Title
Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

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Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Nursing

by

Paula Jean Belson

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ABSTRACT OF THE DISSERTATION

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

by

Paula Jean Belson

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2021

Professor Nancy Pike, Chair

Retinoblastoma (RB) is the most common malignant intraocular tumor occurring in childhood. While survival rates in the United States (U.S.) are high, children are left with the impact of treatment including enucleation, visual impairment or blindness as well as an increased risk of secondary cancer in those with the heritable form. Little is known about the influence of these factors on the health-related quality of life (HRQOL) in RB survivors.

The first manuscript describes an extensive review of the literature on HRQOL in the adolescent and young adult (AYA) RB population. The findings support the need for HRQOL and vision-related quality of life (VRQOL) research in RB survivors.

The second manuscript is a comparative, cross-sectional study of 101 AYA (aged 14-26 years) RB survivors and 97 age-, gender- and race/ethnicity-matched healthy controls. Measures included the Patient Reported Outcomes Measurement Information System PROMIS®-29 Profile, the National Institute of Health (NIH) Toolbox® VRQOL Survey, the Rosenberg Self-Esteem Scale and the Multidimensional Scale of Perceived Social Support. RB survivors

reported worse physical functioning than controls but PROMIS-29 physical and mental health summary scores were comparable. Social support and self-esteem were worse in the RB group with self-esteem significantly associated with better mental and physical HRQOL. Visual acuity and self-esteem accounted for 52% of the variance in the PROMIS-29 physical health summary score.

The third manuscript examines unilateral verses bilateral RB survivors which identified bilateral having worse VRQOL than unilateral survivors on all domains except ocular symptoms and psychosocial well-being. Worse scores were reported on the VRQOL psychosocial and role performance domains than other domains of the VRQOL. The VRQOL domains had medium to large correlations with the majority of PROMIS-29 scales and summary scores. A single-item measure of overall QOL had medium correlations with the VRQOL psychosocial and role performance scales.

The study findings contribute to gaps in our understanding of HRQOL in RB survivors. RB survivors had deficits in physical function and self-esteem with self-esteem and visual acuity as independent predictors of HRQOL. The NIH Toolbox® VRQOL provides more detailed insight into specific vision related effects on daily life of AYA RB.

The dissertation of Paula Jean Belson is approved.

Jo-Ann Eastwood

Mary Lynn Brecht

Ron D. Hays

Nancy Pike, Committee Chair

University of California, Los Angeles

2021

DEDICATION

To my husband Jeff, without his support I could never have accomplished this endeavor

To my children Kate and Liam for their love and understanding throughout the years it took for me to achieve my goal

and

To all the adolescents and young adults with retinoblastoma, your spirit and determination inspire me. Additionally, to the parents of children with retinoblastoma, your dedication to your children and concern for their future well-being motivated me to pursue this endeavor

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CHAPTER ONE: INTRODUCTION

Childhood cancer survivors are at risk for long-term sequelae from the effects of their diagnosis and treatments (Oeffinger et al., 2006; Robison L. L. (2005). Over the past decade, advancements in diagnosis and cancer therapy has improved childhood cancer survival. Attention to the long-term outcomes in survivors has become an essential part of care (Schmiegelow & Frandsen, 2018). The individual's perceptions of their functioning and well-being, or health-related quality of life (HRQOL) has emerged as an important outcome measure to consider in adolescent and young adult (AYA) survivorship care and clinical decision-making.

Retinoblastoma (RB), one type of childhood ocular or eye cancer, is typically diagnosed and treated within the first years of life. Survivors must live with visual impairment, facial deformities, and fear of metastasis or cancer recurrence related to their diagnosis and treatment. However, little is known about the long-term sequalae of RB survivors and the potential impact on HRQOL.

Retinoblastoma

RB is a malignant central nervous system (CNS) tumor that emerges from the developing retina and typically presents in early childhood (Dimaras & Corson, 2018). RB accounts for approximately 11% of cancers diagnosed in the first year of life and is the most common eye cancer in children (Dimaras & Corson, 2018; Wong, Tucker, Kleinerman, & Devesa, 2014). Approximately 300 to 350 children are diagnosed with RB each year in the United States (U.S.) (Gombos, 2012) with a worldwide incidence of one in every 16,000 live births (Dimaras & Corson, 2018). The five-year survival rate for RB is about 98% (Siegel et al., 2012), an increase from approximately 70% in the 1970's (Aziz et al., 2012). This improved survival rate can be attributed to advances in diagnosis and treatment including a shift toward chemotherapy rather

than radiation (Tamboli, Topham, Singh, & Singh, 2015). With advancements in treatment, it is imperative to monitor the effects not only on survival but also HRQOL outcomes.

The etiology of RB can be hereditary or caused by a spontaneous mutation of the RB1 gene. The hereditary form, either inherited from an affected survivor (25%) or the result of a new germline mutation (75%) accounts for 25-35% of all RB patients (Rodriguez-Galindo, Chantada, Haik, & Wilson, 2007). Individuals with heritable RB are more likely to develop tumors in both eyes, be diagnosed at a younger age, and have an increased risk of subsequent or secondary malignancy later in life (Wong et al., 2014).

Clinical Presentation and Treatment

Leukocoria is the most common presenting or clinical sign of RB, which is an abnormal white reflection from the retina of the eye. Initially, leukocoria is variable, meaning visible only with certain lighting and angles, and has often been detected with flash photography. Strabismus, or misalignment of the eyes, is the second most frequent clinical manifestation of RB. However, leukocoria and/or strabismus are not always present and may go undetected (Aerts et al., 2006).

Confirmatory diagnosis of RB occurs when an examination of the ocular fundus is performed under general anesthesia with dilation of the pupils. Ocular ultrasound is commonly performed and magnetic resonance imaging to assess for tumor extension into the extraocular area and brain. RB can also affect one or both eyes.

The primary goal of treatment for RB is the mitigation of cancer with ocular salvage and vision preservation secondary (Delhiwala, Vadakkal, Mulay, Khetan, & Wick, 2015). Options for treatment depend on tumor size and location, laterality, threat of metastatic disease, and visual prognosis (Shields & Shields, 2004). Individualized treatment may include a combination of systemic and/or intra-arterial or intraocular chemotherapy, focal modalities such as laser

photocoagulation and cryotherapy, external beam radiation, and/or enucleation (removal of the eye; Gombos, 2012). If left untreated, RB will spread beyond the eye into the lymph nodes, bone marrow, or CNS (Dimaras & Corson, 2018).

Children with RB require repeated eye examinations under anesthesia to provide treatment and monitor for recurrence of their disease. General anesthesia is provided to assure motionlessness and allow for a thorough examination, which is impossible to achieve in an awake child. Most children can undergo an eye examination without anesthesia by four years of age. However, multiple factors such as anxiety, developmental delay, and ongoing disease activity often necessitate continued examinations under anesthesia (Batra et al., 2014). A child can be exposed to as many as 50 general anesthetics before the age of four (Rodriguez-Galindo et al., 2007). RB survivors require ophthalmology surveillance throughout the lifespan to monitor for reduction or loss of vision in the affected eye. If chemotherapy or radiation is used in treatment, survivors will also be followed by an oncologist due to the increased risk of secondary cancers.

Long-term Outcomes in Retinoblastoma Survivors

There is limited research examining the long-term clinical and psychosocial outcomes of RB survivors. Outcomes are often dependent on age at diagnosis, disease stage at presentation, family history, laterality, and treatment regime (Aziz et al., 2012). RB survivors must live with their chronic disease and the long-lasting effects of treatment. AYA survivors often suffer from visual impairment, facial deformities, and the continual fear of a secondary cancer (van Dijk et al., 2010). Studies in adult RB survivors have reported additional risk factors of subsequent malignant neoplasms, cataracts, severe hearing loss, and thyroid nodules (Friedman et al., 2016).

Besides late effects of treatment, RB survivors must also contend with the long-term

adverse effects of childhood cancer on their HRQOL. An increased incidence of mental health issues such as depression, anxiety, and somatization as well as lower self-esteem were found among survivors of all childhood cancer (Hudson et al., 2003; Li et al., 2013). However, it is unclear if treatment effects impact psychosocial HRQOL in this high-risk subgroup.

Health-Related Quality of Life in Retinoblastoma Survivors

HRQOL is functioning and well-being in physical, mental, and social health (Ruccione, Lu, & Meeske, 2013). Potential benefits of measuring HRQOL in the clinical setting include improving patient-provider communication and patient satisfaction, discovering unknown morbidities, facilitation of clinical decision making, and improving outcomes over time (Cantrell & Kelly, 2015; Snyder et al., 2012). There are few U.S. based studies addressing HRQOL in RB survivors. From a methodologic standpoint, studies that examined HRQOL in those with RB have utilized different vison-targeted verses generic measures and only assessed one or two domains making it difficult to draw definitive conclusions.

Statement of the Study Purpose

The purpose of this study is to examine HRQOL, vision-related quality of life (VRQOL) and overall quality of life (QOL) in adolescent and young adult (AYA) RB survivors.

Specific Aims and Hypotheses

The specific aims and hypotheses for this study are as follows:

Aim 1: Describe patient [age, gender, ethnicity, socioeconomic status (SES), self-esteem and social support] and clinical (age at diagnosis, visual acuity, laterality/ heredity, treatment regime, anesthesia exposure) characteristics, HRQOL, VRQOL and overall QOL in a sample of AYA RB survivors.

Aim 2: Compare HRQOL and overall QOL of AYA RB survivors with those of matched, healthy counterparts.

Hypothesis 2a: HRQOL and overall QOL reported by AYA RB survivors will be worse than that of matched, healthy counterparts.

Aim 3: Identify patient (age, gender, race/ethnicity, SES, self-esteem and social support) and clinical characteristics (age at diagnosis, visual acuity, laterality/ heredity, treatment regime, anesthesia exposure) associated with HRQOL in AYA RB survivors.

Hypothesis 3a: Older age at diagnosis will be associated with worse psychosocial HRQOL than younger age at diagnosis.

Hypothesis 3b: Worse visual acuity will be associated with worse physical HRQOL than normal visual acuity.

Hypothesis 3c: Hereditary status and/or bilateral disease will be associated with worse HRQOL than non-hereditary and/or unilateral disease.

In addition, associations among domains of a VRQOL and generic HRQOL, and overall QOL measure, and estimate associations of the VRQOL and HRQOL domains with overall QOL in the RB population.

Significance of the Research

The findings of this study will contribute to the literature related to the health outcomes of AYA cancer survivors and the RB population. The results can be useful to inform clinical decision-making and the development of interventions to improve modifiable factors associated with HRQOL. Furthermore, this study will provide insight into the applicability of vision-targeted verses generic HRQOL measures to identify specific effects on daily life of RB survivors and correlations with an overall measure of QOL.

Content of the Dissertation: Three Manuscripts

This dissertation is organized into six chapters with chapters two, four, and five as original manuscripts that are published or formatted for publication.

Chapter 1 (this chapter) presents an introduction to RB, clinical presentation, treatment, long-term outcomes, statement of study purpose, significance, research specific aims and hypotheses.

Chapter 2 (first manuscript) provides a critical review of existing literature on HRQOL of RB survivors. This literature review was published in the *Journal of Pediatric Oncology Nursing* in 2020. Permission for reuse of copyrighted content was obtained from SAGE publishing via the Green Open Access policy.

Chapter 3, describes Ferrans, Zerwic, Wilbur, and Larson's (2005) revised HRQOL conceptual framework used to guide this dissertation. The proposed study will examine the relationships between patient and clinical characteristics with physical, mental, and social health domains, and overall QOL in AYA RB survivors.

Chapter 4 (second manuscript), we compare HRQOL, self-esteem, and social support in AYA RB survivors to healthy age-, gender-and ethnicity matched controls. This manuscript is formatted for submission to the *Journal of Pediatric Oncology Nursing*.

Chapter 5 (third manuscript) examines VRQOL in AYA with unilateral versus bilateral RB survivors. We assess associations among the VRQOL and generic HRQOL domains, and overall QOL, and estimate associations of the VRQOL and HRQOL domains with overall QOL. This manuscript is formatted for submission to the journal of *Quality of Life Research.*

Finally, **Chapter 6**, describes the manuscript highlights, implications for clinical practice, recommendations for future research, and conclusions.

Chapter 1 Summary

RB is a childhood cancer that has a unique treatment course in early childhood. While there has been a multitude of literature on HRQOL in survivors of childhood cancer, there is limited data specific to the RB population. With the advances in treatment over the past decade, the assessment of HRQOL and VRQOL is imperative to provide insight into specific vision related effects on daily life of RB survivors and identify modifiable factors that contribute to HRQOL.

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CHAPTER TWO: LITERATURE REVIEW

A Review of the Literature on Health-Related Quality of Life of Retinoblastoma Survivors

Belson, P., Eastwood, J., Brecht, M., Hays, R., and Pike, N. A Review of Literature on Health-Related Quality of Life of Retinoblastoma Survivors. J Pediatr Oncol Nurs 2020 Mar/Apr; 37 (2): 116-127. doi: 10.1177/1043454219888805

A Review of Literature on Health-Related Quality of Life of Retinoblastoma Survivors

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Abstract

Background: Retinoblastoma is a malignant tumor of the eye that typically presents in early childhood and occurs in approximately 1 in 20,000 births. While active treatment of the tumor is typically completed in childhood, survivors often suffer from long-term effects from treatment including visual impairment, facial deformities, and fear of recurrence or secondary cancer. However, little is known how these long-term effects affect their health-related quality of life (HRQOL). **Purpose:** To review the literature on HRQOL in retinoblastoma survivors. **Method:** We searched three electronic databases from January 2005 to December 2018 for original research articles reporting on HRQOL or individual domains such as function, cognition, and psychosocial outcomes in retinoblastoma survivors. **Results:** A total of 59 articles were reviewed and 15 were identified as eligible. Five of the studies reported worse HRQOL in retinoblastoma survivors than controls or general population norms. Parent-proxy ratings were worse than survivors' self-reports. **Conclusion:** Our findings confirm the need for further HRQOL research to assess the factors influencing long-term outcomes associated with treatment in adolescent and young adult retinoblastoma survivors. By identifying any potential deficits in specific domains of HRQOL, early interventions might be developed to improve HRQOL in retinoblastoma survivors.

Keywords

retinoblastoma, cancer, health-related quality of life, quality of life

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Introduction

Childhood cancer survivors, in particular, retinoblastoma, are at risk for long-term sequelae from the effects of their diagnosis and treatments. Retinoblastoma is a malignant tumor of the eye occurring in childhood. The incidence is 1 in 16,000 to 18,000 live births and accounts for approximately 11% of cancers diagnosed in the first year of life (Dimaras & Corson, 2019; Wong, Tucker, Kleinerman, & Devesa, 2014). Currently, the 5-year survival rate for retinoblastoma in the United States is 98% (Siegel et al., 2012). All childhood cancer survivors are at increased risk of secondary malignant neoplasms, however, retinoblastoma survivors have additional concerns regarding the visual and genetic component of their disease. With or without enucleation, they are often left with monocular vision which can have negative effects on motion processing, judging distances, and depth perception as well as an increased risk of visual dysfunction, cataracts, severe hearing loss, and thyroid nodules (D. N. Friedman et al., 2016; Steeves, Gonzalez, & Steinbach, 2008). Other challenges include cosmetic deformities and body image disturbances secondary to enucleation, continued risk and need for surveillance, and increased inherited risks of retinoblastoma in siblings and offspring (D. L. Friedman & Meadows, 2015). However, little is known about the potential effect of these long-term sequela on health-related quality of life (HRQOL) in retinoblastoma survivors.

HRQOL is a multidimensional construct that includes physical, mental, and social components of well-being and function (Ravens-Sieberer et al., 2006). Improvements in treatments and increased survival rates have led to a growing number of childhood cancer survivors and the subsequent need for long-term follow-up due to the potential physical and psychosocial health consequences (Robison et al., 2002). The life-threatening experience of cancer, adverse effects from chemotherapy, radiation, and surgery, and loss of an eye in those with an enucleation can have potential impacts on retinoblastoma survivors' HRQOL. Measuring HRQOL is essential in determining the extent to which cancer and its treatment continues to affect the daily lives of childhood cancer survivors. To date, there are no systematic reviews of HRQOL in the retinoblastoma population. The purpose of this literature review is to document what is known about HRQOL in retinoblastoma survivors and identify gaps in knowledge for future studies.

Method

A literature search was performed in PubMed, Cumulative Index of Nursing and Allied Health Literature, and PsycINFO for peer-reviewed English language articles published from January 2005 to December 2018 using combinations of the following keywords: "health-related quality of life," "quality of life," "outcomes," and "retinoblastoma." This search resulted in a total of 511 articles. An additional seven articles were identified from the reference lists of relevant articles. See Figure 1 for the PRISMA diagram (preferred reporting items for systematic reviews and meta-analyses; Moher, Liberati, Tetzlaff, & Altman, 2009). After removal of duplicates, the first author reviewed 352 titles and abstracts for applicability. Inclusion criteria consisted of studies measuring HRQOL in retinoblastoma survivors, as well as those that examined individual domains such as function (physical, mental/cognitive, or social) and psychosocial outcomes. Exclusion criteria included abstracts, case studies, and articles focusing on medical management and treatment. Articles before 2005 were excluded so treatment era would not affect the perception of HRQOL as higher rates of enucleation were performed before 2005.

Results

A total of 59 articles were examined in detail. Out of the 59 articles, 15 met the inclusion criteria. These 15 studies were from eight different countries and included retinoblastoma survivors from childhood to adulthood (see Table 1).

Health-Related Quality of Life

The literature findings on the impact of retinoblastoma on HRQOL are varied. Five studies identified worse HRQOL in retinoblastoma survivors than the general population (n = 2; Alessi et al., 2007; Sheppard et al., 2005) or controls (n = 3; Batra et al., 2015; Batra et al., 2016; Zhang et al., 2018). An additional five studies reported overall HRQOL similar to normative samples with worse or better outcomes in individual physical, mental, or social/school domains (Mouw et al., 2017; Rueegg et al., 2013; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007; Weintraub et al., 2011). A variety of generic HRQOL instruments were used including the Pediatric Quality of Life Inventory 4.0 Generic Core Scale (PedsQL™ 4.0; Batra et al., 2015; Batra et al., 2016; Mouw et al., 2017; Sheppard et al., 2005; Weintraub et al., 2011; Zhang et al., 2018), the KIDSCREEN-52 (van Dijk, Huisman, et al., 2007), the Medical Outcomes Study 36-Item Short Form Survey (SF-36®; Rueegg et al., 2013; van Dijk, Imhof, et al., 2007), the Children's Health Questionnaire (Weintraub et al., 2011), and the Health Utilities Index Mark III (Alessi et al., 2007). One study used a disease-targeted vision-related quality of life measure, the National Eye

Institute Visual Function Questionnaire (Friedman et al., 2018). Only one study recruited healthy controls (Zhang et al., 2018), while three studies used sibling control groups (Batra et al., 2015; Batra et al., 2016; Rueegg et al., 2013) and six utilized population normative data for comparison (Alessi et al., 2007; Mouw et al., 2017; Sheppard et al., 2005; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007; Weintraub et al., 2011). Two studies reported parent-proxy reports only (Batra et al., 2016; Sheppard et al., 2005), while three included both child/adolescent self-report and parent-proxy (Mouw et al., 2017; van Dijk, Huisman, et al., 2007; Weintraub et al., 2011). Last, only a few studies provided an operational definition or utilized a theoretical or conceptual framework of HRQOL (Batra et al., 2015; Batra et al., 2016; Weintraub et al., 2011).

Zhang et al. (2018) examined HRQOL in retinoblastoma survivors (n = 71) in China who had received an enucleation at least 1 year prior. They found that HRQOL scores were significantly worse ($p < .001$) for these survivors than healthy controls (n = 80). In addition to overall HRQOL, enucleated retinoblastoma survivors reported worse social ($p = .001$) and school ($p < .001$) functioning on the PedsQL. The 5- to 7-year-olds reported significantly worse overall HRQOL ($p = .04$) and school functioning ($p < .001$) than controls, while 8- to 18-year-olds reported significantly worse overall HRQOL ($p = .01$, 8-12 years; $p = .03$, 13-18 years), social ($p = .02$, 8-12 years; $p = .01$, 13-18 years) and school functioning ($p = 0.003$, 8-12 years; $p = .001$, 13-18 years; Zhang et al., 2018).

In a study out of India, both retinoblastoma survivors (n = 122) and their parents (n = 122) reported overall PedsQL scores as significantly worse than sibling controls (n = 50; $p < .001$ for both; Batra et al., 2015; Batra et al., 2016). Survivors reported statistically significant worse scores in emotional ($p = .02$), social ($p < .001$), school ($p < .001$), and psychosocial ($p < .001$) domains than their siblings. However, the physical

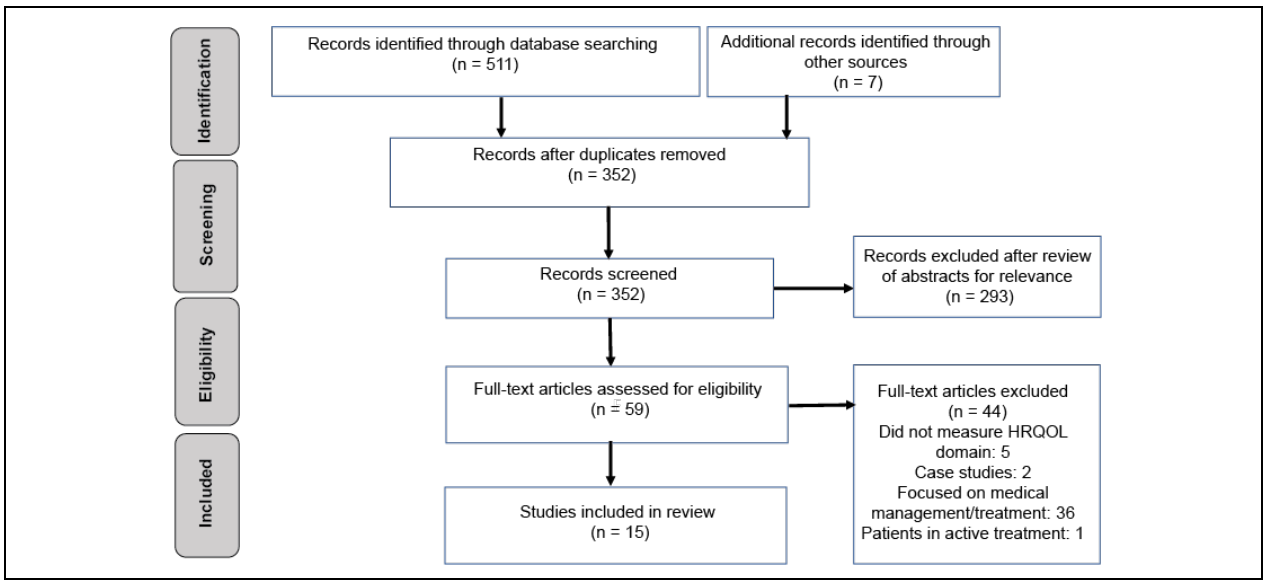

Figure 1. PRISMA diagram of literature search.

Table 1. Studies of Health-Related Quality of Life in Retinoblastoma Survivors.

Citation	Subjects/age/location	Focus	Study design	Methods/measurements	Results/conclusion
Alessi et al. (2007)	644 survivors of childhood cancer age ≥15 years in Italy (19 retinoblastoma survivors)	HRQOL	Childhood Cancer Registry of Piedmont	Health Utilities Index Mark III	Overall HRQOL and each of the eight attributes of health were rated as good by most survivors. RB had the lowest HRQOL scores compared with all cancer survivors with greater impairment in vision, emotion, cognition, and pain than other cancer survivors.
Batra et al. (2016)	122 parents of RB survivors aged 5-20 years with 50 sibling controls in India	HRQOL	Cross-sectional	Parent-proxy reports PedsQL (Hindi) Chart review variables: age, gender, intraocular versus extraocular, previous enucleation, and mother or father HRQOL proxy report	Overall parent-reported HRQOL was significantly worse in RB survivors as compared with controls. All domains were affected. No predictors were identified. Compared with child's self-report, parents reported worse emotional health for their child.
Batra et al./ (2015)	122 RB survivors aged 5-20 years with 50 sibling controls in India	HRQOL	Cross-sectional	Child self-report PedsQL (Hindi) Chart review variables: age at assessment and diagnosis, gender, intraocular versus extraocular disease, surgery or radiation	Overall HRQOL was significantly inferior in RB survivors compared with controls. Mean scores in in all domains were significantly lower except physical domain despite lower energy levels. Age ≤18 months at diagnosis was the only factor that predicted better HRQOL.
Brinkman et al. (2015)	69 adult RB survivors in the United States	Cognitive function and social attainment	Part of St. Jude Lifetime Cohort Study	Cognitive testing included the following: intelligence, academics, memory, attention, processing speed, fine motor dexterity, and executive function. Self-reported behavior rating and social attainment.	RB survivors performed within norms for most cognitive domains except fine motor dexterity, working memory, and task completion. Survivors diagnosed at ≤1 year of age performed significantly better on memory and learning tasks than those diagnosed at >1 year of age. Whole brain radiation exposure was associated with poorer performance on memory tasks. No significant differences in social attainment

					between unilateral and bilateral RB survivors.
Ford et al. (2015)	470 adult RB survivors and 2,820 controls from the CCSS sibling cohort data in the United States		Exploratory cohort study	Various measures: Brief-Symptom Inventory–18, Impact of Events Scale to measure PTSD, posttraumatic Growth Inventory, Fear of Cancer Recurrence. Chronic conditions and satisfaction with facial appearance were self-reported.	Bilateral RB survivors do not experience worse psychosocial functioning than unilateral. Significantly more unilateral survivors reported good to excellent health status, experiencing no pain, and satisfaction with facial appearance than bilateral. Bilateral survivors had more fears of recurrence and worry about offspring than unilateral. Survivors were less likely to report global symptoms, depression, anxiety, somatic distress, and more likely to report symptoms of avoidance and hyperarousal than sibling cohort. There were no differences in posttraumatic growth.
D. N. Friedman et al. (2018)	470 adult RB survivors from 3 medical centers in New York	VRQOL	Cohort from the RB Survivor Study	National Eye Institute Visual Function Questionnaire	Significant differences in VRQOL based on self-reported visual status (complete blindness vs. excellent/good/poor eyesight) and laterality (unilateral vs. bilateral). Overall VFQ scores not affected by radiation exposure. History of bilateral disease and enucleation were associated with inferior overall VRQOL.
Mouw et al. (2017)	12 patients with RB aged 5-22 years who were treated with proton radiation therapy in the United States	HRQOL	Cohort	Child self-report and parent-proxy report on the PedsQL general core and cancer modules.	Only 9 out of the 12 patients and parents completed the PedsQL. No difference between child self- or parent-proxy-reported HRQOL in RB versus population normative values. Cannot rule out that differences were not detected due to lack of power.
Rueegg et al. (2013)	1,593 childhood cancer survivors age ≥16 years with 695 sibling controls (37 retinoblastoma survivors) in Switzerland	HRQOL	Swiss Childhood Cancer Survivor Study	Self-reported HRQOL using the SF-36.	Survivors reported significantly lower physical functioning, general health perception, and physical component summary score and higher mental component summary score than siblings. RB diagnosis was associated with a lower PCS score. Vision impairments affected physical functioning, role physical, general health, and social functioning as well as energy/vitality and role emotional. Chronic health problems had a negative impact on HRQOL.
Sheppard, Eiser, and Kingston (2005)	54 RB survivors, aged 8-16 years in the United Kingdom	HRQOL	Cross-sectional	Parent-proxy report PedsQL	Mothers reported lower HRQOL total scores as well as physical and psychosocial subscales for their children compared with population norms.
van Dijk, Huisman et al. (2007)	65 RB survivors aged 8-18 years and their parents in the Netherlands	HRQOL	Cross-sectional	Child/adolescent self-report and parent-proxy KIDSCREEN–52. Chart review variables: gender, age, parents' marital status, visual acuity, heredity, and type of treatment.	HRQOL was not substantially different than controls. RB survivors reported significantly better HRQOL in "moods and emotions" and "autonomy" with children reporting better "parent relations and home life" and adolescents reporting better "autonomy" than controls. Survivors' and parents' perceptions correlated poorly on all dimensions. Survivors rated their

					"moods and emotions" to be better than parent-proxy ratings. Those with normal vision reported better "physical well-being" than those visually impaired.
van Dijk, Imhof et al. (2007)	87 adult RB survivors in the Netherlands	HRQOL	Cross-sectional	SF-36 (Dutch version) Semistructured interviews to extract data on subjective experience of impairment, being bullied, marital status and life events. Chart review variables: age at diagnosis, current age, gender, hereditary status, laterality, treatment type, visual acuity.	RB survivors scores were significantly lower on mental health subscale; all other scales were comparable to norms. Hereditary RB survivors scored significantly lower on the general health subscale than nonhereditary survivors. Having experienced bullying was an independent predictor of physical functioning, role functioning emotional, role functioning physical and social functioning. Perceived impairment due to RB was an independent predictor of vitality and bodily pain. Having experienced bullying and perceived impairment were both predictors of general health.
van Dijk et al. (2010)	156 RB survivors aged 8-35 years in the Netherlands	Survivors' perceptions of RB-related restrictions in activities of daily life	Cross-sectional	Semistructured interviews. Restrictions were specified according to the International Classification of Functioning, Disability and Health framework developed by the World Health Organization.	55% of young and 54% of adult survivors experience restrictions in school, career, mobility, self-care, and relationships. 84% of restrictions are due to visual impairment. Learning difficulties, fatigue, falling short of expectations, being dependent and different were reported by young survivors. Adult survivors believe their choice of profession was influenced by their RB and 25% experience vision-related restrictions at work.
van Dijk et al. (2009)	148 RB survivors aged 8-35 years in the Netherlands	Subjective experience of behavioral problems	Cross-sectional	Behavioral questionnaires completed by survivors and parents Child Behavior Checklist Youth Self-Report Adult Self-Report	Parents reported 30% of child RB survivors as having behavioral problems, in comparison to self-report by adolescents (9%) and adults (12%). Both parents and survivors define problems as internalizing (anxiety, depression, withdrawal, somatic complaints) rather than externalizing (aggression, rule-breaking behavior).
Weintraub, Rot, Shoshani, Pe'er, and Weintraub (2011)	46 RB survivors aged 2-18 years and their parents in Israel	Participation in daily activities HRQOL	Cross-sectional	Child and Family Follow-up Survey—Parents Child and parent proxy reports of the PedsQL Children's Health Questionnaire—Parents.	Overall HRQOL was similar to the normative sample. Parents perceived general health as lower. Children with RB reported their school QOL significantly lower than age-matched sample. Children who received chemotherapy perceived their physical HRQOL as lower than norms.
Zhang, Gao, and Shen. (2018)	71 enucleated RB survivors aged 5-18 years and 80 healthy controls in China	HRQOL	Cross-sectional	Child self-report of PedsQL (Chinese)	HRQOL scores in RB survivors after enucleation were significantly lower than the control group. School and social domains in 8- to 18-year-olds and school domain in 5- to 7-year-olds was significantly lower than controls. Laterality, age at diagnosis, and ocular prosthesis satisfaction influenced HRQOL.

Note. CCSS = Childhood Cancer Survivor Study; HRQOL = health-related quality of life; PedsQL™ = Pediatric Quality of Life Inventory 4.0 Generic Core Scale; QOL = quality of life; RB = retinoblastoma; SF-36 = Medical Outcomes Study 36-item Short Form Health Survey; VRQOL = vision-related quality of life; PTSD = posttraumatic stress disorder.

health domain did not show significance (p = .15; Batra et al., 2015). Within these domains, survivors reported statistically significant worse energy levels (p < .001), lesser abilities to compete with peer groups (p < .001), higher teasing (p = .002), and a perception of unwillingness of other children to befriend them (p < .001). Significantly higher future worries (p < .001), absenteeism due to sickness and hospital visits (p < .001, both), and difficulties in doing school activities (p < .001) were also reported. Similar significant differences between retinoblastoma survivors and their siblings (worse energy levels, p < .001; lesser abilities to compete with peer groups, p < .001; higher teasing, p = .003; perception of unwillingness of other children to befriend them, p < .001; worries, p < .001; absenteeism, p < .001; difficulties in school activities, p = .007) were reported by parents in addition to more anger (p = .03), impaired memory (p = .001), and difficulty lifting heavy objects (p = .007) in their retinoblastoma surviving child (Batra et al., 2016). These were the only studies that provided an operational definition of HRQOL (Batra et al., 2015; Batra et al., 2016).

Weintraub et al. (2011) utilized the International Classification of Function Disability and Health Framework of the World Health Organization (WHO) to guide their study. This was the only study that used a conceptual or theoretical framework for function or HRQOL. They examined participation of survivors at home, school, and in the community, as well as the relationship between extent of participation and HRQOL perceived by the parents and children. Using the Children's Health Questionnaire, retinoblastoma survivors (n = 46) reported significantly worse school HRQOL (p = .01) than an age-matched normative sample (Weintraub et al., 2011). Parents of survivors rated their children's general health as worse than a normative sample (p < .001; Weintraub et al., 2011). Finally, survivors with normal visual acuity in their nonaffected eye reported better "physical well-being" on the KIDSCREEN than those with impaired vision (p = .038; van Dijk, Huisman, et al., 2007).

While authors reported that the HRQOL of retinoblastoma survivors (n = 65) is not substantially different than the Dutch general population, child and adolescent survivors' KIDSCREEN "moods and emotions" (p = .005) and "autonomy" (p = .043) reports were better than normative data; children aged 8 to 11 years reported better "parent relations and home life" (p = .023) than the age-matched reference group (van Dijk, Huisman, et al., 2007). Adolescent (aged 12-18 years) retinoblastoma survivors reported better "autonomy" (p = .041).

Sheppard et al. (2005) found that mothers (n = 54) in the United Kingdom proxy reported worse physical, psychosocial, and overall HRQOL (all p < .01) for their children on the PedsQL than normative population data for survivors aged 8 to 16 years. Similar results were obtained in a study assessing adult survivors (van Dijk, Imhof, et al., 2007). Adult retinoblastoma survivors scored worse on the SF-36 mental health scale than the Dutch reference group (p < .01), while there were no significant differences on the other seven SF-36 scales (van Dijk, Imhof, et al., 2007).

Rueegg et al. (2013) examined HRQOL in Swiss adult survivors of childhood cancer (n = 1,593), including retinoblastoma (n = 37), and found that they reported significantly worse SF-36 physical component summary scores (p < .001) and better mental component summary scores (p = .017) than siblings. SF-36 scores were significantly worse for survivors for general health perceptions (p < .001), role limitations due to physical health (p = .003), and physical functioning (p < .001). Scores did not differ on bodily pain, vitality, mental health, social functioning, and role limitations due to emotional problems. A diagnosis of retinoblastoma was found to be associated with a worse SF-36 physical component summary score than other cancers, controlling for age, gender, and parents' education.

Moew et al. (2017) examined HRQOL using the PedsQL core and cancer modules following proton radiation therapy for retinoblastoma in a small group of retinoblastoma survivors (n = 9). Mean HRQOL scores as reported by retinoblastoma survivors and their parents did not differ significantly and were slightly better than normative data for child and parent scores (Mouw et al., 2017).

Alessi et al. (2007) found that long-term survivors of all types of childhood cancer (n = 644) in Italy had Health Utilities Index Mark III scores below the North American adult population and retinoblastoma was the worst of all cancer diagnoses. More than half of the 19 retinoblastoma survivors reported HRQOL in the lowest quartile. Compared with survivors of leukemia, retinoblastoma survivors had significantly higher probability of being in the lowest quartile (p < .001). Forty-seven percent of the population reported impairment in vision. Sixty-three percent reported impairment in emotion, 26% in cognition, and 58% in pain (Alessi et al., 2007).

In the only study to measure vision-targeted HRQOL in 470 adult retinoblastoma survivors, Friedman et al. (2018) found that a history of bilateral disease and enucleation (unilateral or bilateral) was associated with worse vision-targeted HRQOL (p < .001). Significant differences on the National Eye Institute Visual Function Questionnaire overall score by visual status (coded as either excellent/good/poor eyesight or complete blindness) were noted (p < .001).

As part of the St. Jude Lifetime Cohort Study, 69 adult retinoblastoma survivors received extensive neurocognitive testing (Brinkman et al., 2015). Survivors performed within test specific standardized norms on most cognitive

domains and were above expectations on nonverbal reasoning abilities and the ability to learn new information over a series of trials. However, they performed 1 standard deviation below the expected mean for fine motor dexterity and self-reported more problems with working memory and task completion than adults of similar age (Brinkman et al., 2015). Survivors with bilateral disease performed significantly better than unilateral survivors on measures of verbal learning (p = .03), short-term memory (p = .01), and long-term memory (p = .02), and better than normative expectations on each of these domains. Age at diagnosis was negatively correlated with verbal learning, short-term verbal memory, and long-term verbal memory. Survivors diagnosed at less than or equal to 1 year of age performed significantly better on short-term verbal memory (p < .01), long-term verbal memory (p = .02), verbal learning (p = .02), and verbal intelligence (p < .01) than those diagnosed at greater than 1 year of age.

Ford et al. (2015) assessed anxiety, depression, somatization, posttraumatic stress and growth, and fear of cancer recurrence in 470 adult retinoblastoma survivors. They used the Brief Symptom Inventory, Impact of Events Scale, Posttraumatic Growth Inventory, and Fear of Cancer Recurrence Questionnaire. Global symptoms of psychological distress were measured by the Global Severity Index. They found that survivors were significantly less likely to report global symptoms (p < .01), anxiety (p < .01), depression (p = .02), and somatic distress (p < .01) than a CCSS sibling cohort. Both survivors and siblings reported fewer symptoms of anxiety, depression, and somatization compared with normative data. Bilateral survivors were significantly more likely than unilateral survivors to experience fears of cancer recurrence (p < .01), worry over their children being diagnosed with retinoblastoma (p < .01), guilt about the possibility of passing retinoblastoma on to their children (p < .01), and avoidance of having children because of these feelings (p < .01; Ford et al., 2015).

The remaining two articles reviewed were both from the same research group in the Netherlands and focused on behavioral functioning and restrictions in daily life in retinoblastoma survivors (van Dijk et al., 2009; van Dijk et al., 2010). Survivors and parents completed either the Youth Self-report, Adult Self-report, or Child Behavior Checklist and scores were compared with American normative data, as Dutch data were unavailable (van Dijk et al., 2009). Results showed that parents reported more behavioral problems (30%) in their children than adolescent (9%) or adult (12%) self-reports. Both survivors and parents reported behavioral problems as internalizing (anxiety, depression, withdrawal, and somatic complaints) rather than externalizing (aggression, rule-breaking behavior). Compared with the normative data, adolescent female retinoblastoma survivors reported less externalizing behavior, rule-breaking, aggressive behavior, and thought problems. Adult males also reported less thought problems, while adult females reported more somatic problems and less total problems, particularly less externalizing problems and aggressive or intrusive behavior. Parents reported significantly higher rates of internalizing problems in boys (p = .037) and somatic complaints in both boys (p = .011) and girls (p = .013). Overall, hereditary retinoblastoma, more intense treatment regime (radiation, chemotherapy, and localized treatments vs. enucleation alone), and single-parent families were associated with behavioral risk, explaining 7% (attention and thought problems) to 60% (aggressive behavior) of the variance (van Dijk et al., 2009).

The final article reported qualitative results from semistructured interviews (n = 156) in the above parent study sample. Fifty-five percent of survivors aged 8 to 35 years reported restrictions in daily life activities due to their retinoblastoma (van Dijk et al., 2010). Problems were mainly due to visual impairment and emotional problems including avoidance. A significantly higher percentage of survivors than the general Dutch population did not attend mainstream education (p < .01) and had significantly lower levels of highest education (p < .01). Forty-eight percent of young survivors reported being bullied at some point compared with 18% in the general population. Anxiety regarding secondary cancer and further loss of vision was reported, as well as fear of being rejected due to cosmetic deformities. No significant differences were found in employment rates between survivors and the general population. However, 26% of survivors considered their choice of profession to be influenced by consequences of their retinoblastoma with 25% experiencing vision-related restrictions at work (van Dijk et al., 2010).

Child Versus Parent Report

Those studies that assessed both parent and child reports found that parents reported worse HRQOL and more behavioral problems than their child's self-report (Batra et al., 2016; Van Dijk, Huisman et al., 2007; Van Dijk et al., 2009; Weintraub et al., 2011). Parent-reported HRQOL was significantly worse in all PedsQL domains for their children previously diagnosed with retinoblastoma compared with sibling controls (p = .05, physical; p < .001, all others; Batra et al., 2016). Parents reported worse emotional HRQOL compared with the child's self-report (p = .02; Batra et al., 2016). Van Dijk, Huisman et al. (2007) found no correlation between parent-proxy and child-self reports of HRQOL in all dimensions of the KIDSCREEN, and retinoblastoma survivors reported significantly better "moods and emotions" than their parents (p = .01).

Correlates of Health-Related Quality of Life

Correlates or predictors of HRQOL in retinoblastoma survivors include age at diagnosis (Batra et al., 2015), age at time of study (van Dijk, Huisman, et al., 2007), visual acuity (van Dijk, Huisman, et al., 2007), having experienced bullying, and perceived impairment related to retinoblastoma (van Dijk, Imhof, et al., 2007). Of interest, gender, intraocular versus extraocular disease, heredity, laterality, and type of treatment were not significantly associated with HRQOL (Batra et al., 2015; Batra et al., 2016; van Dijk, Imhof, et al., 2007).

Age less than or equal to 18 months at diagnosis was associated with better overall HRQOL in one study, with social and school domains significantly better but physical and emotional domains being similar (Batra et al., 2015). Age at the time of study was negatively associated with the KIDSCREEN dimensions of "psychological well-being," "parent relations and home life," and "social support and peers," with adolescents reporting worse HRQOL on these domains than younger children (van Dijk, Huisman, et al., 2007). Visual acuity and age at time of study were negatively associated with the HRQOL "self-perception" dimension (van Dijk, Huisman, et al., 2007). Survivors with normal visual acuity in their nonaffected eye reported better HRQOL on the physical well-being dimension than those that were visually impaired (van Dijk, Huisman, et al., 2007).

In adult survivors, having experienced bullying in childhood was associated with worse "physical functioning," "role-physical functioning," "role-emotional functioning," and "social functioning" (van Dijk, Imhof, et al., 2007). Having experienced bullying and subjective experience of impairment were both associated with worse "general health perceptions" (van Dijk, Imhof, et al., 2007). Perceived impairment (measured as yes or no and extracted by content analysis from semistructured interviews) was associated with "bodily pain" and "vitality" (van Dijk, Imhof, et al., 2007).

Survivors with a hereditary risk for retinoblastoma reported significantly worse SF-36 "general health perceptions" than nonhereditary survivors ($p < .01$; van Dijk, Imhof, et al., 2007). However, heredity, type of treatment, visual acuity, and laterality were not associated with HRQOL. Children who received chemotherapy perceived their HRQOL as worse than those who did not receive chemotherapy (Weintraub et al., 2011).

Discussion

This literature review investigated HRQOL in retinoblastoma survivors. Some studies identified worse HRQOL in survivors compared with controls, while others found similar overall HRQOL but identified significant differences within physical or emotional domains. Eleven of the 15 studies reviewed used comprehensive HRQOL instruments. Nine of which utilized generic profile-based instruments, one study used a preference-based instrument, and one a measure of vision-targeted HRQOL. The remaining four studies measured individual HRQOL domains such as function, cognition, and psychosocial outcomes. All studies were cross-sectional. Three were cohort studies (Brinkman et al., 2015; Friedman et al., 2018; Mouw et al., 2017), and two were large population-based studies of childhood cancer survivors which included retinoblastoma survivors (Alessi et al., 2007; Rueegg et al., 2013).

Better HRQOL in retinoblastoma survivors than population normative data may be attributable to posttraumatic growth or response shift, an adaptation of a person to a change in their health status, which has been previously cited in the pediatric cancer literature (Barakat, Alderfer, & Kazak, 2006; Brinksma et al., 2014; Zamora et al., 2017). Response shift changes the meaning of an individual's perception and causes bias in measurements of HRQOL (Brinksma et al., 2014). The experience of having had cancer causes the survivor to place a higher value on their life, and this can decrease the overall effect of treatment outcomes on their HRQOL ratings. For example, a survivor of osteosarcoma who has had a leg amputation and now must live with a prosthetic, may rate their function and well-being higher than someone without a prosthetic limb. Posttraumatic growth occurs when those who have experienced traumatic events are able to find new meaning in life and their relationships. This in turn can lessen their risk of depression and impairments in other aspects of HRQOL (Arpawong, Oland, Milam, Ruccione, & Meeske, 2013). Better HRQOL in retinoblastoma survivors may be attributable to diagnosis in early childhood and knowing no other way of life or a time without chronic illness.

The findings that adult retinoblastoma survivors scored worse on the SF-36 mental health scale than the Dutch reference group differs from previous findings in child and adolescent survivor studies who scored better on "mood and emotion" domains on the KIDSCREEN. The authors speculate that this discrepancy may be caused by the younger survivors being less informed and thus less aware of the associated risks later in life than adult survivors. In addition, they may possibly be too young to have had experiences that negatively affected their HRQOL (van Dijk, Huisman, et al., 2007).

Many of the studies that found no statistically significant difference in HRQOL between retinoblastoma survivors and the general population had smaller sample sizes than those that found a significant difference. For example,

although results were not statistically significant in the Mouw et al. (2017) study, power analysis suggests that the large effect size found in the study would have been identifiable as significant with a sample size of 26 per group. Unfortunately, the study only had a small sample size ($n = 9$).

All HRQOL studies in retinoblastoma survivors were conducted outside the United States (China, India, Netherlands, United Kingdom, Italy, Switzerland, and Israel) except for one small study with only 12 survivors and the one vision-related quality of life study. The lack of U.S.-based studies can affect the generalizability of the findings to other non-Eurasian populations. Survival rates and treatment options for retinoblastoma are largely dependent on time of diagnosis. Delays in diagnosis and mortality are both significantly higher in lesser developed countries than in developed countries (Singh & Daniels, 2016). Time from onset of symptoms to diagnosis and the start of treatment have been found to vary by country with lag times of 1.5 months (United States) compared with 10 months (East Africa; Singh & Daniels, 2016). The enucleation rate of retinoblastoma patients in China has decreased from 91% to approximately 42% in the past 10 years (Gao et al., 2016; Zhang et al., 2018), while 90% of survivors in the Indian study received an enucleation as treatment for their retinoblastoma (Batra et al., 2015). Conversely, enucleation rates have been reduced at a major treatment facility in the United States to less than 10% due to advances in treatment options (Abramson et al., 2015). The increased proportion of patients with advanced disease in India can contribute to the lower HRQOL results in this study. The reduced resources in this country may have contributed to the low ratings reported for social and school domains. The National Health Service in Europe differs from the health care delivery model in the United States and can have unknown effects on quality and provision of services that could affect HRQOL.

Contradictory findings in HRQOL may be partially attributed to methodological issues and the variety of measurement tools utilized, as well as a lack of conceptual clarity (Fulton, Miller, & Otte, 2012). There is no consensus for any one instrument to serve as the gold standard for measuring HRQOL in children with cancer. Therefore, it is difficult to compare and replicate research, as well as generalize results (Anthony et al., 2014). Many studies have reported childhood cancer survivors having overall HRQOL comparable to nonsurvivors, with the identification of subgroups at increased risk of impairment in individual health domains (Alessi et al., 2007; van Dijk, Huisman, et al., 2007; Zeltzer et al., 2009). Due to the rarity of retinoblastoma, most disease-specific studies have small sample sizes, limiting their statistical power. All studies examining HRQOL in retinoblastoma survivors have been single-institution, cross-sectional studies. Larger cohort studies involving survivors of multiple types of childhood cancers, including retinoblastoma, have greater sample sizes, but are not able to identify outcomes specific to the treatment and course of retinoblastoma. Both large cancer registry studies in this review identified retinoblastoma survivors as having worse HRQOL than the other childhood cancer survivors in these studies (Alessi et al., 2007; Rueegg et al., 2013). There is a lack of studies examining the effect of visual acuity on HRQOL in retinoblastoma survivors and using a disease-targeted measure.

This literature review showed discrepancies between parent-proxy versus child self-reports of HRQOL which has been previously reported (Cremeens, Eiser, & Blades, 2006). Parent reports of worse HRQOL may be due to an overestimation of emotional distress in their child and subsequent underestimation of the ability of their child to adapt to their disease and its treatment (Batra et al., 2016). Other studies of pediatric chronic illnesses have reported similar findings (Forinder, Lof, & Winiarski, 2006; Lambert et al., 2009; Wengenroth et al., 2015). While an older study only assessed parent-reported HRQOL, most current studies recognize the importance of self-reported HRQOL by the survivors. However, parent-proxy report can provide meaningful insight when self-report is not an option. Support for the reliability and validity of parent-proxy reports of HRQOL has been demonstrated (Varni, Limbers, & Burwinkle, 2007) and including them in addition to child self-reports provides a more comprehensive view of HRQOL in survivors of childhood cancer (Wengenroth et al., 2015). Furthermore, a parent's perception of their child's HRQOL is often the driving factor in health care utilization (Janicke, Finney, & Riley, 2001). Since retinoblastoma is diagnosed and treated at a very young age, assessing parents' perception of their child's HRQOL is reasonable. However, the parent's perception may be altered based on their own experience of the cancer diagnosis and treatment.

The reviewed studies used a variety of normative samples as comparative groups, with most studies utilizing siblings or a population sample provided by the selected instrument. Only one study recruited healthy children receiving routine eye examinations as a control group (Zhang et al., 2018). No studies actively recruited gender-, race/ethnicity-, or age-matched control groups. Studies using siblings as controls argue that they are exposed to similar environmental circumstances and share common ethnicity, culture, genetics, and socioeconomic status (Zeltzer et al., 2009). However, siblings can be affected by their relationship with a sibling with cancer and can have an increased risk for psychological distress (Buchbinder et al., 2011; Cantrell, 2010). Furthermore, since siblings would be expected to share similar health outcomes as the survivor (compared with a randomly selected individual from the population), assumptions of independence for statistical analysis of data may be violated if not adjusted for clustering (Leisenring et al., 2009). Population normative data allow for comparison to a standardized sample within a geographical area;

however, these data do not account for individualized differences such as areas overrepresented by certain ethnicities. Currently, no studies have examined HRQOL in retinoblastoma survivors utilizing age-, gender-, and race/ethnicity-matched controls from the same geographic region.

Few studies in the retinoblastoma population have utilized a conceptual or theoretical framework to guide the research. Future studies should address these gaps in order to show congruency in both the operational definition of HRQOL and the instrument selected to measure it.

Summary

This comprehensive review of the literature supports the need for further investigation of HRQOL in the retinoblastoma population who have undergone treatment in the United States. Previous results exemplify the need for additional studies examining individual domains of functioning and well-being in retinoblastoma survivors by utilizing generic and disease-targeted measures. Self-reported HRQOL provides the individual's perspective and eliminates the potential biases associated with proxy reports. Future HRQOL research will become a more critical outcome measure as treatment options change in an attempt to salvage vision and reduce the reoccurrence of malignancies in this high-risk population.

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CHAPTER THREE: CONCEPTUAL FRAMEWORK

This chapter provides an analysis of Wilson and Cleary's HRQOL model (1995) and the modifications by Ferrans and colleagues (2005) to assess individuals with chronic medical conditions. The Ferrans and colleagues revised model will provide the foundation for assessing HRQOL in AYA RB survivors. This chapter will also describe the conceptual differences between HRQOL and overall QOL and the underlying assumptions. Finally, this chapter presents the resulting conceptual framework used in the study examining determinants of HRQOL in AYA RB survivors.

Health-Related Quality of Life versus Overall Quality of Life

The concept of QOL has existed for decades, originating as a factor to consider in health care decision-making especially in times of improved technology and longer life expectancy. Nursing research into QOL has centered on examining and comparing responses to disease and treatment, demonstrating the effects of rehabilitative approaches, and identifying vulnerable periods in the health-illness continuum when QOL is at its low point (Padilla, Grant, & Ferrell, 1992). While the focus on QOL as an outcome in health care is now universally accepted, there is still some debate about its definition (Moons, Budts, & De Geest, 2006). Health-related quality of life is a concept within QOL and indicates functioning and well-being aspects of health (Sandau, Bredow, & Peterson, 2013). While QOL has been conceptualized broadly in many ways such as life satisfaction, happiness, and achievement of goals, HRQOL is often viewed based on the World Health Organization (WHO) definition of health and is operationalized by assessing physical, mental, and social domains (Moons et al., 2006). The WHO's definition of health is "a state of complete physical, mental and social well-being and not

merely the absence of disease or infirmity" (World Health Organization, 1948, p.13). Thus, HRQOL differs from overall QOL.

Both functioning and subjective well-being in physical, mental, and social domains of health are part of HRQOL (Hays & Reeve, 2008). Functioning can be observed and reported by someone other than the target individual, while well-being is an internal, subjective perception, not directly observable by others. Therefore, agreement between proxy and self-reports of HRQOL tend to be better for functional than emotional well-being domains (Magaziner, Zimmerman, Gruber-Baldini, Hebel, & Fox, 1997; Hays & Reeve, 2008).

For this study, HRQOL is defined as a multidimensional construct including physical, mental, and social components of well-being and function as perceived by the individual and/or other observers (Ravens-Sieberer et al., 2006). Overall QOL is defined as life satisfaction, as rated by the individual. This perception is within the context of the culture and value systems in their life as well as goals, concerns, standards, and expectations. Overall QOL can be influenced by a variety of factors including physical and mental health, social relationships, personal beliefs, and the environment (WHO, 1994). While QOL is a global, subjective assessment of one's satisfaction with life, HRQOL describes aspects of life that relate to health, disease, and disability/impairment (Moons, Budts, & De Geest, 2006).

Assumptions

With any theoretical framework, it is important to identify assumptions, or what is accepted as true without the need for evidence or proof. The assumptions for this conceptual framework are listed in Table3.1 and explained below.

Table 3.1: Health-Related Quality of Life (HRQOL) Assumptions

HRQOL is a multidimensional construct
HRQOL is subjective
HRQOL can be positively and negatively influenced
HRQOL is a dynamic construct
Adolescents and young adults have the cognitive capacity to self-evaluate

Health-related quality of life is a multidimensional construct.

Health-related quality of life is a multidimensional construct reflecting physical, mental, and social domains of health (Ravens-Sieberer et al., 2006). While additional domains such as spirituality (Verghese, 2008) have also been evaluated, the three most consistently included dimensions include physical, psychological (mental or emotional), and social. Within these three domains exist multiple components such as symptoms, functioning, and affect. This multidimensionality allows for a large number of points along a continuum where HRQOL can be measured (Testa & Simonson, 1996).

Health-related quality of life is subjective.

Health-related quality of life is the perception of one's life from the view of the individual (Ravens-Sieberer et al., 2006). The same illness can affect different people in different ways. While "objective" indicators are important as measures of HRQOL, they should be considered supplementary to subjective reports (Ferrans,1990). Individuals serve as the best source for evaluation of their HRQOL (Sousa & Williamson, 2003).

Although a patient's self-report of HRQOL is the ideal measurement method, proxy report is often necessary when an individual is unable to self-report due to clinical or

developmental status. Healthcare providers and family members may serve as proxies, but their individual perspective of HRQOL will influence their reports. Proxy respondents tend to underestimate patients' HRQOL (Sprangers & Aaronson, 1992) and agreement is better for observable domains such as physical functioning rather than psychosocial domains (Varni, Limbers, & Burwinkle, 2007). Parent-proxy reports should not be a substitute for child self-reports, because parents' own distress influences their perception of their child's HRQOL (Varni, Limbers, & Burwinkle, 2007).

Health-related quality of life can be positively and negatively influenced.

Historically, HRQOL has been measured in terms of daily limitations due to health without consideration of positive influences (Hyland, 1992). However, illness may be positively perceived depending on an individual's personality or disposition toward life (Moons et al., 2006). A positive outlook after cancer has been attributed to benefit finding, posttraumatic growth, and resilience (Barakat, Alderfer, & Kazak, 2006; Zamora et al., 2017; B. J. Zebrack et al., 2012). Childhood cancer survivors' perception of positive consequences of cancer has been shown to be associated with HRQOL (Castellano-Tejedor et al., 2015; Zebrack & Landier, 2011). In one study, adolescent childhood cancer survivors reported more positive consequences from cancer (such as a changed perspective of life's meaning and a positive self-perception) than negative (Castellano-Tejedor et al., 2015). Thus, the conceptualization of HRQOL should include the possibility of both positive and negative impacts (Moons et al., 2006).

Health-related quality of life is a dynamic construct.

Health-related quality of life is not static and changes over time and depends on the health-illness experience. An individual's assessment of their HRQOL is dependent not only on their developmental stage but also their illness trajectory (Taylor, Gibson, & Franck, 2008). This

change over time occurs because an individual's experiences change their expectations, and individuals evaluate their HRQOL by comparing their expectations with their experience (Carr, Gibson, & Robinson, 2001).

Discrepancies between HRQOL reports in child and adolescent versus adult RB survivors may be due to this change over time. It is possible younger survivors rate their emotional HRQOL higher than adults because they are less knowledgeable of their cancer diagnosis and too young to have yet suffered negative psychological consequences (van Dijk, Huisman, et al., 2007). As this population matures both developmentally and psychologically, their perception of HRQOL may also shift.

Adolescents and young adults have the capacity to self-evaluate.

An underlying assumption of this model is that the individual must have the cognitive capability to self-assess and report their perceptions of HRQOL. Adolescents and young adults can formulate abstract thought and can analyze situations in terms of cause and effect (Piaget, 1962). Adolescents can evaluate their life and the meaning of life and are able to provide meaningful HRQOL reports. This study will incorporate the AYA's perspective of living with their chronic disease and its treatments, and the influence of these factors on their HRQOL.

Health-Related Quality of Life Theoretical Framework: History and Development

Wilson and Cleary (1995) developed a middle-range theory with a broad scope to conceptualize the relationships between clinical variables and measures of HRQOL. Middle-range theories are structures of two or more identified concepts concerning a phenomenon linked by a hypothesized relationship (Cody, 1999). The framework is adaptable to a variety of patients across a spectrum of ages, illnesses, cultures, and backgrounds. However, individuals who are incapable of defining their own QOL such as infants, comatose patients, or those with limited functioning do

not fit this framework. The Wilson and Cleary model is a causal framework that specifies a pathway and proposes fundamental relationships between concepts, categorizing outcome measures according to underlying health concepts. The five main components of this framework include biological and physiological variables, symptom status, functional status, general health perceptions, and overall QOL. Wilson and Cleary (1995) refer to these concepts as levels, each "existing on a continuum of increasing biological, social, and psychological complexity" (p. 60). While the arrows point in only one direction, the authors emphasize that this does not imply that reciprocal relationships cannot exist. Further, although there are not arrows from each box to all others, only from one to the next, this does not mean that there are not relationships between non-adjacent levels. However, the authors believe this model represents the primary underlying relationships between concepts (Figure 3.1

Figure 3.1: Wilson and Cleary's Model of Health-Related Quality of Life

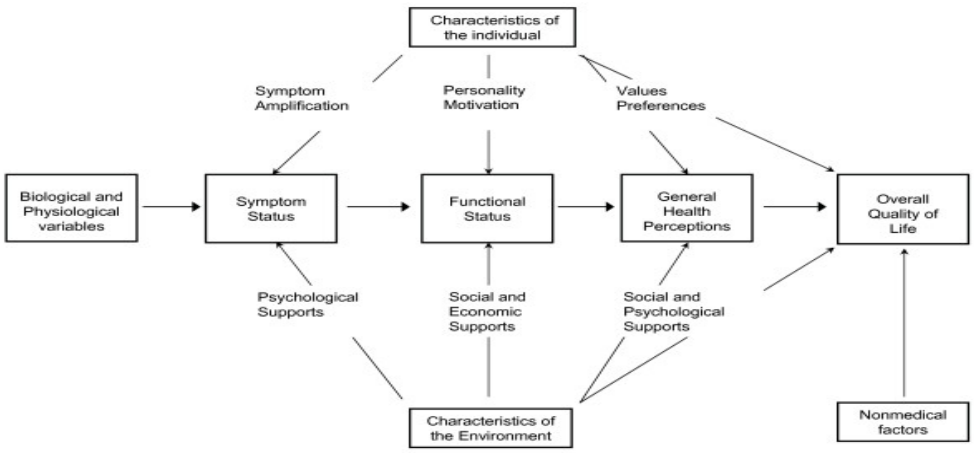


Figure 3.1. Health-related quality of life conceptual model. From "Linking Clinical Variables with Health-Related Quality of Life: A Conceptual Model of Patient Outcomes," by I.B. Wilson and P.D. Cleary, 1995, *JAMA, 273* (1) 59-65. Copyright 1995. Reprinted with permission.

Wilson and Cleary's HRQOL theoretical framework was later modified by Ferrans and colleagues (Ferrans et al., 2005) by adding arrows to show that biological function is influenced by characteristics of the individual and the environment, and deleting non-medical factors and labels on arrows which restricted relationships between concepts (Figure 3.2).

Above and below the main levels are the characteristics of the individual and the characteristics of the environment, respectively. Wilson and Cleary (1995) included these two characteristics in their framework but did not define or describe them within the text. However, Ferrans and colleagues (2005) cover these characteristics extensively, providing a theoretical basis and examples for each. While Wilson and Cleary included labeled examples on the arrows pointing from these two concepts to each of the previous five (excluding biological and physiological variables), Ferrans and colleagues dropped these descriptors in the revised model, because they restrict characterization of the relationships. They also included arrows from characteristics of the individual and environment to biological function (renamed from biological and physiological variables) and deleted the non-medical factors box that had been included as a separate concept influencing overall QOL. All non-medical factors are instead placed in the characteristics of either individual or environment categories. Therefore, the revised model is more concise and clearer than the original and provides a nursing focus (Figure 3.2

Figure 3.2: Revised Wilson and Cleary Model of Health-Related Quality of Life

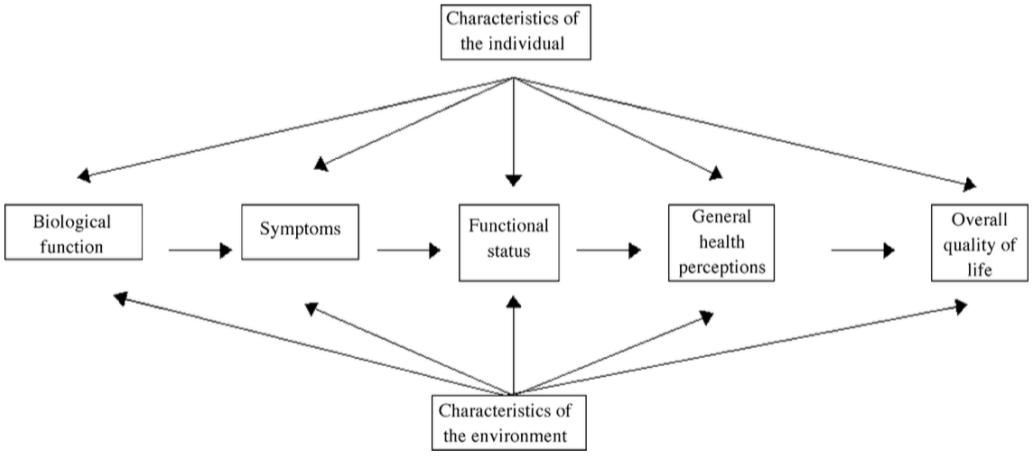


Figure 3.2. Conceptual Model of Health-Related Quality of Life. From "Conceptual Model of Health-Related Quality of Life," by C.E. Ferrans, J.J. Zerwic, J.E. Wilbur, and J.L. Larson, 2005, *J Nurs Scholarship*, 37(4), 336-342. Copyright 2005 by John Wiley and Sons. Reprinted with permission.

Concepts

The basis for the revised HRQOL conceptual model has five main levels of health concepts.

Biological function.

The first concept is biological function. This concept focuses on cells, organs, and organ systems. Examples include diagnoses, laboratory values, physiological function measures, and physical examination findings. Alterations in biological function can affect all aspects of health and any or all concepts that follow in the model (Ferrans et al., 2005).

Symptoms.

A symptom is defined as "a patient's perception of an abnormal physical, emotional, or cognitive state" (Wilson & Cleary, 1995, p. 61). Moving from biological function to symptoms shifts the focus from a cellular to an organism level. The concept of symptoms incorporates

physical, psychophysical, and psychological symptoms and is subjective (Wilson & Cleary, 1995). Symptoms can be measured by a variety of instruments.

Functional status.

Functional status is the third concept in the theoretical framework of HRQOL. It is a multidimensional concept which refers to the ability to perform tasks and incorporates the four domains of physical, social, role, and psychological function (Wilson & Cleary, 1995). Psychological functioning refers to the ability to accomplish a task that requires psychological health (e.g., making an important decision or handling a stressful situation), where psychological symptoms include anxiety/depression (Wilson & Cleary, 1995). Ferrans and colleagues (2005) emphasize optimization of function rather than disability or loss of function.

General health perceptions.

The fourth concept is general health perceptions. This concept is a subjective rating that integrates all the previous concepts in the framework (Wilson & Cleary, 1995). The concept of general health is influenced by biological factors, symptoms, and functional status, but is different than any of these concepts, and thus requires its own measure (Ferrans et al., 2005). General health perceptions can be measured with a single global question rating health on a polytomous response scale from poor to excellent (Ferrans, et al., 2005).

Overall quality of life.

The last main concept in the framework is overall QOL. It is a subjective assessment of well-being and life satisfaction which is related to HRQOL as well as additional life experiences (Wilson & Cleary, 1995). It is a global judgement of how happy or satisfied an individual is with their life overall (Ferrans, et al., 2005). An individual's values and preferences affect their rating of overall QOL (Wilson & Cleary, 1995). For example, an illness that makes one person

feel like life is not worth living, can be considered as only a minor nuisance to someone else. Thus, assessment of overall QOL should also include a measure of the importance of various aspects of life to the individual (Ferrans et al., 2005).

Characteristics of the individual and environment.

The final components of the framework are characteristics of the individual and environment. Characteristics of the individual can be demographic, developmental, psychological, or biological and can affect each of the five main concepts of the framework. Characteristics of the environment are either social or physical and can also affect all concepts (Ferrans et al., 2005). Characteristics of the individual can affect the concept of biological function by influencing an individual's resilience and biological susceptibility (Ferrans et al., 2005). Characteristics of the environmental also influence biological function. For example, exposure to secondhand smoke leads to respiratory ailments, and living in poverty increases risk for nutritional deficiencies. Characteristics of the individual and the environment can also influence the experience, evaluation, and interpretation of symptoms as well as functional status, general health perceptions, and overall QOL (Ferrans et al., 2005). Conversely, in the revised framework, arrows have been added from characteristics of the individual and the environment to each of the five main concepts to demonstrate these relationships (Ferrans et al., 2005).

Evolution of Model

Sousa and Kwok (2006) examined the Wilson and Cleary HRQOL model using structural equation modeling. In patients with human immunodeficiency virus-associated illnesses, the authors demonstrated significant relationships between concepts of the model and found that the hypothesized model fit the data well (Sousa & Kwok, 2006). The authors examined the model both with and without a physiological variable as well as a modified model with an additional

path from symptom status to general health perceptions. The final modified model (Figure 3.3) was rejectable statistically ($\chi^2(130) = 40.16$, $p < 0.0001$) but displayed acceptable comparative fit index (CFI=1.0) and a root mean square error of approximation (RMSEA =0.042) indicated a close fit. The authors found a significant association from symptom status to functional health, suggesting that patients with more symptoms are more likely to perceive a decrease in their functional health. Further, a significant relationship between symptom status and general health perceptions and functional health and general health perceptions suggested that patients with more symptoms and worse functioning had worse general health perceptions. Statistically significant relationships were also shown between symptom status and overall QOL and general health perceptions and overall quality of life, indicating that patients who reported fewer symptoms and better perceived general health reported better overall QOL. Symptom status accounted for 49% of the variance in functional health, while symptom status along with functional health accounted for 63% of general health perceptions. Symptom status and general health perceptions accounted for 38% of the variance in overall QOL (Sousa & Kwok, 2006). Accordingly, the author's analysis supports the hypothesized relationships between the concepts of the Wilson and Cleary HRQOL conceptual model.

Figure 3.3: Alternative model without physiological variables and with an additional path from symptom status to general health perceptions.

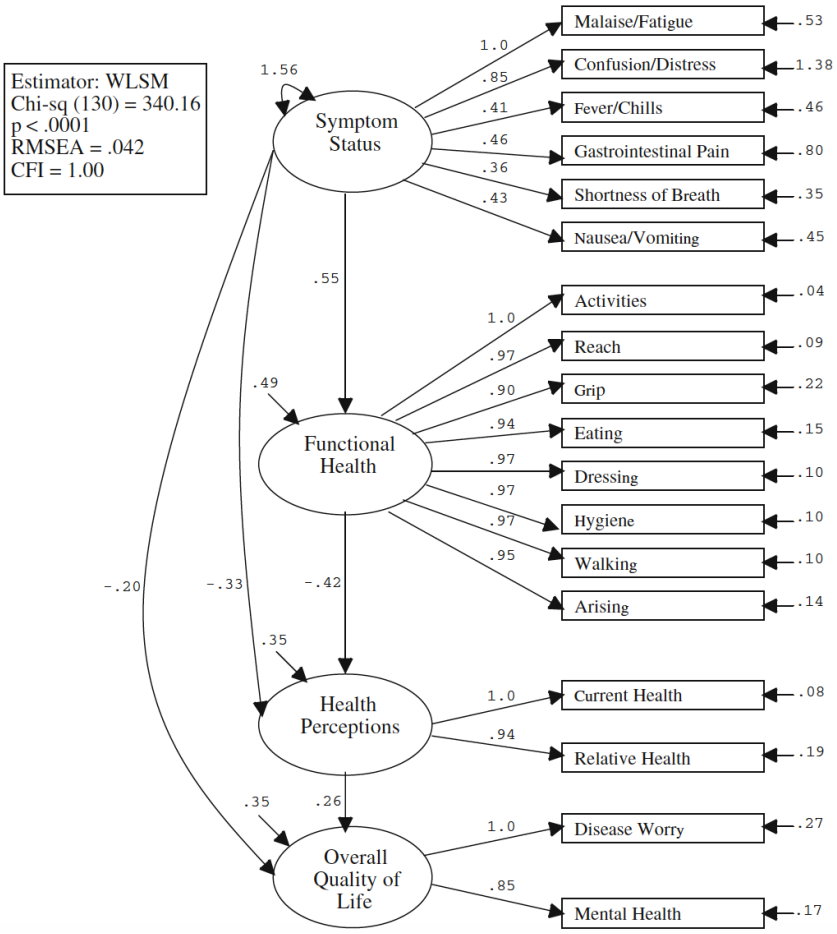


Figure 3.3. Structural equation modeling. From "Putting Wilson and Cleary to the test: Analysis of a HRQOL Conceptual Model using Structural Equation Modeling,'' by K.H. Sousa and O. M. Kwok, 2006, *Quality of Life Research*, *15*(4), 725-737. Copyright 2006 by Springer Nature. Reprinted with permission.

Ojelabi, Graham, Haighton, and Ling (2017) conducted a systematic review of the application of the Wilson and Cleary HRQOL framework in chronic diseases. Twenty-six studies were reviewed for the following three criteria: empirical evidence showing a causal relationship of the dominant concepts as proposed in Wilson and Cleary, whether the model followed a linear unidirectional path, and the relative effect of each variable (Ojelabi, Graham,

Haighton, & Ling, 2017). The findings of the review supported the Wilson and Cleary HRQOL framework. Non-adjacent links among the concepts demonstrated the non-linearity of the framework and indirect effects. For example, direct links were established between symptom status and general health perceptions in nine studies, and between symptom status and HRQOL in seven studies. Meanwhile, functional status was directly associated with overall HRQOL in seven studies (Figure 3.4). The framework explained between 23% and 72% of the variance in overall QOL indicating that modifications may be required to include all possible determinants of QOL in specific populations (Ojelabi et al., 2017).

Figure 3.4: Adjacent and non-adjacent linkages of Wilson and Cleary's model

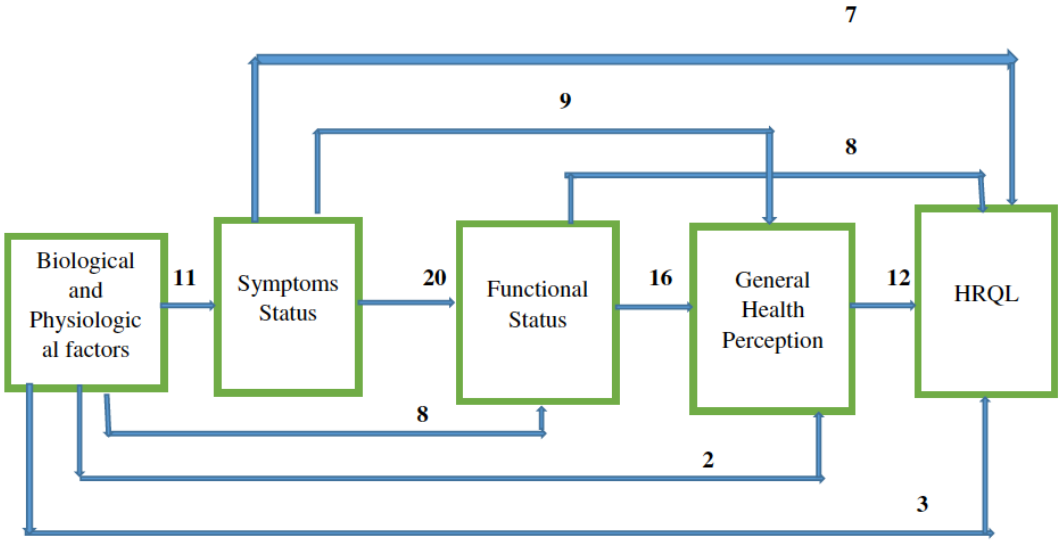


Figure 3.4. Review of the Wilson and Cleary HRQOL model. From, "A Systematic Review of the Application of Wilson and Cleary Health-Related Quality of Life Model in Chronic Diseases," by A. O. Ojelabi, Y. Graham, C., Haighton and J. Ling, 2017, *Health and Quality of Life Outcomes, 15*(1), 241. Copyright 2017 by the authors, open access, http://creativecommons.org/publicdomain/zero/1.0/. Reprinted with author permission.

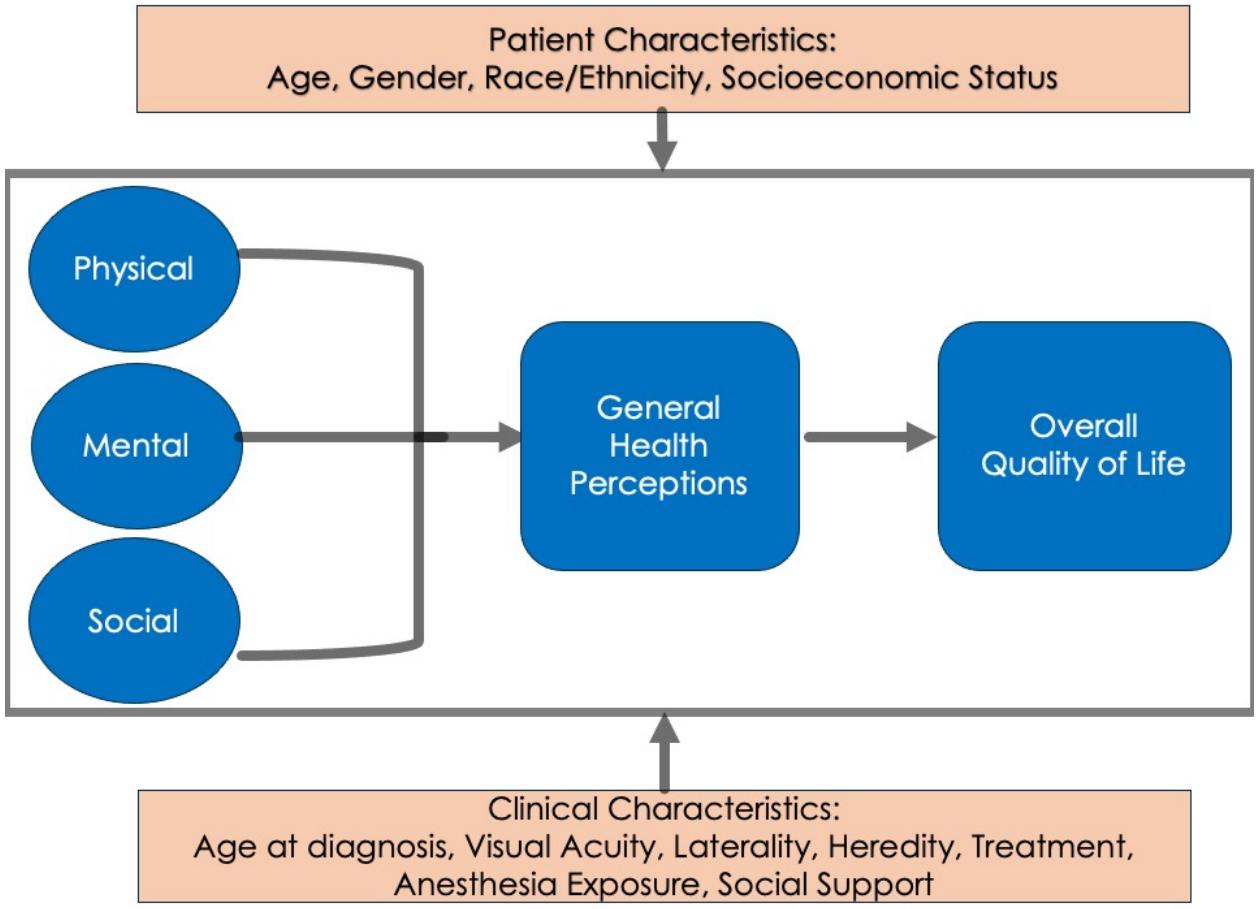
In another systematic review and critique of HRQOL models, Bakas and colleagues (2012) recommend the use of Ferrans and colleagues revised model. The Wilson and Cleary

framework, the Ferrans revised model, and the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF) were all analyzed using Bredow's criteria for evaluating theories including internal and external criticism (Bakas et al., 2012). The Ferrans and colleagues revised model was deemed to be more complete and clearer than the others due to defining of individual and environmental characteristics, clarification of relationships among concepts, and clear conceptual and operational definitions (Bakas et al., 2012). The future use of existing models of HRQOL rather than the development of a new model will allow for additional refinement as necessary while providing structure to the concept in multiple populations.

Conceptual Framework for HRQOL in AYA Retinoblastoma Survivors

The revised Wilson and Cleary HRQOL model by Ferrans and colleagues (2005) will be utilized to guide the conceptual framework for the proposed study addressing HRQOL in AYA RB survivors (Figure 3.5). Some adjustments have been made to the Ferrans and colleagues' model to make it applicable to the AYA RB survivor. The concept of biological function has been removed. Visual acuity is a measure that can represent biological function in RB patients. This measure is represented in the clinical characteristic's category rather than biological function. Symptoms and functional status have been combined to represent physical, mental, and social aspects of HRQOL. Measures of HRQOL include both symptoms and functioning in the domains of physical, mental, and social health.

Figure 3.5: Conceptual Framework of Health-Related Quality of Life for Retinoblastoma Survivors



Patient Characteristics

For this conceptual framework, characteristics of the individual and environment will be represented by patient and clinical characteristics respectively (Figure 3.5). Patient characteristics that would be applicable to the AYA RB population include age, gender, race/ethnicity, and SES. Clinical characteristics will include age at diagnosis, visual acuity, laterality and heredity, treatment exposure including chemotherapy, radiation, and/or enucleation as well as cumulative exposure to general anesthesia for multiple eye examinations as a young

child. These characteristics or variables can all potentially impact the AYA RB survivor's HRQOL.

The role of age as a predictor of HRQOL has been commonly measured in studies examining HRQOL with varying results. Age of the RB survivor was negatively associated with the KIDSCREEN dimensions of "psychological well-being", "parent relations and home life" and "social support and peers" with adolescents reporting worse HRQOL on these subscales than younger children (van Dijk, Huisman, et al., 2007). However, three other studies found no association between age and HRQOL in RB patients using the SF-36 subscales or total Peds QL score (Batra et al., 2016; Batra et al., 2015; van Dijk, Imhof, et al., 2007). The difference in these studies may have been related to the age range being either too broad or narrow (Batra et al., 2016; Batra et al., 2015; van Dijk, Imhof, et al., 2007). In childhood cancer survivors, older age was associated with worse SF-36 mental composite summary scores (Rueegg et al., 2013). These inconsistent findings related to age warrant further investigation as a predictor of HRQOL in the AYA RB survivors.

Gender was also explored as a predictor of HRQOL in the four previously mentioned studies of RB survivors but was not found to be statistically significant (Batra et al., 2016; Batra et al., 2015; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007). From a clinical standpoint, there is no established gender predisposition in RB (Ortiz & Dunkel, 2016). However, female gender was associated with better SF-36 physical and mental composite summary scores (Rueegg et al., 2013) in childhood cancer survivors. Interestingly, most studies of childhood cancer survivors found female gender to be associated with worse HRQOL (Alessi et al., 2007; Langeveld, Grootenhuis, Voute, de Haan, & van den Bos, 2004; Shankar et al., 2005; Zeltzer et al., 2008; Zeltzer et al., 2009). The authors speculate that these results could be

attributed to females being more likely than males to report symptoms (Alessi et al., 2007; Langeveld, et al., 2004). Since there are few studies, specifically examining RB survivors, continued exploration of gender differences in perception of HRQOL is needed.

Race or ethnicity has not been previously examined in HRQOL in RB survivors (Batra et al., 2016; Batra et al., 2015; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007). This may be attributed to the homogeneity of the study populations. The relationship between race/ethnicity and HRQOL in childhood cancer survivors is also unclear. In a population of childhood cancer survivors, Meeske and colleagues (2007) found that Hispanics rated their psychosocial functioning and total score on the PedsQL as significantly worse than non-Hispanics. However, no difference was found between Hispanic and non-Hispanic parent's ratings of their child's HRQOL in a later study (Meeske et al., 2013). Socioeconomic status and ethnicity have been shown to affect HRQOL ratings in other chronic disease populations (Cassedy et al., 2013; Quittner et al., 2010). In the U.S., Hispanic children with RB have been found to present with a greater extent of disease and thus, occur an increased rate of enucleation than non-Hispanic children (Truong, Green, Friedrich, Ribeiro, & Rodriguez-Galindo, 2015). These ethnic differences in diagnosis and treatment can lead to differences in HRQOL outcomes. Race/ethnicity will be included as a characteristic of the individual for this conceptual framework due to the diverse population in the City of Los Angeles.

Socioeconomic status and its relation to HRQOL has not been specifically examined in RB survivors. However, some components of SES (e.g., income, education, and occupation) have been included in previous studies with no significant associations or predictors of HRQOL identified (van Dijk, Imhof, et al., 2007;van Dijk, Huisman, et al., 2007). In contrast, SES factors have been previously found to be strongly positively associated with HRQOL in the

general adult population (Lubetkin, Jia, Franks, & Gold, 2005), and lower SES groups rate their HRQOL worse in those with chronic disease (Mielck, Vogelmann, & Leidl, 2014). The lack of information regarding SES and its correlation with HRQOL in the RB population may be due to previous studies being from countries with little socioeconomic variability. However, in the U.S., low SES has been found to be associated with greater extent of disease at diagnosis (Truong et al., 2015). Since extent of disease dictates treatment options and the chance of eye salvage in RB; these factors can ultimately affect HRQOL. The proposed study will be conducted in a socioeconomically diverse area within the U.S. and will use the Hollingshead Index to calculate SES (Hollingshead, 1975). The Hollingshead Index includes the four factors of education, occupation, sex, and marital status to determine social status.

Clinical Characteristics

Age at diagnosis of RB has long been known to be correlated with stage of disease and survival (Abramson, Ellsworth, Grumbach, Sturgis-Buckhout, & Haik, 1986; Rubenfeld, Abramson, Ellsworth, & Kitchin, 1986). Age at diagnosis has been included as a variable in previous studies of HRQOL in RB survivors with varying results (Batra et al., 2015; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007). Lower age at diagnosis was associated with better overall HRQOL as well as social and school domains in one study (Batra et al., 2015). However, age at diagnosis did not predict HRQOL in the other two studies (van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007). Since outcome in RB is highly correlated with age at diagnosis, this warrants further examination into the association between these two variables.

Maximizing visual acuity or visual function is a goal of treatment and surveillance in RB (Demirci, Shields, Meadows, & Shields, 2005). Visual acuity has previously been shown to be positively correlated with HRQOL and VRQOL in both children and adults (Freedman, Jones,

Lin, Stinnett, & Muir, 2014; van Gestel et al., 2010; Varma, Wu, Chong, Azen, & Hays, 2006). Loss of visual acuity can have a profound effect on an individual's mobility, social interaction, and ability to complete daily activities such as reading and driving (Varma, McKean-Cowdin, Vitale, Slotkin, & Hays, 2013). Visual acuity in child and adolescent RB survivors was negatively associated with the "self-perception" dimension on the KIDSCREEN (van Dijk, Huisman, et al., 2007). Furthermore, survivors with normal visual acuity in their non-affected eye reported better HRQOL on the physical well-being dimension than those that were visually impaired (van Dijk, Huisman, et al., 2007). Poor visual acuity (<20/200) in RB survivors has been found to occur in up to 50% of salvaged eyes but results depend on extent of disease, treatment, and location of tumor (Fabian et al., 2017). Future research is needed to explore the relationship between visual acuity and HRQOL and VRQOL in AYA RB survivors.

Laterality of disease is a variable that is closely associated with heredity in RB. Approximately two thirds of RB cases are unilateral while one third are bilateral (Shields & Shields, 2004). Bilateral RB is caused by a germline mutation which is hereditary (Shields & Shields, 2004). Unilateral RB is usually not hereditary, but 10-15% of children with unilateral disease may have a germline mutation (Shields & Shields, 2004). Even though there is an absent history of familial RB, they can carry a sporadic mutation in the RB gene. Whether or not the disease is sporadic or familial is determined by genetic testing which is not always performed. Hence, the term hereditary or non-hereditary is often used clinically to describe a known previous family history.

Adult survivors with a hereditary risk for RB reported significantly worse HRQOL on the SF-36 general health perceptions scale than non-hereditary survivors (van Dijk, Imhof, et al., 2007). However, heredity and laterality did not predict HRQOL (van Dijk, Imhof, et al., 2007).

Bilateral survivors were significantly more likely than unilateral survivors to experience fears of cancer recurrence, worry over their children being diagnosed with RB, guilt about the possibility of passing RB on to their children and avoidance of having children because of these feelings (Ford et al., 2015). These worries and concerns could potentially contribute to a decrease in HRQOL in familial RB survivors. The effect of laterality and heredity on HRQOL in AYA RB survivors deserves further examination.

Treatment for RB includes chemotherapy, focal treatment such as laser or cryotherapy, radiation, and/or enucleation. Previous studies examined treatment type as a predictor for HRQOL in the RB survivor but found no statistical significance (Batra et al., 2016; Batra et al., 2015; van Dijk, Huisman, et al., 2007; van Dijk, Imhof, et al., 2007). None of these studies reported whether correlations existed between treatment type and HRQOL. Parents of children who received chemotherapy reported that their children were significantly more limited in role and social activities due to emotional problems based on the Children's Health Questionnaire (CHQ-PF50) (Weintraub et al., 2011). Further, parents of children who received an enucleation reported significantly lower self-esteem in their children compared to parents of children who did not have an eye enucleated (Weintraub et al., 2011). Children who received chemotherapy reported significantly worse physical HRQOL on the PedsQL than those who did not receive chemotherapy (Weintraub et al., 2011). Further studies are needed to assess self-report versus parent-proxy report of HRQOL and its relation to treatment type.

Anesthesia exposure has not been examined in HRQOL studies of RB survivors. The RB population is unique in their exposure to anesthesia and can be exposed to as many as 50 general anesthetics before the age of four (Wilson et al., 2006). Children with RB require repeated examinations under anesthesia in order to provide treatment and monitor for recurrence of their

disease. While no studies have assessed the relationship of anesthesia exposure and HRQOL, the risk of general anesthesia exposure, procedural fear / anxiety and neurodevelopmental outcomes is well documented in the pediatric population (Flick et al., 2011; Ing et al., 2012; Stargatt et al., 2006; Wilder et al., 2009). Due to their frequent exposure to anesthesia at a young age and the potential for this exposure to cause long-term effects, anesthesia exposure (e.g., number of exposures and total duration) will be included as a variable. This study will evaluate if any association exists between this early anesthesia exposure and HRQOL as an adolescent or young adult.

The association between social support and HRQOL will also be examined. While social support has not been measured in RB survivors, the importance of social support in adolescent cancer survivors has been previously studied (Decker, 2007). A positive relationship between social support and HRQOL has been found in childhood cancer survivors (Cantrell & Lupinacci, 2008) with family support and peer relationships having the strongest impact (Sedmak et al, 2020). Social relationships are important during adolescence and young adulthood as individuals transition to independence. Social support was found to be a direct predictor of HRQOL in adolescents, reinforcing the importance of social relationships on well-being in this age group (Gomes et al., 2020).

Physical, Mental, and Social Domains

As previously stated, the operational definition of HRQOL for this study includes physical, mental, and social components of well-being and function.

Physical Domain

The physical domain will include *fatigue, pain, physical function, and sleep disturbance*. Low energy levels (Batra et al., 2015) and pain (Alessi et al., 2007) have been reported in RB

survivors. Deficits in physical performance in childhood cancer survivors were associated with poor HRQOL (Ness et al., 2008; Rueegg et al., 2012). Survivors of RB suffering from severe visual impairment or blindness were among the most severely affected by limitations in physical sports and daily activities, with 19% of survivors reporting any type of limitation (Rueegg et al., 2012). While no studies of RB survivors have measured sleep disturbance, a few have identified disordered sleep quality or insomnia in survivors of childhood cancer (Mulrooney et al., 2008; Zhou & Recklitis, 2014), however, none of the cancer-related variables (age at diagnosis, radiation, chemotherapy) predicted disordered sleep (Mulrooney et al., 2008).

Mental Domain

The mental domain will include *anxiety* and *depression.* While only few studies have assessed anxiety and depression in RB patients, mixed reports have been identified. Adults showed no difference compared to controls in one study (Ford et al., 2015) while reporting more anxiety, depression, and feelings of loss of control in another (van Dijk, Imhof, et al., 2007). Overall, adult RB survivors scored worse on the SF-36 mental health scale than the control group (van Dijk, Imhof, et al., 2007). Anxiety and depression have been identified in survivors of childhood cancer (Huang et al., 2017; Zeltzer et al., 2009). Therefore, anxiety and depression will be examined as the mental domain of HRQOL.

Self-esteem will also be included as part of the mental domain. Self-esteem has not been previously studied in the RB population, however studies with childhood cancer survivors have found correlations with HRQOL (Langeveld et al., 2004; Li et al., 2013, Cantrell & Lupinacci, 2008). Self-esteem in the AYA RB population may be influenced by facial appearance due to prothesis and limitations imposed by visual impairment (e.g., sports, career choices; Banerjee et

al., 2019). An individual's self-esteem influences their overall mental health and well-being; thus, it has been included in this study as a patient characteristic.

Social Domain

The social domain will consist of a measure of the *ability to participate in social roles and activities*. Children with RB have been reported to be limited in role/social activities due to emotional or behavioral problems (Weintraub et al., 2011). Children with bilateral RB and those who had received chemotherapy reported having lower participation levels and HRQOL. Authors reported significant correlations between parent-proxy PedsQL physical, social, and total HRQOL and their child's participation in activities (e.g., home, school, community). However, no significant correlation was found between participation and the child's self-reported HRQOL (Weintraub et al., 2011). In a qualitative study of RB survivors and parents, a subtheme that emerged from the data was the impact on social relationships caused by having RB (Hill, Gedleh, Lee, Hougham, & Dimaras, 2018). Vision-related worries may lead parents to limit their child's sporting activities due to fear of injuring their non-affected eye, and enucleated survivors may feel self-conscious about participating in social activities that could bring attention to their prosthetic eye. Limitations in the ability to actively engage socially can affect an individual's perception of their QOL and thus, should be included as part of HRQOL measurement.

General Health Perception

One's perception of health can influence their subjective appraisal of health, thus general health perception comes before overall QOL in the model. General health perception is often a single item measure used in many health status and HRQOL tools such as the SF-36. This single, general self-rated health question such as "In general, how would you rate your health?"

has a strong association with mortality and can help identify those at increased risk (DeSalvo, Bloser, Reynolds, He & Muntner, 2006).

In a study of adult RB survivors, the general health subscale on the SF-36 did not demonstrate a difference between RB survivors and controls, however hereditary survivors rated their general health as significantly more impaired than non-hereditary survivors (van Dijk, Imhof, et al., 2007). The authors reported that this view of general health reflected a realistic view of their situation. Hereditary survivors typically have bilateral disease, undergo more treatments, and have an increased chance of visual impairment and the development of secondary cancers than non-hereditary survivors (van Dijk, Imhof, et al., 2007). In the proposed study, general health perceptions will be measured with a single question asking the individual to rate their health on a scale of poor to excellent.

Overall Quality of Life

Overall QOL is the final concept or outcome of both the Wilson Cleary and Ferrans revised HRQOL model and will be assessed in the proposed study. Weintraub and colleagues (2011) reported overall QOL in RB survivors as similar to their age-peers. This was measured by their total score on the PedsQL. Meanwhile, Batra and colleagues (2016) used the same measure and reported significantly inferior overall QOL as compared to a control group. For this study, overall QOL will be measured using a single item question rating QOL as excellent, very good, good, fair, or poor. This type of measurement allows for the consideration of the components of QOL that are important to that individual. Furthermore, it does not combine the ratings of physical, mental, and social domains together to one total score which can influence overall QOL assessment. Overall summary scores do not allow evaluation of whether the

individual is more affected by their physical, mental, or social health. Thus, overall QOL will be measured separately from each individual health domain.

Chapter Summary

Health-related quality of life is a multi-dimensional, middle-range theory that is practical enough to allow researchers to develop testable hypotheses concerning HRQOL in different patient subgroups (Sandau, Bredow, & Peterson, 2013). The Ferrans and colleagues (2005) revised model of HRQOL provides an appropriate foundation for assessing HRQOL in AYA RB survivors. The proposed conceptual framework will examine the relationships between patient and clinical characteristics with the physical, mental, and social domains of HRQOL as well as the general health perceptions and overall QOL by self-report in AYA RB survivors.

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CHAPTER FOUR: SECOND MANUSCRIPT

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

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Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

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Abstract

Background: Retinoblastoma (RB) is a malignant intraocular tumor diagnosed in early childhood which requires extensive medical and surgical treatment at a young age. Health-related quality of life (HRQOL) is thought to be diminished due to visual impairment, facial deformities, and fear of recurrence or secondary cancer. However, few studies have identified variables associated with HRQOL among those with RB. **Purpose:** To compare HRQOL of adolescents and young adults (AYA) with RB to matched controls and to identify predictors of HRQOL in RB survivors. **Methods:** Using a cross-sectional design, 198 AYA (101 RB and 97 controls) completed HRQOL (PROMIS®-29 profile) and psychosocial questionnaires (Rosenberg Self-Esteem Scale, Multidimensional Scale of Perceived Social Support, and Hollingshead Index for Socioeconomic Status). Clinical variables were extracted from the medical record. Correlates of HRQOL were estimated using linear regression models. **Results:** RB survivors reported similar HRQOL compared to controls. Physical function, social support and self-esteem were lower in the RB group compared to controls., Visual acuity and self-esteem accounted for 52% of the variance in PROMIS physical health summary scores and self-esteem accounted for 38% of the variance in mental health summary scores. **Conclusion:** Despite deficits in physical function and self-esteem HRQOL in RB survivors was comparable to healthy counterparts. However, the majority of RB survivors in this study had normal visual acuity. Clinicians should explore ways to enhance self-esteem in RB survivors.

Key Words: Retinoblastoma, Health-Related Quality of Life, Quality of Life, Adolescent, Young Adult

Introduction

Retinoblastoma (RB) is a malignant central nervous system tumor that emerges from the developing retina and is caused by a hereditary or spontaneous mutation of the RB1 gene (Dimaras & Corson, 2018). RB is the most common intraocular childhood cancer, accounting for approximately 11% of cancers diagnosed in the first year of life with 95% of cases identified before the age of five (Wong, Tucker, Kleinerman, & Devesa, 2014). Between 300 and 350 children are diagnosed with RB each year in the United States (U.S.; Gombos, 2012) and a worldwide incidence of one in every 16,000 live births (Dimaras & Corson, 2018). The overall five-year survival rate has steadily improved to 97 % in the U.S. (Fernandes, Pollock, & Rabito, 2017). This improved survival is attributed to advances in diagnosis and treatment including a shift toward chemotherapy rather than radiation (Fernandes, 2017; Tamboli, Topham, Singh, & Singh, 2015).

The primary goal of RB treatment is the mitigation of cancer, while ocular salvage and vision preservation are secondary (Delhiwala, Vadakkal, Mulay, Khetan, & Wick, 2015). Options for treatment depend on tumor size and location, laterality, threat of metastatic disease, and visual prognosis (Shields & Shields, 2004). RB survivors must live with their chronic disease and treatment effects into adulthood. Survivors often suffer from visual impairment, facial deformities, and the continual fear of a recurrence or secondary cancer (van Dijk et al., 2010). Adult RB survivors have an increased risk of chronic medical conditions including poor visual acuity, malignant neoplasms, cataracts, severe hearing loss, and thyroid nodules (Friedman et al., 2016). While studies have identified long-term medical, visual, and psychosocial outcomes (Ford et al., 2015; Friedman et al., 2016; Narang, Mashayekhi, Rudich, &

Shields, 2012), little is known about health-related quality of life (HRQOL) in RB survivors in the U.S.

HRQOL is a multidimensional construct that includes functioning and well-being in physical, mental, and social health (Ruccione, Lu, & Meeske, 2013). Measuring HRQOL in the clinical setting can improve patient-provider communication and patient satisfaction, uncover unknown morbidities, facilitate clinical decision-making, and improve patient outcomes (Cantrell & Kelly, 2015). A recent literature review on HRQOL in RB survivors found few U.S. based studies with mixed results reflecting both positive and negative outcomes (Belson, Eastwood, Brecht, Hays, & Pike, 2020). The purpose of this study is to describe HRQOL in a U.S. cohort of adolescent and young adult (AYA) RB survivors compared to matched controls, and to identify predictors associated with HRQOL in the RB group.

Methods

Study Design

The study used a comparative, cross-sectional design. Age-, gender-and race/ethnicity-matched AYA with RB and healthy controls participated in the study between June 2019 and December 2020.

Sample and Setting

A convenience sample of AYA RB survivors were recruited from the Children's Hospital Los Angeles (CHLA) Vision Center. This center serves a racial and ethnically diverse population with various levels of medical complexity. Participants were included if they were between the ages of 14-26, had a diagnosis of RB, and were able to speak and read English. RB participants were excluded if they had severe developmental delay precluding active study participation and self-report or current diagnosis of a second malignant neoplasm. When COVID-19 occurred,

procedures were modified. The principal investigator instead mailed recruitment letters and made phone calls to potential RB participants in lieu of on-site recruitment.

Healthy controls were recruited from posted community flyers, word of mouth referrals and contact with controls in other clinical studies in Southern California. Controls were matched on age +/- 2 years, gender, and race/ethnicity, with an RB participant and self-reported no chronic medical (e.g., diabetes, hypertension, asthma) or psychiatric (e.g., depression, anxiety, bipolar) conditions. If eligible in either RB or control group, participation occurred on the same day or a future appointment was made to participate in the study.

Procedures

This study was approved by the Institutional Review Boards at CHLA (IRB # 19-00014) and University of California Los Angeles [UCLA] (IRB # 19-000305). At the time of study participation, written parental permission and child assent was obtained for participants under age 18, and informed consent was obtained from participants aged 18 and over. A study information sheet and consent form were read aloud to blind participants in the RB cohort and/or emailed to them to use with voiceover software if needed. A witnessed signature was obtained for adult blind RB participants and a waiver of signature for blind RB minors. Participants completed all measures utilizing an iPad while in clinic or at another designated location with data collated via Research Electronic Data Capture (REDCap; Harris, 2019; Harris, 2009). When COVID-19 lockdown occurred on March 13, 2020, procedures were modified, and a questionnaire link was emailed to participants. Participants received compensation and parking validation (for those at CHLA). Total time to complete all study measures was approximately 10-30 minutes.

Clinical and demographic data were obtained by participant completion of demographic form and / or medical record review. For RB participants, clinical variables extracted were age at diagnosis, visual acuity, laterality, heredity, treatment regime, and anesthesia exposure. Corrected visual acuity was assessed by the opthalmology team in the participants better eye using the Snellen scale (e.g., 20/20) and transformed to a logarithm of the minimal angle of resolution (logMAR) value by the principal investigator (http://www.myvisiontest.com). Results were categorized according to the World Health Organization International Classification of Diseases (ICD-10) guidelines as normal vision (>0.3 or 20/40), visual impairment (0.05-0.3), and blindness (<0.05 or 20/400; www.who.int). Treatment regime consisted of enucleation, chemotherapy, combination of enucleation/chemotherapy, or combination of enucleation/chemotherapy/radiation. Anesthesia exposure was measured by total duration of inhalational anesthesia in minutes and number of anesthetic exposures.

Measures

Socioeconomic Status

Socioeconomic status (SES) was measured using the Hollingshead Index (Hollingshead, 1975). The four factors of the Hollingshead Index include parental marital status, employment status, educational attainment, and occupational prestige. Education (scale 1-7) and occupation (scale 1-9) scores are assigned to each parent/guardian and then weighted (education X 3, occupation X 5) to obtain a single score (range 8-66). SES was divided into five categories including lower status (8-19), lower-middle status (20-29), middle status (30-39), upper-middle status (40-54), and upper status (55-66).

Health-Related Quality of Life Measure

The generic HRQOL measure used was the Patient Reported Outcomes Measurement Information System PROMIS®-29 profile v2.1 (Craig et al., 2014). The PROMIS® is a 29-item instrument which includes domains in physical (physical function, fatigue, sleep disturbance, pain interference and pain intensity) mental (anxiety, depression), and social (ability to participate in social roles & activities) health. The PROMIS®-29 profile consists of two summary scores (mental and physical health) which are calculated from weighted correlations of the domains (Hays, Spritzer, Schalet, & Cella, 2018). Raw scores are converted to T-scores with a mean of 50 and SD of 10 which is referenced to the U.S. general population average (Liu et al., 2010). Higher T-scores on the mental and physical summary scores indicate better HRQOL. For the functional domains, greater T-scores represent increased or better function while for the symptom domains greater T-scores represent greater symptom burden (e.g., greater anxiety or depression). Internal consistency reliability (coefficent alpha) estimates for the PROMIS®-29 domains range from .77 to .94, and the physical and mental health summary scores at .98 and .97, respectively (Hays et al., 2018). Multiple studies provide evidence of the validity of the PROMIS® measures (Cella et al., 2010; Cook et al., 2016; Rothrock et al., 2010) but they have not been previously used in the RB population. However, previous studies in the general pediatric oncology population support the validity of the PROMIS-29 (Hinds et al., 2013; Hinds, et al., 2019).

General Health Measure

The first question on the PROMIS® Global Health v1.2 scale was used to measure general perceived health (Hays, Schalet, Spritzer, & Cella, 2017). The question is as follows: "*In general, would you say your health is?"* with answer choices including *"excellent", "very good", "good", "fair", and "poor".* This single item has a product-moment correlation with the

PROMIS® four item global physical health scale of .81, and thus can be used alone to estimate the global physical health scores (Hays et al., 2015). However, the marginal reliability was only .52 for the single item compared to .81 for the PROMIS® Global health scale (Hays et al., 2015).

General Overall Quality of Life Measure

The second question on the PROMIS® Global Health v1.2 scale was used to measure overall quality of life (QOL; Hays et al., 2017). The question is as follows: *"In general, would you say your quality of life is?"* with answer choices ranging the same as the previous question. Overall QOL is a single item that measures subjective well-being and is one of four items in the PROMIS® global mental health scale (Hays et al., 2017). Palimaru and Hays (2017) examined associations of the overall QOL item with other PROMIS® global health items to assess the overlap between overall QOL and HRQOL. All correlations were statistically significant ($p <$ 0.001) and ranged from $r = 0.36$ (pain) to $r = 0.82$ (physical health; Palimaru & Hays, 2017).

Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (RSES) is a 10-item instrument and is the most widely used self-esteem scale (Blascovich & Tomaka, 1991; Rosenberg, 1989). The RSES uses an ordinal four-point Likert-type response scale ranging from strongly agree to strongly disagree. Total scores are recorded on a continuous scale with higher scores indicating higher self-esteem. Scores range from 0 to 30 with less than 15 suggesting low self-esteem. The mean internal reliability (Cronbach alpha) of the RSES was found to range from .81 to .91 (Schmitt & Allik, 2005; Sinclair et al., 2010) with test-retest correlations from .82 to .88 (Blascovich & Tomaka, 1991). The RSES has not been previously used in the RB population, however it has been previously used in other childhood cancer survivors (Langeveld et al., 2004; Tonsing & Ow, 2018).

Multidimensional Scale of Perceived Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item questionnaire measuring an individual's perception of their social support (Gregory D. Zimet, Dahlem, Zimet, & Farley, 1988). The MSPSS has three subscales for social support (friends, family, and significant other) and uses a seven-point Likert-type scale ranging from Very Strongly Disagree (1) to Very Strongly Agree (7). The four items for each subscale are summed and divided by four. A total score is created by dividing the sum of all items by 12. The average scores range from one to seven with higher scores representing greater perceived support. Cronbach's alpha reliability was found to be high (.85 to .91) with test-retest values (.72 to .85) indicating good stability (Zimet, Powell, Farley, Werkman, & Berkoff, 1990). The MSPSS has not been used in the RB population but demonstrated good internal consistency in AYA cancer survivors with a Cronbach's alpha of .93 and the subscales of family, friends, and significant others were .91, .89, and .94 respectively (Tremolada et al., 2016).

Data Analysis

An a priori power analysis was performed using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) to determine the sample size for this study. A sample size of 95 in the RB and control groups were determined using a two-tailed *t*-test with a significance level of 0.05 and 80% power to detect an effect size of 0.41. This effect size was based on the results of a previous study of HRQOL where children with RB perceived their QOL related to school (Peds QL) as significantly lower than an age-matched normative sample (t =2.23, $p < 0.01$, Cohen's d =0.41; Weintraub, Rot, Shoshani, Pe'er, & Weintraub, 2011).

Sample characteristics are presented for RB and control participants as means with SD and/or medians with inter-quartile ranges for continuous variables. Variables were examined for

normality and outliers. Outliers were examined for accuracy and representation of the target population and were not removed. The majority of continuous data had non-normal distributions (per Shapiro-Wilk's test of normality), and groups were compared using non-parametric statistics consisting of Mann-Whitney U or Kruskal-Wallis test for all continuous variables and Chi-squared for all categorical variables. Independent sample *t*-tests were used for a few dependent variables that were normally distributed. Transformation (both log and square root) of the physical health summary score was attempted without normality. Physical health summary scores did not have a symmetric distribution and were negatively skewed. Depending on the data distribution of the outcome variable, Pearson product moment or Spearman rank order correlation coefficients between all predictor and the two outcome variables (physical and mental health summary scores) were examined. Variables with p values < 0.15 for the correlations were included in a stepwise multiple regression. The software identified the sequence of entry of covariates into the statistical models using the forward method. Although there was non-normality of the physical health summary scores, linear regression was still performed rather than less robust regression methods. Normality of the residuals was assessed and while Kolmogorov-Smirnov and Shapiro-Wilk have p <0.001, plots of standardized residuals suggest that departure from normality may be only minor and should not substantially affect interpretation of results. Assumptions of multicollinearity and homoscedasticity (equal variance of the residuals) were met. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Version 26.0 for MAC [IBM; Somers, NY].

Results

A total of 184 RB survivors were identified from a clinic database, 61 were unable to be contacted via telephone or letter, and 123 were screened for eligibility. Of the 123 RB survivors,

7 were screened ineligible, 13 declined to participate, and 2 did not complete the study questionnaires for a total of 101 RB survivors enrolled (**Figure 4.1**). Furthermore, a total of 97 healthy controls matched on age +/- two years, gender, and race/ethnicity completed the questionnaires.

Sample Characteristics

Demographic characteristics of the RB and control group are summarized in **Table 4.1**. There were no statistically significant differences in age, gender, race/ethnicity, and SES between groups. There were significant differences in insurance coverage between the groups with more RB survivors receiving state assistance and more controls with private coverage. Retinoblastoma is a California Children's Services (CCS) eligible condition, and CCS provides assistance to families for treatment costs.

The clinical characteristics of the RB group are summarized in **Table 4.2**. The median age at RB diagnosis was 15 months, 43 (42.6%) had bilateral disease and 13 (12.9%) had a previous family history of RB. Out of those who received genetic testing (n=86), 40 (46.5%) had the RB1 gene (8 unilateral and 32 bilateral). For treatment, 40 (39.6%) had a combination of chemotherapy and enucleation, 89 (88%) had at least one eye enucleation, with the majority 87 (86%) having normal vision. The median number of general anesthetics per survivor was 14 (range 3-63 anesthetics), while the median duration of exposure to general anesthesia was 693 minutes (range 226-3603 minutes). Lastly, 19 (18.8%) had another chronic medical condition (e.g., asthma, hearing loss, and thyroid problems), 5 (5%) had a psychological condition (e.g., anxiety, depression, or ADHD), and only 4 (4 %) received treatment for a second malignant neoplasm or previous metastasis.

Health-Related Quality of Life and Psychosocial Variables Between Groups

Internal consistency reliability estimates (Cronbach's alpha) for the PROMIS®-29 domains in this study were as follows: .69 physical function, .86 anxiety, .92 depression, .88 fatigue, .80 sleep, .83 social, and .93 pain interference. Estimated reliabilities of the physical and mental health summary scores were .77 and .96 respectively. Cronbach's alpha for the RSES in this study was .90, and for the MSPSS was .93 for the total score and .94, .90 and .94 for the three subscales (family, friends, and significant other) respectively.

Mean PROMIS-29 physical function scores differed significantly between RB and controls (53.9 vs. 56.3, $p < 0.001$, $d = -0.24$, respectively). RB survivors reported more depressive symptoms than controls (49.7 vs. 47.4, $p = 0.051$, $d = 0.23$). However, the other PROMIS®-29 domains and the physical and mental health summary scores showed no significant differences between RB and controls (**Table 4.3**).

On the single-item measures of general health and overall QOL, RB survivors reported worse mean general health (53.2 vs. 55.1, $p = 0.05$, $d = -0.30$) and overall QOL than controls (50.56 vs. 53.28, $p= 0.011$, $d = -0.35$). Statistically significant lower social support was found in RB survivors compared to controls on all domains of the MSPSS except the family domain (significant others 5.5 vs. 6.0, $p= 0.003$, $d = -.38$; friends 5.3 vs. 5.8, $p = 0.018$, $d = -.33$; and total score 5.5 vs. 5.9, $p = 0.013$, $d = -0.34$). RB survivors reported statistically significantly worse self-esteem than controls (20.63 vs. 22.27, $p = 0.028$, $d = -0.31$).

Health-Related Quality of Life in the Retinoblastoma Group

Mental health summary scores were lower in females than males (53.0 vs. 55.6, $p= 0.042$). Females also reported more depression and anxiety than males. Physical health summary scores were statistically significant between visual acuity groups (normal, impaired, blind) with the visually impaired reporting worse physical health (56.3 vs. 44.1 vs. 47.0, $p <0.001$). While

unilateral survivors reported significantly worse physical function domain than bilateral survivors, the physical health summary scores were not significantly different. None of the other clinical variables (age at diagnosis [<=18 months/ > 18 months], laterality, heredity, chemotherapy, radiation, enucleation) were significantly associated with HRQOL.

Unique Associations of Other Variables with Health-Related Quality of Life

The list of significant variables associated with physical and mental health summary scores in the RB group are listed in **Table 4.4**. Visual acuity, laterality, RSES scores, and total inhalational anesthesia minutes were entered into the stepwise regression for physical health. Gender, MSPSS total scores, and RSES scores were entered for mental health. The final multivariate regression models for physical and mental health summary scores are listed in **Table 4.5**. Visual acuity and self-esteem were independent predictors of physical health, accounting for 52% (adjusted R^2) of the variance. Self-esteem was the only independent predictor of mental health and explained 38% of the variance.

Discussion

Our findings demonstrate that AYA RB survivors perceive their HRQOL similar to their healthy counterparts. Other studies have reported similar HRQOL between RB survivors and controls or normative samples (Feng et al., 2020; Mouw et al., 2017; van Dijk, Huisman, et al., 2007; Weintraub et al., 2011). Despite these findings, physical function was significantly worse in RB survivors compared to controls. This finding was like one study that examined adult survivors of childhood cancer in which the RB group had worse physical component summary scores compared to other cancer types related to visual impairments (Rueegg et al., 2013). However, other studies with RB survivors did not identify physical function deficits (Batra, et al., 2015; van Dijk, Imhof et al., 2007; Zhang, Gao, & Shen, 2018) or worse physical functioning

in the RB group (Feng et al., 2020) which could be due to differences in visual acuity or the lack of visual impairment within the study cohorts. This may explain our findings of similar physical HRQOL even with worse physical function as most of the sample had normal visual acuity in their unaffected eye. Another possible explanation is the lack of other physical functioning ailments associated with the condition. The other domains under physical health such as fatigue, ability to participate in social roles and activities, and pain were not significantly different between RB survivors and controls and contributed to the lack of difference in physical health summary scores. Furthermore, children with congenital birth defects or chronic medical conditions from birth often lack the ability to differentiate their state of wellness from "normal" because their only frame of reference is imbedded within their chronic illness. This is often referred to as the "disability paradox" where those with disabilities perceive a higher QOL due to their ability to produce and maintain a sense of balance between their body, mind, and spirit and adapt and find meaning in their lives (Albrecht & Devlieger, 1999).

RB survivors reported worse general health and overall QOL than controls on the two PROMIS® general health items. While these single questions are highly correlated to the physical and mental health summary scores respectively, reliability is lower and standard error of measurement is higher than the summary scores (Hays, et al., 2015; Hays et al., 2017). Summary scores provide a more comprehensive assessment of physical and mental HRQOL.

Our findings also showed the RB group to have more depressive symptoms than controls but this difference only trended toward significance. No mental health scores were significantly different between these groups. Conversely, one study found significantly worse mental HRQOL in adult RB survivors who reported feeling different from others and had a history of being bullied about their facial appearance and/or visual impairment/blindness (van Dijk, Imhof,

et al., 2007). We did not assess bullying or satisfaction with facial appearance in our study, so it is unclear if that contributed to depressive symptoms in the RB group. Another potential explanation for our findings could be the effects of the COVID-19 global pandemic and civil protests on the mental health of the control group. In the general AYA population, studies have shown increased depression and anxiety due to the COVID-19 pandemic and social isolation (Hawes et al., 2021; Loades et al., 2020; Wang et al., 2020) with females being affected more than males (Hawes et al., 2021). Our study cohort reflects the ethnically diverse Los Angeles community, and the impact of world events may have contributed to the lack of significance between groups as more controls were recruited during this time and females reported more depression and anxiety symptoms.

Our findings differed from three European studies from India, the Netherlands, and China which reported worse HRQOL in RB survivors associated with specific demographic or clinical factors such as disease severity and age at diagnosis (Batra et al., 2015), the age of participants and treatment received (Van Dijk, Imhof et al., 2007) and the socioeconomic status or quality of ocular prosthetics (Zhang et al., 2018). RB survivors in India were older at diagnosis contributing to more advanced stages of disease which limits treatment options and could have explained their findings of worse HRQOL (Batra et al., 2015). Adult RB survivors in the Netherlands had extensive radiation exposure, resulting in long-term effects related to the treatment era compared to current therapies. Radiation can have significant cosmetic effects on the eye resulting in orbital asymmetry and potential dissatisfaction with appearance (Mourits et al., 2018). Furthermore, the potential for dissatisfaction with facial appearance was found in RB survivors in China related to the families' SES and ability to purchase quality ocular prosthetics (Zhang et al., 2018). Our findings reflect a younger age at diagnosis, the current treatment era

with the use of minimal radiation, and predominately middle-class SES with insurance that covers ocular prosthetics. This may explain our findings of similar HRQOL compared to controls based on clinical and SES factors that possibly reflect a healthier RB cohort.

Self-esteem in RB survivors emerged as an independent predictor of physical and mental HRQOL. Other studies with childhood cancer survivors have found moderate to strong correlation between self-esteem and HRQOL (Langeveld et al., 2004; Li et al., 2013, Cantrell & Lupinacci, 2008). Low self-esteem is associated with depression in young adult college students (Choi et al., 2019) and pediatric cancer survivors (Cheung et al., 2019) which can affect HRQOL. Higher self-esteem is associated with better physical health due to decreased health risk behaviors and coping mechanisms which buffer stressors (Lu et al., 2018). Decreased self-esteem in the AYA RB population could be related to facial appearance and limitations imposed by visual impairment (e.g., sports, career choices; Banerjee et al., 2019).

Visual acuity was found to be an independent predictor of physical HRQOL. Since no participants in the unilateral group had visual impairment this finding is driven by the bilateral survivors. Other studies have also found that visual impairment affected physical HRQOL in RB survivors (Alessi et al., 2007; Rueegg et al., 2012; van Dijk, Huisman, et al., 2007) with more than half of RB survivors reporting physical problems due to limited peripheral vision and depth perception (Banerjee et al., 2019). These results emphasize the importance of visual preservation in the treatment of RB. Newer treatment options such as ophthalmic artery chemosurgery have decreased enucleation rates and increased retinal function, showing potential for improved visual function and ultimately HRQOL in the RB population (Abramson et al., 2015; Abramson, Francis, & Gobin, 2019; Brodie, Pierre Gobin, Dunkel, Kim, & Abramson, 2009).

Social support, in particular support from friends and significant others, were significantly different between groups. However, social support from family members may reflect the age of the cohort and most having normal visual acuity making them less dependent on family. Most adolescents and young adults are seeking acceptance from peers and independence from family. Lower perceived social support from friends and significant others in the RB group may be attributed to feelings of being different (e.g., eye prosthesis) and not being able to share with peers about their cancer experience (Lewis, et al., 2013).

Interestingly, we found no significant differences in HRQOL related to clinical variables such as treatment (chemotherapy, radiation, and/or enucleation) or genetic factors (RB1 gene positive). Adult hereditary RB survivors have reported impaired general health perception which can be related to their increased treatment exposure and risk of developing secondary malignancy (van Dijk, Imhof et al., 2007). It is possible our group of AYA may not fully comprehend the later life effects of hereditary RB, as parents have reported difficulties in discussing these consequences with their children (van Dijk, Huisman, et al., 2007). A previous study found that children with RB who received chemotherapy perceived their physical HRQOL to be lower than those who did not receive chemotherapy (Weintraub et al., 2011). Other studies with RB and other pediatric cancer survivors have not found treatment variables to be associated with or predictive of HRQOL (Batra et al., 2015; van Dijk, Imhof, et al., 2007; Zhang et al., 2018, Halvorsen et al., 2018; Meeske et al., 2007). Parents of children diagnosed with RB often have concerns about enucleation and/or the addition of chemotherapy to their child's treatment regime. These results reinforce that regardless of treatment type AYA RB survivors with good visual acuity have similar HRQOL as their peers.

Limitations

The strengths of this study include a relatively large sample size compared to previous studies of RB survivors, adequately powered to detect an effect size previously reported as significant, and the use of a matched control group. Furthermore, this study included a racially and ethnically diverse sample with a majority of participants identifying as Hispanic/Latino. No other HRQOL studies in RB survivors have included this subgroup of the population. However, this study also has some limitations. Although the linear regression models explained a quarter of the variance for physical and mental health, other factors not accounted for in this study contribute to HRQOL. Due to the cross-sectional design, it is not possible to determine any causal relationships between the independent variables and HRQOL. Since survivors were recruited from a single institution, generalizability to RB survivors from other settings is limited. Future multi-institutional studies should be conducted to increase generalizability of findings. In addition, selection bias cannot be ruled out as only survivors seeking active follow-up care and those who responded to letters or phone calls were recruited. Those lost to follow-up and non-participating survivors may have worse HRQOL.

A significant limitation of this study was the occurrence of the COVID-19 pandemic mid-recruitment. The effects of the pandemic on the HRQOL of RB survivors and healthy controls are indeterminant. This could reflect the lack of statistical significance between groups in the mental summary scores considering more controls were recruited during the pandemic than RB survivors which may not be reflective a normative sample.

Conclusions

The findings of this study show that a sample of AYA RB survivors in the U.S. have comparable HRQOL compared to healthy age-, gender- and ethnicity-matched counterparts. Physical function and self-esteem were worse in the RB group compared to controls with only

self-esteem and visual acuity explaining the majority of HRQOL. However, the greater part of our cohort had normal visual acuity. Continued assessment of visual acuity is warranted with aging as are interventions to improve self-esteem. Future use of vision or disease specific measurements may identify more subtle changes or clinical factors that can contribute to HRQOL in RB survivors.

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Figure 4.1

Flow Diagram of Recruitment Process for Retinoblastoma Survivors

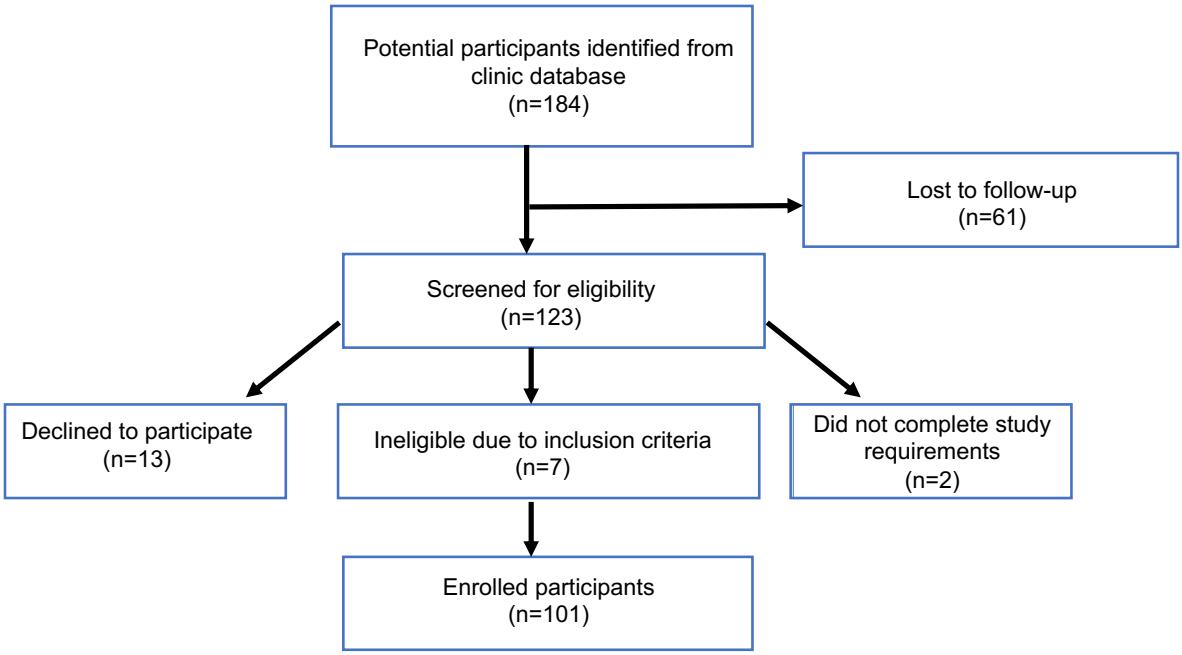

Table 4.1

Comparison of Characteristics Between Retinoblastoma Survivors and Healthy Controls

Characteristic	RB Survivors (n= 101)	Healthy Controls (n= 97)	*P*-value
Age, years (Md, IQR)	17 (15, 19)	17 (16, 19)	.194[a]
	N (%)		
Gender			
Male	50 (49.5)	47 (48.5)	.995[b]
Female	51 (50.5)	50 (51.5)	
Race/Ethnicity			
Latino/Hispanic	66 (65.3)	62 (63.9)	.995[b]
White	16 (15.8)	16 (16.5)	
Black/African American	4 (4)	4 (4.1)	
Asian/Pacific Islander	10 (9.9)	11 (11.3)	
Other	5 (5)	4 (4.1)	
SES			.085[b]
Lower status	14 (14)	14 (14.6)	
Lower-middle status	22 (22)	17 (17.7)	
Middle status	27 (27)	17 (17.7)	
Upper-middle status	25 (25)	22 (22.9)	
Upper status	12 (12)	26 (27.1)	
Unknown	1	1	
Insurance	(N=99)	(N=96)	<0.001[b]
Private (PPO/HMO)	30 (30.3)	48 (50)	
Public (Medi-Cal/CCS)	62 (62.6)	29 (30.2)	
No insurance (self-pay)	5 (5.1)	3 (3.1)	
Unsure	2 (2)	16 (16.7)	

[a]Mann-Whitney test; [b] Chi-square; RB= Retinoblastoma; Md= Median; IQR = Interquartile Range; PPO= Preferred Provider Organization; HMO= Health Maintenance Organization; CCS= California Children's Services

Table 4.2

Clinical Characteristics of Retinoblastoma Survivors (n=101)

Characteristics	***N***	**%**
Age at diagnosis, months (Md, IQR)	15	(8, 23)
Visual acuity		
Normal vision	87	86
Visual impairment	8	7.9
Blindness	6	5.9
Laterality		
Unilateral	58	57.4
Bilateral	43	42.6
Family history of RB		
No	88	87.1
RB 1 mutation, n=86		
Yes	40	46.5
Chemotherapy		
Yes	64	63.4
Radiation therapy		
No	86	85.1
Enucleation		
Yes	89	88.1
Enucleation laterality, n=89		
Unilateral	86	96.6
Bilateral	3	3.4
Treatment regime		
Enucleation only	35	34.7
Chemotherapy only	9	8.9
Enucleation/chemotherapy	40	39.6
Enucleation/chemotherapy/radiation	14	13.9
Other	3	3.0
Anesthesia exposure, n=95, (Md/IQR)		
# anesthetics per patient	14	8, 29
Total inhalational anesthesia (minutes)	693	402, 1405
Chronic medical condition	19	19
Chronic psychiatric condition	5	5
Second malignant neoplasm/ metastasis	4	4

Md= Median; IQR = Inter-Quartile Range

Table 4.3
Comparison of HRQOL between Retinoblastoma Survivors and Healthy Controls

Variables	Mean (SD) and / or Median (IQR) RB (n= 101)	Controls (n=97)	*P*-value
HRQOL (PROMIS®-29 Profile)			
Symptoms‡			
Anxiety	53.3 (8.7)	52.4 (8.1)	0.502[a]
	53.8 (48.2, 59.5)	52.9 (47.9, 57.5)	
Depression	49.7 (8.9)	47.4 (8.0)	**0.051[a]**
	49.1 (42, 56.5)	41 (41, 52.4)	
Fatigue	44.5 (9.2)	44.7 (8.3)	0.803[a]
	45.3 (33.7, 51)	45.9 (39.7, 51)	
Sleep Disturbance	47.8 (8.7)	46.7 (6.8)	0.311[b]
	47.7 (41.2, 53.6)	46.4 (41.8, 51.7)	
Pain Interference	45.4 (6.9)	44.7 (5.6)	0.665[a]
	41.6 (41.6, 50)	41.6 (41.6, 49.5)	
Function+			
Physical Function	53.9 (5.8)	56.3 (2.5)	**<0.001[a]**
	57 (56.7, 57)	57 (57, 57)	
Ability to Participate in Social Roles and	58.0 (7.3)	58. 6 (6.5)	0.731[a]
Activities	58.5 (52.9, 64.2)	63.5 (53.5, 64.2)	
Pain Intensity	**N (%)**		
0	62 (61.4)	56 (57.7)	0.162[a]
1-3	25 (24.8)	32 (33)	
4-6	10 (9.9)	9 (9.3)	
7-10	4 (4)	0 (0)	
Physical Health Summary Score	54.81 (5.9)	57.02 (3.0)	0.099[a]
	57.5 (54.9, 58.6)	57.8 (57.1, 58.6)	
Mental Health Summary Score	54.5 (7.4)	55.27 (6.0)	0.424[b]
	55.3 (50.3, 59.6)	56.0 (51.9, 60)	
(PROMIS® Global Health)			
Question 1: General Health Rating	53.2 (7.0)	55.1 (5.5)	**0.05[a]**
	54 (47, 62)	54 (54, 62)	
Question 2: Overall Quality of Life	50.6 (7.9)	53.3 (7.2)	**0.011[a]**
	51 (44, 61)	51 (51, 61)	
SOCIAL SUPPORT (n=195)			
MSPSS Total	5.5(1.2)	5.9 (1.0)	**0.013[a]**
MSPSS-Significant Other	5.5 (1.4)	6.0 (1.2)	**0.003[a]**
MSPSS-Family	5.6 (1.3)	5.8 (1.2)	0.224[a]
MSPSS-Friends	5.3 (1.5)	5.8 (1.2)	**0.018[a]**
SELF ESTEEM			
RSES	20.6 (5.8)	22.3 (4.6)	**0.028[b]**

‡Higher scores=greater symptom burden; +Lower scores=worse functioning for physical function. [a]Mann-Whitney test; [b] *t*-test; SD=Standard Deviation; IQR=Inter-Quartile Range; HRQOL=Health-Related Quality of Life; QOL=Quality of Life; PROMIS=Patient-Reported Outcomes Measurement Information System; MSPSS= Multidimensional Scale of Perceived Social Support; RSES= Rosenberg Self-Esteem Scale

Table 4.4

Covariates Associated with Physical and Mental Health Summary Scores

Variable	Correlation Coefficient *r*	*p*-Value
Physical Health Summary Score		
RSES	.380	<.001
Laterality	-.157	.118
Visual Acuity	-.485	<.001
Total Inhalation Anesthesia (minutes)	-.179	.082
Mental Health Summary Score		
RSES	.622	<.001
Gender	-.202	.042
MSPSS	.187	.062

r = Spearman's rho for physical health summary and Pearson product moment for mental health summary. RSES= Rosenberg Self-Esteem Scale; MSPSS= Multidimensional Scale of Perceived Social Support

Table 4.5
Final Ordinary Least Squares Regression Models for HRQOL in RB Survivors

Scale	Variable	*β*	R^2	Adjusted R^2	F	*p*-Value
PROMIS ®-29 Physical Health Summary Score	Visual Acuity	-.669	.529	.518	51.600	<.001
	RSES	.362				
PROMIS ®-29 Mental Health Summary Score	RSES	.620	.384	.378	61.088	.000

HRQOL = Health-related quality of life; RB = retinoblastoma; PROMIS® =Patient-Reported Outcomes Measurement Information System; RSES= Rosenberg Self-Esteem Scale

CHAPTER FIVE: THIRD MANUSCRIPT

Vision-related Quality of Life Compared to Generic Measures in Retinoblastoma Survivors

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Vision-Related Quality of Life Compared to Generic Measures in Retinoblastoma Survivors

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Declarations

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Consent to participate: Written parental permission and child assent was obtained for participants under age 18, and informed consent was obtained from participants aged 18 and over.
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Abstract

Purpose: To 1) Compare vision-related quality of life (VRQOL) in adolescent and young adult (AYA) unilateral versus bilateral retinoblastoma (RB) survivors using a vision-targeted measure and a generic health-related quality of life (HRQOL) measure, and 2) Assess associations among VRQOL and generic HRQOL domains and overall QOL and estimate associations of the VRQOL and HRQOL domains with overall QOL.

Methods: The National Institute for Health (NIH) Toolbox® VRQOL instrument, PROMIS®-29 Profile v 2.1, and a single-item QOL measure were administered in a cross-sectional study of RB survivors. Reliability for multi-item scales was estimated. Product-moment and Spearman rank correlation coefficients and stepwise ordinary least squares were used to measure associations of other variables with overall QOL.

Results: Significantly worse VRQOL was reported by bilateral than unilateral RB survivors. Cronbach's alpha coefficients for all VRQOL scales ranged from 0.83 to 0.95. Medium to large correlations were found between all NIH Toolbox® VRQOL scales and the PROMIS®-29 measures. Depression and ability to participate in social roles and activities from the PROMIS®-29 Profile accounted for 38% of the variance in overall QOL with the psychosocial domain of the NIH Toolbox® VRQOL explaining 16% of the variance.

Conclusions: VRQOL is impaired in bilateral RB survivors. VRQOL is associated substantially with the PROMIS-29 generic HRQOL measure but has significant unique associations with overall QOL. The NIH Toolbox® VRQOL measure provides important information about the vision-related effects on daily life of AYA RB survivors.

Introduction

The most common intraocular or eye cancer in childhood is retinoblastoma (RB) [1]. The yearly worldwide incidence is one in every 16,000 live births [1] with an improved survival rate of 97% over the past decade in the United States (U.S.) [2]. Treatment depends on the size and location of the tumor, which can be unilateral or bilateral, resulting from a hereditary or spontaneous gene mutation [3]. While treatment goals include vision preservation and ocular salvage, survivors can be left monocular (unilateral), visually impaired, or blind. RB affects physical, mental, and social health aspects of life. Hence, studies examining health-related quality of life (HRQOL) in RB survivors are needed but to date have been limited [4] with only one previous study utilizing a vision-related quality of life (VRQOL) measure [5].

Assessing HRQOL is important during RB treatment due to decisions negotiated between the provider and the parent. Many parents are hesitant to accept enucleation (surgical removal of the eye), a common treatment for RB, due to fear of social stigma and cultural factors, instead opting for alternate, possibly less-effective therapies [6]. This can result in tumor metastases and often eventual enucleation. Knowledge of HRQOL and VRQOL in RB survivors can be utilized by providers in discussions with parents during early treatment decision making.

Results of HRQOL studies of RB survivors have found varied results that may reflect the use of a variety of measures [4]. Generic HRQOL measures are useful to compare disease groups with healthy counterparts. However, sensitivity to the specific HRQOL effects of the disease may be lacking. There is no disease targeted HRQOL measure that has been psychometrically evaluated for use in the RB population [7]. Limitations in the methodologic quality of pediatric ophthalmology and oncology measures and applicability of content to the RB population have been identified [7]. However, it is uncertain if a generic HRQOL measure will effectively capture the impact of the disease compared to a vision-targeted or single-item QOL measures.

In this study, we compare VRQOL in adolescent and young adult (AYA) unilateral versus bilateral RB survivors. We hypothesize that VRQOL will be worse for those with bilateral than unilateral RB due to more extensive treatment and visual impairment with bilateral disease. In addition, we assess associations among the VRQOL, generic HRQOL and overall QOL, and estimate associations of the VRQOL and HRQOL domains with overall QOL.

Methods

Design, Setting and Sample

A cross-sectional design was used with a convenience sample of 101 AYA RB survivors recruited from a vision center located in a large children's hospital in the City of Los Angeles. Inclusion criteria were age 14 to 26 years, diagnosis of RB, and able to speak and read English. Exclusion criteria included severe developmental delay precluding self-report and/or current diagnosis of second malignant neoplasm.

Data Collection Procedures

Institutional review board (IRB) approval (Children's Hospital Los Angeles [CHLA] IRB # 19-00014 and University of California Los Angeles [UCLA] IRB # 19-000305) was obtained prior to study commencement. Written parental permission and child assent were obtained for participants younger than age 18, and informed consent was obtained from adult participants. A study information sheet and consent form were read aloud to blind participants or emailed to them for voiceover software use if needed. A witness signature was obtained for adult blind participants. Written and/or verbal assent was obtained from minors who were blind and a waiver for signature was obtained.

After consent was obtained, participants completed a demographic form, the Patient Reported Outcome Measurement Information System (PROMIS®)-29 Profile v 2.1 [8, 9], a single question on overall QOL, and the National Institutes of Health (NIH) Toolbox® VRQOL measure

[10] utilizing Research Electronic Data Capture (REDCap®) [11, 12]. Participants independently completed all study measures on an iPad while in clinic with no parental assistance or proxy-reports. When COVID-19 occurred, procedures were modified to allow for remote participation. The principal investigator recruited participants via telephone or letter mailed to last address. Eligible participants completed consent documentation electronically or via mail. REDCap survey invitations were emailed to participants for online completion. A medical chart review was conducted to obtain clinical variables including age at diagnosis, visual acuity, laterality, heredity, and genetic testing. Participants received compensation and parking validation (if completed on-site) for participation.

HRQOL and Overall QOL Measures

PROMIS®-29 Profile v2.1

The generic HRQOL measure was the PROMIS®-29 Profile v 2.1, a 29-item measure with a pain intensity item and four questions for each of the seven domains: physical function, fatigue, sleep disturbance, pain interference, anxiety, depression, and ability to participate in social roles and activities. Item response theory (IRT) pattern-based T-scores were computed (mean of 50 and standard deviation (SD) of 10 in the U.S. general population) [13, 14]. Higher scores represent more of the domain being measured. Thus, higher scores in the functioning domains (e.g., physical function) represent better functioning while higher scores in the symptom domains (e.g., anxiety) represent worse symptoms [15].

Internal consistency reliability (coefficient alpha) estimates for the PROMIS®-29 domains ranged from 0.77 (sleep disturbance) to 0.94 (pain interference) [9]. Estimated reliabilities for the physical health and mental health summary scores (weighted combinations of physial function, pain, social health, fatigue, sleep disturbance, and emotional distress) were 0.98 and 0.97, respectively [9]. Multiple studies have been conducted that provide evidence of the validity of the PROMIS®

measures [16-20]. While the PROMIS®-29 Profile has not been used to date in the RB population, support for the validity of the PROMIS® measures was found in the pediatric oncology population [21].

NIH Toolbox® Vision-Related Quality of Life Survey

The NIH Toolbox® VRQOL is a 53-item measure with six self-reported QOL domains related to visual function: color vision, distance vision, near vision, ocular symptoms, psychosocial well-being, and role performance [10]. While population norms are not available, IRT based on pattern-based scoring reported as T-scores (mean of 50 and SD of 10) relative to the validation sample are estimated, with higher scores representing better VRQOL. Coefficient alphas for the six scales ranged from 0.85 to 0.94 [10]. Product-moment correlations between the National Eye Institute Visual Function Questionnaire (NEI-VFQ) scales and the NIH Toolbox® VRQOL support the validity of this newer measure. Worse NIH Toobox® VRQOL scores were found among those with self-reported visual deficits [10]. The NIH Toolbox® VRQOL is a newer measure and has not been previously used in adolescent or the RB population. Only one previous study has assessed VRQOL in the adult RB population using the NEI-VFQ [5]. The NIH Toolbox® VRQOL measure was chosen due to the advantages of its IRT developmental basis over classical test theory [22] as well as the applicability of the questions to the adolescent RB population.

Overall Quality of Life Item

Overall QOL was measured using the second question on the PROMIS® Global Health v1.2 scale [23]. This question states: *"In general, would you say your quality of life is?"* with answer choices ranging from poor to excellent. Correlations between the overall QOL item with other PROMIS® global health items were statistically significant ($p < 0.001$) and ranged from $r = 0.36$ (pain) to $r = 0.82$ (physical health) [24].

Statistical Analysis

Demographic and clinical characteristics and VRQOL scores by disease laterality were summarized using mean/median, standard deviation, and range for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics between unilateral and bilateral RB survivors were examined using chi-square tests for categorical variables and Mann-Whitney U for continuous variables. Internal consistency reliability (Cronbach's alpha coefficient) [25] was estimated for the NIH Toolbox® VRQOL and PROMIS®-29 domains. IRT pattern-based T-scores for the VRQOL were estimated using the Health Measures Automated Scoring Service and PROMIS HRQOL scales were estimated using the PROMIS® Assessment Center Scoring Service.SM Normality was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Most measurement domains and clinical variables were not normally distributed. Mann-Whitney U tests were used to compare differences in VRQOL between unilateral and bilateral RB survivors.

A correlation of 0.10-0.29 was defined as small, 0.30-0.49 as medium, and >=0.50 as large per Cohen's recommendations [26, 27]. We hypothesize medium to large correlations between NIH Toolbox® VRQOL and PROMIS® domains: 1) psychosocial compared to anxiety, depression, and the mental health summary score; 2) role performance with ability to participate in social roles and activities, physical function, and physical health summary score; and 3) distance and near vision with physical function, ability to participate in social roles and activities, and physical health summary scores, respectively. Product-moment and Spearman rank order correlation coefficients are reported.

Although the dependent variable was ordinal, linear regression was still performed rather than less robust regression methods. A multi-step process was used to build multivariable models for predicting overall QOL from the PROMIS-29® Profile and NIH Toolbox® VRQOL domains. First, the correlations between each PROMIS-29 and VRQOL scale were examined. Scales

associated at $p < .15$ were entered stepwise into the ordinary least squares regression model. The first model included the seven PROMIS® scales, the second model the PROMIS® physical and mental health summary scores and the third model the VRQOL scales. The final model contained all significant predictors in the previous three models. For all analyses, statistical significance was set at a $p < 0.05$.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 26.0 for MAC [IBM; Somers, NY].

Results

Demographic and clinical characteristics of unilateral and bilateral retinoblastoma survivors

Among 101 RB survivors, 57% had unilateral disease and 43% had bilateral disease (**Table 5.1**). The median age of survivors was 17 with a range of 14-26 years, 50% were female, 65% were Latino/Hispanic, and 27% with middle class socioeconomic status. The median age at diagnosis was 15 months (range 1-108), 88% had an enucleation, and 13% had a previous family history of RB. Out of those who received genetic testing (n=86), 40 (46%) had the RB1 gene, and the majority had normal vision (86%); 8% were visually impaired and 6% were blind. There were no statistically significant differences between unilateral and bilateral groups regarding gender, race/ethnicity, and enucleation laterality. Bilateral survivors were older (median 18 versus 16 years) at the time of study and younger (median 9 months versus 20.5) at diagnosis. All unilateral survivors had normal visual acuity while bilateral survivors showed more family history (23%) of RB and the RB1 gene mutation (74%).

VRQOL in RB survivors

Coefficient alpha for the NIH Toolbox® scales in this study were as follows: 0.88 color vision, 0.95 distance vision, 0.93 near vision, 0.84 ocular symptoms, 0.85 psychosocial, and 0.83 role performance. The VRQOL domain scores in unilateral and bilateral RB survivors is listed in

Table 5.2. Unilateral RB survivors had significantly better VRQOL scores for color vision, distance vision, near vision (all $p<.001$) and role performance ($p=.009$) than bilateral survivors. Differences in ocular symptoms and psychosocial domains were not significant between the groups. Bilateral survivors scored worse than the NIH Toolbox developmental sample of 819 adults from an internet panel mean (T score = 50) on all domains except ocular symptoms while unilateral survivors scored below the sample mean only on psychosocial well-being and role performance.

Correlations between the PROMIS®-29 Profile and NIH Toolbox® VRQOL

Coefficient alpha for the PROMIS®-29 Profile scales in this study ranged from 0.69 (physical function) to 0.96 (pain interference). Correlations between the NIH Toolbox® VRQOL, the PROMIS ®-29 profile and the overall QOL measures are shown in **Table 5.3**. All NIH Toolbox® VRQOL scales were significantly correlated with each other except color vision and ocular symptoms. Most scales had medium to large correlations with each other except color vision which had weak correlations with the ocular symptoms and psychosocial scales. The largest correlation ($r = .838$) was between near and distance vision. There were large correlations of the PROMIS® physical function scale with the NIH Toolbox® VRQOL color vision ($r = .623$), distance vision ($r = .532$), and role performance ($r = .570$) scales. Role performance also had a large correlation with the PROMIS® ability to participate in social roles ($r = .509$). Distance vision ($r = .563$), near vision ($r = .527$) and role performance ($r = .578$) were correlated largely with the PROMIS® physical health summary score. There were medium-sized correlations between the NIH Toolbox® VRQOL psychosocial scale and all PROMIS® scales except sleep disturbance (*r's* = .328-.488). The overall QOL measure had a medium correlation with psychosocial ($r = .391$) and role performance scales ($r = .359$) and a small correlation with distance vision ($r = .197$).

Regression Models for Overall Quality of Life on PROMIS®-29 V2.1 and NIH Toolbox® VRQOL

Table 5.4 provides a summary of the multivariate analysis. The scales with correlations ($p < .15$) were entered as predictors of overall QOL into ordinary least squares regression models. The PROMIS®-29 Profile scales explained 38% (adjusted R-square) of the variance in overall QOL, with depression (ß = -.495) and ability to participate in social roles and activities (ß = .216) emerging as significant predictors. The mental health summary score emerged as the only predictor (ß = .575) in the second regression model explaining 32% of the variance in overall QOL. For the VRQOL domains, only distance vision, psychosocial, and role performance domains significantly correlated with overall QOL and were entered into the regression model. The psychosocial domain (ß = .407) emerged as the only significant predictor of overall QOL explaining 16 % of the variance. The final model, with all previous significant predictors, explained 39% of the variance in overall QOL with depression (ß = -.375) and mental health summary score (ß = .303) emerging as significant predictors.

Discussion

VRQOL in the RB population

The results of this study confirm our hypothesis of worse VRQOL for bilateral compared to unilateral RB survivors. Our findings were similar to the only previous study that has reported VRQOL in an adult cohort of RB survivors which showed that the bilateral group had significantly worse scores than the unilateral group on all scales of the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) [5]. Friedman and colleagues reported significant differences on domains that we did not find to have significance (e.g., ocular pain, social functioning, and mental health). This variation could be due to the use of different measures. However, high correlations between the NEI VFQ-25 and the NIH Toolbox® VRQOL were established for these domains [10]. Another explanation could be related to an older historical cohort not reflective of current treatment contributing to more ocular pain (e.g., radiation), some having acquired eye disorders (e.g.,

cataracts, glaucoma), and self-reported visual acuity which can affect social functioning and mental health [28]. Our bilateral RB survivors scored worse than the validation sample means on all domains of the VRQOL except ocular symptoms, indicating their HRQOL assessment may be more reflective of vision problems. Unilateral RB survivors scored worse than the sample means on the psychosocial and role performance domains indicating their well-being and functional status may be more affected by visual field deficits. Though the unilateral survivors had normal monocular visual acuity, there is loss of depth perception and peripheral fields because of eye enucleation. Furthermore, unilateral enucleation early in life results in poor motion processing and oculomotor performance resulting from a lack of visual input to the brain, which can lead to decreased motor function and HRQOL [29, 30]. The cosmetic deformity associated with a prosthetic and its psychosocial impact can affect a child's self-esteem and willingness to participate in certain social activities, negatively influencing their social and role functions [31, 32].

Generic versus Disease Specific HRQOL Measurements

Our analysis provides support for the NIH Toolbox® VRQOL measure in an adolescent population with visual impairment. The domains showed high levels of internal consistency reliability which were similar to previously reported findings [10]. We found significant medium to large correlations between all scales of the NIH Toolbox® VRQOL except the psychosocial and ocular symptom domains with color vision. The original psychometric assessment of the NIH Toolbox® VRQOL reported higher correlations for these domains [10]. This finding may reflect an older sample with more acquired ocular diseases increasing the applicability of these three domains. Large correlations indicate the domains may be measuring the same underlying concept and justify the development of an overall score for the measure. Near and distance vision were very strongly associated (0.838), indicating multicollinearity and the potential that participants were not able to

distinguish the difference between these two domains and that possibly these scales could be consolidated.

Most correlations between the NIH Toolbox® VRQOL and the PROMIS®-29 Profile scales were medium in size. The PROMIS® physical health summary and the physical function scale had large correlations with the VRQOL scales color, near and distance vision and role performance while most correlations with the mental health summary were medium, indicating the NIH Toolbox® VRQOL may be more sensitive to physical than mental HRQOL. The NIH Toolbox® VRQOL scales were not largely correlated with the PROMIS®-29 Profile scales. Conversely, one study compared the Short Form Health Survey (SF-36) and the NEI-VFQ which found only small correlations even among domains that were measuring the same variable [33]. The medium correlations between the NIH Toolbox® VRQOL and the PROMIS® domains were all consistent with our hypotheses, in addition color vision had medium correlations which we had not hypothesized. Per our findings, the high internal consistent reliability and medium to large correlations support the NIH Toolbox® VRQOL as a reliable measure that adds to the assessment of HRQOL in RB survivors.

Relationship between HRQOL, VRQOL, and Overall Quality of Life

Few scales of the NIH Toolbox® VRQOL correlated with a single item assessment of overall QOL. This may be related to single item questions of QOL mostly reflective of mental rather than physical health or well-being [25, 33], and the age and type of ocular disease with limited disease sequela. The color vision domain may not be applicable in this population as it is not a visual deficit associated with the disease or in non-enucleated eyes due to the sparing of the optic nerve in treatment [34]. Thus, color vision deficits in this sample are potentially explained by overall visual impairment or blindness. The other scales in question are distance and near vision in the RB population. One possible explanation is that the distance vision scale contains questions

related to driving. Since driving is a key contributor to adolescents' and young adults' independence, distance vision may have a greater association with their overall QOL than near vision. However, distance vision was only weakly correlated with overall QOL.

The regression models accounted for no more than 39% of the variance of overall QOL with 61% unexplained or not captured in the RB population. Many of the predictive domains were psychosocial, depression or mental health related. Our findings could reflect data collection during a global pandemic and civil unrest affecting mental health more pronouncedly in the AYA age group. The VRQOL appears to not add any additional value to the PROMIS®-29 in predicting overall QOL. While the use of a vision-targeted measure such as the NIH Toolbox® VRQOL does add new data to the assessment of HRQOL in AYA RB survivors by adding vision related issues that can impact their daily life, it does not replace the value of generic measures such as the PROMIS®-29 Profile instrument.

Limitations

While this study adds new information about VRQOL in AYA RB survivors it is not without limitations. Our cross-sectional design precludes the ability to make any causal inferences and limits the interpretation of associations. The lack of a control group for comparison with other types of vision related disorders limits our ability to make unbiased estimates of effect. The generalizability of our findings may be limited due to our ethnically diverse sample from the Los Angeles community compared to most other samples being predominantly Caucasian. Furthermore, our sample reflected the treatment era of a decade ago which may not be reflective of the previous use of radiation and the more current decrease in enucleations. Non-response and selection bias cannot be ruled out as only survivors seeking active follow-up and those who responded to letters and phone calls were recruited. In addition, data was self-reported and with some visually impaired participants requiring assistance in completion of the measures, subjects may have chosen socially

acceptable answers rather than being truthful. Finally, since data collection occurred during the COVID-19 pandemic, psychosocial effects on the AYA population may have played a role in the predominance of mental health factors influencing overall QOL.

Conclusions

Bilateral RB survivors report worse VRQOL than unilateral survivors, but no differences were found in ocular symptoms or psychosocial well-being between groups. Medium to large correlations were found between disease specific (NIH Toolbox® VRQOL) and generic (PROMIS®-29 Profile) HRQOL measures. Our findings indicate that the NIH Toolbox® VRQOL adds to the assessment of HRQOL in AYA RB survivors. Although the NIH Toolbox® VRQOL does not significantly add to the prediction of overall QOL beyond the PROMIS®-29 Profile, it may provide more detailed insight into the specific vision related effects on daily life of AYA RB survivors.

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Table 5.1. Demographic and Clinical Characteristics of Retinoblastoma Survivors

	Overall (n=101)	**Unilateral (n=58)**	**Bilateral (n=43)**	***P*-value***
Age at study (years)				
Mean (SD)	17.5 (3.0)	16.7 (2.1)	18.7 (3.7)	**.008[a]**
Median (range)	17 (14, 26)	16 (14, 22)	18 (14, 26)	
Gender, *N* (%)				
Male	50 (49.5)	26 (44.8)	24 (55.8)	.373[b]
Female	51 (50.5)	32 (55.2)	19 (44.2)	
Race/Ethnicity, *N* (%)				
Latino/Hispanic	66 (65.3)	41 (70.7)	25 (58.1)	.200[b]
White	16 (15.8)	6 (10.3)	10 (23.3	
Black/African American	4 (4)	3 (5.2)	1 (2.3)	
Asian/Pacific Islander	10 (9.9)	4 (6.9)	6 (14)	
Other	5 (5)	4 (6.9)	1 (2.3)	
SES, *N* (%)				
Lower status	14 (14)	6 (10.3)	8 (18.6)	**.019[b]**
Lower-middle status	22 (22)	15 (25.9)	7 (16.3)	
Middle status	27 (27)	18 (31)	9 (20.9)	
Upper middle status	25(25)	16 (27.6)	9 (20.9)	
Upper status	12 (12)	2 (3.4)	10 (23.3)	
Age at diagnosis (months)				
Mean (SD)	18.7 (17.8)	25.2 (20.4)	10.2 (7.8)	**<.001[a]**
Median (range)	15 (1, 108)	20.5 (1, 108)	9 (1, 30)	
Enucleation, *N* (%)				
Unilateral	86 (85.1)	54 (93.1)	32 (74.4)	.112[b]
Bilateral	3 (3)	NA	3 (7)	
Visual Acuity, *N* (%)				
Normal	87 (86.1)	58 (100)	29 (67.4)	**<.001[b]**
Visually Impaired	8 (7.9)	0 (0)	8 (18.6)	
Blind	6 (5.9)	0 (0)	6 (14.0)	
Heredity/Family History, *N* (%)	13 (12.9)	3 (5.2)	10 (23.3)	**.017[b]**
RB 1 gene mutation (n= 86), *N* (%)	40 (46.5)	8 (13.8)	32 (74.4)	**<.001[b]**

RB = Retinoblastoma; SES= Socioeconomic status; [a]Mann-Whitney test; [b]Chi-square; * = *p* value between unilateral and bilateral.

Table 5.2. Vision-related Quality of Life in Retinoblastoma Survivors

	Mean (SD) Median (IQR)			
Scale	**Overall (n=101)**	**Unilateral (n=58)**	**Bilateral (n=43)**	***P* value***
Color vision	49.8 (7.9) 53.9 (53.9, 53,9)	53.2 (2.6) 53.9 (53.9, 53.9)	45.3 (10.1) 53.9 (31.15, 53.9)	**<.001**
Distance vision	50.4 (12.5) 51.28 (43.27, 59.57)	54.7 (9.0) 54.31 (48.07, 64.3)	44.6 (14.2) 44.69 (31.1, 53.69)	**<.001**
Near vision	54.1 (12.1) 58.7 (47.92, 63.37)	58.7 (7.6) 60.84 (52.05, 66.65)	47.7 (14.2) 48.47 (32.96, 60.92)	**<.001**
Ocular symptoms	51.4 (9.0) 52.48 (46.27, 61.29)	51.3 (9.0) 52.79 (46.45, 61.29)	51.5 (9.1) 52.05 (45.69, 61.29)	.925
Psychosocial	47.3 (8.2) 48.12 (41.69, 57.42)	46.9 (8.5) 45.78 (40.11, 57.42)	47.8 (7.9) 49.98 (42.15, 57.42)	.502
Role performance	48.3 (8.3) 55.43 (41.61, 55.43)	50.3 (7.1) 55.43 (46.59, 55.43)	45.7 (9.1) 46.59 (37.81, 55.43)	**.009**

Mann-Whitney test; *= *p* value between unilateral and bilateral

Table 5.3. Correlations between NIH Toolbox® VRQOL and PROMIS®-29 and Overall QOL (n = 101)

Spearman correlations

	CV	DV	NV	OS	PS	RP
NIH TOOLBOX® VRQOL						
Color vision (CV)	—					
Distance vision (DV)	0.596**	—				
Near vision (NV)	0.629**	0.838**	—			
Ocular symptoms (OS)	0.084	0.447**	0.514**	—		
Psychosocial (PS)	0.233*	0.506**	0.476**	0.423**	—	
Role performance (RP)	0.523**	0.645**	0.570**	0.415**	0.630**	—
PROMIS®-29						
Physical function	0.623**	0.532**	0.481**	0.176	0.343**	0.570**
Anxiety	-.076	-.192	-.207*	-.378**	-.357**	-.306**
Depression	-.013	-.204*	-.120	-.316**	-.328**	-.234*
Fatigue	-.111	-.322**	-.399**	-.370**	-.356**	-.303**
Sleep disturbance	0.024	-.150	-.151	-.366**	-.212*	-.178
Social roles	0.323**	0.385**	0.332**	0.314**	0.394**	0.509**
Pain interference	-.273**	-.245*	-.341**	-.404**	-.326**	-.396**
PHS	0.495**	0.563**	0.527**	0.434**	0.488**	0.578**
MHS	0.112	0.320**	0.333**	0.472**	0.413**	0.388**
Overall QOL	0.161	0.197*	0.158	0.176	0.391**	0.359**

Pearson correlations

	CV	DV	NV	OS	PS	RP
NIH Toolbox® VRQOL						
Color vision (CV)	—					
Distance vision (DV)	0.686**	—				
Near vision (NV)	0.753**	0.876**	—			
Ocular symptoms (OS)	0.112	0.433**	0.482**	—		
Psychosocial (PS)	0.200*	0.504**	0.454**	0.495**	—	
Role performance (RP)	0.537**	0.678**	0.653**	0.493**	0.647**	—
PROMIS®-29						
Physical function	0.718**	0.627**	0.636**	0.198*	0.358**	0.642**
Anxiety	-.126	-.203*	-.219*	-.391**	-.369**	-.323**
Depression	-.013	-.159	-.070	-.325**	-.373**	-.262**
Fatigue	-.142	-.290**	-.332**	-.376**	-.374**	-.318**
Sleep disturbance	0.035	-.116	-.088	-.368**	-.201*	-.180
Social roles	0.352**	0.411**	0.402**	0.367**	0.415**	0.557**
Pain interference	-.258**	-.254**	-.318**	-.468**	-.375**	-.387**
PHS	0.695**	0.626**	0.636**	0.279**	0.408**	0.672**
MHS	0.191	0.331**	0.336**	0.495**	0.461**	0.440**
Overall QOL	0.146	0.214*	0.172	0.273**	0.407**	0.357**

NIH = National Institute of Health; VRQOL = Vision-related Quality of Life; PROMIS = Patient-Reported Outcome Measurement Information System®; QOL = Quality of Life; PHS = physical health summary; MHS = mental health summary. *p < .05, **p ≤ 0.001.

Table 5.4. Ordinary Least Squares Regression Models for Overall Quality of Life on PROMIS®-29 V2.1domains, summary scores, and NIH Toolbox® VRQOL

Measure	**Domain**	***β***	**R^2**	**Adjusted R^2**	**F**	***p*-Value**
PROMIS®-29 Domains	Depression	-.495	.391	.378	31.42	<0.001
	Social Roles	.216				
PROMIS®-29 PHS & MHS	MHS	.575	.331	.324	48.96	<0.001
VRQOL Domains	Psychosocial	.407	.166	.158	19.7	<0.001
Overall Model	Depression	-.375	.397	.385	32.24	<0.001
Depression	MHS	.302				
Social roles						
MHS						
Psychosocial						

PROMIS®= Patient Reported Outcome Measurement System; NIH = National Institute of Health; VRQOL= Vision Related Quality of Life; PHS= physical health summary; MHS= mental health summary

CHAPTER SIX: DISSERTATION SUMMARY

Over the past decade, retinoblastoma (RB), like other childhood cancers, has seen an improvement in treatment and survival rates. Treatment modalities for RB have progressed from eye enucleation, external beam radiation, to more modern techniques of chemotherapy (e.g., intraarterial and intravitreal) (Singh & Daniels, 2016). With improved survival comes the importance of measuring long-term medical / treatment outcomes and health-related quality of life (HRQOL; Cantrell, 2010). While there have been a multitude of studies examining HRQOL in survivors of childhood cancer, few have focused on those with RB (Belson, Eastwood, Brecht, Hays, & Pike, 2020).

This dissertation includes three manuscripts that examined the HRQOL literature among those with RB, HRQOL and overall QOL in AYA RB survivors compared to age- gender- and race/ethnicity matched controls, and an examination of VRQOL to generic HRQOL measures.

Manuscript Highlights

Manuscript 1. This manuscript titled *"A Review of Literature on Health-Related Quality of Life of Retinoblastoma Survivors"* was published in the *Journal of Pediatric Oncology Nursing* in 2020. This manuscript was a comprehensive review of the literature on HRQOL in RB survivors. Some studies reported worse HRQOL in RB survivors than controls or population norms while others found no difference or worse/better outcomes in individual domains. We found a variety of HRQOL measures used (disease and generic), older cohort age and era of treatment, study methods issues (no control groups), and the majority of studies were performed in Europe/Asia compromising generalizability of findings to the U.S population. A single study measured VRQOL revealing significant differences based on visual status and laterality of disease. This literature

review identified the need for further investigation of HRQOL in RB survivors using generic and disease-targeted measures.

Manuscript 2. This manuscript, *"Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors,"* is formatted for the *Journal of Pediatric Oncology Nursing.* This was a comparative, cross-sectional study measuring HRQOL in AYA RB survivors compared to an age- gender- and ethnicity matched control group. Participants completed the PROMIS®-29 Profile, single-item general health and overall QOL measures, the Rosenberg Self-Esteem Scale, and the Multidimensional Scale of Perceived Social Support. HRQOL between groups was found to be similar with RB participants reporting worse physical function, social support, and self-esteem. RB survivors reported worse mean general health and overall QOL. Visual acuity was found to be an independent predictor of physical HRQOL while self-esteem was found to be a predictor of both physical and mental HRQOL.

Manuscript 3. This manuscript, *"Vision-Related Quality of Life Compared to Generic Measures in Retinoblastoma Survivors,"* is formatted for the journal *Quality of Life Research*. It compared VRQOL in 101 AYA unilateral versus bilateral RB survivors using both a vision-targeted and generic measure of HRQOL. We also assessed associations among VRQOL and generic HRQOL domains and overall QOL and estimated associations of the VRQOL and HRQOL domains with overall QOL. All participants completed the NIH Toolbox® VRQOL measure, the PROMIS®-29 Profile and a single-item measure of overall QOL. Bilateral RB survivors reported worse VRQOL than unilateral survivors in all domains except ocular symptoms and psychosocial well-being. RB survivors reported worse scores on the psychosocial well-being and role functioning domains than the developmental. The NIH Toolbox® VRQOL measure was found to be reliable with medium to large correlations obtained between the NIH Toolbox® VRQOL and the PROMIS®-29 Profile. Depression and the social roles and activities domains of the PROMIS

accounted for 38 % of the variance in overall QOL with the psychosocial domain of the NIH Toolbox® VRQOL accounting for 16%. The final model, with all previous significant predictors, explained 39% of the variance in overall QOL with depression and mental health summary score emerging as significant predictors. The NIH Toolbox® VRQOL adds to the assessment of HRQOL and may provide more detailed insight into the specific vision related effects on daily life of AYA RB survivors.

Implications for Clinical Practice

HRQOL is an important measure that can improve patient-provider communication and patient satisfaction, reveal unknown morbidities, facilitate clinical decision making and improve healthcare outcomes over time (Cantrell & Kelly, 2015). Our findings that AYA RB survivors have overall similar HRQOL to their peers can provide reassurance to parents of young children diagnosed with RB. No differences were found between treatment regimens with only visual acuity predicting HRQOL. Thus, the continued emphasis on vision preservation during treatment course is warranted.

Routine primary care, ophthalmology or oncology surveillance visits with health care providers should include mental health and psychosocial screening with transitioning to adulthood as depression, self-esteem and social support concerns were highlighted in this study. The use of peer-support groups or camps for the visually impaired to offer interaction with other RB survivors may be beneficial. The ability to meet someone with the same clinical condition provides the opportunity to share experiences and develop acceptance from peers which is especially important during adolescence.

Directions for Future Research

Despite physical and mental HRQOL summary scores in RB survivors being comparable to their healthy counterparts, physical function was found to be worse. Self-esteem and social support

were also lower in RB survivors. Future studies are needed to examine the effect of visual impairment on physical function / activities of daily living (e.g., exercise, driving, school and job performance) in this population. Furthermore, interventions to improve modifiable factors such as self-esteem and social support may improve outcomes. Hence, the need for more quantitative research on body-image and self-esteem, in particular female RB survivors, can provide additional information on the impact of childhood cancer survivorship. The effects of residual cosmetic defects (e.g., enucleation and prosthetic fit), and visual impairment on HRQOL may be better capture in qualitative studies to assess the *"lived experience"* of RB survivors.

As new chemotherapy treatments evolve (intraarterial and intravitreal), future studies will be needed to examine treatment effects on visual acuity which was one of the major predictors of HRQOL identified in this study. The impact of visual acuity deficits (e.g., loss of depth perception and peripheral fields common with monocular vision) and ability for self-care is vital with the transition to adulthood. Lastly, longitudinal studies are needed to examine disease-specific visual deficits with aging and the possible impact on HRQOL in RB survivors.

Conclusion

This research provides further understanding of HRQOL in AYA RB survivors and identified visual acuity and self-esteem as independent predictors of HRQOL. Furthermore, our findings of deficits in physical function, self-esteem and social support contribute new knowledge to the literature and support previous European studies of comparable HRQOL compared to healthy counterparts. However, future studies are needed to further investigate physical limitations, visual acuity with aging, ability for self-care and ways to improve self-esteem in AYA RB survivors.

References

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APPENDIX A: HUMAN SUBJECTS CONSENT FORMS

CHLA CONSENT RETINOBLASTOMA

Children's Hospital Los Angeles

CONSENT/PERMISSION/ASSENT[1] TO PARTICIPATE IN A RESEARCH STUDY

Health-Related Quality of Life in Adolescent and Young Adults with Retinoblastoma

Retinoblastoma Cohort

Subject's Name:	_____		
CHLA medical record #	_____	Birth Date:	_____

KEY INFORMATION

(1) The information in this form is being used to seek your consent for a research study. Being in the study is up to you.

(2) This research is being done to find out how the quality of life of adolescents and young adults with retinoblastoma compares to those with no history of retinoblastoma. Participation will last up to 45 to 60 minutes. Study procedures for this research are:
- Complete a series of questionnaires on your quality of life, how your vision affects your daily life, how you feel about yourself, and some basic demographic information.
- Allow us to record information from your medical records

(3) The most likely risks to you of the research are:
- Feeling uncomfortable answering personal questions about yourself
- Potential of unintentional disclosure of confidential information

➢ Please see the **POTENTIAL RISKS AND DISCOMFORTS** section for a complete list of expected side effects

(4) There is no direct benefit to you from your study participation

(5) The alternative to this research is to not participate.

[1] This form also serves as the permission form for the parent(s) to read and sign. In this case, "You" refers to your child.

INTRODUCTION

You are invited to join a research study led by Paula Belson, CRNA, MSN at Children's Hospital Los Angeles (CHLA), doctoral candidate at the University of California, Los Angeles (UCLA) and Nancy Pike, PhD, Associate Professor, UCLA School of Nursing. This research is paid for by the Association of Pediatric Hematology/Oncology Nurses. You are invited to join this study because you are an adolescent or young adult survivor of retinoblastoma. Up to 125 adolescents/young adults with retinoblastoma will be invited to join the study at CHLA and up to 105 people will be in the study from the Los Angeles community. Please read the information below and ask questions about anything you do not understand before deciding whether or not to participate.

PURPOSE OF THE STUDY

Little is known about the quality of life of adolescent and young adult retinoblastoma survivors. The purpose of this study is to examine the quality of life of this group compared to a group of participants without retinoblastoma (control subjects). The results of your questionnaires will be compared with a control subject who is close to you in age. In doing this, we hope to identify what factors influence your reported quality of life.

PROCEDURES

If you volunteer to be in this study, we will ask you to do the following things:

1. Complete a series of questionnaires about your quality of life, how your vision affects your daily life, how you feel about yourself, and some basic demographic information. This will take 45-60 minutes to complete
2. Allow investigators to review your medical chart regarding your retinoblastoma diagnosis and treatment including the number of anesthetic exposures you have had

INFORMATION ABOUT DATA

The data collected as part of this study will be "coded." This means that the link connecting your identity to your study ID will be kept by the research team at CHLA.

Your data may be used by the researcher conducting this study or other researchers (at CHLA or elsewhere) for future research projects that are unrelated to the purpose of this study. The people conducting the future research will not be given the link connecting your identity to your study ID, so they will only know you by Study ID. This future research may be done without consulting you or obtaining consent (permission) for this additional use.

POTENTIAL RISKS AND DISCOMFORTS

You may feel uncomfortable disclosing personal information in the questionnaires. Some of the questions may cause you to think about difficult times related to yourself or your health. In the rare occasion that you find a question too difficult to answer, you can skip it or end the study.

There is the potential of accidental release of confidential information. There may be additional risks of being in this study that we do not know about and therefore cannot describe.

ANTICIPATED BENEFITS TO SUBJECTS

You should not expect any direct benefit as a result of participating in this research.

ANTICIPATED BENEFITS TO SOCIETY

Through this study, we will learn how adolescents and young adults with retinoblastoma feel about the quality of their life. Information from this study will help to understand the impact of retinoblastoma on the lives of survivors.

ALTERNATIVES TO PARTICIPATION

As this is not a treatment study, the alternative to being in the study is to not be in the study.

PAYMENT FOR PARTICIPATION

To thank you for your time participating in this research, the study team would like to offer you payment. The payment for participation is a $30.00 Target Gift Card. You will be asked to sign a receipt of payment form. If you choose to withdraw from the study and not complete the questionnaires you will not receive the payment. You will also receive hospital parking validation for the date of study completion.

PRIVACY AND CONFIDENTIALITY

The data collected as part of this study will be "coded". Coded means that the data and/or specimens will have your study ID recorded with them, and the link connecting the study ID to your name will be kept separately in a secure location by a member of the research team. Only the members of the study team will be able to see the link or the information that can identify you. Individual responses to survey questionnaires will be destroyed following analysis of data and publication.

People on the research team will know that you are in this research study. All results will be kept confidential, but may be made available to you if you wish. No information about you or provided by you during the research will be disclosed to others without your written permission, except: if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or if required by law (for example, if we learn of child or elder abuse, harm to self or others, or if you have certain infectious disease).

When the results of the research are published or shared with other scientists, no information will be included that would reveal your identity.

Authorized representatives of the CHLA Institutional Review Board (IRB) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you are under the age of 18, consent from the minor and the parent/guardian is required for the minor to participate in the study. Your decision about whether or not to join this research is up to you.

Your decision about whether or not to join this research is up to you. Your choice about whether or not to participate will have no effect on your care, services or benefits at Children's Hospital Los Angeles. If you agree to join the study, but later decide to leave this study, you may do so without affecting your rights to health care, services, or other benefits at Children's Hospital Los Angeles. Please contact the Principal Investigator if you wish to leave the study.

HOW TO OBTAIN INFORMATION

If you have any questions or concerns about the research, please feel free to contact anytime: Principal Investigator: Paula Belson at [redacted]

FINANCIAL INTEREST OF THE INVESTIGATOR

Funding for this research study is provided by the Association of Pediatric Hematology/Oncology Nurses. The amount of funding is not based upon the number of research subjects enrolled. If your doctor is an investigator for this study they are interested in both your healthcare and the conduct of this research. You are not under any obligation to participate in a research study conducted by your doctor.

RIGHTS OF RESEARCH SUBJECTS

You may leave this study at any time without penalty. You are not giving up any legal rights if you decide to be in this research study. If you have questions about the rights of research subjects, have complaints or concerns about the research, or just want to talk to someone other than the Investigator, you may call Children's Hospital Los Angeles, Human Subjects Protection Program office at [redacted]

Contact for future research

May someone from CHLA contact you to invite you to participate in future research? Please provide your initials beside your decision.

_____Yes _____No [for subject to complete, if the subject is 14 years or older]

_____Yes _____No [for parent to complete, if subject is a minor]

SIGNATURE OF RESEARCH SUBJECT (If the subject is 14 years or older)

Your signature below indicates

- You have read this document and understand its meaning;

- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You consent/assent to your participation in this research study; and
- You will be given a signed copy of this form.

_____
Print Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF PARENT(S)/LEGAL GUARDIAN(S) (If the subject is a minor)

Your signature(s) below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your child's participation in this research study;
- You will be given a signed copy of this form.

_____ _____
Print Name(s) of Parent(s)/Legal Guardian(s)

_____ _____
Signature of Parent/Legal Guardian Date

_____ _____
Signature of Parent/Legal Guardian Date

SIGNATURE OF INDIVIDUAL OBTAINING CONSENT

I have explained the research to the subject and/or the subject's parent(s)/legal guardian(s) and have answered all of their questions. I believe that they understand all of the information described in this document and freely give consent/permission/assent to participate.

_____
Print Name of Individual Obtaining Consent

_____ _____

Signature of Individual Obtaining Consent Date

SIGNATURE OF WITNESS (if applicable)

Your signature below indicates:

- I was present for the entire consent conference;
- The information in the consent document and any other written information was accurately explained to the subject and/or the subject's parent(s)/legal guardian(s);
- The subject and/or the subject's parent(s)/legal guardian(s) had an opportunity to ask questions and those questions were answered; and
- The subject and/or the subject's parent(s)/legal guardian(s) voluntarily signed the consent/permission/assent form in my presence.

_____
Print Name of Witness

_____ _____
Signature of Witness Date

Study Team Instructions: Only complete the section below if assent is required, and either only verbal assent was obtained from the subject or assent was not obtained from the subject.
Please check appropriate box and sign below.

☐ The undersigned,_____, hereby certifies that verbal assent was obtained from the subject.

☐ Assent was not obtained from the subject. (Please state the reason. Examples include: subject is an infant; subject is comatose; subject lacks cognitive abilities to understand the information; etc.)

_____

_____

Date:_____

Time:_____ Signature_____

Routing of signed copies of the consent form:

1) Give to the subject, if at least 14 years old (copy)
2) Give to the parent/legal guardian, if subject is a minor (copy)
3) Place in the Principal Investigator's research file (original)

Children's Hospital Los Angeles

CONSENT/PERMISSION/ASSENT[1] TO PARTICIPATE IN A RESEARCH STUDY

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors

Healthy Controls

Subject's Name:	_____
Birth Date:	_____ _____

KEY INFORMATION

(1) The information in this form is being used to seek your consent for a research study. Being in the study is up to you.

(2) This research is being done to find out how retinoblastoma survivors' lives compare to those with no history of retinoblastoma. Participation will last up to 30 to 40 minutes if a subject completes all procedures. Study procedures for this research are:
- Complete a series of questionnaires on your quality of life, how you feel about yourself, and some basic demographic information

(3) The most likely risks to you of the research are:
- Feeling uncomfortable answering personal questions about yourself
- Potential of unintentional disclosure of confidential information

➢ Please see the **POTENTIAL RISKS AND DISCOMFORTS** section for a complete list of expected side effects

(4) There is no direct benefit to you from your study participation

(5) The alternative to this research is to not participate.

[1] This form also serves as the permission form for the parent(s) to read and sign. In this case, "You" refers to your child.

INTRODUCTION

You are invited to join a research study led by Paula Belson, CRNA, MSN at Children's Hospital Los Angeles (CHLA), doctoral candidate at the University of California, Los Angeles (UCLA). You are invited to join this study because we need healthy control to compare to adolescent or young adult survivors of retinoblastoma. This research is paid for by the Association of Pediatric Hematology/Oncology Nurses. Up to 125 people will be invited to join the study at CHLA and up to 105 people will be in the study from the Los Angeles community. Please read the information below and ask questions about anything you do not understand before deciding whether or not to participate.

PURPOSE OF THE STUDY

Little is known about the quality of life of adolescent and young adult retinoblastoma survivors. The purpose of this study is to examine the quality of life of this group compared to a group of participants without retinoblastoma (control subjects). The results of your questionnaires will be compared with a retinoblastoma survivor who is close to you in age. In doing this, we hope to identify what factors influence their reported quality of life.

PROCEDURES

If you volunteer to be in this study, we will ask you to do the following things:

- Complete a series of questionnaires about your quality of life, how you feel about yourself, and some basic demographic information. This will take 30-40 minutes to complete.

INFORMATION ABOUT DATA

The data collected as part of this study will be "coded." This means that the link connecting your identity to your study ID will be kept by the research team at CHLA.

Your data may be used by the researcher conducting this study or other researchers (at CHLA or elsewhere) for future research projects that are unrelated to the purpose of this study. The people conducting the future research will not be given the link connecting your identity to your study ID, so they will only know you by Study ID. This future research may be done without consulting you or obtaining consent (permission) for this additional use.

POTENTIAL RISKS AND DISCOMFORTS

You may feel uncomfortable disclosing personal information in the questionnaires. Some of the questions may cause you to think about difficult times related to yourself or your health. In the rare occasion that you find a question too difficult to answer, you can skip it or end the study.

There is the potential of accidental release of confidential information. There may be additional risks of being in this study that we do not know about and therefore cannot describe.

ANTICIPATED BENEFITS TO SUBJECTS

You should not expect any direct benefit as a result of participating in this research.

ANTICIPATED BENEFITS TO SOCIETY

Through this study, we will learn how adolescent and young adult retinoblastoma survivors feel about the quality of their life. Information from this study will help to understand the impact of retinoblastoma on the lives of survivors.

ALTERNATIVES TO PARTICIPATION

As this is not a treatment study, the alternative to being in the study is to not be in the study.

PAYMENT FOR PARTICIPATION

To thank you for your time participating in this research, the study team would like to offer you payment. The payment for participation is a $30.00 Target Gift Card. You will be asked to sign a receipt of payment form. If you choose to withdraw from the study and not complete the questionnaires you will not receive the payment. You will also receive hospital parking validation for the date of study completion.

PRIVACY AND CONFIDENTIALITY

The data collected as part of this study will be "coded". Coded means that the data and/or specimens will have your study ID recorded with them, and the link connecting the study ID to your name will be kept separately in a secure location by a member of the research team. Only the members of the study team will be able to see the link or the information that can identify you. Individual responses to survey questionnaires will be destroyed following analysis of data and publication.

People on the research team will know that you are in this research study. All results will be kept confidential, but may be made available to you and/or your physician if you wish. No information about you or provided by you during the research will be disclosed to others without your written permission, except: if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or if required by law (for example, if we learn of child or elder abuse, harm to self or others, or if you have certain infectious disease).

When the results of the research are published or shared with other scientists, no information will be included that would reveal your identity.

Authorized representatives of the CHLA Institutional Review Board (IRB) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you are under the age of 18, consent from the minor and the parent/guardian is required for the minor to participate in the study. Your decision about whether or not to join this research is up to you.

Your decision about whether or not to join this research is up to you. Your choice about whether or not to participate will have no effect on your care, services or benefits at Children's Hospital Los Angeles. If you agree to join the study, but later decide to leave this study, you may do so without affecting your rights to health care, services, or other benefits at Children's Hospital Los Angeles. Please contact the Principal Investigator if you wish to leave the study.

HOW TO OBTAIN INFORMATION

If you have any questions or concerns about the research, please feel free to contact anytime: Principal Investigator: Paula Belson at [redacted]

FINANCIAL INTEREST OF THE INVESTIGATOR

Funding for this research study is provided by the Association of Pediatric Hematology/Oncology Nurses. The amount of funding is not based upon the number of research subjects enrolled. If your doctor is an investigator for this study they are interested in both your healthcare and the conduct of this research. You are not under any obligation to participate in a research study conducted by your doctor.

RIGHTS OF RESEARCH SUBJECTS

You may leave this study at any time without penalty. You are not giving up any legal rights if you decide to be in this research study. If you have questions about the rights of research subjects, have complaints or concerns about the research, or just want to talk to someone other than the Investigator, you may call Children's Hospital Los Angeles, Human Subjects Protection Program office at [redacted]

Contact for future research

May someone from CHLA contact you to invite you to participate in future research? Please provide your initials beside your decision.

_____Yes _____No [for subject to complete, if the subject is 14 years or older]

_____Yes _____No [for parent to complete, if subject is a minor]

SIGNATURE OF RESEARCH SUBJECT (If the subject is 14 years or older)

Your signature below indicates

- You have read this document and understand its meaning;

- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You consent/assent to your participation in this research study; and
- You will be given a signed copy of this form.

_____
Print Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF PARENT(S)/LEGAL GUARDIAN(S) (If the subject is a minor)

Your signature(s) below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your child's participation in this research study;
- You will be given a signed copy of this form.

_____ _____
Print Name(s) of Parent(s)/Legal Guardian(s)

_____ _____
Signature of Parent/Legal Guardian Date

_____ _____
Signature of Parent/Legal Guardian Date

SIGNATURE OF INDIVIDUAL OBTAINING CONSENT

I have explained the research to the subject and/or the subject's parent(s)/legal guardian(s) and have answered all of their questions. I believe that they understand all of the information described in this document and freely give consent/permission/assent to participate.

_____
Print Name of Individual Obtaining Consent

_____ _____
Signature of Individual Obtaining Consent Date

SIGNATURE OF WITNESS (if applicable)

Your signature below indicates:

- I was present for the entire consent conference;
- The information in the consent document and any other written information was accurately explained to the subject and/or the subject's parent(s)/legal guardian(s);
- The subject and/or the subject's parent(s)/legal guardian(s) had an opportunity to ask questions and those questions were answered; and
- The subject and/or the subject's parent(s)/legal guardian(s) voluntarily signed the consent/permission/assent form in my presence.

_____
Print Name of Witness

_____ _____
Signature of Witness Date

Study Team Instructions: Only complete the section below if assent is required, and either only verbal assent was obtained from the subject or assent was not obtained from the subject.
Please check appropriate box and sign below.

☐ The undersigned,_____, hereby certifies that verbal assent was obtained from the subject.

☐ Assent was not obtained from the subject. (Please state the reason. Examples include: subject is an infant; subject is comatose; subject lacks cognitive abilities to understand the information; etc.)

_____

_____

Date:_____

Time:_____ Signature

_____

Routing of signed copies of the consent form:

1) Give to the subject, if at least 14 years old (copy)
2) Give to the parent/legal guardian, if subject is a minor (copy)
3) Place in the Principal Investigator's research file (original)

AUTHORIZATION FORM

PERMISSION[1] FOR USE OR DISCLOSURE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

PRINCIPAL INVESTIGATOR (Individual in charge of the research team at CHLA): Paula Belson, CRNA, MSN

TITLE OF STUDY: Health-Related Quality of Life in Adolescents and Young Adults with Retinoblastoma

PURPOSE: The purpose of this study is to examine the quality of life or adolescents and young adults with retinoblastoma and compare then to participants without retinoblastoma.

Patient/Subject Name: _____

Medical Record Number: _____Date of Birth:_____

BACKGROUND and DEFINITIONS

HIPAA stands for the **Health Insurance Portability and Accountability Act**. HIPAA contains federal regulations that govern the privacy and confidentiality of medical information maintained by healthcare providers. Participants in research studies are protected by HIPAA regulations.

[1] This form also serves as the authorization form for parent(s) to read and sign when their child is the subject in a research study. In that case, "you" refers to your child.

Information used in research studies may include data that identifies you. When you decide to take part in a research study, you must give permission for your protected health information to be released from the research team at Children's Hospital Los Angeles and your doctors to the outside researchers involved in conducting the research study.

Protected health information is personal information that can identify you or that can be linked to you. Examples of protected health information include personal information such as your date of birth or where you live and information about your medical condition. Only you or your legal representative can give permission for your protected health information to be released.

By agreeing to sign this authorization form, you are allowing researchers at Children's Hospital Los Angeles to collect your protected health information and share it with others involved in doing this research study as detailed below, consistent with California and Federal laws concerning the privacy of this information.

RESEARCH STUDY INFORMATION

Your protected health information will be used for the following research study:

The protected health information that is needed for this research study includes:

- *Personal demographic information;*
- *History and diagnosis of your medical condition;*
- *Specific information about the treatments you will receive or have received, including treatment(s) you may have had in the past;*
- *Information about other medical conditions that may affect your treatment;*
- *Long-term information about your general health status and the status of your medical condition.*

California law prohibits the disclosure of any protected health information not listed in this authorization unless another authorization form is obtained from you or unless such disclosure is specifically required or permitted by law.

In addition, your medical records may need to be reviewed and the researchers may need to discuss your health information with your healthcare providers. This research also may create new information about you as a result of research procedures, tests, questionnaires, interviews, and visits.

The research team at Children's Hospital Los Angeles *does not receive* payment for your participation in this research study and subsequent use of your protected health information.

DISCLOSURE OF PROTECTED HEALTH INFORMATION

You give permission for the following persons, groups or organizations to use or disclose (release) your protected health information for the research study described in this authorization form.

1. Paula Belson and her research staff
2. Physicians and other healthcare providers
3. The CHLA Institutional Review Board for oversight and compliance purposes

RECEIPT OF PROTECTED HEALTH INFORMATION

You give permission for the following persons, groups or organizations to receive your protected health information for the research study described in this authorization form.

1. Hospital, its representatives, or other accrediting agencies**.**
2. A data safety board that may be formed to monitor the safety of the research.
3. Your health insurer or payer, if necessary, to secure their payment for any covered treatment not paid for by the research.

CONFIDENTIALITY and PRIVACY

Efforts will be made to ensure that your protected health information will not be shared with other persons, groups or organizations outside of the research study. Those persons who receive your health information may not be required by privacy laws to protect it and may share your information with

others without your permission, if permitted by laws governing them. The research team cannot guarantee absolute confidentiality and privacy.

EXPIRATION

This authorization will expire on January 15, 2113. This is because information that is collected for research purposes continues to be analyzed for many years and it is not possible to determine when it will be complete.

YOUR RIGHTS

You may decide not to sign this authorization form. If you do not sign this authorization form, you will not be able to take part in this research study. Your regular healthcare including treatment, payment or enrollment in any health plans or your eligibility for benefits will not be affected if you decide not to sign.

You may revoke your permission at any time for Children's Hospital Los Angeles to use or share your protected health information collected for this research study. However, even if you revoke this authorization, the hospital and the research team may still use information about you that was collected as part of the research project (i.e., side-effects related to the research) between the date you signed the current form, and the date you revoked the authorization. This is to protect the quality, integrity and reliability of the research results. Once you revoke your authorization, no further protected health information will be disclosed.

You must revoke your authorization in writing. You may submit a written request to revoke your authorization or you may request a form for this purpose from the CHLA Human Subjects Protection Program, [redacted]. This document must be signed by you or on your behalf and delivered to the following address: *Paula Belson, CRNA,* Children's Hospital Los Angeles, [redacted]

Your cancellation will be effective upon receipt, but will not be effective to the extent that the Children's Hospital Los Angeles research team or others have acted in reliance upon this Authorization.

You will receive a copy of this Authorization Form.

You have the right to review and/or copy your *medical records* containing your protected health information kept by Children's Hospital Los Angeles.

You will be allowed to review your medical records collected for research at any time, including while the study is ongoing.

You have a right to receive a copy of the blank data forms used for this study.

SIGNATURES

Your signature below indicates: that you give permission for the use and disclosure of your protected health information as described in this document. This authorization form may not be valid if it has not been filled out completely.

Printed Name_____

Signature_____Date____/____/____

Please indicate the relationship:
❑ patient/research subject ❑ legal representative_____
(indicate relationship)

Printed Name of Person Obtaining Permission:

_____

Signature of Person Obtaining Permission:

_____Date____/____/____

Routing: Investigator's file, Subject, Health Information Management (Medical Records)

UCLA RESEARCH INFORMATION SHEET ADULT

University of California, Los Angeles

RESEARCH INFORMATION SHEET

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors
Healthy Controls

Paula Belson, CRNA, MSN, doctoral candidate and Nancy Pike, PhD, RN, CPNP, Associate Professor in the department of Nursing at the University of California, Los Angeles (UCLA) are conducting a research study.

You were selected as a possible participant in this study because you are a young adult and are healthy. Your participation in this research study is voluntary.

Why is this study being done?
Little is known about the quality of life of young adult retinoblastoma survivors. The purpose of this study is to examine the quality of life of this group compared to a group of participants without retinoblastoma (control subjects). The results of your questionnaires will be compared with a retinoblastoma survivor who is close to you in age. In doing this, we hope to identify what factors influence their reported quality of life.

What will happen if I take part in this research study?

If you volunteer to participate in this study, the researcher will ask you to do the following:

- Complete a series of questionnaires about your quality of life, how you feel about yourself, and some basic demographic information. This will take 30-40 minutes to complete.
- This will be completed in a private space.
- Online participation may be possible.

How long will I be in the research study?

Participation will take a total of about 30-40 minutes.

Are there any potential risks or discomforts that I can expect from this study?

You may feel uncomfortable disclosing personal information in the questionnaires. Some of the questions may cause you to think about difficult times related to yourself or your health. In the rare occasion that you find a question too difficult to answer, you can skip it or end the study.

There is the potential of accidental release of confidential information. There may be additional risks of being in this study that we do not know about and therefore cannot describe.

Are there any potential benefits if I participate?

You should not expect any direct benefit as a result of participating in this research.

The results of the research may help us learn how young adult retinoblastoma survivors feel about the quality of their life. Information from this study will help to understand the impact of retinoblastoma on the lives of survivors.

Will I be paid for participating?

To thank you for your time participating in this research, the study team would like to offer you payment. The payment for participation is a $30.00 Target Gift Card. You will be asked to sign a receipt of payment form. If gift card is mailed, a signed receipt will be required via email confirmation. If you choose to withdraw from the study and not complete the questionnaires you will not receive the payment.

Will information about me and my participation be kept confidential?

Any information that is obtained in connection with this study and that can identify you will remain confidential. It will be disclosed only with your permission or as required by law. Confidentiality will be maintained by means of coding of the data collected. Coded means that the data and/or specimens will have your study ID recorded with them, and the link connecting the study ID to your name will be kept separately in a secure location by a member of the research team. Only the members of the study team will be able to see the link or the information that can identify you. Individual responses to survey questionnaires will be destroyed following analysis of data and publication.

People on the research team will know that you are in this research study. All results will be kept confidential but may be made available to you and/or your physician if you wish. No information about you or provided by you during the research will be disclosed to others without your written permission, except: if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or if required by law (for example, if we learn of child or elder abuse, harm to self or others, or if you have certain infectious disease).

When the results of the research are published or shared with other scientists, no information will be included that would reveal your identity.

What are my rights if I take part in this study?

- You can choose whether or not you want to be in this study, and you may withdraw your consent and discontinue participation at any time.
- Whatever decision you make, there will be no penalty to you, and no loss of benefits to which you were otherwise entitled.
- You may refuse to answer any questions that you do not want to answer and still remain in the study.

Who can I contact if I have questions about this study?

- **The research team:**
  If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact: Principal Investigator: Paula Belson at [redacted]

- **UCLA Office of the Human Research Protection Program (OHRPP):**

  If you have questions about your rights as a research subject, or you have concerns or suggestions and you want to talk to someone other than the researchers, you may contact the UCLA OHRPP [redacted]

You will be given a copy of this information to keep for your records.

UCLA RESEARCH INFORMATION SHEET TEEN

UNIVERSITY OF CALIFORNIA, LOS ANGELES

ADOLESCENT (Ages 13-17) RESEARCH INFORMATION SHEET

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors
Healthy Controls

You are asked to participate in a research study conducted by Paula Belson, CRNA, MSN, doctoral candidate and Nancy Pike, PhD, RN, CPNP, Associate Professor in the department of nursing at the University of California, Los Angeles. You were selected as a possible participant in this study because you are an adolescent and are healthy. Your participation in this research study is voluntary.

Why is this study being done?

Little information is known about how retinoblastoma survivors feel about their life as adolescents and young adults. The purpose of this study is to examine the quality of life of this group compared to a group of participants without retinoblastoma (control subjects). The results of your questionnaires will be compared with a retinoblastoma survivor who is close to you in age. In doing this, we hope to identify what factors influence their reported quality of life.

What will happen if I take part in this research study?

Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say “yes” you can still decide not to do this.

If you volunteer to participate in this study, the researcher will ask you to do the following:

- Complete a series of questionnaires about your quality of life, how you feel about yourself, and some basic demographic information. This will take 30-40 minutes to complete.
- This will be completed in a private space.
- Online participation may be possible.

How long will I be in the research study?

Participation in the study will take a total of about *30-40 minutes.*

Are there any potential risks or discomforts that I can expect from this study?

You may feel uncomfortable disclosing personal information in the questionnaires. Some of the questions may cause you to think about difficult times related to yourself or your health. In the rare occasion that you find a question too difficult to answer, you can skip it or end the study.

There is the potential of accidental release of confidential information. There may be additional risks of being in this study that we do not know about and therefore cannot describe.

Are there any potential benefits if I participate?

You should not expect any direct benefit as a result of participating in this research.

The results of the research may help us learn how adolescent and young adult retinoblastoma survivors feel about the quality of their life. Information from this study will help to understand the impact of retinoblastoma on the lives of survivors.

Will I receive any payment if I participate in this study?

To thank you for your time participating in this research, the study team would like to offer you payment. The payment for participation is a $30.00 Target Gift Card. You will be asked to sign a receipt of payment form. If gift card is mailed, a signed receipt will be required via email confirmation If you choose to withdraw from the study and not complete the questionnaires you will not receive the payment.

Will information about me and my participation be kept confidential?

Any information that is obtained in connection with this study and that identify you will remain confidential. It will be disclosed only with your permission or as required by law. Confidentiality will be maintained by means of coding of the data collected. Coded means that the data and/or specimens will have your study ID recorded with them, and the link connecting the study ID to your name will be kept separately in a secure location by a member of the research team. Only the members of the study team will be able to see the link or the information that can identify you. Individual responses to survey questionnaires will be destroyed following analysis of data and publication.

People on the research team will know that you are in this research study. All results will be kept confidential, but may be made available to you and/or your physician if you wish. No information about you or provided by you during the research will be disclosed to others without your written permission, except: if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or if required by law (for example, if we learn of child or elder abuse, harm to self or others, or if you have certain infectious disease).

When the results of the research are published or shared with other scientists, no information will be included that would reveal your identity.

What are my rights if I take part in this study?

You may withdraw your assent at any time and discontinue participation without penalty or loss of benefits to which you were otherwise entitled.

You can choose whether or not you want to be in this study. If you volunteer to be in this study, you may leave the study at any time without consequences of any kind. You are not waiving any of your legal rights if you choose to be in this research study. You may refuse to answer any questions that you do not want to answer and still remain in the study.

Who can answer questions I might have about this study?

In the event of a research related injury, please immediately contact one of the researchers listed below. If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact Principal Investigator: [redacted]

If you have questions about your rights as a research subject, or you have concerns or suggestions and you want to talk to someone other than the researchers, you may contact the UCLA OHRPP [redacted]

UCLA RESEARCH INFORMATION SHEET PARENT

University of California, Los Angeles

PARENT INFORMATION SHEET FOR MINOR TO PARTICIPATE IN RESEARCH

Health-Related Quality of Life in Adolescent and Young Adult Retinoblastoma Survivors
Healthy Controls

Paula Belson, CRNA, MSN, doctoral candidate and Nancy Pike, PhD, RN, CPNP, Associate Professor in the department of Nursing at the University of California, Los Angeles (UCLA) are conducting a research study.

Your child was selected as a possible participant in this study because they are an adolescent or young adult and are healthy. Your child's participation in this research study is voluntary.

Why is this study being done?

Little is known about the quality of life of adolescent and young adult retinoblastoma survivors. The purpose of this study is to examine the quality of life of this group compared to a group of participants without retinoblastoma (control subjects). The results of your child's questionnaires will be compared with a retinoblastoma survivor who is close to your child in age. In doing this, we hope to identify what factors influence their reported quality of life.

What will happen if my child takes part in this research study?

If you agree to allow your child to participate in this study, we would ask him/her to:

- Complete a series of questionnaires about their quality of life, how they feel about themselves, and some basic demographic information. This will take 30-40 minutes to complete.
- This will be completed in a private space.
- Online participation may be possible.

How long will my child be in the research study?

Participation will take a total of about 30-40 minutes.

Are there any potential risks or discomforts that my child can expect from this study?

They may feel uncomfortable disclosing personal information in the questionnaires. Some of the questions may cause them to think about difficult times related to themselves or their health. In the rare occasion that they find a question too difficult to answer, they can skip it or end the study.

There is the potential of accidental release of confidential information. There may be additional risks of being in this study that we do not know about and therefore cannot describe.

Are there any potential benefits to my child if he or she participates?

Your child should not expect any direct benefit as a result of participating in this research.

The results of the research may help us learn how adolescent and young adult retinoblastoma survivors feel about the quality of their life. Information from this study will help to understand the impact of retinoblastoma on the lives of survivors.

Will my child be paid for participating?

To thank your child for their time participating in this research, the study team would like to offer them payment. The payment for participation is a $30.00 Target Gift Card. You will be asked to sign a receipt of payment form. If gift card is mailed, a signed receipt will be required via email confirmation. If your child chooses to withdraw from the study and does not complete the questionnaires, they will not receive the payment.

Will information about my child's participation be kept confidential?

Any information that is obtained in connection with this study and that identifies your child will remain confidential. It will be disclosed only with your permission or as required by law.
Confidentiality will be maintained by means of coding of the data collected. Coded means that the data and/or specimens will have your child's study ID recorded with them, and the link connecting the study ID to your child's name will be kept separately in a secure location by a member of the research team. Only the members of the study team will be able to see the link or the information that can identify your child. Individual responses to survey questionnaires will be destroyed following analysis of data and publication.

People on the research team will know that you are in this research study. All results will be kept confidential, but may be made available to you and/or your child's physician if you wish. No information about your child or provided by your child during the research will be disclosed to others without your written permission, except: if necessary to protect your child's rights or welfare (for example, if your child is injured and needs emergency care); or if required by law (for example, if we learn of child or elder abuse, harm to self or others, or if your child has certain infectious disease).

When the results of the research are published or shared with other scientists, no information will be included that would reveal your child's identity.

What are my and my child's rights if he or she takes part in this study?

- You can choose whether or not you want your child to be in this study, and you may withdraw your permission and discontinue your child's participation at any time.
- Whatever decision you make, there will be no penalty to you or your child, and no loss of benefits to which you or your child were otherwise entitled.
- Your child may refuse to answer any questions that he/she does not want to answer and still remain in the study.

Who can I contact if I have questions about this study?

- **The research team:**
  If you have any questions, comments or concerns about the research, you can talk to the one of the researchers. Please contact: Principal Investigator: Paula Belson [redacted]

- **UCLA Office of the Human Research Protection Program (OHRPP):**
  If you have questions about your rights as a research subject, or you have concerns or suggestions and you want to talk to someone other than the researchers, you may contact the UCLA OHRPP [redacted]

You will be given a copy of this information to keep for your records.

APPENDIX B: CHLA RECRUITMENT LETTER

Date

Dear _____,

My name is Paula Belson and I am working with Dr. Jonathan Kim at CHLA on a research study examining quality of life in retinoblastoma survivors. I am writing to you to see if you/your child would be interested in participating. Participating in this study is completely voluntary.

Participation in the study involves you/your child completing several questionnaires about your/your child's quality of life and allow the study team to look at your/your child's medical record and record some information about your/your retinoblastoma diagnosis and treatment. These questionnaires would be sent to you as a survey link via email. Questions will ask you/your child about the quality of your life, how you feel about yourself, your support systems, and how your vision affects your daily life. These questions will take 45-60 minutes to complete. In addition, you/your child will be administered a cognitive screener, to confirm that you are eligible for study, which takes approximately 10 minutes to complete. The cognitive screener would be done via Facetime or Skype. Upon completion of the study you/your child will be mailed a $30 Target gift card and to thank you for your participation.

If you are interested in participating in the study, please call or email me at the phone/address below. I will need to ask you a few screening questions to determine eligibility for participation and I can answer all questions you may have at that time. Thank you!

Paula
Paula Belson, CRNA, MSN | CRNA Manager
Anesthesiology and Critical Care Medicine
Children's Hospital Los Angeles
[redacted]

APPENDIX C: CHLA PHONE SCRIPT

IRB Phone Screening-RB

Children's Hospital Los Angeles

CONSENT SCRIPT TO SCREEN FOR RESEARCH

Health-Related Quality of Life in Adolescent and Young Adults with Retinoblastoma

Good morning/afternoon,

Hello, my name is Paula Belson and I am working with Dr. Jonathan Kim at CHLA on a research study examining quality of life in retinoblastoma survivors. I am calling to see if you/your child would be interested in participating. Would you like me to tell you more about the study?

Are you interested in being screened for this study?
[If no, thank the person and hang-up].
[If yes, continue with information about screening].

Participation in the study involves you/your child completing several questionnaires about your/your child's quality of life. These questionnaires would be given to you during your next clinic visit at CHLA on _____. Questionnaires will be administered on an IPAD and sufficient time to complete them will be given to you during your visit. Questions will ask you/your child about the quality of your life, how you feel about yourself, your support systems, and how your vision affects your daily life. In addition, you/your child will be administered a cognitive screener which takes approximately 10 minutes to complete. Upon completion of the study you/your child will be given a $30 Target gift card and a validation for same day hospital parking to thank you for your participation.

If you are interested I can email you a copy of the consent for the study which contains all the details involved. You can read it over and discuss it with your family before deciding to participate or not. I will be in the eye clinic on the day of your appointment and you can tell me then if you wish to participate.

The screening will take only a minute. I will ask you a few questions about your child's medical history. You do not have to answer any questions you do not wish to answer or are uncomfortable answering, and you may stop at any time. Your participation in the screening is voluntary.

Your answers will be confidential. No one will know your answers except for the research team. If your child does not qualify for the study, the answers will be kept without their name. Alternately, if they do qualify for the research, and you decide to participate, we will keep the answers with their research record.

Would you like to continue with participating in this telephone screening?
[If no, thank the person and hang-up].

[If yes, continue with the screening].

1. Has your child/have you been diagnosed with retinoblastoma?
2. Has your child/have you received your care for retinoblastoma at CHLA?
3. Does your child/do you have any developmental delay?
4. Does your child/do you have a current diagnosis of a second malignant neoplasm or cancer?
5. Are you/your child able to speak and read English?

Thank you for answering the screening questions.

[Indicate whether the person is eligible, requires additional screening, or is not eligible and explain why.]

Do you have any questions about the screening or the research? I am going to give you a couple of telephone numbers to call if you have any questions later. Do you have a pen? If you have questions about the research screening, you may call me, Paula Belson, [redacted] anytime and I can answer your questions.

If you have questions about your rights as a research subject, please contact the CHLA Human Subjects Protection Program at ([redacted]

Thank you again for your willingness to answer our questions.

CHLA PHONE SCRIPT HEALTHY CONTROLS

IRB Phone Screening-Healthy Controls

Children's Hospital Los Angeles

CONSENT SCRIPT TO SCREEN FOR RESEARCH

Health-Related Quality of Life in Adolescent and Young Adults with Retinoblastoma

Good morning/afternoon,

Hello, my name is Paula Belson and I am working on a research study examining quality of life in retinoblastoma survivors compared to healthy controls. I am calling to see if you/your child would be interested in participating. Would you like me to tell you more about the study?

Are you interested in being screened for this study?
[If no, thank the person and hang-up].
[If yes, continue with information about screening].

Participation in the study involves you/your child completing several questionnaires about your/your child's quality of life. These questionnaires will be administered on an IPAD. Questions will ask you/your child about the quality of your life, how you feel about yourself, your support systems, and how your vision affects. This should take approximately a half hour to complete. Upon completion of the study you/your child will be given a $30 Target gift card to thank you for your participation.

If you are interested I can email you a copy of the consent for the study which contains all the details involved. You can read it over and discuss it with your family before deciding to participate or not. You can contact me at any time later if you wish to participate.

The screening will take only a minute. I will ask you a few questions about your child's medical history. You do not have to answer any questions you do not wish to answer or are uncomfortable answering, and you may stop at any time. Your participation in the screening is voluntary.

Your answers will be confidential. No one will know your answers except for the research team. If your child does not qualify for the study, the answers will be kept without their name. Alternately, if they do qualify for the research, and you decide to participate, we will keep the answers with their research record.

Would you like to continue with participating in this telephone screening?
[If no, thank the person and hang-up].
[If yes, continue with the screening].

1. Has your child/have you been diagnosed with any chronic medical or psychiatric conditions?
2. Are you/your child able to speak and read English?

Thank you for answering the screening questions.

[Indicate whether the person is eligible, requires additional screening, or is not eligible and explain why.]

Do you have any questions about the screening or the research? I am going to give you a couple of telephone numbers to call if you have any questions later. Do you have a pen? If you have questions about the research screening, you may call me, Paula Belson, [redacted] anytime and I can answer your questions.

If you have questions about your rights as a research subject, please contact the CHLA Human Subjects Protection Program at [redacted]

Thank you again for your willingness to answer our questions.

APPENDIX D: ALTAMED APPROVAL LETTER

AltaMed

January 3, 2019

Paula Belson,
MSN, CRNA
[redacted]
Children's Hospital Los

AngelesCC: Nancy Pike,

PhD

Dear Paula,

This letter is to inform you that the AltaMed Research Planning Committee approved therequest to post the research study flyers on the "Retinoblastoma Clinic" on December 14,2018. The research study flyers are approved only at AltaMed CHLA.

Changes to the study should be submitted to research@altamed.org. All changes will undergo a separate review by the committee. We also request that you: 1) inform the Research Planning Committee once you have concluded your study, and 2) share highlightsand key findings from the study in the form of a final report memo or, if relevant, a publication. The Research Planning Committee and the AltaMed Institute of Health Equity takes an interest in learning from the work of our partners. For additional questions, pleasecontact Indira Sanchez, Research Grant Manager, at [redacted]

Sincerely,

Cástulo de la Rocha, J.D.
President/Chief Executive Officer

AltaMed Health Services Corporation
2040 Camfield Avenue
Los Angeles, CA 90040
Tel 323 725 8751
Fax 323 889 7808
AltaMed.org

RETINOBLASTOMA SURVIVORS Needed for CHLA Research Study

Do you have retinoblastoma?

Are you 14 to 26 years old?

If so, do you want to be a part of a research study?

The purpose of the study is to examine the quality of life of retinoblastoma survivors

You will be asked to answer questions about the quality of your life, how you feel about yourself, and how your vision affects your daily life

Your participation is voluntary

Can be done entirely from the safety of your own home!

This will take about 45 minutes

Must be able to speak and read English

You will get a $30 Target gift card when you finish the study

For more information, please contact:

Paula Belson, CRNA, MSN at [redacted]

Healthy Volunteers Needed for a CHLA Research Study

Are you 14 to 26 years old?

Do you have no chronic medical or psychiatric conditions?

If so, you are needed for a research study

The purpose of this study is to examine the quality of life in retinoblastoma survivors compared to healthy adolescents and young adults

You will be asked to answer questions about how you feel about your life and yourself

Your participation is voluntary

This will take about 30 minutes

Must be able to speak and read English

Can be done entirely from the safety of your own home!

You will get a $30 Target gift card when you finish the study

For more information, please contact:

Paula Belson, CRNA, MSN at [redacted]

Disclaimer: This research is not affiliated with AltaMed.

APPENDIX F: RETINOBLASTOMA DATA COLLECTION TOOL

Retinoblastoma Data Collection Tool

Subject Code # _____ Date: _____

Chronic medical conditions:_____

Psychiatric conditions:_____

Medications:_____

Age at diagnosis: _____years _____months

Visual acuity (date): _____(R)_____ (L)_____

Laterality Right / Left

Family history yes / no

Genetic testing yes / no

Treatment history:

Chemo yes / no Agents: Carboplatin/Etoposide/Vincristine/Other_____

cycles_____

Radiation yes / no

Enucleation yes / no Unilateral / bilateral

Prosthesis yes / no

Anesthesia exposure

Total # anesthetics: _____

Eye exams:_____

MRIs:_____

Other:_____

Total duration of inhalational anesthesia (minutes) _____
(interval between recorded anesthesia start and anesthesia stop)

	1	2	3	4	5	6	7	8	9	10
Procedure										
Duration anesthesia										
Sevoflurane										
Isoflurane										
Desflurane										
Midazolam										
Ketamine										
Dexmedetomidine										
Fentanyl										
Morphine										

	11	12	13	14	15	16	17	18	19	20
Procedure										
Duration anesthesia										
Sevoflurane										
Isoflurane										
Desflurane										
Midazolam										
Ketamine										
Dexmedetomidine										
Fentanyl										
Morphine										

	21	22	23	24	25	26	27	28	29	30
Procedure										
Duration anesthesia										
Sevoflurane										
Isoflurane										
Desflurane										
Midazolam										
Ketamine										
Dexmedetomidine										
Fentanyl										
Morphine										

	31	32	33	34	35	36	37	38	39	40
Procedure										
Duration anesthesia										
Sevoflurane										
Isoflurane										
Desflurane										
Midazolam										
Ketamine										
Dexmedetomidine										
Fentanyl										
Morphine										

	41	42	43	44	45	46	47	48	49	50
Procedure										
Duration anesthesia										
Sevoflurane										
Isoflurane										
Desflurane										
Midazolam										
Ketamine										
Dexmedetomidine										
Fentanyl										
Morphine										

APPENDIX G: MEASURES

DEMOGRAPHIC FORM

Subject Code # _____ Date: _____

Subject Type: [Control] [RB]

Demographic Information

Please complete the following information to the best of your knowledge. Remember there is no right or wrong answer. If you have any questions or do not understand a question, please ask the investigator.

Age: _____

Gender:
[ ] Male
[ ] Female
[ ] Other, please specify: _____

Race / Ethnicity:
[ ] White / non-Hispanic
[ ] Latino / Hispanic
[ ] Black / African American
[ ] Asian / Pacific Islander
[ ] Other, please specify: _____

Who currently lives with you in your home? [check all that applies]
[ ] Mother only
[ ] Father only
[ ] Both mother and father
[ ] Step-mother or father
[ ] Siblings [brother(s) and /or sister(s)]
[ ] Extended family [grandparents, aunts/uncles, cousins]
[ ] Other _____

What is your parent[s]current marital status?
[ ] Single, living alone
[ ] Single, living with a partner
[ ] Married, living alone [separated, widowed, deployment]
[ ] Married, living with a spouse
[ ] Other _____

What is your mother's occupation or job title? _____
[Example: stay at home mom, teacher, manager, nurse, lawyer]

What is your father's occupation or job title? _____
[Example: sales representative, electrician, construction worker, cook/chef, dentist]

What is <u>your</u> highest grade completed?
[ ] < 7th grade
[ ] Junior High School (8th or 9th grade)
[ ] Partial High School (10th or 11th grade)
[ ] High School Graduate
[ ] Partial College (at least 1 year) or specialized training
[ ] College or University Graduate
[ ] Graduate Degree [master's, PhD]

What is your <u>mother's</u> highest grade level completed?
[ ] < 7th grade
[ ] Junior High School (8th or 9th grade)
[ ] Partial High School (10th or 11th grade)
[ ] High School Graduate
[ ] Partial College (at least 1 year) or specialized training
[ ] College or University Graduate
[ ] Graduate Degree [master's, PhD]

What is your <u>father's</u> highest grade completed?
[ ] < 7th grade
[ ] Junior High School (8th or 9th grade)
[ ] Partial High School (10th or 11th grade)
[ ] High School Graduate
[ ] Partial College (at least 1 year) or specialized training
[ ] College or University Graduate
[ ] Graduate Degree [master's, PhD]

What is your annual household income?
[ ] < $20,000
[ ] $20,000 to less than $30,000
[ ] $30,000 to less than $50,000
[ ] $50,000 to less than $80,000
[ ] $80,000 to less than $100,000
[ ] > $100,000
[ ] Unsure

What type of health insurance do you have?
[ ] Private [PPO, HMO]

[ ] Public [Medi-Cal / California Children's Services (CCS), Disability or SSI]
[ ] No insurance / out of pocket or self-pay
[ ] Unsure

Have you ever had general anesthesia for surgery or other procedure? If so, approximately how many anesthetics have you had?
[ ] Yes, I've had general anesthesia
[ ] No, I've never had general anesthesia

_____ # of anesthetics

Confidential

PROMIS - 29 Profile v2.0

Please complete the survey below.

Thank you!

Please respond to each item by choosing one answer per statement.

Physical Function

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1. Are you able to do chores such as vacuuming or yard work?....	○	○	○	○	○
2. Are you able to go up and down stairs at a normal pace?....	○	○	○	○	○
3. Are you able to go for a walk of at least 15 minutes?....	○	○	○	○	○
4. Are you able to run errands and shop?....	○	○	○	○	○

Anxiety

In the past 7 days...

	Never	Rarely	Sometimes	Often	Always
5. I felt fearful....	○	○	○	○	○
6. I found it hard to focus on anything other than my anxiety....	○	○	○	○	○
7. My worries overwhelmed me....	○	○	○	○	○
8. I felt uneasy....	○	○	○	○	○

Depression

In the past 7 days...

	Never	Rarely	Sometimes	Often	Always
9. I felt worthless....	○	○	○	○	○
10. I felt helpless....	○	○	○	○	○
11. I felt depressed....	○	○	○	○	○
12. I felt hopeless....	○	○	○	○	○

Fatigue

During the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
13. I feel fatigued....	○	○	○	○	○
14. I have trouble starting things because I am tired....	○	○	○	○	○

15. How run-down did you feel on average?...	○	○	○	○	○
16. How fatigued were you on average?....	○	○	○	○	○

Sleep Disturbance

In the past 7 days...

	Very poor	Poor	Fair	Good	Very good
17. My sleep quality was....	○	○	○	○	○

In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
18. My sleep was refreshing....	○	○	○	○	○
19. I had a problem with my sleep....	○	○	○	○	○
20. I had difficulty falling asleep	○	○	○	○	○

Ability to Participate in Social Roles and Activities

	Never	Rarely	Sometimes	Usually	Always
21. I have trouble doing all of my regular leisure activities with others....	○	○	○	○	○
22. I have trouble doing all of the family activities that I want to do....	○	○	○	○	○
23. I have trouble doing all of my usual work (include work at home)....	○	○	○	○	○
24. I have trouble doing all of the activities with friends that I want to do....	○	○	○	○	○

Pain Interference

In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
25. How much did pain interfere with your day to day activities?....	○	○	○	○	○
26. How much did pain interfere with work around the home?....	○	○	○	○	○
27. How much did pain interfere with your ability to participate in social activities?....	○	○	○	○	○

28. How much did pain interfere with your household chores?....	○	○	○	○	○

Pain Intensity

In the past 7 days...

	No Pain	1	2	3	4	5	6	7	8	9	Worst imaginable pain
29. How would you rate your pain on average?....	○	○	○	○	○	○	○	○	○	○	○

PROMIS SF v1.1 - Global Health

Please complete the survey below.

Thank you!

In general, would you say your health is:	○ Excellent ○ Very good ○ Good ○ Fair ○ Poor
In general, would you say your quality of life is:	○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

Rosenberg Self-Esteem Scale

Please complete the survey below.

Thank you!

Instructions

Below is a list of statements dealing with your general feelings about yourself. Please indicate how strongly you agree or disagree with each statement.

1. On the whole, I am satisfied with myself.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
2. At times I think I am no good at all.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
3. I feel that I have a number of good qualities.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
4. I am able to do things as well as most other people.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
5. I feel I do not have much to be proud of.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
6. I certainly feel useless at times.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
7. I feel that I'm a person of worth, at least on an equal plane with others.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
8. I wish I could have more respect for myself.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree
9. All in all, I am inclined to feel that I am a failure.	○ Strongly Agree ○ Agree ○ Disagree ○ Strongly Disagree

10. I take a positive attitude toward myself.

- ○ Strongly Agree
- ○ Agree
- ○ Disagree
- ○ Strongly Disagree

Multidimensional Scale Of Perceived Social Support

Please complete the survey below.

Thank you!

Instructions: We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you feel about each statement.

	Very Strongly Disagree	Strongly Disagree	Mildly Disagree	Neutral	Mildly Agree	Strongly Agree	Very Strongly Agree
1. There is a special person who is around when I am in need	○	○	○	○	○	○	○
2. There is a special person with whom I can share joys and sorrows	○	○	○	○	○	○	○
3. My family really tries to help me	○	○	○	○	○	○	○
4. I get the emotional help & support I need from my family	○	○	○	○	○	○	○
5. I have a special person who is a real source of comfort to me	○	○	○	○	○	○	○
6. My friends really try to help me	○	○	○	○	○	○	○
7. I can count on my friends when things go wrong	○	○	○	○	○	○	○
8. I can talk about my problems with my family	○	○	○	○	○	○	○
9. I have friends with whom I can share my joys and sorrows	○	○	○	○	○	○	○
10. There is a special person in my life who cares about my feelings	○	○	○	○	○	○	○
11. My family is willing to help me make decisions	○	○	○	○	○	○	○
12. I can talk about my problems with my friends	○	○	○	○	○	○	○