QUALITY OF LIFE AMONG NON-HODGKIN'S LYMPHOMA SURVIVORS

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ABSTRACT

SOPHIA SMITH: Quality of Life among non-Hodgkin's Lymphoma Survivors
(Under the direction of Sheryl Zimmerman, PhD)

Most of the survivorship research to date has been based on the more common types of cancer (e.g., breast, prostate), yet less is known about the quality of life (QOL) of survivors of adult non-Hodgkin's lymphoma (NHL), the sixth most common cancer in the US with an individual lifetime risk of 1 in 50. Therefore, the purpose of this dissertation is to develop a QOL profile of this heterogeneous group of adult NHL survivors. More specifically, the dissertation aims are to: 1) develop prevalence estimates and identify risk factors for PTSD symptomatology in 886 survivors of adult NHL, with a particular focus on potentially modifiable factors (e.g., social support, cognitive appraisals); 2) evaluate whether PTSD and PTG help to explain the role of risk factors in relating to QOL in NHL survivors, thereby enhancing our understanding of the cancer experience so that processes can be targeted for intervention; and 3) compare and contrast the QOL of individuals who reported having active NHL to those who were disease-free short-term (2-4 years post-diagnosis; STS) and long-term (≥5 years post-diagnosis; LTS) survivors. These aims are consistent with the "Cancer Survivorship Research and Quality of Life Act of 2002", federal legislation introduced by the Lance Armstrong Foundation and a bipartisan Congressional group to expand research and quality of life programs for cancer survivors. Finally, given the recent advances in cancer therapies with the

associated transition of cancer to a chronic illness with alternating periods of disease and remission, as is increasingly the case with NHL, this dissertation study also provides a window into the diverse needs of cancer survivors in general. Funding for this dissertation study was provided by the National Cancer Institute (#R03-CA-101492), the American Cancer Society Doctoral Training Grant in Oncology Social Work (#DSW-0321301-SW), and the University of North Carolina at Chapel Hill (University Research Council award).

DEDICATIONS

This dissertation is dedicated to my dad, Nicholas George Kustas, who fueled my eagerness to assist and serve others through his own passion for medicine. It is also dedicated to my husband, Erle Alan Smith, for his unwavering support, encouragement and confidence in me.

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TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

CHAPTER 1

Introduction

The National Cancer Institute[1] now estimates that there are 10.8 million cancer survivors in the US, a size equivalent to the population of Los Angeles, CA and representing about 3.7 percent of the population. Coinciding with this growing population is an increased interest in the quality of life (QOL) of individuals living with a cancer diagnosis. Research studies suggest that long-term survivors who were diagnosed and treated for one of the more common forms of adult cancer report similar QOL to that of the general population,[2-5] but many experience specific difficulties such as sexual dysfunction,[4,6,7] energy level and fatigue,[2,8,9] and post-traumatic stress disorder (PTSD).[10-13] Conversely, a recent focus has emerged on the positive outcomes or post-traumatic growth (PTG) associated with the cancer experience, such as greater appreciation for life, closer personal relationships, and deeper spiritual understanding.[7,14,15]

Most of the above research has been based on breast and prostate cancer survivors, yet less is known about the QOL of survivors of adult non-Hodgkin's lymphoma (NHL), the sixth most common cancer in the US with an individual lifetime risk of 1 in 50. NHL is a heterogeneous group of cancers of the lymphatic system with an overall 5-year survival rate of 50-60%; mortality varies greatly depending on the cell type, stage of disease at the time of diagnosis, and treatment. Indolent lymphomas generally carry a good prognosis (with a median survival of 10 years) but a high rate of relapse, and are usually not curable in advance stages. Treatment plans for the indolent forms include periods of watchful waiting, radiation therapy and chemotherapy. In contrast, many individuals who convert to or present with aggressive forms of NHL can be cured (30-60%) with intensive chemotherapy

regimens but the disease has a shorter natural history, with the greatest risk of relapse within 2 years of treatment cessation.[16]

The incidence rates of NHL have doubled since the early 1970's, partly because of AIDS-related NHL and improved methods of diagnosis. Over the next few years, the increasing average age of the American population together with the growing number of medical advances are expected to add to the incidence rates of NHL.[17] Consequently, and since the number of cancer survivors in the US is rapidly increasing, health care teams would benefit from evidence regarding the needs of this population so that interventions can be designed to improve their overall functioning and QOL. Therefore, the purpose of this dissertation is to develop a QOL profile of this heterogeneous group of adult NHL survivors.

More specifically, the dissertation aims are to: 1) develop prevalence estimates and identify risk factors for PTSD symptomatology in 886 survivors of adult NHL, with a particular focus on potentially modifiable factors (e.g., social support, cognitive appraisals); 2) evaluate whether PTSD and PTG help to explain the role of risk factors in relating to QOL in NHL survivors, thereby enhancing our understanding of the cancer experience so that processes can be targeted for intervention; and 3) compare and contrast the QOL of individuals who reported having active NHL to those who were disease-free short-term (2-4 years post-diagnosis; STS) and long-term (≥5 years post-diagnosis; LTS) survivors. These aims are consistent with the "Cancer Survivorship Research and Quality of Life Act of 2002", federal legislation introduced by the Lance Armstrong Foundation and a bipartisan Congressional group to expand research and quality of life programs for

cancer survivors. Finally, given the recent advances in cancer therapies with the associated transition of cancer to a chronic illness with alternating periods of disease and remission, as is increasingly the case with NHL, this dissertation study also provides a window into the diverse needs of cancer survivors in general.

Funding for this dissertation study was provided by the National Cancer Institute (#R03-CA-101492), the American Cancer Society Doctoral Training Grant in Oncology Social Work (#DSW-0321301-SW), and the University of North Carolina at Chapel Hill (University Research Council award). Approval for all procedures was granted by the Institutional Review Boards at the UNC and Duke Schools of Medicine. Potential study subjects (≥19 years old, diagnosed with NHL, at least 2 years post-diagnosis) were identified through the Duke and University of North Carolina (UNC) Lineberger Comprehensive Cancer Center Tumor Registries and contacted by mail following physician approval. Prospective participants were sent an introductory letter signed by their physician, a self-administered questionnaire which contained several QOL measures, a $2 bill incentive, and thank-you/reminder postcards. Non-respondents were sent replacement mailings and followed up by telephone to confirm receipt of the survey packet. A total of 886 NHL survivors participated, representing a response rate of 74%.

Each of the three chapters (2-4) included in the dissertation correspond with the three aims described above. For example, the purpose of the second chapter, entitled “Post-traumatic Stress Outcomes in Non-Hodgkin’s Lymphoma Survivors”, is to estimate the prevalence of and identify the risk factors for PTSD symptoms in NHL survivors, with a focus on those that are amenable for screening and

modifiable. The prevalence (adjusted for survey non-response) for full PTSD in the sample was 7.9%, with an additional 9.1% meeting criteria for partial PTSD and 39% overall having some level of PTSD symptomatology. Modifiable risk factors that were independently associated with PTSD in a multiple linear regression included less social support, negative appraisals of life threat and treatment intensity, and more employment and insurance issues. Additionally, several demographic characteristics (non-Caucasian race, less education, younger age) and clinical or health-related factors (active disease, more recent diagnosis, more co-morbidity) were independently associated with PTSD.

The third chapter, entitled "The Mediating Role of Cancer-related Trauma Outcomes on Quality of Life", examines how PTSD and PTG might intervene between (i.e., mediate the relationship between) demographic, clinical, health status, and psychosocial stressors (i.e., risk factors) and QOL in cancer survivors. Structural equation modeling (SEM) was used to evaluate competing models in which risk factors were conceptualized as having either direct or indirect (through PTSD and PTG) relationships to QOL. The conceptual models used in this analyses and throughout the dissertation study are based on the information processing[18,19] and stress, coping, and adaptation theories.[20,21] Information processing helps to explain how one's life schema is disrupted by the cancer experience, and how individuals who are able to assimilate or accommodate the life threat into existing schemas are more likely to experience positive outcomes, such as PTG. Conversely, negative outcomes such as PTSD can be explained by stress, coping and adaptation theories, which explain how the stress entailed with a cancer diagnosis and

subsequent treatment may overwhelm an individuals ability cope, as the stressors are appraised as exceeding one's resources and endangering well-being. SEM results revealed that QOL was best explained by the conceptual model in which the relationships of risk factors (e.g., lower social support and education) were partially mediated by PTSD and PTG (RMSEA=.072, CFI=.868, TLI=.865). Furthermore, this model explained a sizable amount of the variance (82%) in QOL for NHL survivors.

The fourth chapter, entitled "Quality of Life among Non-Hodgkin's Lymphoma Survivors", presents a QOL profile of this heterogeneous group of cancer survivors, including a comparison between those who have reported having active disease and being in remission or cured (short-term, 2-4 years, STS; long-term, ≥5 years post-diagnosis, LTS). As expected, those with active disease were found to have poorer QOL than disease-free survivors. By contrast, no statistically significant differences were found in QOL between STS and LTS, and in fact mean differences were no greater than 5% on any measure. Given the recent advances in cancer therapies with the associated transition of cancer to a chronic illness with alternating periods of disease and remission, as is increasingly the case with NHL, this chapter also provides a window into the diverse needs of cancer survivors in general.

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CHAPTER 2

Post-traumatic Stress Outcomes in Non-Hodgkin's Lymphoma Survivors

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INTRODUCTION

A growing body of evidence suggests that the experience of being diagnosed with and treated for cancer, regardless of age, adversely affects functioning and quality of life. However, less is known about the longer-term effects (two years post-diagnosis and beyond) of cancer on survivors' well-being, especially adults with other than breast cancer. Of note, little is known about the needs of individuals diagnosed with non-Hodgkin's lymphoma (NHL), which is the sixth most common cancer in the US and has an overall 5-year survival rate of 63%.

NHL incidence rates have doubled since the early 1970's, an increase that is only partially explained by AIDS-related NHL. The lifetime risk for developing NHL is about 1 in 50, with older adults (median age of 66) at highest risk.[1] Consequently, and since the number of survivors in the US is rapidly increasing due to both medical advances that treat other conditions and the aging of the population, healthcare teams would benefit from evidence regarding the needs of NHL survivors. If indicated, interventions could be provided to improve their well-being.

Cancer-related Traumatic Stress

Post-traumatic Stress Disorder (PTSD) is a set of symptoms (re-experiencing, avoidance, and arousal) following direct exposure to a traumatic stressor where the individual is involved in, witnesses, or learns about threatened death or serious injury. Symptoms of PTSD such as re-experiencing distressing events, avoiding cancer-related experiences, and physiological arousal have been reported by breast cancer survivors, with prevalence estimates ranging from 5-6%[2-5]. Unfortunately, little data are available regarding PTSD in other adult cancers.

A conceptual model for cancer-related PTSD is illustrated in Figure 2.1, in which the cancer diagnosis and associated events such as treatment and general health status are conceptualized as stressors. Demographic characteristics and psychosocial resources relate to the stressors, and these three sets of variables can directly or indirectly influence PTSD. This model is based on Lazarus and Folkman's[6] stress, appraisal and coping theory, which emphasizes the relationship between the person (his/her characteristics) and his/her environment (cancer experience). Of note, cancer-related PTSD differs from more traditional traumas in that the intrusions tend to be future-oriented fears such as about recurrence or treatment. The model reflects risk factors identified in previous studies of adult cancer survivors, including younger age;[7] female gender, negative perceptions of treatment intensity;[8] lower income;[2] less social support and education;[3] and less time since treatment and advanced disease.[4] This paper presents prevalence estimates and risk factors for PTSD, with a particular focus on potentially modifiable factors.

METHODS

Participants and Procedures

Potential study participants were identified through Tumor Registries at the Duke and University of North Carolina at Chapel Hill (UNC) Lineberger Comprehensive Cancer Centers. Patients were eligible if they were diagnosed with NHL, were at least 19 years at diagnosis, and were at least two years post-diagnosis, whether or not they had currently active disease. Each patient's physician granted approval before the researchers requested patient participation. Approval for all procedures was granted by the Institutional Review Boards at the UNC and Duke

University Schools of Medicine. Based on Dillman's method for mailed surveys,[9] prospective subjects were sent a brief pre-notice letter, a self-administered questionnaire with a $2 bill incentive and other study-related materials, and thank-you/reminder postcards. Non-respondents were sent replacements and later telephoned to confirm receipt of the mailed survey packet.

Measures

Demographic and Clinical Characteristics

Self-reported participant demographic information included birthdate, gender, race, ethnicity, marital status, income, and education. Details regarding diagnosis and treatment were obtained from Tumor Registry databases. Histology was categorized as indolent or aggressive based on the updated Revised European American Lymphoma/World Health Organization (REAL/WHO) classification system.[10]

Health Status

The Self-administered Co-morbidity Questionnaire (SCQ), a 12-item self-report version of the Charlson Index, was used to assess other health-related problems.[11] An individual can receive up to 3 points for each of 12 medical conditions (1 point each for presence of the problem, current treatment, and functional limitation). Selected questions related to healthcare use and secondary cancer status were adapted from the Childhood Cancer Survivor Study survey, a large epidemiological study of long-term survivors of childhood cancer.[12]

Psychosocial

Perceived availability of social support was assessed using the 20-item Medical Outcomes Study-Social Support Survey (MOS-SSS).[13] It has been used in various

populations, including long-term breast cancer survivors.[3,14] The standardized score ranges from 20-100 and yielded an α=.97 in this study. The Appraisal of Life Threat and Treatment Intensity Questionnaire (ALTTIQ) assesses the extent to which cancer and its treatment are perceived to be life-threatening and intense in the past and currently.[15] Its six items sum to a score ranging from 6-30 and yielded an α=.80 in the present study. Finally, to assess employment and insurance-related situations and difficulties, 24 items (possible range 0-24, α=.82) were derived from an instrument developed by the Cancer and Leukemia Group B (CALGB) clinical research group.[16] Examples include "I did not change jobs for fear of losing health insurance" and "I was encouraged to leave my job" because of the cancer.

Post-traumatic stress

The PTSD Checklist-Civilian Version (PCL-C) assesses symptomatology in non-combat populations by presenting a self-report symptom checklist that closely mirrors criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders, IV (DSM-IV) for a formal diagnosis of PTSD.[17,18] The instructions were modified so that symptoms were keyed to the particular traumatic stressor of interest; specifically, survivors were asked to rate each PTSD symptom in the past 4 weeks with respect to their diagnosis and treatment for lymphoma. Each of 17 symptoms is rated with respect to intensity on a scale of 1=not at all to 5=extremely bothersome, and item scores are summed to create a total that can range from 17-85. Two approaches were used to identify PTSD: 1) the cut-off method, in which those with scores ≥ 44 are classified as having PTSD;[19] and 2) the symptom cluster method, which follows the DSM-IV criteria for PTSD in that individuals who report

having been at least moderately bothered by (score ≥3) one or more re-experiencing symptoms (of 5; e.g., nightmares), three or more avoidance symptoms (of 7; e.g., evading follow-ups), and two or more arousal symptoms (of 5; e.g., easily startled), are classified as having PTSD.[17] Using the PCL-C cut-off of 44, Blanchard et al.[19] reported a sensitivity of 0.94 and specificity of 0.86 with the Clinician Administered PTSD Scale (CAPS). In other work, the PCL-C demonstrated an α=.97, test-retest reliability of .96, and convergent validity of .93 with the Mississippi Scale in a sample of 123 Vietnam veterans.[18] In this study, the total score yielded an α=.91, and the subscales produced the following internal consistency: re-experiencing α=.88, avoidance α=.82, and arousal α=.78.

Statistical methods

To assure that the PTSD prevalence estimates reflected the Tumor Registry sampling frame, sample prevalence estimates were adjusted for non-response based on race (African American, non-African American), as well as current age and age at diagnosis (in twenty-year increments). While the dataset overall had a small amount of missing data, the level of missingness in three variables, income (10.6%), stage (13.5%), and disease status (10.9%), justified multiple imputation via the Markov chain Monte Carlo (MCMC) algorithm.[20] All variables in the conceptual model were included in the MCMC algorithm, but imputed values for the outcome variable (PCL-C) were not generated. Twenty datasets containing imputed values were used in the multiple linear and logistic regression analyses and standard errors adjusted for imputation were estimated in the SAS MIANALYZE procedure.[21] Bivariate analyses compared mean levels of PCL-C for those with and without a

given potential risk factor using t-tests and ANOVA. Pearson correlations were calculated between the PCL-C and all continuous independent variables. Multiple linear regression was used to estimate the independent associations between candidate variables and the continuous PCL-C score; logistic regression was used to estimate the associations of the same variables with meeting criteria for full or partial PTSD, as defined by the symptom cluster method. Variables were selected for inclusion in the multivariable models if they were at least marginally significant (P<.10) in bivariate analyses. Data management and bivariate analyses were carried out with SPSS Version 14.0. Multiple imputation and multivariable analyses were conducted using SAS Version 9.1.3.

RESULTS

Of the 1312 eligible survivors who were mailed a survey, 117 (9%) of the packages were returned undelivered and tracing attempts were unsuccessful. Of the remaining 1195 survivors who were assumed to have received a survey, 886 (74%) completed and returned their surveys, 258 (22%) did not respond, and 51 (4%) refused participation. Sample bias analyses using demographic information from the registries indicated that participating survivors were less frequently African American (10% vs. 20%, P<.001), older at study enrollment (mean age 62.9 vs. 58.8 years, P<.001), and older at diagnosis (52.6 vs. 48.1 years, P<.001) than non-participants. The 868 survivors who completed the PCL-C were included in further analyses. The sample characteristics are listed in Table 2.1. A similar number of females and males participated, 14% were non-Caucasian, 25% earned less than $30,000 annually, 38% had a college degree, and 40% were employed. Mean age at study

enrollment was 63 and almost half (46%) were older adults (≥ 65 years of age). The majority of subjects reported having received chemotherapy treatment (78%) and that they were not currently in treatment for NHL (85%). The mean age at lymphoma diagnosis was 53 (range, 19-87). The mean interval from diagnosis to study enrollment was 10.2 years (range, 2-44 years). Having received a second primary cancer diagnosis was cited by 14% of the sample, and 4% were currently receiving treatment for it. Participants cited an average of 2.9 co-morbid conditions (SD, 2.1; range, 0-12), primarily back pain (42%), high blood pressure (40%) and heart disease (26%), and 1% had AIDS-related NHL. Scores on the psychosocial variables were: for social support, 83.1 (SD, 16.4; range, 20-100); appraisal of life threat, 19.3 (SD, 6.0; range, 6-30); and cancer-related employment and insurance issues, 1.1 (SD, 2.1; range, 0-17).

The overall mean PCL-C score in this sample was 27.0 (SD=9.9), with subscale scores of 6.9 (3.1) for re-experiencing, 9.3 (3.8) for arousal, and 10.8 (4.4) for avoidance. As shown in Table 2.2, the prevalence of cancer-related PTSD in the sample was similar using the cut-off score (6.9%) and symptom cluster (7.6%) methods. After applying weights to account for non-response bias, the adjusted prevalence rose to 7.4% and 7.9% for each of these methods. Seventeen percent rated at least two of the three PTSD symptom clusters (partial or full PTSD) as occurring moderately to extremely often. Across the symptom clusters, 30% met the criteria for arousal, 20% for re-experiencing, and 14% for avoidance. Overall, 39% met criteria for at least one PTSD symptom cluster.

Relationship of PTSD Symptoms to Other Variables

Bivariate associations between PCL-C scores and the independent variables are shown in Table 2.3. Among demographic and clinical variables, those who were non-Caucasian, had an annual income under $30,000, did not obtain a college degree, were younger, received a bone marrow or stem cell transplant, received biologic treatment, were currently receiving treatment for NHL, had active disease, and experienced at least one NHL recurrence had higher PCL-C scores (all $P \leq .01$). Among the continuous variables, the strongest PCL-C relationships (all $P < .001$) were for co-morbidity ($r = 0.27$), social support ($r = -0.36$), appraisal of life threat and treatment intensity ($r = 0.37$), and cancer-related insurance and employment issues ($r = 0.27$). In addition, significant PCL-C associations were found for age at study enrollment ($r = -0.15$), initial stage of disease ($r = 0.11$), sum of treatment types ($r = 0.13$), number of NHL-related visits to a physician ($r = 0.19$), age at diagnosis ($r = -0.08$), time since diagnosis ($r = -0.11$), and time since last physical exam ($r = 0.08$).

Regression Analyses

Table 2.4 displays the results of a multiple linear regression for the PCL-C score and logistic regression for partial or full PTSD (i.e., at least two symptom clusters) for those variables at least marginally significant in the bivariate analyses ($P < .10$). Non-Caucasian race, less education, younger age at enrollment, having active NHL disease, less time since diagnosis, more co-morbidity, less social support, more negative appraisals, and more insurance and employment issues were independently associated with worse PCL-C scores. For example, survivors with active disease had PCL-C scores 3.7 points higher than those in remission or

cured (*P*=.001). Furthermore, survivors of non-Caucasian race had PCL-C scores 2.4 points higher than those of Caucasian race (*P*=.004). The full model accounted for 38.5% of the variance (*P*<.001).

In the logistic regression model, three risk factors (non-Caucasian race, younger age, active disease status) that were identified in the linear regression were not independently associated with PTSD symptoms, although race remained marginally statistically significant (*P*=.07), with Non-Caucasians having 1.7 times greater odds of having partial or full PTSD than Caucasians. Furthermore, when a logistic model for full PTSD (symptom clusters=3; 7.9% of sample) was estimated, the odds ratio for non-Caucasian race was 2.8 (95%CI=1.4, 5.8) and for active disease was 4.3 (95%CI=1.5, 12.2). Finally, education, time since diagnosis, co-morbidity, and all psychosocial variables (social support, appraisals, and employment and insurance issues) had independent associations with PTSD symptoms.

DISCUSSION

This study is one of the first examinations of well-being among long-term survivors of NHL, who report varying degrees of PTSD symptomatology. Although the prevalence in this sample is somewhat lower than that found in some other traumatized populations, our adjusted prevalence of 7.4%-7.9% is more than three times the 2.4% prevalence in the general adult population.[22,23] While prevalence estimates are highly dependent on the methodology and sample, our finding is similar to breast cancer survivors (for whom PTSD prevalence of 5%-6% has been reported).[3,4] Our prevalence was adjusted upwards by approximately 0.5% (6.9%-

7.4%) when accounting for non-response, suggesting that similar and previous studies of cancer survivors may be under-reporting PTSD if they had response patterns similar to those in our study.

While the majority of survivors (61%) were not symptomatic for PTSD (i.e. had no symptom clusters), the prevalence in certain subgroups is cause for concern. For example, nearly 16% of non-Caucasians qualified for a full PTSD diagnosis. The greater PTSD symptomatology among non-Caucasians persists after adjustment for other demographic and clinical factors, indicating that the discrepancy is not due solely to differences in education or disease status. A possible explanation for this disparity is that individuals exposed to discrimination and prejudice may already be living with a heightened sense of arousal and greater stress.

In two other sub-groups, 15% of those with active NHL disease and 12% of younger survivors (<50 years of age) met criteria for PTSD. Survivors with current disease may experience daily reminders of their illness, such as pain, itchiness, and fever. In support of this finding, Deimling et al.[24] found that current cancer-related symptoms were the strongest predictor of hyper-arousal in a study of 180 adult, long-term cancer survivors. However, it is worth noting that results from a multiple regression that excluded individuals with active disease in our sample were substantively the same. Regarding age, Kornblith et al.[7] suggest that younger survivors have less experience than their older counterparts in dealing with medical crises and life threats, thereby feeling more distressed overall. Furthermore, they may already be faced with more challenges at this earlier stage in the life cycle; for example, younger survivors had significantly more cancer-related employment and

insurance issues than did their older counterparts (mean: 1.7 vs. 0.9, *P*<.001), largely attributable to the higher employment rate (75.8% vs. 31.7%). In addition to increasing age being a protective factor for PTSD, the passage of time seems to mitigate the impact of a cancer diagnosis and treatment. Perhaps least surprising was the finding that other health-related stressors (i.e., co-morbidities) were predictive of PTSD symptomatology.

It is encouraging to consider that the psychosocial factors related to PTSD are potentially modifiable. For example, cognitive behavioral (CBT) and prolonged exposure techniques have been shown to be effective in reducing or eliminating PTSD symptoms in other traumatized populations, such as survivors of sexual assault,[25] but the efficacy of psychosocial treatments on cancer-related PTSD is just beginning to be examined.[26] Interventions that combine therapeutic approaches (e.g., CBT, support groups) may be desirable, as we found social support to be correlated most strongly with avoidance symptoms (*r*=-0.41, *P*<.001) and negative appraisals most related to re-experiencing symptoms (*r*=0.36, *P*<.001).

This study has some limitations, including the absence of a comparison group, a cross-sectional study design, and inclusion only of patients treated at two large comprehensive cancer centers. Without a comparison group it is difficult to determine if these NHL survivors had more or less PTSD symptomatology than a similar group of people who never had NHL. However, the markedly higher PTSD prevalence in our sample compared to general population estimates suggests that NHL survivors have elevated PTSD symptomatology, supporting the need to address it.

The cross-sectional design prevents determination of whether PTSD symptomatology or certain risk factors (e.g., low social support) occurred first. However, it is reasonable to assume that many of the risk factors (e.g., non-Caucasian race, less education) preceded the PTSD. Further, this limitation should not affect the prevalence estimates except to the extent that the sample is a mix of individuals at different places in their course of survivorship. Finally, the inclusion of patients from only two large comprehensive cancer centers may limit the generalizability of our results to survivors living in other regions and treated at smaller hospitals. However, our demographic profile closely mirrors that of the national population of NHL survivors, thereby strengthening the robustness and generalizability of our prevalence estimates. Study strengths include a high response rate (74%), adjustment for non-response, sophisticated and appropriate methodology for accounting for missing data, two methods (linear and logistic regression) for identifying PTSD risk factors, and a balanced gender ratio.

In closing, while the majority of survivors did not exhibit symptoms of PTSD, the impact of diagnosis and treatment for cancer persists for many, such as having physical reactions to reminders (trouble breathing, sweating), difficulties in concentration and sleep, detachment from others, and avoiding medical care. Identification of those at risk (e.g., non-Caucasian, less education) early in the survivorship trajectory could promote screening and treatment to minimize PTSD symptomatology.

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Table 2.1. Characteristics of the Study Sample (N=886)

Demographics	N	%	Clinical Characteristics for NHL	N	%
Gender			Histology		
Male	435	49.1	Indolent	445	50.2
Female	451	50.9	Aggressive	391	44.2
Race			Unknown	50	5.6
Caucasian	758	85.5	Stage at diagnosis		
African-American	91	10.3	Stage I	247	27.9
Multiple race	30	3.4	Stage II	159	17.9
Other	7	.8	Stage III	146	16.5
Ethnicity			Stage IV	214	24.2
Non-Hispanic	873	98.5	Unknown	120	13.5
Hispanic	13	1.5	Types of treatment: mean (SD)	2.1 (1.1)	
Income level			No treatment	45	5.1
< $30,000	225	25.4	Surgery	248	28.0
$30,000 - $59,999	239	27.0	Radiation therapy	418	47.1
$60,000 - $89,999	139	15.7	Chemotherapy	692	78.1
≥ $90,000	189	21.3	Bone marrow/stem cell transplant	132	14.9
Unknown	94	10.6	Biologic therapy	261	29.5
Education			Other therapy	104	11.7
High school or less	250	28.2	Current treatment status		
Some college or trade school	277	31.3	Not in treatment	752	84.9
College degree	199	22.5	Receiving treatment	117	13.2
Post-graduate	138	15.6	Unknown	17	1.9
Unknown	22	2.4	Disease status		
Marital status			In remission or cured	680	76.7
Married	648	73.1	Not in remission	109	12.3
Living with partner	24	2.7	Unknown	97	11.0
Widowed	90	10.2	Number of recurrences		
Separated/divorced	48	5.4	0	562	63.4
Single	67	7.6	≥1	293	33.1
Unknown	9	1.0	Unknown	31	3.5
Employment status			Frequency of visits		
Retired	477	53.8	0	172	19.4
Employed	350	39.5	1-2	126	14.2
Unemployed	46	5.2	3-4	138	15.6
Unknown	13	1.5	5-6	131	14.8
Age at enrollment			7-10	90	10.2
Mean (SD)	62.9 (13.5)		11-20	86	9.7
Range	25–92		>20	113	12.8
25-49	157	17.7	Unknown	30	3.4
50-64	323	36.5	Site of treatment		
65-79	315	35.6	Duke University	750	84.7
80+	91	10.2	University of North Carolina	136	15.3

Health Status		
Secondary cancer (s)		
Yes	120	13.5
No	752	84.9
Unknown	14	1.6
Co-morbidities: mean (SD)	2.9 (2.1)	
0	97	10.9
1-2	326	36.8
3-5	341	38.5
6-8	95	10.7
≥9	12	1.4
Unknown	15	1.7
Years since last physical exam		
<1 year ago	480	54.2
1-2 years ago	186	21.0
3-4 years ago	71	8.0
≥ 5 years ago	128	14.4
Unknown	21	2.4
Age at diagnosis: mean (SD)	52.6 (14.2)	
Range:	19-87	
19-49	370	41.8
50-64	337	38.0
65-79	168	19.0
≥80	11	1.2
Years since diagnosis: mean (SD)	10.2 (7.1)	
Range:	2-44	
2-4 yrs	219	24.7
5-9 yrs	335	37.8
10-14 yrs	150	16.9
15-19 yrs	88	9.9
≥20 yrs	94	10.6
Psychosocial		
Social support: mean (SD)	83.1 (16.4)	
Range:	20-100	
Appraisal of life threat and treatment intensity: mean (SD)	19.3 (6.0)	
Range:	6-30	
Employment and insurance issues related to cancer: mean (SD)	1.1 (2.1)	
Range:	0-17	

Abbreviations: SD, standard deviation; NHL, non-Hodgkin's lymphoma

Table 2.2. Prevalence of Cancer-related Post-Traumatic Stress Disorder (PTSD) (N=868)

Indicator of PTSD [a]	Non-Adjusted		Adjusted for Non-response [b]	
	%	95% CI	%	95% CI
Score ≥ 44	6.9	5.2-8.6	7.4	5.6-9.1
3 Symptom clusters	7.6	5.8-9.4	7.9	6.1-9.7
2 Symptom clusters	8.9	7.0-10.8	9.1	7.2-11.0
1 Symptom cluster	22.2	19.5-25.0	22.3	19.5-25.0
No Symptom clusters	61.3	58.1-64.5	60.7	57.5-64.0

[a] Based on the PTSD Checklist-Civilian Version (PCL-C). Symptom clusters include ≥ 3 avoidance symptoms, ≥ 2 arousal symptoms, and ≥ 1 re-experiencing symptom. All three clusters constitute full PTSD.
[b] Adjusted for current age, age at diagnosis, and race.

Table 2.3. Bivariate Associations of Patient Characteristics with PTSD Symptoms (PCL-C Score) [a]

	n	Mean or correlation	(SD)	*p*-value [b]
Demographics				
Gender				
Male	429	26.8	(9.9)	.511
Female	439	27.2	(9.9)	
Race				
Caucasian	745	26.4	(9.1)	ref[<.001]
African American	85	29.1	(12.8)	.064
American Indian	3	34.7	(6.5)	.118
Asian	2	32.5	(13.4)	.347
Mixed Race	30	33.8	(13.1)	.005
Other	3	43.3	(21.9)	.313
Ethnicity				
Hispanic	13	31.9	(15.7)	.276
Non-Hispanic	855	27.0	(9.8)	
Income		*r* = -.148		<.001
< $30,000	217	29.6	(11.4)	ref[<.001]
$30,000 - $59,999	238	26.6	(9.8)	.003
$60,000 - $89,999	138	26.5	(9.50	.006
≥ $90,000	189	25.3	(8.0)	<.001
Education		*r* = -.110		.001
High school or less	243	28.9	(11.1)	<.001
Some college or trade school	276	27.2	(10.4)	.017
College+	333	25.4	(7.9)	ref[<.001]
Marital status				
Married	642	26.8	(9.8)	ref[.095]
Living with partner	24	29.0	(9.3)	.277
Widowed	88	26.7	(9.3)	.915
Separated	5	37.4	(11.2)	.017
Divorced	43	26.5	(7.8)	.851
Single	63	28.9	(12.2)	.184
Employment status				
Employed	346	26.4	(8.9)	ref[.117]
Unemployed	43	29.6	(12.2)	.106
Retired	466	27.1	(10.1)	.300

Age at enrollment (yrs)		r = -.145		<.001
25-49	152	29.1	(11.5)	ref[<.001]
50-64	317	27.8	(10.2)	.221
65-79	311	25.9	(8.8)	.003
80+	88	24.6	(8.4)	.001
Clinical characteristics for NHL				
Histology				
Aggressive	384	26.7	(9.6)	.491
Indolent	437	27.2	(10.2)	
Stage at diagnosis		r = .106		.004
1	244	25.4	(8.6)	ref[.015]
2	153	27.4	(9.1)	.027
3	145	28.0	(10.3)	.008
4	212	28.0	(10.9)	.006
Sum of treatment types ever		r = .128		<.001
0	35	27.0	(12.2)	ref[<.001]
1	216	26.2	(9.1)	.655
2	338	26.1	(8.8)	.581
3	192	27.4	(10.1)	.840
4	65	31.1	(12.4)	.118
5	19	34.1	(15.5)	.072
6	2	28.0	(4.2)	.912
Surgery				
Yes	245	27.8	(10.5)	.188
No	599	26.8	(9.7)	
Radiation therapy				
Yes	415	27.1	(10.3)	.937
No	453	27.0	(9.6)	
Chemotherapy				
Yes	685	27.3	(9.9)	.100
No	183	26.0	(10.0)	
Bone marrow or stem cell transplant				
Yes	131	30.9	(12.8)	<.001
No	737	26.3	(9.1)	
Biologic treatment				
Yes	260	28.4	(10.9)	.010
No	608	26.5	(9.4)	

Current treatment				
Yes	116	29.1	(10.2)	.012
No	743	26.6	(9.7)	
Active disease				
Yes	107	30.5	(12.1)	.001
No	675	26.1	(9.0)	
Recurrence(s)				
Yes	291	28.5	(10.8)	.002
No	554	26.2	(9.4)	
Frequency of visits		r = .193		<.001
0	167	24.6	(8.2)	ref[<.001]
1-2	125	26.0	(9.1)	.185
3-4	137	26.5	(9.6)	.063
5-6	129	26.4	(8.4)	.066
7-10	89	28.6	(10.9)	.001
11-20	85	28.9	(10.6)	<.001
>20	112	30.8	(12.4)	<.001
Site of treatment				
Duke	735	26.8	(9.6)	.063
UNC	133	28.5	(11.1)	
Age at diagnosis (years)		r = -.083		.015
Time since diagnosis (years)		r = -.108		.001
Health status				
Co-morbidity (0-30)		r = .273		<.001
Time since last physical exam (years)		r = .085		.013
Secondary cancer				
Yes	119	27.0	(9.3)	.989
No	743	27.0	(10.0)	
Psychosocial				
Social support (20-100)		r = -.355		<.001
Appraisal of life threat and treatment intensity (6-30)		r = .369		<.001
Insurance and employment issues related to cancer (0-24)		r = .274		<.001

[a] PTSD Checklist – Civilian Version

[b] P-values shown as superscripts are for the overall F-test for the categorical variable with k-1 degrees of freedom where k is the number of categories.

Abbreviations: SD, standard deviation; UNC, University of North Carolina

Table 2.4. Multiple Linear Regression for PCL-C [a] Score and Logistic Regression for Meeting Symptom Criteria for Full or Partial PTSD (N=868)

	PCL-C			Partial or Full PTSD [f]		
Variable	***Estimate***	***(95% CI)***	***P-value***	***Odds Ratio***	***(95% CI)***	***P-value***
Demographics						
Non-Caucasian race [b]	2.37	(0.75, 3.99)	.004	1.67	(0.96, 2.91)	.070
Income [c]	0.29	(-0.31, 0.90)	.346	1.16	(0.91, 1.47)	.222
Education [d]	-1.46	(-2.26, -0.66)	<.001	0.72	(0.53, 0.97)	.032
Age at enrollment (per 10 years)	-0.60	(-1.05, -0.14)	.010	0.89	(0.75, 1.05)	.169
Clinical characteristics for NHL						
Initial stage of disease (1-4)	-0.01	(-0.52, 0.51)	.978	0.96	(0.79, 1.16)	.652
Bone or stem cell transplant [b]	1.43	(-0.27, 3.14)	.100	0.98	(0.54, 1.79)	.949
Biologic treatment [b]	-0.42	(-1.77, 0.93)	.539	1.10	(0.66, 1.83)	.718
Current treatment [b]	-1.24	(-3.44, 0.96)	.270	0.59	(0.26, 1.33)	.203
Active NHL disease [b]	3.69	(1.49, 5.89)	.001	1.79	(0.86, 3.74)	.121
Any recurrence [b]	0.75	(-0.53, 2.02)	.253	1.19	(0.73, 1.93)	.487
Number of visits	0.29	(-0.04, 0.61)	.089	0.98	(0.86, 1.10)	.693
Time since diagnosis (years)	-0.15	(-0.23, -0.06)	<.001	0.93	(0.89, 0.97)	<.001
Health status						
Co-morbidity [e]	0.44	(0.32, 0.56)	<.001	1.10	(1.06, 1.15)	<.001
Time since last physical (years)	-0.06	(-0.56, 0.44)	.823	0.94	(0.78, 1.14)	.514
Psychosocial						
Social support	-0.17	(-0.21, -0.14)	<.001	0.97	(0.96, 0.98)	<.001
Appraisal of life threat & treatment intensity	0.49	(0.39, 0.59)	<.001	1.12	(1.07, 1.17)	<.001
Insurance/employment issues	0.45	(0.17, 0.73)	.002	1.15	(1.05, 1.25)	.002

NOTE: All analyses conducted with imputed data and adjusted for site of treatment (Duke, UNC). Variables included in this table are those that were significantly associated with the PCL-C score (P<.10) in the bivariate analyses.

[a] PTSD Checklist – Civilian Version

[b] Coded as a dichotomy, yes (1) or no (0)

[c] Coded as 1≤$30,000, 2= $30,000-$59,999, 3= $60,000-$89,999, 4= ≥$90,000

[d] Coded as 1= high school or less, 2= some college, 3= college graduate

[e] Self-Administered Co-morbidity Questionnaire

[f] Number of events/cases= 148/868

Abbreviations: CI, confidence interval

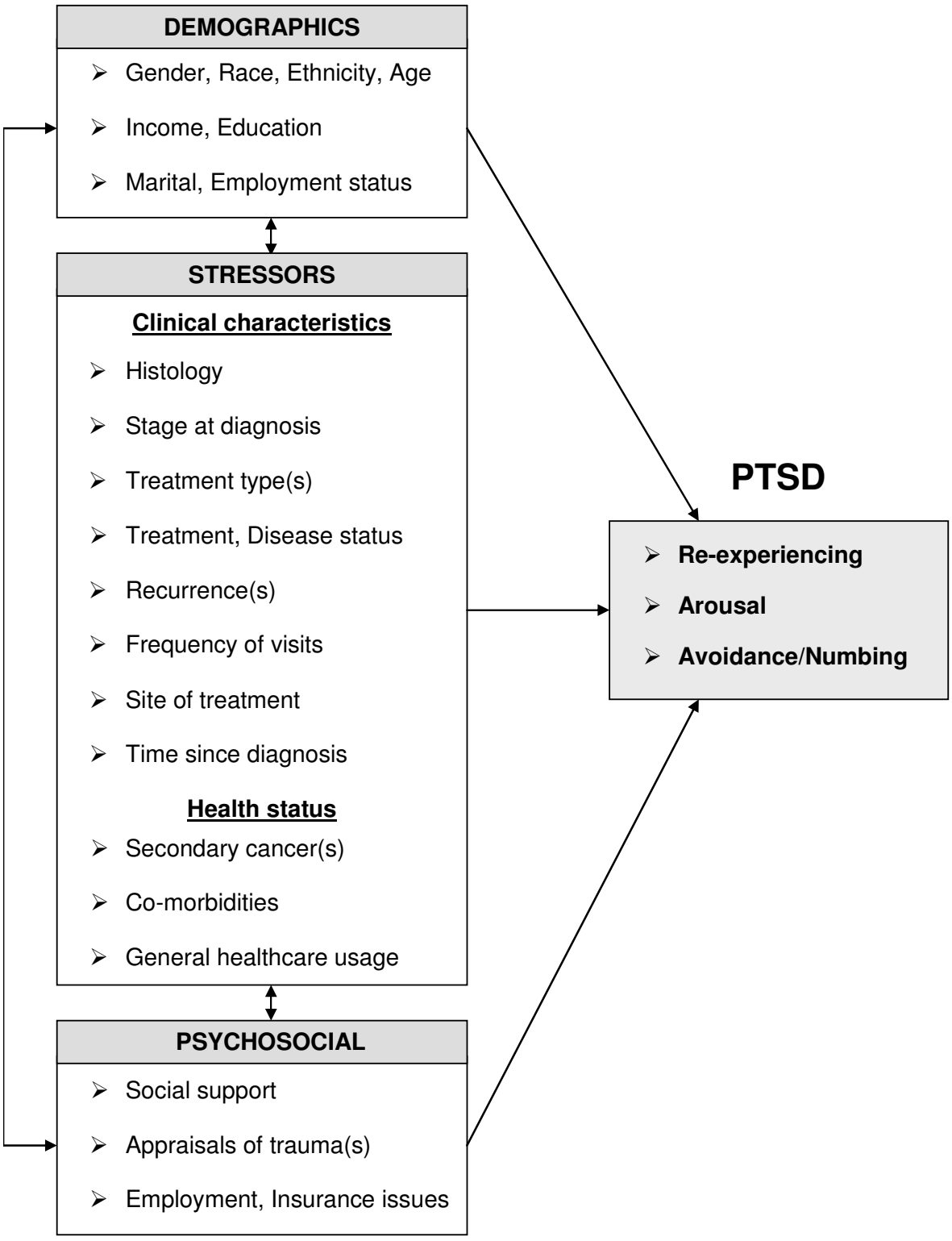

Figure 2.1. Conceptual model of cancer-related Post-Traumatic Stress Disorder

CHAPTER 3

Mediating Role of Trauma Outcomes on Quality of Life

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INTRODUCTION

The devastating message, “you have cancer”, has been delivered to over ten million Americans living today, representing roughly 3.6 percent of the US population.[1] Two-thirds of these individuals were diagnosed more than five years ago, and it is not uncommon for long-term survivors to recall the actual event with strong emotions and in great detail. The cancer experience (diagnosis, treatments, and post-treatment recovery/monitoring) is now categorized as a “traumatic event” according to the Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV),[2] in recognition that survivors are at increased risk for post-traumatic stress disorder (PTSD). PTSD is a set of symptoms (re-experiencing, avoidance, and arousal) following direct exposure to an extreme traumatic stressor where the individual is involved in, witnesses, or learns about threatened death or serious injury.[2] Cancer-related PTSD has been estimated in 5 to 8 percent of the adult survivors studied (Smith, Zimmerman, Williams, Preisser, & Clipp, in review).[3, 4]

While research has largely focused on negative sequelae such as PTSD, a second focus has emerged on the initiation of positive changes and resiliency resulting from the cancer experience; this is generally referred to as post-traumatic growth (PTG). However, the effects of cancer-related outcomes including PTSD and PTG on physical, emotional, social and functional well-being and quality of life (QOL) remain largely unknown, despite the implied urgency brought about by the aging of the US population and subsequent doubling of the annual incidence from 1.3 million new cancer patients in 2000 to over 2.6 million by 2050.[5] Furthermore, little is known about the QOL of individuals diagnosed with non-Hodgkin’s lymphoma (NHL), the sixth most common cancer in the US which has experienced a doubling in incidence

rates since the early 1970's.[6] Therefore, the primary purpose of this paper is to evaluate whether PTSD and PTG help to explain the role of risk factors in relating to QOL in NHL survivors, thereby enhancing our understanding of the cancer experience so that processes could be targeted for intervention.

Cancer-related Trauma and QOL

A conceptual model of QOL among cancer survivors is proposed in Figure 3.1, in which stress, coping, and adaptation theories[7, 8] emphasize the relationship between the person (characteristics of the person including demographics and psychosocial components) and his or her environment (nature of the environmental event, in this case the stressors). Psychological effects are a byproduct of this relationship, one of which occurs when the stress of cancer diagnosis and treatment is appraised as taxing or exceeding one's resources and endangering one's well-being (i.e., PTSD).

Alternatively, the effect can be growth inducing as in the case of PTG, which is characterized by positive changes in an individual as a result of a traumatic event. PTG is best explained by the information processing theory, in which life events are organized into schemas that manage the processing of the traumatic event. When a trauma occurs, an individual's "world schema" is disrupted in which the world may no longer be seen as physically and psychologically safe. In addition, a person's self-schema of being competent and self-reliant may be challenged. When individuals are able to integrate the threat with existing schemas, it is said to represent the "completion tendency".[9] This is accomplished through altering the meaning of the experience to fit into existing schemas (assimilation) or changing the schemas

(accommodation) to conform to the new information. According to Tedeschi and Calhoun,[10] PTG is more likely to develop when cognitive rebuilding takes into account the changed reality of one's life after the trauma and produces schemas that incorporate the trauma and future events, which are then more resistant to being shattered.

Building upon the theoretical base, characteristics identified in previous research studies that were related to QOL, PTSD, and PTG in cancer survivors were incorporated into the conceptual model (Smith, Zimmerman, Williams, Preisser, & Clipp, in review).[3, 11, 12] Clinical characteristics (e.g., cancer treatments, post-treatment monitoring) and health status (e.g., co-morbidity) are conceptualized as stressors, while social support, appraisals and insurance and employment-related issues represent psychosocial characteristics that can influence the outcome of these stressors. For example, the nature and quality of social support can affect the individual's likelihood of timely follow-up, in addition to influencing appraisals of life threat; these can either diminish or enhance the coping strategies employed by the individual, thereby leading to negative (PTSD) and/or positive (PTG) psychological effects.

More specifically, we hypothesize that PTSD and PTG directly relate to QOL and also mediate the effects of demographic, psychosocial, and clinical/health status risk factors (e.g., race, co-morbidity, social support) on QOL. This hypothesis was tested using Structural Equation Modeling (SEM).[13] While the primary aim of this study is to determine whether some or all of the factors have indirect and direct relationships with QOL (i.e., partial mediation), competing models are presented

which examine if QOL can be better explained by the factors having only an indirect relationship (full mediation) or direct relationship (no mediation).

METHODS

Participants and Procedures

Potential study participants were identified through Tumor Registries at the Duke and University of North Carolina (UNC) Lineberger Comprehensive Cancer Centers and were contacted by mail following physician approval. Approval for all procedures was granted by the Institutional Review Boards at the UNC and Duke Schools of Medicine. Individuals were eligible for this study if they were diagnosed with adult NHL (≥19 years old at diagnosis, and ≥2 years post-diagnosis). Prospective participants were sent a letter signed by their physician, a self-administered questionnaire, a $2 bill incentive, and thank-you/reminder postcards. Non-respondents were sent replacement mailings and followed up by telephone to confirm receipt of the survey packet.

Measures

Demographic and Clinical Characteristics

Demographic information such as birth date, gender, race, ethnicity, marital status, income, and education was collected via self-report. The Tumor Registry databases were used to obtain details regarding diagnosis (e.g., date, histology) and treatment history. NHL histology was categorized as indolent or aggressive based on the updated Revised European American Lymphoma/World Health Organization (REAL/WHO) classification system.[14]

Health Status

The Self-administered Co-morbidity Questionnaire (SCQ)[15] was used to assess other non-NHL health-related problems, with up to 3 points for each of 12 conditions, depending on severity. In addition, selected questions related to healthcare use and secondary cancer status were adapted for use from the Childhood Cancer Survivor Study survey.[16]

Psychosocial

The 20-item Medical Outcomes Study-Social Support Survey (MOS-SSS) was used to measure the perceived availability of social support,[17] with scores ranging from 20-100 (α=.97 in this study). The Appraisal of Life Threat and Treatment Intensity Questionnaire (ALTTIQ; six items, range 6-30; α=.80) was used to assess the extent to which cancer and its treatment are perceived to be life-threatening and intense.[18] Finally, to assess employment and insurance-related situations and difficulties, 24 questions (possible range 0-24, α=.82) were derived from an instrument developed by the Cancer and Leukemia Group B (CALGB) clinical research group.[19]

Psychological Effects

The PTSD Checklist-Civilian Version (PCL-C) assesses symptomatology in non-combat populations by presenting a self-report symptom checklist that closely mirrors criteria set forth by the DSM-IV for a formal diagnosis of PTSD.[2, 20] The instructions were modified for the current study to focus on the particular traumatic stressor of interest; specifically, survivors were asked to rate each PTSD symptom in the past 4 weeks with respect to their diagnosis and treatment for lymphoma. The

symptom cluster scoring method was used in the analysis, which maps to the DSM-IV criteria for PTSD.[2] In this study, the total score yielded an α=.91, and the internal consistency of the subscales were α=.88 (re-experiencing), α=.82 (avoidance), and α=.78 (arousal).

The Post-traumatic Growth Inventory (PTGI) is a 21-item scale that was used to measure positive life changes following a cancer-related trauma.[10] The overall α=.96, with the five domains showing strong internal consistency: relating to others (α=.92); new possibilities (α=.88); personal strength (α=.86); spiritual change (α=.89); and appreciation of life (α=.80).

Quality of Life

The Functional Assessment of Cancer Therapy – General Version (FACT-G) is a 27-item self-report measure designed to assess QOL specifically for cancer patients, and has good reported internal consistency.[21] The internal consistency reliability in our sample was excellent: physical well-being (α=.87); emotional well-being (α=.77); functional well-being (α=.88); social/family well-being (α=.80); and FACT-G total score (α=.93).

Statistical Methods

Pearson product moment correlations and associated statistical significance were calculated between QOL, as measured by the FACT-G, and all continuous demographic, clinical, health status and psychosocial variables. T-tests or ANOVA compared mean FACT-G scores for those at different levels of potential categorical risk factors. A multiple linear regression model for the FACT-G score was estimated in order to identify candidates for inclusion in the SEM model. Variables were

selected for inclusion in the multiple linear regression model if they were significant ($P<.05$) in the bivariate analyses. Missing data in three potential risk factors, income (10.6%), stage (13.5%), and disease status (10.9%) justified imputation, although the overall data set had a low level of missingness. Multiple imputation, via the Markov chain Monte Carlo (MCMC) algorithm, was used to impute values for missing data in the independent variables (excluding the mediators).[22] Twenty datasets containing imputed values were used in the multiple linear regression and standard errors adjusted for imputation were estimated in the SAS MIANALYZE procedure.[23]

Variables that were independently associated with the FACT-G score ($P<.05$ in the multiple linear regression model) were selected for inclusion in the SEM model. The hypothesized mediation model of PTSD, PTG and QOL was tested and compared with two alternate models of no mediation and full mediation using MPLUS V4.2[24] with the weighted least square means and variance adjusted method of estimation, an approach used when both categorical and continuous variables are included in a model.

To assess the overall fit of the models, the following indices were examined: the Tucker-Lewis Index (TLI),[25] the comparative fit index (CFI),[26] and the root mean square error of approximation (RMSEA).[27] Good fit is indicated by values of .90 or greater for the TLI and CFI[28] and .05 or smaller for the RMSEA, while values between .05 and .08 represent adequate fit.[29] Data management and bivariate analyses were carried out with SPSS V14.0. Multiple imputation and multiple linear regression analyses were conducted using SAS V9.1.3.

RESULTS

Of the 1195 eligible survivors who were assumed to have received a mailed survey, 886 (74%) returned their surveys. Participating survivors were less frequently African American (10% vs. 20%, *P*<.001), older at study enrollment (mean age 62.9 vs. 58.8 years, *P*<.001), and older at diagnosis (52.6 vs. 48.1 years, *P*<.001) than non-participants. The 830 survivors who completed the FACT-G, PCL-C, and PTGI were included in the analyses; their characteristics are listed in Table 3.1. A similar number of females and males participated; 13.5% were non-Caucasian; 27.3% earned less than $30,000 annually; 40.1% had a college degree; 25.4% were unmarried or not living with a partner; and 40.7% were employed. Mean age at study enrollment was 62.8 and almost half (45.5%) were older adults (≥ 65 years of age). The mean number of treatment types reported was 2.1; most (86.6%) were not receiving treatment; and the majority (78.0%) were in remission or cured. The mean interval from diagnosis to study enrollment was 10.4 years (SD, 7.3; range, 2-44 years). Participants reported an average of 2.9 co-morbid conditions (SD, 2.2; range, 0-12). The mean score for social support was high (83.3; SD, 16.3; range, 20-100), while that for appraisals was more mid-range (19.4; SD, 5.9; range, 6-30), and for cancer-related employment and insurance issues was low (1.1; SD, 2.1; range, 0-17). The mean number of PTSD symptom clusters in this sample was 0.6 (SD=0.9), with 19.2% of the sample meeting the criteria for re-experiencing, 30.0% for arousal, and 13.7% for avoidance. The mean PTGI score was 60.4 (SD, 24.6), with domain mean scores above the mid-range with the exception of new possibilities, which was below (11.0; SD, 6.4; range, 0-25).

Relationship of QOL to Other Variables

Bivariate associations between QOL (FACT-G scores) and the independent variables are also given in Table 3.1. Among demographic and clinical variables, those who were non-Caucasian, had an annual income under $30,000, did not obtain a college degree, were not married, were not employed, were younger, were of a later stage at diagnosis, had more types of treatment, were currently receiving treatment for NHL, had active disease, or had experienced at least one NHL recurrence had lower QOL (FACT-G scores; all $P \leq .01$). Among the remaining variables, the strongest QOL relationships (all at $P < .001$) were for PTSD symptoms ($r = -0.62$), social support ($r = 0.49$), and co-morbidity ($r = -0.39$).

As noted earlier, a multiple linear regression was conducted for the FACT-G total score and for those independent variables significant in the bivariate analyses ($P < .05$). Not having a college degree, not being employed, being a younger age at enrollment, having active NHL disease, more NHL-related visits, less time since diagnosis, more co-morbidity, less social support, more negative appraisals of life threat and treatment intensity, and more insurance and employment issues were significantly related to lower FACT-G scores in the regression. The full model accounted for 50% of the variance ($R^2 = .501$).

Structural Equation Modeling

A correlation matrix (Table 3.2) shows the relationships between demographic, clinical, health status, psychosocial, psychological effect, and QOL variables. The measurement model included three latent variables (variables which are not measured directly): two exogenous variables (a variable that is not caused

by another variable in the model; PTSD symptom clusters, PTG) and one fully endogenous variable (a variable that is caused by one or more variables in the model; QOL). PTSD symptom clusters had three categorical/binary indicators (re-experiencing, avoidance, arousal), PTG had five continuous indicators (relating to others, new possibilities, personal strength, spiritual change, appreciation of life), and QOL had four continuous indicators (physical, emotional, functional, social/family well-being).

The initial measurement model showed statistically significant loadings of each observed indicator on its corresponding latent construct (all at $P<.001$). However, further examination of the loadings suggested that the social/family well-being indicator be dropped from QOL because its R-square (.285) was less than half of those of the remaining FACT-G domains (physical, .600; emotional, .599; functional, .761). Nevertheless, the social/family domain was retained due to theoretical considerations, and all four domains were included in the QOL construct for further analyses.

Initially, a simple, unmediated hybrid model (Model B) was tested which included only direct effects of the independent and mediation (PTSD, PTG) variables with QOL. As shown in Table 3.3, the model fit was poor, RMSEA=.104, CFI=.722, TLI=.723. However, all coefficient paths were statistically significant at $P<.01$, confirming the independent relationship of each variable to QOL. Next, the hypothesized partial mediation model (Model A) was tested, which included paths from the independent variables to PTSD and PTG and from PTSD and PTG to QOL. In addition, to allow for the possibility that the independent variables have

relationships to QOL that are not mediated by PTSD and PTG, direct paths from the independent variables to QOL were included. The model fit was improved from the simple, unmediated Model B; RMSEA=.083, CFI=.827, TLI=.824. The next step was to test the full mediation model (Model C), which included paths from the independent variables to PTSD and PTG and from PTSD and PTG to QOL. The model fit improved from the unmediated Model B, but slightly degraded from that of the partial mediation Model A; RMSEA=.084, CFI=.798, TLI=.818. The hypothesized Model A was trimmed to include only statistically significant paths (P<.05), which resulted in the best fitting model (Model A'), RMSEA=.072, CFI=.868, TLI=.865. In addition, Model A' explained a sizable amount of the variance (81.8%) in QOL in NHL survivors. The final model is displayed in Figure 3.2.

In examining Figure 3.2 and using recommendations by Cohen[30] and Kline[13] about the interpretations of the absolute magnitudes of path coefficients, "small" effect is indicated by standardized values <.10, "typical" or "medium" effect by values around .30, and "large" effects by values ≥ .50, we can conclude that of the mediators, PTG had a small (positive) effect while PTSD symptoms had a large (negative) effect on QOL. More specifically, PTG mediated the relationship between (i.e., intervened between) appraisals, social support, college education, age, and active disease on QOL while PTSD symptoms mediated some of the same variables (appraisals, social support, and education) in addition to co-morbidity, years since diagnosis and employment and insurance issues. Only two of the independent variables (not being employed and NHL-related visits to a physician) were not

mediated by either PTSD symptoms or PTG; each had only a small direct (negative) relationship to QOL.

The direct and indirect relationships of demographic (age, education, employment) and clinical (active disease, NHL-related visits, years since diagnosis) variables to QOL were small to medium, while health status (co-morbidity) and psychosocial (appraisals, social support) variables had greater (medium) direct and indirect relationships. For example, individuals with more social support reported more PTG, fewer PTSD symptoms and greater QOL, while those with more negative appraisals of life threat and treatment intensity reported more PTG and PTSD symptoms and lower QOL (all at $P<.05$), as shown in Figure 3.2. Finally, the unstandardized path coefficients for Model A' are given in Table 3.4, which can be interpreted as regression coefficients.[13]

As demonstrated by these results, PTG and PTSD symptoms were significant mediators between demographic, clinical, health status, and psychosocial characteristics and QOL. This is substantiated by the smaller direct parameter estimates of these variables in the partially mediated model (Model A) than in the unmediated model (Model B). In addition, the paths to and from the mediated variables in Model A' were all statistically significant ($P<.05$). Furthermore, the indirect (mediated) relationships were all statistically significant ($P<.05$), according to the conservative Sobel test.[31]

DISCUSSION

This is the first study to examine the mediating effects of trauma outcomes in explaining QOL in cancer survivors. Our results show that PTSD symptoms and

PTG help to explain the relationship between specific demographic, clinical, health status, and psychosocial variables and QOL. These findings give support to using PTSD as a diagnostic framework (and PTG, to a lesser extent) in understanding symptomatology in this population. However, given the absence of "good fit", it is recommended that these findings be replicated with other measures and in other cancer samples to improve their robustness. With replication, our findings suggest that attention be given to reducing PTSD symptomatology and enhancing PTG in cancer survivors as a way to improve their QOL.

Although there is an absence of comparable studies in cancer survivors, studies of war veterans have similarly found PTSD to mediate the relationship between antecedent variables and QOL.[32-34] Additionally, several studies conducted with cancer survivors found negative relationships between PTSD and QOL,[35-38] yet no such studies were identified in a Medline search of PTG and QOL. The dearth of literature regarding the association between PTG and QOL may be reflective of the more recent development of psychosocial models, as opposed to more traditional medical models that incorporate PTSD as a diagnostic disorder.

The QOL model that we tested (Figure 3.2) explained a large amount of the variance in well-being (82%), indicating that it includes many key variables and is relevant to NHL survivorship. Similar to Northouse et al.,[39] we found that many of the clinical variables (e.g., stage of disease at diagnosis, sum of treatment types, NHL histology) contributed little or no unique variance in the survivors' QOL, while psychosocial variables (social support, appraisals), health status (co-morbidity) and PTSD symptoms were important components of the model. Future screening,

assessment, treatment and research activities need to consider the significant relationship of these variables to survivors' QOL.

The testing of alternative SEM models describing the pathways between the antecedent, mediator and outcome variables led to a reduction in the number of paths, thereby enhancing parsimony. It also elucidated the relationship between variables; for example, we found that some variables had a direct path to QOL (not employed, NHL-related visits to a physician), others had an indirect path (years since diagnosis, employment and insurance-related issues), and still others had both direct and indirect paths to QOL (active disease, age, college education, appraisals, social support, co-morbidity). Examining these pathways is an important exercise in unraveling the complex processes behind QOL so that interventions can be applied, and if necessary, developed for cancer survivors. For example, individuals with active disease or of an older age could be targeted for interventions aimed at enhancing PTG, while those without a college degree, more co-morbidity, more recent diagnosis or more employment and insurance issues related to cancer might benefit from treatments to reduce PTSD symptomatology as a means to improving overall QOL. In addition, individuals with lower social support could benefit from interventions focused on enhancing PTG and social support, and reducing PTSD symptoms.

It is through understanding and testing for mediation that we can begin to untangle the mechanisms and processes by which the cancer experience affects an individual's QOL. As stated by Baron and Kenny,[40] mediator variables are those that "speak to how or why such effects occur", representing processes that could be

targeted for intervention. To translate our findings to practice, treatments could be delivered that aim to reduce PTSD symptoms and enhance PTG. For example, cognitive behavioral (CBT) and prolonged exposure techniques have been shown to be effective in reducing or eliminating PTSD symptoms in survivors of sexual assault.[41] These proven therapies could be modified for use with cancer survivors to include methods that enhance PTG and address the unique features of a cancer-related trauma. For example, targeted treatments could be developed and implemented that minimize future-oriented intrusions (fear of recurrence, test anxiety) and enhance coping skills as survivors navigate through a range of possible aversive events such as treatments, recurrence(s), and medical surveillance.

Several limitations warrant caution in interpreting our findings. First, although our sample was representative of NHL patients treated at two major comprehensive cancer centers in North Carolina, the findings cannot be generalized beyond this specialized population. For example, replication in other geographical areas with different types of cancer diagnoses is needed to confirm the roles of PTSD and PTG in QOL. Second, since this study was cross-sectional, no definitive inferences can be made about the direction of causality between PTSD, PTG and QOL. However, our findings are consistent with the literature regarding the effects of traumatic stress on QOL and our interpretation of these findings is guided by a theoretical framework. Still, longitudinal studies are needed to establish and support evidence of causality. Finally, despite our finding of adequate model fit, other theoretical frameworks may yield equivalent or better fit and could be considered in future research studies. Of note, an additional model was tested (a revision of Model A' without the social/family

QOL domain) which yielded a good fit, RMSEA =.050, CFI=.938, TLI=.932. This would suggest that alternative measures of QOL be considered in replication studies.

Despite these limitations, our findings indicate that PTSD and PTG mediate the relationship between risk factors and QOL. The conceptual model of QOL among cancer survivors accounted for a large amount of variance in the survivors' QOL. In addition, several demographic, clinical, health status, and psychosocial variables were identified that either directly or indirectly through PTSD and/or PTG relate to QOL. Treatments that target PTSD symptom reduction and PTG enhancement may assist individuals in improving their QOL along the survivorship trajectory.

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Table 3.1. Characteristics of the Study Sample and Bivariate Associations with QOL (N=830)

Demographics	**N**	**%**	**QOL [a] Mean or Correl.**	**SD**	***P*-value [b]**
Gender					
Male	418	50.3	85.5	16.9	.917
Female	412	49.7	85.6	16.6	
Race					
Caucasian	718	86.5	86.3	16.3	.002
Non-Caucasian [c]	112	13.5	80.5	18.7	
Ethnicity					
Hispanic	13	1.6	85.5	16.8	.986
Non-Hispanic	817	98.4	85.5	16.8	
Income level			*r* = .225		<.001
< $30,000	205	27.3	79.0	19.5	ref[<.001]
$30,000 - $59,999	229	30.5	86.1	16.5	<.001
$60,000 - $89,999	136	18.1	86.9	14.7	<.001
≥ $90,000	181	24.1	90.0	13.7	<.001
Education			*r* = .115		<.001
High school or less	228	27.8	82.3	18.2	<.001
Some college or trade school	263	32.1	84.9	17.7	.014
College or post-grad	328	40.1	88.3	14.4	ref[<.001]
Marital status					
Married	618	74.6	86.5	16.4	.005
Not married [d]	210	25.4	82.7	17.5	
Employment status					
Employed	334	40.7	87.6	15.7	.005
Not employed [e]	487	59.3	84.3	17.3	
Age at enrollment: mean (SD)	62.8	(13.3)	*r* = .099		.054
25-49	149	18.0	83.4	20.0	ref[.001]
50-64	303	36.5	83.4	16.7	.984
65-79	294	35.4	87.9	15.4	.016
≥80	84	10.1	88.7	13.9	.020
Clinical Characteristics					
NHL histology					
Indolent	414	52.7	84.8	17.3	.097
Aggressive	372	47.3	86.8	16.1	
NHL stage at diagnosis			*r* = .-.077		.038
Stage I	228	31.6	87.8	15.4	ref[<.202]
Stage II	149	20.6	86.2	15.4	.335
Stage III	145	20.1	84.9	18.5	.101
Stage IV	200	27.7	84.7	17.3	.049
Sum of treatment types: mean (SD)	2.1	(1.1)	*r* = -.153		<.001
Current treatment status					
Not in treatment	711	86.6	86.7	16.3	<.001
Receiving treatment	110	13.4	78.6	18.3	

NHL disease status					
In remission or cured	648	78.0	87.8	15.0	<.001
Not in remission	102	12.3	75.2	20.0	
Number of NHL recurrences					
0	534	65.9	86.9	16.3	.003
≥1	276	34.1	83.2	17.4	
Frequency of NHL-related exams			*r* = -.234		<.001
Age at diagnosis: mean (SD)	52.4	(14.1)	*r* = .038		.279
Range:	19-87				
Years since diagnosis: mean (SD)	10.4	(7.3)	*r* = .108		.002
2-4 yrs	202	24.4	84.5	17.1	ref[.010]
5-9 yrs	307	37.0	84.6	17.4	.909
10-14 yrs	143	17.1	85.0	15.9	.772
15-19 yrs	85	10.3	85.8	17.1	.533
≥20 yrs	93	11.2	91.4	13.9	<.001
Health Status					
Secondary cancer					
Yes	113	13.7	83.8	15.8	.205
No	711	86.3	85.9	16.8	
Co-morbidities: mean (SD)	2.9	(2.2)	*r* = -.387		<.001
Years since last physical exam			*r* = -.119		.001
Psychosocial					
Social support: mean (SD)	83.3	(16.3)	*r* = .490		<.001
Range:	20-100				
Appraisal of life threat and treatment intensity: mean (SD)	19.4	(5.9)	*r* = -.285		<.001
Range:	6-30				
Employment and insurance issues related to cancer: mean (SD)	1.1	(2.1)	*r* = -.280		<.001
Range:	0-17				
Psychological Effects					
PTSD symptom clusters: mean (SD)	0.6	0.9	*r* = -.621		<.001
Range:	0-3				
Post-traumatic growth: mean (SD)	60.4	24.6	*r* = .133		<.001
Range:	0-105				

NOTE: Not all variables represent n=830 cases due to missing data; range, 722-830.
[a] Quality of life as measured by the Functional Assessment of Cancer Therapy – General Version (FACT-G).
[b] P-values shown as superscripts are for the overall F-test for the categorical variable with k-1 degrees of freedom where k is the number of categories.
[c] African-American, American Indian/Alaskan, Asian, and multiple races.
[d] Widowed, separated, divorced, and single.
[e] Unemployed and retired.

Abbreviations: SD, standard deviation; UNC, University of North Carolina

Table 3.2. Correlation Matrix

Demographics	***Range***	***M***	***SD***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
1. Some college	0,1	0.33	0.47																						
2. College degree	0,1	0.40	0.49	-0.56																					
3. Not employed	0,1	0.60	0.49	0.07	-0.21																				
4. Age	25-92	62.79	13.32	0.02	-0.15	0.55																			
Clinical																									
5. Active disease	0,1	0.15	0.35	0.03	0.01	-0.02	-0.01																		
6. Frequency of exams		7.35	8.29	0.07	-0.04	0.11	-0.05	0.35																	
7. Yrs since diagnosis	2-44	10.42	7.25	-0.03	-0.04	0.04	0.16	-0.12	-0.24																
Health Status																									
8. Co-morbidity	0-30	5.60	4.89	0.05	-0.16	0.27	0.25	0.05	0.06	0.08															
Psychosocial																									
9. MOS-SSS [a]	20-100	83.28	16.32	-0.05	0.01	0.04	0.05	-0.05	0.00	-0.00	-0.19														
10. ALTTIQ [b]	6-30	19.37	5.98	-0.06	-0.07	-0.01	-0.18	-0.02	0.16	0.02	0.01	0.00													
11. CALGB [c]	0-17	1.09	2.13	-0.01	0.03	-0.16	-0.25	0.06	0.07	0.05	0.11	-0.23	0.20												
PTSD Symptom [d]																									
12. Re-experiencing	0,1	0.19	0.39	-0.08	-0.16	-0.06	-0.22	0.16	0.17	-0.10	0.09	-0.18	0.45	0.24											
13. Avoidance	0,1	0.14	0.34	0.02	-0.08	0.11	-0.05	0.14	0.19	-0.17	0.32	-0.33	0.32	0.23	0.71										
14. Arousal	0,1	0.30	0.46	0.04	-0.12	0.05	-0.11	0.09	0.09	-0.12	0.32	-0.27	0.27	0.24	0.55	0.73									
PTGI [e]																									
15. Relating to others	0-35	21.75	8.64	-0.01	-0.15	0.04	-0.01	-0.14	-0.02	0.03	0.00	0.29	0.22	-0.01	0.11	-0.08	0.03								
16. New possibilities	0-25	10.94	6.44	-0.02	-0.11	-0.06	-0.15	-0.10	-0.06	0.09	0.01	0.16	0.22	0.09	0.18	0.01	0.04	0.79							
17. Personal strength	0-20	11.80	5.15	0.05	-0.14	-0.01	-0.05	-0.12	-0.03	0.10	0.00	0.18	0.22	0.03	0.13	-0.07	0.04	0.82	0.80						
18. Spiritual change	0-10	6.21	3.35	-0.01	-0.19	0.04	-0.04	-0.12	-0.04	0.08	0.07	0.15	0.23	0.04	0.19	-0.03	0.06	0.70	0.67	0.67					
19. Appreciation for life	0-15	9.72	3.81	-0.01	-0.11	-0.06	-0.17	-0.09	0.03	0.02	-0.03	0.14	0.32	0.08	0.25	0.01	0.04	0.74	0.73	0.73	0.66				
FACT-G [f]																									
20. Physical	0-28	22.81	5.57	-0.07	0.21	-0.16	0.04	-0.23	-0.26	0.11	-0.40	0.27	-0.34	-0.23	-0.42	-0.56	-0.49	-0.03	-0.03	-0.02	-0.10	-0.06			
21. Emotional	0-24	19.63	4.14	-0.00	0.08	-0.02	0.15	-0.22	-0.24	0.14	-0.25	0.33	-0.33	-0.20	-0.51	-0.65	-0.53	0.06	0.04	0.08	0.04	-0.02	0.60		
22. Functional	0-28	20.77	6.06	-0.03	0.15	-0.17	0.01	-0.22	-0.22	0.09	-0.42	0.40	-0.22	-0.23	-0.40	-0.60	-0.52	0.14	0.15	0.17	0.07	0.10	0.69	0.63	
23. Social/Family	0-28	22.33	5.00	0.03	-0.03	0.07	0.15	-0.14	-0.06	0.01	-0.14	0.58	-0.07	-0.23	-0.24	-0.45	-0.34	0.33	0.21	0.24	0.20	0.19	0.31	0.46	0.49

NOTE: Analyses conducted with imputed data for independent variables; $r \geq |.07|$, $p < .05$; $r \geq |.09|$, $p < .01$; $r \geq |.12|$, $p < .001$.

[a] Medical Outcomes Study – Social Support Survey total score.

[b] Appraisal of Life Threat and Treatment Intensity Questionnaire total score.

[c] Cancer and Leukemia Group B instrument to assess employment and insurance-related situations and difficulties.

[d] Based on the PTSD Checklist (PCL-C). Means and standard deviations for PTSD Symptom categorical indicators are not equivalent to the values used in MPLUS weighted least square means and variance adjusted parameter estimation technique.

[e] Post-traumatic Growth Inventory.

[f] Functional Assessment of Cancer Therapy – General Version, a measure of quality of life.

Abbreviations: M, mean; SD, standard deviation

Table 3.3. Summary of Goodness-of-Fit Statistics for Comparative Models of QOL

Comparison Models	Description	RMSEA	CFI	TLI
A	Partial mediation	.083	.827	.824
B	No mediation	.104	.722	.723
C	Full mediation	.084	.798	.818
A´	Trimmed Model A	.072	.868	.865

Note: Analyses conducted with imputed data.

Abbreviations: RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker-Lewis Index.

Table 3.4. Weighted Least Square Means and Variance Adjusted Parameter Estimates for the Final Model

Parameter	Estimate	SE	P-value
Direct effects			
PTGI → QOL	0.068	0.014	<.001
PTSDSX → QOL	-2.649	0.246	<.001
ACTIVE DISEASE → PTGI	-2.140	0.799	.007
STUDY AGE → PTGI	-0.066	0.025	.009
SOME COLLEGE → PTGI	-1.187	0.708	.094
COLLEGE → PTGI	-3.087	0.680	<.001
ALTTIQ → PTGI	0.321	0.045	<.001
MOS-SSS → PTGI	0.110	0.016	<.001
SOME COLLEGE → PTSDSX	-0.121	0.090	.178
COLLEGE → PTSDSX	-0.199	0.090	.027
ALTTIQ → PTSDSX	0.048	0.007	<.001
MOS-SSS → PTSDSX	-0.012	0.002	<.001
SCQ → PTSDSX	0.041	0.007	<.001
YEARS SINCE DIAGNOSIS → PTSDSX	-0.019	0.005	<.001
CALGB → PTSDSX	0.052	0.015	<.001
ACTIVE DISEASE → QOL	-1.788	0.315	<.001
STUDY AGE → QOL	0.046	0.010	<.001
SOME COLLEGE → QOL	0.400	0.241	.097
COLLEGE → QOL	0.612	0.265	.021
ALTTIQ → QOL	-0.045	0.020	.022

MOS-SSS → QOL	0.056	0.007	<.001
NOT EMPLOYED → QOL	-0.836	0.255	.001
FREQUENCY OF EXAMS → QOL	-0.047	0.014	<.001
SCQ → QOL	-0.122	0.020	<.001
Factor Loadings			
PTGI → RELATING TO OTHERS	1.000	0.000	
PTGI → NEW POSSIBILITIES	0.726	0.027	<.001
PTGI → PERSONAL STRENGTH	0.593	0.020	<.001
PTGI → SPIRITUAL CHANGE	0.327	0.016	<.001
PTGI → APPRECIATION FOR LIFE	0.403	0.015	<.001
PTSDSX → RE-EXPERIENCING	1.000	0.000	
PTSDSX → AVOIDANCE	1.471	0.111	<.001
PTSDSX → AROUSAL	1.077	0.088	<.001
QOL → PHYSICAL	1.000	0.000	
QOL → EMOTIONAL	0.927	0.047	<.001
QOL → FUNCTIONAL	1.413	0.070	<.001
QOL → SOCIAL/FAMILY	0.830	0.059	<.001

Abbreviations: PTGI, Post-traumatic Growth Inventory; QOL, quality of life; PTSDSX, Post-traumatic Stress Disorder symptoms; ALTTIQ, Appraisal of Life Threat and Treatment Intensity Questionnaire; MOS-SSS, Medical Outcomes Study - Social Support Survey; CALGB, Cancer and Leukemia Group B questionnaire to assess cancer-related employment and insurance issues; SCQ, Self-administered Co-morbidity Questionnaire.

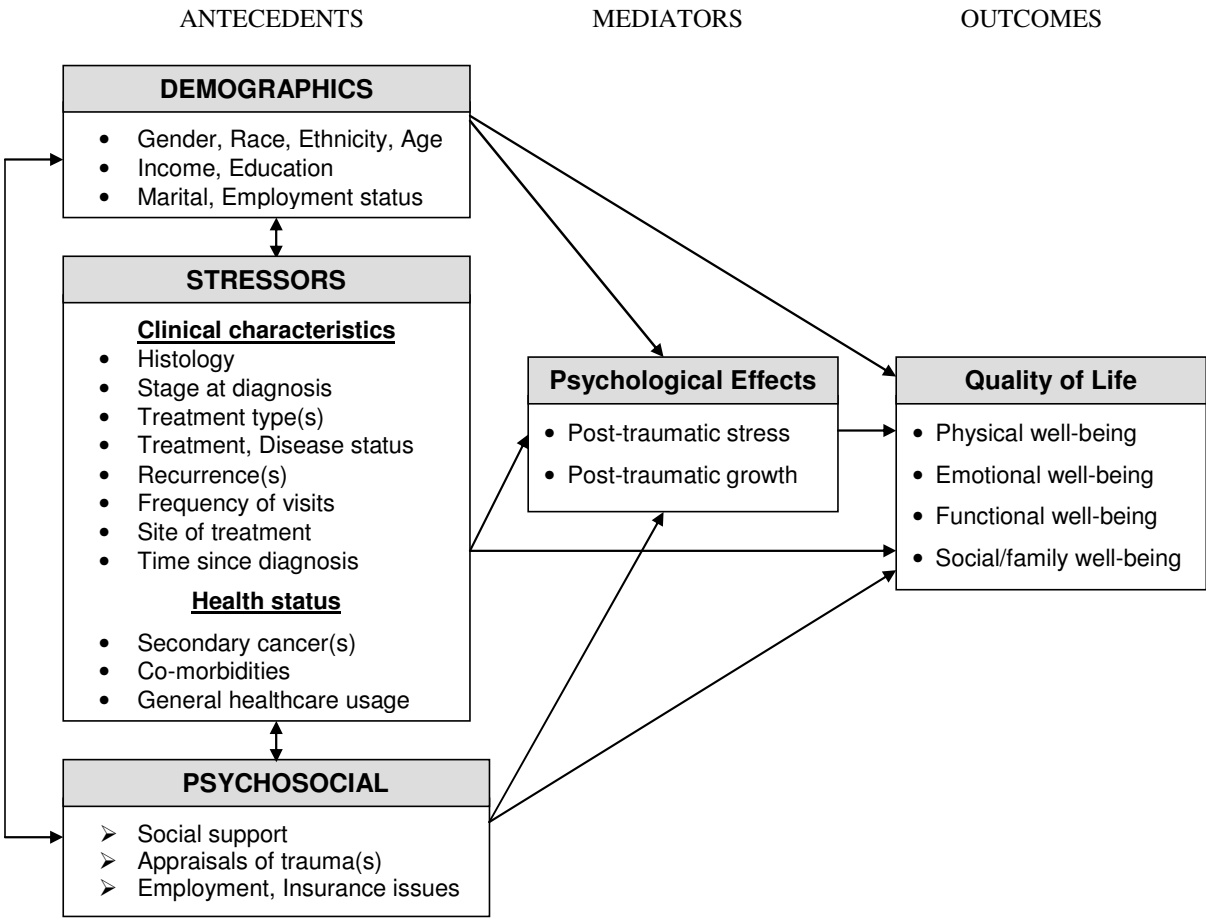
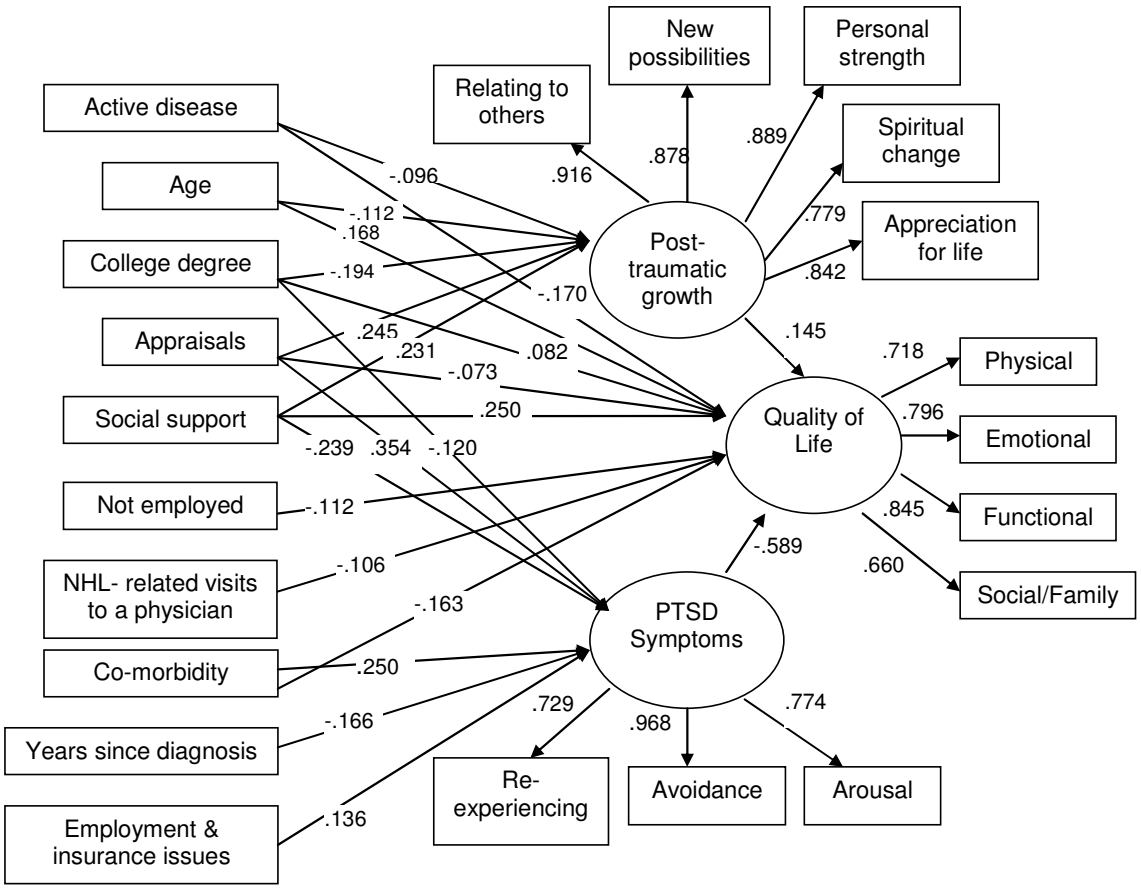


Figure 3.1. Conceptual Model of QOL among Cancer Survivors



RMSEA	CFI	TLI	QOL R^2	PTSDSX R^2	PTGI R^2
.072	.868	.865	.818	.370	.175

Figure 3.2. The Final Model

Note: Weighted least squares estimates for each path are significant at the *P*<.05 level; non-significant paths are excluded. Analyses conducted with imputed data.

Abbreviations: PTSD, Post-traumatic Stress Disorder; RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker-Lewis Index; R^2, proportion of variance in the dependent variable that can be predicted from the independent variables; QOL, quality of life; PTSDSX, PTSD symptoms; PTGI, Post-traumatic Growth Inventory

CHAPTER 4

Quality of Life among Short-term and Long-term non-Hodgkin's Lymphoma Survivors

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INTRODUCTION

Overall, a growing body of evidence suggests that long-term survivors who were diagnosed and treated for one of the more common forms of adult cancer report similar quality of life (QOL) to that of the general population.[1-4] However, specific areas of unresolved concern have been identified in this population, including sexual dysfunction,[3,5,6] low energy level and fatigue,[1,7,8] and psychological distress.[9-12] Conversely, several studies have demonstrated positive outcomes associated with having cancer, such as greater appreciation for life, closer personal relationships, and deeper spiritual understanding.[6,13,14]

Yet, less is known about the QOL of survivors of adult non-Hodgkin's lymphoma (NHL), the sixth most common cancer in the US with an individual lifetime risk of 1 in 50. NHL is a heterogeneous group of cancers of the lymphatic system with an overall 5-year survival rate of 50-60%; statistics vary depending on the cell type, stage of disease at the time of diagnosis, and treatment. Indolent lymphomas generally carry a good prognosis with a median survival of 10 years but also a high rate of relapse, and are usually not curable in advance stages. Treatment plans for the indolent forms include periods of watchful waiting, radiation therapy and chemotherapy. By comparison, many individuals who convert to or present with aggressive forms of NHL can be cured (30-60%) with intensive chemotherapy regimens but the disease has a shorter natural history, with the greatest risk of relapse within 2 years of treatment cessation.[15]

The incidence rates of NHL have doubled since the early 1970's, partly because of AIDS-related NHL and improved methods of diagnosis. Over the next

few years, the increasing average age of the American population together with the growing number of medical advances are expected to add to the incidence rates of NHL.[16] Consequently, and since the number of cancer survivors in the US is rapidly increasing, health care teams would benefit from evidence regarding the needs of this population so that interventions can be designed to improve their overall functioning and QOL, if indicated. Therefore, the primary purpose of this paper is to develop a QOL profile of this heterogeneous group of survivors of adult NHL, including a comparison between those who have active disease and those in remission or cured.

While the majority of survivorship research is conducted with disease-free survivors who are ≥5 years post-diagnosis (LTS),[1,3,4,7] this paper also examines the QOL of those who have active NHL disease and are short-term survivors (STS; those 2-4 years post-diagnosis). With the increasing prevalence of survivors living with cancer as a chronic illness, which is especially the case with indolent lymphomas, our sample was divided by disease status to provide a more comprehensive and accurate profile of this under-studied population. Further, we aim to challenge the conventional 5-year cut-off mark used in survivorship studies by including STS in our sample and comparing their outcomes to those who are further out from diagnosis (i.e., LTS). Finally, due to the limited number of instruments designed for use with LTS, we included three separate outcome measures to capture many of the different components of QOL in our cancer sample. Given the recent advances in cancer therapies (e.g. rituximab, interferon) with the associated transition of cancer to a chronic illness with alternating periods of disease and

remission as is increasingly the case with NHL, this paper provides a window into the diverse needs of cancer survivors across the recovery trajectory.

METHODS

Participants and Procedures

Potential study participants were identified through the Duke and University of North Carolina (UNC) Lineberger Comprehensive Cancer Center Tumor Registries and contacted by mail following physician approval. Individuals were eligible for this study if they were diagnosed with adult (≥19 years old) NHL and were at least 2 years post-diagnosis. Prospective participants were sent an introductory letter signed by their physician, a self-administered questionnaire, a $2 bill incentive, and thank-you/reminder postcards. Non-respondents were sent replacement mailings and followed up by telephone to confirm receipt of the survey packet. Approval for all procedures was granted by the Institutional Review Boards at the University of North Carolina and Duke Schools of Medicine.

Measures

The demographic, clinical, health status, psychosocial and psychological effect variables chosen for inclusion in this study are taken from a conceptual model which is theoretically and empirically-based. Information processing[17,18] and stress, coping, and adaptation theories[19,20] form the base of the model to which characteristics associated with cancer-related QOL, Post-traumatic Stress Disorder (PTSD), and post-traumatic growth (PTG) were added.[3,12,21]

Demographic and Clinical Characteristics

Demographic and clinical information such as race, marital status, income, education, and disease status was collected via self-report. The Tumor Registry databases were used to obtain details regarding diagnosis (e.g., date, histology) and

treatment history. NHL histology was categorized as indolent or aggressive based on the updated Revised European American Lymphoma/World Health Organization (REAL/WHO) classification system.[22]

Health Status

The Self-administered Co-morbidity Questionnaire (SCQ)[23] was used to assess other non-NHL health-related problems, with up to 3 points for each of 12 conditions, depending on severity. In addition, selected questions related to healthcare use and secondary cancer status were adapted for use from the Childhood Cancer Survivor Study survey.[24]

Psychosocial

The 20-item Medical Outcomes Study-Social Support Survey (MOS-SSS) was used to measure the perceived availability of social support,[25] with scores ranging from 20-100 (α=.97 in this study). The Appraisal of Life Threat and Treatment Intensity Questionnaire (ALTTIQ; six items, range 6-30; α=.80) was used to assess the extent to which cancer and its treatment are perceived to be life-threatening and intense.[26] Finally, to assess employment and insurance-related situations and difficulties, 24 questions (possible range 0-24, α=.82) were derived from an instrument developed by the Cancer and Leukemia Group B (CALGB) clinical research group.[27]

Psychological Effects

The PTSD Checklist-Civilian Version (PCL-C) assesses symptomatology in non-combat populations by presenting a self-report symptom checklist that closely mirrors criteria set forth by the DSM-IV for a formal diagnosis of PTSD.[28,29] The instructions were modified for the current study to focus on the particular traumatic stressor of interest; specifically, survivors were asked to rate each PTSD symptom in the past 4 weeks with respect to their diagnosis and treatment for lymphoma. The

continuous scoring method was used, and the three domains and summary demonstrated good reliability: re-experiencing (α=.88); avoidance (α=.82); arousal (α=.78); and total score (α=.91). The Post-traumatic Growth Inventory (PTGI) is a 21-item scale that was used to measure positive life changes following a cancer-related trauma.[18] The overall α=.96, with the five domains showing strong internal consistency: relating to others (α=.92); new possibilities (α=.88); personal strength (α=.86); spiritual change (α=.89); and appreciation of life (α=.80).

Quality of Life

Three measures were used to assess QOL in this sample. First, a general health outcome measure was used to allow for comparisons to general population-based norms; the Medical Outcomes Study- Short Form (SF-36) is comprised of 36 items representing eight sub-scales and two summary scores, the physical health summary (PCS) and the mental health summary (MCS).[30] The internal consistency reliability estimates for the 8 domains ranged from .84 to .95 in the present study. Second, in an effort to capture the more unique issues of cancer patients, the Functional Assessment of Cancer Therapy – Lymphoma Version (FACT-LYM) was used, which is a 27-item general self-report measure (FACT-G) with an additional 15 items to assess NHL-related symptoms.[31] The FACT-G was originally intended to be used to assess QOL in individuals receiving cancer treatment, but is increasingly being used with disease-free samples as well. The internal consistency reliability in our sample was excellent: physical well-being (α=.87); emotional well-being (α=.77); functional well-being (α=.88); social/family well-being (α=.80); FACT-G total score (α=.93); and additional concerns (α=.92). Third, the Impact of Cancer (IOC) is a new instrument that measures certain aspects of long-term survivorship that are not

currently measured by existing tools (e.g., health worries, meaning of cancer). The IOC was tested on 193 long-term survivors of breast, prostate, colorectal cancers, and lymphoma in combination with other well-established measures (SF-36, Quality of Life-Cancer Survivors). A factor analysis of 81 items using the a priori QOL domains yielded ten specific subscales for the IOC instrument, with internal consistency estimates ranging from .67 to .89.[32] Reliability estimates from our study were similar for the two IOC summary scales and their corresponding sub-scales: 1) higher order positive impact summary (α=.91), positive outlook (α=.73), health awareness (α=.69), positive self-evaluation (α=.86), value of relationships (α=.62), meaning of cancer (α=.67); and 2) higher order negative impact summary (α=.90), negative outlook (α=.79), body changes (α=.78), health worry (α=.81), negative self-evaluation (α=.66), and life interferences (α=.76). Higher scores on all of these QOL outcome measures indicate better QOL, except for the IOC higher order negative impact scale, where lower scores indicate better QOL.

Statistical Methods

Descriptive statistics were used to estimate the means and develop a QOL profile for this population, overall and by survivorship status (active disease, STS, LTS). Also, χ^2, ANOVA and t-tests were used to compare distributions and mean levels of demographic, clinical, health status, psychosocial and psychological effect measures across the three survivorship groups. Multiple linear regression analyses were performed for the SF-36 PCS and MCS, FACT-G, FACT-LYM additional concerns and IOC higher order positive and negative impact scales in order to examine the association between survivorship status and QOL, adjusting for demographic, clinical, health status, psychosocial and psychological effect characteristics. For all

comparisons, individuals with active disease were the reference group; however, because disease status was missing for n=97 individuals, these survivors were excluded from further analyses. For each of the five outcomes, sequential series of linear regression models were constructed to examine the association of active disease with QOL. Six models were constructed for each of the five QOL measures, sequentially adding each domain of covariates. For example, the first model tested for the effect of active disease vs. STS and LTS on QOL without adjusting for covariates while the sixth (final) model included all of the covariates from the five domains. Statistical analysis was carried out using SPSS V14.0 software.

RESULTS

For the 1312 eligible survivors who were mailed a survey, 117 packages were returned undelivered and tracing attempts were unsuccessful. Among the remaining 1195 survivors who were assumed to have received their survey, 886 (74.1%) completed and returned the survey. Sample bias was tested between those who did and did not participate using data obtained through the tumor registries. Survivors who participated were older at diagnosis (52.6 years vs. 48.1, $p<.001$), older at study enrollment (62.9 years vs. 58.8 years, $p<.001$), and less frequently African-American (10% vs. 20%, $p<.001$). Slightly more females than males participated, 86% were Caucasian, and almost half (46%) were at least 65 years of age at enrollment.

Table 4.1 lists the information collected via self-report and the tumor registry databases by total sample and survivorship status. Consistent with other survivorship studies, this sample had a mean number of 10.2 (7.1) years post-diagnosis. Study participants reported an average of 2.9 co-morbid conditions (SD,

2.1; range, 0 to 12). Eleven percent reported no co-morbid conditions, 38% reported one or two conditions, 31% reported three or four conditions and 20% reported five or more conditions. Conditions that survivors reported receiving current treatment for include high blood pressure (34%), heart disease (17%), back pain (15%), and osteoarthritis (15%). Fourteen percent of survivors had a history of other non-skin cancers, including prostate (n=22), breast (n=18), melanoma (n=9), colon (n=8) and bladder (n=8). Twenty-four percent reported having been diagnosed with depression in the past, and 13% were currently being treated for it.

Survivors who reported having active NHL disease had a mean number of 8.1 (5.1) years post-diagnosis and were more likely to have been diagnosed with an indolent lymphoma, received biologic therapy, be currently in treatment, had more NHL recurrences and PTSD symptoms, and less PTG than disease-free survivors. In addition, those with active disease were older, had less education, and were more likely to have received radiation and been diagnosed with a secondary cancer than STS. Compared to LTS, those with active disease were more likely to be college educated, were less likely to have received radiation therapy, and were older at diagnosis.

Figure 4.1 displays the means and standard deviations for the QOL outcomes. Those with active disease had poorer QOL than both STS and LTS on each of the six summary measures ($P<.01$). For example, the mean(SD) PCS score was 41.1(11.9) for active disease, compared to 47.0(10.5) and 45.7(10.8) for STS and LTS respectively, and the mean(SD) MCS score was 45.1(11.4) for active disease, compared to 50.0(10.1) and 49.4(11.1) for STS and LTS respectively (all at $P<.001$).

By contrast, no statistically significant differences were found in any of the six summary measures between STS and LTS, and in fact mean differences were no greater than 5% on any measure. Only on two specific subscale measures did LTS have lower mean scores than STS [PCS, bodily pain 50.0(10.5) vs. 52.0(9.8), $P<.05$; and IOC, meaning of cancer 14.5(4.6) vs. 15.4(4.6), $P<.05$].

Tables 4.2 and 4.3 show the regression coefficients for the effects of survivorship status on change in QOL as measured by the FACT-G, IOC, and SF-36 summary scores. The coefficients for the series of six sequential models represent the increase in the mean level of QOL attributable to disease-free survivorship status, after adjusting for the covariates in the model. Consistent with bivariate analyses, Model I indicates that disease-free survivorship status had a strong relationship to better QOL scores (all at $P<.05$). For all models, there was a graded effect with STS experiencing better QOL than LTS. The adjustment for each domain of covariates reduced the magnitude of the survivorship status effect slightly but remained statistically significant, except for the IOC Negative Impact and SF-36 summary scales, where the effects became non-significant after adjustment for demographic, clinical, health status, psychosocial and psychological effect characteristics. Finally, a sizable amount of the variance was explained by the models; for example, 68% of the variance in the cancer-specific FACT-G was explained by the covariates.

DISCUSSION

This study provides one of the first examinations of QOL among NHL survivors overall and by survivorship status. As demonstrated by these findings, NHL survivors are a diverse group with varying levels of QOL. Unexpectedly, no

significant differences were found between STS and LTS on any of the QOL measures, which brings into question the convention of using a 5-year post-diagnosis cut-point in long-term survivorship studies. Additional findings included a strong independent relationship between survivorship status (active disease vs. STS and LTS) and QOL, which was demonstrated for all QOL measures. In addition, after controlling for all covariates, there was still a significant difference between individuals with active disease and those who were disease-free in the FACT-G and IOC Positive Impact summary scales. This finding implies that there remain unidentified characteristics that relate to QOL and differ between those with active disease and those who are disease-free, even in light of large R^2 values (FACT-G, .68; IOC Positive, .65). However, the effects of survivorship status became non-significant in the general QOL measure (SF-36) and IOC Negative Impact summary score, which implies that differences in these QOL measures based on disease status are essentially explained by associated differences in some of the covariates.

A possible explanation for the unexplained characteristics between those with active disease and disease-free survivors after adjusting for all of the covariates is that the FACT-G, a cancer-specific measure, may not measure depression and anxiety symptomatology and physical limitations as thoroughly as the SF-36, which is of some concern. In addition, the IOC was specifically designed for long-term survivors; therefore, the Positive Impact summary may not be assessing for certain outcomes associated with active disease. Across most QOL measures there was evidence of a mediation effect, where the inclusion of the psychological effect

covariates (PTSD, PTG) produced the largest proportional drops in the survivorship status estimates.

When compared to general population-based norms for the SF-36 PCS and MCS (mean=50, SD=10),[33] individuals with active disease scored far lower in both physical (mean=41.0, SD=11.9) and mental (mean=45.4, SD=11.5) health. As expected, disease-free survivors fared better, but still seemed to have worse physical health (STS, mean=47.2, SD=10.5; LTS, mean=45.7, SD=10.8) than the general adult population.[33] However, after comparing our disease-free sample with their corresponding age-stratified normed groupings (25-34, 35-44, 45-54, 55-64, 65-74, ≥75), our sample scored comparably (within ±1.0 point on the PCS). In comparisons to other cancer samples, PCS scores from our disease-free survivors were similar to those from another similarly-aged NHL sample,[34] worse than those from a younger sample of breast cancer LTS,[3] but better than those reported by older LTS of lung and colorectal cancer.[1,2] Regarding mental health, scores from our disease-free survivors on the MCS (STS, mean=50.0, SD=10.1; LTS, mean=49.3, SD=11.3) were close to those from the general population;[33] however, our sample scored lower (≤4.1 points) on the MCS than the corresponding age-stratified groups (except for 35-44 and ≥75), with the largest difference between the 25-34 age groups.[33] Also somewhat disconcerting, our disease-free sample scored consistently worse (1.9-4.0 points lower) on the MCS than other survivors from identified LTS studies that used the SF-36.[1-4] When considering cancer-related QOL, our disease-free sample scored comparably on the FACT-G to other NHL survivors,[35] but worse

in physical and functional well-being in comparisons to younger lymphedema-free breast and bladder cancer LTS,[5,36] which may be an age effect.

The present study was not designed to determine the mechanisms linking survivorship status and QOL. Most likely, however, active disease contributes to worse QOL through the increase in emotional and physical stress that is associated with the disease and treatment-related effects. For example, the largest percentage decrease in the coefficient estimates from the FACT-G, IOC Positive and Negative Impact, and MCS multiple linear regression models occurs when the psychological effect covariates (PTSD, PTG) are added. Furthermore, adding clinical covariates to the PCS model produces the largest percentage decrease in the coefficient estimate.

The impact of having active disease on self-reported QOL has important implications. For example, health care professionals may want to pay closer attention to survivors with chronic (active) disease and screen for QOL-related problems. In addition, psychosocial intervention design and development should consider balancing treatment and control groups based on disease status. For example, individuals with active disease may be more likely to report worse QOL at baseline and may respond differently to specific treatment components than those who are disease-free. Furthermore, our data suggest that a distinguishing characteristic of NHL (alternating between periods of disease and remission) might lead to detriments in mental health, as demonstrated by lower MCS scores when compared to other cancer samples that are not characterized as such. Finally, multiple risk factors related to psychosocial (less social support, negative appraisals,

more cancer-related insurance and employment-related issues) and psychological effects (PTSD, PTG), were shown to have an effect on QOL and are potentially modifiable.

There are several limitations in this study. As is typical for any cross-sectional study, we can not establish a cause-effect relationship between survivorship status and QOL. For example, we cannot ensure that the risk factor (active disease) preceded the outcome (QOL) due to the inability to assess this cohort over time, as is possible in a longitudinal design. Further, the sequential models adjusted for many, although likely not all, of the characteristics that might have confounded the relationship between survivorship status and QOL. In addition, the inclusion of patients from only two large comprehensive cancer centers in NC may limit the generalizability of our results to survivors living in other regions and treated at smaller hospitals. However, our demographic profile closely mirrors that of the national population of NHL survivors, thereby strengthening the robustness and generalizability of our analyses. Finally, without a matched comparison group based on socio-demographic and co-morbid conditions it is difficult to determine if these NHL survivors had better or worse QOL than a similar group of people who never had NHL. However, the results of comparisons to general population norms and LTS studies support the need to address QOL concerns in this population, as evidenced by lower PCS and MCS scores in our sample.

In summary, the use of general health and cancer-specific QOL measures revealed significant differences between NHL survivors who reported having active disease and those who were disease-free. In addition, there were no significant

differences in QOL between STS and LTS, which challenges the current use of the 5-year mark in long-term survivorship research. The data from this study illustrate the value of using multiple instruments that assess areas that are particularly relevant to cancer survivors and of studying subgroups of survivors with differing disease status.

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Table 4.1. Characteristics of the Study Sample

	All survivors N= 886		Active disease n=109		Short-term survivor n=159		Long-term survivor n=521		
Demographics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	***P*-value**
Gender									
Male	435	49.1	54	49.5	76	47.8	263	50.5	.838
Female	451	50.9	55	50.5	83	52.2	258	49.5	
Race									
Caucasian	758	85.5	88	80.7	140	88.0	455	87.3	.111
African-American	91	10.3	15	13.8	11	6.9	44	8.5	
Multiple race	30	3.4	5	4.6	6	3.8	17	3.3	
Other	7	.8	1	0.9	2	1.3	5	0.9	
Ethnicity									
Non-Hispanic	873	98.5	107	98.2	157	98.7	513	98.5	.930
Hispanic	13	1.5	2	1.8	2	1.3	8	1.5	
Income level									
< $30,000	225	28.4	28	28.0	34	23.6	128	27.4	.769
$30,000 - $59,999	239	30.2	32	32.0	43	29.9	142	30.3	
$60,000 - $89,999	139	17.6	21	21.0	28	19.4	80	17.1	
≥ $90,000	189	23.8	19	19.0	39	27.1	118	25.2	
Education									
High school or less	250	28.9	29	27.6	28	17.7	158	30.8	**.031**
Some college or trade school	277	32.1	31	27.5	58	36.7	157	30.6	
College or post-grad	337	39.0	45	47.9	72	45.6	198	38.6	
Marital status									
Married	648	73.9	81	75.0	126	79.3	387	74.4	.462
Not married [d]	229	26.1	27	25.0	33	20.7	133	25.6	
Employment status									
Unemployed	46	5.3	6	5.6	9	5.7	23	4.5	.545
Retired	477	54.6	63	58.3	78	49.7	291	56.5	
Employed	350	40.1	39	36.1	70	44.6	201	39.0	

	All survivors N= 886		Active disease n=109		Short-term survivor n=159		Long-term survivor n=521		
	N	%	N	%	N	%	N	%	*P*-value
Age at enrollment: mean (SD)	62.9 (13.5)		62.7 (12.6)		59.7 (14.1)		63.7 (13.1)		**.005**
25-49	157	17.7	20	18.3	40	25.2	80	15.4	.122
50-64	323	36.5	44	40.4	57	35.8	189	36.3	
65-79	315	35.6	34	31.2	48	30.2	197	37.8	
≥80	91	10.2	11	10.1	14	8.8	55	10.5	
Clinical Characteristics									
NHL histology									
Indolent	445	53.2	85	81.0	66	44.0	232	47.3	**<.001**
Aggressive	391	46.8	20	19.0	84	56.0	259	52.7	
NHL stage at diagnosis									
Stage I	247	32.2	29	34.1	42	29.6	145	31.2	.300
Stage II	159	20.8	10	11.7	32	22.5	103	22.1	
Stage III	146	19.1	23	27.1	26	18.3	86	18.5	
Stage IV	214	27.9	23	27.1	42	29.6	131	28.2	
Sum of treatment types: mean (SD)	2.1 (1.1)		2.4 (1.3)		2.2 (1.1)		2.1 (1.0)		**.013**
Surgery	248	28.0	25	22.9	48	30.2	162	31.1	.256
Radiation	418	47.2	48	44.0	65	40.9	268	51.4	**.042**
Chemotherapy	692	78.1	83	76.2	124	78.0	428	82.2	.240
Bone marrow/stem cell transplant	132	14.9	16	14.7	29	18.2	79	15.2	.615
Biologic therapy	261	29.5	60	55.1	65	40.9	110	21.1	**<.001**
Current treatment status									
Not in treatment	752	86.5	38	35.5	149	94.3	499	96.3	**<.001**
Receiving treatment	117	13.5	69	64.5	9	5.7	19	3.7	
Number of NHL recurrences									
0	562	65.7	51	47.7	121	76.6	349	67.9	**<.001**
≥1	293	34.3	56	52.3	37	23.4	165	32.1	

	All survivors N= 886		Active disease n=109		Short-term survivor n=159		Long-term survivor n=521		
	N	%	N	%	N	%	N	%	*P*-value
Age at diagnosis: mean (SD)	52.6 (14.2)		54.5 (13.2)		55.9 (14.2)		50.8 (14.0)		**<.001**
Range:	19-87		20-82		22-87		19-82		
Years since diagnosis: mean (SD)	10.2 (7.1)		8.1 (5.1)		3.8 (0.7)		12.9 (7.4)		**<.001**
2-4 yrs	219	24.7	32	29.4	109	100.0			
5-9 yrs	335	37.8	48	44.0			247	47.4	
10-14 yrs	150	16.9	19	17.4			113	21.7	
15-19 yrs	88	9.9	6	5.5			75	14.4	
≥20 yrs	94	10.6	4	3.7			86	16.5	
Health Status									
Secondary cancer									
Yes	120	13.5	16	14.8	12	7.6	81	15.6	**.035**
No	752	84.9	92	85.2	147	92.4	439	84.4	
Co-morbidities: mean (SD)	2.9 (2.1)		3.0 (2.2)		2.5 (2.1)		3.0 (2.1)		.070
Psychosocial									
Social support: mean (SD)	83.1 (16.4)		81.7 (16.1)		85.0 (15.7)		83.5 (16.2)		.268
Range:	20-100		34-100		22-100		26-100		
Appraisal of life threat and treatment intensity: mean (SD)	19.3 (6.0)		19.0 (6.5)		18.8 (5.9)		19.6 (5.8)		.330
Range:	6-30		6-30		6-30		6-30		
Employment and insurance issues related to cancer: mean (SD)	1.1 (2.1)		1.2 (2.2)		1.0 (2.0)		1.0 (2.0)		.636
Range:	0-17		0-12		0-11		0-17		
Psychological Effects									
PTSD symptom clusters: mean (SD)	0.6 (0.9)		0.8 (1.1)		0.6 (0.9)		0.6 (0.9)		**.013**
Range:	0-3		0-3		0-3		0-3		
PTSD symptoms: mean (SD)	27.0 (9.9)		30.5 (12.1)		26.3 (8.2)		26.0 (9.2)		**<.001**
Range:	17-78		17-71		17-55		17-78		
Post-traumatic growth: mean (SD)	60.5 (24.7)		52.0 (26.0)		61.5 (23.5)		62.3 (24.4)		**<.001**
Range:	0-105		0-99		0-105		0-105		

Note: Individuals without a disease status classification (n=97) are included in the total sample (n=886) but excluded from further analysis. The active disease group represents individuals who self-reported having current NHL disease;

the short-term survivor group represents individuals who are 2-4 years post-diagnosis and have reported being disease-free; long-term survivor group represents individuals who are at least 5 years post-diagnosis and have reported being disease-free.

Table 4.2. Regression Coefficients for the Effects of Survivorship Status on Cancer-related Quality of Life (n=503)

Model Covariates	FACT-G			IOC Positive Impact			IOC Negative Impact		
	R^2	STS vs. Active Est. (Std error)	LTS vs. Active Est. (Std error)	R^2	STS vs. Active Est. (Std error)	LTS vs. Active Est. (Std error)	R^2	STS vs. Active Est. (Std error)	LTS vs. Active Est. (Std error)
I. SS	.054	11.6 (2.5) ****	10.8 (2.1) ****	.024	1.64 (0.50) ***	1.38 (0.43) ***	.019	-0.97 (0.41) **	-1.10 (0.35) ***
II. SS+DEM	.127	11.1 (2.4) ****	10.5 (2.1) ****	.153	1.68 (0.47) ****	1.44 (0.41) ***	.084	-0.97 (0.40) **	-1.10 (0.34) ***
III. SS+DEM+CLN	.173	10.7 (2.8) ****	7.9 (2.6) ***	.202	1.76 (0.56) ***	1.72 (0.52) ***	.201	-0.56 (0.45)	-0.21 (0.42)
IV. SS+DEM+CLN+ HTH	.290	10.2 (2.6) ****	8.7 (2.5) ****	.214	1.74 (0.55) ***	1.65 (0.52) ***	.256	-0.51 (0.44)	-0.30 (0.41)
V. SS+DEM+CLN+ HTH+PSO	.494	8.6 (2.2) ****	8.5 (2.1) ****	.330	1.89 (0.51) ****	1.66 (0.48) ***	.405	-0.26 (0.39)	-0.29 (0.37)
VI. SS+DEM+CLN+ HTH+PSO+ PSY	.683	4.7 (1.8) ***	3.9 (1.7) **	.648	1.10 (0.38) ****	0.80 (0.35) **	.583	0.24(0.33)	0.32 (0.31)

Table 4.3. Regression Coefficients for the Effects of Survivorship Status on Health-related Quality of Life (n=503)

Model Covariates	SF-36 Physical Component Summary			SF-36 Mental Component Summary		
	R^2	STS vs. Active Est. (Std error)	LTS vs. Active Est. (Std error)	R^2	STS vs. Active Est. (Std error)	LTS vs. Active Est. (Std error)
I. SS	.028	6.1 (1.7) ****	5.0 (1.4) ***	.016	4.8 (1.7) ***	3.2 (1.5) **
II. SS+DEM	.224	5.0 (1.5) ***	4.8 (1.3) ****	.069	4.7 (1.7) ***	3.2 (1.5) **
III. SS+DEM+CLN	.256	3.9 (1.8) **	2.6 (1.7)	.100	4.6 (2.0) **	2.2 (1.9)
IV. SS+DEM+CLN+HTH	.443	3.4 (1.6) **	3.1 (1.5) **	.184	4.3 (1.9) **	2.7 (1.8)
V. SS+DEM+CLN+HTH+PSO	.445	3.3 (1.6) **	3.1 (1.5) **	.306	3.5 (1.8) *	2.6 (1.7)
VI. SS+DEM+CLN+HTH+PSO+PSY	.458	2.6 (1.6)	2.3 (1.5)	.507	0.9 (1.5)	-0.5 (1.4)

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; IOC, Impact of Cancer; SF-36, Medical Outcomes Study-Short form; STS, Short-term disease-free survivor(<5 years) ; LTS, long-term disease-free survivor (≥5 years); SS = Survivorship status; DEM, demographics (gender, race, ethnicity, age, income, education, marital status, employment status); CLN, Clinical (histology, stage, surgery, radiation therapy, chemotherapy, bone marrow/stem cell transplant, biologic therapy, NHL treatment status, recurrence, number of visits to an MD for NHL, site of treatment); HTH, Health status (other diagnosed cancer

excluding skin, co-morbidity, time since last physical exam); PSO, Psychosocial (social support, appraisal of life threat and treatment intensity, employment and insurance issues); PSY, Psychological effects (Post-traumatic Stress Disorder symptoms, post-traumatic growth).

*p<.10; **p<.05; ***p<.01; ****p<.001.

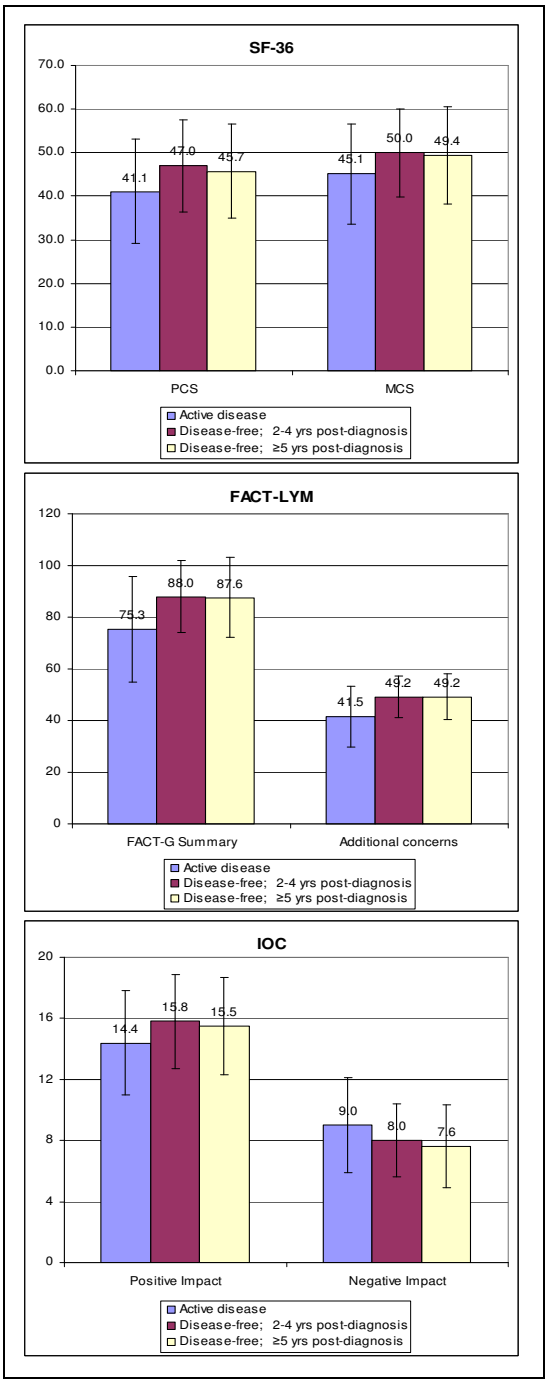

Figure 4.1. Quality of Life in non-Hodgkin's Lymphoma Survivors

Note: Higher scores indicate better QOL except for the IOC Negative Impact summary; error bars represent 1 standard deviation from mean; all comparisons between active and disease-free survivors are statistically significant at P< .01; no statistical difference between short-term and long-term disease-free survivors (P>.05); Mean (SD) scores for the entire sample (n=886) are: PCS, 45.3 (11.1); MCS, 48.7 (11.2); FACT-G, 85.5 (17.0); Additional concerns, 47.8 (9.9); IOC Positive, 15.4 (3.3); IOC Negative, 8.0 (2.8).

CHAPTER 5

Conclusion

This dissertation study was conducted to enhance the understanding of and thereby improve the quality of life of cancer survivors by demonstrating findings to inform research and practice. While the majority of survivors did not exhibit symptoms of PTSD, the impact of the diagnosis and treatment for cancer persists for many, as evidenced by symptoms in 39% of this NHL sample. Further research into understanding cancer-related PTSD, such as longitudinal studies that track symptomatology over the survivor trajectory in a recently diagnosed cohort and replication efforts that test the novel conceptualization of PTSD and PTG as mediators (SEM analysis) with different cancer samples is needed to inform the design of a phased-approach intervention with considerations to the optimal timing for treatment delivery. Early identification of those at risk (e.g., non-Caucasian, low social support) could promote screening and treatments that target PTSD symptom reduction and PTG enhancement to assist individuals in improving their QOL along the survivorship trajectory. A more detailed discussion of the implications for research and practice follow below.

Implications for Research

Several implications for cancer survivorship research have emerged following this dissertation study. First, despite the call for research and increasing evidence of the prevalence of PTSD symptomatology in cancer survivor populations, there remains a paucity of information concerning the natural history of PTSD symptomatology over the course of survivorship, including timing of onset, natural resolution, and specific areas of need. For example, Smith et al.[1] argued that longitudinal research in cancer-related PTSD is important conceptually and for treatment purposes, and Stuber et al.[2] discussed the need to examine the types of

intrusive thoughts and avoidant objects present at each stage of the cancer experience to guide selection of empirically-tested PTSD interventions. Mullan[3] describes these stages as “seasons of survivorship”, representing the acute (diagnosis, treatments), extended (initial treatment cessation, “watchful waiting”, follow-up exams, remission of disease), and permanent (cure) phases of survivorship.

Empirical data suggest that PTSD symptoms may increase and decrease over time (re-activated PTSD)[4-6] Yet, in other longitudinal studies of PTSD such as those conducted with war veterans,[7] burn injury survivors,[8] and 9/11,[9] the findings have been inconsistent. For example, significant decreases in PTSD symptoms were found between two assessments 4 and 16 months following exposure to natural disaster, and individuals residing in Manhattan reported a decrease in PTSD symptoms following 9/11. In contrast, combat-related PTSD symptomatology remained constant or increased across assessments 1 month–2 years following return from the Persian Gulf War. Also, the proportion of burn victims meeting PTSD diagnostic criteria increased at one year following injury.[8] These mixed results are not surprising, given the different types of traumatic events studied coupled with the differences in the timing of the symptom assessments.

Longitudinal assessments of cancer survivors that capture times of major life events (e.g., treatment cessation, job re-entry, recurrences, and changes in medical surveillance) would help determine the direction of causality between PTSD, PTG and QOL, and bolster the identification of risk factors to guide identification of patients and the selection and timing of phase-specific psychosocial treatments to

alleviate distress and enhance PTG. In addition, from what is known of the risk factors identified in cancer-related longitudinal studies[10-12] and in this dissertation study, there are opportunities to intervene early in the cancer experience, as many of these factors are modifiable (e.g., poor social support, negative appraisals). For example, in one of only three relevant studies identified in a MEDLINE search, breast cancer patients were assessed for PTSD 14 months after treatment completion and reassessed 12 months later.[10] PTSD symptoms remained stable and did not diminish over time. In another study, breast cancer patients were assessed at 6 weeks and 1 year post-operatively and the frequency of PTSD symptoms was reduced at the one-year mark.[11] In the third study, head and neck and lung cancer patients were assessed at 6 and 12 months post-diagnosis, and symptoms gradually subsided with no evidence of delayed-onset.[12] Risk factors for persistent PTSD included less social support, more traumatic stressors prior to diagnosis, pre-morbid health conditions, and personality type of high emotional reactivity. Determining the optimal timing and administration of the applicable components of the treatment plan could accelerate not only the reduction of PTSD symptoms for cancer survivors, but enhance their overall QOL as well.

Second, results from the SEM analyses in Chapter 2 demonstrated that PTSD symptoms and PTG help to explain the relationship between specific demographic, clinical, health status, and psychosocial variables and QOL. These findings give support to using PTSD as a diagnostic framework (and PTG, to a lesser extent) in understanding symptomatology in this population. However, given the absence of "good fit", it is recommended that these findings be replicated with other measures

and in other cancer samples to improve their robustness. With replication, our findings suggest that attention be given to reducing PTSD symptomatology and enhancing PTG in cancer survivors as a way to improve their QOL.

Third, the impact of having active disease on self-reported QOL, regardless of the amount of time post-diagnosis, has important research design implications as described in Chapter 3. For example, psychosocial intervention design and development research might consider separate treatments based on disease status. In addition, further research is needed to understand how the distinguishing characteristics of NHL (alternating between periods of disease and remission) might lead to detriments in mental health. For example, our sample scored consistently lower on the SF-36 mental component summary measure than other cancer samples that are not characterized by these characteristics. As stated earlier, findings like these are relevant for cancer survivors in general, but particularly relevant for patients who are living with cancer as a chronic illness with alternating periods of active disease and remission.

Implications for Practice

Two areas of focus regarding psychosocial support and treatment for this population are described here. First, while interventions have been developed, tested and shown to reduce PTSD in trauma populations such as adolescent cancer[13] and sexual assault,[14] no specific therapies for PTSD in the cancer setting have been developed for adult survivors, according to the NCI[15] and literature review. In other populations, such as rape survivors, cognitive behavioral therapy (CBT) and prolonged exposure (PE) have been shown to be an effective treatment for PTSD.[14]

However, cancer-related trauma has distinct features that could drive modification to existing therapies used to treat PTSD in other populations.

Kangas, Henry & Bryant[12] have identified several clinical issues resulting from the distinctive features of the cancer stressor. For example, a major issue relates to the ongoing nature of the trauma (e.g., treatments, medical surveillance, aversive side effects), which puts into question the timing of using PE in this population. If deemed appropriate, exposure activities should be conducted only after the demanding aspects of the medical treatment have ended. Furthermore, cognitive restructuring and anxiety management may be more beneficial than exposure in facilitating adaptive coping. The issues related to interventions with cancer survivors, combined with what is already known about the unique features of cancer-related PTSD and the knowledge gained from the dissertation study about the mediating effects of PTSD and PTG (see Chapter 2), suggest that psychosocial interventions be developed and tested to treat PTSD and enhance PTG in cancer survivors.

Secondly, the risk factor analyses in Chapters 1 and 2 suggest that screening tools be developed and tested to identify those at risk for PTSD. Currently, the National Coalition of Cancer Networks Distress Management Screening Measure (DMSM) is being used in many oncology clinics to screen for general distress and impacts to daily functioning. However, this measure does not specifically assess for PTSD; therefore, this disorder may go undetected in a large number of survivors. Perhaps more disconcerting is that many survivors are followed up by their primary care physicians who may be unaware of the increased risk for PTSD in this population. Oncology social workers should consider discussing these issues with

their patients while they are still in active treatment or at treatment cessation before leaving the care of an oncology setting. Furthermore, findings from the QOL analyses in Chapter 3 comparing survivors with active disease to those that are disease-free suggest that health care professionals may want to pay close attention to survivors with active disease and screen for QOL-related problems as well.

In summary, it was demonstrated in Chapter 1 that PTSD symptomatology is prevalent in this sample of cancer survivors. Given this identification, Chapter 2 explored how PTSD and PTG mediate the relationship between various stressors (risk factors) and QOL. Finally, a more in-depth examination of QOL across three different survivorship statuses (active NHL, STS, LTS) was presented in Chapter 3, with findings of worse QOL for those who reported having active disease when compared to survivors who were in remission or cured. Overall, it is encouraging to consider that many of the psychosocial factors identified in this dissertation study that were significantly related to PTSD and worse QOL are potentially modifiable. Oncology social workers are in the unique position to identify those at risk and provide support and treatment to minimize PTSD symptomatology and enhance PTG, ultimately leading to improved QOL for this vulnerable, yet resilient, population.

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