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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

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.

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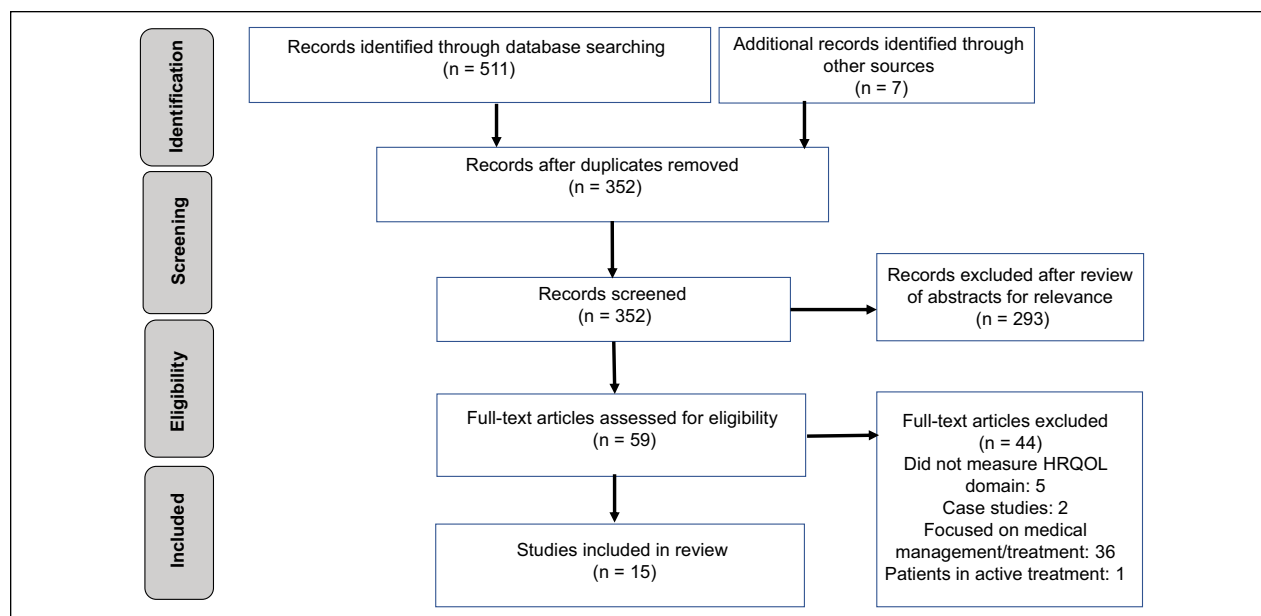


Figure 1. PRISMA diagram of literature search.

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

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 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. |

(continued)

Table 1. (continued)

| Citation | Subjects/age/location | Focus | Study design | Methods/measurements | Results/conclusion |
|--------------------------------------|---|---|---------------------------------------|---|--|
| 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). |

(continued)

Table 1. (continued)

| Citation | Subjects/age/location | Focus | Study design | Methods/measurements | Results/conclusion |
|---|---|--|-----------------|--|--|
| 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.

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 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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