Higher Levels of Acute and Chronic Stress are Associated with Worse Morning and Evening Fatigue Profiles in Oncology Patients Receiving Chemotherapy

Kord M. Kober, PhD
University of California, San Francisco

Christine Miaskowski, RN, PhD
University of California, San Francisco

Fay Wright, RN, PhD
New York University

Background

- Cancer-related fatigue is the most common symptom associated with cancer and its treatment.
- CRF has a negative impact on patient's ability to tolerate treatments and on their quality of life.
- Oncology patients receiving chemotherapy (CTX) rarely experience a single symptom.
- While stress has significant negative effects on physical and emotional well-being, little is known about the effects of stress on fatigue severity

Background

- Fatigue is an adaptive response to acute stress to conserve energy and maintain homeostasis.
- With repeated stressful events or cumulative exposure to stressful life events, the autonomic nervous system (ANS) and hypothalamic-pituitary axis (HPA) experience increased allostatic load which results in increased levels of fatigue.
- Patients' perceptions of stress and their use of adaptive or maladaptive coping strategies may influence fatigue severity during CTX.
- Higher self-reported levels of perceived stress were associated with higher levels of fatigue in previous studies.

Study Purposes

In a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of CTX that were previously categorized into subgroups identified with distinct profiles of morning and evening fatigue using latent profile analysis (LPA), the purposes were to:

- Evaluate for differences between subgroups in the subjective measures of acute and chronic stress.

Design and Methods

- This study is part of a larger, longitudinal study.
- Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.
- Inclusion criteria:
  - ≥18 years of age
  - Diagnosis of breast, GI, GYN, or lung cancer
  - Received CTX within the preceding four weeks
  - Scheduled to receive at least two additional cycles of CTX
  - Able to read, write, and understand English
  - Gave written informed consent
- Patients (n = 1331) completed study questionnaires in their homes, a total of six times over two cycles of CTX.

Timing of the Assessments

- Prior to CTX administration (i.e., recovery from previous cycle - assessments 1 and 4)
- ~1 week after CTX administration (i.e., acute symptoms – assessments 2 and 5)
- ~2 weeks after CTX administration (i.e., potential nadir, assessments 3 and 6)

Lee Fatigue Scale (LFS)

- 18-items designed to assess physical fatigue and energy.
- Each item was rated on a 0 to 10 numeric rating scale.
- LFS score was calculated as the mean of the 18 items.
- Using separate LFS questionnaires, patients rated each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue) and prior to going to bed (i.e., evening fatigue).
- Clinically meaningful levels of fatigue are ≥3.2 for morning fatigue and ≥5.6 for evening fatigue
- The LFS has well-established validity and reliability and is easy to administer. In this study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue.

Life Stressor Checklist-Revised (LSC-R)

- 30-items designed to assess lifetime exposure to stressful, potentially traumatic events.
- LSC-R total score was obtained by summing the number of events endorsed and can range from 0 (no events) to 30 (all events).
- For each event that was endorsed, patients indicated how much that stressor affected their live **in the past year** and ranged from 1 (“not at all”) to 5 (“extremely”)
- LSC-R “affected” score the average of these responses
- The LSC-R has good to moderate test-retest reliabilityand good criterion-related validity with diverse populations.

Perceived Stress Scale (PSS-14)

- 14-items designed to measure global perceived stress over the **previous four weeks**.
- Each item was rated on a 0 (never) to 4 (very often) numeric rating scale.
- 7 of the 14 items are considered negative and 7 are considered positive
- PSS-14 total score can range from 0 (lower stress) to 56 (greater stress).
- The PSS has well-established validity and reliability. In the current study, the Cronbach's alpha for the PSS total score was 0.85.

Impact of Event Scale-Revised (IES-R)

- 22-items designed to measure cancer-related stress in response to specific potentially traumatic events.
- Each item was rated on how stressful each potential traumatic event was for them in the past on a 0 (not at all) to 4 (extremely) numeric rating scale.
  - Three subscales (i.e.., intrusion, avoidance, and hyperarousal)
- IES-R total score was the sum of the subscale and ranges from 8 to 88 (>33 represents probable PTSD, >37 suggests high levels of PTSD)
- The IES-R has well-established validity and reliability. In the current study, the Cronbach's alpha for the IES-R total score was 0.91.

Impact of Event Scale-Revised (IES-R) Subscales

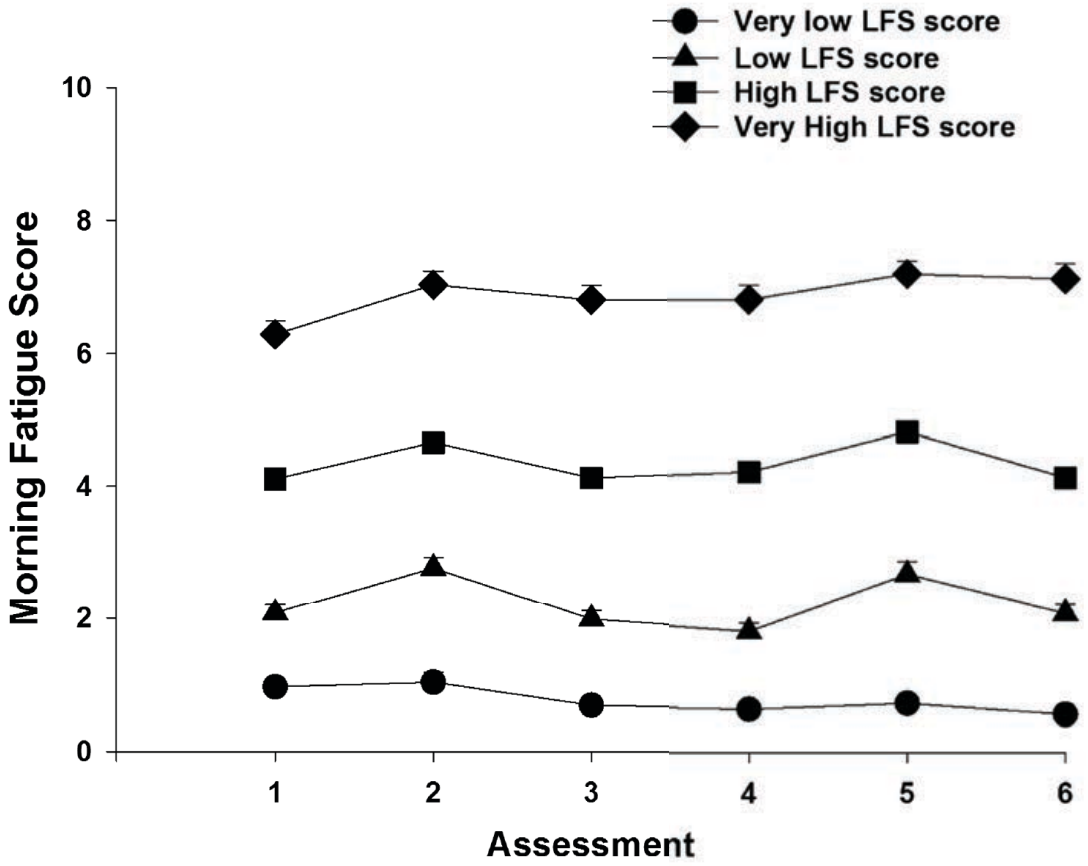
- Intrusion is the degree to which the patient's awareness of their cancer diagnosis negatively impacts their daily life.
- Avoidance is the degree the patient tries to avoid thinking about their cancer diagnosis.
- Hyperarousal is feeling vigilant and on guard.

Data Analysis

- LPA previously identified the profiles of morning and evening fatigue that characterized unobserved groups (i.e., latent classes) of patients over the six assessments.

- Differences in the demographics, clinical, stress characteristics were evaluated using analysis of variance (ANOVA), Kruskal-Wallis, or Chi-square test.

Changes in Morning Fatigue Over Six Time Points



Differences in Demographics – Morning Fatigue

Characteristics	Very Low (0) n=261 (19.6%)	Low (1) N=403 (30.2%)	High (2) n=528 (39.6%)	Very High (3) n=141 (10.6%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age 0 and 1 > 2 and 3	**59.8 (10.9)**	**58.8 (12.8)**	**55.3 (12.5)**	**54.6 (11.5)**
	% (n)	**% (n)**	**% (n)**	**% (n)**
Female 1, 2 and 3 > 0; 2 > 1	**65.5 (171)**	**76.4 (308)**	**83.7 (442)**	**83.0 (117)**
Married or Partnered 0 and 1 > 2 and 3	**73.9 (190)**	**68.8 (274)**	**58.8 (306)**	**54.7 (76)**
Lives Alone 2 and 3 > 0; 3 > 1	**14.4 (37)**	**19.0 (76)**	**23.7 (123)**	**33.6 (47)**
Currently employed 1 > 3	**37.5 (96)**	**39.1 (156)**	**33.4 (175)**	**25.7 (36)**
Annual household income **Less than $30,000** **$30,000 to $70,000** **$70,000 to $100,000** **Greater than $100,000** 3 > 0, 1, and 2; 2 > 1	 **13.3 (29)** **20.6 (45)** **20.2 (44)** **45.9 (100)**	 **11.9 (43)** **21.3 (77)** **14.1 (51)** **52.8 (191)**	 **20.1 (97)** **22.0 (106)** **18.7 (90)** **39.2 (189)**	 **38.2 (50)** **18.3 (24)** **13.0 (17)** **30.5 (40)**
Childcare responsibilities NS post-hoc contrasts	**17.3 (44)**	**19.5 (77)**	**25.3 (131)**	**27.0 (37)**

Differences in Clinical Characteristics – Morning Fatigue

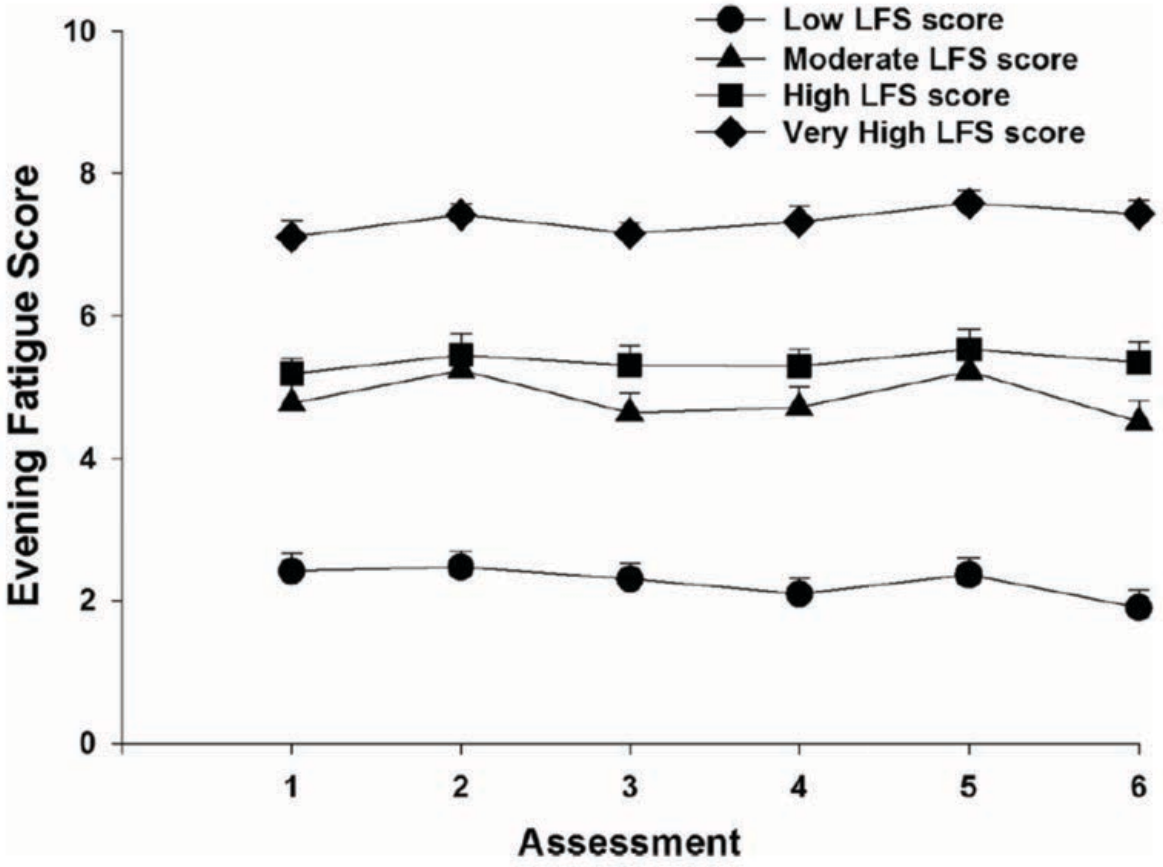
Characteristics	Very Low (0) n=261 (19.6%)	Low (1) N=403 (30.2%)	High (2) n=528 (39.6%)	Very High (3) n=141 (10.6%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BMI 0 and 1 < 3	**25.6 (4.8)**	**26.0 (5.3)**	**26.3 (5.8)**	**27.6 (7.2)**
KPS score 0 > 1 > 2 > 3	**86.3 (11.3)**	**83.1 (11.3)**	**76.9 (11.7)**	**70.7 (12.1)**
SCQ score 0 and 1 < 2 and 3; 2 < 3	**4.5 (2.6)**	**5.0 (2.7)**	**5.9 (3.2)**	**7.3 (4.3)**
Hemoglobin, g/dL 0 > 1 and 2	**11.8 (1.4)**	**11.5 (1.4)**	**11.5 (1.4)**	**11.5 (1.5)**
Hematocrit, % 0 > 1 and 2	**35.4 (4.1)**	**34.4 (4.2)**	**34.3 (4.0)**	**34.4 (4.5)**
	% (n)	**% (n)**	**% (n)**	**% (n)**
Exercise on a regular basis 3 < 0, 1, and 2	**77.6 (201)**	**75.6 (298)**	**68.9 (357)**	**50.8 (67)**
Cancer diagnosis				
Breast 1 and 2 > 0	**31.4 (82)**	**41.9 (169)**	**43.8 (231)**	**40.4 (57)**
Gastrointestinal 0 > 1, 2, and 3	**44.4 (116)**	**27.8 (112)**	**25.6 (135)**	**29.1 (41)**
Gynecological NS	**13.8 (36)**	**18.1 (73)**	**18.6 (98)**	**18.4 (26)**
Lung NS	**10.3 (27)**	**12.2 (49)**	**12.1 (64)**	**12.1 (17)**

Wright et al., Cancer Nursing 2018

Differences in Stress Measures For Morning Fatigue

Instrument	Very Low (0) 261 (19.6%)	Low (1) 403 (30.2)	High (2) 528 (39.6%)	Very High (3) 141 (10.6%)	Statistic; p-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
LSC-R Affected	8.71 (8.59)	9.64 (9.25)	13.4 (11.4)	19.3 (14.7)	F=25.8, <0.001 0 and 1 < 2 < 3
LSC-R Total score	5.22 (3.62)	5.39 (3.44)	6.41 (4.12)	8.48 (4.63)	F=17.9, <0.001 0 and 1 < 2 < 3
Perceived Stress Scale score	13.5 (6.21)	16.5 (7.14)	20.6 (7.61)	26.0 (8.34)	F=111, <0.001 0 < 1 < 2 < 3
IES-R Avoidance mean subscale score	.73 (.59)	.91 (.64)	1.01 (.67)	1.25 (.79)	F=20.5, <0.001 0 < 1 < 2 < 3
IES-R Intrusion mean subscale score	.56 (.52)	.76 (.56)	1.04 (.74)	1.48 (.82)	F=70.8, <0.001 0 < 1 < 2 < 3
IES-R Hyperarousal mean subscale score	.30 (.38)	.48 (.46)	.80 (.68)	1.31 (.86)	F=104, <0.001 0 < 1 < 2 < 3
IES-R Total score (≥33)	12.0 (9.27)	16.3 (10.3)	21.2 (13.4)	29.9 (15.9)	F=75.3, <0.001 0 < 1 < 2 < 3

Changes in Evening Fatigue Over Six Time Points



Differences in Demographics – Evening Fatigue

Characteristics		Low (0) n=186 (14.0%)	Moderate (1) n=230 (17.2%)	High (2) n=479 (36.0%)	Very High (3) n=437 (32.8%)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years) 0 > 1, 2, and 3; 2 > 3		**61.4 (11.6)**	**57.0 (12.5)**	**57.2 (12.5)**	**55.0 (11.9)**
Education (years) 1 < 3		**15.9 (3.3)**	**15.8 (2.9)**	**16.2 (3.0)**	**16.5 (3.0)**
		% (n)	**% (n)**	**% (n)**	**% (n)**
Female 0 and 2 < 1 and 3		**68.3 (127)**	**82.6 (190)**	**72.9 (349)**	**84.9 (371)**
Ethnicity					
White	0 & 1 < 2 & 3	**59.0 (108)**	**59.6 (134)**	**71.3 (338)**	**77.1 (334)**
Black	0 > 2 & 3; 1 > 2	**12.0 (22)**	**11.6 (26)**	**4.9 (23)**	**5.5 (24)**
Asian or Pacific Islander	0, 1 & 2 > 3	**16.9 (31)**	**16.0 (36)**	**13.7 (65)**	**7.6 (33)**
Hispanic Mixed or Other	NS	**12.0 (22)**	**12.9 (29)**	**10.1 (48)**	**9.7 (42)**
Annual household income					
Less than $30,000		**19.4 (31)**	**19.5 (41)**	**18.0 (76)**	**17.8 (71)**
$30,000 to $70,000		**23.8 (38)**	**25.7 (54)**	**22.0 (93)**	**16.8 (67)**
$70,000 to $100,000		**18.8 (30)**	**20.0 (42)**	**14.5 (61)**	**17.3 (69)**
Greater than $100,000 1 > 3		**38.1 (61)**	**34.8 (73)**	**45.5 (192)**	**48.3 (193)**
Childcare responsibilities (% yes) 0 < 3		**14.6 (27)**	**19.4 (43)**	**20.8 (97)**	**28.4 (122)**

Differences in Clinical Characteristics – Evening Fatigue

Characteristics	Very Low (0) n=261 (19.6%)	Low (1) N=403 (30.2%)	High (2) n=528 (39.6%)	Very High (3) n=141 (10.6%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
KPS score 0 > 1, 2 and 3; 1 and 2 > 3	**85.7 (11.9)**	**80.8 (12.7)**	**80.7 (12.0)**	**76.4 (12.1)**
SCQ score 0 < 2 and 3	**4.7 (2.8)**	**5.3 (3.1)**	**5.5 (3.0)**	**5.9 (3.5)**
	% (n)	**% (n)**	**% (n)**	**% (n)**
Cancer diagnosis				
Breast 0 < 1, 2, and 3	**26.3 (49)**	**43.0 (99)**	**39.5 (189)**	**46.0 (201)**
Gastrointestinal 0 > 1, 2, and 3	**46.8 (87)**	**26.1 (60)**	**30.5 (146)**	**25.6 (112)**
Gynecological NS	**15.1 (28)**	**18.3 (42)**	**17.1 (82)**	**18.3 (80)**
Lung NS	**11.8 (22)**	**12.6 (29)**	**12.9 (62)**	**10.1 (44)**

Differences in Stress Measures For Evening Fatigue

Instrument	Very Low (0) 261 (19.6%)	Low (1) 403 (30.2)	High (2) 528 (39.6%)	Very High (3) 141 (10.6%)	Statistic; p-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
LSC-R Affected	8.18 (6.81)	12.0 (10.3)	10.7 (9.82)	14.8 (13.5)	F=12.5, p<0.001 0 and 1 and 2 < 3, 0<1
LSC-R Total score	5.07 (3.28)	5.91 (3.69)	5.59 (3.92)	7.10 (4.3)	F=10.7, p<0.001 0 and 1 and 2 < 3
Perceived Stress Scale score	14.1 (7.12)	17.2 (8.14)	18.2 (7.25)	21.4 (8.5)	F=41.5, p<0.001 0 < 1 and 2 and 3, 0 and 1 and 2 < 3
IES-R Avoidance mean subscale score	.82 (.67)	.96 (.64)	.96 (.67)	.98 (.70)	F=2.65, p<0.047 0<3
IES-R Intrusion mean subscale score	.60 (.57)	.83 (.68)	.91 (.66)	1.08 (.78)	F=21.3, p<0.001 0 < 1 and 2 and 3, 0 and 1 and 2 < 3
IES-R Hyperarousal mean subscale score	.36 (.42)	.59 (.64)	.63 (.58)	.85 (.78)	F=26.0, p<0.001 0 < 1 and 2 and 3, 0 and 1 and 2 < 3
IES-R Total score (≥33)	13.4 (10.4)	17.8 (12.5)	18.8 (12.3)	21.7 (14.6)	F=17.7, p<0.001 0 < 1 and 2 and 3, 0 and 1 and 2 < 3

Conclusions – Morning Fatigue

Four distinct Morning Fatigue classes (Very Low (19.6%), Low (30.2%), High (39.6%), Very High (10.6%)) were evaluated.

General Stress

- Patients had higher PSS associated with increasing MF class (i.e. Very High>High>Low>Very Low).

Cumulative Life Stress

- Patients in the Very High and High Morning Fatigue classes reported higher LSC-R Affected and LSC-R total scores compared to the Low and Very Low classes.

Cancer-Specific Stress

- Patients had higher IES-R subscale and total scores associated with increasing MF class (i.e. Very High>High>Low>Very Low).

Conclusions – Evening Fatigue

Four distinct Evening Fatigue classes (Low (14.0%), Moderate (17.2%), High (36.0%), Very High (32.8%)) were evaluated.

General Stress

- Patients in the Very High Evening Fatigue class had significantly higher PSS compared to the Moderate and High classes.

Cumulative Life Stress

- Patients in the Very High Evening Fatigue class had significantly higher LSC-R Affected subscale and total scores compared to the Moderate and High classes.

Cancer-Specific Stress

- Patients in the Very High Evening Fatigue class had significantly higher IES-R Intrusion, Hyperarousal, and total scores compared to the Moderate and High classes.

Limitations

- Sample was predominately:
  - Female
  - White
  - College educated
  - Had metastatic disease
- Patients were not recruited prior to initiation of CTX
- Patients received various CTX regimens at different frequencies (14-, 21-, 28-day cycles)
- Our study included only subjective measures of morning and evening fatigue and acute and chronic stress

Implications for Practice

- Stress in oncology patients should be assessed throughout the continuum of CTX (i.e., before, during, and after treatment).
- Clinicians who care for oncology patients receiving CTX need to perform an in-depth assessment of stress and common co-occurring symptoms to identify high-risk patients.

Implications for Research

- Future longitudinal studies should enroll patients prior to the initiation of CTX and follow them to the completion of CTX.
- Additional research is needed to evaluate for interactions between coping strategies and whether their impact on stress are associated with higher levels of fatigue.
- More studies are warranted to evaluate the efficacy of specific interventions to improve stress throughout the continuum of CTX.
- Studies are warranted to evaluate for molecular characteristics (e.g., epigenetic) associated with fatigue and stress.

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Co-Directors:

Christine Miaskowski, RN, PhD, FAAN - Chris.Miaskowski@ucsf.edu

Sandra J. Weiss, RN, PhD, DNSc FAAN - Sandra.Weiss@ucsf.edu

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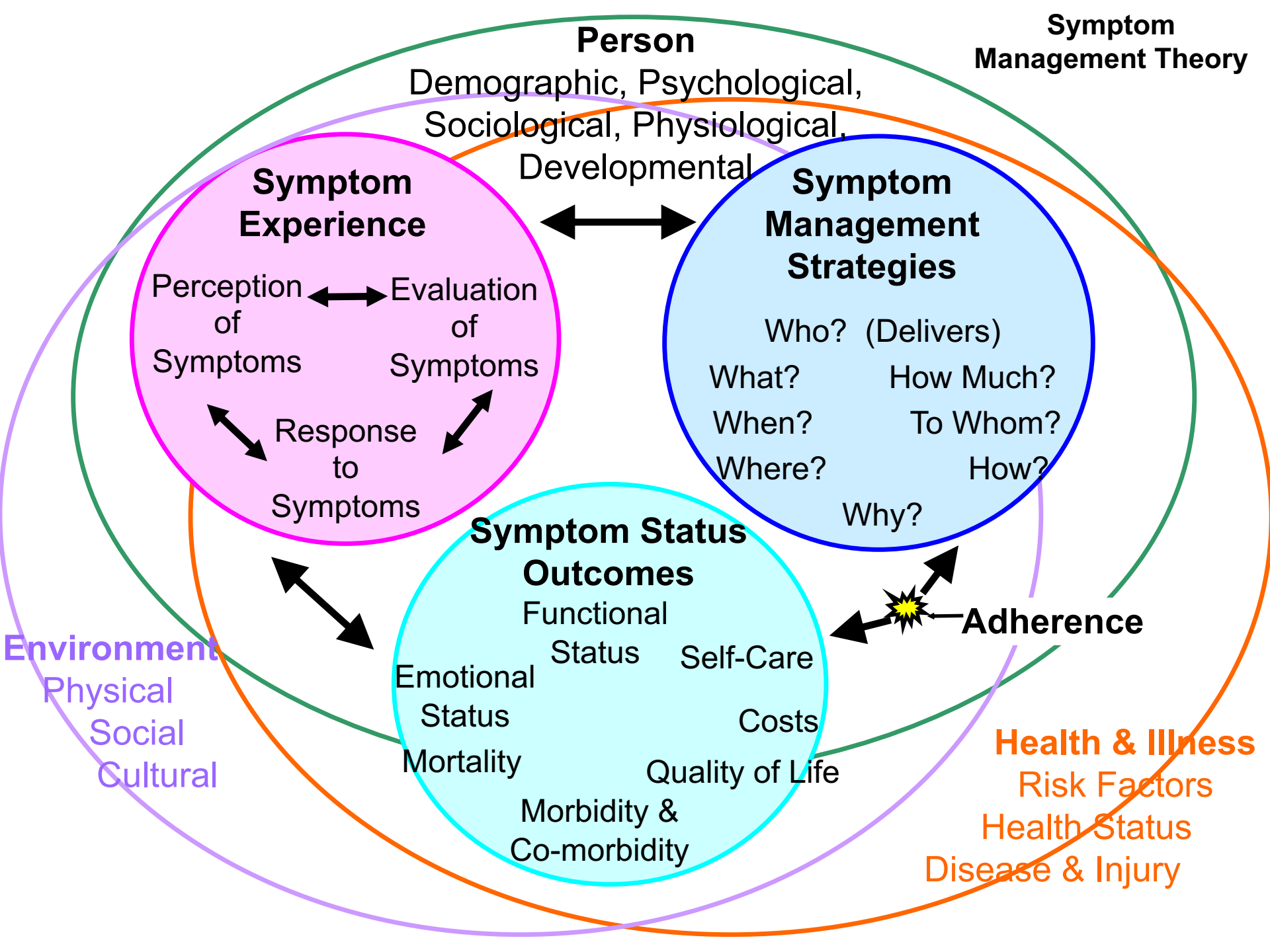
Surplus Materials


Symptom Management Theory
Person
Demographic, Psychological, Sociological, Physiological, Developmental
Symptom Experience
Perception of Symptoms
Evaluation of Symptoms
Response to Symptoms
Symptom Management Strategies
Who? (Delivers)
What?
How Much?
When?
To Whom?
Where?
How?
Why?
Symptom Status Outcomes
Functional Status
Self-Care
Emotional Status
Costs
Mortality
Quality of Life
Morbidity & Co-morbidity
Adherence
Environment
Physical
Social
Cultural
Health & Illness
Risk Factors
Health Status
Disease & Injury

Design and Methods

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- Inclusion criteria:
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  - Received CTX within the preceding four weeks
  - Scheduled to receive at least two additional cycles of CTX
  - Able to read, write, and understand English
  - Gave written informed consent

Study Procedures

- Written informed consent was obtained from all patients.
- Patients (n = 1331) completed study questionnaires in their homes, a total of six times over two cycles of CTX.

- ❑ **Demographic questionnaire**
- ❑ **Karnofsky Performance Status (KPS)**
- ❑ **Self-Administered Comorbidity Questionnaire (SCQ)**
- ❑ **Lee Fatigue Scale (LFS) (morning energy, evening energy)**
- ❑ **Life Stressor Checklist-Revised (LSC-R)**
- ❑ **Perceived Stress Scale (PSS-14)**
- ❑ **Impact of Event Scale-Revised (IES-R)**
- ❑ **Medical records were reviewed**

This is the current working location.