

PATIENTS, CAREGIVERS, AND ILLNESS UNCERTAINTY: INFLUENCES ON COPING  
AND QUALITY OF LIFE

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## **ABSTRACT**

TING GUAN: Patients, Caregivers, and Illness Uncertainty: Influences on Coping and Quality of Life

(Under the direction of Dr. Mimi V. Chapman)

Illness uncertainty is defined as “the inability of a person to determine the meaning of illness-related events”. Patients’ and caregivers’ individual experiences of illness uncertainty adversely affect their quality of life (QOL). The relationship between uncertainty and QOL have been examined extensively for either the patient or caregiver, but not among the patient-caregiver dyads. This three-paper dissertation fills gaps in the literature by examining the independent and interdependent relationships between illness uncertainty and QOL using the patient-caregiver dyad as a unit of analysis.

The first paper presented a systematic review and meta-analysis of 21 articles that reported correlates of illness uncertainty in patients with cancer and caregivers. Notable effect sizes were observed in the correlations between illness uncertainty and social support, QOL, depression, and anxiety among patients with cancer. Insufficient data precluded examining the effect size of correlates of illness uncertainty among caregivers.

The second paper using the actor -partner interdependence model, examined the independent and interdependent relationships between illness uncertainty and QOL among patients with advanced cancer and caregivers and assessed whether these relationships differed according to the patient-caregiver relationship and the type of cancer. Results demonstrated that patients’ and caregivers’ illness uncertainty was negatively associated with their own QOL.

Patients' illness uncertainty was negatively associated with caregivers' QOL. These independent and interdependent relationships between illness uncertainty and QOL did not differ by patient-caregiver relationship, but did differ by type of cancer.

The third paper using actor-partner interdependence mediation model, examined independent and interdependent relationships among patients' and family caregivers' illness uncertainty, coping, and QOL. Significant actor and partner effects were present: each person's illness uncertainty and coping were significantly associated with their own QOL; caregivers' illness uncertainty was positively associated with patients' avoidant coping. The mediation effects of active and avoidant coping on the relationships between illness uncertainty and QOL among patients and caregivers were partially verified.

Collectively, the findings emphasized the need to support patients and caregivers as one unit of care and underscore the potential value of targeting family-oriented interventions to enhance QOL for patients and caregivers as they manage the stress of cancer.

I dedicate this dissertation to my Mom and Dad, Pengfei Liu, Ruitong Liu, and Ruilin Liu.

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## TABLE OF CONTENTS

LIST OF TABLES .....	x
LIST OF FIGURES .....	xi
LIST OF ABBREVIATIONS .....	xii
INTRODUCTION.....	1
Reference: Introduction .....	5
PAPER I: CORRELATES OF ILLNESS UNCERTAINTY IN PATIENTS WITH CANCER AND FAMILY CAREGIVERS: A SYSTEMATIC REVIEW AND META-ANALYSIS .....	6
Introduction.....	7
Methods .....	7
Results .....	10
Discussion.....	15
Conclusion .....	21
REFERENCES: PAPER I.....	22
PAPER II: ILLNESS UNCERTAINTY AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER AND FAMILY CAREGIVERS: AN ACTOR-PARTNER INTERDEPENDENCE MODEL ANALYSIS.....	36
Introduction.....	36
Methods .....	38
Results .....	42
Discussion.....	45
Conclusion .....	48
REFERENCES: PAPER II .....	49



PAPER III: ILLNESS UNCERTAINTY, COPING, AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER AND FAMILY CAREGIVERS: USING THE ACTOR-PARTNER INTERDEPENDENCE MEDIATION MODEL.....	58
Introduction.....	58
Methods .....	61
Results .....	64
Discussion.....	66
Conclusion .....	70
REFERENCES: PAPER III.....	71
SUMMARY .....	81
APPENDIX 1: MISHEL UNCERTAINTY IN ILLNESS SCALE .....	84
APPENDIX 2: FUNCTIONAL ASSESSMENT OF CANCER THERAPY -GENERAL .....	85
APPENDIX 3: SYMPTOM DISTRESS SCALE .....	86
APPENDIX 4: BRIFE COPE.....	87
APPENDIX 5: TWO-FACTOR STRUCTURE OF COPING .....	90

## LIST OF TABLES

Table 1.1 - Description of Population Characteristics ( $n = 21$ ).....	26
Table 1.2 - Description of Study and Outcomes ( $n = 21$ ) .....	28
Table 1.3 - Meta-analysis Results for Correlates with Illness Uncertainty.....	32
Table 1.4 - Methodological Quality of Included Studies .....	33
Table 2.1- Characteristics of Patients and Caregivers ( $N = 484$ dyads) .....	52
Table 2.2 - Means, Standard Deviations, Range, and Correlations for Illness Uncertainty and QOL among Patients and Caregivers ( $N = 484$ Dyads).....	53
Table 3.1 - Characteristics of Patients and Caregivers ( $N = 484$ dyads).....	76
Table 3.2 - Means, Standard Deviations, Range, and Correlations for Illness Uncertainty, Active Coping, Avoidant Coping, and QOL among Patients and Caregivers ( $N = 484$ Dyads).....	77
Table 3.3 - Parameter Estimate.....	78

## LIST OF FIGURES

Figure 1.1 - PRISMA 2009 Flow Diagram .....	34
Figure 1.2 - Results of Individual Studies and Overall Effect Size for Correlates of Illness Uncertainty.....	35
Figure 2.1 - Modified Uncertainty in Illness Theory Model.....	54
Figure 2.2 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Caregiver Dyads ( $N = 484$ ).....	54
Figure 2.3 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Spousal Caregiver Dyads ( $n = 339$ ).....	55
Figure 2.4 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Non-Spousal Caregiver Dyads ( $n = 123$ ).....	55
Figure 2.5 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Breast Cancer Patient-Caregiver Dyads ( $n = 156$ ).....	56
Figure 2.6 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Prostate Cancer Patient-Caregiver Dyads ( $n = 63$ ).....	56
Figure 2.7 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Lung Cancer Patient-Caregiver Dyads ( $n = 141$ ).....	57
Figure 2.8 - Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Colorectal Cancer Patient-Caregiver Dyads ( $n = 123$ ).....	57
Figure 3.1 - Modified Uncertainty in Illness Theory Model.....	79
Figure 3.2 - Actor-Partner Interdependence Mediation Model of Illness Uncertainty, Coping, and Quality of Life among Patient-Caregiver Dyads ( $N = 484$ ).....	80

## LIST OF ABBREVIATIONS

APIM	Actor-Partner Interdependence Model
APIMeM	Actor-Partner Interdependence Mediation Model
CFI	Comparative Fit Index
CINAHL	Cumulative Index to Nursing and Allied Health Literature
FACT-G	Functional Assessment of Cancer Therapy-General
FIML	Full Information Maximum Likelihood Estimation
MUIS	Mishel Uncertainty in Illness Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QAT-OCCSS	Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies
QOL	Quality of Life
RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modeling
SRMR	Standardized Root Mean Square Residual
TLI	Tucker-Lewis Index
UIT	Uncertainty in Illness Theory

## INTRODUCTION

### PATIENTS, CAREGIVERS, AND ILLNESS UNCERTAINTY: INFLUENCES ON COPING AND QUALITY OF LIFE

*Illness uncertainty* is the cognitive state created when a person cannot determine the meaning of illness-related events because of insufficient information (Mishel, 1988). It can persist across the cancer trajectory from the time of diagnosis, through treatment, to long-term survivorship (Garofalo et al., 2009), and can be exacerbated by disease progression (Guan et al., 2020a). Illness uncertainty is widely recognized as a common and significant source of psychosocial stress not only for patients with cancer (Ghodraty Jabloo et al., 2017), but also for their family caregivers, who in fact experience illness uncertainty at greater rates than patients themselves (Guan et al., 2020a).

To comprehensively understand this phenomenon, this dissertation is grounded in Mishel's (1988) Uncertainty in Illness Theory (UIT), which posits that illness uncertainty has three antecedent components: *stimuli frame*, *structure providers*, and *cognitive capacities* (Mishel, 1988). The stimuli frame is the form, composition, and structure of an individual's perceived stimuli, consisting of symptom pattern, event familiarity, and event congruency. Research has found significant associations between patients' levels of illness uncertainty and their cancer-specific symptoms (Guan et al., 2020a). Structure providers are the personal and environmental resources that aid in stimuli formation, including credible authorities (e.g., healthcare providers), social support, and education (Mishel & Braden, 1988). A recent study

found that patients who lacked social support reported elevated levels of illness uncertainty (Kang & Choi, 2019). Cognitive capacities refer to the individual's information-processing ability and any physiological difficulties that might impair their ability to cognitively process information. Mishel's UIT also provides a model of how an individual's appraisal of their illness uncertainty (i.e., dangerous or beneficial) influences their coping, which in turn affects their adaptation (Mishel, 1988). Patients' high levels of illness uncertainty are associated with avoidant coping strategies (Guan et al., 2020b), often adversely affecting quality of life (QOL) (Kang & Choi, 2019; Lee et al., 2020).

Research examining illness uncertainty in adults with cancer has grown considerably in the past three decades. However, only one scoping review published to date has focused on factors influencing illness uncertainty among older patients with cancer and its effects on patient outcomes (Ghodraty Jabloo et al., 2017). The authors reviewed 44 studies (published 1995–2015) and reported illness uncertainty (1) was associated with a number of demographic and clinical factors, and (2) adversely affected patients' QOL. However, the review did not include literature published after 2015 or studies focused on caregivers' illness uncertainty. Since 2015, research examining illness uncertainty in adults with cancer and their caregivers has also grown considerably, suggesting that a systematic review and meta-analysis summarizes the current illness uncertainty literature among adult patients with cancer and their caregivers will be a significant and timely contribution to the literature. To this end, the present study conducts a systematic review that consolidates and summarizes the current illness uncertainty literature among adult patients with cancer and their caregivers.

In addition, patients' and caregivers' experiences of illness uncertainty adversely affect their QOL. Yet previous studies seeking ways to mitigate that illness uncertainty have typically

focused either on the patient or on the caregiver, rather than on the patient-caregiver dyad. This focus on individuals overlooks a key insight of interdependence theory: namely, that people in close relationships influence each other's emotions, behaviors, cognition, and outcomes (Rusbult & Van Lange, 2008). Strikingly, no study to date has analyzed the possible interdependent relationships between illness uncertainty and QOL using the patient-caregiver dyad as a unit of analysis. According to Mishel's UIT, an individual's appraisals of illness uncertainty influence their methods of coping, which can in turn influence their QOL. However, the role of patients' and caregivers' coping in the relationship between illness uncertainty and QOL has largely been neglected in the context of the patient-caregiver dyad.

### **Organization of the Dissertation**

This dissertation uses a three-paper format to address different domains of illness uncertainty among patients with cancer and their family caregivers. The first paper, "Correlates of Illness Uncertainty in Patients with Cancer and Family Caregivers: A Systematic Review and Meta-Analysis," is a systematic review and meta-analysis that synthesizes the evidence from prior research on the correlates of illness uncertainty in patients with cancer and their family caregivers.

The second paper, "Illness Uncertainty and Quality of Life in Patients with Advanced Cancer and Family Caregivers: An Actor-Partner Interdependence Model Analysis," aims to (1) to examine the independent and interdependent relationships between illness uncertainty and QOL among patients with advanced cancer and caregivers; and (2) examine the moderating effects of the patient-caregiver relationship and type of cancer on these independent and interdependent relationships. This study is a secondary analysis of the baseline data from a randomized clinical trial for patients with advanced cancer and their family caregivers that tested

the efficacy of a psycho-educational program on psychosocial outcomes. The present study used the Actor-Partner Independence Model to achieve the research aims.

The third paper, “Illness Uncertainty, Coping, and Quality of Life in Patients with Advanced Cancer and Family Caregivers: Using the Actor-Partner Interdependence Mediation Model,” examines the independent and interdependent relationships among patients’ and family caregivers’ illness uncertainty, coping, and QOL using the actor-partner interdependence mediation model. This study utilized the same cross-sectional data as the second paper.

The new evidence generated from the dissertation work will lead to a better understanding of the psychosocial process of cancer survivorship and outcomes for both patients and caregivers. The findings highlight the importance of dyad- and family-focused approaches to improve QOL for cancer patient-caregiver dyads.



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## PAPER I

### CORRELATES OF ILLNESS UNCERTAINTY IN PATIENTS WITH CANCER AND FAMILY CAREGIVERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

#### Introduction

The cognitive state of illness uncertainty occurs when a person has insufficient information to understand illness-related events (Mishel, 1988). Commonly reported among cancer survivors (Garofalo et al., 2009), illness uncertainty is widely recognized as a psychosocial stressor not only for patients with cancer (Ghodraty Jabloo et al., 2017) but also their family caregivers, who experience higher levels of illness uncertainty than patients (Guan et al., 2020a).

To comprehensively understand this phenomenon, Mishel's Uncertainty in Illness Theory (UIT) was used. The UIT posits illness uncertainty has 3 antecedent components: *stimuli frame*, *structure providers*, and *cognitive capacities* (Mishel, 1988). The stimuli frame is the form, composition, and structure of an individual's perceived stimuli, consisting of symptom pattern, event familiarity, and event congruency (Mishel, 1988). Research has found significant associations of patients' levels of illness uncertainty and their cancer-specific symptoms (Guan et al., 2020a). Structure providers are the personal and environmental resources that aid in stimuli formation, including credible authorities (e.g., healthcare providers), social support, and education (Mishel & Braden, 1988). A recent study found patients lacking social support reported elevated levels of illness uncertainty (Kang & Choi, 2019). Cognitive capacities refers to the individual's information-processing ability and any physiological malfunction that might

impair their ability (Mishel, 1988). Mishel's UIT also provides a model of how an individual's appraisal of their illness uncertainty (i.e., dangerous or beneficial) influences their coping, which in turn, affects their adaptation (Mishel, 1988). Patients' high levels of illness uncertainty are associated with avoidant coping strategies, often adversely affecting quality of life (QOL) (Sammarco, 2001; Wonghongkul et al., 2006).

One scoping review that focused on factors influencing illness uncertainty among older patients with cancer and its effects on patient outcomes was identified in the previous literature (Ghodraty Jabloo et al., 2017). The authors reviewed 44 studies (published 1995–2015) and reported illness uncertainty (1) was associated with a number of demographic and clinical factors; and (2) adversely affected patients' QOL. However, the review did not include literature published after 2015 or studies focused on caregivers' illness uncertainty. Since 2015, research examining illness uncertainty in adults with cancer and their caregivers has also grown considerably, suggesting that a systematic review and meta-analysis summarizes the current illness uncertainty literature among adult patients with cancer and their caregivers will be a significant and timely contribution to the literature. To this end, the aim of this paper is to identify the sociodemographic, physical, and psychosocial correlates associated with illness uncertainty in these populations.

## **Methods**

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), and the protocol was registered with PROSPERO (CRD42020216230).

## **Inclusion Criteria**

Articles selected for review met the following inclusion criteria: (1) The study targeted adult patients ( $\geq 18$  years) with cancer or caregivers of adult family members with cancer; (2) illness uncertainty was assessed quantitatively; (3) the study reported numerical estimate of correlation, association, or effect between illness uncertainty and demographic, physical, and psychosocial variables; (4) the study used an observational, non-intervention design (e.g., cohort study, cross-sectional study); and (5) the study is published in English between January 1, 2015 and December 31, 2020. Articles were excluded if the study focus was specific to “diagnostic uncertainty” (i.e., primarily reflects a clinician’s subjective perceptions) (Bhise et al., 2018) or “intolerance of uncertainty” (i.e., focused on a patient’s cognitive, emotional, and behavioral reactions to uncertainty) (Freeston et al., 1994).

## **Search Methods**

A health sciences librarian was consulted to identify databases and to develop the following search terms: *uncertainty AND cancer OR neoplasm OR tumor OR myeloma OR oncolog\* AND patient OR patients OR caregiv\* OR family OR families*. Six scholarly databases were searched: PubMed, Scopus, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and Cochrane Database of Systematic Reviews. Additionally, forward- and backward-citation chaining and Web of Science and Google Scholar searches were conducted.

## **Assessment of Risk of Bias in the Included Studies**

The risk of bias for each study was assessed using the 14-item Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QAT-OCCSS) (National Heart, Lung, and Blood Institute, 2021), which evaluates methodological and reporting parameters to appraise

study quality. Dichotomous ratings (*yes = 1, no = 0*) indicate which of the 14 quality indicators are present, with greater total scores indicating higher study quality and robust reporting. Two authors worked independently to rate each study; disagreements in risk assessments were resolved by discussion. When needed, a third reviewer was called on.

### **Data Abstraction and Synthesis**

Study data were abstracted by myself, and checked by another doctoral student. Abstraction included study details, method/characteristics, sample characteristics, illness uncertainty metric, measure of correlates, and effect size for correlates. Data synthesis was based on UIT (Mishel, 1988), including 3 antecedent components (i.e., stimuli frame, structure providers, and cognitive capacities), coping, and adaptation (e.g., QOL, depression, and anxiety).

### **Meta-Analysis**

The meta-analysis used Person's  $r$  as the effect size metric, and we followed Cohen's definitions of small ( $r = 0.2$ ), medium ( $r = 0.5$ ), and large ( $r = 0.8$ ) effect sizes (Sullivan & Feinn, 2012). If a study reported a nonsignificant correlation but not the value of the point estimate, we recorded the effect size as 0. Knowing this conservative approach might underestimate effect size (Rosenthal, 1995), efforts to obtain unreported data from authors were conducted. When unable to obtain additional data, Peterson and Brown's (2005) suggestion to convert standardized  $\beta$  weights to  $r$  (if  $\beta$  weights ranged  $-0.5$ – $0.5$ ) were followed. A random-effects model provided a weighted-mean estimate of the correlation between each variable and illness uncertainty (Borenstein et al., 2021). When relevant data were available from at least 3 studies, effect sizes were calculated using R software. Thus, forest plots were created to examine the distribution of effects across studies. The  $I^2$  statistic was produced for each analysis to determine extent of heterogeneity. Higgin's variability ranges were employed to estimate 4

categories of heterogeneity: minimal ( $I^2$  range: 0%-40%), moderate (40%-60%), substantial (50%-90%), and considerable heterogeneity (75%-100%) (Higgins et al., 2019). Lower heterogeneity indicates higher consistency and generalizability of meta-analytic findings. Small subsample sizes (< 10 studies) precluded subgroup analyses of effects and publication bias.

## Results

Figure 1.1 summarizes the systematic search yielding 21 articles, of which 9 studies provided sufficient data for meta-analysis.

### Participants Characteristics

Of 21 reviewed studies, 18 focused on patients with cancer, one focused on family caregivers, and 2 included patients and family caregivers (Table 1.1). Patient samples ranged from 14 to 484, with a mean age (across all studies) of 56.8 years (range = 44.2–67.2). Female-only samples were included in 7 studies and 4 studies included only male patients. Nine other studies included participants of both genders/sex but samples were predominantly male ( $n = 6$ ) or female ( $n = 3$ ). Diagnoses reported mixed types of cancer ( $n = 2$ ) or one homogenous type of cancer ( $n = 19$ ) (e.g., breast cancer [ $n = 6$ ], prostate cancer [ $n = 5$ ], hematologic cancer [ $n = 2$ ]). Of the 14 studies reporting cancer stage, 9 included patients at all stages (64%). Phase of cancer survivorship was reported in 17 studies as during treatment ( $n = 9$ ), posttreatment ( $n = 3$ ), or at various points in illness trajectory ( $n = 4$ ). One study focused on patients during active surveillance ( $n = 1$ ). Among the 3 studies that included caregivers, sample sizes ranged from 134–484 (majority female); the mean age of caregivers was 58.7 years (range: 56.7–60). All 6 US-based studies reported participants' race, with a majority (84%) identifying as White.

## Study Characteristics

Table 1.2 summarizes study characteristics of the 21 reviewed studies, of which 15 were cross-sectional and 6 were longitudinal. Studies were conducted in the United States ( $n = 6$ ), South Korea ( $n = 4$ ), China ( $n = 3$ ), Malaysia ( $n = 3$ ), Colombia ( $n = 1$ ), Norway ( $n = 1$ ), Germany ( $n = 1$ ), Iran ( $n = 1$ ), and Japan ( $n = 1$ ). Almost half of the studies were guided by theoretical frameworks, including UIT ( $n = 7$ ), theory of comfort ( $n = 1$ ) (You, et al., 2020), generalized unsafety theory of stress ( $n = 1$ ) (Park & Kim, 2020), transactional theory of stress ( $n = 1$ ) (Song, et al., 2020), and Bodenmann's Systemic Transactional Model ( $n = 1$ ) (Varner et al., 2019). One study used 2 theoretical frameworks: UIT and Systemic Transactional Model (Varner et al., 2019).

## Illness Uncertainty Assessment

Among 21 studies, twenty studies measured illness uncertainty used different versions of the Mishel Uncertainty in Illness Scale (MUIS), including the MUIS-adult version and the MUIS-short version. This scale has also been translated into different language versions, such as Chinese, Japanese, Malaysian, Norwegian, Iranian, and Korean. One study measured illness uncertainty using the cancer- and treatment-specific distress uncertainty subscale (Kuba et al., 2017) (Table 1.2).

## Correlates of Illness Uncertainty in Patient with Cancer

**Sociodemographic factors.** Illness uncertainty was associated with age, gender, race, location, family income, employment status, and change in employment. Age was negatively associated with illness uncertainty (i.e., younger age associated with elevated illness uncertainty) (Tarhani et al., 2020; Zhang et al., 2015). Female gender was associated with higher levels of illness uncertainty (Kuba et al., 2017). Non-White patients reported higher levels of illness

uncertainty than White patients (Guan et al., 2020a). Patients from urban areas reported lower levels of illness uncertainty as compared to patients from rural areas (Tarhani et al., 2020). Patients with lower incomes reported higher levels of illness uncertainty (Jeon et al., 2016; Zhang et al., 2015). Patients employed part- or full-time had higher levels of illness uncertainty than unemployed patients (Shun et al., 2018; Tarhani et al., 2020). As compared with patients became unemployed due to illness, patients whose employment did not change had significantly lower illness uncertainty scores (Lin et al., 2015).

**Stimuli frame.** Stimuli frame consists of symptom pattern, event familiarity and event congruency. Regarding symptom pattern, illness uncertainty was positively associated with higher levels of symptoms (Guan et al., 2020a; Park & Kim, 2020), pain (Kang & Choi, 2019), and fatigue (Park & Kim, 2020); those experiencing more cancer-specific symptoms reported higher levels of illness uncertainty (Guan et al., 2020a). Regarding event familiarity (i.e., experiences with cancer), illness uncertainty was associated with family history of cancer, treatment history, comorbidity, illness phase, and survivorship phase. Findings were mixed regarding the influence of family history of cancer on illness uncertainty level (Adarve & Osorio, 2020; Jeon et al., 2016). Patients who received radiation therapy reported high illness uncertainty levels (Adarve & Osorio, 2020). Patients with comorbid conditions (e.g., diabetes, hypertension) reported low illness uncertainty levels (Zhang et al., 2015). Comparison by stage of prostate cancer (i.e., localized versus advanced or recurrent) showed advanced or recurrent cancer was associated with higher illness uncertainty (Guan et al., 2020a). In contrast, comparison of diagnosis phase showed newly diagnosed patients had higher levels of illness uncertainty than patients under treatment or in follow-up stage (Lin et al., 2015). However, a separate study found as compared with newly diagnosed patients, patients diagnosed for one year reported higher



levels of illness uncertainty (Hagen et al., 2015). Relative to event congruency among patients with prostate cancer, illness uncertainty was associated with higher prostate-specific antigen levels (Guan et al., 2020a). Illness uncertainty was negatively associated with locus of control (i.e., extent individual perceives internal or external factors control life events) (Sharif, 2017). Patients with high unmet care needs had high illness uncertainty levels (Shun et al., 2018).

**Structure provider.** A significant small and negative association between illness uncertainty and social support (weighted  $r = -0.40$ ; 95% CI [-0.51, -0.28]) was found based on  $k = 3$  studies ( $n = 392$ ), with a moderate level of heterogeneity ( $I^2 = 34.5\%$ ) (Table 1.3, Figure 1.2). All studies reported negative associations (range:  $r = -0.33 - -0.51$ ). One study of couples facing prostate cancer found patients' illness uncertainty was negatively related to partner-caregivers' social support (Varner et al., 2019). Findings were mixed regarding the association between illness uncertainty and patients' level of education, with results showing positive (Jeon et al., 2016), negative (Adarve & Osorio, 2020; Lee & Park, 2020; Tarhani et al., 2020), and no association (Guan et al., 2020a). Illness uncertainty was also predicted by the quality of information from healthcare providers (Hagen et al., 2015).

**Coping.** Studies categorized coping in various ways, including problem focused (e.g., instrumental support, religion), active emotional (e.g., positive reframing), and avoidant emotional (e.g., denial) (Ahadzadeh & Sharif, 2018; Sharif et al., 2017). One study distinguished between only active or avoidant coping (Guan et al., 2020b). No studies reported a relationship between and problem-focused coping (Ahadzadeh & Sharif, 2018; Sharif et al., 2017), and the relationships found between illness uncertainty and active-emotional coping were either nonsignificant (Ahadzadeh & Sharif, 2018) or negative (ie, higher illness uncertainty related to less active-emotional coping) (Sharif et al., 2017). Data from  $k = 3$  studies ( $n = 533$ ) reported a

small positive association between illness uncertainty and avoidant coping (weighted  $r = 0.24$ ), but this was nonsignificant (95% CI [-0.03, 0.47]). Additionally, one study reported patients' self-care was negatively correlated with illness uncertainty (Zhang et al., 2015). Considerable heterogeneity ( $I^2 = 90.7%$ ) was found across studies. The study of patient-caregiver couples facing prostate cancer found patients' illness uncertainty was positively related to caregivers' non-supportive behaviors (e.g., avoiding patient when patient was not feeling well) (Varner et al., 2019).

**Adaptation.** Illness uncertainty was associated with adaptation outcomes including QOL, anxiety, and depression. A significant, small, and negative association between illness uncertainty and QOL (weighted  $r = -0.47$ ; 95% CI [-0.61, -0.29]) as indicated by data from  $k = 5$  studies ( $n = 646$ ) was identified. Despite considerable heterogeneity ( $I^2 = 84.5%$ ), all studies reported negative associations (rang:  $r = -0.31$  to  $-0.73$ ). Additionally, uncertainty was negatively associated with prostate-specific QOL (Parker et al., 2016), functional QOL (Kang & Choi, 2019), symptom QOL (Kang & Choi, 2019), and QOL subdomains such as physical well-being and emotional/mental well-being (Hagen et al., 2015). Data from  $k = 4$  studies ( $n = 377$ ) indicated a significant, medium positive association between illness uncertainty and anxiety (weighted  $r = 0.51$ ; 95% CI [0.21, 0.72]). These studies had considerable heterogeneity ( $I^2 = 91.2%$ ). Data from  $k = 4$  studies ( $n = 377$ ) indicated a significant, medium positive association between illness uncertainty and depression (weighted  $r = 0.54$ ; 95% CI [0.25, 0.74]) also with considerable heterogeneity ( $I^2 = 90.8%$ ).

Additionally, a few studies specified illness uncertainty was associated with other adaptations such as perceived stress (Park & Kim, 2020), posttraumatic stress syndrome (Kuba et al., 2017), and fear of disease progression (Parker et al., 2016). Illness uncertainty was negatively

associated with comfort in the physical, psychological, social, and environmental contexts (You et al., 2020), and with perceived recovery (Jeon et al., 2016).

### **Correlates of Illness Uncertainty in Cancer Caregiver**

Only 3 articles focused on illness uncertainty among caregivers of patients with various cancer diagnoses. As compared with non-White partner-caregivers, White partner-caregivers reported higher levels of illness uncertainty (Guan et al., 2020a). One study found caregivers' illness uncertainty was associated with caregivers' general health, caregivers' perceptions of the influence side effects on themselves, patients' prostate-specific antigen levels, and caregivers' perceived levels of social support (Guan et al., 2020a). Another study showed caregivers' illness uncertainty was negatively associated with their QOL (Song et al., 2020).

### **Risk of Bias Assessment**

Calculation of a total quality score (based 14 items) for each reviewed study (range 6–10; average quality = 8) indicated methodological quality was fair overall (Table 1.4). Regarding specific QAT-OCCSS items, all studies had clearly articulated research questions, clearly specified study populations and sample eligibility criteria, and defined independent and dependent variable measures. The most common methodological limitation was the lack of a sample size justification or a power calculation for the analysis. The majority of studies did not report whether the participant rate of eligible persons was at least 50%. Most studies were cross-sectional; therefore, exposures were not measured before outcomes, and study periods were insufficient to observe associations between exposure and outcome.

## **Discussion**

Based on UIT, findings identified distinct correlates for illness uncertainty in patients with cancer, including sociodemographic factors, stimuli frame, structure providers, coping, and

adaptation. Notable effect sizes were observed for relationships between illness uncertainty and social support, QOL, depression, and anxiety. Caregivers' illness uncertainty was associated with race, caregivers' general health, caregivers' perceptions of the influence side effects on themselves, patients' prostate-specific antigen levels, social support, and QOL. However, insufficient data precluded to examine the effect size of correlates of illness uncertainty in family caregivers.

### **Correlates of Illness Uncertainty**

For stimuli frame, illness uncertainty was positively associated with patients' symptoms. As UIT suggests, when patients experience a greater numbers of symptoms, it increases difficulty in tracking and distinguishing between symptom cause (disease or treatment). In turn, difficulty in distinguishing symptom cause prevents patients from recognizing symptom patterns, contributing to illness uncertainty (Mishel & Braden, 1988). Results were mixed regarding the associations between illness uncertainty and family history of cancer. Although a family history of cancer might increase patients' familiarity with cancer, which might decrease illness uncertainty, such family history can also evoke fear and risk of cancer, which might increase illness uncertainty. Mishel's reconceptualized UIT (1990) suggests illness uncertainty evolves over time, positing the longer a patient lives with illness and continual uncertainty, the more positively they appraise uncertainty. In other words, patients find meaning in learning to live with illness uncertainty. This claim is supported by research showing patients newly diagnosed with cancer had higher illness uncertainty scores than patients in post-treatment (Mishel, 1990). However, a separate study was contradictory: patients who had lived with a cancer diagnosis for 1 year reported higher levels of illness uncertainty than those newly diagnosed (Hagen et al., 2015). Further longitudinal research is needed to detect changes in illness uncertainty over time.

According to UIT, education as a structure provider helps patients know where and how to get health information, thereby reducing illness uncertainty. However, we found evidence conflicting with Mishel's view of education, which is corroborated by results of a previous review examining older patients with cancer (Ghodraty Jabloo et al., 2017). Further research is needed to determine the reasons for the variability in these associations. This systematic review supports the effect of social support as a structure provider that decreases illness uncertainty. As UIT holds, social support from a patient's social network can alleviate illness uncertainty by providing health information, clarifying situations, and sharing characteristics and environments. Also based on UIT, information provided by healthcare providers and other credible authorities influences illness uncertainty. However, this review found only one study exploring this relationship (Hagen et al., 2015). Given the important role of healthcare providers in patients' ability to deal with illness, future research should address this variable.

The current literature has provided inconsistent findings regarding the link between illness uncertainty and active-emotional coping. This review found no statistically significant relationship between illness uncertainty and avoidant-coping strategies. The complicated relationship between coping and illness uncertainty is supported by UIT. This theory proposes when illness uncertainty is evaluated as a danger, then threat is reduced by using problem-focused coping strategies. If that method cannot be used, then emotional-coping strategies are used to respond to illness uncertainty (Mishel, 1988). These inconsistent and complex findings suggest the relationship between illness uncertainty and coping warrant further exploration.

Despite the mixed findings on the antecedents of illness uncertainty in the literature, results were clearer regarding the outcomes of illness uncertainty. The significant link between illness uncertainty and QOL confirms the UIT tenet that patients' illness uncertainty influences

their adaptation (Mishel, 1988). This significant negative association is also supported in Ghodraty and colleagues' (2017) scoping review. However, because few studies controlled for potential confounding variables, it remains unknown whether illness uncertainty is an independent predictor of QOL (Ghodraty Jabloo et al., 2017). In contrast, this review controlled for potential confounding variables in all the included studies and the findings indicate illness uncertainty independently influences aspects of QOL. Similarly, the literature has reported significant positive relationships between illness uncertainty and anxiety and depression (Ghodraty Jabloo et al., 2017), which might be explained as illness uncertainty being an intolerable state that interferes with the individual's ability to prepare for negative events, thereby causing such events to seem more stressful (Grupe & Nitschke, 2011).

Another important finding was that surprisingly few studies had examined caregivers' illness uncertainty. This gap is troubling given that caregivers reported not only higher levels of illness uncertainty than patients (Guan et al., 2020a) but also that they lacked sufficient information about managing illness uncertainty (Ervik et al., 2013). The study of partner-caregivers caring for a patient with prostate cancer demonstrated the significant relationship between patients' illness status and caregivers' illness uncertainty, which validates the importance of considering characteristics of patients' illness when studying caregivers' illness uncertainty (Guan et al., 2020a). Additionally, this work also found a positive association between caregivers' illness uncertainty and caregivers' health symptoms, suggesting healthcare providers need to thoroughly question caregivers to understand the impact of illness uncertainty on caregivers' health, symptoms, and capacity to provide care. Similarly, we found caregivers' adaptation to cancer demonstrated a negative relationship between illness uncertainty and QOL.

However these conclusions were based on a small sample of studies and suggest future research should explore how illness uncertainty influences caregivers.

As mentioned, one study with couples facing prostate cancer used dyadic data to explore associations between illness uncertainty and psychosocial constructs (Varner et al., 2019). Patients' sustained illness uncertainty was positively related to decreased supportive behaviors from caregivers (e.g., avoiding patient interaction when patient was not feeling well) (Varner et al., 2019). These findings not only demonstrated the association between illness uncertainty and marital functioning but also supported interdependence theory by showing the response of each partner to an event influenced outcomes of the other partner (Rusbult & Van Lange, 2003). This dyadic perspective is uncommon in cancer research, yet the findings demonstrate the value of this perspective. In addition to examining illness uncertainty at the individual level, future research should identify illness uncertainty within couple dyads.

### **Methodological Quality of the Included Studies**

Study findings should be considered in the context of several methodological limitations. Overall, the 21 reviewed studies were assessed as having fair quality reporting of their findings. It is noteworthy that much of what we know about patients' illness uncertainty comes from patients with breast or prostate cancer, whereas little is known about illness uncertainty among those experiencing other cancer types. This reality highlights the need for researchers to include a more diverse range of patients. Additionally, most available illness uncertainty studies have used cross-sectional designs, making it difficult to draw causal inferences about the relationships between illness uncertainty and other variables. Longitudinal studies should be undertaken to clarify these relations and to examine if and how illness uncertainty changes over time (Mishel,

1990) and to determine if illness uncertainty is associated with other variables at various points in the cancer trajectory.

### **Strengths and Limitations**

This is the first meta-analysis of the illness uncertainty literature on adult patients with cancer and their family caregivers. The two main study strengths are its contributions to the literature (1) by synthesizing illness uncertainty among family caregivers; and (2) by assimilating and analyzing a large amount of empirical data through meta-analysis. The meta-analysis provides a better representation of the average effect size across studies than a narrative review. However, this review also has limitations. First, only quantitative studies were included. Although qualitative studies provide important perspective, quantitative studies were used to determine the average effect size across studies, which is missing in the literature. However, many studies did not report an effect size; therefore, the reported effects may not be representative of all extant research in this area. Second, given this meta-analysis included only 9 studies, the moderators of the relationship between illness uncertainty and other variables could not be examined.

### **Clinical Implications**

Knowing the correlates of illness uncertainty among patients with cancer and their caregivers can inform efforts to improve strategies for managing illness uncertainty and addressing its sources. For example, whereas prior studies underscored social support as helping patients with cancer manage illness uncertainty (Guan et al., 2021), study findings revealed a negative association between illness uncertainty and caregivers' social support. Thus, this study provides promising findings regarding the relationship between illness uncertainty and QOL for patients and caregivers and suggests illness uncertainty can be managed with a likely positive



impact on QOL. The dyadic impact of illness uncertainty on marital and family functioning not only highlights the importance of dyad- and family-focused approaches to improving outcomes for cancer patient-caregiver dyads but also provides sound evidence for integrating caregivers into healthcare delivery teams.

### **Research Implications**

This review highlights the need for more research on correlates of illness uncertainty among patients with cancer and their caregivers. Future research needs to include a greater diversity of cancer types to better understand how the disease influences participants' illness uncertainty. Additionally, more research attention should be given to the correlates of illness uncertainty among caregivers. Similarly, additional research is needed 1) to clarify the roles played in illness uncertainty by family history of cancer, survivorship phase, education, and coping strategies; and 2) to identify moderators of the relation of illness uncertainty to correlates that might have different implications for patients with different cancer stages and phases. Last, longitudinal studies are needed to describe the trajectory of illness uncertainty and the interrelationships of predictive variables and illness uncertainty over time.

### **Conclusion**

This systematic review and meta-analysis identified correlates of illness uncertainty among patients with cancer and their family caregivers. These findings contribute to the growing literature on managing illness uncertainty among the patients with cancer and their family caregivers.

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**Table 1.1 Description of Population Characteristics (n = 21)**

First Author Year	Country	N	Age	Gender	Race	Cancer type	Stage	Phase of Cancer Survivorship
Adarve 2020	Colombia	50	44.8	58% female	NR	Hematologic	NR	Undergoing hematopoietic stem cell transplantation
Ahadzadeh 2018	Malaysia	135	52.1	100% female	51.9% Chinese	Breast	Stage I- III	NR
Guan, Guo 2020	US	PT: 134 CG: 134	PT: 62.57 CG: 58.92	pt: 100% male cg: 100% female	PT: 85% White; CG: 83% White	Prostate	All stages	At various points in the illness trajectory
Guan, Santacroce 2020	US	263	63.1	100% male	83.3% White	Prostate	All stages	At various points in the illness trajectory
Hagen 2015	Norway	209	57.9	100% female	NR	Breast	NR	In curative treatment
Jeon 2016	South Korea	146	54.66	63% male	NR	Gastric	All stages	After gastrectomy
Kang 2019	Korea	110	NR	55.5% female	NR	Multiple myeloma	NR	Receiving chemotherapy
Kuba 2017	Germany	239	50.4	62% male	NR	Hematologic	NR	Undergoing hematopoietic stem cell transplantation
Lee 2020	Korea	148	51.87	100% female	NR	Breast and thyroid	All stages	In treatment
Lin 2015	US	186	44.2	53% male	80% White	Brain	All stages	At various points in the illness trajectory
Park 2020	South Korea	210	48.09	100% female	NR	Breast	All stages	Undergoing radiotherapy
Parker 2016	US	180	67.2	100% male	86.1% White	Prostate	NR	Undergoing active surveillance

US							
Sasai 2017 Japan	14	60.5	57% male	NR	Lung	IV	After initial treatment; chemotherapy or/and radiation therapy
Sharif, Ahadzadeh 2017 Malaysia	135	51.18	100% female	51.9% Chinese	Breast	Stage I- III	NR
Sharif 2017 Malaysia	118	50.95	100% female	49.2% Chinese	Breast	Stage I- III	NR
Shun 2018 China	90	62.53	72.2% male	NR	Live	NR	Receiving medical treatment
Song^ 2020 US	Prostate CG: 263; Advanced cancer CG: 484	Prostate CG: 59; Advanced cancer CG: 56.7	Prostate CG: 100% female; Advanced cancer CG: 55.8% female	Prostate CG: 83% White; Advanced cancer CG: 82.5% White	Prostate; lung, colorectal, breast, and prostate	All stages; Stage III or IV	At various points in the illness trajectory
Tarhani 2020 Iran	163	52.41	66.3% female	NR	mixed types	All stages	NR
Varner 2019 US	PT:165; CG:165	PT: 63 CG: 60	PT:100% male; CG: 96.4% female	PT: 87% White CG: 88% White	Prostate	Stage I or II	Undergoing open radical prostatectomy
You 2020 China	21	45.24	66.7% male	NR	Leukemia	NR	After chemotherapy treatment
Zhang 2015 China	97	51.76	100% female	NR	Breast	All stages	Receiving chemotherapy/radiotherapy

Note. ^ This study included 2 data samples. NR = Not reported; PT = Patient; CG = Caregiver

**Table 1.2 Description of Study and Outcomes (n = 21)**

First author Year	Study Design	Theoretical Frameworks	Uncertainty Measurement	Correlates	Scale	Results
Adarve 2020	Cross-sectional	UIT	MUIS-Spanish	Education, family history of cancer, and history of radiotherapy treatment	NA	Higher level of uncertainty was associated with education up to high school (OR = 4.1), family history of cancer (OR = 6.9), and previous radiotherapy treatment (OR = 0.12).
Ahadzadeh# 2018	Cross-sectional	NR	SF-MUIS-Malaysia	QOL, coping	FACT-B, Brief COPE	Uncertainty was related to QOL ( $\beta = -0.362, P < .001$ ) and was not significantly related to active emotional, avoidant emotional, and problem-focused coping. Uncertainty for patients and partners was associated with general symptoms ( $\beta = 0.67, P < 0.001$ ); prostate cancer-specific sexual ( $\beta = -1.05, P < 0.05$ ) and hormonal symptoms ( $\beta = -1.38, P < 0.01$ ); prostate-specific antigen ( $\beta = 0.01, P < 0.01$ ); and levels of internal (ie, dyadic communication about cancer) ( $\beta = -4.47, P < 0.001$ ) and external social support (ie, support from others) ( $\beta = -0.12, P < 0.001$ ). Compared to patients with localized prostate cancer and their partners, patients with advanced or recurrent prostate cancer and their partners reported higher levels of illness uncertainty ( $P < 0.001$ ). Uncertainty for patients was associated with urinary symptoms ( $\beta = -3.13, P < 0.001$ ) and uncertainty for partner was associated with patients' urinary symptoms ( $\beta = -0.83, P < 0.05$ ). Uncertainty was not associated with education. Non-White partners had the lowest levels of illness uncertainty, whereas non-White patients had the highest levels of illness uncertainty.
Guan#, Guo 2020	Longitudinal	UIT	MUIS	General symptoms, prostate cancer-specific symptoms, internal social support, social support from others, PSA, cancer stage, education, race	Subscale of the Risk of Distress Scale, EPIC, MIS, PRQ	Uncertainty was associated with avoidant coping ( $\beta = 0.297, P < .001$ ), physical well-being ( $\beta = -0.263, P < .001$ ) and mental well-being ( $\beta = -0.244, P < .001$ ). Uncertainty was not significantly associated with active coping.
Guan#, Santacroce 2020	Cross-sectional	UIT	MUIS	Coping, QOL (physical well-being and mental well-being)	Brief COPE, SF-12	Uncertainty was associated with anxiety ( $r = 0.35, P < .01$ ), depression ( $r = 0.28, P < .01$ ), social support ( $r = -0.27, P < .01$ ), emotional well-being ( $r = 0.30, P$
Hagen# 2015	Cross-sectional	NR	SF-MUIS-Norwegian	Anxiety and depression, social support, emotional well-being, quality of information provided	HADS, FACT-E subscales, QPI	



Jeon 2016	Cross-sectional	NR	MUIS -Korea	Education, income, family history of cancer, perceived recovery	Self-developed scale	< .01), and quality of information provided ( $r = 0.46$ , $P < .01$ ). Participants with an education level of high school graduate or less ( $P < .001$ ), with a lower monthly income ( $P = .024$ ), and without family history of gastric cancer ( $P = .024$ ) showed higher levels of uncertainty.
Kang# 2019	Cross-sectional	NR	MUIS-Korea	QOL (global, functional symptom), pain, anxiety and depression, social support	EORTC-QLQ-C30, HAQ Pain Scale, PG-VAS, HADS; 6-item scale developed by Korean scholar	Uncertainty was associated with global QOL ( $r = -0.73$ , $P < .001$ ), functional QOL ( $r = -0.52$ , $P < .001$ ), symptom QOL ( $r = 0.60$ , $P < .001$ ), anxiety ( $r = 0.74$ , $P < .001$ ), depression ( $r = 0.75$ , $P < .001$ ), social support ( $r = -0.51$ , $P < .001$ ).
Kuba 2017	Prospective	NR	Cancer and treatment specific distress-uncertainty subscale	Gender, PTSS	PCL-C	Uncertainty was associated with gender ( $\beta = 0.38$ , $P = .000$ ) and PTSS ( $\beta = 0.38$ , $P = .000$ ).
Lee 2020	Cross-sectional	NR	MUIS-Korea	QOL, social support, education, satisfaction with financial status, smoking	EORTC QLQ-C30, MSPSS	Uncertainty was higher for patients with less than a high school education ( $t = 4.048$ , $P < .001$ ), dissatisfied with their financial status ( $F = 3.760$ , $P = .027$ ), and smokers smoking ( $t = 2.195$ , $P = .030$ ). Uncertainty was correlation with social support ( $r = -.335$ , $P < .001$ ) and QOL ( $r = -.312$ , $P < .001$ ).
Lin 2015	Cross-sectional	UIT	MUIS	Phases of treatment process; employment change	NA	Compared to newly diagnosed patients, patients at treatment and follow-up had significantly lower total scores of uncertainty. Patients whose employment status did not change due to the illness had a significantly lower MUISBT score (ie, lower by -7.36) than that of those without employment due to the illness.
Park# 2020	Cross-sectional	Generalized Unsafety Theory of Stress	MUIS-Korea	Anxiety and depression, symptom assessment, social support, perceived stress, fatigue	HADS, MSAS-SF, MSPSS, PSS, FACIT-fatigue scale	Uncertainty was associated with anxiety and depression ( $\beta = 0.69$ , $P = 0.004$ ), symptom assessment ( $\beta = 0.35$ , $SE = 0.18$ , $P = 0.004$ ), social support ( $\beta = -0.08$ , $SE = 0.06$ , $P = 0.005$ ), perceived stress ( $\beta = 0.35$ , $SE = 0.18$ , $P = 0.004$ ), and fatigue ( $\beta = 0.39$ , $SE = 0.09$ , $P = 0.004$ )
Parker 2016			MUIS	QOL (physical well-being and mental well-being),	SF-12, EPIC,	

	Longitudinal	NR		prostate-specific QOL, fear of disease progression	MAX-PC-fear of recurrence subscale	Uncertainty was associated with physical well-being ( $\beta = -0.099, P < 0.001$ ), mental well-being ( $\beta = -0.128, P < 0.001$ ), all of the prostate-specific QOL (urinary, $\beta = -0.115, P < 0.001$ ; bowel, $\beta = -0.063, P = 0.02$ ; sexual, $\beta = -0.177, P = 0.004$ ; hormonal, $\beta = -0.142, P < 0.001$ ; satisfaction, $\beta = -0.529, P < 0.001$ ), and fear of disease progression ( $\beta = 0.072, P < 0.001$ ).
Sasai 2017	Cross- sectional	NR	MUIS-Japan	Emotions	POMS-Brief Form	Uncertainty was associated with emotion ( $r = 0.735, P = 0.003$ ).
Sharif#, Ahadzadeh 2017	Cross- sectional	UIT	SF-MUIS- Malaysia	QOL, coping, anxiety and depression	FACT-B, Brief COPE, HADS	Uncertainty also was correlated with QOL ( $r = -0.406, P < 0.01$ ), anxiety ( $r = 0.274, P < 0.01$ ) and depression ( $r = 0.319, P < 0.01$ ), avoidant coping ( $r = 0.218, P < 0.05$ ), active emotional coping ( $r = -0.297, P < 0.01$ ). No significant relationship between problem-focused coping and uncertainty.
Sharif# 2017	Cross- sectional	NR	SF-MUIS- Malaysia	Locus of control, QOL, anxiety and depression	Levenson's Locus of Control Scale short form, FACT-B, HADS	Uncertainty was associated with an external locus of control ( $r = -0.285, P < 0.01$ ), QOL ( $r = -0.406, P < 0.01$ ), anxiety ( $r = 0.287, P < 0.01$ ) and depression ( $r = 0.321, P < 0.01$ ).
Shun 2018	Longitudinal	UIT	MUIS-Chinese	Employment status, supportive care needs	SCNS-Short form	Patients with part- or full-time jobs had higher levels of uncertainty ( $\beta = 2.215, P = 0.022$ ). Those patients with higher levels of unmet care needs and those with higher levels of uncertainty before discharge had higher levels of uncertainty over time ( $\beta = 0.080, P = 0.000$ ).
Song 2020	Cross- sectional	Transactional Theory of Stress	SF-MUIS/ MUIS	QOL	Caregiver FACT-G	Uncertainty was associated with caregiver QOL ( $r = -0.53, P < 0.0001$ ).
Tarhani 2020			MUIS-A-Iran	Age, education, job type, inhabitation, therapy type	NA	The average uncertainty score of patients who were 60 years of age or more was less than the average uncertainty score of patients below 60 years of age ( $P = 0.007$ ). The average uncertainty average score in lower-education patients was more than those with a high school diploma or above ( $P = 0.018$ ). The average uncertainty score for employed patients was lower than for unemployed patients ( $P < 0.05$ ). The average uncertainty score for in city inhabitants was lower than for rural inhabitant patients ( $P = 0.025$ ). The average uncertainty average score for patients

	Cross-sectional	NR				undergoing other therapies was lower than for those undergoing chemotherapy ( $P = 0.027$ ). Those undergoing chemotherapy and surgery experienced higher uncertainty than those undergoing only chemotherapy ( $P = 0.049$ ).
Varner 2019	Longitudinal	STM	MUIS	Non-supportive behaviors, perceived support	Non-supportive Behaviors Scale, SPS	Uncertainty among patients was related to more non-supportive behaviors from partners ( $\beta = 0.27$ , $P < .001$ ) and partners' perceived support ( $\beta = -0.28$ , $P < .001$ ). A person's own change in illness uncertainty did not have any significant effects on their own assessment of their partner's non-supportive behaviors.
You 2020	UIT		MUIS-Chinese	Comfort	GCQ	Uncertainty was associated with comfort ( $\beta = -0.989$ , $P < 0.001$ ).
Zhang 2015	Longitudinal	Theory of comfort	MUIS-A-Chinese	Age, family income, type of therapy, comorbidity, self-care behavior	ASAS-R	Uncertainty was associated with age ( $r = -0.280$ , $P < 0.01$ ), family income ( $r = -0.321$ , $P < 0.01$ ), type of therapy ( $r = 0.294$ , $P < 0.01$ ), comorbidity ( $r = -0.247$ , $P < 0.05$ ), self-care behavior ( $r = -0.314$ , $P < 0.01$ ).

Note. # = included in the meta-analysis

NR = Not reported; UIT = Uncertainty in Illness Theory; STM = Systemic Transactional Model

OR = Odds ratio

NA = Not Applicable; MUIS = Mishel Uncertainty in Illness Scale; SF-MUIS = Mishel Uncertainty in Illness Scale-Short form; QOL = Quality of life; FACT-B = Functional Assessment of Cancer Therapy-Breast; EPIC = Expanded Prostate Cancer Index Composite; MIS = Lewis' Mutuality and Interpersonal Sensitivity Scale; PRQ = Personal Resource Questionnaire; SF-12 = 12-Item Short Form Health Survey; HADS = Hospital Anxiety and Depression Scale; QPI = Quality of Patient Information; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire; HAQ = Health Assessment Questionnaires; PG-VAS = Patient Global Visual Analogue Scale; PTSS = Posttraumatic stress syndrome; PCL-C= PTSD Checklist-Civilian Version; MSPSS= Multidimensional Scale of Perceived Social Support; MSAS-SF = Memorial Symptom Assessment Scale-Short Form; PSS = Perceived Stress Scale; FACIT = Functional Assessment of Chronic Illness Therapy; MAX-PC = Memorial Anxiety Scale for Prostate Cancer; POMS = Profile of Mood States-Brief Form; SCNS = Supportive Care Needs Survey; FACT-G = Functional Assessment of Cancer Therapy General; SPS = Social Provisions Scale; GCQ = General Comfort Questionnaire; MUIS-A = Mishel Uncertainty in Illness Scale- Adult version; ASAS-R = Appraisal of Self-Care Agency Scale Revised

**Table 1.3 Meta-analysis Results for Correlates with Illness Uncertainty**

Correlate	<i>k</i>	<i>n</i>	<i>r</i>	95% CI for <i>r</i>		<i>I</i> <sup>2</sup> %
				Lower	Upper	
Social support	3	392	-0.40	-0.51	-0.28	34.5
Avoidant coping	3	533	0.24	-0.03	0.47	90.7
Quality of life	5	646	-0.47	-0.61	-0.29	84.5
Anxiety	4	377	0.51	0.21	0.72	91.2
Depression	4	377	0.54	0.25	0.74	90.8

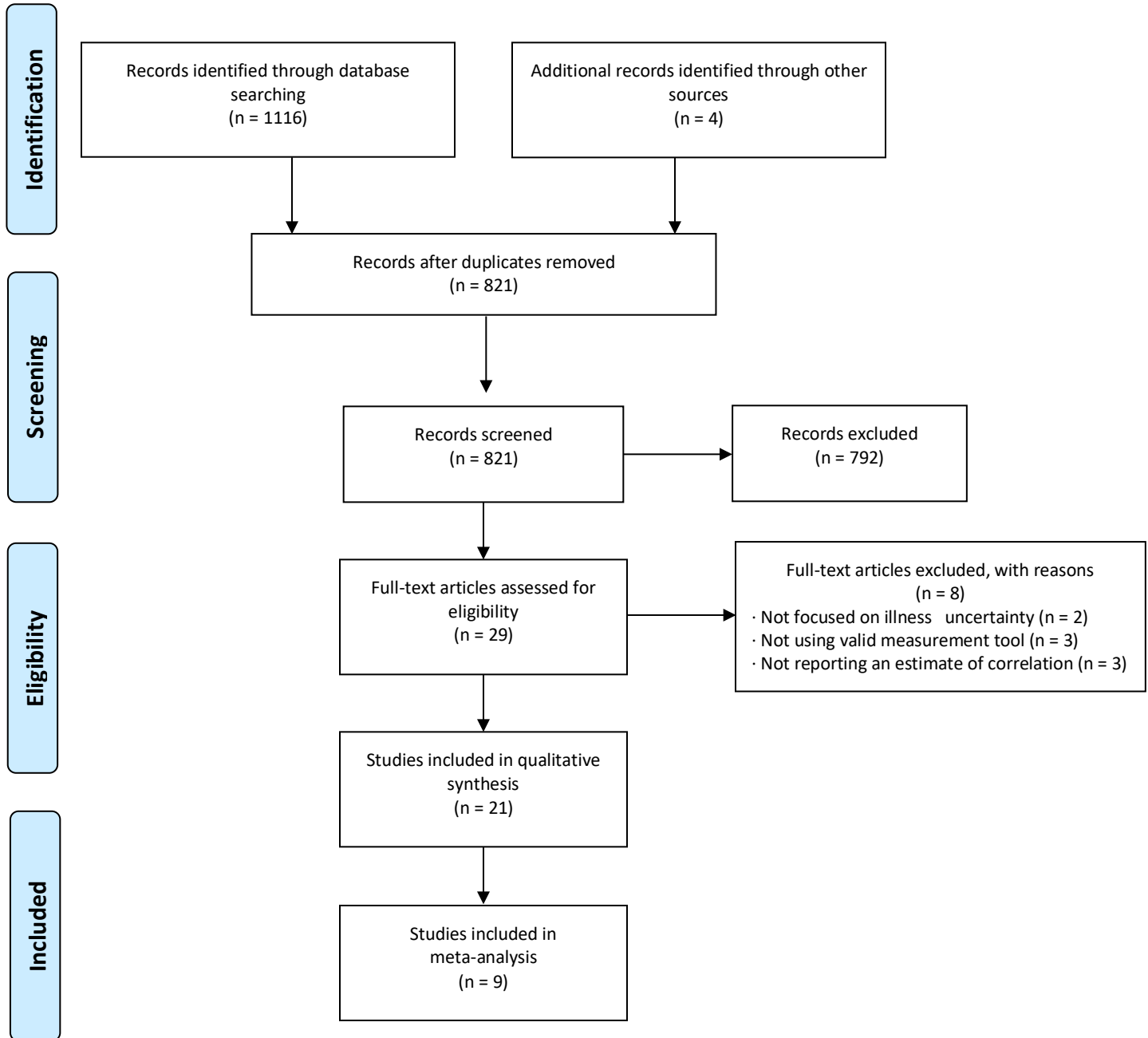
*Note.* *k* = number of studies; *n* = sample size; CI = confidence interval; *r* = effect size.

**Table 1.4 Methodological Quality of Included Studies**

First Author, Year	Research question	Study population	Eligible rate	Uniform eligibility criteria	Sample size justified	Exposure assessed before outcome measured	Sufficient timeframe to observe effect	Different levels of exposure of interest	Exposure measure and assessment	Repeated exposure assessment	Outcome measure	Masked outcome to assessors	Follow-up rate	Statistical analyses	Total Score
Adarve, 2020	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7
Ahadzadeh, 2018	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7
Guan & Guo, 2020	1	1	0	1	0	0	0	1	1	1	1	NA	1	1	9
Guan & Santacroce, 2020	1	1	1	1	0	0	0	1	1	0	1	NA	NA	1	8
Hagen, 2015	1	1	1	1	1	0	0	1	1	0	1	NA	NA	1	9
Jeon, 2016	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	N	6
Kang, 2019	1	1	NR	1	1	0	0	1	1	0	1	NA	NA	1	8
Kuba, 2017	1	1	NR	1	0	1	1	1	1	1	1	NA	0	1	10
Lee, 2020	1	1	1	1	1	0	0	1	1	0	1	NA	NA	1	9
Lin, 2015	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7
Park, 2020	1	1	NR	1	1	0	0	1	1	0	1	NA	NA	1	8
Parker, 2017	1	1	NR	1	0	0	0	1	1	1	1	NA	0	1	8
Sasai, 2017	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	N	6
Sharif & Ahadzadeh, 2017	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7
Sharif, 2017	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7
Shun, 2018	1	1	1	1	0	0	0	1	1	1	1	NA	1	1	9
Song, 2020	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	N	6
Tarhani, 2020	1	1	NR	1	1	0	0	1	1	0	1	NA	NA	1	8
Varner, 2019	1	1	NR	1	0	1	1	1	1	0	1	NA	NA	1	9
You, 2020	1	1	1	1	0	0	0	1	1	1	1	NA	1	1	10
Zhang, 2015	1	1	NR	1	0	0	0	1	1	0	1	NA	NA	1	7

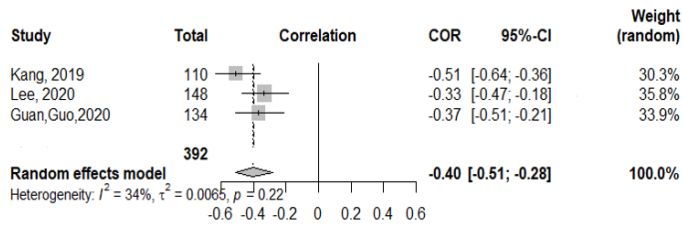
Note. 1 = Yes; 0 = No; NA = Not Applicable; NR= Not reported.

Figure.1.1 PRISMA 2009 Flow Diagram

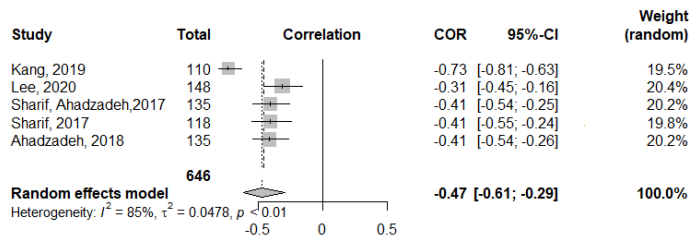


**Figure.1.2 Results of Individual Studies and Overall Effect Size for Correlates of Illness Uncertainty Among Patients with Cancer**

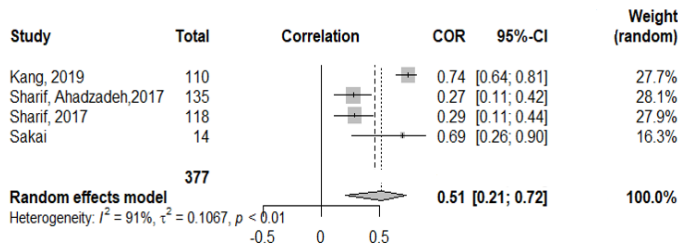
**Social support**



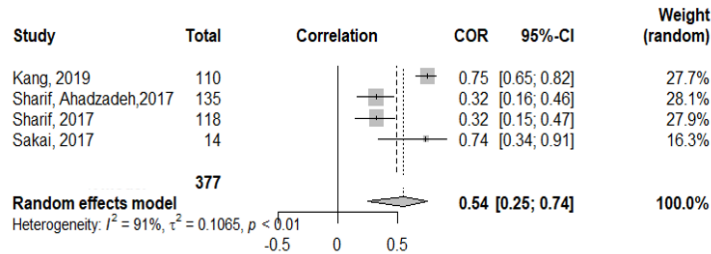
**Quality of life**



**Anxiety**



**Depression**



## **PAPER II**

### **ILLNESS UNCERTAINTY AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER AND FAMILY CAREGIVERS: AN ACTOR-PARTNER INTERDEPENDENCE MODEL ANALYSIS**

#### **Introduction**

The diagnosis of advanced cancer poses a significant stressor to patients and their family caregivers (Martinez et al., 2020; Moghaddam et al., 2016; Wang et al., 2018). Patients with advanced cancer may experience the challenge of have an inaccurate understanding of their own prognosis (Nipp et al., 2017), difficult decisions regarding further treatment, and unpredictable future outcomes (Thorne et al., 2013). This lack of information contributes to illness uncertainty, which is defined as “the cognitive state created when patients cannot determine the meaning of illness-related events (Mishel, 1988). As patients’ illness progress, such illness uncertainty also extends to their family caregivers (Mazanec et al., 2011).

A considerable amount of research has demonstrated that patients’ experiences of illness uncertainty adversely affect their quality of life (QOL) (Guan et al., 2020; Kang & Choi, 2019; Lee et al., 2020). Similarly, other research confirmed that the same association exists among family caregivers (Song et al., 2020). Yet previous studies examining the relationship between illness uncertainty and QOL have typically focused either on the patient or on the caregiver, rather than on the patient-caregiver dyad (Guan et al., under review). This focus on individuals overlooks a key insight of interdependence theory: namely, that people in close relationships influence each other’s emotions, behaviors, cognition, and outcomes (Rusbult & Van Lange, 2008). Strikingly, no study to date has analyzed the possible independent and interdependent



relationships between illness uncertainty and QOL simultaneously using the patient-caregiver dyad as a unit of analysis.

Furthermore, the interaction of patients and caregivers can be complex and is influenced by many factors. A meta-analysis has also revealed considerable differences between caregivers' roles. For example, compared to adult children, spousal caregivers were at higher risk for perceiving burden associated with their caregiving responsibilities (Pinquart & Sorensen, 2011). Moreover, the responsibilities and subjective experience of caregivers vary depending on the patient's type of cancer, stage of illness, and other treatment-related conditions (LeSeure & Chongkham-Ang, 2015). However, it remains unknown whether the possible influence of patients' and caregivers' illness uncertainty on each other's QOL will differ by patient-caregiver relationship and type of cancer. Understanding the heterogeneity within and across patient-caregiver dyads may offer useful findings for developing tailored interventions in clinical and research settings.

To fill these gaps, the present study used the actor-partner independence model (APIM) (Kenny et al., 2020) in a sample of patients with advanced cancer and their family caregivers to (1) examine whether an individual's (either a patient or caregiver) illness uncertainty was associated with their own QOL (i.e., an actor effect) and their partner's QOL (i.e., a partner effect) (Figure 2.1); (2) examine the moderating effects of patient-caregiver relationship (i.e., spouse vs. non-spouse such as children, other relatives) on the actor and partner effects of illness uncertainty on QOL; and (3) examine the moderating effects of the type of cancer (i.e., breast, lung, colorectal, and prostate cancer) on the actor and partner effects of illness uncertainty on QOL. The three hypotheses for this study are as follows:

**Hypothesis 1:** Illness uncertainty in patients and caregivers will be negatively associated with their own QOL (actor effect) and the QOL of their dyadic partner (partner effect).

**Hypothesis 2:** These actor and partner effects differ by patient-caregiver relationship (i.e., spouse vs. non-spouse).

**Hypothesis 3:** These actor and partner effects differ by type of cancer (i.e., breast, lung, colorectal, and prostate cancer).

## **Methods**

### **Study Design**

In this cross-sectional study, secondary analysis was used to analyze the baseline data from a randomized clinical trial that examined the effects of a dyadic-based psycho-educational intervention on psychological outcomes for patients with advanced cancer and their family caregiver (Clinicaltrial.gov registration number: NCT00709176). Details about the study design and procedure have been published elsewhere (Northouse et al., 2013). Institutional Review Board approval was obtained from the patient's cancer centers and the University of Michigan (coordinating site). This secondary analysis of the extant deidentified data involved no direct contact with participants and was exempted by the Institutional Review Board at the University of North Carolina at Chapel Hill.

### **Sample**

This study sample included patients with advanced cancer and their family caregivers at the baseline ( $N = 484$  dyads). Eligible patients had either a new diagnosis of advanced lung, colorectal, breast, or prostate cancer (i.e., stage III or IV) during the previous 6 months or a progression of their advanced disease during this time frame. Patients also had to have a life

expectancy greater than or equal to 6 months (as indicated by their oncologist), be 21 years of age or older, live within 75 miles of one of the four participating cancer centers, and have a family caregiver willing to participate in the study. Patients diagnosed with multiple primary cancer sites were excluded from the study. Family caregivers had to be 18 years or older and identified by patients as their primary provider of emotional and/or physical care. Caregivers diagnosed with a cancer within the past year or who were receiving active treatment for cancer were excluded.

## **Measurement**

The study variables were measured using a set of well-established instruments. Illness uncertainty was measured with a brief version of the Mishel Uncertainty in Illness Scale (MUIS) (Mishel & Epstein, 1990) (Appendix 1). The MUIS included 9 items with a 4-point Likert-type response that ranges from 1 (not at all) to 4 (a lot). Participants' responses were averaged across items to reflect patients' and caregivers' levels of illness uncertainty, with higher scores indicating greater levels of illness uncertainty. In this study, the internal consistency reliability as indicated by Cronbach  $\alpha$  was 0.74 and 0.58 for patients and caregivers, respectively.

Patients' QOL was measured using the general Functional Assessment of Cancer Therapy (version 4) (Appendix 2), a cancer-specific instrument that assesses QOL (Cella et al., 1993). Caregivers completed a slightly modified version of the Functional Assessment of Cancer Therapy that asked caregivers to report on their own QOL (Song et al., 2020). This measure included 27 items to assess four domains: social, emotional, functional, and physical well-being using a 5-point Likert-type response that ranges from 0 (not at all) to 4 (very much). We averaged participants' responses across items, with higher scores indicating better QOL. The internal consistency Cronbach  $\alpha$  for patients and caregivers was 0.90 in this study.

Patient and caregiver demographic and health-related variables were included in the analyses as potential covariates of QOL. Covariates included patients' and caregivers' age (age in years); gender (male, female); race (recoded as White, Black, others); education (highest level of education in years); income (recoded as  $\leq$  \$50,000,  $>$  \$50,000); patients' types of cancer (breast, lung, colorectal, prostate); time since diagnosis (recoded as  $<$  1 year, 1 to  $<$  2 year, 2 to  $<$  3 year, 3 to  $<$  4 year, 4 to  $<$  5 year,  $\geq$  5 year); treatment (chemotherapy, hormone therapy, radiation, surgery, other treatment, not specified); and patients' and caregivers' general physical and mental symptoms. Patients' general physical and mental symptoms were measured using the 19-item Symptom Distress Scale (Appendix 3), a subscale of the Risk of Distress scale, which assessed symptoms such as fatigue, pain, sexual difficulties, and mental distress (Mood et al., 2007). The Symptom Distress Scale has a 3-point Likert-type response that ranges from 0 (no trouble) to 2 (a lot of trouble). Caregiver's general symptoms were measured using the same scale but without the item regarding lymphedema (i.e., swollen arms or legs due to cancer treatment). The participants' responses across items were averaged, with higher scores indicating more general symptoms.

### **Data Analysis**

We used descriptive statistics, including means, standard deviations, range, frequency, and percentages, to describe the study sample characteristics and the study measures in patients and caregivers using Stata version 15. The relationships between patients' and caregivers' measures were investigated using paired t-tests and Pearson correlation coefficients.

The APIM was used to achieve research aim 1. The APIM takes into account the non-independence of the data coming from partners of a dyads: in this case, a patient and a caregiver. (Kenny et al., 2020). This model consisted of two pairs of variables corresponding to each dyad

member. The independent variables were illness uncertainty and the dependent variables were QOL of patients and their caregivers. APIM allowed for a concurrent evaluation of one dyad member's illness uncertainty on their own QOL (actor effect) and on the other dyad member's QOL (partner effect). Patients' and caregivers' illnesses uncertainty was simultaneously regressed on to their own QOL, as well as on to their dyadic partner's QOL, while controlling for the correlations of the paired variables between the patients and caregivers. There was no missing data for the main study variables (i.e., illness uncertainty and QOL). The theoretical APIM is illustrated in Fig. 2.1 with a detailed explanation.

A number of patient and caregiver demographic and health-related variables were included in the analyses as potential covariates. There was a small percentage of missing data for covariates (0.21% - 14.05%). To account for missing data, full information maximum likelihood estimation (FIML) was utilized (Enders & Bandalos, 2001). Structural equation modeling (SEM) with FIML was used to estimate the APIM model parameters using MPlus version 8 (Kelloway, 2014). We initially included all the potential covariates in the APIM model. To simplify the model, the nonsignificant covariates were removed, so that only covariates significantly associated with patients' and caregivers' QOL (i.e., patient and caregiver age, patient and caregiver gender, caregiver race, and patient and caregiver general symptoms) were included.

Multigroup structural equation models were used to achieve research aim 2 and aim 3. For aim 2, the fit of the multi-group models was investigated using patient-caregiver relationship (i.e., spouse vs. non-spouse) as a grouping variable. The patient and caregiver age, patient and caregiver gender, caregiver race, and patient and caregiver general symptoms were included as covariates. Next, the strengths of each of the actor and partner effects were compared between the patient-spousal caregiver dyads and patient-non-spousal caregiver dyads. For aim 3, we used

the same method to test whether the model differed by different types of cancer (i.e., breast, lung, prostate, and colorectal). Patient and caregiver age, caregiver gender, caregiver race, and patient and caregiver general symptoms were included as covariates. We did not include patient gender as covariates because of multicollinearity: namely, patient gender and cancer type were highly linearly related in the sample (all the patients with breast cancer were female; all the patients with prostate cancer were male).

We used the following goodness-of-fit indices to examine model fit: the comparative fit index (CFI) and the Tucker-Lewis index (TLI) ( $> 0.95$  indicating an excellent fit); standardized root mean square residual (SRMR) ( $\leq 0.08$  indicating a good fit); and root mean square error of approximation (RMSEA) ( $< 0.06$  indicating a good fit) (Hu & Bentler, 1999). Unstandardized (b) regression coefficients were used to describe the models. The statistical significance level was set at  $p \leq 0.05$  throughout all analyses.

## **Results**

### **Characteristics of patients and caregivers**

The primary randomized clinical trial included 484 patient and family caregiver dyads. Demographic and medical information of patients and family caregivers is presented in Table 2.1. The average age of cancer patients was 60.5 years (SD = 11.5; range 26–95) and the average age of caregivers was 56.5 years (SD = 13.4; range 18–88). Approximately 62% of patients and 56.8% caregivers were female. A majority of patients (78.9%) and caregivers (79.6%) were White. Patients were diagnosed with advanced breast (32.4%), lung (29.1%), colorectal (25.4%), and prostate cancer (13.0%). Approximately 41% patients had been diagnosed for less than one year at the time of study enrollment.

## **Illness uncertainty and QOL in patients and caregivers**

Table 2.2 shows descriptive statistics for illness uncertainty and QOL variables as well as the correlations between these two variables. The mean scores of illness uncertainty for patients and caregivers were 2.27 (SD = 0.53) and 2.23 (SD = 0.51). The mean scores of QOL for patients and caregivers were 2.80 (SD = 0.62) and 2.82 (SD = 0.59). No significant differences were found in illness uncertainty and QOL between patients with advanced cancer and caregivers. Results revealed a small degree of correlations between patients' and caregivers' illness uncertainty ( $r = 0.232$ ) and between patients' and caregivers' QOL ( $r = 0.357$ ).

### **Aim 1: Actor and partner effects**

The model had excellent fit to the data:  $\chi^2(8, N = 484) = 13.558, p = .0940$ ; CFI = .994; TLI = .984; RMSEA = .038 (90% CI [.000, .072]); SRMR = .011. As displayed in Figure 2.2, the model showed significant actor and partner effects after controlling for covariates.

Results demonstrated significant actor effects: patients' illness uncertainty was negatively associated with their own QOL ( $b = -.422; p < .001$ ) and caregivers' illness uncertainty was negatively associated with their own QOL ( $b = -.408; p < .001$ ).

In terms of partner effects, patients' illness uncertainty was negatively associated with caregivers' QOL ( $b = -.095; p < .01$ ). No partner effect was found for caregivers, meaning that taken in aggregate, caregivers' illness uncertainty did not appear to be affecting the patients' QOL.

### **Aim 2: Actor and partner effects differed by patient-caregiver relationship**

The model had excellent fit to the data:  $\chi^2 (32, N = 459) = 40.960, p = .1332$ ; CFI = .990; TLI = .986; RMSEA = .035 (90% CI [.000, .063]); SRMR = .025. Figures 2.3 and 2.4 show the APIM model results among patient-spousal caregiver dyads and patient-non-spousal caregiver dyads after controlling for covariates.

The actor effects did not vary by type of patient-caregiver relationship. Specially, the effect of patients' illness uncertainty on their own QOL among patient-spousal caregiver dyads ( $b = -.464; p < .001$ ) was not significantly different from the effect among patient-non-spousal caregiver dyads ( $b = -.322; p < .001$ ). Similarly, the effect of caregivers' illness uncertainty on their own QOL among patient-spousal caregiver dyads ( $b = -.409; p < .001$ ) was not significantly different from the effect among patient-non-spousal caregiver dyads ( $b = -.425; p < .001$ ).

The partner effects did not vary by different types of patient-caregiver relationship. The effect of patients' illness uncertainty on caregivers' QOL among patient-spousal caregiver dyads ( $b = -.082; p < .05$ ) was not significantly different from the effect among patient-non-spousal caregiver dyads ( $b = -.150; p < .05$ ).

### **Aim 3: Actor and partner effects differed by type of cancer**

The model had acceptable fit to the data:  $\chi^2 (28, N = 483) = 67.472, p = .0000$ ; CFI = .958; TLI = .887; RMSEA = .108 (90% CI [.075, .141]); SRMR = .027. Figures 2.5, 2.6, 2.7 and 2.8 show the APIM model results among breast cancer patient-caregiver dyads, prostate cancer patient-caregiver dyads, lung cancer patient-caregiver dyads, and colorectal cancer patient-caregiver dyads after controlling for covariates.



The actor effects varied by type of cancer. Specially, there was significant difference in caregivers' actor effects between lung cancer patient-caregiver dyads and prostate cancer patient-caregiver dyads ( $p < .05$ ): the caregivers' actor effect among lung cancer patient-caregiver dyads ( $b = -.471$ ) was significantly larger than that among prostate cancer patient-caregiver dyads ( $b = -.241$ ). There was also significant difference in caregivers' actor effects between breast cancer patient-caregiver dyads and prostate cancer patient-caregiver dyads ( $p < .05$ ): the caregivers' actor effect among breast cancer patient-caregiver dyads ( $b = -.470$ ) was significantly larger than that among prostate cancer patient-caregiver dyads ( $b = -.241$ ).

The partner effects varied by type of cancer. Results show a significant difference in caregivers' partner effects between colorectal cancer patient-caregiver dyads and breast cancer patient-caregiver dyads ( $p < .05$ ): the caregivers' partner effect among breast cancer patient-caregiver dyads ( $b = -.137$ ) was significantly larger than that among colorectal cancer patient-caregiver dyads ( $b = .037$ ).

## Discussion

Using the APIM, this study examined the independent and interdependent relationships between illness uncertainty and QOL in dyads of patients with advanced cancer and their caregivers. Findings demonstrated that patients' and caregivers' illness uncertainty was negatively associated with their own QOL (actor effects). Patients' illness uncertainty was negatively associated with caregivers' QOL (partner effect). The actor and partner effects did not differ by patient-caregiver relationship but they did differ by type of cancer.

As expected, patients' illness uncertainty was negatively associated with their own QOL after controlling for patient characteristics and symptoms. Although this finding is consistent with previous study results (Ahadzadeh & Sharif, 2018; Guan et al., 2020; Lee & Park, 2020),

most of these prior studies focused on patients at all cancer stages. This study provides valuable insights about illness uncertainty and the QOL of patients with advanced cancer specifically. In addition, this finding expands on prior research suggesting that there is a negative association between illness uncertainty and QOL among family caregivers. Collectively, these findings provide further evidence to support targeted interventions to manage uncertainty and ultimately improve QOL among patients with advanced cancer and their family caregivers.

The study builds upon the burgeoning dyadic research by examining interdependent relationships between illness uncertainty and QOL. Results show that patients' illness uncertainty significantly influenced family caregivers' QOL. This finding provides evidentiary support to a key tenet of interdependence theory: namely, that in the context of cancer disease, patients' experience of adversity (i.e. illness uncertainty) is not limited to themselves, but affects the QOL of family caregivers as well. These findings underscore the potential value of targeting family-based illness uncertainty management interventions to enhance QOL when managing the stress of advanced cancer.

Interestingly, findings demonstrated that the actor and partner effects did not differ according to patient-caregiver relationships, which were contrary to the study hypothesis. Although previous studies have demonstrated that the needs and burdens of spousal caregivers and non-spousal caregivers vary (Jeong et al., 2020 ), no significant differences in actor and partner effects were found between patient-spousal caregiver dyads and patient-non-spousal caregiver dyads. A possible explanation might be that in the context of advanced cancer, the caregiving role may be prolonged for many months or even years. Whether they are spouses or non-spouses, family caregivers play a similar critical role in supporting patients with cancer. Family caregivers could be deeply involved in a considerable caregiving workload and

experience equal stress whether they were spouses or non-spouses (Lund et al., 2014).

Qualitative research could explore the dynamics operating in the patient-spousal caregiver dyads and patient-non-spousal caregiver dyads, providing useful insights into how spousal caregivers and non-spousal caregivers deal with illness uncertainty. These findings suggest that managing illness uncertainty is crucial not only for spousal caregivers but also for the non-spousal caregivers. Given that previous family-based illness uncertainty interventions focused on patient-spousal caregiver dyads (Guan et al., 2021), further interventions aimed at managing caregivers' illness uncertainty should be tailored to non-spousal caregivers.

In contrast, the actor and partner effects differed by type of cancer. For example, the presence of actor effects for caregivers varied across cancer types: the effect of caregivers' illness uncertainty on their own QOL was the largest among caregivers of patients with lung cancer. Several possible reasons have been suggested: caregivers of patients with lung cancer experience increased caregiving strain (Braun et al., 2007) and lower confidence in assisting the patient with symptom management (Porter et al., 2008) than caregivers of patients with other cancer types. Additionally, the study findings indicated that the effect of caregivers' illness uncertainty on patients' QOL among breast patient-caregiver dyads was larger than that in colorectal patient-caregiver dyads. By highlighting the different associations across specific subgroups of patient-caregiver dyads, these findings may help health providers identify different needs of cancer patients-caregivers dyads and provide tailored interventions.

Study findings provide foundational data for future intervention development to improve QOL for patients with advanced cancer and their family. The findings indicate that illness uncertainty is a key variable to address in interventions offered to patients with advanced cancer and their caregivers. Similar to the recommended distress screening for cancer patients, health

providers should ideally incorporate a routine assessment of patient and caregiver illness uncertainty in practice and provide interventions when needed. Further, interventions may be most effective if they address the illness uncertainty faced by patients with particular types of cancer and their family caregivers.

### **Strengths and limitations**

There are several strengths of this study. This study is the first to examine independent and interdependent relationships between patients' and caregivers' illness uncertainty and their QOL simultaneously using the patient-caregiver dyad as a unit of analysis. The results lay the necessary foundation for continued research on family-based illness uncertainty management in patients with advanced cancer and their caregivers. This study has several limitations. First, given that the majority of the patients and caregivers were females over the age of 56, the findings may not be generalizable to other, more diverse populations. Second, the current study included a sample that was predominantly White, and therefore did not allow us to explore differences across minority populations. In addition, this study's cross-sectional design prohibits the ability to determine how these relationships change over time.

### **Conclusion**

This study extends previous research by examining the independent and interdependent relationship between illness uncertainty and QOL in patients with advanced cancer and their family caregiver. The findings highlight the importance of viewing patient-caregiver dyad as one unit of care. Understanding different patterns of relationships between illness uncertainty and QOL that exist in patient-caregiver dyads with different backgrounds could facilitate the tailoring of interventions to maximize impact based on the dyads' characteristics.

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**Table 2.1 Characteristics of Patients and Caregivers (N = 484 dyads)**

Characteristics	Patient (N = 484)			Caregiver (N = 484)		
	Mean	SD	Range	Mean	SD	Range
<b>Age</b>	60.5	11.5	26-95	56.5	13.4	18-88
<b>Education in years</b>	14.5	2.7	7-22	14.6	2.8	7-22
<b>Gender</b>	<b>N</b>	<b>%</b>		<b>N</b>	<b>%</b>	
Female	300	62.0		275	56.8	
Male	184	38.0		208	43.0	
<b>Race</b>						
American Indian/Alaskan Native	1	0.2		0	0	
Asian	5	1.0		6	1.2	
Black	70	14.5		73	15.1	
Pacific Islander	1	0.2		0	0	
White	382	78.9		385	79.6	
Multiracial	25	5.2		17	3.5	
<b>Ethnicity</b>						
Hispanic	8	1.7		9	1.8	
Non-Hispanic	476	98.3		475	98.2	
<b>Types of cancer</b>						
Breast	157	32.4				
Lung	141	29.1				
Colorectal	123	25.4				
Prostate	63	13.0				
<b>Cancer treatment type</b>						
Chemotherapy	283	58.5				
Hormone therapy	71	14.7				
Radiation	37	7.6				
Surgery	14	2.9				
Other treatment/not specified	79	16.3				
<b>Years since diagnosis</b>						
< 1 year	199	41.1				
1 to < 2 years	67	13.8				
2 to < 3 years	51	10.5				
3 to < 4 years	36	7.4				
4 to < 5 years	22	4.6				
≥ 5 years	109	22.5				
<b>Income</b>						
< \$5,000	26	5.4		21	4.3	
\$5,000- \$15,000	40	8.3		19	3.9	
\$15,001-\$30,000	59	12.2		55	11.4	
\$30,001-\$50,000	84	17.4		73	15.1	
\$50,001-\$75,000	82	16.9		97	20.0	
> \$75,001	133	27.5		151	31.2	



**Relationship to patient**

Spouse	339	70.0
Daughter/son	73	15.1
Sister/brother	2	0.4
Other relative	27	5.6
Friend	20	4.1
Unknown	23	4.8

**Table 2.2 Means, Standard Deviations, Range, and Correlations for Illness Uncertainty and QOL among Patients and Caregivers (N = 484 Dyads)**

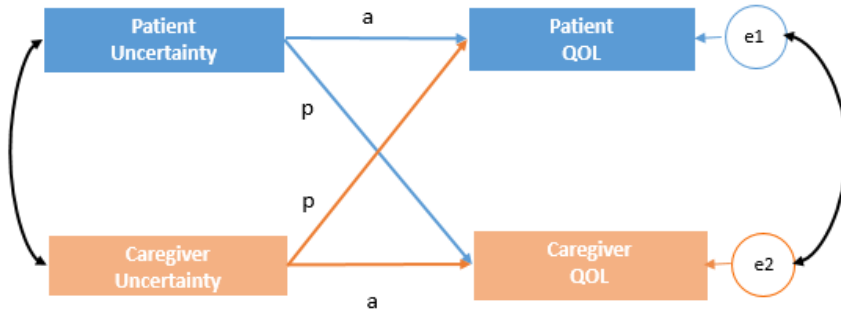
Construct	Illness uncertainty		QOL	
	PT	CG	PT	CG
Mean	2.27	2.23	2.80	2.82
SD	0.53	0.51	0.62	0.59
Range	1.00-3.56	1.11-3.89	0.62-4	0.77-4
Difference test <sup>a</sup>	$p = .190$		$p = .435$	
PT illness uncertainty	1			
CG illness uncertainty	.232***	1		
PT QOL	-.617***	-.222**	1	
CG QOL	-.287***	-.559***	.357***	1

Note. CG = Caregiver; PT = Patient; QOL = Quality of life

<sup>a</sup> Paired sample t test

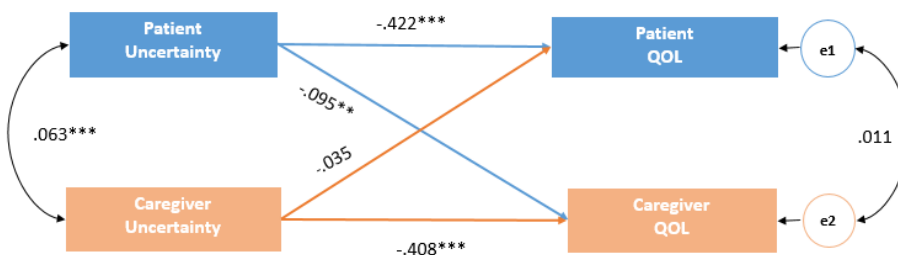
\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.1 Modified Uncertainty in Illness Theory Model**



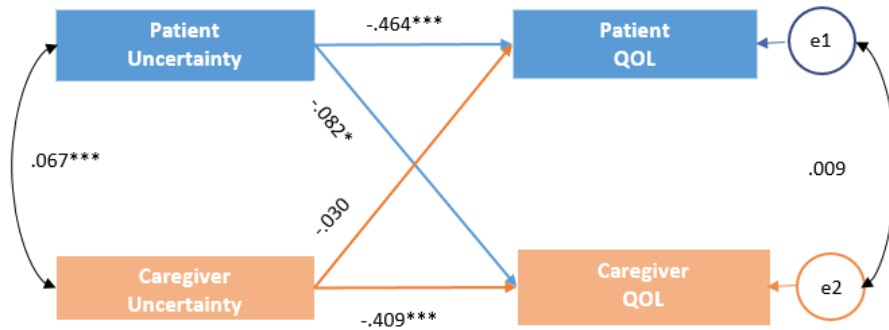
*Note.* a = actor effect; p = partner effect. In the graphical representation of the actor-partner interdependence model, the rectangles represent the independent and dependent variables; the two circles represent the latent error terms; and the arrows describe the actor and partner effects. The curved double-headed arrow on the left represents the covariances between the independent variables, and the curved double-headed arrow on the right represents the correlation between the two error terms.

**Figure 2.2 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Caregiver Dyads ( $N = 484$ )**



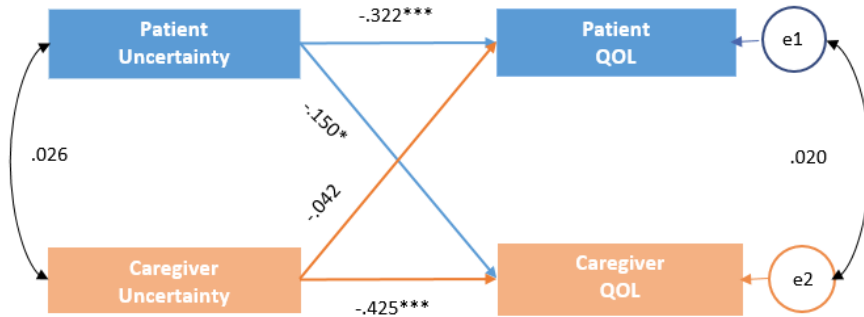
*Note.* We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, gender, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.3 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Spousal Caregiver Dyads (n = 339)**



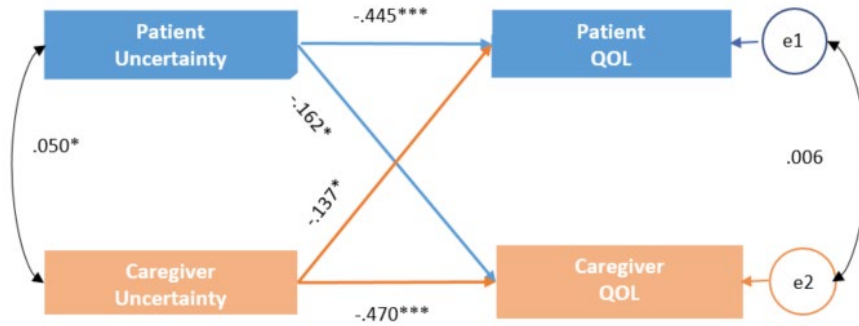
Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, gender, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.4 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Patient-Non-Spousal Caregiver Dyads (n = 123)**



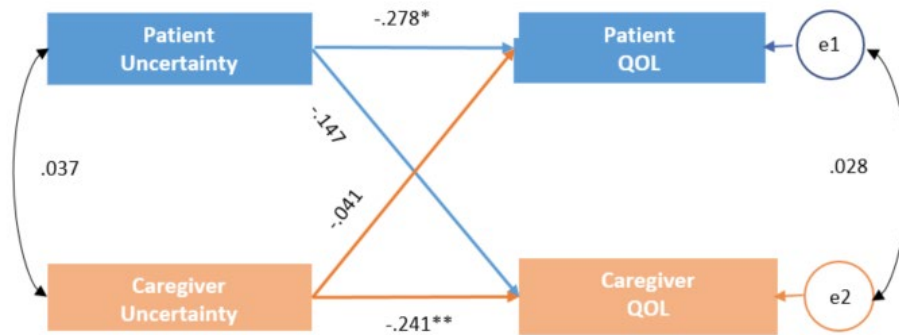
Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, gender, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.5 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Breast Cancer Patient-Caregiver Dyads (n = 156)**



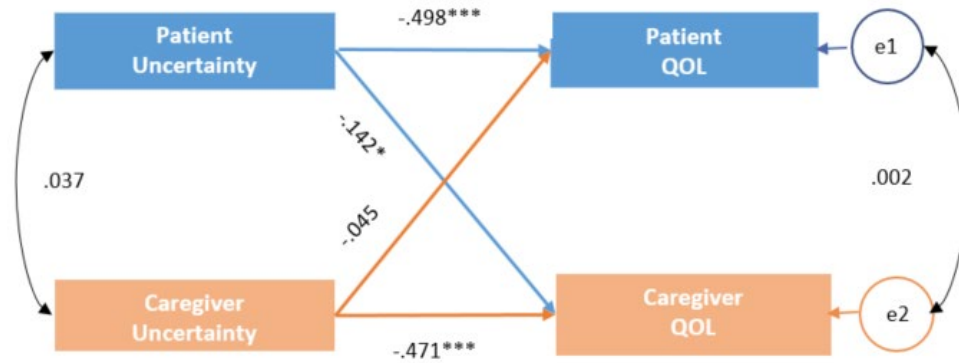
Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.6 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Prostate Cancer Patient-Caregiver Dyads (n = 63)**



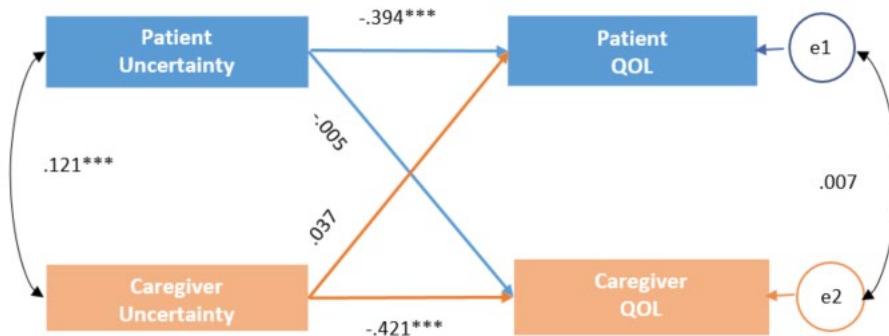
Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.7 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Lung Cancer Patient-Caregiver Dyads ( $n = 141$ )**



Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Figure 2.8 Actor-Partner Interdependence Model of Illness Uncertainty and Quality of Life among Colorectal Cancer Patient-Caregiver Dyads ( $n = 123$ )**



Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**PAPER III**  
**ILLNESS UNCERTAINTY, COPING, AND QUALITY OF LIFE IN PATIENTS WITH  
ADVANCED CANCER AND FAMILY CAREGIVERS: USING THE ACTOR-  
PARTNER INTERDEPENDENCE MEDIATION MODEL**

**Introduction**

Illness uncertainty, or difficulty determining the meaning of illness-related cues or events (Mishel, 1988), has long been recognized as a common and significant source of psychosocial stress for patients across the course of cancer survivorship (Guan et al., under review). Patients living with advanced cancer reported higher levels of illness uncertainty than those who were diagnosed at earlier stages because they often experienced a greater symptom burden related to their life-threatening illness (Guan et al., 2020a; Teunissen et al., 2007). Previous research has demonstrated that illness uncertainty in patients with advanced cancer not only adversely affects their own quality of life (QOL) but also influences their family caregivers' QOL.

Mishel's Uncertainty in Illness Theory (UIT) provides a conceptual framework for understanding the mechanism through which illness uncertainty impacts patient and caregiver adaptation (e.g., QOL) (Mishel, 1988). According to this theory, in response to illness uncertainty, an individual can use different coping strategies, which can in turn influence their adaptation (Mishel, 1988). Coping, defined as the cognitive and behavioral efforts that individuals use to manage stress (Folkman & Moskowitz, 2004), can be categorized as (1) active coping, such as seeking instrumental support or positively reframing difficult experiences, or (2) avoidant coping such as denying the reality of the illness or ignoring symptoms or medical

advice. If the coping strategies are effective for an uncertain event, adaptation will occur (Mishel, 1988).

A growing body of research details the coping responses to illness uncertainty among the general cancer population and suggests that patients reporting higher levels of illness uncertainty are more likely to use avoidant coping (Ahadzadeh & Sharif, 2018; Guan et al., 2020b; Sharif et al., 2017), which adversely affects their QOL (Guan et al., 2020b; Nipp et al., 2016). Previous studies have shown that when facing advanced cancer, patients use multiple forms of coping across the disease trajectory (Greer et al., 2020). Yet the relationship between illness uncertainty, coping, and QOL has not been fully evaluated among patients with advanced cancer. In addition, although illness uncertainty caused by advanced cancer is shared by family caregivers, little is known about family caregivers' coping strategies or the relationship between levels of illness uncertainty, coping, and QOL (Guan et al., under review). This represents a significant knowledge gap in light of evidence that caregivers cope with stressors differently than patients (Kershaw et al., 2007).

Furthermore, the shared stressors caused by advanced cancer require patients and caregivers to cope in ways that facilitate their ability to work together through a period of intensive caregiving. Several studies have demonstrated that patients and caregivers may react as one unit rather than as individuals in the face of cancer (Traa et al., 2015). However, the role of coping in the relationship between illness uncertainty and QOL has largely been neglected in the patient-caregiver dyad. By further understanding the links that may exist between illness uncertainty and QOL and how partners impact each other, findings can inform the development of dyadic interventions for managing illness uncertainty and improving QOL for both patients and caregivers affected by advanced cancer.

## **Aims and Hypotheses**

Given the aforementioned knowledge gaps, this cross-sectional study examined independent and interdependent relationships among patients' and family caregivers' illness uncertainty, coping, and QOL using the actor-partner interdependence mediation model (APIMeM) (Ledermann et al., 2011). APIMeM is adapted from the actor-partner interdependence model (APIM), which takes into account the non-independence of the data coming from partners of a dyad (i.e., patient, caregiver). It can simultaneously estimate the impact of a person's independent variable on his/her own dependent variable (actor effect) and on the dependent variable of his/her partner (partner effect). APIMeM extends the model of APIM by adding a third variable pair to assess the mediation effects in dyadic data (Ledermann et al., 2011). Figure 3.1 depicts the conceptual framework used for this study. This study's specific hypotheses are as follows:

***Hypothesis 1:*** Illness uncertainty in patients and caregivers will be related to patients' QOL (actor effect) and caregivers' QOL (partner effect).

***Hypothesis 2:*** Illness uncertainty in patients and caregivers will be related to patients' coping (actor effect) and caregivers' coping (partner effect).

***Hypothesis 3:*** Coping in patients and caregivers will be related to patients' QOL (actor effect) and caregivers' QOL (partner effect).

***Hypothesis 4:*** Coping will mediate the relationships between patients' and caregivers' illness uncertainty and their QOL (both actor and partner effects).



## Methods

### Participants and Procedures

The current study utilized the baseline data from a randomized clinical trial for patients with advanced cancer and their family caregivers. The trial tested the efficacy of a psycho-educational program (FOCUS: Family Involvement, Optimistic Attitude, Coping Effectiveness, Uncertainty Reduction, and Symptom Management) on psychosocial outcomes (Clinicaltrial.gov registration number: NCT00709176) (Northouse et al., 2013). The study was approved by the Institutional Review Board at the University of Michigan (coordinating site) and multiple cancer centers served as recruitment sites. Detailed information about the study design and procedures have been published previously (Northouse et al., 2013). This secondary analysis of the extant deidentified data involved no direct contact with participants and was exempted by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Patients were eligible if they were at least 21 years; had a new diagnosis of stage III or IV lung, colorectal, breast, or prostate cancer during the previous 6 months or had experienced a progression of their advanced disease during this time frame; had a life expectancy of at least 6 months (as assessed by their oncologist); and had a family caregiver willing to participate in the study. Patients diagnosed with multiple primary cancer sites were excluded from the study. Family caregivers (e.g., spouses, siblings, adult children) were eligible if they were aged 18 years or older and identified by patients as their primary source of physical or emotional care. Caregivers were excluded if they had been diagnosed with a cancer within the past year and/or were receiving active treatment for cancer.

## Measures

**Illness Uncertainty.** The-9 item Mishel Uncertainty in Illness Scale (MUIS) (Appendix 1) was used to assess patients' and caregivers' levels of illness uncertainty (Mishel & Epstein, 1990). MUIS has a four-item Likert-type response ranging from 1 (not at all) to 4 (a lot). Responses were averaged, with higher scores indicating greater levels of illness uncertainty. In this study, the internal consistency reliability as indicated by Cronbach  $\alpha$  was 0.74 and 0.58 for patients and caregivers, respectively.

**Coping.** Patients' and caregivers' coping were measured with the Brief Coping (Appendix 4), a shorter version of the original 60-item COPE scale developed by Carver (Carver, 1997). The Brief Coping has 28 items that assess 14 different coping strategies (e.g., self-distraction, planning, denial, positive reframing). Each strategy was measured using two items. Respondents were asked to indicate how much they used different coping strategies within the past month ranging from 1 (I usually don't do this at all) to 4 (I usually do this a lot). The internal consistency Cronbach  $\alpha$  for the Brief COPE was 0.84 and 0.75 for patients and caregivers in the study sample, respectively. A previous RCT study has conducted higher-order exploratory factor analyses of the data to determine the underlying factor structure of the 14 coping strategies (Northouse et al., 2013). The results supported a two-factor structure: active coping (i.e., use of emotional support, positive reframing, active coping, planning, acceptance, and use of instrumental support) and avoidant coping (i.e., denial, self-distraction, behavioral disengagement, venting, and self-blame) (Northouse et al., 2013) (Appendix 5). Responses were averaged, with higher scores indicating greater use of either active or avoidant coping.

**Quality of Life.** Patients' QOL was measured using the Functional Assessment of Cancer Therapy-General (FACT-G; version 4) (Appendix 2) (Cella et al., 1993). Caregivers

completed a slightly modified version of the FACT-G that asked caregivers to report on their own QOL (Northouse et al., 2002). The FACT-G consists of 27 items measuring four domains of QOL: physical, emotional, social, and functional well-being. Respondents were asked to indicate their QOL within the past 7 days ranging from 0 (not at all) to 4 (very much). Responses were averaged, with higher scores indicating better QOL. The Cronbach  $\alpha$  for both patients and caregivers in this study was 0.90.

**Covariates.** Several patient and caregiver demographic and health-related variables have been explored in previous analyses as potential covariates of QOL. This study included covariates significantly associated with patients' and caregivers' QOL, including patient and caregiver age (age in years), patient and caregiver gender (male, female), caregiver race (recoded as White, Black, other), and patient and caregiver general physical and mental symptoms. Patients' general physical and mental symptoms were measured using the 19-item Symptom Distress Scale (Appendix 3), a subscale of the Risk of Distress Scale (Mood et al., 2007). The Symptom Distress Scale assessed symptoms (e.g., fatigue, pain, urinary incontinence, sexual difficulties, and mental distress) using a three-item Likert-type response ranging from 0 (no trouble) to 2 (a lot of trouble). Caregivers also indicated their general symptoms using the same scale but without the item of lymphedema (i.e., swollen arms or legs due to cancer treatment). Responses were averaged, with higher scores indicating more general symptoms. In this study, the internal consistency reliability for patients and caregivers was 0.77 and 0.82, respectively.

## **Data Analysis**

Using Stata version 15, descriptive statistics including means, standard deviations, ranges, frequency, and percentages were computed to describe study sample characteristics and study measures in patients and caregivers. Paired t-tests were used to compare the means of

variables among patients and caregivers. Pearson's bivariate correlations between variables for patients and caregivers were also calculated using Stata version 15.

The APIMeM was used to achieve research aims. This model consists of three pairs of variables corresponding to each dyad member: independent variables (illness uncertainty); mediator variables (coping); and dependent variables (QOL). There was no missing data for the main study variables (illness uncertainty, coping, and QOL). There was a small percentage of missing data for covariates (0.21% - 0.62%). To account for missing data, full information maximum likelihood estimation (FIML) was utilized (Enders & Bandalos, 2001). Structural equation modeling (SEM) with FIML was used to estimate the APIMeM model parameters using MPlus version 8 (Kelloway, 2014). Four fit indices were used to examine the model fit: the comparative fit index (CFI) and the Tucker-Lewis index (TLI) ( $> 0.95$  indicating an excellent fit); standardized root mean square residual (SRMR) ( $\leq 0.08$  indicating a good fit); and root mean square error of approximation (RMSEA) ( $< 0.06$  indicating a good fit) (Hu & Bentler, 1999). Unstandardized (b) regression coefficients were used to describe the models. The statistical significance level was set to  $p \leq 0.05$  throughout all analyses.

## **Results**

### **Characteristics of Participants**

This study included 484 dyads. The mean age of patients was 60.5 years (SD = 11.5; range 26–95); for caregivers, it was 56.5 (SD = 13.4; range 18–88). A majority of patients (62%) and caregivers (56.8%) were female. The mean education for patients and caregivers was 15 years. A majority of patients (78.9%) and caregivers (79.6%) were White. Patients had advanced breast (32.4%), lung (29.1%), colorectal (25.4%), and prostate cancer (13.0%). Approximately 41% patients have been diagnosed for less than one year. Patients were currently receiving

chemotherapy (58.5%), hormone therapy (14.7%), radiation (7.6%), surgery (2.9%), or other treatment/not specified (16.3%). Most caregivers were spouses (70%).

Table 3.2 provides the means, standard deviations, and ranges for illness uncertainty, coping, and QOL variables, as well as the correlations among these variables. Results show no significant differences in illness uncertainty, avoidant coping, and QOL between patients and caregivers. A significant difference was found between patients' and caregivers' active coping ( $p = .000$ ): namely, patients were more likely to use active coping than caregivers.

### **Results of APIMeM**

The model had good fit to the data:  $\chi^2 (49, N = 484) = 118.500, p = .000$ ; CFI = .956; TLI = .933; RMSEA = .054 (90% CI [.042, .067]); SRMR = .044. Table 3.3 and Figure 3.2 provide unstandardized estimates for the APIMeM after controlling for a series of significant covariates.

***Hypothesis 1: Illness uncertainty → QOL.*** Patients' illness uncertainty was negatively associated with their own QOL ( $b = -.339; p < .001$ ). Caregivers' illness uncertainty was negatively associated with their own QOL ( $b = -.308; p < .001$ ). No partner effects were found for patients and caregivers, meaning one's illness uncertainty was not associated with another's QOL.

***Hypothesis 2: Illness uncertainty → Coping.*** Patients' illness uncertainty was positively associated with their own avoidant coping ( $b = .384; p < .001$ ). Caregivers' illness uncertainty was positively associated with their own active coping ( $b = .097; p < .05$ ) and positively associated with their own avoidant coping ( $b = .330; p < .001$ ). Patients' illness uncertainty was not significantly associated with caregivers' active and avoidant coping. Caregivers' illness

uncertainty was not significantly associated with patients' active coping. Caregivers' illness uncertainty was positively associated with patients' avoidant coping ( $b = .113; p < .01$ ).

**Hypothesis 3: Coping → QOL.** Patients' active coping was positively associated with their QOL ( $b = .207; p < .001$ ), and their avoidant coping was negatively associated with their QOL ( $b = -.248; p < .001$ ). Similarly, caregivers' active coping was positively associated with their QOL ( $b = .255; p < .001$ ), and their avoidant coping was negatively associated with their QOL ( $b = -.424; p < .001$ ).

**Hypothesis 4: Illness uncertainty → Coping → QOL.** Patients' avoidant coping partially mediated the relationship between their level of illness uncertainty and QOL. Specifically, the direct effect of illness uncertainty on QOL was  $-.339 (p < .001)$ . The indirect effect of illness uncertainty on QOL via avoidance coping was  $-.095 (p < .001)$ . Caregivers' active coping and avoidant coping partially mediated the relationship between their illness uncertainty and QOL. Specifically, the direct effect of illness uncertainty on QOL was  $-.308 (p < .001)$ . The indirect effect of illness uncertainty on QOL via active and avoidance coping was  $-.115 (p < .001)$ .

## Discussion

The current study was the first to use a dyadic approach to investigate the independent and interdependent relationships between patients' and caregivers' illness uncertainty, coping, and QOL by applying the APIMeM. A theory-based analytic approach was used to simultaneously examine the effects of patients' and caregivers' illness uncertainty and coping on their own QOL (actor effects) and on their caregiver's QOL (partner effects), as well as the mechanisms underlying these relationships (mediation). The findings supported most theorized actor effects: each person's illness uncertainty and coping were significantly associated with

their own QOL. The findings also demonstrated the partner effects: higher levels of illness uncertainty among caregivers was associated with patients' avoidant coping. The hypotheses for the mediating role of active and avoidant coping between illness uncertainty and QOL among patients and caregivers were partially verified.

Consistent with recent evidence (Guan et al., under review) and previous research, the results indicated that illness uncertainty was directly associated with QOL both for patients and for their caregivers. In addition to illness uncertainty, we also found that patients' and caregivers' active and avoidant coping were directly associated with their own QOL. Active coping (e.g., instrumental support, positive reframing) correlated with better QOL, whereas the use of avoidant coping was associated with poorer QOL. The findings support previous results of studies among patients with advanced cancer (Nipp et al., 2016; Sorato & Osorio, 2015), and provide valuable new insights about the relationships between coping and QOL in a large sample of family caregivers of patients with advanced cancer. Future interventions that target specific coping strategies may promote better QOL for patients and caregivers, even if it is each individual's coping that mainly affects their own QOL.

It is not surprising that, among the population of patients with advanced cancer, avoidant coping played a significant mediating effect between illness uncertainty and QOL. This finding corroborates findings from Guan's study of a sample of patients with prostate cancer (Guan et al., 2020b). Advanced cancer can be an extremely stressful and uncertain experience. In fact, a qualitative study that explored how patients diagnosed with advanced cancer cope with an uncertain disease trajectory also indicated that most patients avoided thinking about their situation and did not wish to discuss the prognosis or have detailed information on disease

progression (Lobb et al., 2015). Chronic illness uncertainty contributes to patients' increased avoidant coping, which in turn, adversely impacts their QOL.

This study also expands on prior research by examining the mediating role of coping between illness uncertainty and QOL among family caregivers. Interestingly, both active and avoidant coping played significant mediating roles between illness uncertainty and QOL for family caregivers. Specially, when caregivers reported a higher level of illness uncertainty, they were more likely to use active and avoidant coping. As a result, caregivers who engaged in active coping reported better QOL whereas caregivers who engaged in avoidant coping reported poorer QOL. The complicated relationship between illness uncertainty and coping is supported by UIT (Mishel, 1988). This theory proposes illness uncertainty can be evaluated either a danger or an opportunity. When uncertainty is appraised as an opportunity, avoidant coping strategies are used to maintain it. In contrast, when illness uncertainty is evaluated as danger, active coping is employed to reduce it (Mishel, 1988). The study findings demonstrated that caregivers experience a duality of hope and worry due to their illness uncertainty (Petrillo et al., 2021). Further qualitative studies should be conducted to elucidate caregivers' experiences of illness uncertainty and how coping responses may differ across context and time.

It is noteworthy that the present study also found one significant partner effect: when caregivers reported higher levels of illness uncertainty, patients were more likely to use avoidant coping. This finding demonstrates the dyadic interdependence of illness uncertainty and coping in patient-caregiver dyads coping with cancer, and underlines the fact that we cannot examine one dyad member's coping efforts without considering the effects of the other dyad member. This interdependence may partially contribute to the fact that family caregivers play a critical role in the supporting and caring for patients with cancer, especially at advanced cancer stages.



When family caregivers experience higher levels of illness uncertainty, this cognition can spill over into the relationship, causing patients to experience illness uncertainty as well. The complex dyadic interdependence of illness uncertainty and coping is worthy of further in-depth investigation. Given the significant impact of caregivers' illness uncertainty on patients' and caregivers' coping, understanding and addressing caregivers' illness uncertainty is needed in order to improve both patients' and caregivers' QOL.

There are several limitations to the present study. First, because this was a cross-sectional study, it is hard to reach conclusions about the causal relationships among illness uncertainty, coping, and QOL. However, according to Mishel's UIT, an individual's appraisals of illness uncertainty influence their coping strategies, which can in turn influence their adaptation. Additional longitudinal studies are needed to elucidate the causal relationships among the associations found in this study. Second, although this study was a multicenter study, patients and caregivers had relatively high levels of education and income, which may influence their coping strategies. In addition, future studies should also examine these findings in a multiethnic population of patients and caregivers as well as among patients and caregivers with lower incomes. Families with different demographic characteristics may have different patterns in responding to illness uncertainty (Zhang et al., 2018).

Despite these limitations, this study has many strengths. First, the findings lend support to Mishel's UIT. Second, this is the first study to report the interdependent relationships among illness uncertainty, coping, and QOL in patients with advanced cancer and family caregivers. The findings about these relationships provide foundational data for developing interventions to help patients with advanced cancer and caregivers cope with advanced cancer and improve their QOL. Future research is needed to develop and test family-based interventions to manage illness

uncertainty and enhance coping skills. Such interventions would ideally improve patients' and caregivers' QOL while enhancing the use of effective coping behaviors.

### **Conclusion**

This study offers evidence of the independent and interdependent relationships among the illness uncertainty, coping, and QOL in patient-caregiver dyads. The findings emphasize the need to support patients and caregivers as one unit of care and underscore the potential value of targeted interventions involving family-based illness uncertainty management and coping skills training to enhance QOL when managing the stress of advanced cancer.

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**Table 3.1 Characteristics of Patients and Caregivers (N = 484 dyads)**

Characteristics	Patient (N = 484)			Caregiver (N = 484)		
	Mean	SD	Range	Mean	SD	Range
<b>Age</b>	60.5	11.5	26-95	56.5	13.4	18-88
<b>Education in years</b>	14.5	2.7	7-22	14.6	2.8	7-22
<b>Gender</b>	<b>N</b>	<b>%</b>		<b>N</b>	<b>%</b>	
Female	300	62.0		275	56.8	
Male	184	38.0		208	43.0	
<b>Race</b>						
American Indian/Alaskan Native	1	0.2		0	0	
Asian	5	1.0		6	1.2	
Black	70	14.5		73	15.1	
Pacific Islander	1	0.2		0	0	
White	382	78.9		385	79.6	
Multiracial	25	5.2		17	3.5	
<b>Ethnicity</b>						
Hispanic	8	1.7		9	1.8	
Non-Hispanic	476	98.3		475	98.2	
<b>Types of cancer</b>						
Breast	157	32.4				
Lung	141	29.1				
Colorectal	123	25.4				
Prostate	63	13.0				
<b>Cancer treatment type</b>						
Chemotherapy	283	58.5				
Hormone therapy	71	14.7				
Radiation	37	7.6				
Surgery	14	2.9				
Other treatment/not specified	79	16.3				
<b>Years since diagnosis</b>						
< 1 year	199	41.1				
1 to < 2 years	67	13.8				
2 to < 3 years	51	10.5				
3 to < 4 years	36	7.4				
4 to < 5 years	22	4.6				
≥5 years	109	22.5				
<b>Income</b>						
< \$5,000	26	5.4		21	4.3	
\$5,000- \$15,000	40	8.3		19	3.9	
\$15,001-\$30,000	59	12.2		55	11.4	
\$30,001-\$50,000	84	17.4		73	15.1	
\$50,001-\$75,000	82	16.9		97	20.0	
> \$75,001	133	27.5		151	31.2	



**Relationship to patient**

Spouse	339	70.0
Daughter/son	73	15.1
Sister/brother	2	0.4
Other relative	27	5.6
Friend	20	4.1
Unknown	23	4.8

**Table 3.2 Means, Standard Deviations, Range, and Correlations for Illness Uncertainty, Active Coping, Avoidant Coping, and QOL among Patients and Caregivers (N = 484 Dyads)**

Construct	Illness uncertainty		Active coping		Avoidant coping		QOL	
	PT	CG	PT	CG	PT	CG	PT	CG
Mean	2.27	2.23	2.87	2.67	1.55	1.52	2.80	2.82
SD	0.53	0.51	0.55	0.54	0.51	0.46	0.62	0.59
Range	1.00-3.56	1.11-3.89	1.28-4	1.11-3.94	1-3.63	1-3.44	0.62-4	0.77-4
Difference test <sup>a</sup>	$p = .190$		$p = .000$		$p = .269$		$p = .435$	
Correlations								
PT illness uncertainty	1							
CG illness uncertainty	.232***	1						
PT active coping	.034	.007	1					
CG active coping	.001	.089	.108*	1				
PT avoidant coping	.441**	.210***	.171***	.080	1			
CG avoidant coping	.178***	.483***	.039	.231***	.309***	1		
PT QOL	-.617***	-.222**	.058	-.084	-.503***	-.289***	1	
CG QOL	-.287***	-.559***	-.042	.096*	-.309***	-.609***	.357***	1

Note. CG= Caregiver; PT= Patient; QOL= Quality of life

<sup>a</sup> Paired sample t test

\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

**Table 3.3 Parameter Estimate**

	Path	Estimate	P value	% of effect
<b>Actor effects</b>				
Patient	Illness uncertainty → active coping	-	-	
	Illness uncertainty → avoidant coping	.384	.000	
	Active coping → QOL	.207	.000	
	Avoidant coping → QOL	-.248	.000	
Caregiver	Illness uncertainty → QOL	-.339	.000	
	Illness uncertainty → active coping	.097	.037	
	Illness uncertainty → avoidant coping	.330	.000	
	Active coping → QOL	.255	.000	
	Avoidant coping → QOL	-.424	.000	
	Illness uncertainty → QOL	-.308	.000	
<b>Partner effects</b>				
	Patient illness uncertainty → caregiver active coping	-	-	
	Patient illness uncertainty → caregiver avoidant coping	-	-	
	Patient illness uncertainty → caregiver QOL	-	-	
	Patient active coping → caregiver QOL	-	-	
	Patient avoidant coping → caregiver QOL	-	-	
	Caregiver illness uncertainty → patient active coping	-	-	
	Caregiver illness uncertainty → patient avoidant coping	.113	.005	
	Caregiver illness uncertainty → patient QOL	-	-	
	Caregiver active coping → patient QOL	-	-	
	Caregiver avoidant coping → patient QOL	-	-	
<b>Mediation testing</b>				
<b>Actor effects</b>				
Patient	Total effect (Direct + indirect)	-.434	.000	100%
	Direct effect: patient illness uncertainty → patient QOL	-.339	.000	78%
	Indirect effects (mediation)	-.095	.000	22%
	Patient illness uncertainty → patient active coping → patient QOL	-	-	
	Patient illness uncertainty → patient avoidant coping → patient QOL	-.095	.000	
	Patient illness uncertainty → caregiver active coping → patient QOL	-	-	
Caregiver	Patient illness uncertainty → caregiver avoidant coping → patient QOL	-	-	
	Total effect (Direct + indirect)	-.423	.000	100%
	Direct effect: caregiver illness uncertainty → caregiver QOL	-.308	.000	73%
	Indirect effects (mediation)	-.115	.000	27%
	Caregiver illness uncertainty → patient active coping → caregiver QOL	-	-	
	Caregiver illness uncertainty → patient avoidant coping → caregiver QOL	-	-	
	Caregiver illness uncertainty → caregiver active coping → caregiver QOL	.025	.043	
	Caregiver illness uncertainty → caregiver avoidant coping → caregiver QOL	-.140	.000	
<b>Partner effects</b>				
Patient	Total effect (Direct + indirect)	-	-	
	Direct effect: patient illness uncertainty → caregiver QOL	-	-	
	Indirect effects (mediation)	-	-	
	Patient illness uncertainty → patient active coping → caregiver QOL	-	-	
	Patient illness uncertainty → patient avoidant coping → caregiver QOL	-	-	
	Patient illness uncertainty → caregiver active coping → caregiver QOL	-	-	
Caregiver	Patient illness uncertainty → caregiver avoidant coping → caregiver QOL	-	-	
	Total effect (Direct + indirect)	-	-	
	Direct effect: caregiver illness uncertainty → patient QOL	-	-	
	Indirect effects (mediation)	-	-	
	Caregiver illness uncertainty → patient active coping → patient QOL	-	-	
	Caregiver illness uncertainty → patient avoidant coping → patient QOL	-	-	
	Caregiver illness uncertainty → caregiver active coping → patient QOL	-	-	
	Caregiver illness uncertainty → caregiver avoidant coping → patient QOL	-	-	

Figure 3.1 Modified Uncertainty in Illness Theory Model

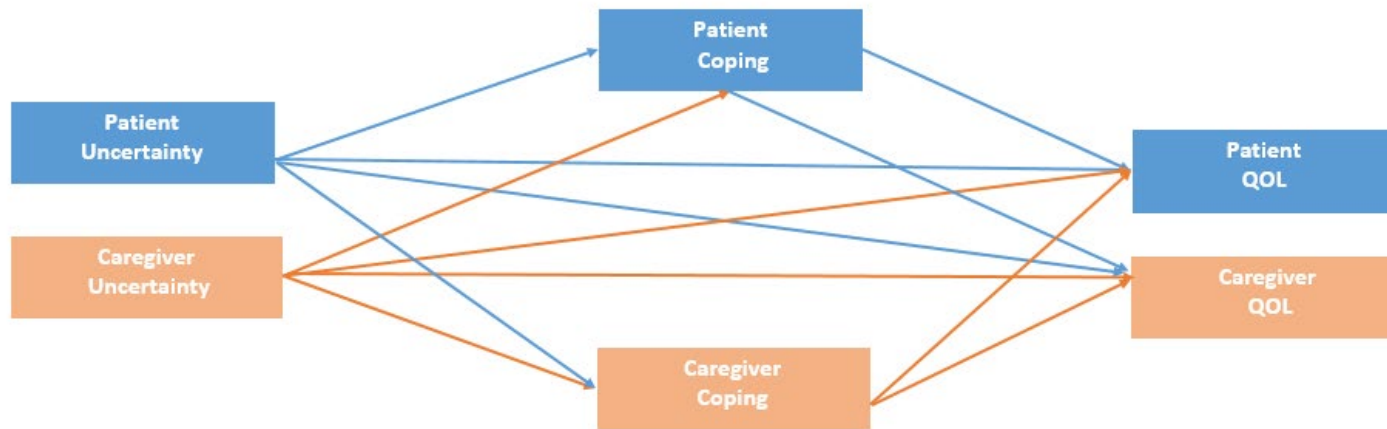
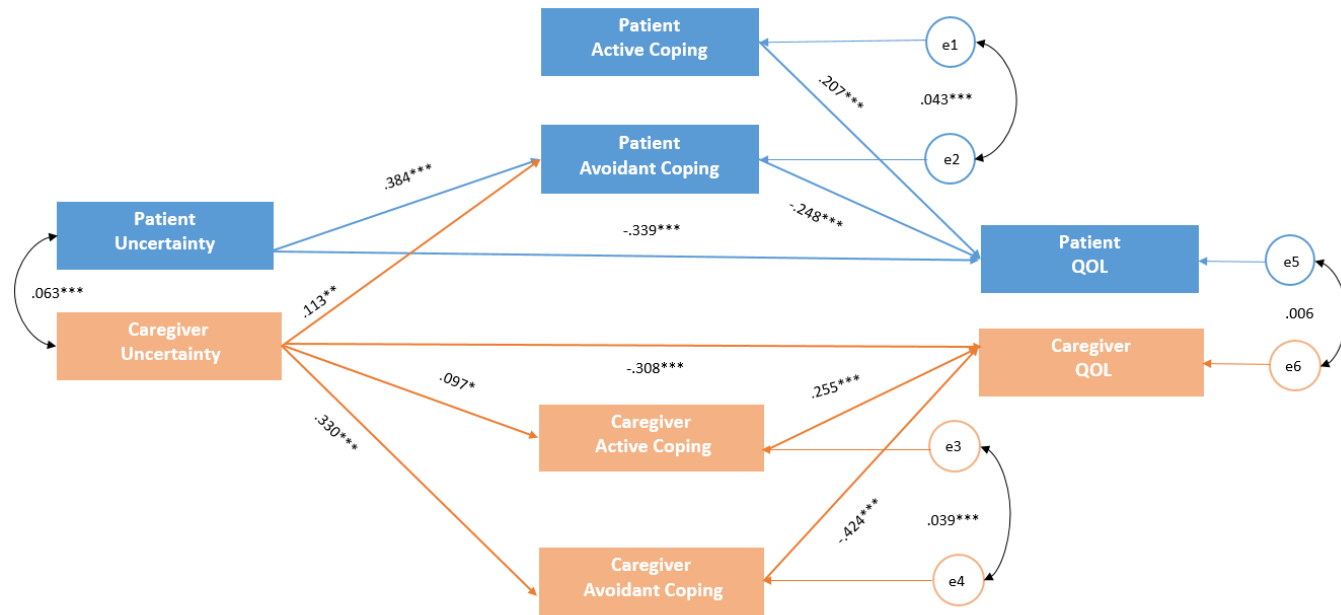


Figure 3.2 Actor-Partner Interdependence Mediation Model of Illness Uncertainty, Coping, and Quality of Life among Patient-Caregiver Dyads (N = 484)



Note. We have controlled for the effects of significant covariates, including patient characteristics (i.e., age, gender, symptoms) and caregivers characteristics (i.e., age, gender, race, symptoms). \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$

## SUMMARY

The driving purpose of this dissertation was to investigate the independent and interdependent relationships between illness uncertainty and quality of life (QOL) simultaneously, using the patient-caregiver dyad as the unit of analysis. To achieve this goal, three studies were conducted. First, a systematic review examined prior scholarship on the correlates of illness uncertainty in adult patients with cancer and their caregivers and synthesized evidence using meta-analysis. Second, an empirical study examined the independent and interdependent relationships between illness uncertainty and QOL among patients with advanced cancer and their caregivers (i.e., the patient-caregiver dyad) and assessed whether these relationships differed according to the patient-caregiver relationship and the type of cancer. Third, an empirical study assessed whether and how patients' and caregivers' coping strategies mediated those independent and interdependent relationships.

### **Key Findings**

This dissertation has several notable findings that fill gaps in the literature regarding illness uncertainty among patients with cancer and their family caregivers. First, findings identified distinct correlates for illness uncertainty in patients with cancer, including sociodemographic factors (e.g., age, gender, race), stimuli frame (e.g., symptom, family history of cancer), structure providers (e.g., education), coping, and adaptation. Notable effect sizes were observed in the correlations between illness uncertainty and social support, QOL, depression, and anxiety. Caregivers' illness uncertainty was associated with race, caregivers' symptoms,

prostate-specific antigen levels, social support, and QOL. However, the data was insufficient to examine the effect size of correlates of illness uncertainty in family caregivers. Findings from the second study indicate that patients' and caregivers' illness uncertainty were negatively associated with their own QOL. Patients' illness uncertainty was negatively associated with caregivers' QOL. In addition, the independent and interdependent relationships between illness uncertainty and QOL did not differ by patient-caregiver relationship, but differed by type of cancer. Namely, the presence of actor effects for caregivers varied across cancer type, and the effect of caregivers' illness uncertainty on patients' QOL among breast patient-caregiver dyads was larger than that in colorectal patient-caregiver dyads. Additionally, findings from the third study supported most theorized actor effects: each person's illness uncertainty and coping were significantly associated with their own QOL. The findings also demonstrated the hypothesized partner effects: caregivers' illness uncertainty was positively associated with patients' avoidant coping. The hypotheses regarding the mediating role of active and avoidant coping between illness uncertainty and QOL among patients and caregivers were partially verified.

### **Limitations and Implications for Future Research**

This dissertation research had several limitations that should be addressed in future research. First, the first systematic review and meta-analysis revealed that the majority of studies focused on patients' illness uncertainty, especially patients with breast or prostate cancer. Future research needs to include a greater diversity of cancer types to better understand how the disease and its particular characteristics and treatment considerations influence participants' illness uncertainty. Second, more research attention should be given to the correlates of illness uncertainty among caregivers. Third, the second and third studies used a cross-sectional design. Additional longitudinal studies are needed to elucidate the causal relationships among the

associations found in this study. Finally, in these studies, most of the participants are White. Future studies should also examine these findings using a multiethnic population of patients and caregivers as well as patients and caregivers with lower incomes.

### **Implication for Future Practice**

First, the verified negative association between illness uncertainty and QOL provides further evidence to support illness uncertainty as an intervention target and ultimately to improve QOL among patients with cancer and their family caregivers. Second, the mediating role of coping between illness uncertainty and QOL suggests that future interventions should target specific coping strategies, which may promote better QOL for patients and caregivers. The finding regarding the partner effect of caregivers' illness uncertainty on patients' coping highlights the importance of family-based interventions to manage illness uncertainty and enhance coping skills among patients with cancer and their family.

The three papers presented in this dissertation make an important contribution to understanding the phenomenon of illness uncertainty among patients with cancer and their family caregivers. First, the findings lend support to Mishel's UIT. Second, this dissertation is the first study to apply the actor-partner interdependence (mediation) model to examine the association between illness uncertainty, coping, and QOL among patients with advanced cancer and family caregivers. Third, the findings emphasize the need to support patients and caregivers as one unit and underscore the potential value of designing family-based illness uncertainty management and coping skill training interventions to enhance QOL for patients and caregivers managing the stress of advanced cancer.

## APPENDIX 1: MISHEL UNCERTAINTY IN ILLNESS SCALE

### 1-4 Scale:

1 = Not at all

2 = A little

3 = Some

4 = A lot

1. I have a lot of questions about my illness.
2. I am unsure if the treatment I am getting for my cancer is helping.
3. I know what side effects to expect from my treatment.
4. I feel uncertain about the future because of my illness.
5. Because of my illness, I am unsure what activities I will be able to do from day-to-day.
6. I am bothered by the uncertainty caused by my illness.
7. The plan for treating my cancer is clear to me.
8. I can manage the uncertainty that my illness creates.
9. I understand all of the information I have received about my illness.



## APPENDIX 2: FUNCTIONAL ASSESSMENT OF CANCER THERAPY -GENERAL (VERSION 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<b><u>PHYSICAL WELL-BEING</u></b>		<b>Not at all</b>	<b>A little bit</b>	<b>Some-what</b>	<b>Quite a bit</b>	<b>Very much</b>
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
<b><u>SOCIAL/FAMILY WELL-BEING</u></b>		<b>Not at all</b>	<b>A little bit</b>	<b>Some-what</b>	<b>Quite a bit</b>	<b>Very much</b>
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

<b><u>EMOTIONAL WELL-BEING</u></b>		<b>Not at all</b>	<b>A little bit</b>	<b>Some-what</b>	<b>Quite a bit</b>	<b>Very much</b>
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

<b><u>FUNCTIONAL WELL-BEING</u></b>		<b>Not at all</b>	<b>A little bit</b>	<b>Some-what</b>	<b>Quite a bit</b>	<b>Very much</b>
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

### APPENDIX 3: SYMPTOM DISTRESS SCALE

Pain Symptoms	0= No trouble, 1= Some, 2= A lot
Energy loss, fatigue	0= No trouble, 1= Some, 2= A lot
Weight loss (unintentional)	0= No trouble, 1= Some, 2= A lot
Sleeping problems	0= No trouble, 1= Some, 2= A lot
Skin problems	0= No trouble, 1= Some, 2= A lot
Bodily sensations (sense of touch)	0= No trouble, 1= Some, 2= A lot
Difficulty moving arms and/or legs	0= No trouble, 1= Some, 2= A lot
Stomach problems	0= No trouble, 1= Some, 2= A lot
Bowel problems	0= No trouble, 1= Some, 2= A lot
Urinating, incontinence	0= No trouble, 1= Some, 2= A lot
Breathing problems	0= No trouble, 1= Some, 2= A lot
Heart or blood pressure problems	0= No trouble, 1= Some, 2= A lot
Sexual problems	0= No trouble, 1= Some, 2= A lot
Mental distress	0= No trouble, 1= Some, 2= A lot
Mental fatigue (too tired to think)	0= No trouble, 1= Some, 2= A lot
Appetite	0= No trouble, 1= Some, 2= A lot
Concentration	0= No trouble, 1= Some, 2= A lot
Hot flashes	0= No trouble, 1= Some, 2= A lot
Lymphedema	(Swollen arms or legs due to cancer treatment), 0= No trouble, 1= Some, 2= A lot

## APPENDIX 4: BRIEF COPE

These items deal with ways you've been coping with the stress in your life since you found out you were going to have to have this operation. There are many ways to try to deal with problems. These items ask what you've been doing to cope with this one. Obviously, different people deal with things in different ways, but I'm interested in how you've tried to deal with it. Each item says something about a particular way of coping. I want to know to what extent you've been doing what the item says. How much or how frequently. Don't answer on the basis of whether it seems to be working or not—just whether or not you're doing it. Use these response choices. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

- 1 = I usually don't do this at all
- 2 = I've been doing this a little bit
- 3 = I've been doing this a medium amount
- 4 = I've been doing this a lot

1. I've been turning to work or other activities to take my mind off things.
2. I've been concentrating my efforts on doing something about the situation I'm in.
3. I've been saying to myself "this isn't real."
4. I've been using alcohol or other drugs to make myself feel better.
5. I've been getting emotional support from others.
6. I've been giving up trying to deal with it.
7. I've been taking action to try to make the situation better.
8. I've been refusing to believe that it has happened.
9. I've been saying things to let my unpleasant feelings escape.
10. I've been getting help and advice from other people.
11. I've been using alcohol or other drugs to help me get through it.
12. I've been trying to see it in a different light, to make it seem more positive.
13. I've been criticizing myself.
14. I've been trying to come up with a strategy about what to do.
15. I've been getting comfort and understanding from someone.
16. I've been giving up the attempt to cope.
17. I've been looking for something good in what is happening.
18. I've been making jokes about it.
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.
20. I've been accepting the reality of the fact that it has happened.
21. I've been expressing my negative feelings.
22. I've been trying to find comfort in my religion or spiritual beliefs.
23. I've been trying to get advice or help from other people about what to do.
24. I've been learning to live with it.
25. I've been thinking hard about what steps to take.
26. I've been blaming myself for things that happened.
27. I've been praying or meditating.
28. I've been making fun of the situation.

Scales are computed as follows:

- Self-distraction, items 1 and 19
- Active coping, items 2 and 7
- Denial, items 3 and 8
- Substance use, items 4 and 11
- Use of emotional support, items 5 and 15
- Use of instrumental support, items 10 and 23
- Behavioral disengagement, items 6 and 16
- Venting, items 9 and 21
- Positive reframing, items 12 and 17

Planning, items 14 and 25  
Humor, items 18 and 28  
Acceptance, items 20 and 24  
Religion, items 22 and 27  
Self-blame, items 13 and 26

## APPENDIX 5: TWO-FACTOR STRUCTURE OF COPING

<b>Factor</b>	<b>Coping strategies</b>	<b>Items</b>
Active Coping	Use of emotional support	I've been getting emotional support from others.  I've been getting comfort and understanding from someone.
	Positive reframing	I've been trying to see it in a different light, to make it seem more positive.  I've been looking for something good in what is happening.
	Active coping	I've been concentrating my efforts on doing something about the situation I'm in. I've been taking action to try to make the situation better.
	Planning	I've been trying to come up with a strategy about what to do. I've been thinking hard about what steps to take.
	Acceptance	I've been accepting the reality of the fact that it has happened.  I've been learning to live with it.
	Use of instrumental support	I've been getting help and advice from other people.  I've been trying to get advice or help from other people about what to do.
Avoidant coping	Denial	I've been saying to myself "this isn't real."  I've been refusing to believe that it has happened.
	Self-distraction	I've been turning to work or other activities to take my mind off things.  I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.
	Behavioral disengagement	I've been giving up trying to deal with it.  I've been giving up the attempt to cope.
	Venting	I've been saying things to let my unpleasant feelings escape.  I've been expressing my negative feelings.
	Self-blame	I've been criticizing myself.  I've been blaming myself for things that happened.