

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BACKGROUND: Research into the clustering of symptoms may improve the understanding of the underlying mechanisms that affect survivors' symptom burden. This study applied network analyses in a balanced sample of cancer survivors to 1) explore the clustering of symptoms and 2) assess differences in symptom clustering between cancer types, treatment regimens, and short-term and long-term survivors. **METHODS:** This study used cross-sectional survey data, collected between 2008 and 2018, from the population-based Patient Reported Outcomes Following Initial Treatment and Long Term Evaluation of Survivorship registry, which included survivors of 7 cancer types (colorectal cancer, breast cancer, ovarian cancer, thyroid cancer, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma). Regularized partial correlation network analysis was used to explore and visualize the associations between self-reported symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) and the centrality of these symptoms in the network (ie, how strongly a symptom was connected to other symptoms) for the total sample and for subgroups separately. **RESULTS:** In the total sample (n = 1330), fatigue was the most central symptom in the network with moderate direct relationships with emotional symptoms, cognitive symptoms, appetite loss, dyspnea, and pain. These relationships persisted after adjustments for sociodemographic and clinical characteristics. Connections between fatigue and emotional symptoms, appetite loss, dyspnea, and pain were consistently found across all cancer types (190 for each), treatment regimens, and short-term and long-term survivors. **CONCLUSIONS:** In a heterogenous sample of cancer survivors, fatigue was consistently the most central symptom in all networks. Although longitudinal data are needed to build a case for the causal nature of these symptoms, cancer survivorship rehabilitation programs could focus on fatigue to reduce the overall symptom burden. ***Cancer* 2021;127:4665-4674**.

KEYWORDS: cancer, networks, symptoms, survivorship.

INTRODUCTION

Although only 1 in 5 cancer survivors lives in good health (ie, without cancer [treatment] complications or comorbid conditions),[1] the majority experience (long-term) sequelae from cancer or its treatment.[2] Commonly experienced symptoms include fatigue, feelings of depression or anxiety, pain, cognitive problems, and sleep difficulties.[2] To date, studies on symptoms in cancer typically focus on a single symptom as either a dependent variable or an independent variable.[3] However, patients rarely experience only 1 symptom at a time, and clustering of symptoms is common.[3-6] For example, there is evidence for a neuropsychological clustering of fatigue, depression, and sleep problems in cancer survivors.[7,8] Other common symptom clusters seen in cancer survivors include gastrointestinal symptoms (GI; ie, nausea, vomiting, and lack of appetite) and aerodigestive symptoms (ie, dyspnea, dysphagia, and cough).[8,9] Although the literature on factors involved in the development or persistence of single symptoms is elaborate, few studies have been conducted on antecedents of symptom clusters.[10]

To date, we know that older age, being female, and receiving chemotherapy are related not only to a higher prevalence of single symptoms but also to stronger clustering of symptoms.[11-13] However, previous studies have been conducted mostly shortly after or during treatment,[13] whereas clustering of long-term symptoms such as fatigue, cognitive

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impairments, and emotional problems may develop over time or persist for years after diagnosis and treatment.[14-16] Yet, there is little evidence about the underlying biological, behavioral, or psychological mechanisms of symptom clusters among cancer survivors. Research focusing on antecedents of symptom clusters across a variety of tumor types is needed to guide the identification of those prone to experiencing symptom burden, to uncover underlying mechanisms, and ultimately to improve the quality of life of patients with cancer. Network analysis is a relatively new method that provides a unique opportunity to assess and visualize symptom clusters as dynamic systems of mutually interacting symptoms[17] and to compare patterns of clustering between study populations.[18] This allows us to study symptoms in their full complexity[19] and can guide future research into the complex, underlying biophysiological mechanisms of symptom clusters.

We have aimed to 1) explore the clustering of symptoms in a large population-based sample of cancer survivors and 2) assess differences in symptom clustering among 7 cancer types (ie, colorectal cancer, breast cancer, ovarian cancer, thyroid cancer, chronic lymphocytic leukemia [CLL], Hodgkin lymphoma [HL], and non-Hodgkin lymphoma [NHL]) and treatment regimens by examining clusters of symptoms via network modeling.

MATERIALS AND METHODS

Study Design and Setting

This study is a secondary analysis of data from the Patient Reported Outcomes Following Initial Treatment and Long Term Evaluation of Survivorship (PROFILES) registry and the Netherlands Cancer Registry (NCR).[20] The PROFILES registry collects patient-reported outcomes of individuals diagnosed with cancer in the Netherlands, which can be linked with clinical data from the NCR.[20]

Study Population

The current study combined several cohorts from the PROFILES registry: survivors of colorectal cancer, thyroid cancer, breast cancer, ovarian cancer, HL, NHL, or CLL as the primary cancer.[21] Survivors were included between 2008 and 2018 with a primary cancer diagnoses (all cancer stages) between 1990 and 2016.[21] Eligible participants were ≥18 years old at their cancer diagnosis. In deliberation with their (former) attending specialist, patients were excluded if they were not able to complete a questionnaire (ie, because they had severe cognitive impairments, were too ill, or were not sufficiently fluent in Dutch). Ethical approval was obtained for all study samples separately from local Dutch certified medical ethics committees. For each participant, informed consent was obtained.

Data Collection

The data collection has been described previously.[20] In short, all cancer survivors were informed about the study via a letter from their (former) attending specialist. This letter contained an informed consent form and a secure link to a web-based informed consent form and an online questionnaire. Patients could return a postcard to request a paper and pencil questionnaire. In total, 66% of the survivors (5171 of 7811) who were invited to participate in one of the PROFILES cohorts completed a questionnaire (see the flowchart in Supporting Fig. 1). Nonparticipants in PROFILES were more often female and younger (<60 years) or older (>70 years), more often had a low socioeconomic status, had more comorbidities, and were more often more than 3 years from their diagnosis.[21]

Measures

Sociodemographic and clinical characteristics

Patients' marital status, educational level, and employment were self-reported. Clinical data were obtained from the NCR. Cancer stages were classified according to the TNM classification of malignant tumors,[22] the International Federation of Gynecology and Obstetrics classification[23] (ovarian cancer), or the Ann Arbor Code (HL, NHL, and CLL).[24] Primary treatment was classified as surgery, chemotherapy, and radiotherapy. The number of comorbidities was assessed with the adapted Self-Administered Co-Morbidity Questionnaire, which assesses 14 predefined conditions and 3 "other, please specify" conditions in the past 12 months (yes or no),[25] and they were summed and categorized as 0, 1 or >1 comorbidities.

Symptoms

Symptoms were measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30),[26] a 30-item questionnaire comprising 5 functional scales, a global quality-of-life scale, 3 symptom scales, and 6 single-symptom items. For the purposes of assessing symptom clusters, we included the EORTC QLQ-C30 symptom scales (ie, fatigue, pain, dyspnea, constipation, lack of appetite, diarrhea, and nausea/vomiting) together with the emotional and cognitive functioning scales measuring emotional and cognitive symptoms. The single-item scale for financial difficulties was excluded because it does not reflect

symptoms. We recoded the emotional and cognitive functioning scales so that higher scores were indicative of more emotional and cognitive symptoms. For the interpretation of mean scores, all scales were linearly transformed and scored from 0 to 100 in accordance with the manual,[26] with a higher score representing worse symptomatology. For network analyses, nontransformed ordinal data were used. Small sample sizes of cancer type–specific networks limited the possibility of including individual EORTC QLQ-C30 items as nodes.

Statistical Analyses

To ensure equal sample sizes between cancer types in the current study, which were needed to enable comparisons between networks, cohorts of 190 patients were randomly selected for each cancer type because this was the smallest cancer-type sample that was available to us (n = 190 for ovarian cancer). We used Floyd's ordered hash table algorithm for simple random sampling (PROC SURVEYSELECT in Statistical Analysis System, version 9.4).[27]

Descriptive analyses were performed. Regularized partial correlation network analyses with polychoric correlations suitable for ordinal data[19] were conducted to assess clustering of symptoms for the total sample (including and excluding covariates) and for each of the cancer types, treatment regimens (ie, chemotherapy and radiotherapy [yes or no]), and short-term and long-term survivors (<5 vs ≥5 years after diagnosis) separately. Each network model was a graphical representation of dependencies between variables; it was visualized by nodes representing variables and edges representing pairwise interactions.[28] The graphical lasso tuned with the extended Bayesian information criterion was used to create a sparse network; the hyperparameter γ was set at 0.5 to minimize spurious connections.[29] Age, sex, time since diagnosis, cancer type, chemotherapy, radiotherapy, and comorbidities were selected a priori as covariates.[30,31] Covariates were included in the total sample network model but not for subgroup networks because of variations between cohorts. To identify the symptoms that were most central in the network, centrality analyses were conducted. Centrality measures included strength (ie, the sum of all edge strengths to or from a node), betweenness (ie, based on the shortest path length connecting any 2 nodes), and closeness (ie, the inverse of all shortest path lengths between a node and all other nodes). The most central symptom was identified on the basis of the highest centrality coefficient. Bootstrapping (nBoots = 1000) was used to evaluate the stability of centrality measures.

To assess differences in network structure and strength between the cancer types, between treatment regimens, and between short-term and long-term survivors, network comparison tests were conducted. We calculated the global strength invariance (ie, the overall level of connectivity is equal across groups), the network invariance (ie, the overall structure of the network is equal across groups), and the edge strength invariance (ie, the edge strength of a specific edge is equal across groups).[18] Monte Carlo simulations were conducted to assess the post hoc statistical power of the network comparison tests conducted on the cancer-type networks, particularly to detect a given number of edge differences, with 190 observations and 10 nodes in each network. Networks were visualized with the layout (ie, position of nodes) fixed at the network of the total sample. Partial correlations between 2 nodes were considered small ($r = \pm 0.1$), medium ($r = \pm 0.3$), or large ($r = \pm 0.5$).[32]

Statistical analyses were conducted with R version 3.6.2 with the qgraph package[17] for network visualization, bootnet for stability analyses, and NetworkComparisonTest for network comparison tests.[18] One of the authors (K.V.D.) wrote the syntax for the Monte Carlo simulations of network comparisons tests (https://github.com/katrijnvandeun/NCTSimulations).

RESULTS

Sociodemographic and clinical characteristics of survivors by cancer type are described in Table 1.

Overall, the symptoms with the highest mean scores (0-100) were fatigue (mean, 27.1; SD, 25), insomnia (mean, 23.3; SD, 30), pain (mean, 18.3; SD, 25), cognitive symptoms (mean, 16.6; SD, 22), and emotional symptoms (mean, 16.3; SD, 20). The highest mean scores for insomnia (mean, 29.8; SD, 33) and cognitive symptoms (mean, 19.9; SD, 23) were found in breast cancer, the highest mean scores for pain (mean, 21.1; SD, 28) and constipation (mean, 12.8; SD, 22) were found in ovarian cancer, and the highest mean scores for diarrhea (mean, 10.9; SD, 22) were found in colorectal cancer (Table 2).

Overall Network

The partial correlation network models (Fig. 1) showed that in the total sample (n = 1330), fatigue had moderate connections with pain ($r = 0.30$), emotional symptoms ($r = 0.23$), cognitive symptoms ($r = 0.25$), appetite loss ($r = 0.20$), and dyspnea ($r = 0.33$). In addition, there were moderate to strong connections between appetite loss and nausea/vomiting ($r = 0.43$) and between cognitive and

TABLE 1. Sociodemographic and Clinical Characteristics of the Study Sample and by Cancer Type

	Total (n = 1330)	Colorectal (n = 190)	Breast (n = 190)	Ovarian (n = 190)	Thyroid (n = 190)	HL (n = 190)	NHL (n = 190)	CLL (n = 190)
Age at questionnaire, mean (SD), y	61 (15)	70 (9)	62 (10)	64 (12)	56 (15)	46 (16)	63 (14)	68 (11)
Sex, No. (%)								
Male	494 (37)	97 (51)	0 (0)	0 (0)	49 (26)	100 (53)	113 (59)	135 (71)
Female	835 (63)	93 (49)	190 (100)	190 (100)	141 (74)	89 (47)	77 (41)	55 (29)
Education, No. (%)								
Lower/primary education	164 (12)	32 (17)	10 (5)	31 (17)	23 (12)	13 (7)	26 (14)	29 (16)
Secondary education (high school)	336 (26)	59 (31)	49 (26)	50 (27)	40 (21)	42 (22)	46 (24)	50 (27)
Secondary vocational education	470 (36)	63 (34)	83 (44)	63 (34)	74 (39)	74 (39)	57 (30)	51 (27)
Higher (vocational) education, university	343 (26)	34 (18)	47 (25)	34 (18)	52 (28)	52 (28)	59 (31)	56 (30)
Employment, No. (%)								
Employed	410 (33)	25 (13)	71 (39)	45 (26)	94 (50)	98 (56)	47 (27)	30 (17)
Retired	525 (39)	124 (65)	78 (37)	37 (19)	48 (25)	30 (16)	88 (46)	120 (63)
Unemployed	29 (2)	4 (2)	9 (5)	4 (2)	1 (0)	4 (2)	4 (2)	3 (2)
Disabled	106 (8)	15 (8)	7 (4)	13 (7)	15 (8)	22 (12)	23 (12)	11 (6)
Marital status, No. (%)								
Married/living together	975 (74)	134 (71)	154 (81)	119 (64)	145 (76)	140 (74)	134 (71)	149 (79)
Single/divorced	343 (26)	54 (29)	35 (19)	67 (36)	45 (24)	49 (26)	54 (29)	39 (21)
Years from diagnosis, median (range)	4.2 (0-21)	4.8 (1.5-10.9)	3.10 (0.8-5.7)	5.7 (1.7-12.1)	8.2 (1.9-20.7)	3.4 (0.5-10.2)	2.8 (0.4-9.9)	2.4 (0.5-10.5)
Stage, No. (%)[a]								
I	464 (35)	55 (29)	90 (47)	110 (58)	116 (61)	33 (17)	54 (28)	6 (3)
II	340 (26)	64 (34)	81 (43)	21 (11)	32 (17)	99 (52)	35 (18)	8 (4)
III	227 (17)	60 (32)	19 (10)	48 (25)	30 (16)	35 (18)	29 (15)	6 (3)
IV	126 (13)	7 (4)	0 (0)	6 (3)	7 (4)	19 (10)	57 (30)	30 (16)
Unknown	173 (13)	4 (2)	0 (0)	5 (3)	5 (3)	4 (8)	15 (8)	140 (74)
Surgery, No. (%)[a]	761 (57)	181 (95)	190 (100)	189 (99)	189 (99)	1 (1)	8 (4)	3 (2)
Chemotherapy, No. (%)	624 (47)	55 (29)	86 (45)	129 (68)	0 (0)	179 (94)	135 (71)	40 (21)
Radiotherapy, No. (%)	493 (37)	49 (26)	148 (78)	2 (1)	132 (69)	111 (58)	47 (25)	4 (2)
Comorbidities, No. (%)								
0	396 (31)	47 (26)	67 (36)	60 (32)	44 (24)	91 (51)	50 (28)	37 (21)
1	378 (30)	50 (28)	67 (36)	46 (24)	58 (31)	48 (27)	53 (29)	56 (31)
≥2	504 (39)	83 (46)	52 (28)	82 (44)	83 (44)	40 (22)	77 (43)	87 (48)

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.
Percentages may not always add up to 100 because they have been rounded off to whole numbers.
[a]At the time of diagnosis. Tumor and treatment data at the time of study enrollment were unavailable.

TABLE 2. Mean Scores and SDs of EORTC QLQ-C30 Symptom Scales by Cancer Type

Symptom Scale (0-100)	Total (n = 1330)	Colorectal (n = 190)	Breast (n = 190)	Ovarian (n = 190)	Thyroid (n = 190)	HL (n = 190)	NHL (n = 190)	CLL (n = 190)
Fatigue	27.1 (25)	22.8 (24)	27.1 (26)	24.6 (25)	28.0 (25)	28.6 (28)	25.8 (24)	25.4 (27)
Insomnia	23.3 (30)	21.1 (29)	29.8 (33)	26.7 (31)	21.0 (28)	19.2 (28)	20.6 (28)	22.4 (32)
Pain	18.3 (25)	17.1 (24)	19.6 (24)	21.1 (28)	17.4 (24)	13.0 (23)	17.9 (25)	16.3 (25)
Cognitive symptoms[a]	16.6 (22)	15.8 (21)	19.9 (23)	15.3 (21)	18.9 (23)	17.4 (22)	15.5 (21)	13.9 (20)
Emotional symptoms[a]	16.3 (20)	14.5 (19)	18.1 (21)	17.0 (20)	16.8 (21)	17.8 (23)	13.3 (18)	13.0 (20)
Dyspnea	14.5 (24)	17.1 (27)	12.7 (23)	13.4 (25)	15.1 (22)	14.0 (24)	14.1 (23)	16.7 (25)
Constipation	9.3 (20)	6.8 (18)	9.1 (21)	12.8 (22)	8.9 (19)	6.2 (18)	7.8 (19)	7.6 (18)
Lack of appetite	7.5 (20)	5.7 (18)	7.3 (18)	7.1 (19)	6.0 (18)	6.3 (20)	6.7 (19)	8.5 (21)
Diarrhea	7.4 (18)	10.9 (22)	4.7 (14)	6.1 (18)	6.9 (17)	4.7 (13)	7.8 (18)	8.2 (21)
Nausea/vomiting	4.3 (13)	3.0 (9)	3.7 (12)	5.5 (15)	4.4 (12)	3.7 (11)	3.7 (11)	4.3 (14)

Abbreviations: CLL, chronic lymphocytic leukemia; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.
[a]These scales have been reversed; higher scores indicate more symptoms for all scales (range, 0-100).

emotional symptoms ($r = 0.29$). Weak connections were found between fatigue and nausea/vomiting ($r = 0.08$), between fatigue and sleep problems ($r = 0.15$), between pain and constipation ($r = 0.14$), between diarrhea and nausea/vomiting ($r = 0.14$), between diarrhea and pain ($r = 0.09$), and between nausea/vomiting and dyspnea ($r = 0.10$). After the addition of covariates to the network, the connections between fatigue and nausea/vomiting and between diarrhea and pain were no longer present (Fig. 1).

Cancer-Type Network Comparison

Monte Carlo simulations showed adequate statistical power to detect at least 1 edge difference between cancer-type networks (190 for each) in network comparison tests (Supporting Table 1). Network comparison tests showed that the structure of the breast cancer network was different from those of colorectal cancer ($P < .01$), ovarian cancer ($P < .01$), NHL ($P < .01$), and CLL ($P = .01$). This was mostly due to a connection between nausea/vomiting and appetite loss that was present in all cancer types ($r = 0.24$-0.65) but breast cancer. In addition, a direct connection between fatigue and nausea/vomiting found in breast cancer ($r = 0.26$) was not present in NHL ($P = .02$) or CLL ($P = .04$). Furthermore, the connection between fatigue and cognitive symptoms found in breast cancer ($r = 0.39$) was not present in CLL ($P = .03$), whereas the connection between fatigue and emotional symptoms was stronger in CLL than breast cancer ($r = 0.35$ vs $r = 0.15$; $P = .04$). Other differences between the cancer types were connections found between nausea/vomiting and diarrhea in ovarian cancer ($r = 0.34$) and HL ($r = 0.25$) but not in colorectal cancer ($P = .03$ and $P = .01$, respectively). Furthermore, NHL showed an additional connection between emotional symptoms and pain ($r = 0.19$) that was not found in colorectal ($P = .03$) or thyroid cancer ($P < .01$; Fig. 2).

Treatment Regimen Network Comparison

The network model of survivors who had received radiotherapy (n = 493) versus those who had not (n = 837) showed an additional connection between cognitive symptoms and appetite loss ($r = 0.15$; $P = .01$) and a stronger connection between fatigue and nausea/vomiting ($r = 0.13$ vs $r = 0.10$; $P = .04$). In contrast, the network of survivors who had not received radiotherapy showed an additional connection between nausea/vomiting and dyspnea ($r = 0.15$; $P = .04$) in comparison with the network of those who did. Similarly, survivors who had received chemotherapy (n = 624) showed the

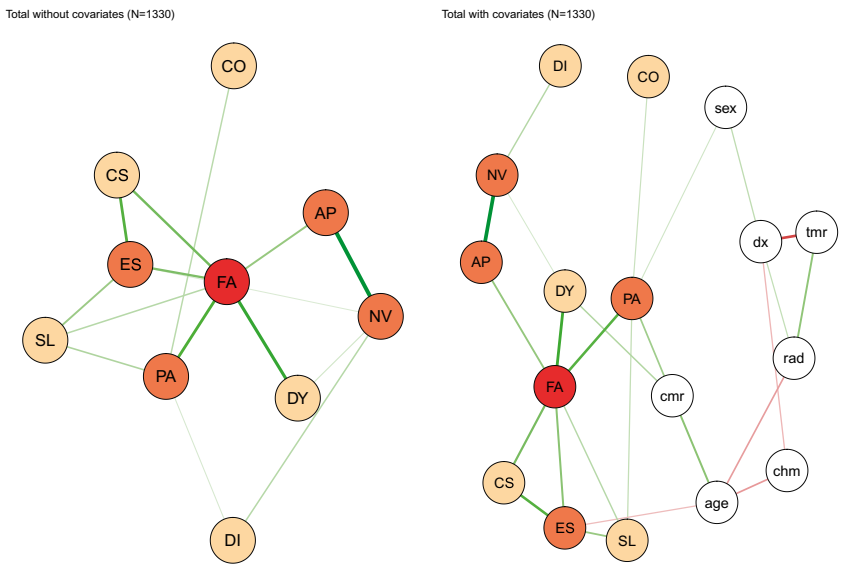

Figure 1. Symptom networks of the total sample (n = 1330) with and without covariates. A red node represents the highest node strength, an orange node represents node strength > 0, and a cream node represents node strength < 0. A green edge indicates a positive relationship, and a red edge indicates a negative relationship; thicker edges indicate stronger relationships. AP indicates appetite loss; chm, received chemotherapy; cmr, number of comorbidities; CO, constipation; CS, cognitive symptoms; DI, diarrhea; dx, time since diagnosis; DY, dyspnea; ES, emotional symptoms; FA, fatigue; NV, nausea/vomiting; PA, pain; rad, received radiotherapy; SL, sleep problems; tmr, tumor type.

same connection between nausea/vomiting and diarrhea ($r = 0.23$); however, survivors who had not received chemotherapy (n = 706) did not ($P = .04$; Fig. 3).

Short-Term and Long-Term Survivor Network Comparison

The network model of short-term survivors (<5 years; n = 797) versus long-term survivors (≥5 years; n = 531) showed stronger but not statistically different connections between fatigue and cognitive symptoms, emotional symptoms, appetite loss, dyspnea, and pain and an additional weak connection between pain and diarrhea ($r = 0.12$; $P = .04$). The network model of long-term survivors showed additional weak connections between emotional symptoms and appetite loss ($r = 0.13$; $P < .01$) and between sleep problems and diarrhea ($r = 0.13$; $P = .02$; Fig. 4).

Centrality Analyses

The results of our centrality analyses (see the supporting information including Supporting Table 2) indicated that on the basis of strength (ie, the sum of all edge strengths to or from a node), fatigue was the most central symptom in all of the networks (indicated in red in Figs. 1-4). Nodes with medium node strength (>0) were emotional symptoms, pain, appetite loss, nausea/vomiting, and sleep problems (indicated in orange in Figs. 1-3; see the supporting information).

DISCUSSION

In a heterogenous sample of survivors of 7 cancer types, our symptom network analyses provided evidence for a cluster of fatigue, pain, emotional symptoms, appetite loss, and dyspnea that was prevalent across all cancer types and treatment regimens and in short-term and long-term survivors. A cluster of GI symptoms including appetite loss, nausea/vomiting, dyspnea, and diarrhea was found only in survivors who had received chemotherapy and was, therefore, mainly present in survivors of ovarian cancer and HL and in short-term survivors.

Literature on the clustering of symptoms is limited, with much heterogeneity in the statistical analysis techniques used. As a result, there is little consistency in symptom clusters between studies.[8,10,33] The well-established cluster of fatigue, insomnia, and depression[7,8] was confirmed in our total sample. In the cancer type–specific networks, sleep problems were not consistently associated with emotional symptoms or fatigue, possibly because of the small sample sizes in the current study. Fatigue, sleep problems, and emotional symptoms were also directly or indirectly associated with cognitive symptoms and pain; this was previously defined as the psychoneurological symptom cluster and explained by common biological pathways, including increases in proinflammatory cytokines, disturbed

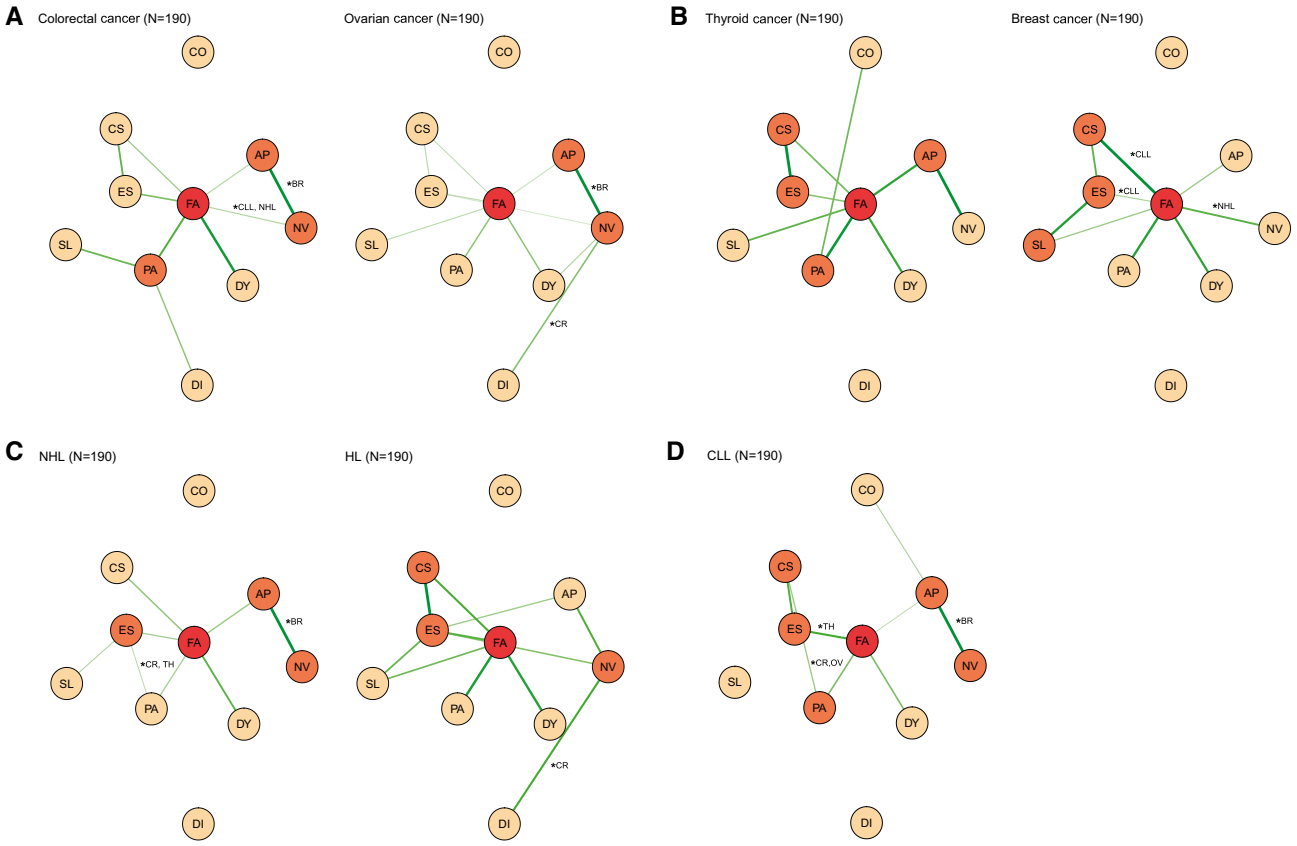

Figure 2. Symptom networks by cancer type. *P < .05 edge difference in network comparisons tests, compared with CR, BR, OV, TH, NHL, HL, or CLL. Note that only edge differences that are visible with the extended Bayesian information criterion parameter set to 0.5 are shown. A red node represents the highest node strength, an orange node represents node strength > 0, and a cream node represents node strength < 0. A green edge indicates a positive relationship, and a red edge indicates a negative relationship; thicker edges indicate stronger relationships. AP indicates appetite loss; BR, breast cancer; CLL, chronic lymphocytic leukemia; CO, constipation; CR, colorectal cancer; CS, cognitive symptoms; DI, diarrhea; DY, dyspnea; ES, emotional symptoms; FA, fatigue; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NV, nausea/vomiting; OV, ovarian cancer; PA, pain; SL, sleep problems; TH, thyroid cancer.

hypothalamic-pituitary-adrenal axis function, and monoamine neurotransmission imbalances.[34,35]

The association between cognitive symptoms and fatigue was notably strong in breast cancer survivors, possibly because 57% of the patients with breast cancer in this sample had received antihormonal therapy,[36] which is known to affect cognitive function and fatigue.[37] However, decreased cognitive function could alternatively be caused by fatigue.[35]

Breast cancer was the only cancer type in our analyses that presented no clustering of the GI symptoms appetite loss and nausea/vomiting, whereas these symptoms have previously been associated together in 3 of 5 studies in a review of symptom clusters in breast cancer.[33] This may be due to the timing of the questionnaire in our study (~3 years after cancer diagnosis), whereas these symptoms are most prominent during and immediately after chemotherapy.[33] Furthermore, the GI symptom constipation did not cluster with other GI symptoms in our analysis, possibly because of a different biological pathway (ie, chemotherapy-related autonomic dysfunction that results in a slowing down of gastric motility).[38] However, other mechanisms may explain the association of constipation and pain in thyroid cancer survivors; for example, many of these patients need lifelong hormone replacement therapy.[39]

Limitations

Our analyses included various cancer types and were based on a random selection of our population-based PROFILES cohorts[20]; therefore, our results are highly generalizable to survivor populations. Although we did not include information on nonparticipants in the current study, a previous publication has shown that the samples

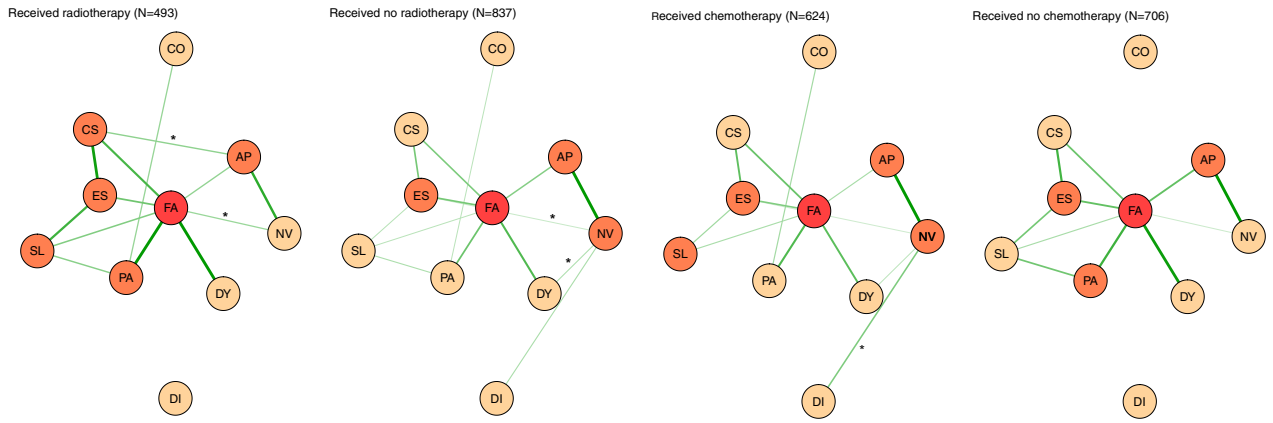

Figure 3. Symptom networks by treatment regimen. *P < .05 for edge differences in network comparison tests of chemotherapy versus no chemotherapy and radiotherapy versus no radiotherapy networks. AP indicates appetite loss; CO, constipation; CS, cognitive symptoms; DI, diarrhea; DY, dyspnea; ES, emotional symptoms; FA, fatigue; NV, nausea/vomiting; PA, pain; SL, sleep problems.

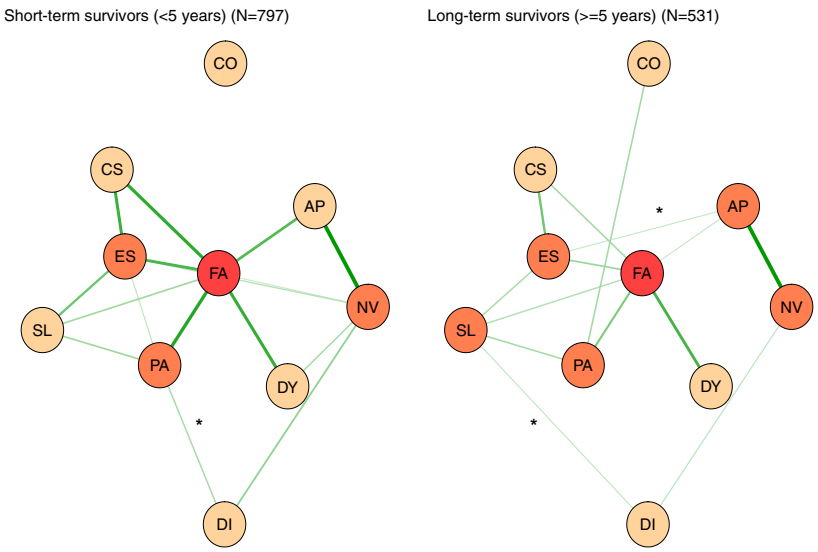

Figure 4. Symptom networks by a short (<5 years) or long term (≥5 years) from diagnosis. *P < .05 for edge differences in network comparison tests of networks for "chemotherapy" versus "no chemotherapy," and "radiotherapy" versus "no radiotherapy." AP indicates appetite loss; CO, constipation; CS, cognitive symptoms; DI, diarrhea; DY, dyspnea; ES, emotional symptoms; FA, fatigue; NV, nausea/vomiting; PA, pain; SL, sleep problems.

included in the current study may represent the healthier patient.[21] Furthermore, we could not account for changes in symptom experience over time because of our cross-sectional analysis and the heterogeneity of time since diagnosis within our cohorts. In addition, we did not have information on whether the reported symptoms were attributable to the cancer, treatments, or comorbidities. Repeated sampling of the symptom experience, preferably using intensive longitudinal data obtained through experience sampling,[40] could reveal individual changes in the symptom burden and provide evidence for the causality of symptom clustering. Second, we could not account for covariates in our cancer type–specific networks because they were not consistently applicable across cancer types,

as network comparison tests are possible only when all variables (nodes) in the networks are identical.[18] However, covariates did not change the clustering of symptoms in the total sample and were, therefore, not expected to heavily affect our subgroup networks. Third, no data were available with regard to disease status (ie, metastasis or recurrence) at the time of the questionnaire, although it is known that disease status, including the treatment phase, is related to experiencing symptoms or clustering thereof. Hence, clustering of symptoms may differ across phases of the cancer trajectory.[16] Although our sample is heterogenous in this respect, the high consistency of findings across survivor groups suggests that symptoms cluster, regardless of disease status. However, the stratification of short-term and long-term survivors by the time since the primary cancer diagnosis rather than disease status may have diluted the differences between these groups. Longitudinal research starting shortly after diagnosis is warranted to study individual changes in symptom clustering over time. Furthermore, the sparsity of the networks is sensitive to the sample size, and this results in less sparse networks of the cancer type–specific networks in comparison with the larger group networks. However, the consistency of the network structures between smaller and larger sample sizes suggests that the findings are rather stable and independent of the sample size. In addition, small sample sizes of cancer type–specific networks limited the possibility of including individual EORTC QLQ-C30 items as nodes. Therefore, a more detailed examination of symptoms is warranted in future research to gain insights into differential mechanisms of individual symptoms.

Future Directions

Although previous methods applied in symptom cluster research, such as path analysis, principal components analysis, and common factor analysis,[10,14] assume that symptoms cluster because of a common underlying factor, network analysis provides a more dynamic approach with the assumption that symptoms cluster because they mutually interact.[19] The only exception is hierarchical cluster analysis, which, though most often applied to group patients who are similar according to a predefined set of symptoms, also allows us to assess the clustering of symptoms in a population based on correlations similarly to network analysis.[41] However, the visualization of correlations as similarity measures in hierarchical cluster analysis (ie, a dendrogram) is less flexible in showing pairwise correlations between all symptoms in a cluster and in minimizing spurious correlations. Therefore, network analysis provides a unique opportunity to study symptoms in their full complexity.[19] Although associations between single symptoms and underlying mechanisms have been increasingly reported, our network analyses provide evidence on multiple interrelated symptoms that may share underlying pathophysiological mechanisms, such as accelerated aging,[42] increased levels of inflammation, or disruption of the hypothalamic-pituitary-adrenal axis.[34,35] In addition, our symptom networks suggest that the symptom burden among cancer survivors persists through the mutual reinforcement of symptoms in a cluster. An increased understanding of the mechanisms involved in symptom clusters could provide directions for future treatment of multiple symptoms at the same time to reduce the overall symptom burden in cancer survivors.

In conclusion, our finding that fatigue is consistently central (ie, most strongly connected to other symptoms) in a cluster with pain, emotional symptoms, appetite loss, and dyspnea, across various cancer types and treatment regimens, suggests that fatigue could be an important target for reducing the overall symptom burden in cancer survivors. Even though patterns of causality may be highly individual, if mutual connectedness of symptoms is assumed, interventions targeting fatigue may reduce multiple other symptoms through negative feedback loops via other connected symptoms. Moreover, knowledge of symptom clusters as a whole and the identification of central symptoms shed light on possible underlying pathophysiological and behavioral mechanisms.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Belle H. de Rooij: Conceptualization, funding acquisition, methodology, writing of the manuscript, and formal analysis. **Simone Oerlemans:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Katrijn van Deun:** Conceptualization, funding acquisition, methodology, writing of the manuscript, and formal analysis. **Floortje Mols:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Kelly M. de Ligt:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Olga Husson:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Nicole P. M. Ezendam:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Meeke Hoedjes:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Lonneke V. van de Poll-Franse:** Conceptualization, funding acquisition, methodology, and writing of the manuscript. **Dounya Schoormans:** Conceptualization, funding acquisition, methodology, writing of the manuscript, supervision, and formal analysis.

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