

Correlates of illness uncertainty in cancer survivors and family caregivers: a systematic review and meta-analysis

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Abstract

Purpose Illness uncertainty is widely recognized as a psychosocial stressor for cancer survivors and their family caregivers. This systematic review and meta-analysis aimed to identify the sociodemographic, physical, and psychosocial correlates that are associated with illness uncertainty in adult cancer survivors and their family caregivers.

Methods Six scholarly databases were searched. Data synthesis was based on Mishel's Uncertainty in Illness Theory. Person's r was used as the effect size metric in the meta-analysis. Risk of bias was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Results Of 1116 articles, 21 articles met the inclusion criteria. Of 21 reviewed studies, 18 focused on cancer survivors, one focused on family caregivers, and 2 included survivors and family caregivers. Findings identified distinct correlates for illness uncertainty in cancer survivors, 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, quality of life, depression, and anxiety. Caregivers' illness uncertainty was associated with their race, general health, perception of influence, social support, quality of life, and survivors' prostate-specific antigen levels. Insufficient data precluded examining effect size of correlates of illness uncertainty among family caregivers.

Conclusion This is the first systematic review and meta-analysis to summarize the literature on illness uncertainty among adult cancer survivors and family caregivers. Findings contribute to the growing literature on managing illness uncertainty among cancer survivors and family caregivers.

Keywords Illness uncertainty · Cancer survivors · Family caregiver · Systematic review · Meta-analysis · Quality of life

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Introduction

Illness uncertainty is the cognitive state created when a person cannot determine the meaning of illness-related events because of insufficient information [1]. It is widely recognized as a psychosocial stressor not only for cancer survivors [2] but also their family caregivers [3]. Although illness uncertainty is acknowledged as an enduring and common experience in cancer survivorship [4] and significantly affects quality of life (QOL) [5], evidence-based interventions regarding how to manage illness uncertainty for cancer survivors and family caregivers are sparse [6]. Managing uncertainty is still reported as one of the most prevalent unmet needs among cancer survivors [7].

Illness uncertainty has been conceptualized using the Mishel's Uncertainty in Illness Theory (UIT) [1]. This theory posits that illness uncertainty has 3 antecedent

components: *stimuli frame*, *structure providers*, and *cognitive capacities* [1]. The stimuli frame is the form, composition, and structure of an individual's perceived stimuli, consisting of symptom pattern, event familiarity, and event congruency [1]. For example, illness uncertainty was associated with cancer-specific symptoms [3]. Structure providers are the personal and environmental resources that aid in stimuli formation, including credible authorities (e.g., healthcare providers), social support, and education [1]. Cancer survivors lacking social support reported elevated levels of illness uncertainty [8]. Cognitive capacities refer to the individual's information-processing ability and any physiological malfunction that might impair their ability [1]. Moreover, 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 [1]. Cancer survivors' high levels of illness uncertainty are associated with avoidant coping strategies, often adversely affecting QOL [5][9].

Despite an early scoping review examined factors influencing illness uncertainty among older adults with cancer [2], this review did not include literature published after 2015 and focused on older adults with cancer. Furthermore, to date, no systematic review has been conducted to explore illness uncertainty among family caregivers. Since 2015, research examining illness uncertainty in cancer survivors and their caregivers has also grown considerably. Therefore, an updated and more comprehensive review of the current illness uncertainty literature among adult cancer survivors and their caregivers will be a significant and timely contribution to the literature. The current review aimed to identify the sociodemographic, physical, and psychosocial correlates associated with illness uncertainty in these populations.

Methods

This systematic review and meta-analysis protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020216230).

Inclusion criteria

Articles selected for review met the following inclusion criteria: (1) The study targeted adult cancer survivors or their adult family caregivers (≥ 18 years of age) or both; (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 design (e.g., cohort study, cross-sectional study); the baseline information from the intervention studies was

also included because these can be treated as observational data; and (5) the study was 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) [10] or "intolerance of uncertainty" (i.e., focused on a patient's cognitive, emotional, and behavioral reactions to uncertainty) [11].

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 survivor 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) [12], 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 one author and checked by another author. Data synthesis was based on UIT [1], 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 [13]. If a study reported a nonsignificant correlation but not the value of the point estimate, we recorded the effect size as 0. This represents a conservative approach that may underestimate the true effect size [14]. Four eligible studies reported Spearman coefficients or used multivariate regression analyses with variables of interest but did not report all variables in a format that would allow an effect size to be computed. These authors were contacted for the

original correlation coefficients. For those not provided, Peterson and Brown's suggestion to convert standardized β weights to r (if β weights ranged -0.5 – 0.5) was followed [15]. A random-effects model provided a weighted-mean estimate of the correlation between each variable and illness uncertainty [16]. When relevant data were available from at least 3 studies, effect sizes were calculated using R software. 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%) [17]. Lower heterogeneity indicates higher consistency and generalizability of meta-analytic findings. Subgroup analyses of effects and publication bias were not able to be conducted because the number of studies for these domains was less than 10.

Results

Figure 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 cancer survivors, one focused on family caregivers, and 2 included survivors and family caregivers (Table 1). Survivor samples ranged from 14 to 484, with a mean age of 56.8 years (range = 44.2–67.2). Female-only samples were included in 7 studies and 4 studies included only male survivors. Nine other studies included participants of both genders/sexes, 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 survivors 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 survivors during active surveillance ($n = 1$). Among the 3 studies that included caregivers, sample sizes ranged from 134 to 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.

Fig. 1 PRISMA 2009 flow diagram

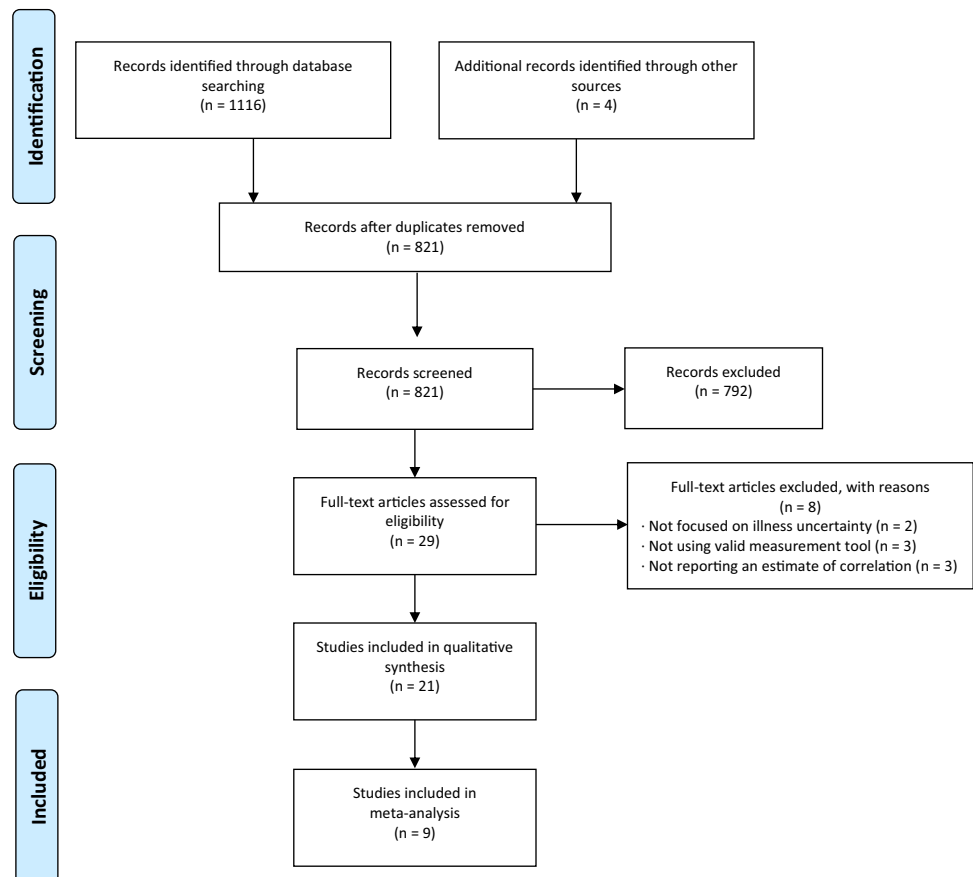


Table 1 Description of population characteristics ($n = 21$)

First author Year Country	<i>N</i>	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	Stages I–III	NR
Guan, Guo 2020 US	CS: 134 CG: 134	CS: 62.57 CG: 58.92	CS: 100% male CG: 100% female	CS: 85% White; CG: 83% White	Prostate	All stages	At various points in the illness trajectory
Guan, Santac- roce 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
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	Stages I–III	NR
Sharif 2017 Malaysia	118	50.95	100% female	49.2% Chinese	Breast	Stages I–III	NR
Shun 2018 China	90	62.53	72.2% male	NR	Live	NR	Receiving medical treatment

Table 1 (continued)

First author Year Country	<i>N</i>	Age	Gender	Race	Cancer type	Stage	Phase of cancer survivorship
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	CS:165 CG:165	CS: 63 CG: 60	CS:100% male CG: 96.4% female	CS: 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; CS, cancer survivor; CG, caregiver

Study characteristics

Table 2 summarizes study characteristics of the 21 reviewed studies, of which 15 were cross-sectional and 6 were longitudinal. Studies were conducted in the USA ($n = 6$), 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 ($n = 1$) [18], generalized unsafety theory of stress ($n = 1$) [19], transactional theory of stress ($n = 1$) [20], and Bodenmann's Systemic Transactional Model ($n = 1$) [21]. One study used 2 theoretical frameworks: UIT and Systemic Transactional Model [21].

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. One study measured illness uncertainty using the cancer- and treatment-specific distress uncertainty subscale [22] (Table 2).

Correlates of illness uncertainty in cancer survivors

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) [23, 24]. Female

gender was associated with higher levels of illness uncertainty [22]. Non-White survivors reported higher levels of illness uncertainty than White survivors [3]. Survivors from urban areas reported lower levels of illness uncertainty as compared to survivors from rural areas [23]. Survivors with lower incomes reported higher levels of illness uncertainty [24, 25]. Survivors employed part- or full-time had higher levels of illness uncertainty than unemployed survivors [23, 26]. As compared with survivors became unemployed due to illness, survivors whose employment did not change had significantly lower illness uncertainty scores [27].

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 [3, 19], pain [8], and fatigue [19]; those experiencing more cancer-specific symptoms reported higher levels of illness uncertainty [3]. 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 [25, 28]. Survivors who received radiation therapy reported high illness uncertainty levels [28]. Survivors with comorbid conditions (e.g., diabetes, hypertension) reported low illness uncertainty levels [24]. Comparison by stage of prostate cancer (i.e., localized versus advanced or recurrent) showed advanced or recurrent cancer was associated with higher illness uncertainty [3]. In contrast, comparison of diagnosis phase showing newly diagnosed survivors had higher levels

Table 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 ($\beta = -0.362, P < 0.001$) and was not significantly related to active emotional, avoidant emotional, and problem-focused coping
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 for survivors 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 survivors with localized prostate cancer and their partners, survivors with advanced or recurrent prostate cancer and their partners reported higher levels of illness uncertainty ($P < 0.001$). Uncertainty for survivors was associated with urinary symptoms ($\beta = -3.13, P < 0.001$) and uncertainty for partner was associated with survivors' 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 survivors had the highest levels of illness uncertainty

Table 2 (continued)

First author Year	Study design	Theoretical frameworks	Uncertainty measurement	Correlates	Scale	Results
Guan [#] , Santacroce 2020	Cross-sectional	UIT	MUIS	Coping, QOL (physical well-being and mental well-being)	Brief COPE, SF-12	Uncertainty was associated with avoidant coping ($\beta = 0.297, P < 0.001$), physical well-being ($\beta = -0.263, P < 0.001$), and mental well-being ($\beta = -0.244, P < 0.001$). Uncertainty was not significantly associated with active coping
Hagen [#] 2015	Cross-sectional	NR	SF-MUIS- Norwegian	Anxiety and depression, social support, emotional well-being, quality of information provided	HADS, FACT-E sub-scales, QPI	Uncertainty was associated with anxiety ($r = 0.35, P < 0.01$), depression ($r = 0.28, P < 0.01$), social support ($r = -0.27, P < 0.01$), emotional well-being ($r = 0.30, P < 0.01$), and quality of information provided ($r = 0.46, P < 0.01$)
Jeon 2016	Cross-sectional	NR	MUIS -Korea	Education, income, family history of cancer, perceived recovery	Self-developed scale	Participants with an education level of high school graduate or less ($P < 0.001$), with a lower monthly income ($P = 0.024$), and without family history of gastric cancer ($P = 0.024$) 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 ($r = -0.73, P < 0.001$), functional QOL ($r = -0.52, P < 0.001$), symptom QOL ($r = 0.60, P < 0.001$), anxiety ($r = 0.74, P < 0.001$), depression ($r = 0.75, P < 0.001$), and social support ($r = -0.51, P < 0.001$)
Kuba 2017	Prospective	NR	Cancer and treatment specific distress-uncertainty subscale	Gender, PTSS	PCL-C	Uncertainty was associated with gender ($\beta = 0.38, P = 0.000$) and PTSS ($\beta = 0.38, P = 0.000$)

Table 2 (continued)

First author Year	Study design	Theoretical frameworks	Uncertainty measurement	Correlates	Scale	Results
Lee 2020	Cross-sectional	NR	MUIS-Korea	QOL, social support, education, satisfaction with financial status, smoking	EORTC QLQ-C30, MSPSS	Uncertainty was higher for survivors with less than a high school education ($t = 4.048, P < 0.001$), dissatisfied with their financial status ($F = 3.760, P = 0.027$), and smokers smoking ($t = 2.195, P = 0.030$) Uncertainty was correlation with social support ($r = -0.335, P < 0.001$) and QOL ($r = -0.312, P < 0.001$)
Lin 2015	Cross-sectional	UIT	MUIS	Phases of treatment process; employment change	NA	Compared to newly diagnosed survivors, survivors at treatment and follow-up had significantly lower total scores of uncertainty. Survivors whose employment status did not change due to the illness had a significantly lower MUISBT score (i.e., 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	Longitudinal	NR	MUIS	QOL (physical well-being and mental well-being), prostate-specific QOL, fear of disease progression	SF-12, EPIC, 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 ($\beta = 0.072, P < 0.001$)

Table 2 (continued)

First author Year	Study design	Theoretical frameworks	Uncertainty measurement	Correlates	Scale	Results
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 ($r = 0.218$, $P < 0.05$), and 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	Survivors with part- or full-time jobs had higher levels of uncertainty ($\beta = 2.215$, $P = 0.022$). Those survivors 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 ($r = -0.53$, $P < 0.0001$)

Table 2 (continued)

First author Year	Study design	Theoretical frameworks	Uncertainty measurement	Correlates	Scale	Results
Tarhani 2020	Cross-sectional	NR	MUIS-A-Iran	Age, education, job type, inhabitance, therapy type	NA	The average uncertainty score of survivors who were 60 years of age, or more was less than the average uncertainty score of survivors below 60 years of age ($P = 0.007$). The average uncertainty average score in lower-education survivors was more than those with a high school diploma or above ($P = 0.018$). The average uncertainty score for employed survivors was lower than for unemployed survivors ($P < 0.05$). The average uncertainty score for in city inhabitants was lower than for rural inhabitant survivors ($P = 0.025$). The average uncertainty average score for survivors 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 survivors was related to more non-supportive behaviors from partners ($\beta = 0.27$, $P < 0.001$) and partners' perceived support ($\beta = -0.28$, $P < 0.001$). 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 ($\beta = -0.989$, $P < 0.001$)

Table 2 (continued)

First author Year	Study design	Theoretical frameworks	Uncertainty measurement	Correlates	Scale	Results
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 ($r = -0.314$, $P < 0.01$)

[#]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 Questionnaire; 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; POMIS, 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

of illness uncertainty than survivors under treatment or in follow-up stage [27]. However, a separate study found that as compared with newly diagnosed survivors, survivors diagnosed for 1 year reported higher levels of illness uncertainty [29]. Relative to event congruency among survivors with prostate cancer, illness uncertainty was associated with higher prostate-specific antigen levels [3]. Illness uncertainty was negatively associated with locus of control (i.e., extent individual perceives internal or external factors control life events) [30]. Survivors with high unmet care needs had high illness uncertainty levels [26].

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 3). All studies reported negative associations (range: $r = -0.33$ to -0.51). One study of couples facing prostate cancer found survivors' illness uncertainty was negatively related to partner-caregivers' social support [21]. Findings were mixed regarding the association between illness uncertainty and survivors' level of education, with results showing positive [25], negative [23, 28, 31], and no association [3]. Illness uncertainty was also predicted by the quality of information from healthcare providers [29].

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) [32, 33]. One study distinguished between only active or avoidant coping [34]. No studies reported a relationship between and problem-focused coping [32, 33], and the relationships found between illness uncertainty and active-emotional coping were either nonsignificant [32] or negative (i.e., higher illness uncertainty related to less active-emotional coping) [33]. 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]) (Table 3). Additionally, one study reported survivors' self-care was negatively correlated with illness uncertainty [24]. Considerable heterogeneity ($I^2 = 90.7%$) was found across studies. The study of survivor-caregiver couples facing prostate cancer found survivors' illness uncertainty was positively related to caregivers' non-supportive behaviors (e.g., avoiding survivor when survivor was not feeling well) [21].

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 (Table 3). Despite considerable heterogeneity ($I^2 = 84.5%$), all studies reported negative associations (range: $r = -0.31$ to -0.73). Additionally, uncertainty was nega-

tively associated with prostate specific QOL [35], functional QOL [8], symptom QOL [8], and QOL subdomains such as physical well-being and emotional/mental well-being [29]. 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]) (Table 3). 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 ($I^2 = 90.8\%$) (Table 3).

Additionally, a few studies specified illness uncertainty was associated with other adaptations such as perceived stress [19], posttraumatic stress syndrome [22], and fear of disease progression [35]. Illness uncertainty was negatively associated with comfort in the physical, psychological, social, and environmental contexts [18] and with perceived recovery [25].

Correlates of illness uncertainty in cancer caregiver

Only 3 articles focused on illness uncertainty among caregivers of survivors with various cancer diagnoses. As compared with non-White partner-caregivers, White partner-caregivers reported higher levels of illness uncertainty [3]. One study found caregivers' illness uncertainty was associated with caregivers' general health, caregivers' perceptions of the influence side effect on themselves, survivors' prostate-specific antigen levels, and caregivers' perceived levels of social support [3]. Another study showed caregivers' illness uncertainty was negatively associated with their QOL [20].

Risk of bias assessment

Calculation of a total quality score for each reviewed study indicated that methodological quality was fair overall. 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 cancer survivors, 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 effect on themselves, survivors' 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 survivors' symptoms. As UIT suggests, when survivors experience a greater number of symptoms, it increases difficulty in tracking and distinguishing between symptom cause (disease or treatment). In turn, difficulty in distinguishing symptom cause prevents survivors from recognizing symptom patterns, contributing to illness uncertainty [1]. Results were mixed regarding the associations between illness uncertainty and family history of cancer. Although a family history of cancer might increase survivors' familiarity with cancer, which might decrease illness uncertainty, such family history can also evoke fear and risk of cancer, which might increase illness uncertainty. Similarly, findings were mixed regarding the relationship between illness uncertainty and time since diagnosis. It is possible that these mixed findings reflect diverse cancer trajectories and stages at diagnosis. For example, a patient with a new early-stage cancer diagnosis may grow to learn more about their illness, and living with good prognostic

Table 3 Meta-analysis results for correlates with illness uncertainty

Correlate	k	n	r	95% CI for r		I^2 %
				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

indicators may ultimately resolve their illness uncertainties. On the other hand, a patient with an advanced stage diagnosis may have increasing uncertainty over time as they struggle with existential questions. Further longitudinal research is needed to detect changes in illness uncertainty over time in the complexity of the cancer context.

According to UIT, education as a structure provider helps survivors 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 cancer survivors [2]. 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 survivor'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 [29]. Given the significant role of healthcare providers in survivors' 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 that 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 [1]. 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 survivors' illness uncertainty influences their adaptation [1]. This significant negative association is also supported in the previous scoping review [2]. However, because few studies controlled for potential confounding variables in the previous review, it remains unknown whether illness uncertainty is an independent predictor of QOL [2]. In contrast, this review indicates illness uncertainty independently influences QOL because all the included studies controlled for potential confounding variables. Moreover, consistent with previous review [2], illness uncertainty was associated with anxiety and depression, 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 [37].

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 survivors [3], but also that they lacked sufficient information about managing illness uncertainty [38]. The study of partner-caregivers caring for prostate cancer survivors demonstrated the significant relationship between survivors' illness status and caregivers' illness uncertainty, which validates the importance of considering characteristics of survivors' illness when studying caregivers' illness uncertainty [3]. Additionally, this study 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. However, these conclusions were based on a small sample of studies and suggest that 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 [21]. Survivors' sustained illness uncertainty was positively related to decreased supportive behaviors from caregivers (e.g., avoiding survivor interaction when survivor was not feeling well) [21]. 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 [39]. 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 survivors' illness uncertainty comes from survivors 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 survivors. 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 [36] and to determine if illness uncertainty is associated with other factors at various points across the cancer trajectory.

Strengths and limitations

This is the first systematic review and meta-analysis of the illness uncertainty literature on adult cancer survivors 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 are 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. Lastly, this systematic review only included the articles published between 2015 and 2020. We will further update the literature in our research paper which is currently under review.

Clinical implications

Knowing the correlates of illness uncertainty among cancer survivors 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 cancer survivors manage illness uncertainty [6], 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 survivors and caregivers and suggests that 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 survivor-caregiver dyads but also provides sound evidence for integrating caregivers into healthcare delivery teams.

Research implications

This study highlights the need for more research on correlates of illness uncertainty among cancer survivors 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 survivors 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 study identified correlates of illness uncertainty among cancer survivors and their family caregivers. These findings contribute to the growing literature on managing illness uncertainty among the cancer survivors and their family caregivers.

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Declarations

Ethics approval This is a systematic review and meta-analysis study. No ethical approval is required.

Consent to participate This study involved secondary analysis of publicly available articles; hence, formal consent is not required.

Consent for publication Not applicable; this is a systematic review and meta-analysis study. Data were abstracted from published articles.

Competing interests The authors declare no competing interests.

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