Examination of Quality of Life in Cancer Survivorship

By

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Abstract

Background: Cancer is a leading cause of death in the United States and worldwide. However, people with cancer are also living longer. In order to understand the experience of cancer survivorship in both life-limiting as well as long-term cancer, quality of life (QOL) should be of the utmost concern. QOL is an overarching concept assessing cancer survivor's well-being and includes domains of physical, psychological, social, and spiritual health. Cancer and its treatment have the potential to significantly impact the QOL of cancer survivors, yet there remain aspects of QOL in cancer survivorship that are understudied and unknown.

Purpose: The purpose of this dissertation was to examine QOL in cancer survivorship from close to death to long-term survivorship and to examine the relationship between domains of QOL and a previously understudied subdomain of social well-being (perceived financial insecurity). Ferrell's model of QOL was used as the theoretical framework. The specific aims of this dissertation are to: 1) identify how QOL is defined and measured in a life-limiting cancer (hepatocellular carcinoma); (2) identify the impact of patient-reported financial insecurity on physical and mental health and symptoms in cancer survivors; and (3) describe and analyze QOL in the long-term cancer survivorship literature.

Methods: To address the first aim, a systematic review of the literature was completed examining QOL in the hepatocellular carcinoma literature using PRISMA guidelines. The second aim was addressed with a secondary analysis of a cross-sectional study of young and middle-aged cancer survivors who had been diagnosed with cancer 1 to 3 years prior. This study quantified the relationship between perceived financial insecurity and physical and mental health and symptoms while controlling for demographics. The final aim was completed with a meta-analysis of QOL in long-term cancer survivorship.

Results: The cumulative results of this dissertation demonstrate the significant impact of cancer and its treatment on QOL across the entire disease trajectory and provide greater insight into QOL in cancer survivorship. Specifically, the key findings include: (1) A diagnosis of cancer has a life-long impact on survivors' QOL; (2) There is a lack of a clear definition of QOL; (3) the domains of QOL are closely integrated with each other and must all be considered in order to have a clear view of QOL; and (4) The spiritual domain of QOL is understudied in cancer survivorship.

Conclusions: This work demonstrates the continued impact of cancer and its treatment on QOL in cancer survivorship and the need for continued attention in research. Key gaps were demonstrated that have the potential to guide future research and advance our understanding of QOL in cancer survivorship. The findings of this work have significant implications for clinical practice as not only the number of long-term cancers survivors are increasing, but also the number of adults with some life-limiting cancer are increasing. Due to this, cancer survivors are being seen in more areas of health care and it is vital that cancer survivors' specific QOL implications are clearly understood to all health care providers.

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Chapter I

Introduction

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Background and Significance

Cancer is a leading overall cause of death in the United States (U.S.) second only to heart disease; it is the leading cause of death for Hispanic, Asian Americans, and adults between the ages of 60 to 79 years (DeSantis et al., 2014; Jemal et al., 2017; Noone, 2018; Siegel, Miller, & Jemal, 2018; Zeng et al., 2015). Nearly 40% of U.S. residents will be diagnosed with cancer during their lifetime (DeSantis et al., 2014; Siegel et al., 2018). While over 1.7 million new cancer incidences are expected in the U.S. in 2019 (approximately 4,700 new cancer diagnoses every day), only 606,880 (~36%) cancer-related deaths are projected. These numbers show that while cancer is prevalent, more people with cancer are living longer in the U.S. (American Cancer Society, 2019; Jemal et al., 2017; D. K. Mayer, Nasso, & Earp, 2017; Siegel et al., 2018; van Leeuwen et al., 2018). With more people living longer *with* cancer, quality of life (QOL) becomes a vital consideration in understanding cancer survivorship experiences, with the lasting and often long-term impact both from the cancer and its treatment (Dow, Ferrell, Haberman, & Eaton, 1999; Ferrell, 1996; Ferrell & Hassey Dow, 1997).

Historically, the primary focus of cancer treatment has been on overall survival; however, understanding the impact of cancer and its treatment on an individual’s QOL is also a vital consideration (Khan, Akhtar, & Sheikh, 2005; Shrestha et al., 2019). QOL has been described as an overarching concept that includes all aspects of being (Peplau, 1994). The World Health Organization defines QOL as more than simply the absence of disease, but as “a state of complete physical, mental, and social well-being” (World Health Organization, 2019). QOL comes from the experience of life as a whole rather than from its parts (Phillips, 1995). It is fundamental in the wholeness of living, things flow and change in life creating a pattern that gives life meaning and purpose. QOL is a dynamic as opposed to static process, dependent on individual perceptions and experiences and varying greatly within and across cancer survivors (Ferrell & Hassey Dow, 1997). It is clear that due to its effects on almost every aspect of an individual's being that the diagnosis and treatment of cancer can have a significant impact on survivors' QOL (Dow et al., 1999).

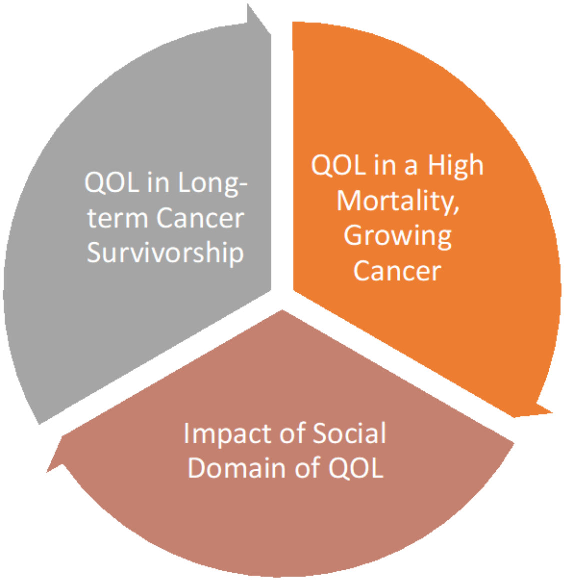
New advances in the ability to diagnose and treat cancer have increased survival rates in most cancers; however, cancer survivors face new challenges, such as recurrence, development of a secondary cancer, long-term adverse effects from cancer treatment, and psychosocial impact of living with a cancer diagnosis and treatment sequalae (Salas-Vega, Iliopoulos, & Mossialos, 2017; Wilbur, 2015). The lasting effects from cancer treatment can include organ toxicity, resulting in loss of organ function, endocrine and reproductive difficulty, mental health issues, and financial and relationship strains (Ganz, 2001; Treanor & Donnelly, 2014). Although those adverse cancer treatment effects that present early generally decrease with time, adverse effects that develop later tend to be progressive, irreversible, and have the potential to have an ongoing impact on an individual's QOL (Langendijk et al., 2008). For long-term cancer survivors, cancer shifts from being an acute illness to become a chronic, lifelong disease. As Ganz (2001) wrote, "Once a cancer patient, always a cancer patient" (p. 241). For long-term cancer survivors, QOL is impacted across the disease trajectory from diagnosis to death. Those cancer survivors who experience the ongoing and/or late-onset adverse effects of cancer and cancer treatment, have significantly poorer physical and mental health and are at greater risk for having unmet care needs when compared with survivors who do not experience them (Given, 2015; Treanor, Santin, Mills, & Donnelly, 2013; Treanor & Donnelly, 2014). Yet, there remains a gap in our knowledge surrounding the impact of the ongoing and/or long-term effects of cancer and its treatment on QOL on cancer survivors as they receive little guidance and support as they adjust to their "new normal". The various trajectories related to QOL remain unclear, especially moving forward into the chronic phase of cancer survivorship (Given, 2015). Such knowledge is needed to develop tailored interventions focused on improving QOL for long-term cancer survivors.

At the same time, not all cancers are seeing an increase in survival rates; however, QOL is impacted across the disease trajectory for these survivors too. Cancer and its treatment can have a significant impact on the QOL of these individuals, even in the short term (Brown et al., 2017; Lee et al., 2016). One such cancer is hepatocellular carcinoma (HCC). The incidence of HCC and HCC-related deaths has significantly increased in the U.S. and worldwide (American Cancer Society, 2019; Jemal et al., 2017). HCC is the most common form of liver cancer and the second leading cause of cancer-related mortality worldwide (McGlynn, Petrick, & London, 2015). In the U.S., HCC is estimated to be the fifth highest cancer-related death for men, and ninth for women, with a 5-year survival rate of only 18% for both men and women (American Cancer Society, 2019; Jemal et al., 2017a). HCC is the most rapidly increasing cancer in the U.S. with an increasing rate of 3% per year (American Cancer Society, 2019). Further, there is a significant symptom burden associated with HCC not only from the disease itself, but also from the accompanying comorbidities (i.e. liver cirrhosis) and treatment (Fitzmorris, Shoreibah, Anand, & Singal, 2015; Harris, Harman, Card, Aithal, & Guha, 2017; Thomas, Poultsides, Pawlick, & Thomas, 2011). As such, HCC is a key example of why QOL is important to understand, even in a life-limiting cancer. Yet, there is little understanding of how QOL is defined and used in the HCC literature. By having a clear understanding, we will be able to identify gaps in the QOL literature for this group of high-mortality cancer survivors and lay the groundwork for future implementation studies to improve the QOL of this understudied, yet highly impacted population.

Living with cancer as a survivor can have a substantial impact on physical, psychological, social, and spiritual health; however, QOL in cancer research primarily focuses on physical and psychological well-being, which is a limited focus and results in a partial understanding of QOL in cancer survivorship (Flannery, 2017). Common cancer QOL measurement tools, such as the *European Organization for Research and Treatment of Cancer* (EORTC), the *Medical Outcomes Short Form* (SF-36) and the *Functional Assessment of Cancer Therapy* (FACT) address physical, psychological, and limited social and role well-being (King, Bell, Costa, Butow, & Oh, 2014; van Leeuwen et al., 2018). In total, the EORTC, SF-36, and the FACT include 73 questions, excluding symptom items. Of those 73 questions, 45% (n=33) address the physical domain of QOL, 30% (n=22) address the psychological domain, and only 15% (n=11) address the social domain (remaining 10% (n=7) address global QOL) (Cella et al., 1993; Phillips et al., 2015; Ware, Snow, Kosinski, & Gandek, 1993). None of these three measures address the spiritual domain. Exploration of QOL has been incomplete, creating a gap in understanding regarding the impact and interactions of some of the subtler domains of QOL (e.g. social and spiritual). Further, is there a lack of a clear and consistent definition of QOL being used (Flannery, 2017).

Therefore, this dissertation's focus is to explore the identified gaps in current knowledge in: 1) the definition and use of QOL in the HCC literature, 2) the impact of perceived financial insecurity, an understudied aspect of the social domain of QOL, and its relationship to the physical and psychological domains of QOL, and 3) QOL in long-term cancer survivorship (Figure 1).

Figure 1. Identified Gaps in our Knowledge



Literature Review

Cancer Survivorship

The term cancer "survivor" is applied to individuals who have been diagnosed with cancer throughout the remainder of their lives, including those seeking curative and palliative treatment at any stage of disease (Frick et al., 2017; Mayer et al., 2017). The term and concept of cancer "survivorship" was first defined by Mullan (1985) in the *New England Journal of Medicine* (Mayer et al., 2017; Mullan, 1985). Mullan identified three phases of cancer survivorship: 1) *acute*, which includes diagnosis; 2) *extended*, which includes treatment; and 3) *permanent*, which included long-term remission. Due to the high mortality of cancer, there are many short-term survivors who do not reach the permanent phase, as such it is important that their QOL needs be addressed during their short survivorship. As survivors transition from the extended to the permanent phase, their needs continue due to the ongoing and late onset effects of cancer and its treatment, yet they often may experience a decrease in supportive resources they receive from their healthcare providers, family, and friends during active treatment (Mayer et al., 2017). This decrease in supportive resources can result in a decrease in QOL, depression, anxiety, and decreased physical and mental health, further compounding the ongoing and later-onset effects of cancer and its treatment (Beckjord et al., 2008; Beckjord et al., 2014; Cheng, Wong, & Koh, 2016).

Effects of Cancer

Physical and psychological impact.

Cancer survivors, living longer are at increased risk for experiencing ongoing and later-onset effects of cancer and its treatment. Of note is that survivors report the first years *after* treatment ends as more difficult than the cancer treatment itself (Mayer et al., 2017). The later-onset and ongoing effects of cancer and its treatment have been well documented. Horick et al. (2018) found that even at a median of 7.6 years post diagnosis, 70% of survivors experienced ongoing adverse physical symptoms relating to their cancer or treatment. Additional findings of rare-cancer survivors (i.e. ovarian, gastrointestinal, thyroid, hematologic, and CNS cancers) demonstrated that a median of seven symptoms persisted more than five years after diagnosis (Horick, Muzikansky, Gutierrez, Boyd, & Finkelstein, 2018). Breast cancer survivors reported a decreased QOL compared to the general population and continued to report pain 12 months after treatment (Tian, Schofield, Gough, & Mann, 2013). A large systematic review reported that at an average of 7 years post diagnosis, up to 100% of ovarian cancer survivors under the age of 40 experienced ongoing and later-onset effects of cancer treatment due to treatment-induced menopause, 92% experienced peripheral neuropathy, 85% experienced hyperthyroidism, and 77% experienced sexual dysfunction (Stava, Jimenez, & Vassilopoulou-Sellin, 2007). A second large study conducted with esophagogastric cancer survivors found that only 12.2% of patients reported depression and anxiety within the 12 months prior to cancer diagnosis compared to 41.1% who reported depression and anxiety two years after diagnosis (Bouras et al., 2017). It is estimated that up to 75% of cancer survivors experience cognitive impairment, such as changes in memory abilities, ability to learn new things, concentrating, daily decision making, and ongoing cognitive impact as a result of their cancer treatment (Treanor et al., 2016).

Social and spiritual impact.

As previously mentioned, QOL cancer research mainly focuses on physical and psychological domains, but the effects of cancer and its treatment can also have significant impact on the social and spiritual domains of QOL. Spiritual and religious practices, such as mindfulness, have been shown to be valuable coping strategies for cancer survivors and to decrease depression, fear of recurrence and promote greater well-being (Adams et al., 2017; Gonzalez et al., 2014; Salsman, Fitchett, Merluzzi, Sherman, & Park, 2015; Wang & Lin, 2016); however, patients report that while oncology clinicians report that their own spirituality influences their practice, these same clinicians provide spiritual care infrequently (Peteet & Balboni, 2013). The spiritual domain of QOL has also been found to be positively associated with physical well-being, and negatively associated with anxiety and depression (Bai & Lazenby, 2015; Mohebbifar, Pakpour, Nahvijou, & Sadeghi, 2015; Walker et al., 2017). Wang & Lin (2016) found that spiritual well-being was negatively associated with cancer symptom severity and that cancer symptom severity was also negatively associated with QOL, demonstrating that increasing spiritual well-being may decrease symptom severity in cancer survivors and thus improve QOL.

The social domain of QOL is often combined with the psychological domain (psych-social domain), but it is in itself its own domain within QOL. The social domain of QOL includes items such as: support, roles, relationships, and finances. The positive impact social support has on increasing QOL in cancer survivorship has been well documented (Colloca & Colloca, 2016; Gonzalez-Saenz de Tejada et al., 2017; Luszczynska, Pawlowska, Cieslak, Knoll, & Scholz, 2013; Pfaendler, Wenzel, Mechanic, & Penner, 2015; Warner et al., 2016). In a study of adults with HCC, changes in role function were identified as the worst scoring QOL subdomain and yet the most significant contributor to overall QOL (Meier et al., 2015). Survivors' QOL has been shown to be positively associated with caregivers' QOL (Bauer et al., 2018; Li & Loke, 2014; Sterba, Zapka, Cranos, Laursen, & Day, 2016). Long-term sexual dysfunction is seen in over 50% of individuals with pelvic and breast cancers, and 25% in other forms of cancer, which could be due to damage to the nerves, blood vessels, hormone disturbances, or psychological factors (Schover et al., 2014). The presence of sexual dysfunction has been linked to depression, anxiety, relationship conflict, loss of self-esteem, and infertility (Schover et al., 2014). One understudied subdomain within the social domain of QOL is the financial impact of cancer.

Financial Impact of Cancer

Cancer is one of the costliest medical conditions in the U.S. (Guy et al., 2013; Yabroff et al., 2016). Further, the cost to treat cancer continues to increase with the emergence of precision care, new chemotherapy agents, biologics, targeted therapies, and other, new cancer treatments (Banegas et al., 2016; Yabroff et al., 2016). In fact, the cost of cancer care is increasing two to three times the rate of other medical care (Banegas et al., 2016). Along with the overall cost of treatment, the out-of-pocket expenses for patients with cancer continues to grow, especially over time. Insurers are shifting the higher cost burden of treatment to the patient/family through ever-increasing copayments and higher deductibles (Yabroff et al., 2016; Zafar et al., 2013). The collateral impact on patients and families, such as lost income from work, transportation costs, and childcare costs, further broaden the wide financial impact of cancer and its treatment on survivors (Guy et al., 2013; Sharp, Carsin, & Timmons, 2013; Whitney et al., 2016).

Employment and bankruptcy

The projected increase in treatment costs represents a limited portion of the financial impact of a cancer diagnosis and its treatment. Cancer survivors' ability to maintain, return to, and/or function at work may have lasting effects due to reduced employee-based health insurance options and decreased resources to pay for medical care (Banegas et al., 2016; Yabroff et al., 2016). Some cancer survivors have needed to file for bankruptcy, which is more likely to occur two years out from the completion of treatment (Banegas et al., 2016). A cancer diagnosis and its treatment may also have a lasting negative effect on employment, which impacts future earnings, career development, and retirement (Banegas et al., 2016; Yabroff et al., 2016). Whitney et al. (2016) found that almost half of employed/working cancer survivors report having to make at least one work modification due to their cancer, including 15% who also reported having to make long-term work modification (Whitney et al., 2016). Yabroff et al. (2016) reported that 42% of working cancer survivors under the age of 65 took extended paid, nonpaid leave, and/or decreased to part time work after their cancer diagnosis. Banegas et al. (2016) found 33% of cancer survivors had gone into debt with 3% having filed for bankruptcy (Banegas et al., 2016). Financial hardship has even been linked with survival, with lung cancer patients five years after diagnosis having the highest incidence of bankruptcy and lowest survival (S. D. Ramsey et al., 2016). Financial hardship is significantly higher for cancer survivors under the age of 65 compared to survivors over the age of 65 (Whitney et al., 2016; Yabroff et al., 2016). Yet, cancer survivors ages 18 to 54 are significantly more likely to go into debt than those ages

55 to 64 (Banegas et al., 2016). For this younger group of cancer survivors, the financial impact may increase over time and extend long after completion of treatment (Whitney et al., 2016; Yabroff et al., 2016).

Financial Impact on Physical and Psychological Domains QOL

The additional financial burden of cancer clearly impacts survivors' physical and psychological health. Depression and/or anxiety is associated with financial stress when controlling for income at diagnosis and insurance status (Sharp et al., 2013). Kale and Carroll (2016) found both physical and mental health related QOL were significantly lower in cancer survivors who reported financial hardship compared with survivors with no financial hardship. In fact, a significant linear relationship exists between physical and psychological health related QOL and financial hardship, signifying the greater the financial hardship the greater the negative impact on QOL (Kale & Carroll, 2016).

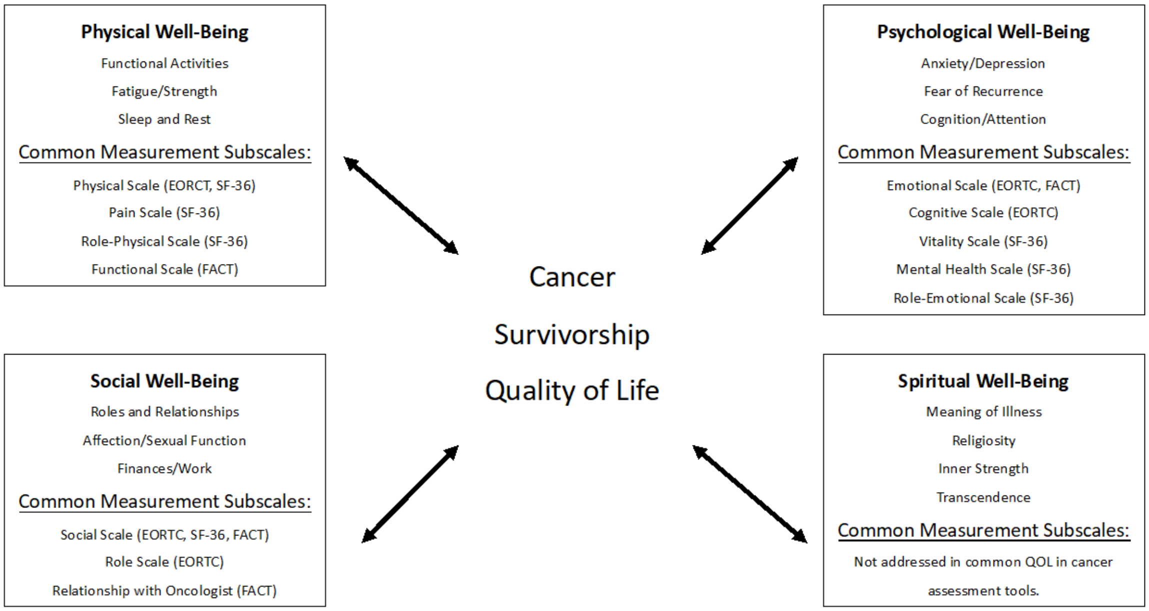
Cancer as a Chronic Disease

In 2017, Dizon wrote that we are no longer fighting a war with cancer; cancer is now a disease that people can, and are, living with (Dizon, 2017). It is estimated that by 2024, there will be 19 million cancer survivors in the U.S. (DeSantis et al., 2014). With the increase in cancer survivorship and survival time, an emerging diagnosis of *chronic* cancer has developed (Frick et al., 2017). The Centers for Disease Control and Prevention (CDC) defines a chronic disease as one lasting longer than one year and requiring ongoing medical attention or alterations to activities of daily living (Center for Disease Control and Prevention, 2019). Many cancer survivors are transitioning from surviving an acute, life-threatening illness to living with a chronic illness. *Chronic* cancer is defined as those survivors who are living with the late-onset and ongoing effects of cancer, recurrent disease and metastatic disease, and secondary cancers as well as those with chronic leukemias (Frick et al., 2017). Individuals with chronic cancer are distinguished from those survivors receiving active treatment (e.g. chemotherapy, radiation, immunotherapy, or surgery) and/or those at the end of life (Harley, Pini, Bartlett, & Velikova, 2012). Frick et al (2017) found in a large sample of over 38,000 cancer survivors that individuals with chronic cancer were significantly more likely to experience fatigue, cognitive changes, dyspnea, kidney problems, liver dysfunction, peripheral neuropathy, lymphedema, and erectile dysfunction compared to those currently receiving active treatment. The population of adults with chronic cancer is expected to grow, and there is a corresponding need for a clearer understanding of these individuals' QOL (American Cancer Society, 2019).

Theoretical Framework

Cancer has specific impacts on QOL that are not typically experienced outside of cancer or other life-limiting diseases. Peplau (1994) examined QOL as a global concept and her framework is widely used; but Peplau's work does not specifically address the needs of adults with a diagnosis of cancer. Ferrell's Quality of Life Model (1996). Ferrell's model is specifically designed to assess the QOL of adults with cancer (Figure 2) as it addresses the complexity and inter-relationship of the human experience and individual domains involved in cancer survivorship. Figure 2 presents examples of latent constructs within each domain of QOL, the subscales of common measurement tools that roughly map onto the subdomains of each domain are presented at the bottom of each box. Ferrell (1996) describes four vital domains to consider with QOL in cancer research: 1) *physical well-being*, 2) *psychological well-being*, 3) *social well-being*, and 4) *spiritual well-being*. All four domains must be considered in order to have a complete and holistic understanding of an individual's QOL.

Figure 2. Quality of Life Theoretical Framework (Ferrell & Hassey Dow, 1997)



Physical well-being.

Physical well-being focuses on the control of side-effects and symptoms in order to maintain the highest level of functioning and independence possible (Ferrell, 1996). The assessment of physical well-being of survivors can include the impact of fatigue, pain, dyspnea, and physical decline, and although these symptoms are not life-threatening, their presence greatly impacts the physical well-being and overall QOL (Ferrell & Hassey Dow, 1997). For cancer survivors, physical well-being is much greater than the symptoms of the cancer itself, but it is greatly impacted by the side-effects of cancer treatment, as a single untreated physical symptom frequently leads to a cascade of symptoms that can impact QOL more than the impact of the cancer diagnosis itself (Ferrell, 1996). Describing physical well-being, a cancer survivor stated:

> I think a new terminology should identify post-cancer syndrome, which could encompass chronic fatigue, loss of energy, fibromyalgia, susceptibility to illness (e.g., colds), pain in the

> original surgical site (if surgery was done) on a physical level and depression, anxiety, and social isolation on an emotional/mental level. (Ferrell, 1996, p. 910)

Psychological well-being.

Psychological well-being is the ability to seek control when facing a possible terminal illness (Ferrell, 1996). It embodies emotional challenges, life impact, and fear of the unknown, but psychological well-being in the face of cancer can also be characterized by positive impact on life (Ferrell, 1996). Though there are many symptoms that impact psychological well-being in survivorship; the most commonly reported include anxiety, depression, fear of recurrence, uncertainty, loneliness, and isolation (Ferrell & Hassey Dow, 1997). These symptoms can continue in cancer survivorship and expand to include such phenomena as uncertainty, fear of recurrence, and fear of the unknown (Appleton, Poole, & Wall, 2018). Describing psychological well-being, a cancer survivor stated: “It’s not better right now, except I’m damn grateful to be alive. My awareness of smaller, insignificant things (stop and smell the roses) is more acute. I appreciate things more than I did before.” (Ferrell, 1996, p. 911)

Social well-being.

Social well-being is the way in which cancer survivors are recognized as people with cancer, including their roles and relationships (Ferrell, 1996). Female breast cancer survivors have described difficulty in re-establishing their roles in their life and relationship, even five years after completion of treatment (Keesing, Rosenwax, & McNamara, 2018). Social well-being also includes the financial impact of cancer along with work-related issues (Ferrell & Hassey Dow, 1997). Economic factors may force survivors to continue employment even when facing the trauma of cancer and its treatment (Ferrell, 1996). Describing social well-being, a cancer survivor stated:

> People come to me. I can’t go to them. It’s been going on so long [that] I adjusted to my declining health. My biggest problem is my children because I see the hurt and pain in their eyes and I feel as though I let them down or something. It hasn’t changed my quality of love. (Ferrell, 1996, p. 911)

Spiritual well-being.

Spiritual well-being is the ability to draw meaning from the cancer experience that is exemplified by uncertainty. It can include, but is not limited to, religion and spiritual support, it is transcendence (Ferrell, 1996). Personal awareness and meaning from cancer are also key elements to spiritual well-being along with religiosity and spirituality. The desire to find meaning from cancer can be seen as desire to understand the diagnosis of cancer and its consequences. This search for meaning can change the survivors outlook of both life and death and can lead to a survey of one’s life (Ferrell & Hassey Dow, 1997). Spiritual pain and spirituality have been found to independently predict a lower and higher global QOL respectively (Bovero, Leombruni, Miniotti, Rocca, & Torta, 2016; Kruizinga et al., 2016; Perez-Cruz et al., 2019). Describing spiritual well-being, a cancer survivor stated: “Cancer has put me in touch with my own vulnerability, my own impermanence. It has taught me to live with that understanding while I carry on with my life. I want to spend only a short time dying and most all my time living” (Ferrell, 1996, p. 913).

Cancer QOL Measurement Tools

In cancer research, there are three common, valid, reliable tools used to measure global QOL: the European Organization for Research and Treatment of Cancer (EORTC), the Functional Assessment of Cancer Therapy (FACT), and the Short-Form 36 (SF-36) with the EORTC as the most frequently used tool (Heydarnejad, Hassanpour, & Solati, 2011; Luckett et al., 2011; Tax, Steenbergen, Zusterzeel, Bekkers, & Rovers, 2017). The EORTC is a research tool designed to assess QOL of cancer survivors as a research outcome (Scott, 2008). The EORTC also has 28 subscales for specific cancer populations (Scott, 2008). The EORTC is the only tool that also includes nine single questions regarding common cancer symptoms: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (Scott, 2008). The second commonly used tool to measure QOL is the FACT. Similar to the EORTC, the FACT was specifically designed for clinical trials in cancer, though there is current scale development outside of the cancer population (Cella et al., 1993). Additional disease and symptoms specific modules are available for the FACT as well. However, unlike the EORTC, the general FACT does not include any questions regarding symptoms. As opposed to the EORTC and the FACT, the SF-36 was not specifically designed as a measurement tool for cancer, but as a general tool to capture patients' perspective of QOL for use in health care outcome (Ware et al., 1993). The SF-36 is used frequently due to its global view of QOL, however, it lacks specificity to the special needs of cancer survivors due to their specific symptoms and does not offer any disease-specific scales. Ferrell has also developed a QOL measurement tool based on the model of QOL, however it is not commonly used. Ferrell's tool includes 40 questions and was designed specifically for the cancer population and includes subdomains for each of the four areas of well-being in Ferrell's model of QOL (Ferrell, Hassey Dow, & Grant, 2012). Of note, Ferrell's QOL tool is the only described tool that includes the spiritual domain of QOL. In all of these measurement tools, a higher score corresponds to higher QOL.

Table 1. Domains of QOL in common cancer QOL measurement tools.

Measure	Physical	Psychological	Social	Spiritual
EORTC (30 items)	-Physical Scale	-Emotional Scale -Cognitive Scale	-Role Scale -Social Scale	Not addressed*
SF-36 (36 items)	-Physical Scale -Role-Physical Scale	-Vitality Scale -Mental Health Scale -Role-Emotional Scale	-Social Scale	Not addressed
FACT-G (27 items)	-Functional Scale	-Emotional Scale	-Social Scale -Relationship with doctor	Not addressed*
Ferrell QOL Tool (40 items)	-Physical Well-being	Psychological Well-being	-Social Concerns	Spiritual well-being

* Primary scale does not include the spiritual domain but a separate spirituality specific scale is available.

Dissertation Purpose and Aims

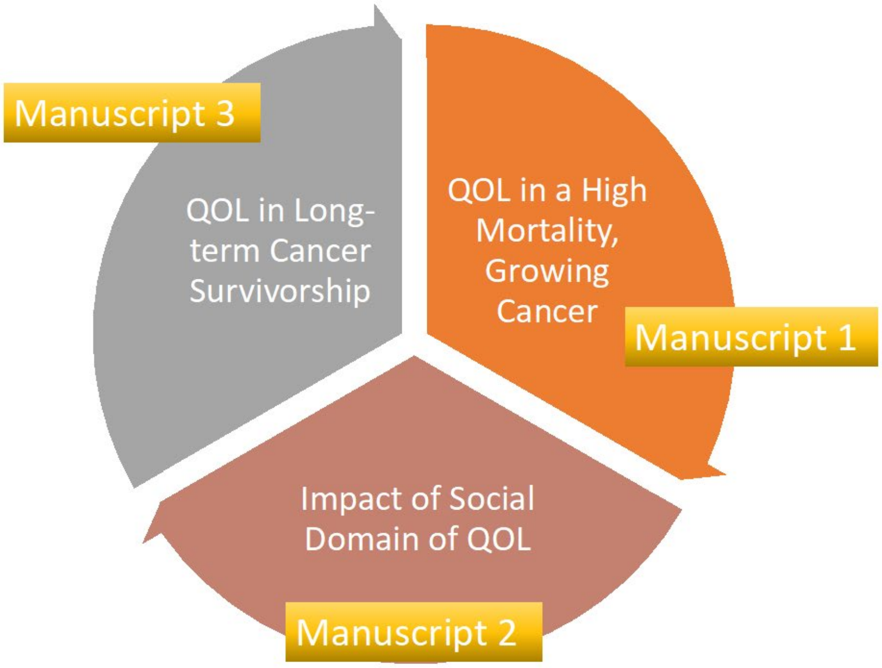
The overall purpose of this research is to create a deeper understanding of QOL in cancer survivorship from close to death to long term survivorship in various types of cancer. This dissertation seeks to examine QOL as a whole concept. To accomplish this purpose, three specific aims with corresponding manuscripts are proposed (Table 2). These manuscripts include an in-depth literature review of quantitative research on all domains of QOL in HCC, a life-limiting cancer, a secondary analysis exploring an understudied aspect of the social domain of QOL (financial insecurity) and its relationship to the physical and psychological domains of QOL, and a meta-analysis of QOL in long-term cancer survivorship (Figure 3).

Chapters and Aims

Table 2 Chapters and aims

Chapter Title	Aims
Chapter 2: A Closer Look at QOL in the HCC Literature (Systematic Review of the Literature)	Aim 1: Identify how QOL is defined and measured in the HCC literature based on Ferrell's model of QOL.
Chapter 3: Impact of Perceived Financial Insecurity on Physical and Mental Health and Symptoms in Cancer Survivors (Secondary Analysis)	Aim 2: Identify the impact of patient-reported financial insecurity on physical and mental health and symptoms in cancer survivors.
Chapter 4: QOL in Long-Term Cancer Survivorship: A Meta-Analysis	Aim 3: Describe and analyze QOL in the long-term cancer survivorship literature.

Figure 3. Manuscripts Addressing Gaps in Our Knowledge



Aim 1. The first aim of this body of work is to identify how QOL is defined and measured in the HCC literature based on Ferrell's model of QOL. This aim will be completed with a systematic review of the literature of research studies reporting on the QOL in hepatocellular carcinoma. Completion of this aim will help to describe how QOL is currently being defined and used in the cancer literature and identify any emerging shifts in understanding.

Aim 2. The second aim is to explore an understudied aspect of the social domain of QOL by identifying the impact of patient-reported financial insecurity on physical and mental health and symptoms in cancer survivors. This aim will be accomplished with a secondary analysis of a cross-sectional survey from a cohort of Oregon cancer survivors. Completion of this aim will bridge the gap of the disconnect between these domains of QOL to establish a more comprehensive understanding of the QOL of the cancer survivors by quantifying a portion of the potential relationship between the domains of QOL.

Aim 3. The third aim of this body of work is to describe and analyze QOL in the long-term cancer survivorship literature. This aim will be accomplished with a meta-analysis of published literature of cancer survivorship. The research hypothesis for this aim is that QOL continues to be significantly impacted in cancer survivors even two or more years after diagnosis. Completion of this aim will increase our understanding of QOL in chronic cancer, and potentially identify gaps in current literature leading to future research.

Implications for Nursing

This body of research has several potential implications for nursing. First, by identifying how QOL is defined and measured in the HCC literature, we will better understand QOL in adults with HCC and potentially other life-limiting cancer. We will also be able to identify potential domains, groups of individuals, and aspects of QOL that are understudied in the HCC population. This knowledge will help guide future research to better our understanding of the QOL of cancer survivors with HCC and possibly other life-limiting cancers.

The second implication for nursing is a clearer understanding of the relationship between the social, physical, and psychological domains of QOL. Examining the impact of an aspect of the social domain on the physical and psychological domains of QOL will increase our understanding of QOL as a whole, along with the interrelatedness of the domains of QOL. In examining the relationships between the QOL of domains, gaps in our knowledge may be exposed, demonstrating future research needs into the relationships of the domains of QOL in cancer survivorship.

Finally, by examining QOL in chronic cancer is a systematic way, we may identify gaps in our knowledge and understanding regarding QOL in chronic cancer, guiding future research. We will also show that cancer survivorship should be viewed as a chronic condition and not as an acute condition where QOL returned to baseline after active treatment is completed, but instead that the QOL continues to be negatively impacted as cancer becomes a chronic condition.

Summary

QOL is an integral aspect of the human experience of cancer survivorship. As such, it is important to understand how QOL is described and used in the cancer literature. This dissertation seeks to increase the understanding of the usage and impact of QOL on cancer survivorship and help to identify gaps in the QOL literature of cancer survivorship. Ferrell's QOL model is used as a theoretical lens as it is specifically designed for the special needs of cancer survivors. The three manuscripts explored QOL in the HCC literature based on the described QOL model. We also examined the impact that financial insecurity has on key physical and mental health and symptoms in cancer survivors. Finally, we will analysis QOL in chronic cancer. As a whole, this dissertation increased our understanding of how QOL is used in cancer survivorship and identify further opportunities to study and examine QOL in cancer research.

References for Chapter I (See Cumulative References)

CHAPTER II

A Closer Look at Quality of Life in the Hepatocellular Carcinoma Literature

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This manuscript represents a significant contribution to the Dissertation work. Ms. Firkins is the primary author on the paper and Dr. Hansen is the senior author on this paper. This manuscript has been submitted to Quality of Life Research (QOLR) journal. QOLR is a peer-reviewed journal focusing on all quality of life aspects of treatment, care, and rehabilitation. QOLR published original research, theoretical articles, reviews, and methodological reports related to any aspect of quality of life. At the time of this Dissertation proposal, QOLR has an impact factor of 2.392.

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Abstract

Adults with hepatocellular carcinoma (HCC) have a high symptom burden. Their quality of life (QOL) has been shown to be significantly impacted by both the disease and its treatment, adding to the high symptom burden that these patients experience. The primary aims of this paper are: (1) to identify how QOL is being defined in HCC literature, and (2) to identify how QOL is being measured in the HCC literature using Ferrell's model of QOL. A systematic review was completed of relevant studies published after 2014, using PubMed, CINHAL, and PsychInfo. Relevant studies were reviewed by 2 reviewers using PRISMA guidelines. From a total of 1312 papers obtained in the initial database search, 30 met inclusion criteria and are included in this review. From the included articles, 10% included a definition of QOL and 3% addressed the spiritual domain of QOL. Majority of study participants were in the early stage of HCC, though the majority of adults with HCC are diagnosed in the advanced stage. Only 3% of included studies included greater than 22% population of advanced stage of HCC. The results of this systematic review demonstrate the need for future research into QOL in the advanced stage of QOL. It also identified gap in the literature concerning the definition of QOL in HCC and the spiritual domain of QOL in HCC.

Introduction

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) making up 80% of all liver cancers (Bray et al., 2018; McGlynn et al., 2015; Thomas et al., 2011). The highest incidence of liver cancer is seen in Asia which makes up an estimated 75% of the world's liver cancer burden. In the United States (U.S.), which has one of the lowest incidences of liver cancer in the world, HCC is the fifth highest cancer-related death for men, and ninth highest for women, with a 5-year survival rate of only 18% (Center for Disease Control and Prevention, 2019; Jemal et al., 2017; McGlynn et al., 2015). While the death rate in most cancers is decreasing, HCC cancer deaths are increasing in the U.S. and worldwide (Jemal et al., 2017; McGlynn et al., 2015). This increase may be largely due to the parallel increased incidence of hepatitis and liver cirrhosis, the primary etiologies of HCC (McGlynn et al., 2015; Thomas et al., 2011).

Approximately 44% of adults with HCC are diagnosed when the disease is localized to the liver alone and still has available curative options, such as liver transplant (American Cancer Society, 2019); the majority(56%) are diagnosed in the advanced stages of the disease, when curative options are no longer an option (American Cancer Society, 2019; Mudumbi et al., 2018). All adults have a high symptom burden as symptoms of HCC can coexist with those of severe hepatic dysfunction such as: abdominal pain, hypoglycemia, diarrhea, nausea, vomiting, jaundice, cholangitis, fever, and peritonitis (Center for Disease Control and Prevention, 2019; Harris et al., 2017). Adults with HCC also frequently suffer from hepatic encephalopathy, further adding to the already high symptom burden of HCC (Fitzmorris et al., 2015; Harris et al., 2017; Thomas et al., 2011). Due to the high symptom burden and mortality for adults with HCC, ensuring optimal quality of life (QOL) should be in the forefront of care efforts.

Quality of Life (QOL)

QOL is a multifaceted concept that embodies all aspects of a person's life and can be defined as an individual's perception of well-being (Ferrell, 1996; Haas, 1999). QOL is a vital metric when considering patient outcomes in both clinical care and research and needs to be moved to the forefront alongside survival (Gandhi, Khubchandani, & Iyer, 2014; Liu, Mittendorf, & von der Schulenburg, 2010; Mayer, 1995; Moinpour, 1994; Slevin, 1992). In cancer research, Ferrell's (1996) model of QOL in cancer survivors defines the four domains, physical, psychological, social, and spiritual well-being, that impact QOL (Figure 1) (Ferrell, 1996). Each of the domains plays a vital role in determining the overall QOL and well-being of all adults living with cancer, including HCC. Both generic QOL measurement tools, along with liver/HCC disease-specific measurement tools, have been developed in order to capture a comprehensive evaluation of QOL. Evaluating the use of these measurement tools is needed in order to appropriately and accurately determine how overall QOL is addressed in the HCC population, as well as its four sub-domains.

In adults with HCC, QOL has been shown to be significantly impacted by both the disease and its treatment, adding to the high symptom burden that these patients experience (Fan, Eiser, & Ho, 2010; Gandhi et al., 2014; Liu et al., 2010). However, it is not well understood *how* QOL is defined, or *how* QOL is being measured in this population. Due to these gaps in understanding, along with an increase in the incidence and mortality of HCC in the U.S. and worldwide, the primary aims of this paper are to: (1) identify how QOL is being defined in HCC literature, and (2) identify how QOL is being measured in the HCC literature using Ferrell's model of QOL. To address these aims, a systematic review of the literature was undertaken.

Methods

For this review, two investigators performed a search of three electronic databases (CINAHL, PubMed, PsycINFO) using the search terms “quality of life” (OR “QOL” OR “HRQOL” OR “health related quality of life”) AND “hepatocellular carcinoma”. The search term “hepatocellular carcinoma” was used (rather than the generic “liver cancer”) because 80% of adults diagnosed with liver cancer have HCC. Search results were imported into Rayyan, a web-based systematic review application, and duplicates were removed (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). The reviewers then independently reviewed titles and abstracts of articles and identified those to be included, based on the following criteria: (1) quantitative methodology, (2) data-based original research, (3) participants with exclusively HCC patients or with results for patients with HCC separated from results from patients with other diagnoses in papers with mixed samples, (4) published within the previous 15 years, and (5) available in English. Case studies, narrative reviews, commentaries, letters, non-patient reported metrics (i.e. Karnofsky Performance Status), or validation of measures studies were excluded.

Full articles were then obtained and reviewed. After both reviewers had completed independent, blinded reviews, Rayyan was unblinded and 100% consensus of articles that met inclusion criteria was reached (Figure 2). Data extraction was then conducted. Extraction categories included: (1) participant demographics; (2) geographical location of participants; (3) participant disease stage; (4) QOL definition; (5) QOL measurement tool; (6) inclusion of the four domains of QOL (i.e. physical, psychological, social, spiritual), and (7) disease specific measurements.

Results

A total of 30 quantitative studies met inclusion criteria (Table 1).

Demographics

Sample size for included studies ranged from 21 to 538 participants with HCC (*M*= 180) for a total of 5583 participants included in this review. The average age of study participants per study ranged from 49 to 71 years (*M*=62). As HCC is more commonly diagnosed in males rather than females, with an estimated proportion of 75% male worldwide (McGlynn et al., 2015), the studies in this review aligned with the global gender distribution of HCC (M=82% male; Range 68%-100% male). This finding does however create a gap in our understanding regarding the female perspective of QOL in HCC, which may be significantly overshadowed and/or uniquely different.

Geographic Location

Of the 30 studies, 17 (57%) included participants from Asia, 7 (23%) from Europe, and 6 (20%) from North America. Gill et al (2018) included participants from 13 countries across North and South America, Europe, Asia, and Australia. None of the studies included participants from Africa.

Disease Stage

For our review, the Child-Pugh score (CPS) was used to describe disease stage. CPS is used to assess prognosis in liver disease by scoring total bilirubin, serum albumin, prothrombin time, international normalized ratio, ascites, and hepatic encephalopathy (Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973). Total scores are graded as class A, B, or C with a corresponding prognostic survival for one- and two-year survival as: 100% and 85% for class A, 80% and 60% for class B, and 45% and 35% for class C (Pugh et al., 1973). Of the 30 included studies, 20 (67%) provided description of participants CPS and 6 (32%) studies included an exclusive participants of class A and B. Five studies (17%) included participants of more than 50% class A. Of the 14 (70%) studies that included participants in class C, only one (5%) study included more than 22% of class C. Of note was Bonnetain et al (2008), who included exclusively participants with class C, found that QOL was an independent prognostic factor for survival in adults with end-stage HCC.

QOL Definition

In Ferrell's (1996) model of QOL, QOL is defined as, "a personal sense of well-being encompassing physical, psychological, social, and spiritual dimensions" (p. 915). A clear definition of QOL was provided in only 3 (10%) of the reviewed articles. Fan et al (2012) introduced QOL as a broad concept that included the domains of physical, psychological, and social well-being. They further defined QOL as an "integrative-index" merging objective functioning and subjective well-being. Phillips et al (2015) defined QOL as, "Patient's perceptions of their well-being in various areas such as physical, psychological, social, financial, and somatic" (p. 895). Finally, Steel et al (2005) based their definition of QOL on the World Health Organization (WHO) definition that QOL is the subject's perception of their lives in the context of their environment, in relation to their goals and expectations. The remaining 27 articles did not offer a definition for the term QOL.

QOL Measurement Tool

The large majority *n*=28; 93% of the studies used a validated, reliable measurement tool for QOL. The most commonly used (*n*=14; 47%) tool was the *European Organization for Research and Treatment of Cancer* (EORTC). The *Functional Assessment in Cancer Treatment* (FACT) was used in 10 (33%) studies, while the *Medical Outcomes Short Form 36* (SF-36), or the *Medical Outcomes Short Form 8* (SF-8), was used in 5 (17%) studies. The remaining studies (*n*=2) did not use a standard QOL measurement tool. For example, Gill et al (2018) simply asked participants to describe their QOL as either “excellent”, “good”, or “poor”, while Ueno et al (2002) used a 14-item questionnaire asking participants to rate their physical, mental, and social health and symptoms as “good”, “fair”, or “poor” or “never”, “sometimes” or “often” based on the question.

QOL Domains

The model of QOL for this review included four sub-domains of well-being: physical, psychological, social, and spiritual. A breakdown of the QOL measurement tools used in the articles for this review are presented in Table 2. All 30 (100%) of the studies addressed *physical* and *psychological* well-being and 29 (97%) included some measurement of the *social* domain of QOL; however, only one (3%) study specifically addressed the *spiritual* domain of QOL in any way.

Disease-Specific Measurement

Adults with HCC have a very specific set of symptoms resulting in a high symptom burden. One way to assess these symptoms is through a disease-specific QOL subscale; such a subscale was included in 17 (57%) studies. For example, both the EORTC and the FACT have disease-specific subscales appropriate for the HCC population; however, there is no relevant disease-specific subscale for the SF-36. The EORTC disease-specific subscale (EORTC HCC 18) was used in seven (23%) of studies and the FACT hepatobiliary (FACT-Hep) disease-specific subscale was used in nine (30%) studies. Kondo et al (2007), who used the SF-36, added a chronic liver disease questionnaire to address the specific needs of the HCC population.

Discussion

The primary aims of this review were to identify how QOL is being defined and measured in the HCC literature, using Ferrell's model of QOL and sub-domains as a guiding lens. There were four insights and/or gaps identified.

First, only 10% of the studies included a definition for QOL. All three of these studies provided a definition of QOL that included aspects of physical, psychological, and social health; however, none of the definitions provided specifically addressed the spiritual well-being aspect of QOL. Without a clear or shared comprehensive definition of QOL, it is difficult to make inferences within/across research studies. The definition closely aligned with Ferrell's was the WHO definition (Steel et al.,2005), which states that QOL is much more than simply the absence of disease, but encompasses physical, mental, and social well-being (World Health Organization, 2019). However, The WHO definition of QOL does not specifically address the spiritual well-being as a fourth domain of QOL.

Second, there was the lack of attention to the *spiritual* domain of QOL in the HCC literature. Spiritual well-being was addressed in only one study. This absence may be because the spiritual domain has previously been housed or subsumed within the psychological domain of QOL; however, Ferrell asserts that it is its own separate domain (Ferrell, 1996). According to Ferrell, the spiritual domain embodies more than religiosity and includes such topics as hope, inner strength, spirituality, uncertainty, transcendence, and meaning in illness (Ferrell, 1996). In fact, a large study of adults with cancer found that spiritual well-being was a significant protective factor against psychological distress at the end of life (Bernard et al., 2017). A study of Italian cancer survivors found that faith, meaning, and peace became more important the closer survivors were to death (Bovero et al., 2016). Clearly, addressing the spiritual domain of QOL should be seen as essential, especially in life-limiting cancers, such as HCC (Wang, Chow, & Chan, 2017). Of note, the most commonly used QOL measurement tools (e.g. EORTC, FACT, SF-36(8)) focus on the physical, psychological, and social domains, but do not specifically contain the spiritual domain. Both the EORTC and the FACT do have separate, spirituality-specific measurement tools, but these tools are only provided as a secondary questionnaire for study participants to complete. By separating this domain and only assessing it with the addition of another measurement tool, not only marginalizes this overlooked domain, but also increases the participant burden during research.

Third, there is a disproportionate geographic representation in HCC QOL research. HCC is endemic and a leading cause of cancer-related deaths in Eastern Asia (e. g., Mongolia, China), South-Eastern Asia, Northern and Western Africa, and Micronesia (Bray et al., 2018). In fact, Asia is responsible for approximately 75% of the worldwide incidence of HCC, yet only 60% of the articles included in this review included participants from Asia. Worldwide, Mongolia has the highest incidence and mortality from HCC, which accounts for almost half of all cancer deaths in that country, yet no studies included participants from Mongolia (Znaor et al., 2018). Another large geographic location that was not represented was Africa, which was not represented in any of the study populations of this review yet HCC is prevalent throughout Africa, specifically in Northern and Western Africa where HCC is endemic (Lemoine & Thursz, 2017). In order to have a complete understanding of QOL in HCC, research in QOL in these areas of high HCC prevalence should be completed. In addition, the specific impact of HCC on QOL for these populations may be uniquely different.

Fourth and last, there was a lack of focus on QOL in the end-stage (Class C) HCC literature. Adults with HCC who are diagnosed and treated early (Classes A & B) have a greater rate of long-term survival and curative treatment available than those diagnosed late in class C. However, the majority of adults with HCC continue to be diagnosed in the late stages of disease, when long-term, curative treatment is no longer an option, and 1-year survival is less than 50% (Fateen & Ryder, 2017). As such, end-stage HCC patients could possible present a uniquely different perspective on QOL than their early-stage counterparts. Only 68% of studies included in this review included Class C HCC participants. Further, while 68% of the studies included Class C, 92% had less than 25% Class C participants. This under-representation is important in that the impact of HCC on QOL in end-stage disease may be at its highest, not only due to the increasing symptom burden experienced as patients approach death, but also because of an increase in self-awareness for anyone in the midst of facing death.

The most commonly used QOL tools were the EORTC and the FACT. The EORTC includes five sub-domains: physical, emotional, cognitive, social, and role health (Scott, 2008). The FACT includes three sub-domains: functional, emotional, and social health, plus a single item relating to the relationship with oncologist (Cella et al., 1993). The EORTC addresses eight specific symptoms related to cancer and its treatment: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea (Phillips et al., 2015). Though these eight symptoms are not pulled out as part of scoring, as with the EORTC, the FACT also includes items regarding symptoms, such as fatigue, nausea, and pain within the functional health sub-domain (Cella et al., 1993). As adults with HCC are known to have a high symptom burden, the EORTC may be a more appropriate measurement tool based on its ability to address more of symptoms experienced by adults with HCC.

While the majority of patients diagnosed with HCC are diagnosed in the advanced stage, the majority of QOL research is completed with those in the early stage of HCC. This skew in participation may reflect the high symptom burden and overt inability of patients in end-stage HCC to participate. However, it is worth noting as the experience in these individuals, again, may be distinctly different. Curative treatments, such as liver resection, liver transplant and ablation, are available for adults with HCC in the earlier stages, (Mudumbi et al., 2018; Schlachterman, Craft, Hilgenfeldt, Mitra, & Cabrera, 2015). When curative treatments are no longer an option, palliative treatment options may be offered, including: transarterial chemoembolization, chemotherapy (Sorafenib), and radiotherapy (Schlachterman et al., 2015). Side effects of these palliative treatments can be very similar to the symptoms of HCC, adding to, rather than decreasing symptom burden (Schlachterman et al., 2015). Though the EORTC and the FACT address the symptoms of fatigue, nausea, vomiting, pain, dyspnea, appetite changes, and diarrhea, these tools do not address other common symptoms as hypoglycemia, fever, cholangitis, peritonitis, and encephalopathy. In order to capture the overall experience of QOL in HCC, additional measures from the EORTC and FACT are needed or these tools need to be revisited as we learn more about HCC across its disease trajectory. Both the EORTC and the FACT have additional subscales available to address these specific needs of the HCC population; however, these measures may not always be appropriate, due to survey burden for study participants.

There are several limitations that need to be highlighted. First, we excluded articles that were not available in English. This exclusion may have underrepresented studies HCC-endemic areas, such as Asia, Though HCC is increasing in English-speaking countries, it is possible that research examining QOL has been done in these areas that is not available in English. Second, this review excluded research using qualitative methods due to our focus on investigating the definition of QOL being used and how QOL is measured in the HCC literature. The inclusion of qualitative studies may not only provide a deeper view of what QOL means to the patient with HCC, but also provide additional insights into how existing tools could capture QOL across domains and disease stages. Finally, this review shows clear gaps in the literature for the HCC population, which may not be generalizable to other types of cancers that are not increasing in incidence and mortality. Similar studies should be conducted in other life-limiting cancers, such as pancreatic cancer, to explore similarities and differences.

Conclusion

As the incidence and mortality of HCC continues to increase worldwide, the need to examine QOL in adults with HCC is increasingly important. This systematic review was completed to begin to investigate the current state of knowledge around QOL and HCC, with a focus on how QOL is currently defined and measured in the HCC literature. We also examined the inclusion of four QOL sub-domains using the model put forth by Ferrell et al (1996). We found that in QOL studies in HCC, the physical, psychological, and social domains are well represented, but there was a lack of research into the spiritual domain of QOL. Of particular note, we found a lack of a clear definition of QOL in the overwhelming majority of the studies. This lack of definition may be due to the complex nature of the concept of QOL or an assumption that everyone knows what QOL means. Yet, even when definitions of QOL are included, there was a lack of specific attention to spirituality. This oversight clearly needs attention as research increasingly defines spirituality as a prognostic predictor of QOL. Finally, there is a need to explore QOL across the HCC experience, especially in end-stage disease and differences between/among genders, including those who self-identify as gender minorities, such as the LGBTQ populations. Each of these limitations provide an avenue for future research.

Figure 1. Conceptual Model of QOL in Cancer (B. R. Ferrell, 1996)

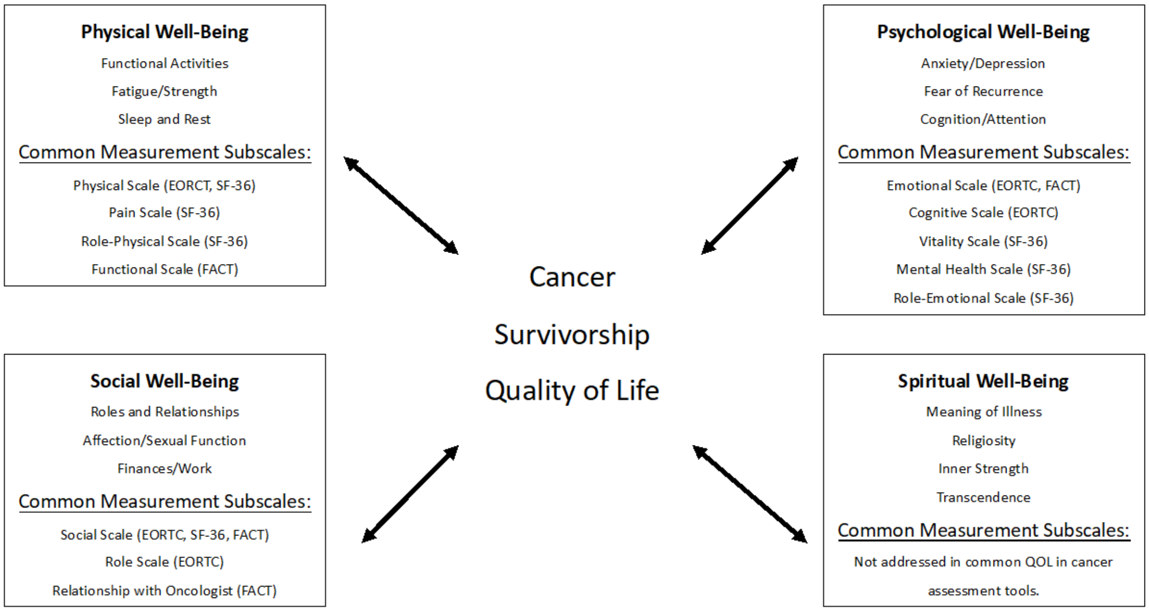

Figure 2. Flow diagram of literature review

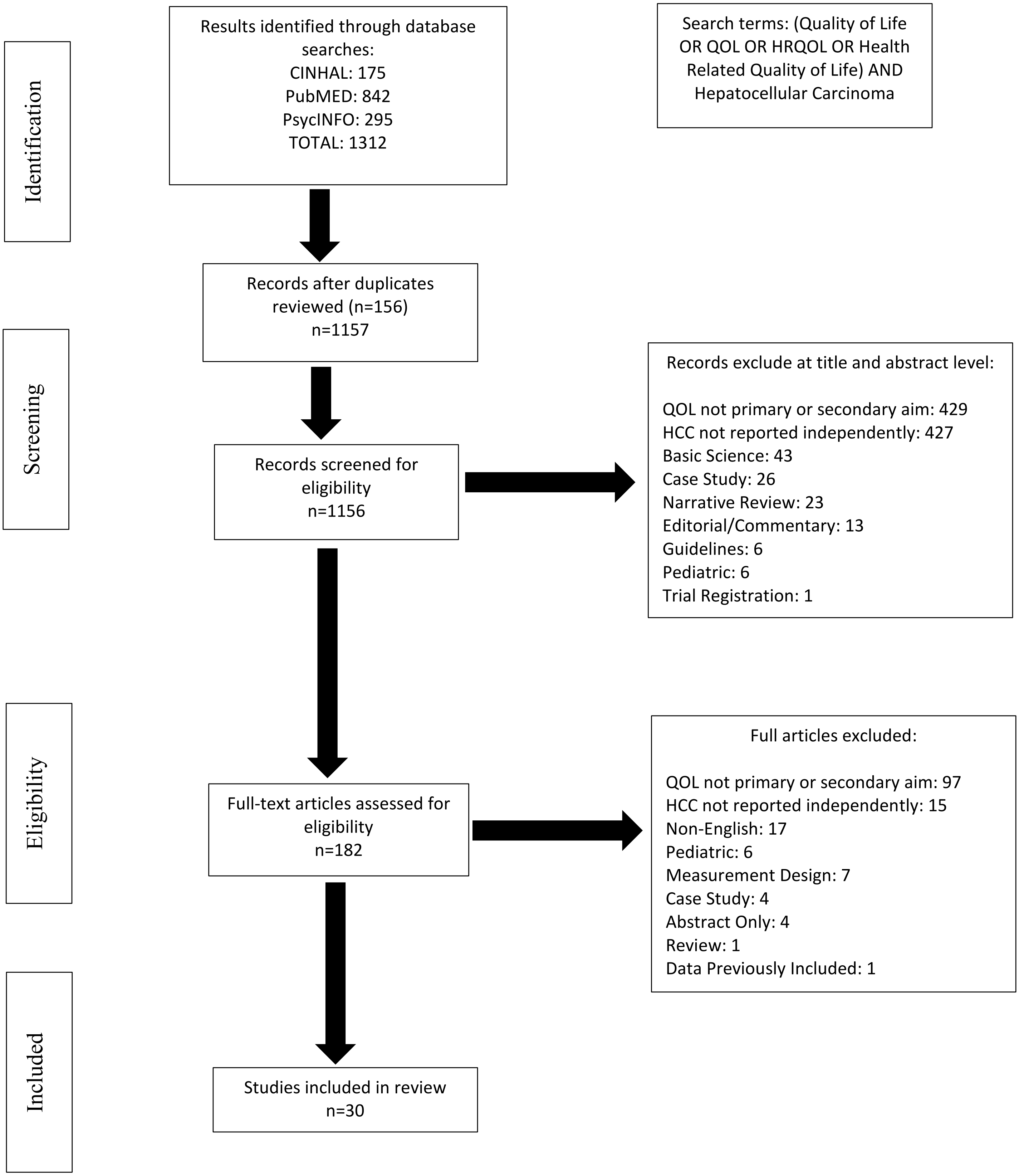

Table 1. Characteristics of the included studies

Reference	Location	QOL Definition	QOL Measure	Disease Stage	Sample Size	Sample Demographics
(Bianchi et al., 2003)	Europe	Not Provided	SF-36	Child-Pugh A 35% B 43% C 22%	101	Mean Age 66 Males 74%
(Bonnetain et al., 2008)	Europe	Not Provided	EORTC	Child-Pugh C 100%	538	Age ≥ 65: 63% Male 88%
(Chie et al., 2017)	Europe Asia	Not Provided	EORTC	Child-Pugh A 79% B/C 18% Missing 3%	227	Mean Age 62 Male 76%
(Diouf et al., 2013)	Europe	Not Provided	EORTC	Child-Pugh A 67% B 24% C 1% D 8%	271	Age ≥ 65: 66% Male 75%
(Fan, Eiser, Ho, & Lin, 2013)	Asia	Provided	EORTC	Child-Pugh A 78% B 15% C 6% Missing 1%	286	Mean Age 60 Male 76%
(Gill et al., 2018)	International	Not Provided	Patient reported: ‘excellent’, ‘good’, or ‘poor’ to describe their QOL	Unknown	256	Age ≥ 60: 66% Male 70%
(Gmur, Kolly, Knopfli, & Dufour, 2018)	Europe	Not Provided	FACT	Child-Pugh A 67% B 29% C 4%	242	Median Age 64 Male 85%
(Hsu, Tsai, Chan, Wang, & Chung, 2012)	Asia	Not Provided	EORTC	Child-Pugh A 67% B 29% C 4%	300	Age ≥ 65: 44% Male 80%
(Jie, Qiu, Feng, & Zhu, 2016)	Asia	Not Provided	EORTC	Qualify for curative treatment	218	Mean Age 50 Male 86%
(G. A. Kim et al., 2019)	Asia	Not Provided	EORTC FACT	Child-Pugh A 91% B 9%	300	Mean Age 55 Male 88%
(Kondo et al., 2007)	Asia	Not Provided	SF-36	Child-Pugh A/B 100%	194 total 97 HCC	Mean Age 68 Male 68%
(Lam et al., 2009)	Asia	Not Provided	SF-36	Child-Pugh A 68% B 8% C 3%	520 total 123 HCC	Mean Age 57 Male 85%

(L. Li et al., 2019)	Asia	Not Provided	EORTC	Child-Pugh A 68% B 27% C 5%	472	Age ≤ 65: 69% Male 89%
(Meier et al., 2015)	North America	Not Provided	EORTC	Not Specified	130	Mean Age 57 Male 78%
(Mikoshiba, Miyashita, Sakai, Tateishi, & Koike, 2013)	Asia	Not Provided	EORTC	Child-Push A 76% Remaining 24% not specified	127	Mean Age 69 Male 81%
(Palmieri et al., 2015)	Europe	Not Provided	SF-36	Child-Pugh A 87% B 13%	66 total 24 HCC	Median Age 71 Male 75%
(R. Phillips et al., 2015)	Asia	Provided	EORTC	Not Specified	167 HCC	Mean Age 56 Male 86%
(Qiao et al., 2012)	Asia	Not Provided	EORTC	Child-Pugh A 60% B 21% C 19%	140	Median Age 52 Male 95%
(Ryu et al., 2010)	Asia	Not Provided	FACT	Child-Pugh A 60% B 21% C 19%	180	Mean Age 55 Male 89%
(Shiraki et al., 2013)	Asia	Not Provided	SF-8	Child-Pugh A 55% B 23% C 22%	114 total 62 HCC	Not separated for HCC
(J. L. Steel, Eton, Cella, Olek, & Carr, 2006)	North America	Not Provided	FACT	Not Specified	158	Mean Age 64 Male 75%
(J. L. Steel, Chopra, Olek, & Carr, 2007)	North America	Not Provided	FACT	Child-Pugh A 51% B 26% C 1% Missing 22%	272 total 83 HCC	Mean Age 58 Male 77%
(J. Steel, Hess, Tunke, Chopra, & Carr, 2005)	North America	Not Provided	FACT	Child-Pugh A 73% B 18% C 0% Missing 9%	44 total 21 HCC	Mean Age 65 Male 100%
(J. L. Steel, Geller, & Carr, 2005)	North America	Provided	FACT	Not Specified	82 triads (patient, caregiver, oncologist)	Mean Age 59 Male 78%
(Sternby Eilard et al., 2018)	Europe	Not Provided	EORTC	Child-Pugh A 70% B 27% C 3%	185	Mean Age 67 Male 77%
(Sun et al., 2008)	North America	Not Provided	FACT FACIT-Spirituality	Not Specified	55 total 22 HCC	Age not provided

						Male 72%
(Ueno et al., 2002)	Asia	Not Provided	Non-validated measure	Child-Pugh A 94% B 6%	96	Age ≤ 65: 68% Male 81%
(Wong & Fielding, 2008)	Asia	Not Provided	FACT	Not Specified	578 total 253 HCC	Mean Age 57 Male 82%
(Yeo et al., 2006)	Asia	Not Provided	EORTC	Child-Pugh A 69% B 27% C 4%	233	Median Age 57 Male 91%
(Zheng, Wu, Xiao, & Guo, 2013)	Asia	Not Provided	FACT	Not Specified	62	Mean Age 49 Male 84%

Table 2. Included domains of quality of life

Reference	QOL Measure	Physical Domains	Psychological Domain	Social Domain	Spiritual Domain	Liver Specific Measure
Bianchi, G., Loguercio, C. et al (2003)	SF-36	Yes	Yes	Yes	No	None
Bonnetain, F., Paoletti, X. et al (2008)	EORTC	Yes	Yes	Yes	No	None
Chie, W.C., Blazeby, J.M. et al (2017)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18
Diouf, M., Bonnetain, F. et al (2015)	EORTC	Yes	Yes	Yes	No	None
Fan, S., Eiser, C. et al (2013)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18
Gill, J., Baiceanu, A. et al (2018)	Patient reported: ‘excellent’, ‘good’, or ‘poor’ to describe their QOL	Yes	Yes	No	No	None
Gmür, A., Kolly, P. et al (2018)	FACT	Yes	Yes	Yes	No	FACT-Hep
Hsu, W., Tsai, A. et al (2012)	EORTC	Yes	Yes	Yes	No	None
Jie, B., Qiu, Y. et al (2015)	EORTC	Yes	Yes	Yes	No	None
Kim, G., Kim, H. et al (2019)	EORTC FACT	Yes	Yes	Yes	No	EORTC HCC 18
Kondo, Y., Yoshida, H. et al (2007)	SF-36	Yes	Yes	Yes	No	None
Lam, E., Lam, C. et al (2009)	SF-36	Yes	Yes	Yes	No	Chronic Liver Disease Questionnaire
Li, L., Mo, F. et al (2019)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18
Meier, A., Yopp, A. et al (2015)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18
Mikoshiba, N., Miyashita, M. et al (2013)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18
Palmieri, V., Santovito, D. et al (2015)	SF-36	Yes	Yes	Yes	No	None
Phillips, R., Gandhi, M. et al (2015)	EORTC	Yes	Yes	Yes	No	None
Qiao, C., Zhai, X. et al (2012)	EORTC	Yes	Yes	Yes	No	FACT-Hep
Ryu, E., Kim, K. et al (2010)	FACT	Yes	Yes	Yes	No	FACT-Hep
Shiraki, M., Nishiguchi, S. et al (2013)	SF-8	Yes	Yes	Yes	No	None
Steel, J., Eton, D. et al (2006)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Chopra, K. et al (2007)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Hess, S. et al (2005)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Geller, D. & Carr, B. (2005)	FACT	Yes	Yes	Yes	No	FACT-Hep
Sternby Eilard, M., Hagström, H. et al (2017)	EORTC	Yes	Yes	Yes	No	EORTC HCC 18

Sun, V., Ferrell, B. et al (2008)	FACT FACIT-Spirituality	Yes	Yes	Yes	Yes	FACT-Hep
Ueno, S., Tanabe, G. et al (2002)	Non-validated measure	Yes	Yes	Yes	No	None
Wong, W. & Fielding, R. (2008)	FACT	Yes	Yes	Yes	No	None
Yeo, W., Mo, F. et al (2006)	EORTC	Yes	Yes	Yes	No	None
Zheng, W., Wu, J. et al (2013)	FACT	Yes	Yes	Yes	No	FACT-Hep

References for Chapter II (See Cumulative References)

Chapter III

Impact of Perceived Financial Insecurity on Physical and Mental Health and Symptoms in Cancer Survivors

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Abstract

Purpose: A diagnosis of cancer carries a significant economic burden. Studies have shown that out-of-pocket medical expenses are responsible for 17-50% of all bankruptcies in the United States, creating devastation for cancer survivors and their families. Yet there has been little study between perceived financial insecurity and physical and mental health and symptoms of cancer survivors in the United States.

Methods: Study sample included 57 cancer survivors 1 to 3 years post diagnosis. Study measures included: SF-36 v2 (physical and mental health), Functional Assessment in Chronic Illness Therapy (fatigue), pain severity, Center for Epidemiological Studies Depression scale, and the SCL-90 anxiety subscale. Perceived financial insecurity was assessed by asking survivors to select if they: Have more than enough to make ends meet; Have enough to make ends meet; Do not have enough to make ends meet. A hierarchical 2-step process was used for analysis.

Results: The mean age of survivors was 42 (SD 9.14) years with the majority being female (68%) and married (91%). When controlling for age, gender, years since cancer diagnosis, and number of children, perceived financial insecurity was found to be a significant predictor of physical health (β=-15.038, p=0.001, ΔR^2=.197), fatigue (β=-21.716, p<.001, ΔR^2=.314), pain severity (β=3.245, p<.001, ΔR^2=.321), mental health (β=-14.230, p=0.002, ΔR^2=.173), (depression (β=13.025, p=0.001, ΔR^2=.155) and of anxiety (β=5.983, p=0.004, ΔR^2=.134).

Conclusion: This study showed that perceived financial insecurity plays a key role in cancer survivor’s overall physical and mental health and symptoms 1-3 years post-diagnosis.

Introduction

It is estimated that there are over 15 million cancer survivors in the United States and the number of survivors is expected to increase to over 20 million by 2026 (American Caner Society, 2019). Cancer survivorship has been associated with an increase in fatigue (Berger et al., 2015; Wagner & Cella, 2004), pain (Bennett et al., 2012; Caraceni, Martini, Zecca, & Fagnoni, 2012), depression (Sotelo, Musselman, & Nemeroff, 2014; Watts et al., 2014), and anxiety (Maass, Roorda, Berendsen, Verhaak, & de Bock, 2015; Watts et al., 2014; Watts, Prescott, Mason, McLeod, & Lewith, 2015). Age has also been associated with physical and mental health needs of cancer survivors, with younger survivors having more unmet physical and mental health needs than older cancer survivors (de Rooij et al., 2018). Recent literature shows that these symptoms may persist long after cancer treatment is completed, putting even long-term cancer survivors at risk for unmet physical and mental health needs (Berger et al., 2015; de Rooij et al., 2018; Duijts et al., 2014; Mitchell, Ferguson, Gill, Paul, & Symonds, 2013). Furthermore, a diagnosis of cancer carries a significant economic burden. Studies have shown that out-of-pocket medical expenses are responsible for 17-50% of all bankruptcies in the United States with 3% of all cancer survivors filing for bankruptcy due to medical costs (Banegas et al., 2016; Ramsey et al., 2013), creating devastation for cancer survivors and their families (Dranove & Millenson, 2006; Himmelstein, Warren, Thorne, & Woolhandler, 2005). Despite this, there has been little study of the relationship between perceived financial insecurity and physical and mental health and symptoms, particularly among young adult and middle age cancer survivors.

The impact of other limitations such as lost income from work, transportation costs, and childcare costs further broaden the wide financial impact of cancer on survivors (Guy et al., 2013; Sharp et al., 2013; Whitney et al., 2016). The impact of a cancer diagnosis on survivors' ability to work may have lasting effects due to reduced employee-based health insurance options and decreased resources to pay for medical care (Banegas et al., 2016; Yabroff et al., 2016). Cancer survivors who file for bankruptcy are more likely to be more than two years beyond completion of treatment compared with cancer survivors who do not file for bankruptcy (Banegas et al., 2016). A cancer diagnosis and its treatment may also have a lasting negative effect on employment impacting future earnings, career development, and retirement (Banegas et al., 2016; Yabroff et al., 2016). There is strong evidence that cancer survivors who are female, member of a racial or ethnic minority, lower socioeconomic status, and/or under the age of 65 are at greater risk of financial hardship due to their cancer diagnosis (Banegas et al., 2016; Ell et al., 2008; Kale & Carroll, 2016; Ramsey et al., 2016; Whitney et al., 2016; Yabroff et al., 2016).

Physical and mental health symptoms play an important role in the quality of life and mortality of cancer survivors (Naughton & Weaver, 2014), thus a thorough understanding of the causes of and factors impacting these symptoms is required. In particular, research on the role of economic hardship or financial insecurity has been lacking. Yet, understanding the impact that financial insecurity has on health symptoms may lead to better ways to address the supportive needs of cancer survivors and their families. The purpose of this paper is to identify the impact of patient reported financial insecurity on physical and mental health and symptoms in cancer survivors controlling for demographic and social factors including age, gender, education, years since cancer diagnosis, and number of children. This paper will address two research questions: 1) What is the impact of patient reported financial insecurity on physical health and symptoms in cancer survivors, controlling for demographic and social factors, and 2) What is the impact of patient reported financial security on mental health and symptoms in cancer survivors, controlling for demographic and social factors?

Methods

Participants

This paper reports on a secondary analysis of a quantitative, cross-sectional study. The sample included 57 cancer survivors and their significant others. Of the cancer survivors, 68% were female and the mean age was 42.5 (SD=9.14) years. Potential subjects were identified using a statewide cancer registry. Subjects were eligible if they were between the ages of 21 to 55, had been diagnosed with cancer within 12 to 36 months of study entry, and were able to speak and understand English. Potential subjects were first contacted by registry staff with a letter describing the study and a reply form to return to the registry. Potential subjects who returned forms were then contacted by phone by study investigators to determine eligibility. Once subjects verbally consented to participate, surveys and consent forms were mailed to cancer survivors and their significant others with separate return mail envelopes. Couples were instructed to complete their interviews separately. As the purpose of this paper was to examine the impact of financial insecurity on the outcomes of the patient, only patient data were included in the analysis. The institutional review board at Oregon Health & Science University approved this study.

Measures

1. Physical Function

   The Short Form 36 (SF-36, v.2), 10-item physical function sub-scale was used to measure subject's physical function (Ware, 2005). Scores were converted to US norm-based scores (i.e., mean of 50 and standard deviation of 10)(Ware, 2005). For this scale, higher scores indicated better physical function. The physical function subscale of the SF-36 demonstrated strong internal consistency in this sample (Cronbach α=.89).

2. Fatigue

Patient fatigue was measured using the 13-item Functional Assessment in Chronic Illness Therapy measure (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Subjects responded from 0 (not at all) to 4 (very much) based on their fatigue over the previous week. Eleven items were reverse coded and all items were summed for a total score between 0 and 52 with higher scores indicating less fatigue. The fatigue scale demonstrated excellent internal consistency in this sample (α=.96).

3. Pain Severity

Subjects rated their pain severity using a 4-item sub-scale of the Brief Pain Inventory (Cleeland & Ryan, 1994). Subjects rated current pain level, average pain level over the past week, as well as highest and lowest pain level over the past week using a scale of 0 – no pain to 10 – worst pain. These four responses were averaged creating a summary score where higher scores indicated greater pain severity. The pain severity scale demonstrated strong internal consistency in this sample (α=.92).

4. Mental Health

The Short Form 36 (SF-36, v.2), mental health sub-scale was used to measure subject’s mental health (Ware, 2005). Scores were converted to US norm-based scores (i.e., mean of 50 and standard deviation of 10) (Ware, 2005). For this scale, higher scores indicated better mental health. The SF-36, v.2 demonstrated strong internal consistency in this sample (α=.83).

5. Anxiety (SCL-90 Anxiety subscale)

Anxiety was measured using the anxiety subscale of the symptom checklist. This 10-item, 5-point scale from 1 (not at all) to 5 (extremely) assessed subjects anxiety over the previous week (Derogatis, Lipman, & Covi, 1973). Items were totaled with higher scores indicating increased anxiety. The anxiety subscale demonstrated strong internal consistency in this sample (α=.89).

6. Depressive Symptoms

Depressive symptoms experienced within the previous week were measured using the 20-item Center for Epidemiological Studies-Depression (CESD) scale (Radloff, 1977). Response options range from 0 (rarely or none of the time) to 3 (most or all of the time). The measure involves the sum of the scores which ranges from 0 to 60. Scores with higher values indicating increased depressive symptomatology. The CESD demonstrated strong internal consistency in this sample (α=.91).

7. Perceived Financial Insecurity was assessed by asking survivors to select one of three responses to “Financially, would you say you: 1. Have more than enough to make ends meet; 2. Have enough to make ends meet; 3. Do not have enough to make ends meet”. Perceived financial insecurity had a Pearson’s correlation coefficient of r=0.55 with reported household income, signifying that income was not strongly correlated with perceived financial security. Using perceived financial insecurity as a categorical variable assumes that there is an equal amount of financial insecurity between having more than enough to having enough as there is between having enough and not having enough to make ends meet, which is not an appropriate assumption in this case. Due to this, a dichotomous variable was created for data

analysis combining those who stated they had enough or more than enough to compare with those who stated they did not have enough to make ends meet[1].

Analysis Plan

To test the research question, six hierarchical 2-step analyses were completed, one each for the physical and mental health summary scores and one for each of the four symptom variables (fatigue, pain, depression and anxiety). For step 1, a multiple linear regression was conducted using the covariates of age, gender, education, years since cancer diagnosis, and number of children. In step 2, the variable of interest, financial insecurity, was added to the linear regression to determine patient's perception of having enough versus not having enough impact on the outcome variables when controlling for demographics and patient characteristics. The change in R^2 between step 1 and step 2 is reported in order to describe the amount of outcome variance contributed by patient reported financial insecurity and an effect size using an adjusted Cohen's D was calculated for each model.

Results

Demographics

Cancer survivor's demographics and characteristics are presented in Table 1. The mean age of the cancer survivors was 42 (SD 9.14) years. The majority of cancer survivors were female (68%), married (91%), had completed a college degree (68%), and were Non-Hispanic White (88%). The cancer survivors had a mean of 1.4 (SD 1.23) children and had been diagnosed with cancer an average of 2.17 (SD 0.52) years previous to study. The majority of cancer survivors were employed (61%) and lived in an urban setting (59%). Cancer survivors

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[1] Model was also run using perceived financial insecurity as a categorical variable with three categories with similar results.

reported having more than enough financially (32%), having enough (54%), and not having enough financially (14%).

Physical Health and Symptoms (Fatigue and Pain)

The first step of the hierarchical regression for physical health and symptoms (fatigue and pain) using the covariates of age, gender, years since cancer diagnosis, and number of children explained 18% of the variance of physical functioning, 16% of the variance of fatigue, and 14% of the variance of pain severity. The addition of perceived financial insecurity explained an additional variance of 20% in physical functioning (β=-15.038, p=0.001, Cohen's D=0.335), 31% of fatigue (β=-21.716, p<.001, Cohen's D=0.598), and 32% of pain severity (β=3.245, p<.001, Cohen's D=0.600) (Table 2).

Mental Health and Symptoms (Depression and Anxiety)

The first step of the hierarchical regression for mental health and symptoms (depression and anxiety) using the covariates of age, gender, years since cancer diagnosis, and number children explained 18% of the variance of the mental health summary score, 27% of the variance of depression, and 23% of the variance of anxiety. The addition of perceived financial insecurity explained an additional variance of 17% of the mental health summary score (β=-14.230, p=0.002, Cohen's D=0.268), 16% of the variance of depression (β=13.025, p=0.001, Cohen's D=0.273), and 13% of the variance of anxiety (β=5.983, p=0.004, Cohen's D=0.211) (Table 3)

Discussion

We know that a diagnosis of cancer can have a significant financial impact on survivors (Azzani, Roslani, & Su, 2015). However, the impact that perceived financial insecurity can have on physical and mental health and symptoms was unclear. This secondary analysis showed that perceived financial insecurity plays a key role in survivors overall physical and mental health and symptoms even 1-3 years post-diagnosis. Survivor reported financial insecurity had the largest impact on overall fatigue and pain severity. Financial insecurity accounted for 32% of the variability in survivor pain severity and 31% of the variability in fatigue when controlling for demographic and socioeconomic factors. Pain is the most common symptom of cancer (van den Beuken-van Everdingen et al., 2007), and pain continues to be extremely difficult to treat, with treatment focusing predominantly on analgesics (Breivik et al., 2009). However, the results of this study may demonstrate that in addition to an assessment of pain etiology, effective treatment may need to include addressing the impact of socioeconomic factors on subjects' pain and pain management such as survivor's ability to fill pain medication prescriptions due to cost.

It is also important to consider, however, that pain, along with fatigue may impact financial security by limiting survivors in their ability to work and earn income. Working cancer survivors report having to make at least one work modification due to their cancer, including 15% who reported having to make long-term work modification due to their cancer (Whitney et al., 2016). The impact of a cancer diagnosis on survivors' ability to work may have lasting effects due to reduced employee-based health insurance options and decreased resources to pay for medical care (Banegas et al., 2016; Yabroff et al., 2016), leading to increased financial burden and increased financial insecurity for the cancer survivor. Further studies are needed to not only explore the role that financial insecurity has with pain and fatigue in cancer survivors, but also the impact that pain severity and fatigue has on financial insecurity.

Financial hardship has also been shown to be significantly higher for cancer survivors under the age of 65 compared to survivors over the age of 65 (Whitney et al., 2016; Yabroff et al., 2016). Cancer survivors ages 18 to 54 are also significantly more likely to go into debt than those ages 55 to 64 (Banegas et al., 2016). The average age of this sample was 42.54 years (SD

9.14) while the average age of a cancer diagnosis is 65 years (American Cancer Society, 2019). This sample captures a younger group of cancer survivors and demonstrates a relationship between financial insecurity and physical and mental health and symptoms. This relationship with financial insecurity may increase over time and extend long-term in part due to the younger age of this sample (Whitney et al., 2016; Yabroff et al., 2016). The maximum age for this sample was 55 years and age was not found to be a significant factor in our model, so it is unclear the precise relationship age has in our model and if the results of this study would be equally significant in an older sample.

Though this study did have positive results, there are limitations and needs for future research. Given that this was a small, pilot study, larger future studies should be completed to confirm these finding and investigate potential interventions. For our sample, 14% reported not having enough to make ends meet, additional studies with larger sample sizes should be competed to confirm results. This study also limited cancer survivors to those who had been diagnosed within 36 months, thus it is unknown the impact that these finding have on long term cancer survivorship. This study did not address the presence and/or absence of medical insurance as an aspect of financial insecurity. Especially in light of recent changes to the availability and cost of health insurance in the United States, this should be an important consideration in future research on financial insecurity among cancer survivors.

Prior research and interventions that overlooked this crucial stressor may have limited power to understand the full impact of physical and mental health symptoms in cancer survivors. As the number of cancer survivors continues to increase, a clearer understanding of the impact of financial insecurity on physical and mental health and symptoms is needed in order to address the long-term effects of cancer and to improve quality of life for cancer survivors. By better understanding the significant role that financial insecurity has on physical and mental health symptoms, tailored interventions can be designed to address the supportive needs of cancer survivors.

Table 1. Demographics and characteristics of cancer survivors

	Subjects(n=57)
Age (years)	42.54 ± 9.14
Gender (% female)	39 (68%)
Marital status (% married)	52 (91%)
Education (% completed college)	39 (68%)
Ethnicity (% Non-Hispanic)	50 (88%)
Financial Status	
Have more than enough	18 (32%)
Have enough	30 (53%)
Do not have enough	8 (14%)
Number of Children	1.4 ± 1.23
Years since cancer diagnosis	2.17 ± .52
Health	
SF-36 Physical Component Summary	48.92 ± 11.50
SF-36 Mental Component Summary	45.08 ± 11.40
Symptoms	
Depression	15.05 ± 10.73
Fatigue	36.47 ± 12.91
Anxiety	4.11 ± 5.20
Pain Severity	2.05 ± 1.83

SF-36: Short Form Health Survey (36 items)

Table 2: Hierarchical multiple regression of financial insecurity on survivor's physical health variables

Step and Variable	Step 1			Step 2				
SF-36 Physical Function	β	SE	R^2	β	SE	R^2	ΔR^2	Cohen's d
Age	-0.356	0.184	.179	-0.260	0.164	.385	.197	
Gender	0.122	3.372		2.935	3.066			
Education (completed College)	3.318	3.681		0.180	3.351			
Years since Cancer Diagnosis	4.939	2.951		3.271	2.637			
Number of Children	0.825	1.415		0.807	1.246			
Financial Insecurity				-15.038*	2.014			.335
Fatigue								
Age	-0.045	0.204	.161	0.076	0.165	.475	.314	
Gender	-3.429	3.788		0.397	3.118			
Education (completed College)	7.797	4.101		2.881	3.414			
Years since Cancer Diagnosis	6.292	3.266		3.990	2.649			
Number of Children	0.217	1.584		0.167	1.267			
Financial Insecurity				-21.716**	4.185			.598
Pain Severity								
Age	0.026	0.031	.144	0.008	0.025	.465	.321	
Gender	0.202	0.566		-0.369	0.465			
Education (completed College)	-1.142	0.612		-0.407	0.510			
Years since Cancer Diagnosis	-0.533	0.488		-0.189	0.395			
Number of Children	-0.090	0.237		-0.082	0.189			
Financial Insecurity				3.245**	0.625			.600

*$p<.01$

**$p<.001$

Table 3: Hierarchical multiple regression of mental health variables

Step and Variable	Step 1			Step 2				
SF-36 Mental Health Summary	β	SE	R^2	β	SE	R^2	ΔR^2	Cohen's d
Age	0.031	0.187	.182	0.122	0.170	.355	.173	
Gender	-1.291	3.417		1.371	3.170			
Education (completed College)	8.482*	3.730		5.512	3.465			
Years since Cancer Diagnosis	4.441	2.991		2.863	2.727			
Number of Children	1.363	1.434		1.346	1.288			
Financial Insecurity				-14.230 **	4.235			.268
Depression								
Age	0.005	0.162	.273	-0.061	0.146	.429	.155	
Gender	3.224	3.018		0.705	2.803			
Education (completed College)	-9.903*	3.338		-6.504*	3.150			
Years since Cancer Diagnosis	-6.273*	2.580		-4.849*	2.350			
Number of Children	-0.123	1.256		-0.158	1.126			
Financial Insecurity				13.025***	3.764			.273
Anxiety								
Age	-0.084	0.083	.231	-0.117	0.077	.365	.134	
Gender	2.827	1.531		1.773	1.448			
Education (completed College)	-4.527**	1.657		-3.172	1.585			
Years since Cancer Diagnosis	-1.933	1.320		-1.299	1.230			
Number of Children	-0.733	0.640		-0.719	0.588			
Financial Insecurity				5.983**	1.943			.211

*$p<.05$
** $p<.01$
***$p=0.0$

References for Chapter III (See Cumulative References)

Chapter IV

Meta-Analysis of Quality of Life in Chronic Cancer

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This manuscript represents a significant contribution to the Dissertation work. Ms. Firkins is the primary author on the paper and Dr. Dieckmann is the senior author on this paper. This manuscript is in preparation to be submit to the European Journal of Oncology Nursing (EJON). The EJON is a peer-reviewed journal which published research directly related to patient care, nurse education, management, and policy development. At the time of this Dissertation proposal, EJON has an impact factor of 1.812. It is anticipated that this manuscript will be submitted to EJON the week of September 16th, 2019.

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Abstract

A new concept of chronic cancer is emerging in cancer survivorship. With more cancer survivors living longer, they are now facing the long-term consequences of cancer and its treatment. As people are living longer with cancer, QOL becomes a vital consideration in understanding cancer survivorship and the long-term impact of cancer and its treatment. The primary aims of this review is to describe QOL in cancer survivors two or more years from diagnosis. A meta-analysis was completed of relevant studies assessing QOL in long-term cancer survivorship using PubMed, CINHAL, and PsychInfo. A total of 64 articles met inclusion criteria and were included for analysis. Standardized effect sizes and errors were calculated using previously published standard QOL pass rates in order to compare QOL across measurement tools and calculate cumulative effect sizes (CES). Fixed-effect or random-effects models were used based on the presence of significant heterogeneity of ≤0.10. Physical health (CES= -0.894, CI: -1.472, -0.316), role-physical health (CES= -2.039, CI: -2.643, -1.435), and mental health (CES= -0.870, CI: -1.447, -0.292) had large, negative cumulative effect sizes signifying worse QOL compared with acceptable QOL rates. Tested moderators, cancer type, average age, country of origin, time since diagnosis, or decade of diagnosis, were not significant to explain heterogeneity between included studies. More research is needed to determine possible moderators of QOL in long-term cancer survivors. This analysis found that QOL is significantly impacted two to 26 years after cancer diagnosis.

Introduction

An emerging concept in clinical cancer care is that cancer is considered not only an acute disease, but a chronic disease as well (Berlinger & Flamm, 2009; Thong et al., 2019; van Dipten, Hartman, Biermans, Assendelft, & Olde Hartman, 2016). The concept of *chronic* cancer is the result of the progress seen in oncology practices and outcomes over the past 10 years (Arndt et al., 2017; Damaskos & Gerbino, 2014). With new drugs and therapeutic approaches, patients diagnosed with cancer are not only living longer, but also facing the long-term consequences of cancer and its treatment (American Cancer Society, 2019; Arndt et al., 2017; Berlinger & Flamm, 2009; Damaskos & Gerbino, 2014; Harpham, 2009). In 1979, the five-year cancer survival was approximately 49%, however the current five-year survival is now approximately to 70% (Miller, Mehta, Abraham, Opneja, & Jain, 2017; Noone, 2018). Patients living with cancer as a chronic disease have described the integration of ongoing medical matters into their everyday lives (Harpham, 2009). Where there was once elusive hopes and dreams, there are now goals more within a patient's reach, such as: pain control, managing side effects, maintaining/obtaining remission, managing metastatic disease, and navigating new treatment options (Damaskos & Gerbino, 2014; Harley, Pini, Kenyon, Daffu-O'Reilly, & Velikova, 2019; Harpham, 2009). With more people with cancer living longer, quality of life (QOL) becomes a vital consideration in understanding cancer survivorship and the lasting and often long-term impact both from the cancer and its treatment.

Cancer's impact on the survivor's life does not end after the completion of primary treatment, but has the potential to affect every aspects of the survivor's life (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010; Siegel et al., 2018). The long-term effects of cancer and its treatment are well documented and can include osteoporosis, hypertension, heart failure, atherosclerosis, diabetes, hypothyroidism, cognitive dysfunction, chronic pain, endocrine dysfunction, sexual dysfunction, psychosocial changes, and/or secondary cancers (Arndt et al., 2017; Gonzalez et al., 2014; Schover et al., 2014; Stava et al., 2007; Tian et al., 2013). However, a comprehensive understanding of the long-term impact that the ongoing effects of cancer and its treatment have on patients' QOL is lacking (Harley et al., 2019). To improve the experience and QOL of patients with chronic cancer, a firm understanding of the long-term impact of cancer on survivors is essential (Harley et al., 2019). Meeting the needs of the increasing long-term cancer survivorship population requires a clear understanding of the impact of long-term cancer survivorship on these individual's QOL (Harley et al., 2012). Accordingly, this review examines what we now know about the QOL of cancer survivors two or more years after diagnosis. Our hypothesis was that QOL continues to be significantly impacted in long-term cancer survivors, even more than two years post diagnosis.

Methods

This review and analysis were completed adhering to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA) (Liberati et al., 2009). A literature search was conducted using CINHAL, PubMED, and PsycINFO (Appendix A). A research librarian was consulted to assist with identifying and refining search terms. Inclusion criteria included: available in English, report primary data, participants diagnosed with cancer as an adult, and include a population of cancer survivors greater than two years post diagnosis. Studies with patients on long-term maintenance chemotherapy or immunotherapy were included; however, study populations receiving other acute therapies, such as radiation, surgery, non-maintenance treatment medications were excluded, along with intervention studies.

Only articles that used standard, global QOL measurement tools and reported the means and standard deviations (SD) of the QOL domains were included in order to compare study results as part of the meta-analysis. In cancer research, there are three common, valid, reliable tools used to measure global QOL: the European Organization for Research and Treatment of Cancer (QLQ-C30), the Functional Assessment of Cancer Therapy (FACT), and the Short-Form 36 (SF-36) with historically the EORTC as the most frequently used tool (Heydarnejad et al., 2011; Luckett et al., 2011; Tax et al., 2017). Articles that only used a disease-and/or symptom-specific measurement tool (without a global QOL measurement tool) were excluded. Authors of studies that met inclusion criteria but did not report the means and SD of QOL subdomains were contacted and asked to provide the information. A reverse search of the references was also completed and common authors were identified and contacted regarding possible unpublished data that fit within the search parameters. The authors of abstract-only publications that potentially matched the search parameters were also contacted. Data, such as the number participants, country or origin, types of cancer, mean ages, sex/gender distribution, time since cancer diagnosis, QOL measurement tool, and QOL means and SDs, were extracted from the included articles to include in the analysis.

Statistical Analysis

Study effect sizes were calculated by standardizing the mean differences between the subdomains of QOL of included studies and previously published thresholds for acceptable QOL. The previously published thresholds for acceptable QOL values were based on the primary measurement tool reliability and validity testing by the measurement tool's primary authors (Scott, 2008; Ware et al., 1993). As opposed to a traditional meta-analysis, this analysis excluded intervention studies and only included observational studies. In order to calculate the effect size, the previously published thresholds for acceptable QOL value was subtracted from mean of each of the corresponding study QOL subdomains and the difference was divided by the SD of the mean of the corresponding study QOL subdomain. Based on this, a negative effect size corresponded to a lower, or worse QOL while a positive effect size corresponded to a high, or better QOL compared to previously published thresholds for acceptable QOL. Standard errors were calculated by divided the SD of the study QOL subdomain by the square root of the study sample size. The 95% confidence intervals (CI) for each individual study QOL study subdomains were determined by multiplying the standard error of the study QOL subdomain by 1.96 (for the 95% CI). This result was added to the standardized effect size of the upper 95% CI and subtracted from the standardized effect size for the lower 95% CI. By calculating standardized effect sizes in this manner, the results from multiple different QOL measurement tools could be analyzed using a comparable measure to determine the cumulative effect sizes of QOL in long-term cancer survivorship.

For this paper, a two-step analysis was planned. The first step tested for heterogeneity using a Chi-Square test. A *p* value of 0.10 for the Chi-Square test was used to determine significance as recommended in the Cochrane Handbook for Systematic Reviews (Higgins & Green, 2011). If there was no significant heterogeneity across studies, a fixed effect model was used, with the individual means being weighted by the inverse-variance method. In the second step, assuming there was heterogeneity in the effect sizes, a random-effects model was estimated with the DerSimonian-Laird method (Veroniki et al., 2016). Other models such as Sidik-Jonkman, Hedges, Hunter & Schmidt, and maximum likelihood were considered; however due to difficulty with convergence and the large variability between study sample size the DerSimonian-Laird was preferred (Veroniki et al., 2016). Due to issues with convergence, the overall effect sizes of each QOL subdomain were compared between fixed and random effects and found to be similar. Potential moderators of the random-effects model included: type of cancer, mean age of population, country of origin, time since diagnosis, decade of diagnosis, and QOL tool used. If three or more qualifying studies reported changes in QOL over time, a repeat of the above analysis would be completed based on the change of QOL as the effect measure; however only two of the included studies reported QOL results over time. When reporting cumulative effect sizes, the following guidelines were used: small ≥ 0.20, medium ≥ 0.50, large ≥ 0.80 (Cohen, 1992).

Each of the commonly used global QOL measurement tools (QLQ-C30, SF-36 and, FACT-G) include subdomains of physical health, emotional health, and social health. For this review, studies that included multiple global QOL measures tools, only the results for the SF-36 were used in the subdomains of physical, emotional, and social health for analysis (Table 2). For included studies that reported longitudinal data on the same independent sample, the latest timepoint was used for analysis due to the focus on this review being on the long-term QOL of survivors. For studies that stratified results based on survival time, but included an independent study sample at each timepoint, all timepoint groups were included for analysis. For studies that stratified results other than by time and included an independent sample in each group (i.e. cancer type, treatment type, or type of provider), the groups of means within each study QOL subdomain were combined by weighting the mean by sample size and used to calculated the standardize effect sizes and standard error. In order to calculate the weighted means, each stratified group mean within an individual study QOL subdomain was multiplied by the sample size of the stratified group, these values were added together for each of the QOL subdomains within each individual study and divided by the total sample size of all the stratified groups for the QOL subdomain within the study (Figure 1). The weighted means were then used to calculate standardized effect sizes and standard errors to use in the analysis using the method described above.

Results

A total of 63 articles were included for analysis (Table 1). As previously mentioned, additional authors were contacted for unpublished and unreported means and SD that fit within the search parameters. One author responded and the subsequent data was included for analysis.

Number of Participants and Geographical Location

The number of study participants ranged from 11 to 7369 (mean, 444; median, 220) in included studies. A total of 28,423 participants were included in the analysis. Of the included articles, 39 (62%) included a sample population from Europe, 14 (22%) from North American, 7 (11%) from Asia, 2 from Australia (3%), and 1 (<1%) from South America (Figure 3).

Types of Cancer (Figure 4)

The most common cancer type included in the review was breast cancer. Of the included studies, 20 (31%) were exclusively female breast cancer participants. Colorectal cancer made up 14% of included studies and oropharynx cancer 8%. Prostate cancer and lung cancer participants were exclusively reported in four (6%) studies each. Three studies (5%) had nasopharyngeal/esophageal cancer population, two studies (3%) each reported gastric and ovarian cancer. Single studies (1.5%) reported participants exclusively with liver cancer, head and neck, melanoma, thyroid, laryngeal, and head and neck squamous cell carcinoma. Eight (12%) studies included a mix of various cancer types, however, the study with the largest sample size (n=7,369) did not provide a description of the cancer types included in the study.

Age and Gender Distribution

The average age range of study participants was 45 to 80 years (mean, 61 years; median, 60.5 years). Twenty-six (41%) of the included studies sample population was exclusively female or male, due to the focus of either breast, ovarian or prostate cancer. Though breast cancer can occur rarely in males, there were no males included in the breast cancer study populations of the included studies. The remaining studies ranged from 8% to 79% female and 21% and 92% male study populations. The average female population was 61% (median 51%) and the average male population was 66% (median 63%) based on the remaining studies.

Follow-up Time

Time since cancer diagnosis ranged from 2 to 26 years (mean, 6 years; median, 5 years).

QOL Measurement Tool

Twenty-nine (45%) included studies measured QOL with the QLQ-C30, 27 (42%) studies used the SF-36, 4 (6%) studies used the FACT, and 4 (6%) studies used both the QLQ-C30 and the SF-36.

Cumulative QOL Effect Sizes

Global QOL

The global QOL assessed study participants perception of their overall QOL, this element in included in the QLQ-C30, SF-36, and FACT. Significant heterogeneity ($p<0.00001$, $I^2=92\%$) and a moderate, negative effect size was found for the cumulative global QOL subdomain (cumulative effect size [CES]= -0.650, CI: -1.198, -0.103) (Figure 5). No significant difference was seen in global QOL between cancer type (p=0.476), average age (p=0.60), country of origin (p=0.99), time since diagnosis (p=0.30), or decade of diagnosis (p=0.14).

Physical domain

The physical subdomain of QOL is a subdomain included in the QLQ-C30, SF-36, and FACT. It assesses cancer survivor's ability to move, such as walking and climbing stairs, along with performing basic activities of daily living such as ability to bathe and dress themselves. Significant heterogeneity ($p<0.00001$, $I^2=93\%$) and a large, negative effect size was found in the cumulative physical health subdomain (CES= -0.894, CI: -1.472, -0.316) (Figure 6). No significant difference was seen in cumulative physical health based on cancer type ($p=0.401$), average age ($p=0.375$), country of origin ($p=0.861$), time since diagnosis ($p=0.345$), or decade of diagnosis ($p=0.326$).

The role-physical subdomain is specific to the SF-36, which was included in 31 of the included studies. The role-physical subdomain expands on the physical subdomain (which is also included in the SF-36, to assess cancer survivor's ability to perform activities of daily living beyond walking, bathing, and dressing themselves and includes items regarding work and other activities. Significant heterogeneity ($p<0.00001$, $I^2=61\%$) and a very large, negative effect size was found in the cumulative role-physical health subdomain (CES= -2.039, CI: -2.643, -1.435) (Figure 7). No significant difference was seen in the cumulative role-physical health based on cancer type ($p=0.077$), average age ($p=0.504$), country of origin ($p=0.106$), time since diagnosis (0.088), or decade of diagnosis ($p=0.475$).

Psychological domain

The cognitive health subdomain is specific to the QLQ-C30, which was included in 33 of the included studies. The cognitive health subdomain assesses survivor's ability to concentrate and assesses for memory difficulties. A small, negative effect size was found in the cumulative cognitive health subdomain with no significant heterogeneity (CES= -0.048, CI: -0.533, 0.437, p=0.845) (Figure 8).

The emotional health subscale is included in the QLQ-C30, SF-36, and FACT however, six of the included studies did not report the results of this subdomain. The emotional health subscale assesses for emotional problems such as depression and/or anxiety. Significant heterogeneity ($p<0.00001$, $I^2=93\%$) and a medium, negative effect size was found in the cumulative emotional health subdomain (CES= -0.685, CI: -1.271, -0.099) (Figure 9). No significant difference was seen in the cumulative emotional health based on cancer type (p=0.099), average age (p=0.830), country of origin (0.798), time since diagnosis (p=0.115), or decade of diagnosis (p=0.190)

The mental health subdomain is specific to the SF-36, which was included in 31 of the included studies. The mental health subdomain expounds on that of the emotional subdomain by further assessing survivors for depression and/or anxiety. Significant heterogeneity ($p<0.00001$, $I^2=86\%$) and a large, negative effect size was found in the cumulative mental health subdomain (CES= -0.870, CI: -1.447, -0.292) (Figure 10). No significant difference was seen in the cumulative mental health based on cancer type (p=0.142), average age (p=0.895), country of origin (p=0.336), time since diagnosis (p=0.133), or decade of diagnosis (p=0.707).

The vitality subdomain is specific to the SF-36, which was included in 31 of the included studies. Vitality is a unique subdomain which assesses survivor’s energy levels. Significant heterogeneity ($p=0.0059$, $I^2=43\%$) and a moderate, negative effect size was found in the cumulative vitality subdomain (CES=-0.590, CI: -0.900, -0.281) (Figure 11). No significant difference was seen in the cumulative vitality subdomain based on cancer type (p=0.420), average age (p=0.300), country of origin (p=-.866), or decade of diagnosis (p=0.326).

Social domain

The social health subscale is included in the QLQ-C30, SF-36, and FACT; however, three of the included studies did not report the results of this subdomain. The social health subdomain assesses if survivors are able to participate in their typical social interactions with family and friends. Significant heterogeneity ($p<0.00001$, $I^2=91\%$) and a medium, negative effect size was found in the cumulative social health subdomain (CES= -0.677, CI: -1.272, -0.083) (Figure 12). No significant difference was seen in the cumulative social health subdomain based on cancer type (p=0.309), average age (p=0.594), country of origin (p=0.930), times since diagnosis (0.284), or decade of diagnosis (p=0.381).

Discussion

The results of this analysis demonstrate that QOL continues to be significantly impacted in long-term cancer survivorship. Of the eight QOL subdomains assessed in this review, seven (88%) resulted in medium to large negative CES, signifying worse QOL compared with previously published thresholds for acceptable QOL. The remaining subdomain, cognitive health, resulted in a small, negative CES. Physical, role-physical, and mental health had large, negative effect sizes and global, emotional, vitality, and social health resulted in medium, negative CES. The largest impact in QOL was seen in the role-physical health, with a very large CES of -2.039. Role-physical health is a subdomain of the SF-36 which specifically addresses survivors ability to work and perform normal activities of daily living outside of eating, bathing, or dressing (Ware et al., 1993). For the cancer survivors, this demonstrates a significantly lower physical and mental health compared to acceptable QOL thresholds. The large, negative CES for general physical health signify that the cancer survivors included in this analysis are less able to perform activities of daily living such as bathing, dressing, walking, and climbing stairs than has been previously published as acceptable. The subdomain of role-physical health expands on physical health to demonstrate that cancer survivor's ability to work continues to be significantly negatively impacted at an average of 6 years after diagnosis. The second largest CES was that of the overall physical health subdomain. These results suggest that long-term cancer survivorship has the greatest impact on the physical domain of QOL compared with the other domains of QOL. Meaning that long-term cancer survivors continue to have their physical function negatively impacted even over two years and perhaps up to over twenty years after diagnosis. However, time since diagnosis was not found to be a significant moderator of either of the physical health subdomains so it is unclear if there is variation in physical function in cancer survivorship based on length of survivorship or if the decreased physical health is a constant result of cancer and its treatment. However, 36% of the included studies had a wide range of time since diagnosis (3 to 24 years) without stratification of results based on time since diagnosis. This means that time since diagnosis may in fact be a significant moderator of heterogeneity, but that our analysis did not pick it up due to the lack of precision of time since diagnosis in the results of the included studies.

As possible moderators of the CES, the variables of cancer type, average age of study participants, country of origin, time since diagnosis, and decade of diagnosis were examined. However, none of these variables were found to be moderators for any of the QOL subdomains. This indicates the need for further investigation into the moderators that may be impacting the negative CES of QOL in these results. Two potential moderators to our results is treatment the cancer survivor completed and the presence of comorbidities. Cancer treatment can include surgery, radiation, chemotherapy, immunotherapy, and/or targeted therapy. Four (6%) of the studies included in this analysis stratified QOL results based on prior treatment. Pourel et al

(2002) examined prior treatment in oropharynx cancer survivors and found that global QOL and emotional health were impacted by treatment type in long-term cancer survivorship. Survivors who had upfront surgery and radiotherapy had higher emotional health than those treated with radiotherapy with and without brachytherapy. Global health was worse for survivors who were treated with radiotherapy with brachytherapy compared to the other treatment modalities. Korfage et al (2005) compared long-term QOL in prostate cancer survivors who were treated with surgery or radiotherapy and found that males who had radiotherapy had significantly lower QOL than those treated with surgery only. Thong et al (2011) compared QOL in long-term rectal cancer survivors who were treated with surgery alone and radiotherapy prior to surgery and found no significant differences in QOL based on treatment. Mandelblatt et al (2003) compared QOL in long-term breast cancer survivors who were treated with breast-conserving surgery and radiation, total mastectomy, or breast-conserving surgery only, and found that those will breast-conserving surgery only reported lower mental health compared with the other treatment modalities. These results suggest that treatment modalities may have a significant impact on long-term QOL in cancer survivorship and should be further studied. The impact of treatment modalities on long-term QOL is important to consider as cancer survivors are living longer and more treatment options are available, understanding the long-term impact of cancer treatments will assist patients and health care providers in make treatment related decisions that will treat their cancer but also perhaps maintain their QOL.

Comorbidities may also be a significant moderator of CES in QOL in long-term cancer survivorship. A study of colorectal cancer survivors found that the presence of limiting comorbidities were significant predictors of worse QOL compared with no or non-limiting comorbidities (Cummings et al., 2018). In breast cancer survivors, comorbidities have been correlated with a decrease in QOL that increased over time even when the number of comorbidities remained constant (Schoormans, Czene, Hall, & Brandberg, 2015). In older adults, comorbidities were associated with worse QOL after surgery for cancer compared with older adults without comorbidities (Sun, Burhenn, Lai, & Hurria, 2017). Outside of cancer survivorship, comorbidity such as heart disease, depression, and osteoarthritis have been shown to correlate with a decrease in QOL independently (Beaudart et al., 2018; Hofmann, Curtiss, Carpenter, & Kind, 2017; Jing et al., 2018; Muhammad, He, Kowitlawakul, & Wang, 2016). It is unclear if the impact of comorbidities on QOL in cancer survivorship is due to the impact of comorbidities on QOL alone or if there is an exponential relationship between comorbidities and cancer survivorship resulting in a significantly worse QOL for cancer survivors with comorbidities compare with adults with comorbidities alone. More research is needed in this area in order to clearly understand the potential impact of comorbidities on long-term cancer survivorship.

Though many cancers have limited survival, many cancer such as lymphoma, melanoma, breast, prostate, thyroid, and endometrial have over 80% 5-year survival rates (American Cancer Society, 2019). In this analysis, over 40% of the included study participants were female breast cancer survivors, over 10% were colorectal cancer survivors, and over 5% were prostate cancer survivors. Yet, it is estimated in 2019, that only 20% of cancer survivors have a history of breast cancer, 3% a history of colorectal cancer, and 12% a history of prostate cancer (American Cancer Society, 2019). This demonstrates that the makeup of cancer types in this analysis are not consistent with the makeup of cancer type in long-term cancer survivorship. More research is needed to explore the possible relationship between cancer type and QOL in long-term cancer survivorship.

There are several limitations of this meta-analysis. The primary limitation is lack of access to unpublished data that may have fit without the inclusion criteria. Though potential authors with unpublished data were connected regarding access to data that met inclusion criteria, we did not receive any responses. Another potential limitation is that 26% of the total number of participants included in this analysis came from a single study (Baker, Denniston, Haffer, & Liberatos, 2009). Baker et al (2009) not only had a large sample size, but it was a much older sample with an average age of 80 years. Of the studies included in this review, 35% included a sample with an average age of over 65 years, meaning that these results may not be generalizable to younger, and middle age cancer survivors. Also, due to the increased average age of the study samples, it is unknown if the large, significant decrease in physical and mental health is due to the normal aging process. An additional limitation of this meta-analysis is that there were no comparison groups in the included articles due to excluding intervention studies. Finally, this study was not able to explain the heterogeneity between studies. More research is needed to explore possible moderators of QOL in long-term cancer survivorship.

Conclusion

With the continued increase in early detection and cancer treatment options, the number of long-term cancer survivors will continue to increase worldwide. As the number of cancer survivors continues to grow, QOL will continue to be a key concern in understanding the long-term impact of cancer and its treatment on survivors. This meta-analysis was completed to examine the QOL in long-term cancer survivorship, with a focus in survivors more than two years from diagnosis. This analysis found that QOL is significantly impacted two to 26 years after cancer diagnosis. The largest impact to QOL was found in physical and mental health. However, the potential moderators tested, cancer type, average age, country of origin, time since diagnosis, and decade of diagnosis, did not explain a significant amount of the heterogeneity between studies. More research is needed in order to explore the impact and potential moderators of long-term cancer survivorship on QOL.

Figure 1. Formula for weighted means by sample size

$$\overline{\mathrm{X}}_{\mathrm{W}}=\frac{\sum_{i=1}^{n}(xi*wi)}{\sum_{i=1}^{n} wi}$$

x_i=stratified mean; w_i=sample size

Figure 2. Flow diagram of literature review

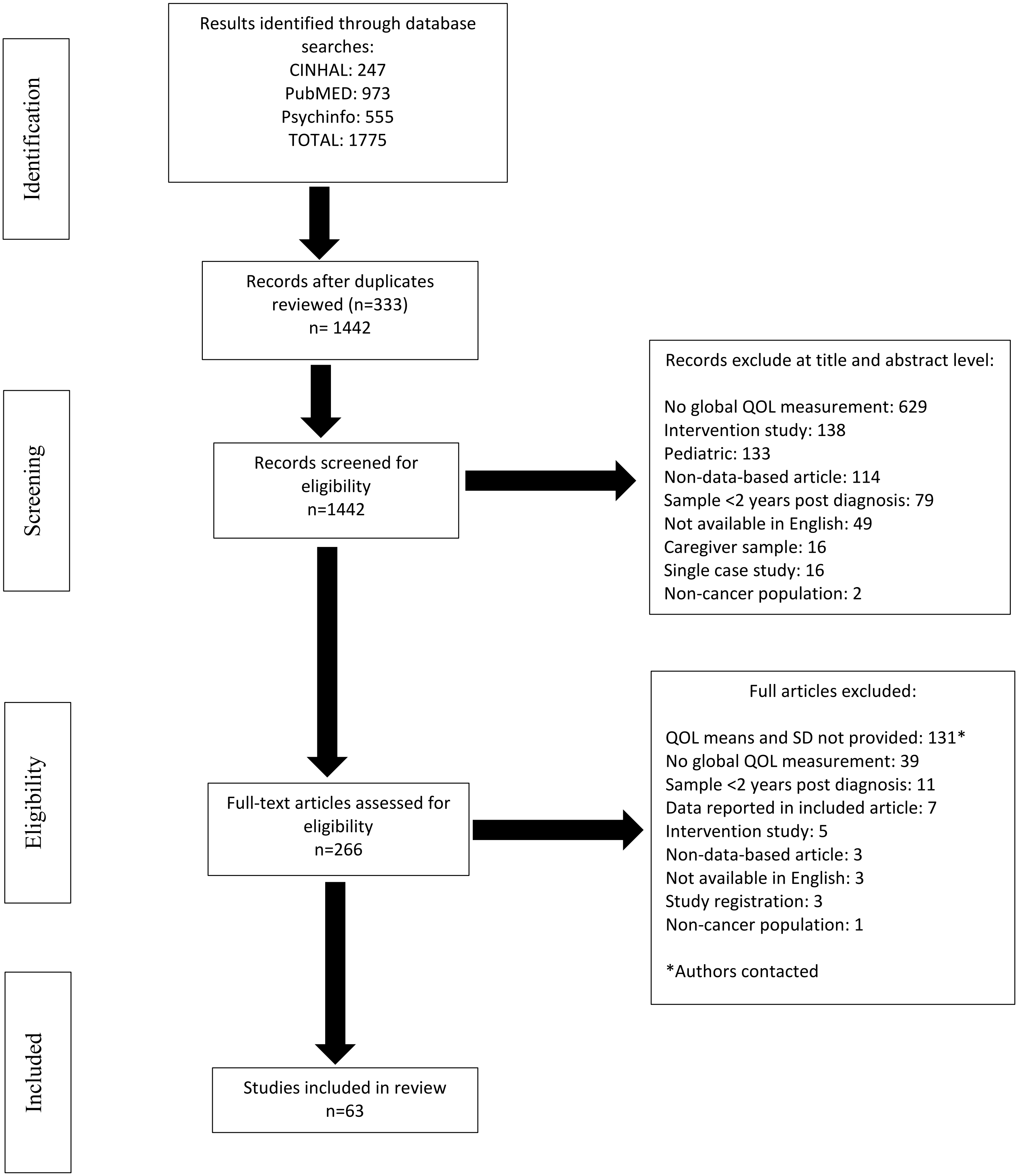


Table 1. Characteristics of included studies

Citation	Country of Origin	Cancer Population	Sample Size (included in this review)	Average Age	Female	Male	Follow-up Time (in years)	QOL Tool
(E. Adams et al., 2014)	United Kingdom	Rectal: 30% Endometrial: 28% Prostate: 24% Cervical: 10% Bladder: 8% Vaginal: 1%	413	71	53%	47%	2-11	QLQ-C30
(Alfano et al., 2007)	United States	Breast: 100%	545	58	100%		2	SF-36
(Andersen, Bowen, Morea, Stein, & Baker, 2009)	United States	Breast: 100%	636	55	100%		2-10	SF-36
(Baena-Canada et al., 2013)	Spain	Breast: 100%	98	63	100%		5	SF-36
(Baker et al., 2009)	United States	Not Provided	7369	77	45%	55%	>2	SF-36
(Beatty, Lee, & Wade, 2009)	Australia	Breast: 100%	210	52	100%		4	SF-36
(Beutel et al., 2015)	Germany	Melanoma: 100%	689	60	51%	49%	6-12	QLQ-C30
(Bloom, Stewart, Chang, & Banks, 2004)	United States	Breast: 100%	185	45	100%		5	SF-36
(Bruheim et al., 2010)	Norway	Rectal: 100%	535	69	40%	60%	2-12	QLQ-C30
(Chambers et al., 2012)	Australia	Colorectal: 100%	763	65	46%	54%	5	FACT-G
(Chu et al., 2016)	France	Breast: 100%	188	58	100%		5	QLQ-C30 SF-12
(Davis et al., 2014)	United States	Prostate: 100%	518	75		100%	7	FACT-G
(De Aguiar, Bergmann, & Mattos, 2014)	Brazil	Breast: 100%	549	59	100%		4	QLQ-C30
(Gotze, Taubenheim, Dietz, Lordick, & Mehnert, 2018)	Germany	Prostate: 25% Breast: 22% Gynecological: 10% Other: 42%	1002	67	47%	53%	5 and 10	QLQ-C30

(Greimel, Daghofer, & Petru, 2011)	Austria	Ovarian: 100%	11	56	100%		10	QLQ-C30
(Hammerer & Wirth, 2018)	Germany	Prostate: 100%	536	80		100%	4-20	QLQ-C30
(Hartl et al., 2010)	Germany	Breast: 100%	186	60	100%		2	QLQ-C30
(Hedman, Djarv, Strang, & Lundgren, 2016)	Sweden	Thyroid: 100%	279	51	78%	22%	14-17	SF-36
(Herce-Lopez, Rollon-Mayordomo, Lozano-Rosado, Infante-Cossio, & Salazar-Fernandez, 2013)	Spain	Oral: 100%	60	65	18%	82%	5	SF-36
(Hoerske, Weber, Goehl, Hohenberger, & Merkel, 2010)	Germany	Rectal: 100%	97	61	38%	62%	2-14	QLQ-C30
(Holzner et al., 2001)	Austria	Breast: 100%	57	54	100%		2-8	QLQ-C30
(Huguenin et al., 1999)	Switzerland	Head and Neck: 100%	87	61	28%	72%	5	QLQ-C30
(Jansen, Hoffmeister, Chang-Claude, Brenner, & Arndt, 2011)	Germany	Colorectal: 100%	483	67	38%	62%	5	QLQ-C30
(Joly, Espie, Marty, Heron, & Henry-Amar, 2000)	France	Breast: 100%	122	54	100%		6-16	QLQ-C30
(Kendall, Mahue-Giangreco, Carpenter, Ganz, & Bernstein, 2005)	United States	Breast: 100%	371	50	100%		10-16	SF-36
(Klein et al., 2011)	France	Breast: 100%	317	65	100%		5	QLQ-C30 SF-36
(Klug et al., 2002)	Austria	Oropharynx: 100%	67	56	27%	73%	2-10	QLQ-C30
(Kool et al., 2015)	Netherlands	Breast: 100%	339	60	100%		6-8.5	QLQ-C30
(Korfage et al., 2005)	Netherlands	Prostate: 100%	314	65		100%	5	SF-36

(Krouse et al., 2009)	United States	Rectal: 100%	246	72	40%	60%	5+	SF-36
(S. S. Lee, Chung, Kwon, & Yu, 2014)	Korea	Gastric: 100%	143	60	27%	73%	5	QLQ-C30
(Lehmann, Oerlemans, van de Poll-Franse, Vingerhoets, & Mols, 2011)	Netherlands	Prostate: 505 Lymphoma: 30% Endometrial: 20%	1299	58	35%	65%	6-15	SF-36
(Lei, Yan, Wang, Zhu, & Li, 2016)	China	Liver: 100%	205	45	14%	86%	>2	SF-36
(Macdonald, Bruce, Scott, Smith, & Chambers, 2005)	United Kingdom	Breast: 100%	54	56	100%		7-12	SF-36
(Mandelblatt et al., 2003)	United states	Breast: 100%	1812	73	100%		4	SF-36
(McLarty et al., 1997)	United States	Esophageal: 100%	64	62	24%	76%	5-23	SF-36
(Mehnert & Koch, 2008)	Germany	Breast: 100%	1083	62	100%		2-5	SF-36
(Metreau, Louvel, Godey, Le Clech, & Jegoux, 2014)	France	Pharyngolaryngeal: 100%	47	58	11%	89%	2-8	QLQ-C30
(Mirabeau-Beale et al., 2009)	United States	Ovarian: 100%	121	57	100%		5	QLQ-C30
(Moller & Sartipy, 2012)	Sweden	Lung: 100%	166	65	48%	52%	2	SF-36
(Mols, Coebergh, & van de Poll-Franse, 2007)	Netherlands	Lymphoma: 20% Endometrial: 25% Prostate: 55%	1112	70	55%	45%	7	SF-36
(Mosher et al., 2009)	United States	Breast: 43% Prostate: 42% Colorectal: 15%	753	73	52%	53%	5-26	SF-36
(Muzzatti, Flaiban, Surbone, & Annunziata, 2015)	Italy	Breast: 60% Lymphoma: 23% Other: 17%	265	60	79%	21%	10	QLQ-C30 SF-36
(Ozturk, Sarihan, Ercan, & Karadag, 2009)	Turkey	Lung: 100%	28	55	8%	92%	4	QLQ-C30
(Paskett et al., 2008)	United States	Breast: 100%	245	63	100%		12.5	SF-36

(Phipps, Braitman, Stites, & Leighton, 2008)	United states	Colorectal: 100%	30	69	50%	50%	5	SF-36
(Pierre et al., 2014)	France	Oropharynx: 100%	64	58	27%	73%	2-10	QLQ-C30
(Pourel et al., 2002)	France	Oropharynx: 100%	113	62	14%	86%	5	QLQ-C30
(Rauch, Miny, Conroy, Neyton, & Guillemin, 2004)	France	Rectal: 100%	121	64	35%	65%	5	QLQ-C30
(Rauma, Sintonen, Rasanen, Salo, & Ilonen, 2015)	Finland	Lung: 100%	230	63	47%	53%	2-11	QLQ-C30
(Roeloffzen et al., 2010)	Netherlands	Prostate: 100%	127	65		100%	6	QLQ-C30 SF-36
(Rogers, Hannah, Lowe, & Magennis, 1999)	United Kingdom	Oropharynx: 100%	37	58	34%	66%	5-10	QLQ-C30
(Sackey et al., 2015)	Sweden	Breast: 100%	420	59	100%		3	SF-36
(Sarna et al., 2004)	United States	Lung: 100%	142	71	54%	46%	10	SF-36
(Scharloo et al., 2010)	Netherlands	Head and Neck Squamous Cell: 100%	94	60	24%	76%	2	QLQ-C30
(Sehlen et al., 2012)	Germany	Gastrointestinal: 18% Breast: 16% Head/Neck: 14% Lymphoma: 12% Urogenital: 12% Lung: 10% Other: 16%	930	58	43%	57%	5	FACT-G
(Taira et al., 2011)	Japan	Breast: 100%	170	53	100%		2	FACT-G
(M. S. Thong, Mols, Coebergh, Roukema, & van de Poll-Franse, 2009)	Netherlands	Prostate: 63% Lymphoma: 29% Endometrial: 8%	232	69	Not Provided		>5	SF-36
(M. S. Thong et al., 2011)	Netherlands	Rectal: 100%	340	68	63%	37%	2-10	SF-36
(Tsai et al., 2014)	Taiwan	Nasopharyngeal: 100%	242	46	31%	69%	>5	QLQ-C30

(Valls-Mateus et al., 2016)	Spain	Laryngeal: 100%	62	69	13%	87%	5	SF-12
(van Roekel et al., 2017)	Netherlands	Colorectal: 100%	104	64	40%	60%	2-10	QLQ-C30
(Yu, Park, Chung, Kwon, & Lee, 2016)	Korea	Gastric: 100%	254	55	37%	63%	5	QLQ-C30
(Zhang et al., 2009)	China	Breast: 100%	42	50	100%		3 and 5	QLQ-C30

[1] Original manuscript did not include mean and SD of QOL domains, corresponding author provided means and SD to include in analysis.

Table 2. Breakdown of Number of Questions Per QOL Domain

	Global Health	Physical Health	Role-Physical Health	Cognitive Health	Emotional Health	Mental Health	Vitality	Social Health
QLQ-C30	2 items	5 items		2 items	4 items			2 items
SF-36	5 items	10 items	4 items		3 items	5 items	4 items	2 items
FACT	7 items	7 items			5 items			7 items

Figure 3. Study geographical locations

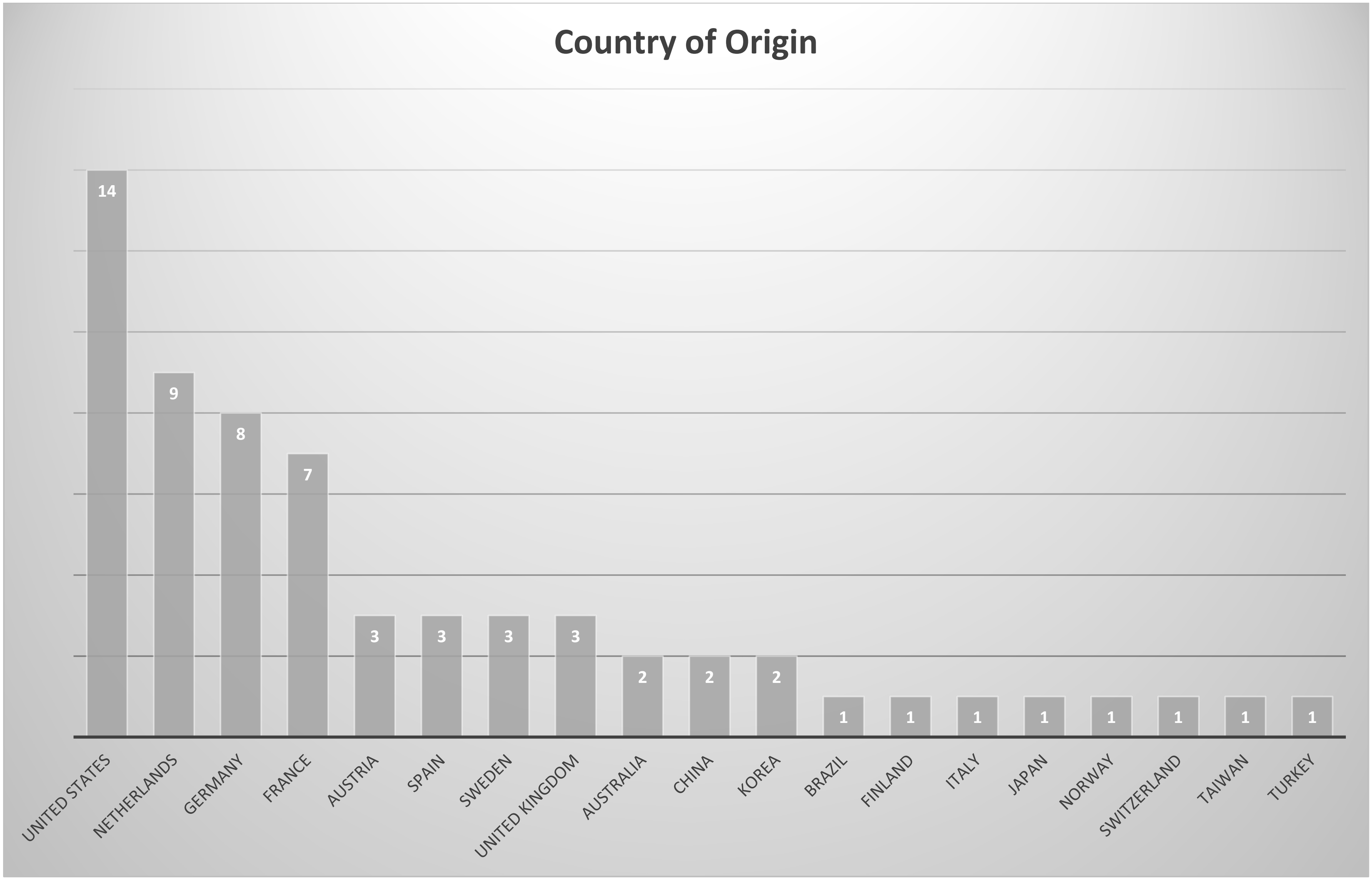


Figure 4. Number of studies by cancer type

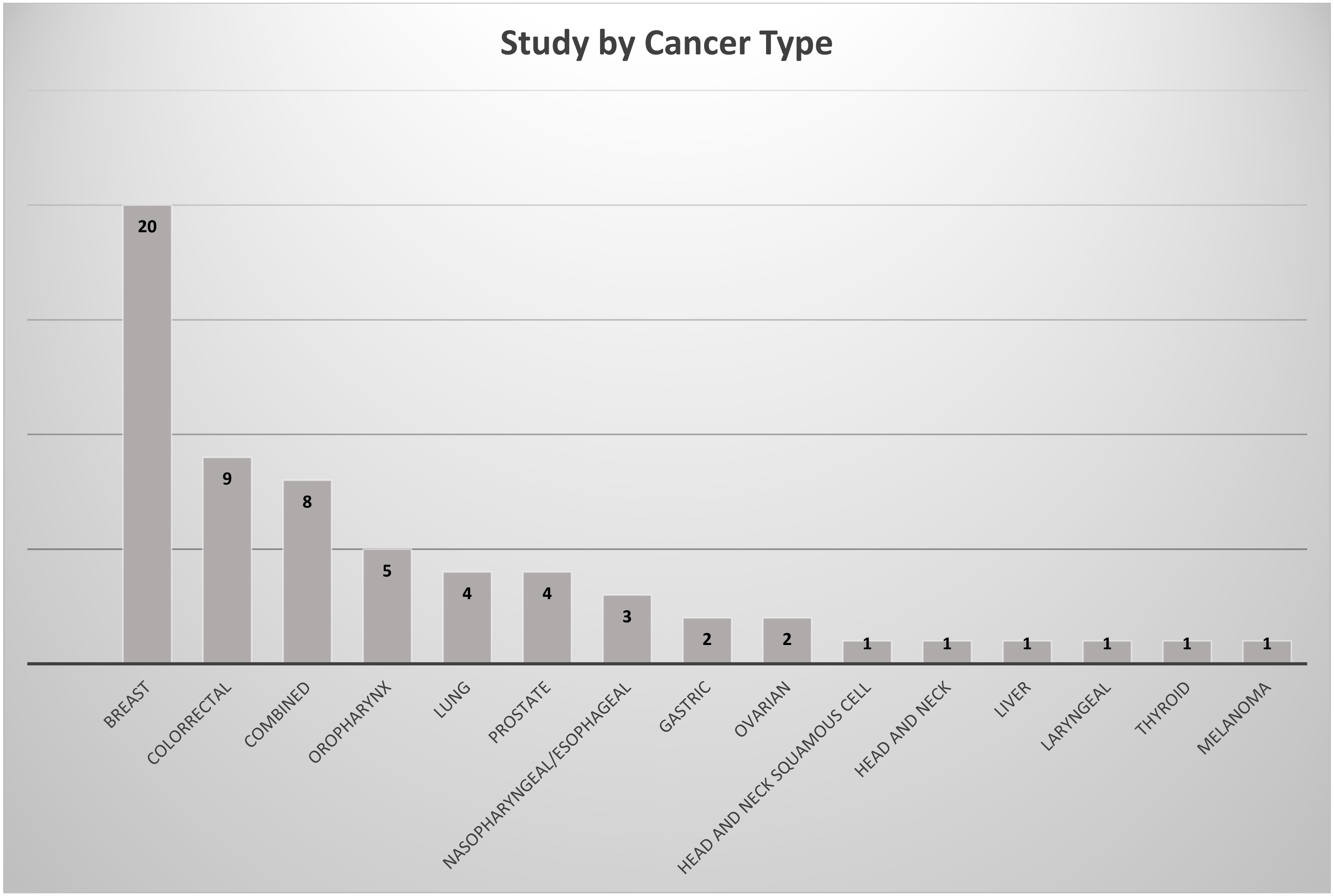
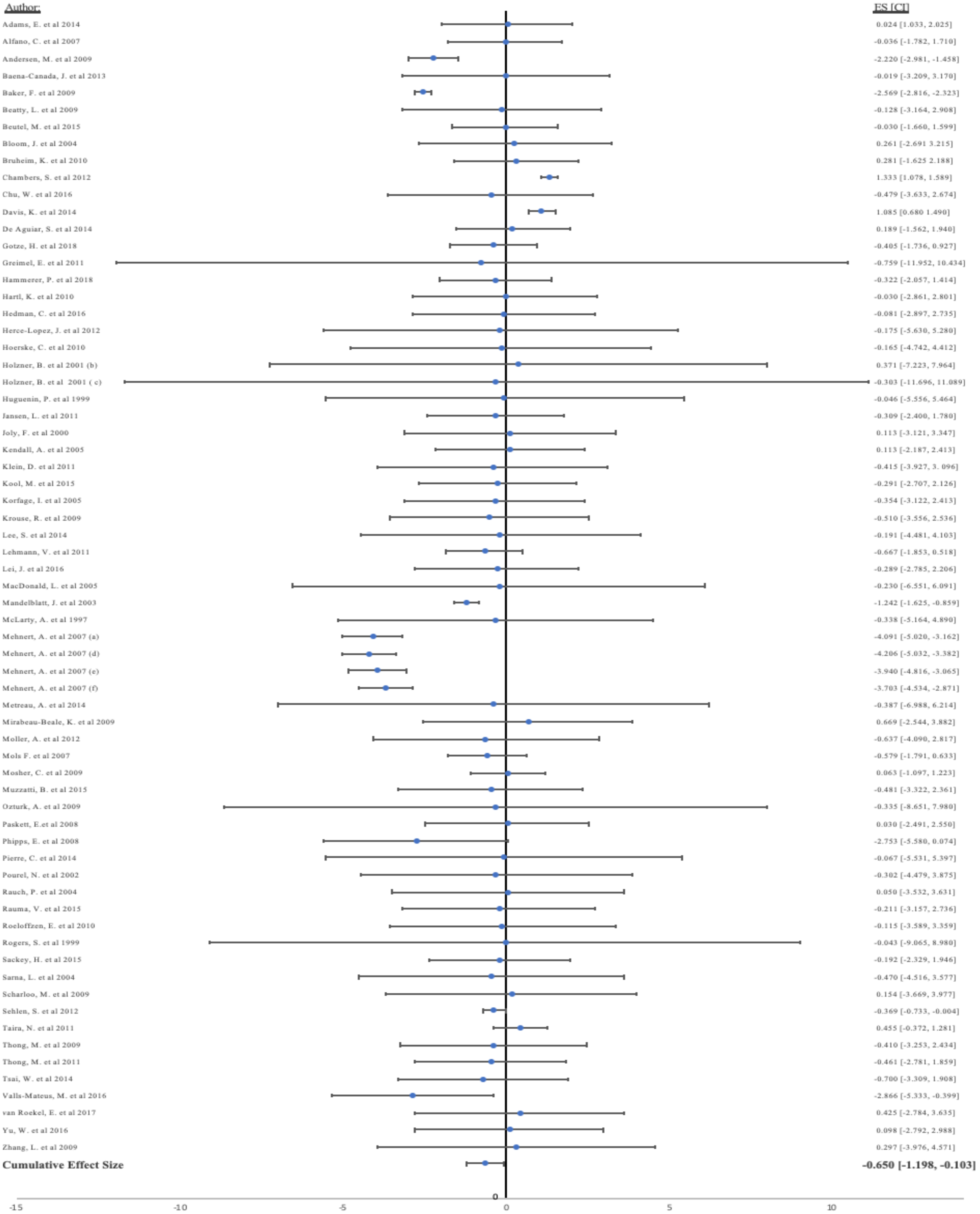
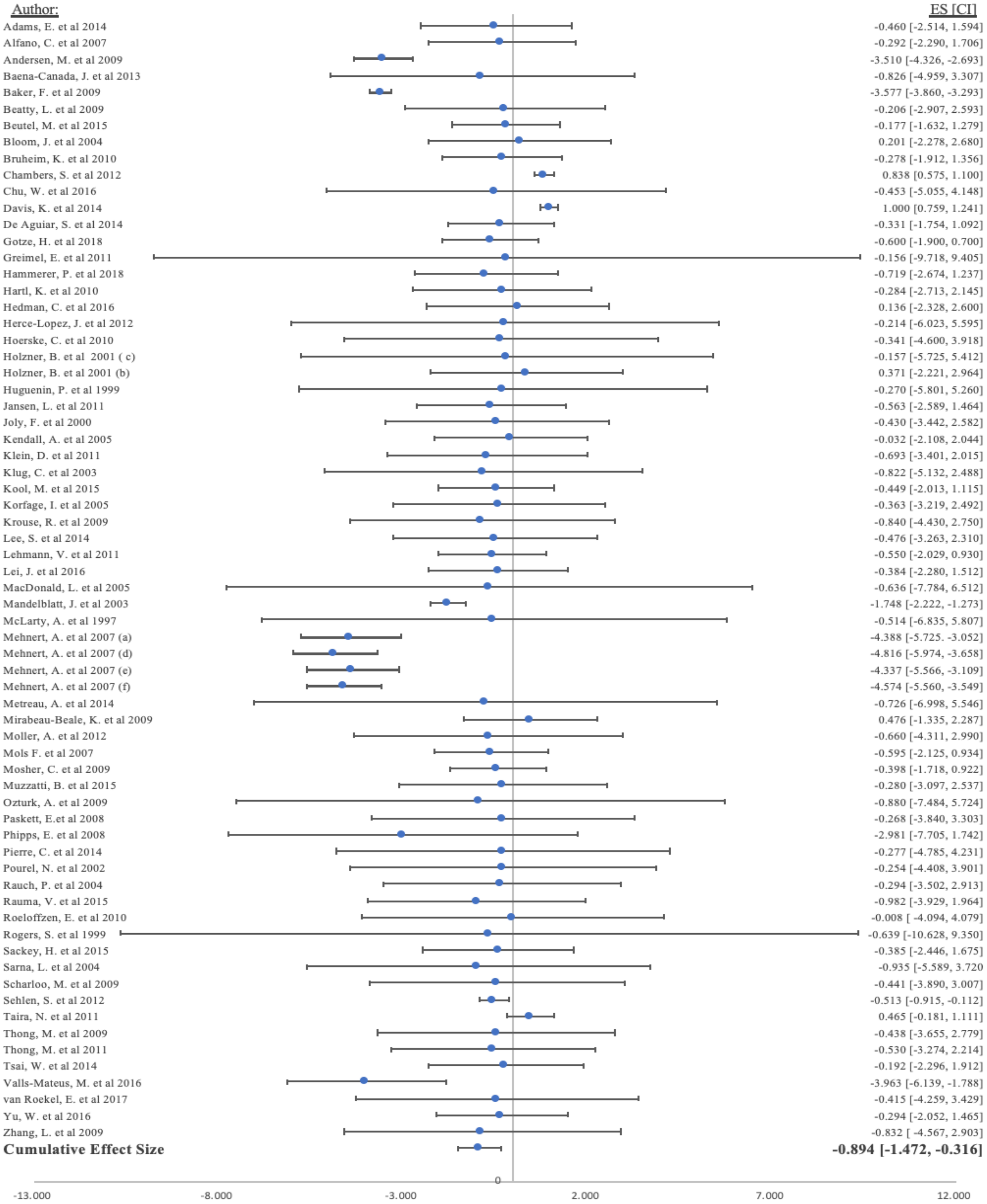


Figure 5. Forest plot of cumulative effect size for global health



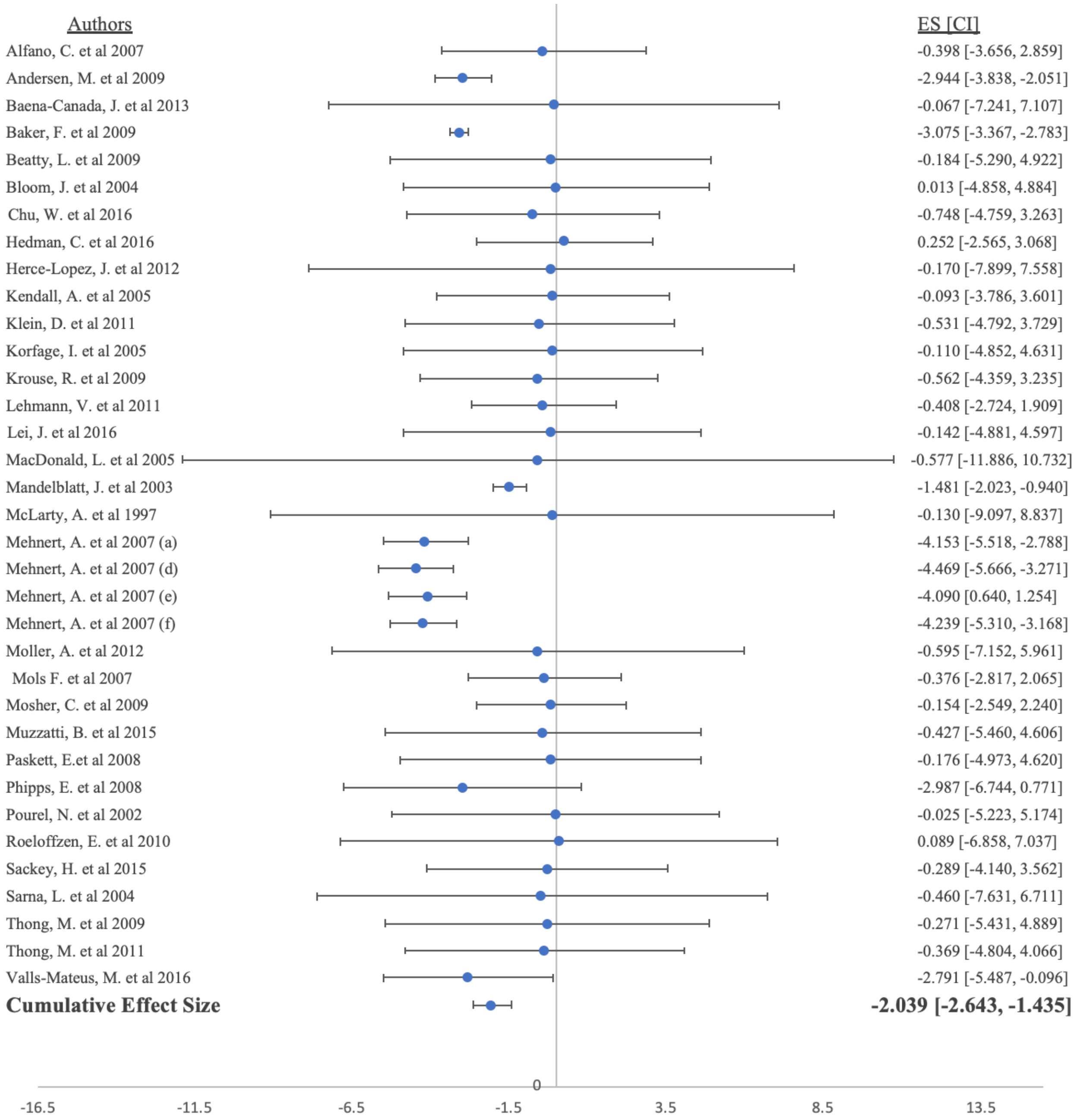
Key: (a) 5-year follow-up, (b) 10-year follow-up, (c) 2 to 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

Figure 6. Forest plot of cumulative effect size for physical health



Key: (a) 5-year follow-up, (b) 10-year follow-up, (c) 2 to 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

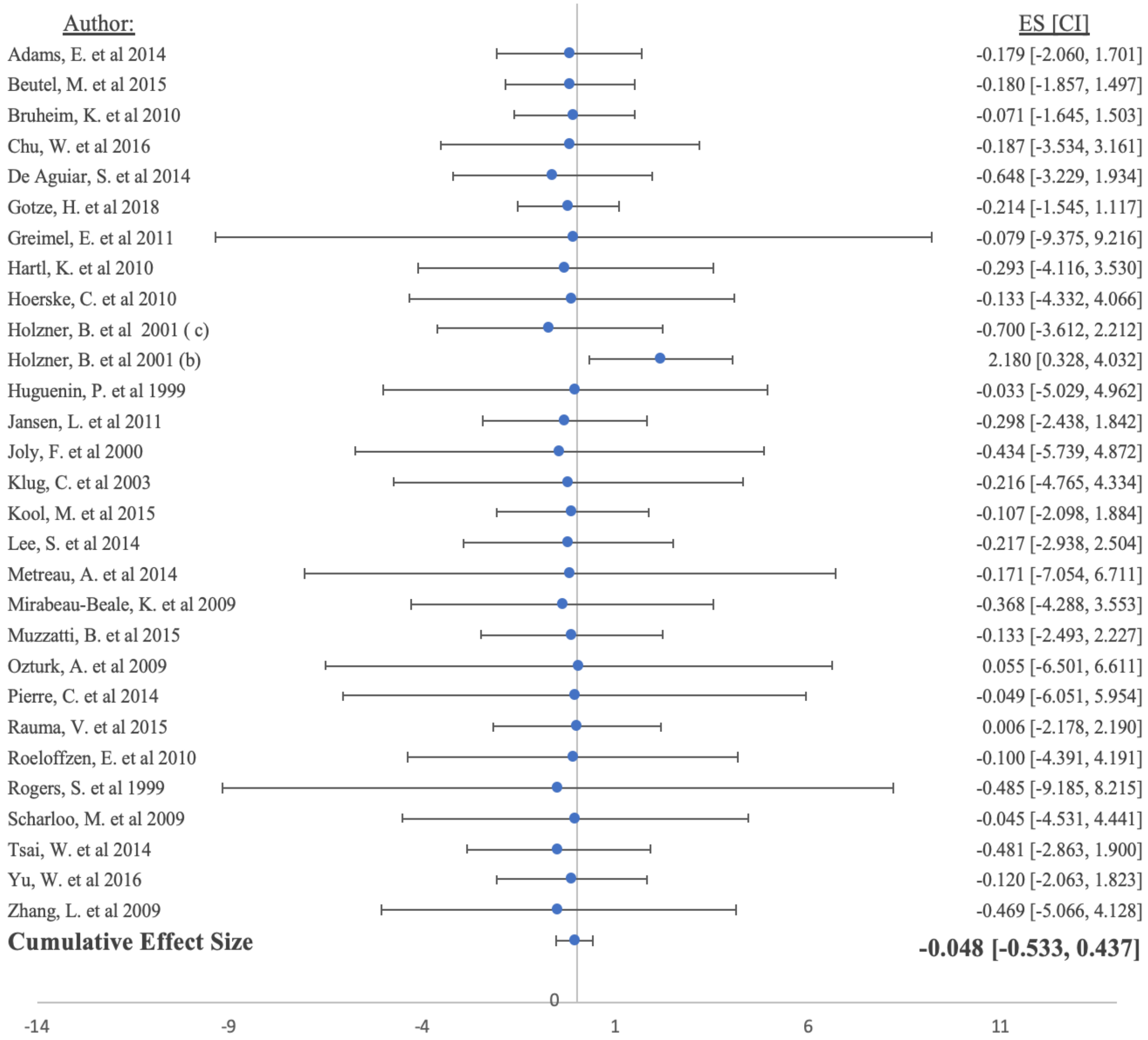
Figure 7. Forest plot of cumulative effect size for role-physical health



Authors	ES [CI]
Alfano, C. et al 2007	-0.398 [-3.656, 2.859]
Andersen, M. et al 2009	-2.944 [-3.838, -2.051]
Baena-Canada, J. et al 2013	-0.067 [-7.241, 7.107]
Baker, F. et al 2009	-3.075 [-3.367, -2.783]
Beatty, L. et al 2009	-0.184 [-5.290, 4.922]
Bloom, J. et al 2004	0.013 [-4.858, 4.884]
Chu, W. et al 2016	-0.748 [-4.759, 3.263]
Hedman, C. et al 2016	0.252 [-2.565, 3.068]
Herce-Lopez, J. et al 2012	-0.170 [-7.899, 7.558]
Kendall, A. et al 2005	-0.093 [-3.786, 3.601]
Klein, D. et al 2011	-0.531 [-4.792, 3.729]
Korfage, I. et al 2005	-0.110 [-4.852, 4.631]
Krouse, R. et al 2009	-0.562 [-4.359, 3.235]
Lehmann, V. et al 2011	-0.408 [-2.724, 1.909]
Lei, J. et al 2016	-0.142 [-4.881, 4.597]
MacDonald, L. et al 2005	-0.577 [-11.886, 10.732]
Mandelblatt, J. et al 2003	-1.481 [-2.023, -0.940]
McLarty, A. et al 1997	-0.130 [-9.097, 8.837]
Mehnert, A. et al 2007 (a)	-4.153 [-5.518, -2.788]
Mehnert, A. et al 2007 (d)	-4.469 [-5.666, -3.271]
Mehnert, A. et al 2007 (e)	-4.090 [0.640, 1.254]
Mehnert, A. et al 2007 (f)	-4.239 [-5.310, -3.168]
Moller, A. et al 2012	-0.595 [-7.152, 5.961]
Mols F. et al 2007	-0.376 [-2.817, 2.065]
Mosher, C. et al 2009	-0.154 [-2.549, 2.240]
Muzzatti, B. et al 2015	-0.427 [-5.460, 4.606]
Paskett, E.et al 2008	-0.176 [-4.973, 4.620]
Phipps, E. et al 2008	-2.987 [-6.744, 0.771]
Pourel, N. et al 2002	-0.025 [-5.223, 5.174]
Roeloffzen, E. et al 2010	0.089 [-6.858, 7.037]
Sackey, H. et al 2015	-0.289 [-4.140, 3.562]
Sarna, L. et al 2004	-0.460 [-7.631, 6.711]
Thong, M. et al 2009	-0.271 [-5.431, 4.889]
Thong, M. et al 2011	-0.369 [-4.804, 4.066]
Valls-Mateus, M. et al 2016	-2.791 [-5.487, -0.096]
Cumulative Effect Size	**-2.039 [-2.643, -1.435]**

Key: (a) 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

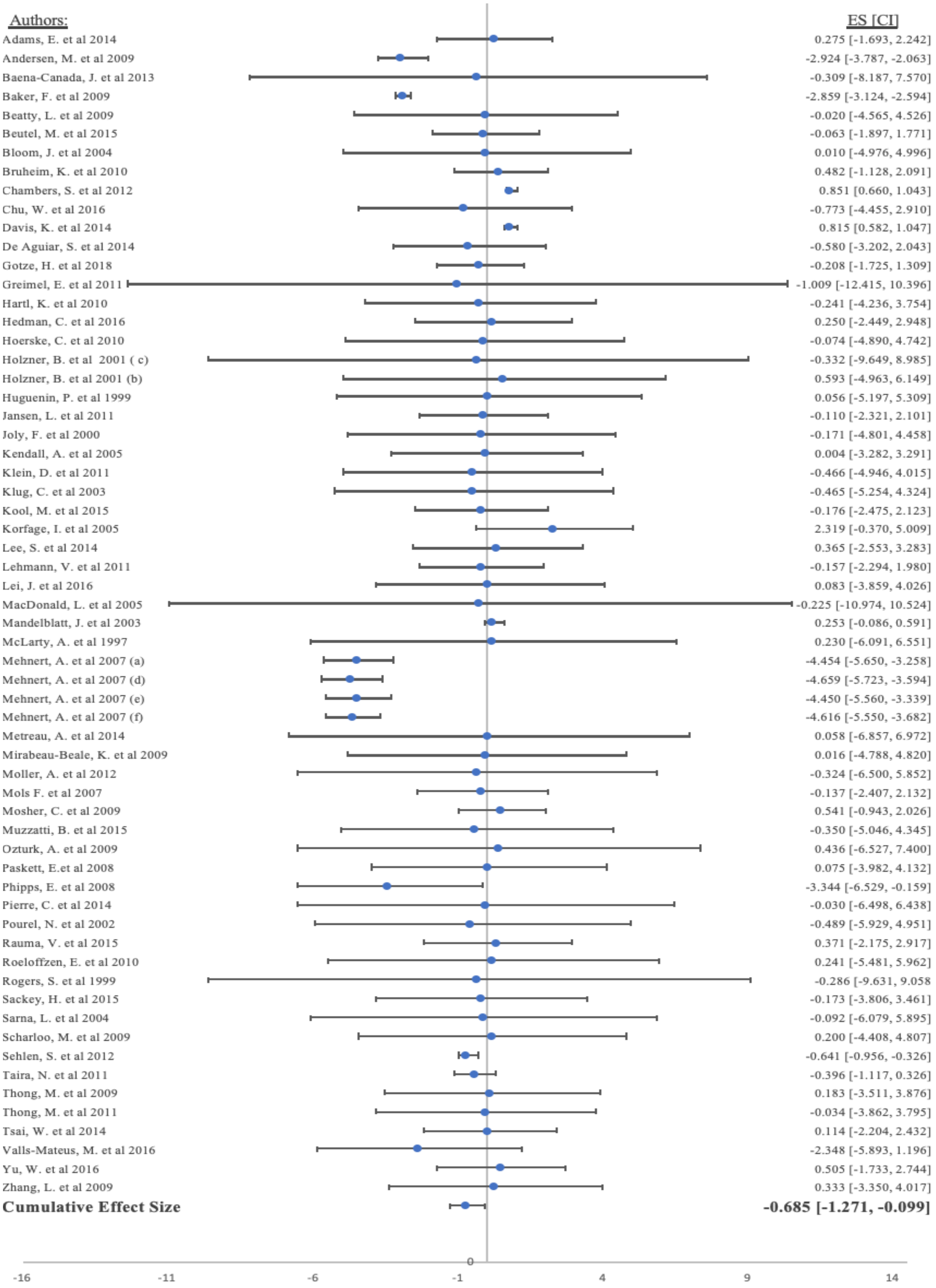
Figure 8. Forest plot of cumulative effect size for cognitive health



Author:	ES [CI]
Adams, E. et al 2014	-0.179 [-2.060, 1.701]
Beutel, M. et al 2015	-0.180 [-1.857, 1.497]
Bruheim, K. et al 2010	-0.071 [-1.645, 1.503]
Chu, W. et al 2016	-0.187 [-3.534, 3.161]
De Aguiar, S. et al 2014	-0.648 [-3.229, 1.934]
Gotze, H. et al 2018	-0.214 [-1.545, 1.117]
Greimel, E. et al 2011	-0.079 [-9.375, 9.216]
Hartl, K. et al 2010	-0.293 [-4.116, 3.530]
Hoerske, C. et al 2010	-0.133 [-4.332, 4.066]
Holzner, B. et al 2001 (c)	-0.700 [-3.612, 2.212]
Holzner, B. et al 2001 (b)	2.180 [0.328, 4.032]
Huguenin, P. et al 1999	-0.033 [-5.029, 4.962]
Jansen, L. et al 2011	-0.298 [-2.438, 1.842]
Joly, F. et al 2000	-0.434 [-5.739, 4.872]
Klug, C. et al 2003	-0.216 [-4.765, 4.334]
Kool, M. et al 2015	-0.107 [-2.098, 1.884]
Lee, S. et al 2014	-0.217 [-2.938, 2.504]
Metreau, A. et al 2014	-0.171 [-7.054, 6.711]
Mirabeau-Beale, K. et al 2009	-0.368 [-4.288, 3.553]
Muzzatti, B. et al 2015	-0.133 [-2.493, 2.227]
Ozturk, A. et al 2009	0.055 [-6.501, 6.611]
Pierre, C. et al 2014	-0.049 [-6.051, 5.954]
Rauma, V. et al 2015	0.006 [-2.178, 2.190]
Roeloffzen, E. et al 2010	-0.100 [-4.391, 4.191]
Rogers, S. et al 1999	-0.485 [-9.185, 8.215]
Scharloo, M. et al 2009	-0.045 [-4.531, 4.441]
Tsai, W. et al 2014	-0.481 [-2.863, 1.900]
Yu, W. et al 2016	-0.120 [-2.063, 1.823]
Zhang, L. et al 2009	-0.469 [-5.066, 4.128]
Cumulative Effect Size	**-0.048 [-0.533, 0.437]**

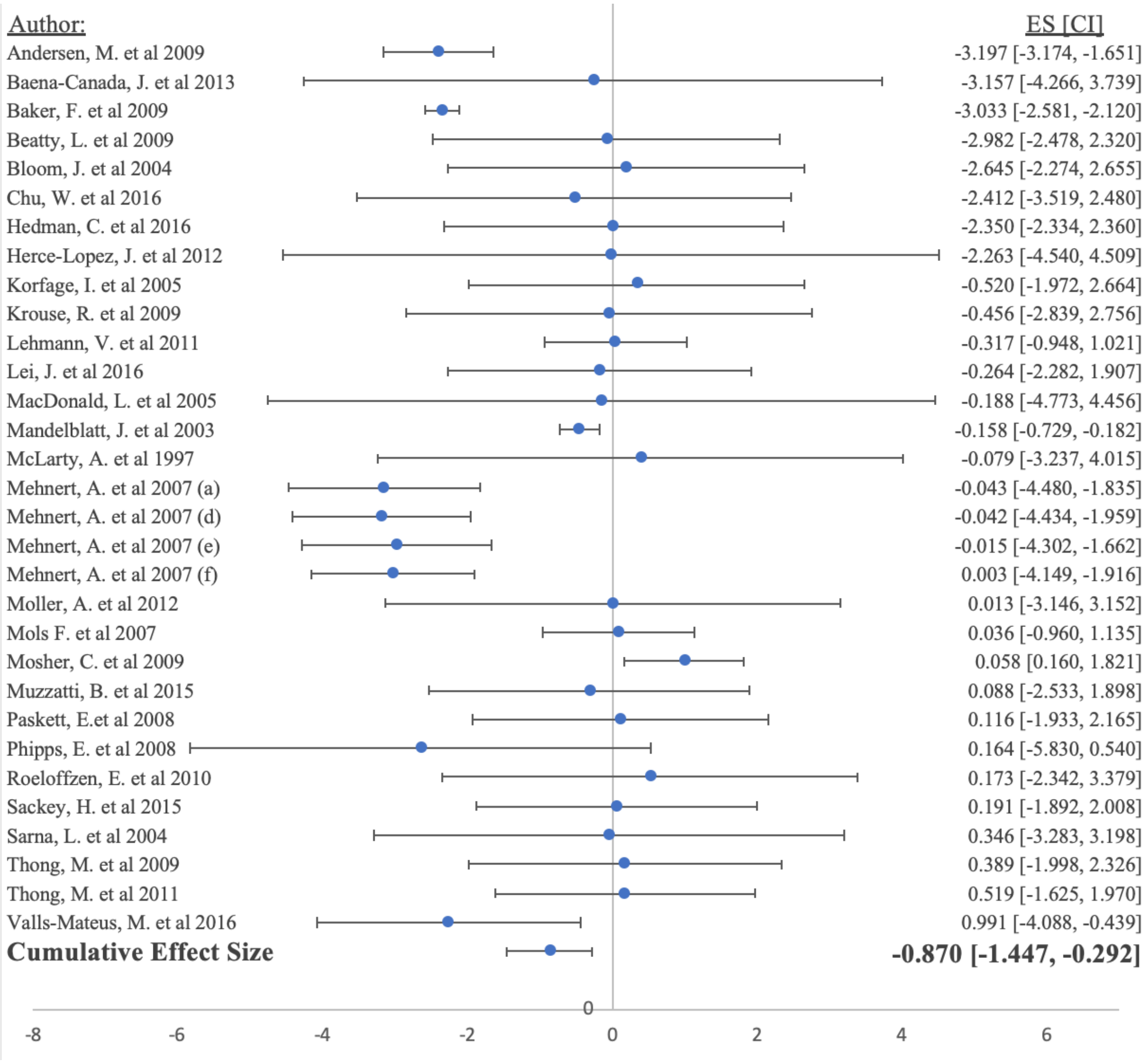
Key: (c) 2 to 5-year follow-up, (d) >5-year follow-up

Figure 9. Forest plot of cumulative effect size for emotional health



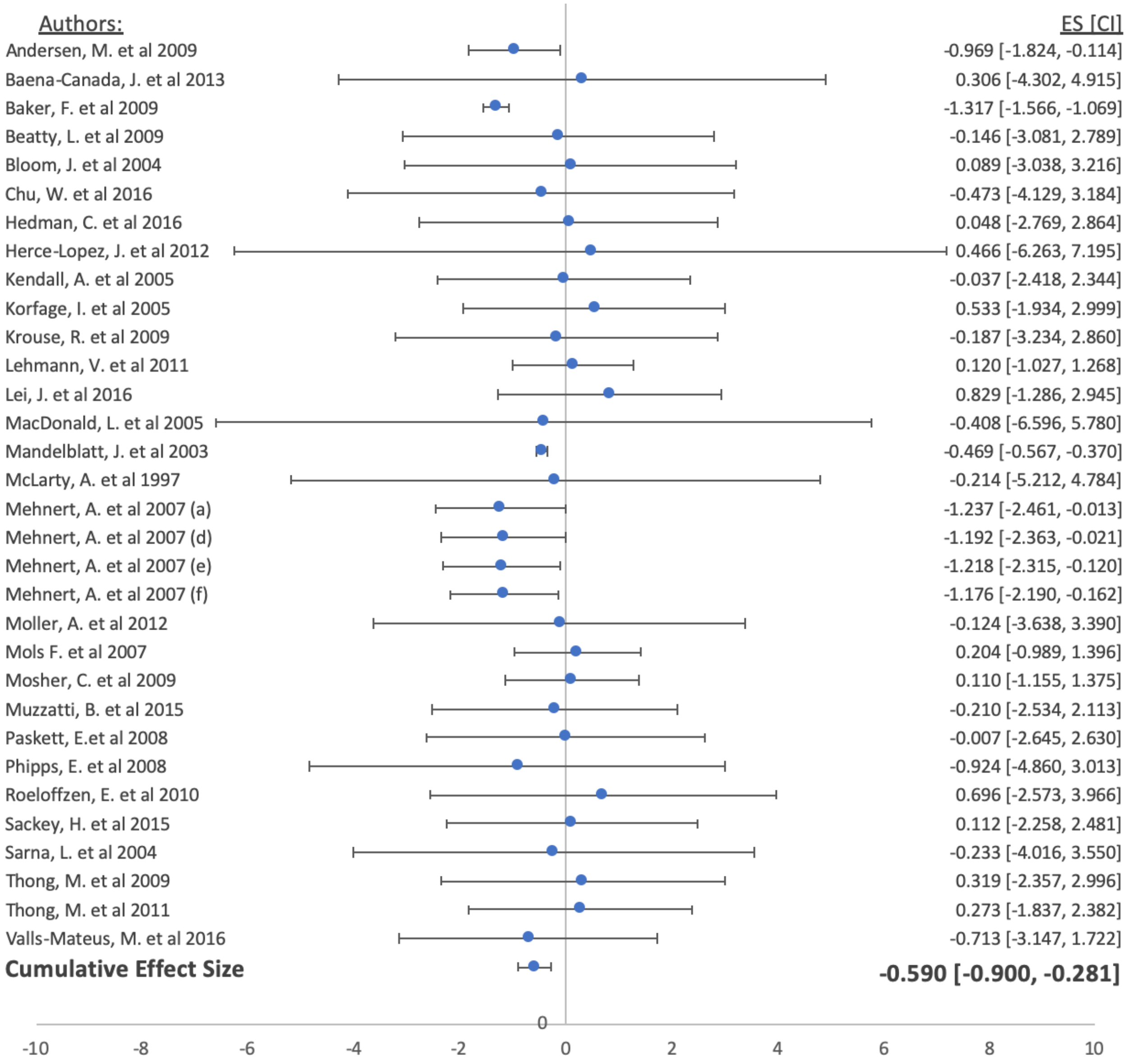
Key: (a) 5-year follow-up, (b) 10-year follow-up, (c) 2 to 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

Figure 10. Forest plot of cumulative effect size for mental health



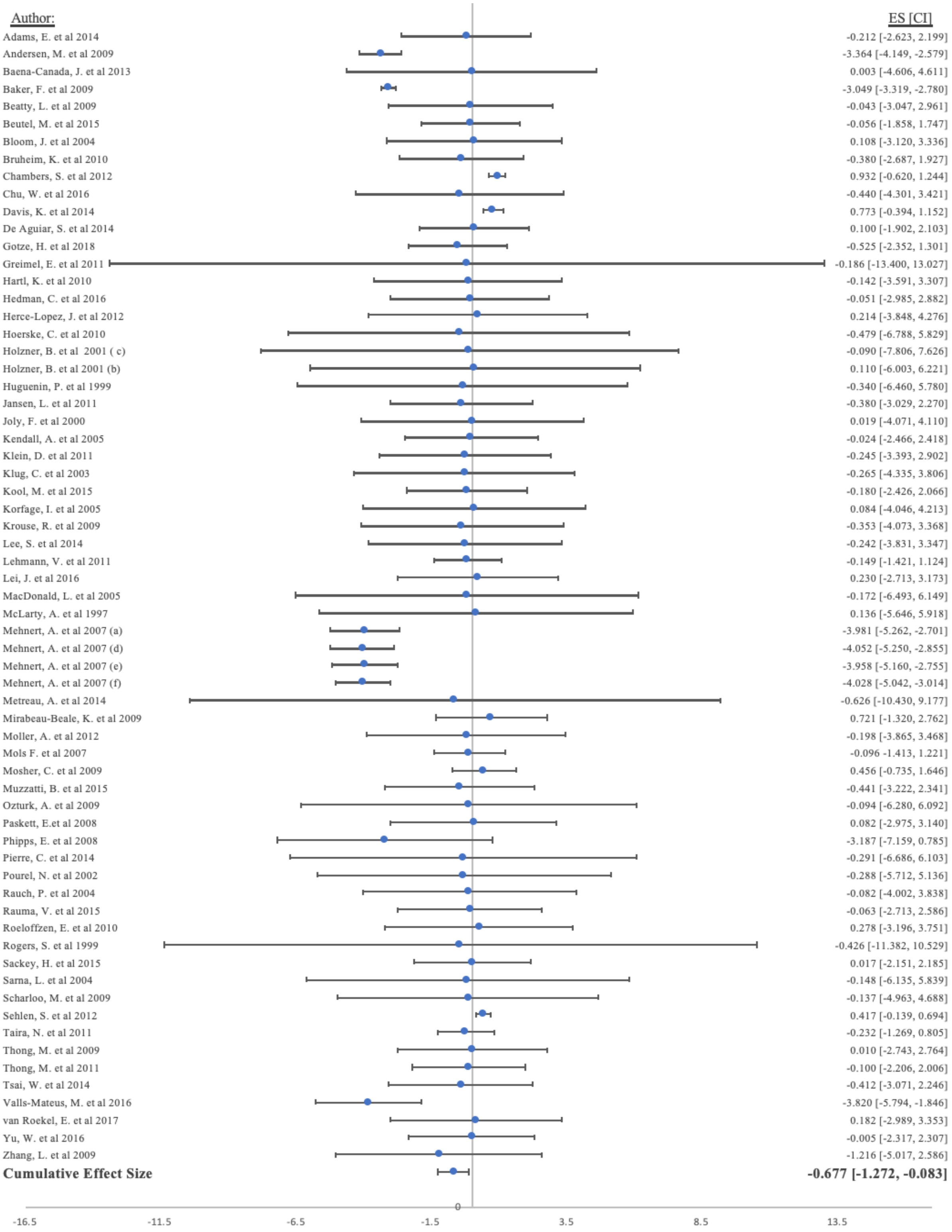
Key: (a) 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

Figure 11. Forest plot of cumulative effect size for vitality



Key: (a) 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

Figure 12. Forest plot of cumulative effect size for social health



Key: (a) 5-year follow-up, (b) 10-year follow-up, (c) 2 to 5-year follow-up, (d) >5-year follow-up, (e) 3 year-follow-up, (f) 4-year follow-up

References for Chapter IV (See Cumulative References)

Chapter V

Discussion, Summary, and Implications

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Discussion

The number of cancer survivors will continue to grow in the U.S. and cancer will continue to be a leading cause of death (Bray et al., 2018; Jemal et al., 2017; Siegel et al., 2018). QOL is a fundamental aspect of the human experience that can be dramatically impacted by a diagnosis of cancer and cancer treatment (Dow et al., 1999; Ferrell & Hassey Dow, 1997; Khan et al., 2005; Shrestha et al., 2019). As such, QOL should be closely examined and understood in the cancer survivorship population. The purpose of this dissertation was to create a deeper understanding of the usage and impact of QOL in cancer survivorship from close to death to long-term survivorship in various types of cancer. This study was accomplished by examining QOL in cancer survivorship from three separate vantage points in order to create a clearer vision of QOL in cancer survivorship as a whole: (a) identifying how QOL is defined and measured in the HCC literature using Ferrell's model of QOL, (b) identifying the impact of patient reported financial insecurity on physical and mental health and symptoms in cancer survivors, and (c) describing and analyzing QOL in the long-term cancer survivorship literature. Three manuscripts are included in this dissertation, one for each of the dissertation aims. The manuscripts include one systematic review of the literature (**Chapter 2 [Aim 1]**), a secondary analysis of a cross sectional study (**Chapter 3 [Aim 2]**), and a meta-analysis of the literature (**Chapter 4 [Aim 3]**). These three manuscripts used a variety of methodological approaches and statistical analyses to address their individual primary aims and the overall purpose of this dissertation.

Overview of Findings

The three manuscripts of this dissertation provide greater insight into QOL in cancer survivorship. They also identify gaps in our understanding that have the potential of directing future research. The key findings of this dissertation are: (a) a diagnosis of cancer has a life-long impact on survivors QOL, (b) there is a lack of a clear definition of QOL, (c) the domains of QOL are closely integrated with each other and must all be considered in order to have a clear view of QOL as a whole, and (d) the spiritual domain of QOL is understudied in cancer survivorship (see Table 1). This chapter will synthesize these key findings and describe the theoretical and clinical implications of this dissertation work. The strengths, limitations, and future research will also be discussed.

Table 1. Chapter aims and findings

	Aims	Findings
QOL in a Life Limiting Cancer	Aim 1: Define how QOL is measured in the HCC literature using Ferrell's model of QOL.	1. In published studies of QOL in HCC, QOL is not clearly defined. Only 10% of studies included in this review have a definition of QOL. 2. The spiritual domain of QOL was not well represented in the QOL in HCC literature. Only 1 of the included studies address spirituality of participants. A potential key reason for this is that the standard QOL measurement tools do not include an innate measurement of QOL. 3. In the studies included in this review, the geographic distribution of study participants did not reflect the geographic distribution of adults with HCC. 4. The majority of adults diagnosed with HCC are diagnosed in the advanced stage of the disease, yet the majority of study participants in this review were in the early stage of HCC.

Understudied Aspect of QOL	Aim 2: Identify the impact of patient reported financial insecurity on physical and mental health and symptoms in cancer survivors.	1. Perceived financial insecurity plays a key role in overall physical and mental health and symptoms in cancer survivors one to three years post diagnosis. 2. Financial insecurity accounted for 32% of the variability of cancer survivors pain severity and 31% of the variability in fatigue when controlling for demographic and socioeconomic factors. 3. A significant relationship exists between an aspect of the social domain of QOL in perceived financial insecurity and the physical and psychological domains of QOL.
QOL in Chronic Cancer	Aim 3: Describe and analyze QOL in the long-term cancer survivorship literature.	1. A large, negative cumulative effect size was found in the physical and mental subdomains of QOL in long-term cancer survivorship. 2. The variables of cancer type, average age of study participants, country of origin, time since diagnosis and decade of diagnosis were not found to be significant moderators to explain the heterogeneity of the subdomains of QOL in long-term cancer survivorship. 3. The distribution of cancer types analyzed was disproportionate to the distribution of cancer survivors in the general population.

Life-long impact of cancer on QOL

In this dissertation we examined QOL in a life-limiting cancer, recent cancer survivors, and long-term chronic cancer survivorship. Across the trajectory of cancer survivorship, QOL remained important and was impacted by cancer and its treatment from diagnosis to end of life. In **Chapter 2,** QOL was examined in a life-limiting cancer using the Ferrell model of QOL in cancer survivorship. Though the results of the individual studies were not reported in **Chapter 2,** all of the included studies reported a lower or decreased QOL in adults with HCC. In **Chapter 3** we examined the relationship between perceived financial insecurity and the physical and psychological domains of QOL. This manuscript specifically addressed recent cancer survivors that had been diagnosed between one and three years previously and demonstrated that QOL continues to be impacted once upfront treatment is completed and up to 3 years after diagnosis. **Chapter 4** builds upon the results of **Chapters 2 and 3** by further describing QOL in chronic, long-term cancer survivorship. In **Chapter 4,** cancer survivorship was examined in a meta-analysis of long-term cancer survivors. The results of this analysis demonstrate that QOL continues to be negatively impacted even two to 26 years after cancer diagnosis. Together, the three manuscripts of this dissertation demonstrate that QOL is impacted along the entire trajectory of cancer survivorship.

In addition, it was identified in **Chapter 2** that there is a lack of literature addressing QOL in advanced HCC. Research in common cancers such as lung (Choi & Ryu, 2018), breast (Hamer et al., 2017), prostate (Adamowicz, 2017), and colorectal (Mayrbaurl et al., 2016) cancers has found that QOL worsens as cancer progresses to more advanced, terminal stages. However, research describing the QOL of advanced HCC and other life-limiting cancers, such as pancreatic cancer, is limited. It is vital to specifically understand QOL in advanced, life-limiting cancers as research has shown that adults with advanced cancers may prioritize improving QOL over lengthening survival (Malhotra et al., 2017; Meropol et al., 2008; Shrestha et al., 2019; Voogt et al., 2005).

Results of **Chapter 3** confirm those of Bouras et al. that psychological health is negatively impacted 12 months after cancer diagnosis and increases our understanding that perceived financial insecurity may play a role in negatively impacting both psychological and physical well-being in cancer survivorship. The results of **Chapter 3** also validate the findings of Tian et al. (2013) that perceived financial insecurity is a factor associated with pain in cancer survivorship. Previous research has demonstrated the impact that a diagnosis of cancer can have on survivor’s ability to work and thus their income (Banegas et al., 2016; Yabroff et al., 2016).

Banegas et al (2016) found that survivors are more likely to report financial hardship and file for bankruptcy two years after completion of treatment compared with less than 2 years after treatment, demonstrating that financial insecurity continues after cancer treatment and may even be at its most significant two or more years after diagnosis. **Chapter 3** specifically examined financial insecurity of early cancer survivors from one to three years after diagnosis, meaning that our results may have captured the perceived financial insecurity of cancer survivors at the height of their financial insecurity being impacted by cancer and its treatment. The findings from **Chapter 3** of the significant relationship between perceived financial insecurity and pain and fatigue may further explain the relationship to bankruptcy and financial hardship in early cancer survivors. For example, survivors may be unable to return to work or may miss work due to the pain and fatigue related to cancer and its treatment. These results would confirm those of Whitney et al (2016) that over half of cancer survivors report missing work due to the side effects of cancer and its treatment. However, this study's results do not explain directionality or causality of the relationship between perceived financial insecurity with physical and psychological health and symptoms.

The results of **Chapter 4** further confirm the potential impact that cancer survivorship has on survivor's ability to work and could assist in understanding the results of **Chapter 3**. On the SF-36 QOL scale, the subdomain of role-physical health explores survivors' ability to work, along with other physical activities. The analysis of **Chapter 4** found that role-physical health was the most significantly impacted QOL subdomain in long-term cancer survivorship. This demonstrates that cancer survivor's ability to work may continue to be significantly negatively impacted in long-term survivorship, which may have an impact on survivors perceived financial insecurity and thus their physical and mental health.

Chapter 4 found that there was a large, negative cumulative effect size for physical functioning and mental health in long-term cancer survivorship, signifying a decrease in QOL. There was also a medium, negative cumulative effect size for vitality, global, emotional, and social health in long-term cancer survivorship. However, possible moderators of these effect sizes remain unclear. The moderators tested in **Chapter 4:** cancer type, average age of study participants, country of origin, time since diagnosis, and decade of diagnosis, did not show any significant results. Two potential moderators that were not examined in this work is cancer treatment and comorbidities, future research is needed to examine if treatment type and number and types of comorbidities explain some of the heterogeneity in QOL in long-term cancer survivorship.

Horick et al. (2018) also found that physical QOL continued to be decreased in long-term cancer survivorship, which is in line with the results from **Chapter 4**. Findings from **Chapter 4** support previous results of the long-term psychological and social impact of cancer and its treatment (Arambasic, Sherman, & Elder, 2019; Pfaendler et al., 2015). Arambasic et al (2019) found that psychological health is negatively impacted in long-term breast cancer survivorship, which confirms our results of medium, negative cumulative effect sizes in the psychological subdomains of emotional health and vitality and the large, negative cumulative effect size of the mental health subdomain. Our results expand on those of Arambasic by including the results to all cancer types in long-term survivorship, and found that type of cancer was not a significant moderator in the QOL subdomains of psychological health. Pfaendler et al (2015) found that cervical cancer survivors who received radiation as part of their treatment were more likely to have negative, long-term psychological and social effects compared with cancer survivor who did not receive radiotherapy. The results of Pfaendler et al (2015) further suggest that treatment type may be a significant moderator of QOL in long-term cancer survivorship.

Other possible important variables to the effect of cancer survivorship on QOL in both life-limiting cancer in **Chapter 2** and long-term cancer survivorship in **Chapter 4** is stigma and survivors' guilt. Stigma has been defined as both a *process* and as an *attribute* with three key actions: (1) negative labels are applied to specific human differences, (2) the negative labels are connected to negatively perceived social stereotypes, and (3) negative labels and perceptions create stigma which results in separation, loss, and discrimination (Link & Phelan, 2006). Stigma has been identified as a challenge for cancer survivors in the work environment due to concerns around death and ability to perform work activities (Stergiou-Kita, Pritlove, & Kirsh, 2016). High levels of stigma have also been reported by lung-cancer survivors (Hamann, Ver Hoeve, Carter-Harris, Studts, & Ostroff, 2018; Weiss et al., 2017). Hamann et al (2018) found that across the disease trajectory, stigma negatively affect lung cancer survivor's psychosocial health and communication outcomes. Weiss et al (2017) reported that lung cancer survivors experienced stigma from the general population, particularly lung cancer survivors who had never smoked. Stigma in cancer survivorship has been associated with a decrease in QOL (Ernst, Mehnert, Dietz, Hornemann, & Esser, 2017; Yeung, Lu, & Mak, 2019). In a survey of over 800 cancer survivors, Ernst et al (2017) found that an inverse relationship between stigma and QOL, such that increased stigma correlated with decreased QOL. Yeung et al (2019) examined stigma and QOL in Chinese-American breast cancer survivors and found that stigma was associated with a reduced physical and emotional QOL. Adults with HCC have a high likelihood of experiencing stigma due to HCC being primary the result of hepatitis and/or cirrhosis resulting from alcohol abuse (McGlynn et al., 2015; Thomas et al., 2011). However, to the best of the knowledge of the author, no studies have been done examining the impact of stigma in HCC. Due to stigma being associated with a decreased QOL in other types of cancer, stigma and its relationship to QOL in HCC should been assessed in order to obtain a complete understanding of QOL in HCC.

Survivors' guilt may also be impacting QOL in both life-limiting and long-term cancer survivors. Survivors' guilt is an interpersonal process of surviving disease or tragedy when others do not (Hutson, Hall, & Pack, 2015). In cancer survivorship, survivors' guilt is experienced due to cancer survivors continuing to live while others are dying from cancer (Glaser, Knowles, & Damaskos, 2019). Survivors' guilt was recognized as a concern in cancer survivorship in the National Action Plan for Cancer Survivorship published in 2004, yet little research has been done surrounding this concept and the possible impact on QOL (Center for Disease Control and Prevention, 2004). In the limited available research, 64% of lung cancer survivors were found to have significant survivors' guilt (Perloff, King, Rigney, Ostroff, & Johnson Shen, 2019). Perloff et al (2019) found that lung cancer survivors frequently wanted to discuss the death of other cancer survivors and frequently questioned "why not me?", regarding other cancer survivors' deaths. Lung cancer survivors with a history of smoking are at increased risk for survivors' guilt compared with non-smoker due to reporting that they feel as if they brought lung cancer on themselves due to smoking (LoConte et al., 2008). Yet the impact of survivors' guilt on QOL remains unknown.

Definition of QOL

One of the key findings from **Chapter 2** was that only 10% of included articles provide a QOL definition. QOL is a global, human concept, yet a clear and concise definition of QOL has yet to be established. Peplau (1994) defined QOL as an overarching theme that includes all aspects of being. Further definitions explains that QOL is fundamental in the wholeness of living, thing flow and change in life creating a pattern that gives meaning and purpose to life (Phillips, 1995). The WHO further specified the definition of QOL as more than simply the absence of disease, but that QOL encompasses physical, mental, and social well-being. The definition of QOL presented in Ferrell's model of QOL, specific to cancer survivorship, is that QOL is a personal sense of well-being and embodies physical, psychological, social, and spiritual domains. Though all of these definitions have slight variations concerning the specific domains of QOL, the key elements that they share is that QOL is an overarching term used to describe the wholeness of the human experience, and that the definition of QOL comes back to the individual. Individual cancer survivors define what QOL means to them. One key finding that all definitions of QOL have in common is that QOL is determined by the individual's experience. QOL is determined by the patient and not by the health care provider; QOL is whatever the cancer survivor feels that it is (B. R. Ferrell, 1996).

Spiritual domain of QOL

An element of QOL that is lacking across all three manuscripts of this dissertation is the spiritual domain of QOL. Of the 30 articles included in **Chapter 2,** only one addressed the spiritual domain of QOL. Though **Chapter 3** examined the relationship between the social, physical, and psychological domains of QOL, the spiritual domain of QOL was not addressed in the analysis. In **Chapter 4**, the spiritual domain of QOL was only addressed in one (2%) of the included articles on long-term cancer survivorship. In the three most commonly used QOL measurement tools (EORTC, FACT, SF-36), the physical, psychological, and social domains of QOL are addressed. However, none of these three-measurement tools included any questions to address the spiritual domain of QOL. This limits not only our understanding of the spiritual domain of QOL in cancer survivorship, but it also creates a gap in our knowledge concerning the relationship between spirituality and the other domains of QOL.

Research has shown that spirituality does impact survivors' QOL. Adams et al (2017) found that in a study of African American breast cancer survivors that spirituality and religion were essential to their coping and accepting of their cancer, yet the survivors felt that spirituality was not well understood or encouraged by their health care providers. Peteet and Balboni (2013) also found that cancer survivors reported their health care providers discussed spiritual well-being infrequently with them. Gonzalez et al (2014) found that increased spiritual well-being was a significant coping mechanism that offers protection against depression and that additional research is needed to identify the relationship between spiritual and psychological well-being. A study of health care providers and adults with advanced illnesses found that providers frequently 'miss the moment' to address spiritual well-being with patients due to feeling that spiritual care is not something that they, the health care provider, could provide (Selby, Seccaraccia, Huth, Kurppa, & Fitch, 2017). Additionally, an international qualitative study found that a key research priority for adults with life-limiting diseases was spirituality and provider education regarding addressing patient spirituality (Selman et al., 2018).

Spirituality has been described as an essential component of health and well-being and that spirituality can be a bridge between hopelessness and meaningfulness in life in adults at the end of life with cancer and HIV/AIDS (Fryback & Reinert, 1999). A study of those at the end of life with cancer and HIV/AIDS found that finding meaning in illness improved their QOL to be even higher than it was prior to their diagnosis (Fryback & Reinert, 1999). A systematic review found that spirituality had a positive association with clinical outcomes in adults with HIV (Doolittle, Justice, & Fiellin, 2018). A meta-analysis of all diseases at the end of life (primarily cancer, HIV/AIDS, cardiovascular disease, and amyotrophic lateral sclerosis) found that spirituality is fundamental to QOL, particularly at the end of life (Williams, 2006) and in a systematic review of spirituality it was found that increased spiritual well-being decreased the suffering experienced by adults with advanced heart failure (Clark & Hunter, 2019).

Though there may be many reasons for not addressing spiritual well-being in the cancer survivorship literature, a basis for its absence might be that previously, spirituality was considered an aspect of the psychological domain of QOL. Though spirituality has been previously included in the psychological domain of QOL, it should actually be a separate and independent domain. Spirituality is the way that cancer survivors find and give meaning to their lives and existence and encompass origins and purpose, these feelings and beliefs guide cancer survivors interactions with the world and with others (Timmins & Caldeira, 2017). The key and distinct difference between spiritual well-being and psychological well-being is the concept of transcendence, concepts within the spiritual domain of QOL contain an underlying assumption of something existential outside of oneself. Spirituality focuses on finding one’s purpose, meaning, and hope outside of oneself as opposed to psychological forces finding purpose, meaning, and hope from within oneself (Steinhauser et al., 2017).

Another reason for spirituality being understudied in cancer survivorship literature is perhaps that spirituality is thought to be synonymous with religiosity, when in fact they are very different concepts (McSherry, 2000; McSherry & Cash, 2004; Mishra, Togneri, Tripathi, & Trikamji, 2017; Puchalski, Vitillo, Hull, & Reller, 2014). A qualitative study of patients with end stage renal disease and HIV/AIDS reported feeling uncomfortable with the term ‘spirituality’ and had difficulty separating the meaning of spirituality from one’s personal religious beliefs (Molzahn et al., 2012). One study did however show a relationship between spirituality and religion; cancer survivors at the end of life found that the psychological benefits of religion were primarily due to spirituality rather than religious practices (Nelson, Rosenfeld, Breitbart, & Galietta, 2002).

Theoretical Implications

This study closely examined QOL in the HCC literature. This dissertation work is based on the theoretical framework of Ferrell's model of QOL in cancer survivorship. Ferrell's model centers around the four domains of QOL being physical well-being, psychological well-being, social well-being and spiritual well-being. This work both confirms concepts in Ferrell's model as well as identifies gaps in her model. Physical and psychological well-being were addressed in all of the reviewed articles. The majority of articles (97%) also addressed the social aspects of QOL. However, only 3% of the articles addressed the spiritual aspects of QOL. These results demonstrate a need for additional research in spirituality with adults with HCC so as to better understand Ferrell's conceptual model as a whole.

A theoretical implication brought to light in **Chapter 4** is the impact that cancer and its treatment continues to have in long-term cancer survivorship, demonstrating that Ferrell's model may continue to be applicable even up to 26 years after cancer diagnosis. **Chapter 3** explored the interrelatedness of two sets of the domains of QOL (physical and social well-being, and psychological and social well-being). The results of **Chapter 3** expand Ferrell's model by exploring the relationships and interdependence between the domains of QOL. Ferrell's current model does not reflect the interrelatedness of the domains of QOL. Much research has been done demonstrating the strong relationship between the physical and the psychological domains of QOL. Physical activity is known to positively impact psychological health both for those with and without cancer (Gavin et al., 2016; Kim et al., 2019; Patsou, Alexias, Anagnostopoulos, &

Karamouzis, 2018; White et al., 2017). However, the relationships of the social and spiritual domains with the physical and psychological domains in cancer survivorship remains understudied.

Clinical Implications

Though a vital purpose of research is to expand and add to our knowledge, it is also vital to consider the practical, clinical implications of research. This dissertation does have some notable clinical implications. One of the key clinical implications is the need for nurses and other health care providers to address QOL in every stage of cancer survivorship. The need for QOL to be discussed and addressed with cancer survivors does not end with the completion of active treatment. As discussed in **Chapter 4,** QOL is impacted years after diagnosis. This has clinical importance both in and outside the field of oncology. Findings demonstrate that QOL is affected at over 10 years after diagnosis, by this timepoint, cancer survivors are more commonly being followed predominantly, if not exclusively, by the primary care providers (PCP) and less by their oncology specialists. This means that PCP in the community need to be aware of the issues and concerns regarding QOL that may still be impacting this patient population. However, the impact of cancer survivorship in the community outside of oncology providers is unclear. A study of PCP in the US found that none of the PCP provided any type of cancer survivorship support or services, citing the lack of actionable information regarding the clinical needs of cancer survivorship (Rubinstein et al., 2017). Research, education, and training is needed regarding QOL in cancer survivorship for both oncology and non-oncology health care providers.

Financial insecurity was shown in **Chapter 3** to impact physical and psychological health and symptoms, as such, it is important that health care providers assess the financial security of recent cancer survivors. Assessing recent survivor’s financial security may provide an opportunity to provide resources and/or support that may improve QOL. These resources may include e.g., financial counseling, debt consolidation, and education on the long-term financial impact of cancer survivorship.

These results also highlight the need for patient-centered care. It is important to consider that QOL is a patient determined and centered measurement, meaning that the health care providers focus on QOL should be in line with what is important and meaningful for the cancer survivor. QOL can be impacted by multiple factors, as such, it is vital that health care providers' focus on the aspects of QOL that are most important to the cancer survivors as part of patient-centered care.

Strengths and Limitations

The three manuscripts included in this dissertation have added to the understanding and appreciation of QOL in cancer survivorship. This dissertation may be the first of its kind to both explore how QOL is examined and defined in the HCC literature as well as expose key gaps in the literature. The manuscripts in this dissertation highlight the impact of cancer on QOL across the disease trajectory. **Chapter 3** addressed an understudied aspect of QOL in cancer survivorship in perceived financial insecurity. Previous research has examined the cost and financial impact of cancer (Banegas et al., 2016; Banegas & Yabroff, 2013; Yabroff et al., 2016; Zafar et al., 2013). Additional research demonstrated the relationship of financial hardship to physical and psychological health (Kale & Carroll, 2016; Sharp et al., 2013). This research explores a previously unstudied aspect of perceived financial insecurity – one's household income - which did not strongly correlate with one's perceived financial insecurity. Results demonstrate that not only a cancer survivor's income but their view of their financial status has an impact on physical and psychological well-being.

However, there are several limitations to this dissertation work. First, the study does not include primary data collection and reported on an exclusively adult cancer survivorship population not addressing childhood and adolescent cancer survivorship. It is a secondary analysis of the literature. In addition, there are methodological limitations to all of the included manuscripts due to the nature of research. In **Chapter 2**, a key limitation identified was the exclusion of qualitative research studies from the review. Qualitative studies may have provided a deeper and richer understanding of QOL in the life-limiting cancer of HCC. Another limitation of the study is that the findings may not be generalizable to other types of life-limiting cancers do to the high symptoms burden and advanced stage of HCC. Also, in **Chapter 2,** articles not available in English were excluded from the review. This limitation may have impacted one of the key findings in **Chapter 2** that there was a lack of studies from Africa and parts of Asia where HCC is endemic. It is possible that research into the QOL in HCC in these populations has been completed but is unavailable in English. In addition, **Chapter 2** highlighted a small pilot study of young and middle age cancer survivors in Oregon, making it difficult to generalize our results to other populations of cancer survivors. The primary limitations of **Chapter 3** are that it was a pilot study with a limited sample size and this study did not address the presence or absence of health insurance coverage or amount of debt, which may be a significant confounding factor in our results. Lastly, the limitation with **Chapter 4** was the lack of access to unpublished data. It is possible that data exists that met inclusion parameters but was not published and therefore did not appear in our search results. Though authors were contacted regarding unpublished data, only a single response was received, and that was not related to completely unpublished data. In their study, Scharloo et al (2010) did not report the means and SD of the cancer survivorship population, but reported the results of regression analyses only. The corresponding author was contacted and shared the means and SD of the population included in their study.

Implications for Future Research

The results of **Chapter 2** demonstrate the need for additional research into the QOL of HCC, these results also demonstrate the need for continued research into the QOL of other life-limiting cancers to confirm if these results can be generalizable to other life-limiting cancers. Future work needs to focus on the identified gaps in the literature. Four gaps in the literature were identified in **Chapter 2**: 1) a lack of a clear definition of QOL in the HCC literature, 2) a lack of research in the spiritual domain of QOL in the HCC literature, 3) the unknown QOL of adults with HCC in areas of high prevalence of HCC such as Mongolia, Africa, and Micronesia, and 4) the understudied aspect of QOL in advanced HCC. A key element to addressing these gaps in the HCC literature is for QOL research to be encouraged and supported in areas of high prevalence of HCC, such as Asian and Africa, along with the U.S. where HCC is increasing in incidence and mortality.

What is also not reflected in the literature is research describing QOL and the stage of HCC. Almost half of adults who are diagnosed with HCC are diagnosed in the advanced stage, meaning that the research in QOL in advanced HCC does not correlate with that of the HCC population. Additional research is needed in order to better understand the impact of advanced disease on QOL in cancer survivors.

In **Chapter 3** a relationship between perceived financial insecurity and physical and psychological health and symptoms was identified. However, the directionality, along with potential confounders, of this relationship are unknown. Future studies are needed in order to determine the directionality of the relationship between perceived financial insecurity and physical and psychological health and to address potential confounding factors such as access to health insurance, financial assets, and financial debt.

As **Chapter 4** demonstrated, there is a continued negative impact on QOL in long-term cancer survivorship, yet the current available literature and research may not be reflective of the varied cancer types seen in long-term cancer survivorship. Additional research is needed to examine QOL in long-term cancer survivorship that is reflective of the cancer types seen in long-term survivorship. To determine if cancer type has a significant impact on QOL in long-term survivorship. The moderators examined in **Chapter 4** did not results in a significant finding. Additional research is needed in order to explore other possible moderators such as cancer type, treatments received, and comorbidities. In addition, only two of the articles included in **Chapter 4** included a longitudinal sample. Longitudinal research of long-term cancer survivorship will help our understanding of the transition from to chronic cancer survivorship and the impact this change has on the QOL of the survivor.

Additionally, the concept of stigma and survivors' guilt and their relationship to QOL in cancer survivorship is not well understood. The concepts of stigma and survivors' guilt are important to understand in both life-limiting and long-term cancer survivorship. Stigma and survivors' guilt have the potential to significantly impact QOL in cancer survivorship, as such, a thorough understanding of these concepts are required in order to truly understand QOL in cancer survivorship. More research is needed to not only understand the phenomena of stigma and survivors' guilt in cancer, but also their impact on QOL in cancer survivorship.

And finally, a key area for future research would be to examine the relationship of spirituality both within and to QOL. Spiritual well-being is one of the four domains of QOL in cancer survivorship, yet, all three manuscripts demonstrated a lack of research concerning spirituality in cancer survivorship. The spiritual domain is not well understood as an independent domain outside of psychological well-being. Additional research is needed to explore the differences between these two domains in order to have a better understanding of the spiritual domain of QOL. Another area for future research is the role spirituality itself plays in QOL and spiritualities relationship to the other domains of QOL.

Conclusion

The work done for this dissertation demonstrates that QOL is impacted by cancer and its treatment across the disease trajectory and throughout survivorship. Important advances in theoretical and clinical implications have been presented. Lastly, key gaps have been identified in the literature that provide potential paths for future research – research that is needed in order to advance our understanding of the important relationships between the QOL domains and cancer survivorship across the entire disease trajectory.

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