

## Adolescent Psychopathology and Adult Health Behaviors in Long-term Survivors of Childhood Cancer

Lana L Harder, PhD<sup>1</sup> and Kevin R Krull, PhD<sup>2</sup>

1. Pediatric Neuropsychologist, Children's Medical Center of Dallas, and Assistant Professor, University of Texas Southwestern Medical School;

2. Associate Member, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital

### Abstract

As rates of childhood cancer survival increase and survivors reach adulthood, research aims to understand the unique ongoing difficulties for this burgeoning population. Survivors are at heightened risk for late effects associated with cancer and its treatment including those related to physical health, psychological wellbeing (i.e. cognitive and emotional functioning), and social outcomes (e.g. education, employment). Additionally, survivors are at greater risk for maladaptive health-related behaviors (e.g. tobacco use, excessive sun exposure, physical inactivity), which serve to amplify risk for late effects and secondary cancers. While risk associated with a medical history significant for childhood cancer is a stable factor, those associated with health-related behaviors are fortunately modifiable. Research efforts have yielded important findings linking cognitive and emotional difficulties with maladaptive health behaviors, which are detailed in this review. Such findings afford opportunity for targeted prevention and intervention programs to improve outcomes for survivors; however, limited research has evaluated interventions to address maladaptive health behaviors in pediatric cancer survivors and further investigation is warranted. The importance of long-term multidisciplinary follow-up is emphasized and associated challenges are discussed.

### Keywords

Adolescent psychopathology, adult outcomes, Childhood Cancer Survivor Study, health-related behaviors, late effects, oncology, psychological problems, survivorship

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**Correspondence:** Kevin R Krull, PhD, Associate Member, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS 735, Memphis, TN 38105-3678. E: kevin.krull@stjude.org

Due to advances in medical treatment over the last few decades, rates of childhood cancer survivorship have reached almost 80%.<sup>1,2</sup> The goal of treatment is to eliminate disease with the least compromise to subsequent health and quality of life.<sup>3</sup> Approximately one in every 640 young adults between 20 and 39 years of age is a survivor of childhood cancer.<sup>4</sup> As survivors reach adulthood at growing rates, research efforts have focused on long-term outcomes and have identified a number of late effects associated with cancer and its treatment. Late effects are defined as any physical, psychological, or social consequence of the disease or treatment that can emerge months or years after treatment,<sup>2</sup> often when survivors are no longer a part of the pediatric follow-up system.<sup>5</sup> It has been established that long-term survivors are at increased risk for a host of chronic medical problems stemming from damage to organ systems by chemotherapy and radiation.<sup>6</sup> Recent reports have revealed important information about the unique ongoing difficulties faced by long-term survivors. Findings from the Childhood Cancer Survivor Study (CCSS), a long-term retrospective cohort study, have revealed multiple medical late effects including those related to second cancers, cardiac disease, stroke, and reproductive issues.<sup>6</sup> Survivors of childhood cancer are also at increased risk for the development of psychopathology<sup>7</sup> and maladaptive health-related behaviors,<sup>8</sup> further

compromising overall survivor health. Moreover, emotional and cognitive difficulties have been linked to maladaptive health behaviors and provide possible targets for intervention efforts.<sup>9,10</sup> Overall, findings highlight the importance of long-term multidisciplinary follow-up care, although research has revealed multiple challenges related to such ongoing care, particularly as survivors transition to adulthood.<sup>5</sup>

### Medical Outcomes and Health-related Behavior—Adult Health Status

Survivors of childhood cancer are at greater risk for long-term morbidity and late mortality compared with the general population.<sup>1,6</sup> The majority of such problems do not become apparent until several years after diagnosis.<sup>4</sup> Individual survivor risk is determined by multiple factors including cancer diagnosis, age during treatment, treatment regimen, genetic predisposition, and health-related behaviors (e.g. level of physical activity).<sup>4</sup> Survivors of pediatric central nervous system (CNS) malignancies are at the highest risk for late mortality.<sup>11</sup> Armstrong and colleagues<sup>1</sup> found that the risk for death increased 13-fold in survivors of CNS malignancies compared with that of the general population. The most common cause of death was recurrence or progression of the primary disease, followed by medical causes of death such as second

neoplasms, cardiac disease, and pulmonary disease. Functional impairment is most closely associated with survivors of CNS tumors.<sup>12</sup>

In a study of over 10,000 adult survivors, increased incidence of chronic health problems such as second cancers, cardiovascular disease, renal dysfunction, musculoskeletal problems, and endocrine deficiencies was observed across time.<sup>6</sup> The incidence of a chronic health condition 30 years after cancer diagnosis was nearly 75%. More than 40% had a serious health problem and approximately 33% had multiple conditions. Groups at highest risk and likely to have multiple conditions were bone tumors, CNS tumors, and Hodgkin's lymphoma. Patient characteristics also influence health outcomes: females are at greatest risk for poor health status,<sup>6,12</sup> while patients diagnosed and treated at a younger age, those from racial minor groups, and those from lower socioeconomic status are more likely to experience poor health outcomes than those treated at an older age.<sup>13</sup> Overall findings underscore the importance of long-term follow-up for childhood cancer survivors. Pediatric oncology has led the development of guidelines for long-term follow-up care plans for patients.<sup>5</sup> Such guidelines are provided through the Children's Oncology Group (COG; [www.survivorshipguidelines.org/](http://www.survivorshipguidelines.org/)) and provide information on risk for late effects associated with cancer therapy as well as guidelines for healthy behavior of survivors of childhood cancer.<sup>14</sup>

### Psychological Outcomes

Survivors of childhood cancer experience adverse psychosocial outcomes including those related to emotional wellbeing, cognitive functioning, and academic and vocational difficulties.<sup>4</sup> For example, research has shown that survivors are more likely than sibling controls to exhibit symptoms of social withdrawal, depression, anxiety, and antisocial behavior in adolescence.<sup>7,9</sup> Childhood cancer survivors have also been shown to be at increased risk for a diagnosis of stress-related mental disorders such as post-traumatic stress disorder (PTSD), acute stress disorder, or adjustment disorder.<sup>12</sup> Additionally, adult survivors of childhood cancer are at increased risk for suicidal ideation.<sup>15</sup> Such risk was associated with cancer diagnosis, depression, and poor health. Identifying such associations affords opportunity for targeted prevention and intervention programs to improve outcomes for survivors of childhood cancer.

Neurocognitive functioning is another area vulnerable to the effects of childhood cancer and its treatment. Reduced cognitive functioning is thought to be related to white matter damage associated with cranial irradiation<sup>16</sup> as well as high-dose antimetabolite chemotherapy.<sup>17</sup> Among survivors, studies have documented poorer performance and decline across time in the area of intelligence.<sup>18,19</sup> This finding is believed to be associated with survivors' failure to learn at the rate of peers rather than a loss of previously acquired knowledge.<sup>20</sup> The rate of intelligence quotient (IQ) decline has been associated with risk factors including age at time of treatment, female sex, radiotherapy dose, and the volume of brain involved in treatment.<sup>20</sup> Armstrong and colleagues<sup>1</sup> found that after treatment with radiation, survivors of CNS malignancies showed higher rates of neurocognitive impairment compared with siblings. More than 40% of survivors of medulloblastoma or primitive neuroectodermal tumors had deficits in attention and/or processing speed. Survivors of astrocytoma and glial tumors showed the same deficits, with additional deficits in memory. In general, higher doses of cranial radiotherapy were

related to increased cognitive difficulty. However, survivors treated with chemotherapy only are also at risk for neurocognitive impairment.<sup>21</sup> In adulthood, survivors of childhood cancer endorse significantly more neurocognitive impairment compared with sibling controls.<sup>22</sup> Neurocognitive impairment in survivors of childhood cancer is thought to affect psychosocial outcomes related to education and employment. For example, neurocognitive deficits, greater special education service utilization, and difficulty with school progression (i.e. high school graduation) are more common for survivors treated with radiation therapy and were observed among 70% of brain tumor survivors diagnosed before six years of age.<sup>23</sup> Survivors of brain tumors treated with higher doses of radiation are less likely to complete high school, be employed, or live independently. Greater radiation dose and younger age at treatment increased vulnerability.<sup>19,24</sup>

### Predictors of Adult Health-related Behavior

Given the multiple medical risks associated with cancer and its treatment, it is of the utmost importance that survivors of childhood cancer make decisions to promote overall health. While a medical history of childhood cancer and associated risk for late effects is a stable factor, those associated with health-related behaviors are fortunately modifiable. Risk for late effects may be amplified by maladaptive health-related behaviors. Those clinicians providing long-term follow-up care to survivors should monitor for maladaptive health-related behaviors such as tobacco use, physical inactivity, obesity, and excessive sun exposure, any of which is likely to have synergistic effects on short- and long-term overall health. Research evaluating cardiovascular risk in survivors of childhood cancer revealed several associated factors.<sup>25</sup> In addition to factors that are not subject to intervention (e.g. medical history significant for radiation exposure), a sedentary lifestyle was associated with increased cardiovascular risk. It is important to note that this factor is modifiable and that change in this area may lower risk and promote overall health. It was also found that survivors of childhood acute lymphoblastic leukemia (ALL) were less likely to be physically active, further increasing their risk for adverse medical outcomes.<sup>8</sup> In this study, patients treated with increased doses (>20Gy) of radiotherapy were at greater risk. Given the heightened risk for health problems in cancer survivors, the importance of engaging in physical activity is great. Given the impact of maladaptive health-related behavior on overall health, it is important to understand what predicts these behaviors to inform appropriate and effective intervention to promote healthy habits in survivors of childhood cancer. As reviewed above, survivors of childhood cancer are at risk for the development of psychological problems.<sup>7</sup> While research has linked psychological problems to poor health behavior, few studies have investigated such associations in survivors of childhood cancer.<sup>9</sup>

Despite heightened risk for adverse medical outcomes, childhood cancer survivors reportedly engage in smoking at a comparable rate to the general population.<sup>26</sup> Kahalley and colleagues<sup>10</sup> explored whether cognitive deficits predicted smoking in adult survivors of childhood cancer. Findings indicated that childhood attention problems were a predictor of adult smoking. Additionally, adult survivors with executive dysfunction in the areas of memory and emotional regulation were more likely to smoke. These findings underscore the importance of early detection and intervention for cognitive late effects of childhood cancer. In a study of 6,440 survivors of childhood cancer, cognitive and emotional problems

were associated with health behaviors (Krull K et al. Neurocognitive functioning, health behaviors and health care utilization in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study, under review). Specifically, results showed that impaired attention or organization skills were associated with lower rates of physical activity, while significant rates of anxiety predicted higher rates of physical activity. In this study, the authors note that it is unclear whether physical activity promotes cognitive functioning or if those with cognitive impairment struggle to manage a regular schedule that allows for time dedicated to physical activity. The results of this study also revealed that survivors with impaired organization or increased somatization were less likely to receive regular dental care. Obesity was related to lower rates of adherence to recommended medical screening exams. Overall, survivors engaged in low rates of protective health behaviors.

A recent study examined the relationship between parental reports of psychological problems during adolescence and adult health status and health-related behavior.<sup>9</sup> The results indicated that social withdrawal during adolescence increased survivors' risk for obesity in adulthood. Additionally, the use of stimulant medication during adolescence was associated with an increased risk for adulthood obesity. Social withdrawal and use of antidepressants were associated with physical inactivity in adulthood. A considerable percentage of adult survivors reported low levels of physical activity and limited or no sunscreen use, although they did not show increased risk compared with siblings. Nevertheless, this is concerning, as survivors should take extra precautions when making health-affecting decisions given that they are more vulnerable to adverse medical outcomes. The results of this study link increased psychological problems during adolescence with increased risk for health problems in adulthood. Early identification and treatment of psychological problems may serve to lower overall health risk.

## Interventions to Address Health-related Behavior

Given that many outcomes associated with childhood cancer and its treatment (i.e. risk for second malignancies, cardiovascular problems) are stable and, thus, not subject to intervention, it is important to identify and address those factors that are subject to modification to potentially contribute to the overall health of survivors. Few studies have evaluated interventions to address maladaptive health-related behavior in pediatric cancer survivors.<sup>27</sup> One study aimed to reduce intention to use tobacco by providing intensive late effects risk counseling, educational materials, goal setting, and follow-up telephone counseling.<sup>28</sup> Compared with controls, subjects in the intervention group showed significantly greater knowledge, higher perceived vulnerability, and lower intention to use tobacco at 12 months

post-intervention. Another study evaluated a behavioral intervention to change survivors' health knowledge, health perceptions, and practice of health-protective behaviors.<sup>29</sup> While the results showed no significant difference between the treatment group and controls, exploratory analysis revealed greater health knowledge in female survivors. Further longitudinal investigation is warranted to evaluate the efficacy of lifestyle intervention in increasing healthy behavior across time. Literature suggests that survivor knowledge of increased vulnerability to health problems is not associated with the practice of healthy behaviors and that knowledge is required but not adequate to influence behavioral change.<sup>27</sup> Hudson and Findlay<sup>27</sup> emphasize the importance of clinician recognition of the complex developmental phase of adolescence, including denial and sense of invulnerability, which affects motivation to engage in healthy habits.

## Conclusions and Future Directions

Longitudinal research evaluating survivors of childhood cancer provides important information regarding their complex needs across medical, psychological, and behavioral areas. Research has begun to identify factors related to maladaptive health-related behaviors, often evident during childhood or adolescence, revealing that a lack of identification and/or treatment for psychological problems intensifies risk for poor health status and adverse health outcomes in adulthood. Childhood cancer survivors can benefit from early diagnosis, intervention or preventive care to address an array of conditions influenced by cancer and its treatment.<sup>27</sup> The findings presented in this review emphasize the importance of long-term follow-up with a multidisciplinary approach including regular contact with physicians and other specialists.<sup>30</sup> Unfortunately, such care is not the norm for survivors, especially during the adult years,<sup>31</sup> and medical visits tend to decrease as the age of the survivor increases.<sup>32</sup> Many survivors of childhood cancer are lost to follow-up care as they age, leave the care of their parents, and take charge of their own medical care.<sup>5</sup> Moreover, many of the institutions where childhood cancer patients are treated are pediatric centers that do not provide care to patients once they become adults,<sup>1</sup> which highlights the importance of a successful transition to adult-oriented healthcare for survivors of childhood cancer<sup>2</sup> and emphasizes the role of the primary care physician in risk-based care of survivors.<sup>4</sup>

Finally, it is important to acknowledge that, as treatment protocols change across time, late effects are expected to also evolve. Modern therapeutic regimens that utilize more chemotherapy to decrease or limit radiation are likely to improve long-term outcomes and lower the risk for late effects.<sup>1</sup> Efforts such as the CCSS allow for the longitudinal study and monitoring of such changes. ■

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