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Life Milestones and Cancer-related Late Effects among Young Adult Survivors of Childhood
Cancers

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

In Epidemiology

by

Yoonji Kim

Dissertation Committee:
Professor Joel Milam, Chair
Professor Michael Hoyt
Associate Professor Michelle Fortier

2024

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As a childhood cancer survivor myself, this dissertation is deeply personal. My life has been a journey of survivorship, and this research extends from my personal experience to my professional career. I am thankful for the opportunity to merge my lived experience with my academic pursuits, contributing to the field of childhood cancer survivorship research.

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ABSTRACT OF THE DISSERTATION

Life Milestones and Cancer-related Late Effects among

Young Adult Survivors of Childhood Cancers

by

Yoonji Km

Doctor of Philosophy in Epidemiology

University of California, Irvine, 2024

Professor Joel Milam, Chair

Given significant advancements in cancer treatment, close to 85% of children and adolescents diagnosed with cancer have long-term survival. In the United States, there are approximately 500,000 childhood cancer survivors looking forward to many years ahead. Yet, the aftermath of cancer poses substantial challenges, including cancer-related late effects, psychosocial struggles, and financial burdens. The objective of this dissertation is to further our understanding of life milestones (e.g., employment, educational attainment, living arrangement, relationship status) and cancer-related late effects among Young Adult Childhood Cancer Survivors (YACCS) using a population-based sample from the Los Angeles Cancer Surveillance Program, the Surveillance, Epidemiology, and End Results (SEER) Cancer Registry covering Los Angeles County.

Study 1 aimed to examine the prevalence of life milestones among YACCS and non-cancer population-based cohort controls. The study conducted a matched-cohort case control to compare YACCS and a non-cancer comparison group from the California Health Interview

Survey (CHIS) (matched by age, sex, year of survey, and race/ethnicity) on the prevalence of life milestones (e.g., full-time employment, educational attainment, living independently, relationship status). The results showed that YACCS were less likely to have a college degree, have a full-time employment, and married/partnered compared to their peers without a cancer history. In contrast, they were more likely to be unemployed, have a part-time employment, and live with a parent.

The objective of study 2 was to assess the relationship between delays in achieving life milestones and depressive symptoms over time in YACCS. The study used linear regression model with depressive symptoms as the outcome variable and delay in life milestone as the exposure variable. Delays in educational attainment was a significant predictor of depressive symptoms, even when demographic factors and baseline depressive symptoms were controlled.

The aim of study 3 was to identify the subgroups of YACCS based on their cancer-related late effects and how each subgroup is associated with life milestone achievement. The study used latent class analysis and logistic regression models. The latent class analysis revealed multimorbidity group and resilient group based on cancer-related late effects reported by the survivors. The multimorbidity group were less likely to have a college degree and be employed full-time compared with the resilient group after adjusting for demographic factors, years since diagnosis, and treatment intensity.

This research is a population-based study that utilizes a diverse sample of recently treated YACCS in Los Angeles County. It offers valuable insights into their post-cancer experiences during a period marked by medical and treatment advancements in childhood cancers. The significance of this research lies in its potential to positively impact cancer survivorship research by enhancing our understanding of the risk and protective factors that affect the achievement of

life milestones among YACCS. It also offers a window into the long-term effects of childhood cancer on the social determinants of health and wellbeing. The findings from this study not only contribute to the existing body of knowledge but also lay the groundwork for future research aimed at developing targeted interventions. These interventions will be tailored to the age-specific needs of survivors, focusing on promoting social integration and independence, which are pivotal in securing a high-quality survivorship experience.

CHAPTER 1: Introduction

Background

In the United States, nearly half a million individuals have survived childhood cancer (1). While close to 85% of children diagnosed with cancer achieve long-term survival or cure (2) they continue to face substantial health challenges as they age. This group of young adult childhood cancer survivors (YACCS) is uniquely vulnerable, navigating a complex landscape of ongoing medical, psychosocial, and developmental needs.

Research by the National Cancer Institute (NCI) estimates that childhood cancer survivors (CCS) have fivefold increased risk of negative health outcomes compared to their non-cancer siblings (16). Additionally, half of the CCS have reported experiencing health complications, with about a quarter facing severe or life-threatening issues (17). According to the Childhood Cancer Survivor Study (CCSS), 73% of childhood cancer survivors will have at least one chronic physical health issue by age 40. Additionally, 42% will either develop a serious, life-threatening, or disabling condition, or die from a chronic illness. (18). Long-term complications may encompass secondary cancers, chronic illnesses, and neurocognitive deficits (19-21). Thus, CCS are ten times more likely to die earlier compared to the overall population. (22,23).

Adolescence and young adulthood are a time of growth, opportunity, and critical developmental milestones, including pursuing educational and vocational opportunities, exploring intimate relationships, and separating from parents (3,4). Consequently, cancer is particularly disruptive for YACCS not only because disrupted higher education or career goals can compromise their future earning potential but also because interruptions during their developmental trajectory may exacerbate psychological distress (5,6).

YACCS experience significantly higher emotional distress and depression compared to control groups (7-10). Younger cancer survivors also experience greater financial toxicity and job insecurity which can jeopardize their long-term earning potential and lead to prolonged financial distress (11, 13). Such challenges can undermine their personal independence, sometimes resulting in a "failure to launch" into adulthood (14). Financial barriers, for instance, can extend their dependence on parents (12). Furthermore, delays or absences in achieving life milestones are linked with poorer psychological and social outcomes (14). Vocational, educational, financial, and interpersonal development are crucial for high-quality survivorship (15), but these issues remain under-researched in the YACCS population.

Educational Challenges for YACCS

Educational attainment plays a pivotal role in predicting future employment prospects, earnings, and societal integration, thus serving as a crucial quality-of-life indicator for long-term cancer survivors. However, cognitive impairments resulting from treatments, combined with the loss of schooling time due to treatment schedules, can leave survivors academically behind (3, 38-42, 50). Irregular school attendance patterns can persist for years after treatment ends, compounding the educational challenges these survivors confront (88, 59).

A recent systematic review highlighted the risk YACCS face in terms of adverse socioeconomic outcomes, particularly concerning education attainment and income level (37). Population-based studies have consistently demonstrated lower educational attainment among YACCS compared to their general population counterparts (38-40). Findings from the CCSS revealed that CCS had a higher utilization of special education services than their non-cancer siblings (41). Furthermore, neurocognitive deficits have been identified as a significant factor

associated with educational difficulties in YACCS (42), particularly among survivors of CNS

tumors and leukemia who are at a higher risk for educational underachievement (37). Similarly,

survivors of non-Hodgkin lymphoma and neuroblastoma were more likely to report not

completing high school than other survivors (41). Enhancing educational opportunities is thus

critical for YACCS, given the strong association between educational attainment and future

vocational opportunities and earning potential.

Employment and Financial Independence in YACCS

Stable employment and financial independence are key milestones of adulthood (31).

Research underscores that financial aspirations increase during young and established adulthood

(32,33), with an inverse relationship observed between the value placed on wealth and well-

being (34). Conversely, income levels have been positively correlated with well-being (35, 36),

especially for those who are just starting to be financially self-sufficient. This suggests that

financial milestones are intimately linked to well-being.

YACCS are more likely to face unemployment or to be engaged in lower-skilled jobs

compared to non-cancer controls (4, 43). Two systematic reviews and meta-analyses focusing on

work life and employment indicated that survivors had double the likelihood of unemployment

than their non-cancer peers (4,43). A more recent meta-analysis reported that YACCS have a

50% greater likelihood of unemployment relative to the general population (44-47). Notable risk

factors for unemployment among this demographic include female sex, younger age at diagnosis,

cranial radiation treatment (CRT), CNS tumor diagnosis, and cancer-related late effects.

The long-term impact of childhood cancer can significantly influence the employment

prospects of adult survivors. Chronic health issues, psychological and physical impairments, and

the risk of secondary malignancies can obstruct educational achievements and job opportunities (41, 88). Late effects may limit survivors' ability to maintain steady employment or pursue specific careers. The cancer experience can also alter survivors' educational and vocational aspirations, and concerns about future prospects may inhibit their transition into further education and work (3-5). CNS tumor survivors, in particular, face persistent difficulties due to their treatment, with higher unemployment rates in adulthood (4). Studies have found that YACCS have lower overall income compared to the general population, a disparity more pronounced among CNS tumor survivors or those who underwent CRT (48-50). Lower educational attainment and unemployment adversely affect the survivors' financial potential, which is significantly less than their siblings or the general population (51-53).

Relationships and Independent Living in YACCS

Emerging into young adulthood is characterized by the pursuit of goals such as completing education and starting a career (33). However, as individuals transition to established adulthood, milestones such as living independently, forming close social relationships, and starting a family become more central (54,55). Individuals with more significant social connections during established adulthood report greater midlife well-being (56).

YACCS often report adverse impacts on relationships (57). They are less likely to be married or in a partnership compared to non-cancer controls (58), with the percentage of ever-married survivors slightly lower than the broader population in comparable age brackets (88). Female survivors and those who have overcome brain tumors are particularly less likely to be married, with a significantly higher proportion of brain tumor survivors never marrying compared to the overall survivor group (88).

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YACCS experience delays in psychosexual development, such as having a first romantic partner or engaging in sexual intimacy at an older age relative to their non-cancer peers (58). Previous research indicates that survivors are twice as likely to reside with their parents compared to their siblings (59), a trend most pronounced among survivors of CNS tumors and leukemia. The increased risk of dependent living can be attributed to the effects of cranial radiation therapy, which has detrimental impacts on neurocognitive, physical, and behavioral functioning. These effects indirectly contribute to dependency through impacts on neurocognitive late effects, the requirement for targeted neurological medications, and mental health issues. Neurocognitive difficulties, particularly task efficiency, lead to dependency through mental health challenges like depression and somatization (59-62).

Psychological distress is also a factor affecting the ability to live independently. A robust correlation between depression and dependent living highlights the debilitating effects of mental health issues. Although most childhood cancer survivors adapt well post-treatment, a notable subset continues to struggle with emotional distress, leading to deficits in adaptive skills and dependent living. The stress associated with dependency may further exacerbate depressive symptoms (59).

Psychological distress and developmental challenges in YACCS

Lower income, lower education, female sex, cancer-related late effects, and unpartnered status have been positively associated with psychological distress among YACCS (64). However, the direction of these effects remains unclear, as mental health issues may be either a predictor or a consequence of these factors. Poor mental health has been consistently associated with poor physical health outcomes, including pain and chronic health conditions among

YACCS (65-67). Given the strong relationship between mental and physical health, cancer-related late effects can significantly hamper psychological adjustment. CNS tumor survivors and those with a history of intensive treatment, including CRT, are associated with poor adjustment and psychological symptoms (64,66,68). Survivors of bone cancer are at a heightened risk of psychosocial problems, likely because on physical mobility and pain (64,68).

Delays in life milestone achievement and the resulting adverse socioeconomic outcomes in YACCS may stem from or be compounded by the childhood cancer diagnosis and treatment. Childhood cancers exhibit diverse patterns of etiology (69), incidence (70), treatment, survival rates (71), supportive care, and late effects (72,73), suggesting that patterns of socioeconomic outcomes may differ across cancer types. Further research is essential to investigate the impact of various clinical characteristics of YACCS on their ability to reach life milestones. Survivors with lower educational attainment and income are at increased risk of not engaging in cancer-related follow-up care (74). Those experiencing financial hardship, particularly those with limited health insurance access or high out-of-pocket medical expenses, are more inclined to skip survivorship care (75, 76). Lower educational attainment, reduced income, and chronic health conditions have been positively linked to the risk of financial burden (77). The implications of a cancer diagnosis and treatment for socioeconomic achievements tend to negatively impact YACCS compared to older adult survivors, as YACCS are more likely to miss out on educational and occupational opportunities prior to the cancer occurrence.

Conceptual Model and Study Overview

The dissertation study aims to examine the relationship between cancer-related late effects and delays in life milestones affecting adverse social outcomes for YACCS using a

population-based sample from the Los Angeles Cancer Surveillance Program. This approach utilizes an adapted social determinants of health conceptual framework (Figure 1) to demonstrate pathways of life milestones and socioeconomic factors impacting the health and well-being of YACCS. This original model has been effectively used to explore patterns of health and the health inequalities at the population level for children with neurodisabilities (81).

The conceptual model illustrates the relationship between cancer-related late effects and life milestones as social determinants of health, with a focus on the reciprocal influence between these factors over time. The diagram shows two main components: cancer-related late effects and life milestones as social determinants of health. The model highlights two specific aims. Aim 2 investigates how delays in achieving life milestones are associated with psychological late effects of cancers. Aim 3 examines how different subgroups of cancer-related late effects are related to achieving life milestones. The direction is represented by arrows indicating Aim 2 (left arrow) and Aim 3 (right arrow), with an additional time dimension shown to emphasize the longitudinal nature of these relationships.

Life milestones such as education, employment, living arrangement, and relationship status are critical social determinants of health. These milestones significantly impact an individual's overall well-being and health outcomes. Education provides knowledge and skills that influence employment opportunities and socioeconomic status. Employment affects financial stability, access to healthcare, and stress levels. Living arrangements contribute to physical safety and mental health, while relationship status and social capital provide emotional support and connectedness. Therefore, these milestones are integral to understanding health disparities and outcomes in cancer survivors.

The model recognizes a bidirectional relationship between life milestones and depressive symptoms. Cancer-related late effects, including depressive symptoms, can hinder the achievement of key life milestones. For example, health complications and depressive symptoms may limit educational attainment and stable employment. Conversely, the failure to achieve these milestones can exacerbate depressive symptoms, creating a vicious cycle. For instance, unemployment or unstable living arrangements may increase stress and depression, further impacting physical health.

Research indicates that educational and vocational achievements are crucial for long-term socioeconomic stability and health (37). Social-developmental factors like living arrangements and relationship status are essential for mental health and social support, which are particularly important for cancer survivors dealing with long-term physical and psychological effects. The model aims to capture the complexity and interdependence of these factors, providing a comprehensive framework to guide interventions and improve outcomes for cancer survivors.

The adapted conceptual model demonstrates the dynamic and reciprocal relationship between cancer-related late effects and life milestones as social determinants of health. By addressing these interconnected pathways, the model underscores the importance of a holistic approach to improving health outcomes for cancer survivors, acknowledging both the direct impact of late effects and the crucial role of achieving key life milestones.
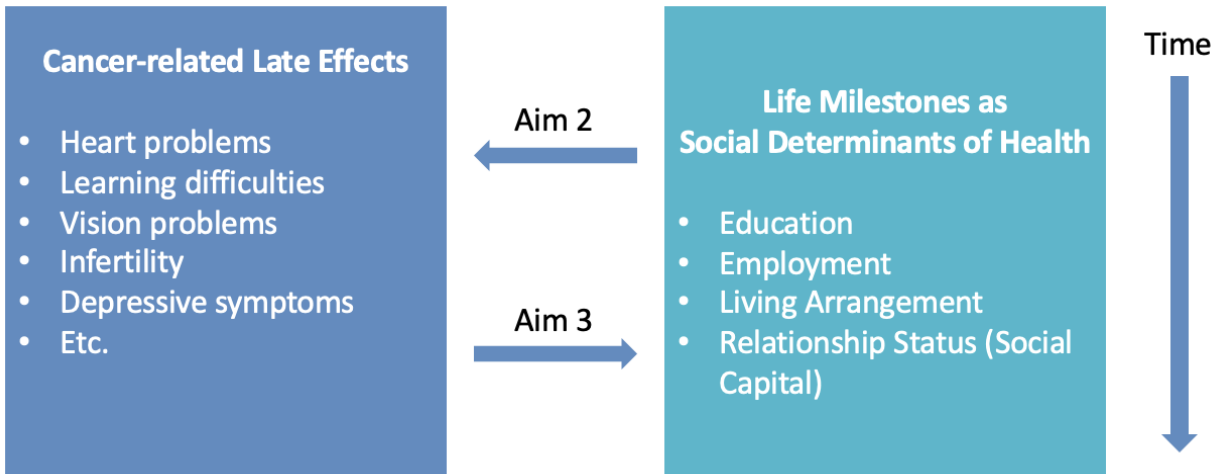
Figure 1. Adapted Social Determinants of Health Conceptual Model and Overview of Specific Aims 2 and 3.

This study has greater representation of YACCS from various cultural backgrounds and clinical characteristics than previous research, which enhances its generalizability. Los Angeles County is the most populous county in the United States with over 10 million residents. It offers a uniquely diverse population with significant variations in population density and socioeconomic status. The Los Angeles Cancer Surveillance Program, with its strong representation across ethnicities, urban/rural settings, and healthcare facilities, will provide valuable insights into psychosocial development, health disparities, and socioeconomic inequalities among YACCS. This study focuses on a vulnerable and understudied population, examining the associations of physical and psychological late effects with life milestone achievements of YACCS. Additionally, this study employs a large population-based approach, presenting a unique opportunity to examine potential health and socioeconomic inequities between YACCS and their non-cancer peers.

Cancer survivorship care for young adults should extend beyond the physical and cognitive dimensions of the disease, focusing also on optimizing the psychosocial function of

YACCS, such as developing autonomy and establishing meaningful social relationships (78-80).

These studies will contribute to our understanding of potential risks that could interrupt the

psychosocial development of YACCS. The results of the study can inform healthcare

professionals in supporting the psychosocial well-being of YACCS, ultimately helping them in

achieving life milestones.

CHAPTER 2: Life Milestone Attainment in YACCS Compared to Non-Cancer Peers

2.1 Introduction

Family, work, financial self-sufficiency, relationships, and health domains are important life milestones during young adulthood. While there may be differences in the value of each domain between individuals, each life milestone is a hallmark of life-long wellbeing (24-26). The relationship between the pursuit of life milestones and wellbeing is generally stronger when the achievement aligns with societal expectations of what should be pursued at different stages in the lifespan (27-29). However, YACCS are at risk for disrupted psychosocial development secondary to their cancer diagnosis, treatment, and cancer-related late effects. The impact of the protracted time course spanning cancer diagnosis, treatment, and survivorship may result in psychological distress, adjustment difficulties, delays in educational attainment, and missed vocational and relationship opportunities (30). Many YACCS experience difficulties related to the development of mental health symptoms, failure to meet expected life milestones, such as inability to achieve autonomy and financial self-sufficiency (30).

As the YACCS population continues to grow, research into their long-term psychosocial development becomes increasingly critical. In contrast to the adverse socioeconomic outcomes and health inequalities experienced by YACCS, the research on their long-term health and life milestone achievement remains underexamined. Studies on long-term survivors of childhood cancer are invaluable for optimizing care and providing insights into potential targets for future interventions and policy strategies aimed at reducing childhood cancer-related health disparities (63).

Study 1 is designed as a matched-cohort analysis to assess the probability of achieving life milestones among YACCS compared to a non-cancer cohort. The comparison group is

selected from the California Health Interview Survey (CHIS), with matching based on age, sex, year of survey, and race/ethnicity. The life milestone variables include employment (full-time, part-time, unemployed), educational attainment (having a college degree), living with a parent, and relationship status (married/partnered vs. single).

HYP1a: YACCS will be less likely to hold at least a college degree compared with non-cancer controls.

HYP1b: YACCS will be less likely to have full-time employment and more likely to have part-time employment or be unemployed compared with non-cancer controls.

HYP1c: YACCS will be more likely to live with a parent compared with non-cancer controls.

HYP1d: YACCS will be less likely to be married or partnered compared with non-cancer controls.

HYP1e: YACCS will be less likely to achieve life milestones as treatment intensity increases.

2.2 Methods

Participants

The data originated from the Project Forward Cohort, which is a population-based study examining risk and protective factors of cancer-related follow-up care in YACCS (82). These participants were recruited via Los Angeles Cancer Surveillance Program, which is the cancer registry for Los Angeles County (part of the Surveillance, Epidemiology, and End Results program, SEER). The study included childhood cancer survivors who were between the ages of 18 and 39 when the study launched in 2015. Eligible participants were those diagnosed with cancer before the age of 19 during the years 1996 to 2010 in Los Angeles and Orange County,

with a cancer stage of 1 or higher for brain cancers, stage 2 or higher for other types, and who were at least five years beyond their initial diagnosis.

CHIS is a population-based telephone survey conducted among California's residential, non-institutionalized population (113). CHIS gathers extensive information across all age groups on various health-related topics, including health status, conditions, behaviors, insurance access, health care services, and other related issues. The comparison data were specifically drawn from the Los Angeles County samples from the 2015, 2016, and 2017 survey years, accessed through the Data Access Center at the UCLA Center for Health Policy Research.

Procedures

Eligible and interested participants were provided with a study questionnaire through internet, mail, or phone. Recruitment methods involved sending initial postcards and a bilingual (English and Spanish) self-report survey. Out of 2,788 eligible childhood cancer survivors, 1,106 responded to the questionnaire. There were 1,426 individuals who did not participate (e.g., lost after all efforts, declined to participate) and 196 were considered ineligible (e.g., incompetent, or deceased). The final analytical sample included 1,106 young adult CCS, excluding 60 individuals who had undergone cancer treatment within two years before the study. Responder analyses were conducted using the demographic and clinical variables available from the registry. No differences were observed between non-responders and responders in age at diagnosis, years since diagnosis, current age, cancer type, and stage of disease. The study procedures were approved by the California State Committee for the Protection of Human Subjects, the Institutional Review Board at the University of Southern California, and the California Cancer Registry.

Measures

Demographic and Clinical Characteristics. The study captured a range of demographic and clinical variables, including age at diagnosis, age at the time of survey, and years since diagnosis. The types of cancer were categorized into specific groups such as leukemia, lymphoma, and thyroid, among others. These variables were sourced from clinical records and the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Demographic information such as gender, race/ethnicity, and the socioeconomic status (SES) of the neighborhood at the time of diagnosis were derived from the SEER registry complemented by self-reported questionnaires to enhance accuracy and detail.

Neighborhood Socioeconomic Status. Participants' socioeconomic status (SES) was ascertained based on their residence's census tract at the time of the survey. Specifically, data from the census tract were employed to construct a SES composite score, which was composed of seven indicators: the education index, the percentage of individuals exceeding 200% of the poverty line, the percentage of individuals in blue-collar occupations, the percentage of individuals employed, the median rental cost, the median value of owner-occupied housing units, and the median household income. The composite scores were assigned on a quintile scale ranging from 1 to 5, with 1 representing the lowest SES quintile and 5 representing the highest.

Relationship Status. Current relationship status was self-reported by participants, operationalized as a binary variable to denote whether an individual was married or in a partnership versus being single.

Educational Attainment. Participants provided self-reported data on their highest level of educational attainment. This was dichotomized into whether participants had achieved a college degree or higher education level.

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Employment Status. Employment status was assessed by self-report, where participants indicated if they were engaged in full-time, part-time employment, or if they were unemployed at the time of the survey.

Living Arrangements. The survey also included questions about current living arrangements. A binary variable indicated whether participants were residing with at least one parent.

Treatment Intensity. The Intensity of Treatment Rating Scale 2.0 (ITR-2) was employed to gauge treatment intensity, synthesizing information from the cancer registry, medical records, and survivors' self-reports of treatment and relapse. This scale differentiates treatment into four levels of intensity: 'Least intensive' which might include singular treatments such as surgery, 'Moderately intensive' involving single-mode treatments like chemotherapy or radiation, 'Very intensive' that combines two or more treatment modalities, and 'Most intensive' for treatments inclusive of relapse protocols (97).

Statistical Analysis

The comparison group was selected from the CHIS, matching for demographic characteristics. Matching was done on a 1:3 ratio with CHIS participants matched on current age, sex, year of survey, and race/ethnicity with the YACCS cohort. Neighborhood socioeconomic status was adjusted in logistic regression analyses. For each cohort, proportions were computed for demographic characteristics and, where applicable, cancer and treatment attributes, in relation to key life milestones. Conditional logistic regression was utilized to investigate the relationship between being a case or control and the attainment of life milestones, with a dichotomous outcome variable (achievement: yes/no). This analysis facilitated the estimation of odds ratios

(ORs) along with 95% confidence intervals (95% CIs) to gauge the strength and precision of the associations.

Additional stratified analyses were conducted on demographic and clinical factors such as years since diagnosis, sex, treatment intensity, age category, and race/ethnicity to test hypotheses within subgroups. All statistical procedures were conducted using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC). Significance testing was two-tailed with an alpha level set at 0.05, with p-values below this threshold deemed to indicate significant differences.

2.3 Results

Comparisons of YACCS with Matched Non-cancer Controls

The descriptive analysis of YACCS and their matched controls are presented in Table 2.1. A variety of cancer types were reported among survivors, with leukemia being the most common (36.1%). The years since diagnosis for survivors showed that 52.2% had been diagnosed 15 or more years ago, 32.0% between 10-14 years ago, and 15.8% less than 10 years ago. In terms of treatment intensity, 49.2% of survivors underwent very intensive treatment, and 13.4% underwent the most intensive treatment.

Significant differences were observed in neighborhood socioeconomic status (nSES) of neighborhoods, with a lower percentage of survivors living in the highest SES neighborhoods compared to controls (18.1% vs. 12.2%, p < .0001). Marital status also showed significant differences, with fewer survivors being married or partnered compared to controls (28.1% vs. 33.3%, p = .002). More survivors were single (never married) (69.0% vs. 62.2%, p < .0001) and living with a parent (52.3% vs. 32.8%, p < .0001).

Educational attainment was similar between the two groups (29.0% of survivors held at least a college degree compared to 30.4% of controls, $p = .35$). Employment status showed significant differences, with more survivors unemployed (34.2% vs. 22.8%, p < .0001) and fewer employed full-time (42.9% vs. 63.4%, p < .0001) or part-time (21.2% vs. 13.8%, p < .0001).

Table 2.1. Descriptive statistics of YACCS and their matched controls.

Characteristic		Survivors n = 1,106	Control n = 3,292	*P*-value
Year of survey completed N (%)				
	2015	275 (25.0)	823 (25.0)	
	2016	429 (38.6)	1271 (38.6)	
	2017	401 (36.4)	1198 (36.4)	
Age at survey mean (SD), range		26.2 (4.9), 18-39	26.2 (4.9), 18-39	
Age category N (%)				
	18-20	131 (11.9)	392 (11.9)	
	21-25	422 (38.3)	1260 (38.3)	
	26-29	339 (30.4)	1017 (30.4)	
	30-39	213 (19.4)	639 (19.4)	
Years since diagnosis N (%)				
	< 10	174 (15.8)	NA	
	10-14	354 (32.0)	NA	
	15+	577 (52.2)	NA	
Sex N (%)				
	Female	562 (50.9)	1675 (50.9)	
	Male	543 (49.1)	1617 (49.1)	
Race/ethnicity N (%)				
	Non-Hispanic White	324 (29.3)	972 (29.3)	
	Hispanic/Latinx	570 (51.6)	1704 (51.6)	
	Asian	107 (9.7)	311 (9.7)	
	Other	104 (9.4)	305 (9.4)	
Neighborhood SES N (%)				
	Lowest	247 (25.1)	847 (25.8)	
	Low	195 (19.8)	765 (23.3)	
	Medium	188 (19.1)	682 (20.8)	<.0001
	High	178 (18.1)	592 (18.0)	

Highest	178 (18.1)	401 (12.2)	
Cancer type N (%)			
Leukemia	392 (36.1)	NA	
Lymphoma	240 (21.7)	NA	
Brain & other nervous system	169 (15.2)	NA	
Endocrine system	60 (5.1)	NA	
Bones & joints	56 (5.0)	NA	
Skin	41 (3.5)	NA	
Genital system	56 (5.2)	NA	
Other[a]	92 (8.2)	NA	
Treatment intensity N (%)			
Low-modest	413 (37.3)	NA	
Very intensive	544 (49.2)	NA	
Most intensive	148 (13.4)	NA	
Married or partnered N (%)	311 (28.1)	1097 (33.3)	.002
Single (never married) N (%)	751 (69.0)	2047 (62.2)	<.0001
Living with a parent N (%)	568 (52.3)	1080 (32.8)	<.0001
Hold at least a college degree N (%)	316 (29.0)	1001 (30.4)	.35
Employment N (%)			
Full-time	474 (42.9)	2087 (63.4)	<.0001
Part-time	234 (21.2)	454 (13.8)	<.0001
Unemployed	378 (34.2)	751 (22.8)	<.0001

Note. The percentages are from the total number of participants who provided data for each variable, not from the total number of individuals in each cohort; percentages may not add up to 100 due to rounding. NA denotes not applicable.

[a] Oral cavity & pharynx, digestive system, respiratory system, soft tissue including heart, urinary system, eye & orbit, miscellaneous

Main Outcomes

The matched logistic regression analyses for the case-control study are reported in Table 2.2. For marital status, being married or partnered was associated with lower odds among YACCS in both unadjusted and adjusted models, with an odds ratio (OR) of 0.75 (95% CI: 0.63-0.88, $p = .0005$) and 0.69 (95% CI: 0.58-0.82, $p < .0001$), respectively. Conversely, being single

was associated with higher odds in YACCS, with an unadjusted OR of 1.49 (95% CI: 1.26-1.76, $p < .0001$) and an adjusted OR of 1.62 (95% CI: 1.35-1.94, $p < .0001$).

YACCS were also more likely to be living with a parent, as indicated by an OR of 2.87 (95% CI: 2.42-3.39, $p < .0001$) unadjusted and 3.34 (95% CI: 2.78-4.00, $p < .0001$) adjusted.

Regarding educational attainment, the likelihood of having a college degree was not significantly different in the unadjusted model (OR: 0.92, 95% CI: 0.78-1.09, $p = .32$). However, after adjustment, YACCS were less likely to have a college degree compared to controls (OR: 0.79, 95% CI: 0.66-0.95, $p = .0142$).

For employment status, YACCS were substantially less likely to have full-time employment, with both unadjusted (OR: 0.40, 95% CI: 0.34-0.46, $p < .0001$) and adjusted (OR: 0.39, 95% CI: 0.33-0.45, $p < .0001$) models showing a strong association. They were more likely to be in part-time employment, indicated by an OR of 1.71 (95% CI: 1.43-2.05, $p < .0001$) unadjusted and 1.67 (95% CI: 1.38-2.02, $p < .0001$) adjusted. Additionally, the likelihood of unemployment was higher among YACCS, with an unadjusted OR of 1.81 (95% CI: 1.55-2.11, $p < .0001$) and an adjusted OR of 1.89 (95% CI: 1.61-2.23, $p < .0001$).

Table 2.2. Odds Ratio of Life Milestones among YACCS, as Compared with Controls.

	Unadjusted OR (CI 95%)	*P*-value	Adjusted OR (CI 95%)	*P*-value
Married/Partnered	**0.75 (0.63-0.88)**	.0005	**0.69 (0.58-0.82)**	<.0001
Single	**1.49 (1.26-1.76)**	<.0001	**1.62 (1.35-1.94)**	<.0001
Living with a parent	**2.87 (2.42-3.39)**	<.0001	**3.34 (2.78-4.00)**	<.0001
College degree	0.92 (0.78-1.09)	.32	**0.79 (0.66-0.95)**	.0142
Full-time employment	**0.40 (0.34-0.46)**	<.0001	**0.39 (0.33-0.45)**	<.0001
Part-time employment	**1.71 (1.43-2.05)**	<.0001	**1.67 (1.38-2.02)**	<.0001
Unemployment	**1.81 (1.55-2.11)**	<.0001	**1.89 (1.61-2.23)**	<.0001

Note. Each row represents an individual regression model, adjusted for nSES. Bold font indicates statistical significance ($p<.05$).

Exploratory Analyses: Comparisons among YACCS

Exploratory analyses were conducted to examine how clinical and demographic factors influence the achievement of life milestones among YACCS. These factors include the number of years since diagnosis, treatment intensity, race/ethnicity, and sex. This approach allows for the examination of diverse influences within the cohort, considering the variation in treatment intensity and time since diagnosis. These factors are crucial as they significantly impact the survivors' ability to reach certain life milestones post-treatment. Furthermore, stratifying the data by race/ethnicity and sex provides detailed information on subgroups of YACCS who might require additional support to achieve these milestones. This stratified analysis may help identifying specific needs and developing targeted interventions to improve outcomes for all survivors.

The analysis of life milestones among YACCS in relation to the years since diagnosis reveals varying patterns when compared to controls, as shown in Table 2.3. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for different milestones across three timeframes since diagnosis: less than 10 years, 10-14 years, and 15 years or more.

For YACCS who are less than 10 years post-diagnosis, the likelihood of being married or partnered was slightly lower than controls (OR = 0.84, 95% CI: 0.51-1.37), though this difference was not statistically significant. However, as time since diagnosis increased, the odds of being married or partnered decreased significantly. Those 10-14 years post-diagnosis had 49% lower odds (OR = 0.51, 95% CI: 0.37-0.71), and those 15 or more years post-diagnosis had 23% lower odds (OR = 0.77, 95% CI: 0.61-0.97).

Conversely, the odds of being single increased with time since diagnosis. Survivors less than 10 years post-diagnosis did not have significantly higher odds of being single (OR = 1.22,

95% CI: 0.75-1.97), but those 10-14 years post-diagnosis had more than twice the odds (OR = 2.06, 95% CI: 1.49-2.85), and those 15+ years post-diagnosis had 51% higher odds (OR = 1.51, 95% CI: 1.18-1.93).

Living with a parent showed a clear trend with increasing odds as time since diagnosis lengthened. Survivors less than 10 years post-diagnosis had more than twice the odds of living with a parent (OR = 2.41, 95% CI: 1.63-3.56), which further increased to almost three times for those 10-14 years post-diagnosis (OR = 2.85, 95% CI: 2.11-3.84) and over four times for those 15+ years post-diagnosis (OR = 4.46, 95% CI: 3.36-5.91).

The odds of holding at least a college degree were lower among survivors less than 10 years post-diagnosis, but the difference was not statistically significant (OR = 0.61, 95% CI: 0.37-1.01). The odds gradually approached that of controls over time, with survivors 15+ years post-diagnosis having odds that were not substantially different from controls (OR = 0.88, 95% CI: 0.68-1.13).

Employment outcomes also varied significantly. Full-time employment was markedly less likely among survivors compared to controls, with the odds being lowest for those less than 10 years post-diagnosis (OR = 0.26, 95% CI: 0.17-0.39) and increasing over time, but remaining significantly lower even for those 15+ years post-diagnosis (OR = 0.46, 95% CI: 0.37-0.58). Part-time employment was more likely across all timeframes, with the highest odds for those less than 10 years post-diagnosis (OR = 1.98, 95% CI: 1.30-3.00). Unemployment followed a similar trend to living with a parent, with higher odds for survivors less than 10 years post-diagnosis (OR = 2.40, 95% CI: 1.61-3.58) which decreased over time, yet remained higher than controls even 15+ years post-diagnosis (OR = 1.52, 95% CI: 1.21-1.92).

In summary, the years since diagnosis appear to be associated with the likelihood of achieving various life milestones among YACCS. The trends suggest that while the odds of being single, living with a parent, and unemployment decrease over time, they remain significantly higher compared to controls. Conversely, the likelihood of being married or partnered and full-time employment increases over time but still remains significantly lower compared to controls.

Table 2.3. Odds Ratio of Life Milestones among YACCS, according to Years Since Diagnosis, as Compared with Controls (n=1,106).

	< 10	10-14	15+
		OR (CI 95%)	
Married/Partnered	0.84 (0.51-1.37)	**0.51 (0.37-0.71)**	**0.77 (0.61-0.97)**
Single	1.22 (0.75-1.97)	**2.06 (1.49-2.85)**	**1.51 (1.18-1.93)**
Living with a parent	**2.41 (1.63-3.56)**	**2.85 (2.11-3.84)**	**4.46 (3.36-5.91)**
College degree	0.61 (0.37-1.01)	0.74 (0.53-1.04)	0.88 (0.68-1.13)
Full-time employment	**0.26 (0.17-0.39)**	**0.34 (0.26-0.46)**	**0.46 (0.37-0.58)**
Part-time employment	**1.98 (1.30-3.00)**	**1.44 (1.02-2.05)**	**1.74 (1.33-2.29)**
Unemployment	**2.40 (1.61-3.58)**	**2.37 (1.77-3.18)**	**1.52 (1.21-1.92)**

Note. Each row represents an individual regression model, adjusted for nSES. Bold font indicates statistical significance ($p<.05$).

The investigation into the association between treatment intensity and the achievement of life milestones among YACCS reveals notable differences when compared to controls, as outlined in Table 2.4. The odds ratios (OR) with 95% confidence intervals (CI) have been calculated for varying levels of treatment intensity: low-modest, very intensive, and most intensive.

Among YACCS who underwent low-modest intensity treatment, the likelihood of being married or partnered was modestly lower than that of controls (OR = 0.73, 95% CI: 0.55-0.98). For those receiving very intensive treatment, this likelihood decreased further (OR = 0.65, 95% CI: 0.50-0.84), although the difference was not statistically significant for the most intensive treatment group (OR = 0.71, 95% CI: 0.43-1.16).

The odds of being single were higher across all treatment intensities compared to controls, with significant differences observed for low-modest (OR = 1.47, 95% CI: 1.10-1.97) and very intensive treatments (OR = 1.74, 95% CI: 1.34-2.26). The most intensive treatment group had a higher odd as well, but this was not statistically significant (OR = 1.56, 95% CI: 0.96-2.57).

Living with a parent showed a positive correlation with treatment intensity; the odds increased from 2.59 (95% CI: 1.93-3.47) for low-modest intensity to 4.10 (95% CI: 2.47-6.80) for the most intensive treatment, suggesting a significant impact of treatment intensity on this aspect of survivors' living arrangements.

Holding at least a college degree appeared less likely among YACCS who received very intensive treatment (OR = 0.69, 95% CI: 0.52-0.90) compared to controls, with no significant differences noted for the low-modest and most intensive treatment categories.

In terms of employment, full-time employment was significantly less likely for survivors across all treatment intensities, with the lowest odds reported for those who underwent the most intensive treatment (OR = 0.26, 95% CI: 0.17-0.41). Part-time employment odds were higher for those who received very intensive treatment (OR = 1.95, 95% CI: 1.47-2.57) and significantly so for low-modest intensity treatment (OR = 1.46, 95% CI: 1.07-1.98), but not for the most intensive category.

Unemployment showed a substantial increase in likelihood with the most intensive treatment (OR = 3.00, 95% CI: 1.91-4.71), suggesting a strong association between treatment intensity and the ability to be employed.

The data indicates that as the intensity of cancer treatment increases, YACCS are less likely to be married or partnered and employed full-time, and more likely to be living with

parents and unemployed. The relationship between treatment intensity and educational

attainment, as well as being single, appears less consistent.

Table 2.4. Odds Ratio of Life Milestones among YACCS, according to Treatment Intensity, as Compared with Controls (n=1,106).

	Low-modest Intensity	Very Intensive	Most Intensive
		OR (CI 95%)	
Married/Partnered	**0.73 (0.55-0.98)**	**0.65 (0.50-0.84)**	0.71 (0.43-1.16)
Single	**1.47 (1.10-1.97)**	**1.74 (1.34-2.26)**	1.56 (0.96-2.57)
Living with a parent	**2.59 (1.93-3.47)**	**3.80 (2.93-4.92)**	**4.10 (2.47-6.80)**
College degree	0.97 (0.71-1.31)	0.69 (0.52-0.90)	0.76 (0.47-1.23)
Full-time employment	**0.45 (0.35-0.59)**	**0.38 (0.30-0.48)**	**0.26 (0.17-0.41)**
Part-time employment	**1.46 (1.07-1.98)**	**1.95 (1.47-2.57)**	1.66 (1.00-2.73)
Unemployment	**1.72 (1.31-2.26)**	**1.77 (1.40-2.24)**	**3.00 (1.91-4.71)**

Note. Each row represents an individual multivariable regression model, adjusted for nSES. Bold font indicates statistical significance ($p<.05$).

The examination of life milestones among YACCS, according to race/ethnicity,

demonstrates distinct patterns when compared with controls in corresponding race/ethnicity

groups, as shown in Table 2.5. Non-Hispanic White survivors were less likely to be married or

partnered than NHW controls (OR = 0.70, 95% CI: 0.50-0.98), as were Hispanic/Latino

survivors (OR = 0.69, 95% CI: 0.54-0.87) compared with Hispanic/Latino controls. Asian

survivors had a significantly lower likelihood of being married or partnered (OR = 0.29, 95% CI:

0.13-0.68) than Asian controls.

Being single was more likely among Non-Hispanic White survivors (OR = 1.68, 95% CI:

1.18-2.40) and Hispanic/Latino survivors (OR = 1.59, 95% CI: 1.25-2.01), with Asian survivors

showing the highest odds (OR = 3.71, 95% CI: 1.60-8.63).

The likelihood of living with a parent was higher for all groups compared to controls,

with the highest odds observed among Asian survivors (OR = 4.62, 95% CI: 2.48-8.62),

followed by Hispanic/Latino survivors (OR = 4.10, 95% CI: 3.19-5.26). Non-Hispanic White

and 'Other' racial/ethnic groups also showed increased likelihood but to a lesser extent.

Attainment of a college degree was significantly less likely among Asian survivors (OR = 0.34, 95% CI: 0.19-0.61), and there was a non-significant trend towards lower likelihood among the 'Other' category (OR = 0.56, 95% CI: 0.30-1.04). Non-Hispanic White and Hispanic/Latino survivors did not exhibit significant differences from controls in educational attainment.

In terms of employment, all racial/ethnic groups of survivors were less likely to be in full-time employment compared to controls, with similar odds across the groups (Non-Hispanic White OR = 0.47, Hispanic/Latino OR = 0.43, Asian OR = 0.43, 'Other' OR = 0.45). Part-time employment was more likely among Non-Hispanic White (OR = 1.54), Hispanic/Latino (OR = 1.76), and Asian survivors (OR = 2.04), while the 'Other' group was not significantly different from controls.

Unemployment was more likely among Non-Hispanic White (OR = 1.62), Hispanic/Latino (OR = 2.09), and 'Other' survivors (OR = 2.19), with Asian survivors not showing a significant difference from controls in this outcome (OR = 1.29). Race/ethnicity appears to play a significant role in the achievement of life milestones among YACCS compared to controls. The patterns indicate that Non-Hispanic White, Hispanic/Latino, and Asian survivors face unique challenges with marriage/partnership, living with parents, educational attainment, and employment, with the degree of impact varying by race/ethnicity.

Table 2.5. Odds Ratio of Life Milestones among YACCS, according to Race/Ethnicity, as Compared with Controls (n=1,106).

	Non-Hispanic White	Hispanic/Latino	Asian	Other
		OR (CI 95%)		
Married/Partnered	**0.70**	**0.69**	**0.29**	1.18
	(0.50-0.98)	**(0.54-0.87)**	**(0.13-0.68)**	(0.67-2.07)
Single	**1.68**	**1.59**	**3.71**	1.00
	(1.18-2.40)	**(1.25-2.01)**	**(1.60-8.63)**	(0.57-1.75)
Living with a parent	**2.12**	**4.10**	**4.62**	**1.83**
	(1.48-3.02)	**(3.19-5.26)**	**(2.48-8.62)**	**(1.02-3.26)**
College degree	0.90	0.93	**0.34**	0.56

		(0.65-1.24)	(0.71-1.22)	**(0.19-0.61)**	(0.30-1.04)
Full-time employment		**0.47** **(0.34-0.65)**	**0.43** **(0.28-0.43)**	**0.43** **(0.25-0.74)**	**0.45** **(0.27-0.74)**
Part-time employment		**1.54** **(1.05-2.26)**	**1.76** **(1.37-2.27)**	**2.04** **(1.09-3.83)**	1.12 (0.57-2.21)
Unemployment		**1.62** **(1.16-2.28)**	**2.09** **(1.68-2.61)**	1.29 (0.79-2.11)	**2.19** **(1.28-3.74)**

Note. Each row represents an individual multivariable regression model, adjusted for nSES. Bold font indicates statistical significance (*p*<.05).

The analysis of life milestones among YACCS by sex shows significant disparities when compared to controls as shown in Table 2.6. Female survivors were significantly less likely to be married or partnered than controls, with an OR of 0.57 (95% CI: 0.44-0.73). This contrasts with male survivors, for whom the likelihood of being married or partnered was not significantly different from controls (OR = 0.89, 95% CI: 0.68-1.16).

When it came to being single, female survivors had an OR of 1.96 (95% CI: 1.53-2.52), indicating they were nearly twice as likely to be single compared to controls. Male survivors also had a higher likelihood of being single, but this was not statistically significant (OR = 1.25, 95% CI: 0.96-1.63).

Living with a parent was significantly more likely for both female and male survivors compared to controls, with ORs of 3.06 (95% CI: 2.38-3.92) and 3.64 (95% CI: 2.80-4.73), respectively. This suggests that both female and male survivors are more likely to live with a parent post-diagnosis.

Educational attainment, measured by holding at least a college degree, was less likely among female survivors with an OR of 0.75 (95% CI: 0.57-0.97), indicating a small but significant difference. For male survivors, the odds were not significantly different from controls (OR = 0.81, 95% CI: 0.62-1.06).

Employment outcomes showed that both female and male survivors were less likely to be employed full-time compared to controls (OR = 0.50, 95% CI: 0.41-0.63 for females and OR = 0.30, 95% CI: 0.23-0.38 for males). This difference was more pronounced for males. Regarding part-time employment, females had a slightly higher likelihood of being employed part-time (OR = 1.30, 95% CI: 1.00-1.68), and this likelihood was significantly higher for males (OR = 2.40, 95% CI: 1.80-3.21). Unemployment was more likely among both female (OR = 1.62, 95% CI: 1.30-2.02) and male survivors (OR = 2.04, 95% CI: 1.59-2.62) compared to controls. The increased odds for unemployment were more significant for male survivors.

Table 2.6. Odds Ratio of Life Milestones among YACCS, according to Sex, as Compared with Controls (n=1,106).

	Female	Male
	OR (CI 95%)	
Married/Partnered	**0.57 (0.44-0.73)**	0.89 (0.68-1.16)
Single	**1.96 (1.53-2.52)**	1.25 (0.96-1.63)
Living with a parent	**3.06 (2.38-3.92)**	**3.64 (2.80-4.73)**
College degree	**0.75 (0.57-0.97)**	0.81 (0.62-1.06)
Full-time employment	**0.50 (0.41-0.63)**	**0.30 (0.23-0.38)**
Part-time employment	1.30 (1.00-1.68)	**2.40 (1.80-3.21)**
Unemployment	**1.62 (1.30-2.02)**	**2.04 (1.59-2.62)**

Note. Each row represents an individual multivariable regression model, adjusted for nSES. Bold font indicates statistical significance ($p<.05$).

2.4 Discussion

This study sought to understand the disparities in life milestones among young adult cancer survivors (YACCS) compared to controls by examining a range of factors including time since diagnosis, treatment intensity, race/ethnicity, and gender. These findings suggest that YACCS face significant challenges in achieving key life milestones related to relationship status, living arrangements, education, and employment when compared to their peers without a history of cancer. These results align with previous findings that reported delayed life milestone outcomes among YACCS compared to their non-cancer peers or siblings (11-15, 31-47, 54-59).

The temporal distance from diagnosis was a significant factor, with those further out from diagnosis generally faring better in terms of employment status, though still less likely to be married or partnered compared to controls. This suggests a long-term effect of cancer on personal relationships and highlights the need for targeted support for relationship-building post-diagnosis. Additionally, the persistent likelihood of living with parents and increased odds of being single many years post-diagnosis may affect potential challenges in achieving independence and forming new family.

Treatment intensity emerged as a prominent factor affecting the survivors' life trajectories. Those received very intensive, or the most intensive treatments had markedly lower odds of full-time employment and higher odds of living with parents, underscoring the enduring nature of treatment-related disruptions. These findings are consistent with previous research suggesting that more aggressive treatments can lead to long-term physical and psychological sequelae, which in turn can impact social and professional milestones (30, 42, 47, 60).

Race/ethnicity also played a significant role, particularly for Hispanic/Latino and Asian survivors, who faced increased odds of living with parents and decreased odds of marriage/partnership and full-time employment. This underscores the importance of culturally sensitive support programs that consider the varied experiences of cancer survivors from different racial and ethnic backgrounds.

Gender differences were pronounced, with female survivors less likely to be married or partnered and more likely to be single and unemployed compared to male survivors. Female survivors are significantly less likely to be married or partnered and to hold a college degree, and both female and male survivors exhibit difficulties in living independently and securing full-time employment. Males, however, face higher odds of part-time employment and unemployment,

which could point to more substantial disruptions in their career trajectories compared to female survivors. Female survivors might be particularly vulnerable to adverse employment situations. Prior studies observed an increased incidence of health-related unemployment in female survivors, with minority female survivors more likely to be jobless and actively seeking employment (44). Female survivors often experience worse health outcomes and are at an increased risk of suffering from neurocognitive impairments compared to male survivors (47).

The relationship between treatment intensity and socioeconomic outcomes indicates a dose-response effect, where survivors who underwent more intensive treatments are less likely to be married or partnered, have a college degree, and be employed full-time. This gradient effect highlights the need for ongoing support and interventions, particularly for those who have experienced the most intense treatments. A recent literature review also found that radiation therapy and chemotherapy were both positively associated with delayed educational attainment and employment (83).

Across all stratified analyses, the consistent challenge appears to be the attainment of full-time employment. This may be due to physical or cognitive late effects of treatment, the need for ongoing medical care, or discrimination in the workplace. The implications of this are profound, as full-time employment is often a gateway to other milestones, such as financial self-sufficiency and healthcare benefits. While survival rates for childhood cancer have improved, the journey beyond survival is complex and the challenges are likely extended into adulthood. The findings underscore the importance of comprehensive survivorship care that includes psychosocial support and addresses the unique needs of survivors as they progress through different life stages and treatments. Future research should continue to explore these dynamics, with a focus on developing targeted interventions that can assist survivors in overcoming these

long-term challenges and achieving a quality of life comparable to their peers without a history of cancer.

One of the limitations of this study is that societal views on relationship status among young adults have evolved over the decades (109). There is a noticeable decline in marriage rates, and an increase in the number of young adults in the US choosing to remain single (110, 111). Being unmarried or unpartnered is no longer solely seen as a failure to achieve life milestones but rather as a personal choice. Despite these societal changes, being married is considered important in terms of lifespan development due to its association with several positive outcomes. Studies have shown that married individuals often enjoy better physical health, higher socioeconomic status (SES), and improved mental health (112). This study acknowledges that individuals may have various reasons for not seeking marriage or long-term relationships. The study focuses on comparing the relationship status of YACCS with their non-cancer peers. Future studies may investigate how having cancer influences their ability to form and maintain new relationships.

Another limitation is the methodological differences between the Project Forward Cohort and the CHIS cohort data. Although both are population-based studies, Project Forward collected data via telephone, mail, and internet, while CHIS used random-digit dialing. The comparison between the study group and the general population can be challenging because the general population may also include childhood cancer survivors. The differing recruitment methods and target populations between the two cohorts may limit the validity of direct comparisons.

This study represents a significant contribution to the field of childhood cancer survivorship, particularly in the domain of young adult survivors, a relatively understudied population. Unlike previous research, which has often examined educational attainment,

employment status, relationship status, and living arrangements in isolation, this investigation provides a holistic view of adulthood life milestone achievement. By doing so, it underscores the socio-developmental determinants of health and well-being, offering a comprehensive understanding of the survivorship experience.

This study is unique in its integrative approach, considering multiple aspects of life milestones together, rather than in isolation. By conducting stratified analyses by years since diagnosis, sex, treatment intensity and race/ethnicity, the research allows for a more detailed examination of how survivors are coping in comparison to their non-cancer peers. Such an approach not only illuminates the general trends in survivorship but also uncovers the disparities within subgroups, identifying populations that may be more vulnerable and in need of targeted interventions.

Research on the long-term social effects of childhood or adolescent cancer is still evolving. Generally, data on social outcomes are limited, and there is a significant need for comprehensive studies on social functioning and adaptation throughout life. Comparing life milestones between YACCS and their non-cancer peers reveals the potential negative impact of the cancer and its treatments on the lives of YACCS. However, most current findings are based on cross-sectional studies, which do not provide clear insights into the specific causes and progression of psychosocial challenges in cancer survivors. To improve the psychosocial well-being of survivors, it is crucial to gain a deeper understanding through longitudinal studies. The data presented offer valuable information for researchers and clinicians to develop and implement targeted interventions aimed at enhancing social outcomes for YACCS. Future psychosocial research should focus on integrating existing knowledge about risk profiles into clinical management and social contexts, such as schools and workplaces.

By integrating these dimensions, the study highlights the importance of considering the heterogeneity of the survivor population. Health care professionals, educators, and policymakers can use these findings to develop tailored support services that address the specific needs of survivors as they navigate the critical transition to adulthood. In essence, the study adds a valuable perspective to the existing body of research by providing a comprehensive analysis of life milestones in young adult survivors of childhood cancers. It not only advances the understanding of the long-term outcomes for this unique population but also underscores the necessity for continued research and tailored support to enhance survivorship care and promote positive health outcomes.

CHAPTER 3: Delays in achieving life milestones and depressive symptoms among YACCS

3.1 Introduction

The significant achievement in childhood cancer treatments has shifted research towards understanding the long-term outcomes and quality of life of YACCS. Among the various challenges faced by YACCS, delayed life milestones and depressive symptoms emerge as critical areas of concern that warrant further investigation. Delayed life milestones, including educational achievement, employment status, independent living, marriage/partnership, and parenthood, are pivotal components of an individual's transition into adulthood and societal integration. For YACCS, these milestones can be significantly impacted by the long-term effects of their disease and its treatment. The disruption in normal development and the prolonged periods spent in healthcare settings can hinder their social, educational, and psychological growth, potentially leading to delays in achieving these important life stages.

Depressive symptoms represent another critical issue for this population. The psychological burden of surviving cancer, coupled with the challenges of reintegration into "normal" life, may affect survivors across a range of mental health issues, including depression. Depressive symptoms not only affect the survivors' quality of life but also influence their ability to achieve and value life milestones. The relationship between delayed life milestones and depressive symptoms is complex and bidirectional. The inability to achieve expected life milestones can lead to feelings of inadequacy, low self-esteem, and social isolation, contributing to depressive symptoms (30, 47). In contrast, depressive symptoms can hinder motivation, social interaction, and overall functioning, further delaying the achievement of these milestones (95).

Recent longitudinal data suggest that disparities in life milestone achievement and socioeconomic conditions observed throughout adulthood may be a result of persistent

depression (89). Changes in social conditions, such as job loss and divorce, are associated with depression in the general population (90, 91). However, more research is needed in finding how socioeconomic and social-developmental changes are associated with mental health among YACCS, who are vulnerable to health declines.

Protective and risk factors of life milestones among YACCS support a conceptual model of psychological functioning which considers the dynamic relationships between biological, psychological, and social factors (i.e., biopsychosocial framework) (92). Importantly, a longitudinal approach allows for identification of risk and protective factors that may influence individual difference in life milestones and socioeconomic/social-developmental outcomes. Knowledge of how life milestones change over time, as well as factors that influence such change, are essential to guide the psychosocial development and interventions to address social and mental health disparities among YACCS.

Adult survivors of childhood cancer were significantly less likely to be married, have achieved higher education levels, or be employed full-time compared to their siblings and age-matched peers from the general population. This research highlighted the need for targeted interventions to support survivors in overcoming educational and vocational hurdles (6). Childhood cancer survivors reported higher levels of depressive symptoms than the general population, with factors such as treatment intensity and the presence of chronic health conditions being significant predictors of their mental health outcomes (98). This study underscored the importance of ongoing mental health support for survivors, tailored to address their unique experiences and challenges. Delays in educational and vocational achievements were strongly correlated with higher levels of depressive symptoms, suggesting a bidirectional relationship where each factor exacerbates the other. While survivors often lead productive lives, they face

unique challenges that can impact their quality of life, including difficulties in social relationships, educational attainment, and employment. These challenges are closely linked to their psychological well-being, with depressive symptoms being both a cause and a consequence of these difficulties.

Prior studies underscore the multifaceted challenges faced by YACCS as they transition into adulthood and there is a need for holistic support services that address not only the physical but also the psychological and social aspects of survivorship. Interventions aimed at facilitating educational and vocational achievements, alongside mental health support, are critical in helping survivors overcome these hurdles and improve their overall quality of life. This study aims to explore the relationship between delayed life milestones over time and depressive symptoms among YACCS.

This study aims to identify risk and protective factors of depressive symptoms and support mechanisms that can improve the long-term psychosocial outcomes for these individuals. Understanding these dynamics is crucial for developing targeted support services that address the unique needs of childhood cancer survivors, facilitating their successful transition into adulthood and enhancing their overall well-being.

HYP2a: Changes in life milestones will be associated with changes in depressive symptoms over time.

3.2 Methods

Participants and Procedures

The Project Forward longitudinal dataset is a subset of the Project Forward pilot study (109) and the Project Forward 2 cohort study. Initial survey measures were completed between

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2007 and 2009 (Time 1), with follow-up surveys distributed and completed between 2015 and 2018 (Time 2). The mean time between surveys was 5.1 (SD: 0.56) years. A total of 135 YACCS participated in both the Project Forward cohort studies, which were identified through the LA cancer registry covering Los Angeles County. Project Forward pilot study included YACCS from two large pediatric medical centers. The participants were between the age of 0-18 years at diagnosis, and diagnosed between 2000 and 2007, at least 2 years from diagnosis. The Project Forward cohort population-based study had larger inclusion criteria which is detailed in Aim 1.

Measures

Life milestone achievements. Participants' educational achievement (e.g., hold at least a college degree), employment status (e.g., employed full-time, employed part-time, unemployed, student), livings arrangement (e.g., living with a parent), relationship status (e.g., single, married, partnered) were dichotomized at both Time 1 and Time 2.

Depressive Symptoms. The Center for Epidemiologic Studies Depression Scale (CES-D) is a self-report scale developed by the National Institute of Mental Health to measure depressive symptomatology (α = .92) (93). Comprising 20 items rated on a four-point Likert scale, it assesses symptoms such as depressive mood, feelings of guilt and worthlessness among others. The response scale is structured as follows: 1 = seldom or never (< 1 day), 2 = occasionally or a minor portion of the time (1–2 days), 3 = sometimes or a moderate quantity of the time (3–4 days), and 4 = frequently or the entirety of the time (5–7 days). The total score ranges from 0 to 60, with higher scores indicating greater depressive symptomatology and a conventional cutoff of 16 used to identify individuals at risk for clinical depression.

Demographic variables. Covariates included current age, sex, race/ethnicity, and neighborhood SES. Participants' socioeconomic status (SES) was ascertained based on their residence's census

tract at the time of the survey. Specifically, data from the census tract were employed to construct a SES composite score, which was composed of seven indicators: the education index, the percentage of individuals exceeding 200% of the poverty line, the percentage of individuals in blue-collar occupations, the percentage of individuals employed, the median rental cost, the median value of owner-occupied housing units, and the median household income. The composite scores were assigned on a quintile scale ranging from 1 to 5, with 1 representing the lowest SES quintile and 5 representing the highest. This methodology has been previously utilized in research on cancer survivors and was included in this study due to the documented correlation between SES and the incidence of cancer.

Statistical Analysis

Descriptive data were examined, including the prevalence of life milestone variables at each time point. Linear regression models were utilized to explore the associations between life milestones and depressive symptoms. The primary dependent variable was the level of depressive symptoms, which was measured at Time 2. Depressive symptoms measured at Time 1 (baseline depressive symptoms), the age at Time 2, sex, race/ethnicity, and the neighborhood socioeconomic status (nSES) at Time 2 was controlled in the multivariable analyses. The CES-D scores were transformed using the Box-Cox transformation method to ensure the linearity of the relationship between the independent variables and the dependent variable. This statistical technique is designed to stabilize variance and make the data more closely adhere to the assumptions of linear regression. The data analyses were conducted using SAS statistical software, Version 9.4.

3.3 Results

A total of 163 YACCs participated in this study and 132 were included in the regression analyses due to 132 had CES-D scores at Time 2. Descriptive statistics of participant characteristics at both time points are shown in Table 3.1. At Time 1, the average age of survey participants was 19.5 years, with a standard deviation of 2.8 years, ranging from 15 to 25 years old. By Time 2, participants had aged to an average of 25.2 years, with the same standard deviation, ranging from 20 to 31 years old. The age at diagnosis was reported as an average of 12.8 years, with a standard deviation of 2.8 years, and a range from 5 to 19 years.

Regarding sex distribution, the sample at Time 1 consisted of 94 females (57.7%) and 69 males (42.3%). Race/ethnicity was diverse, with non-Hispanic Whites constituting nearly half of the participants (49.7%), followed by Hispanics (23.3%), Asians (16.6%), and others (10.4%).

The types of cancer these individuals had been diagnosed with included brain and other nervous system cancers (29.5%), leukemia (30.1%), lymphoma (19.6%), endocrine cancers (7.4%), and other types (13.5%).

In terms of neighborhood socioeconomic status (nSES), the distribution was relatively even across the five levels at Time 1, with the lowest SES representing 41.7% of the cohort and the highest SES 11.0%.

The mean score for depressive symptoms at Time 1 was 13.1, with a standard deviation of 10.7 and a range from 0 to 47. This decreased slightly by Time 2 to a mean of 12.3, also with a standard deviation of 10.5 and the same range. Time 1 depressive symptoms and Time 2 depressive symptoms were moderately correlated (r=0.59, $p<.0001$; n=133). Preliminary analysis showed that 35% reported lower depressive symptom at Time 2, 25% reported higher depressive symptoms at Time 2, and 45% reported no change in depressive symptoms.

With respect to life milestones, at Time 1, 12.3% were employed full-time, 27.0% part-time, and a substantial 60.1% were unemployed. The majority of the sample (68.1%) were students, and only a small fraction (7.4%) were married or partnered. By Time 2, there was a significant increase in full-time employment (39.3%), a decrease in part-time employment (19.6%), and a notable reduction in unemployment (27.6%). The proportion of students decreased to 6.75%, and the number of married or partnered individuals had more than doubled to 16.0%.

Table 3.1. Descriptive Statistics of YACCS at Time 1 and 2 (n=169).

	Time 1	Time 2
Sex – N (%)		
Female	94 (57.7)	NA
Male	69 (42.3)	NA
Age at survey mean (SD), range	19.5 (2.8), 15-25	25.2 (2.8), 20-31
Age at diagnosis mean (SD), range	12.8 (2.8), 5-19	NA
Race – N (%)		
Non-Hispanic White	81 (49.7)	NA
Hispanic	38 (23.3)	NA
Asian	27 (16.6)	NA
Other	17 (10.4)	NA
Cancer Type – N (%)		
Brain and other nervous system	48 (29.5)	NA
Endocrine	12 (7.4)	NA
Lymphoma	32 (19.6)	NA
Leukemia	49 (30.1)	NA
Other[a]	22 (13.5)	NA
nSES – N (%)		
1 (lowest)	68 (41.7)	63 (42.9)
2	30 (18.4)	23 (15.7)
3	21 (12.9)	19 (13.0)
4	26 (16.0)	25 (17.0)
5 (highest)	18 (11.0)	17 (11.6)
Depressive Symptoms Mean (SD), range	13.1 (10.7), 0-47	12.3 (10.5), 0-47
Life Milestones – N (%)		
Full-time	20 (12.3)	64 (39.3)
Part-time	44 (27.0)	32 (19.6)
Unemployed[b]	98 (60.1)	45 (27.6)

Student	111 (68.1)	11 (6.75)
Married/Partnered	12 (7.4)	26 (16.0)
Living with a parent		

Note. The percentages are from the total number of participants who provided data for each variable, not from the total number of individuals in each cohort; percentages may not add up to 100 due to rounding. NA denotes not applicable.
[a] Oral cavity & pharynx, digestive system, respiratory system, soft tissue including heart, urinary system, eye & orbit, miscellaneous
[b] includes unemployed students.

Table 3.1a shows an overview of changes in the employment status of YACCS, between two points in time, Time 1 and Time 2. Of those who were students at Time 1, 32 participants (19.6%) remained students at Time 2. 39 participants (23.9%) transitioned from being students to full-time employment. 23 participants (14.1%) moved from being students to part-time employment, while 13 participants (8.0%) became unemployed. For those who were unemployed at Time 1, 6 participants (3.7%) became students by Time 2. 5 participants (3.1%) transitioned from being unemployed to full-time employment, and 7 participants (4.3%) moved to part-time employment. Meanwhile, 8 participants (4.9%) remained unemployed.

Table 3.1a. Prevalence of Life Milestone Achievement Change at Time 1 and 2 (n=169) among YACCS.

Time 1 Status	Time 2 Status	N(%)
Student	Student	32 (19.6)
Student	Full-time employment	39 (23.9)
Student	Part-time employment	23 (14.1)
Student	Unemployed	13 (8.0)
Unemployed	Student	6 (3.7)
Unemployed	Full-time employment	5 (3.1)
Unemployed	Part-time employment	7 (4.3)
Unemployed	Unemployed	8 (4.9)

Main Outcomes

In univariable analyses, being unemployed ($\beta = 0.24$, $p < .01$) and still being at school at time 2 ($\beta = 0.24$, $p < .01$) were significantly associated with higher depressive symptoms at Time 2. The initial parameters of the study categorized participants as unemployed if they were not

engaged in either full-time or part-time work. It is important to note that within this definition, 'unemployed' also included individuals who were full-time students. Given a majority of sample was in their twenties, it was deemed pertinent to further analyze the relationship between student status and the progression of depressive symptoms over time.

This reclassification showed that when full-time students were stratified from the general unemployed group, the remaining subset of unemployed individuals—those not in full-time education—shrank to only eight individuals. Within this refined group, the association between unemployment and an increase in depressive symptoms over time was not statistically significant.

No college education also showed a significant association ($\beta = 0.18$, $p < .05$). However, living with parents ($\beta = 0.06$) and not being married or partnered ($\beta = 0.02$) at both Time 1 and 2 did not show a significant relationship with depressive symptoms over time.

In multivariable analyses, which controlled for Time 1 depressive symptoms, age, sex, race/ethnicity, and neighborhood socioeconomic status (SES), the significant relationship between unemployment and depressive symptoms remained ($\beta = 0.16$, $p < .05$), as did the association with still being at school ($\beta = 0.17$, $p < .05$). However, the relationship between having no college education and depressive symptoms was no longer significant in the multivariable context ($\beta = 0.03$). Similarly, living with parents ($\beta = 0.03$) and not being married or partnered ($\beta = 0.03$) were not significantly associated with depressive symptoms in the multivariable analyses.

Table 3.2. Regression analyses for delays in life milestones and depressive symptoms at Time 2 (n = 132).

Life milestones	Univariable analyses		Multivariable analyses			
	b (SE b)	β	b (SE b)	β	F Value	Adj R^2
Unemployed[a]	**0.92 (0.33)**	**0.24****	**0.60 (0.29)**	**0.16***	**12.98*****	0.38
No college degree	**0.78 (0.37)**	**0.18***	0.14 (0.34)	0.03	11.82***	0.36

Living with a parent	0.20 (0.30)	0.06	0.10 (0.26)	0.03	11.82	0.36
Not married/partnered	0.07 (0.35)	0.02	0.12 (0.32)	0.03	11.82	0.36

Note. Each row is a separate model. Multivariable analyses controlled for Time 1 depressive symptoms, age, sex, race/ethnicity, and neighborhood SES.
[a] includes unemployed students.
*$p < .05$, **$p < .01$, ***$p < .001$.

Table 3.3. Consolidated Multivariable Regression Model between Life Milestones and Depressive Symptoms at Time 2 (n = 115).

	b (SE)	β	p
Variables			
Unemployed	.62 (.29)	.17	.035
No college degree	-.22 (.32)	.06	.493
Living with a parent	.18 (.29)	.05	.536
Not married/partnered	-.27 (.35)	-.07	.434
Covariates			
Age (at Time 2)	-.03 (.05)	-.06	.485
Female (vs. Male)	-.12 (.26)	-.04	.652
Hispanic/Latino (vs. Non-H/L)	-.75 (.35)	-.20	.032
nSES	.12 (.10)	.11	.227

Note. Time 1 depressive symptoms was controlled as the baseline of the outcome variable.

Sensitivity analysis

Sensitivity analyses were performed to further understand the impact of employment status changes over time on depressive symptoms among YACCS. The analysis showed that being consistently employed at both Time 1 and Time 2 (n=56; 34%) was significantly associated with lower depressive symptoms (β = -0.17, $p < .05$). Conversely, individuals who were unemployed at Time 1 and then gained employment by Time 2 (n=62; 38%) did not show a significant association with depressive symptoms.

Further analysis was conducted on unemployment, excluding students who were neither in full-time nor part-time employment. The newly coded unemployment status indicated 11 YACCS, compared to 36 YACCS in the original coding. Regression analysis showed that being unemployed at both Time 1 and 2 was not associated with depressive symptoms (β = 0.08, p

> .05) after controlling for Time 1 depressive symptoms, age, sex, race/ethnicity, and neighborhood socioeconomic status (SES).

3.4 Discussion

The findings of this study describe the relationship between delayed life milestones and depressive symptoms among young adult survivors of childhood cancer. It was observed that certain milestones, such as marital status and living arrangements, did not significantly correlate with depressive symptoms. However, delayed educational attainment without subsequent employment were identified as significant predictors of depression. These findings underscore the necessity for specialized survivorship care and highlight the complex psychosocial factors impacting these survivors, as they suggest that delayed educational attainment without subsequent employment may not just be an outcome of depressive states but a contributing factor to the psychological distress experienced by survivors. The absence of employment, closely tied to self-worth and societal position, may contribute to feelings of isolation and low self-value, potentially aggravating the psychological challenges that survivors encounter as they progress into later stages of life (4, 44).

Interestingly, the transition from unemployment to employment within the study's timeframe did not significantly affect depressive symptoms. This could imply that the mental health benefits of employment are delayed or dependent on other unmeasured variables. However, maintaining stable employment over the two time points seems to offer some protection against depressive symptoms, underscoring the role of consistent work in supporting mental health.

The study also highlights a potential connection between delays in educational attainment and heightened depressive symptoms among YACCS. This points to the possibility that

educational delays may act as stressors, contributing to the mental strain on this population. Thus, stable employment and timely educational achievements are crucial in potentially reducing depressive symptoms.

A transition towards more stable employment and partnership statuses over time was observed, potentially correlating with age-related development and recovery trajectories post-treatment. A concurrent slight decline in depressive symptoms suggests a potential improvement in mental health as these individuals age.

The methodology necessitates careful consideration of how employment status is defined, particularly in research with younger cohorts for whom education is a significant pursuit. The reevaluation of the impact of unemployment on mental health, especially when factoring in student status, indicates that its influence may be less significant than previously thought.

The adjustment in the analysis highlights the necessity for careful consideration of the criteria used to define employment status in research, especially in studies involving younger populations where educational engagement is a common and significant activity. The findings prompt a reevaluation of the implications of unemployment on mental health within this demographic, suggesting that the impact may be less pronounced when accounting for student status.

The association between ongoing education and increased depressive symptoms could reflect the struggle to maintain educational demands amidst the challenges posed by their post-cancer experience. This may be indicative of the need for additional educational support services for YACCS, recognizing that their trajectory through the education system may be different from their peers. Interestingly, the lack of a college education, living with parents, and being unmarried or unpartnered did not maintain a significant association with depressive symptoms in

the multivariable analyses. This could be reflective of the sample's young average age (mean age was 20 at Time 1 and 25 at Time 2), where such milestones are not yet expected to be achieved, and therefore, their absence is not as psychologically impactful.

Clinical Implications for Survivorship Care

Results provide some guidance for the survivorship care programs. There is a clear indication that supportive interventions should prioritize employment assistance and educational support for YACCS. Job crafting/employment support programs provide career counseling, job training, and placement services tailored to the capabilities and limitations of survivors could help mitigate the impact of unemployment on mental health. The programs may help with adapting work tasks, relationships, and perceptions to better fit their personal strengths, capabilities, and health needs, fostering a more meaningful and satisfying work experience (101, 102). Establishing partnerships with employers to create work opportunities that are accommodating to the unique needs of survivors is crucial.

Educational institutions should be equipped with the knowledge and resources to offer support to survivors, including flexible schedules, tailored learning plans, and mental health services (e.g., DSP). Scholarship programs and financial aid can also alleviate the pressure of ongoing education and support timely graduation. Furthermore, routine mental health screening and accessible psychological services should be integrated into survivorship care. This can enable the early identification and treatment of depressive symptoms, thereby preventing a potential cascade of psychosocial challenges.

The results of this study support for continuous long-term follow-up care for YACCS as they progress through different life stages and help identify those at risk of developing depressive symptoms. This approach will allow for timely interventions and support adjustments

as survivors age and their expectations and societal roles evolve. This study highlights the importance of considering employment and educational support as critical components of survivorship care for young adult childhood cancer survivors. By addressing these factors, healthcare providers can significantly contribute to the reduction of depressive symptoms and enhance the overall quality of life for this vulnerable population.

Limitations

This study, while contributing valuable insights into the experiences of YACCS is subject to several limitations that warrant consideration. The sample size was relatively small, which may limit the statistical power of the study and the robustness of the findings. Additionally, the sample may not adequately represent the diversity of the YACCS population in terms of race, ethnicity, socioeconomic status, or cancer type, which can affect the generalizability of the results to all survivors.

The association between depressive symptoms at Time 2 and unemployment, both with and without including unemployed students, showed different results, warranting further investigation. When those with an unemployed student status were excluded from the unemployed group, the analytic sample size decreased, and the previously observed positive association was no longer statistically significant.

The self-reported data for depressive symptoms and life milestones could introduce response bias. The follow-up period may not have been extensive enough to capture the long-term effects of employment and educational attainment on mental health. The study may not account for broader economic and social changes that could influence the job market and educational opportunities over time, which can impact the employment and educational experiences of survivors.

Although depression is conceptualized as the predictor in the model, the reverse relationship could also be possible. Future studies may examine the reciprocal nature of this relationship. It's important to note that the average depressive symptoms scores at both Time 1 and 2 were below the clinical thresholds.

The selection of participants who are willing and able to participate in the study might introduce survivorship bias, as these individuals may differ in significant ways from those who did not or could not participate. Specifically, mental health issues may be more prevalent among those who did not respond to the survey. Moreover, the current health status and potential late effects of cancer treatment on the participants were not comprehensively assessed, which could significantly influence both mental health and achievement of life milestones.

The findings of this study demonstrates that YACCS are at risk for adverse socioeconomic outcomes over the course of survivorship following their original cancer diagnosis. These findings offer important implications for developing optimal psychosocial intervention among health care providers caring for long-term YACCS. The findings highlight the need for regular, repeated assessment of socioeconomic outcomes and mental health in YACCS. Such repeated assessments may be particularly important for survivors who develop late medical morbidities that result in reduced health status.

CHAPTER 4: Cancer-related Late Effect Clusters and Life Milestones among YACCS

4.1 Introduction

Over the last fifty years, significant advancements have been made in creating treatments that cure cancer in children. These improvements in survival rates can be attributed to the development of more effective and targeted therapies, as well as early diagnosis and comprehensive care strategies. However, the increased survival rate brings with it a new set of challenges, as survivors often face the risk of late effects—long-term or delayed adverse effects of the cancer and its treatment. These effects can emerge months to years after the completion of cancer treatment. These late effects can significantly impact the quality of life and overall well-being of Young Adult Childhood Cancer Survivors (YACCS). While the physical late effects of cancer treatment, such as cardiovascular, endocrine, and neurocognitive deficits, are well-established, the social consequences for those who had cancer as children need more study (103). These social late effects include educational attainment, employment, personal relationships, and mental health (103, 104). A deeper understanding of these areas is crucial to develop tailored survivorship intervention for YACCS. This study aims to describe the landscape of childhood cancer late effects, with a particular focus on the impact on their social outcomes.

Significance of Late Effects

Late effects are complications, disabilities, or adverse outcomes that appear months to years after cancer treatment has ended. These effects can range from physical complications such as cardiotoxicity, endocrine disorders, and second cancers, to psychosocial issues including emotional distress, cognitive impairments, and challenges in social integration (105). The significance of these late effects cannot be overstated, as they have the potential to impact nearly every aspect of a survivor's quality of life. Psychosocial late effects, such as anxiety, depression,

and difficulties with social relationships, are particularly concerning, as they can affect educational attainment, employment opportunities, and overall well-being (103, 104). The growing population of childhood cancer survivors, estimated to be in the millions worldwide, underscores the importance of addressing these late effects as part of survivorship care.

Efforts to mitigate the impact of late effects include the development of long-term follow-up guidelines for survivors, which recommend regular health screenings and assessments to detect and manage late effects proactively (105). Additionally, there is a growing emphasis on the need for multidisciplinary care that addresses not only the physical but also the psychological and social needs of survivors (103, 104).

Medical Late Effects

A significant body of research has documented the range of medical late effects experienced by survivors of childhood cancer. Cardiac late effects are among the most serious, with studies indicating an increased risk of cardiomyopathy, congestive heart failure, and coronary artery disease in survivors, particularly those treated with anthracycline chemotherapies or chest radiation (105, 106). Endocrine disorders, including growth hormone deficiency, hypothyroidism, and gonadal dysfunction, have been frequently reported, often resulting from cranial radiation or alkylating agent chemotherapy (105, 106).

Other organ systems are also affected, with survivors facing increased risks of pulmonary dysfunction, renal impairment, and second malignancies. For example, bleomycin has been linked to pulmonary fibrosis, while radiation therapy increases the risk of developing secondary cancers such as sarcomas and breast cancer (105, 106). The cumulative incidence of these late effects supports lifelong monitoring and intervention, underscoring the need for tailored survivorship care plans.

Psychosocial Late Effects

Beyond physical health, childhood cancer survivors often encounter psychosocial challenges. Studies have documented elevated levels of anxiety, depression, and post-traumatic stress disorder (PTSD) compared to their healthy peers (5, 6, 19). These psychological outcomes can significantly affect survivors' quality of life, influencing their social relationships, educational attainment, and employment opportunities.

Educational impacts manifest in various forms, including increased absenteeism, learning disabilities, and lower overall academic achievement, particularly in those who received central nervous system-directed therapies (3, 84). Employment challenges are similarly prevalent, with survivors facing higher rates of unemployment and underemployment, often due to physical limitations or employers' perceptions of their health (44).

Social relationships, including familial bonds and peer interactions, can also be strained by the childhood cancer experience. Survivors report difficulties in forming and maintaining close relationships (107). There is a need for more longitudinal studies that follow survivors into late adulthood to understand the full spectrum of late effects over the lifespan. Research on interventions to mitigate these late effects is also limited, particularly in terms of psychosocial support and long-term follow-up programs for YACCS.

The primary aim of this research is to identify distinct categories of YACCS based on the presence and type of late effects—both physical and psychological—that persist into adulthood. Defined subgroups, according to their unique clinical profiles, can then be investigated in relation to key life milestones to assess potential unique impacts. Previous studies conducted latent class analysis on YACCS and the indicators for identifying subgroups were resilience (94), depression (95-97), anxiety (96), somatization (96), posttraumatic stress (97), fear of recurrence

(96). Studies successfully identified subgroups of YACCS and found significant associations with their demographic and clinical characteristics such as perception of physical health, and pain (94-97).

This research aims to identify subgroups of YACCS based on physical and psychological cancer-related late effects and to examine life milestones of each class membership. By doing so, it seeks to fill existing gaps in our understanding and provision of care for this population. Furthermore, it underscores the importance of long-term follow-up and integrated support systems in facilitating the transition into adulthood and beyond.

HYP 3a: There will be distinct subgroups categorized by differing cancer-related late effects (e.g., resilient group, multimorbidity group, etc.).

HYP 3b: The subgroup experiencing multimorbidity will be more likely to experience challenges in achieving life milestones. Individuals in the multimorbidity subgroup will endorse lower rates of full-time employment and educational attainment, are more likely to reside with parents, and are less likely to be married or in a committed partnership compared to their counterparts who experience fewer or no late effects.

4.2 Methods

Participants and Procedure

The analysis in this project utilized the population-based data from the Project Forward cohort, consistent with the methodology used in Study 1 (82).

Measures

Self-reported late effects of cancer treatment. Cancer-related late effects included 10 binary response variables categorized based on Late Effects of Treatment for Childhood Cancer

(PDQ®) (106). The late effect categories include neurocognitive (difficulty learning and memory), endocrine (weight gain), respiratory (difficulty breathing), cardiac (heart problem), sensory (eyesight, hearing), reproductive (infertility, early menopause, sexual dysfunction), neoplasm, psychological (depressive symptoms), musculoskeletal (bone fracture), digestive (liver damage). Items were selected based on the most prevalent chronic conditions previously reported among CCS. A CES-D cutoff score of 16 was used to indicate clinically significant depression as a psychological late effect.

Treatment intensity. Treatment intensity was evaluated using a method modeled after the Intensity of Treatment Rating Scale 2.0 (ITR-2) (97). This scale combines cancer registry data and the survivors' self-reported treatment and relapse information to categorize treatments into four levels of intensity: 1 = "Least intensive" (e.g., surgery only), 2 = "Moderately intensive" (e.g., chemotherapy or radiation), 3 = "Very intensive" (e.g., two or more treatment modalities), and 4 = "Most intensive" (e.g., relapse protocols).

Demographic and socioeconomic variables. The covariates included sex, age at survey completion, race/ethnicity, living status (living with a parent), employment status (full-time, part-time, unemployed), educational attainment (having obtained a college degree), and relationship status (single, married/partnered).

Statistical Analysis

Class Selection

Latent class analysis (LCA) serves as a multiple-group SEM where the group variable was unobserved, used to discern different groups of YACCS based on the hypothesis of group differences, though the exact number and nature of the groups were not predetermined. Class

memberships were derived from observed data. To ensure a global solution, each class model was replicated using multiple starting values and different random starts. Model interpretability and theoretical meaningfulness were also pivotal in the selection of the best fitting model. Missing data were addressed using the full information maximum likelihood method, with latent class variables treated as missing at random. The fit of the latent class models was evaluated using an array of fit indices. The log-likelihood (LL) indicated the goodness-of-fit, with higher values signifying a better fit. Degrees of freedom (DF) reflected the complexity of the model, with more degrees indicating a less complex model. G^2, the likelihood-ratio chi-square statistic, was considered where lower values suggested a better fit. The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Consistent Akaike's Information Criterion (CAIC), and Adjusted Bayesian Information Criterion (ABIC) all penalized for model complexity, with lower values indicating a more parsimonious fit. Entropy was utilized as a measure of classification quality, with higher values indicating a clearer delineation of classes. Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) was applied, with p-values less than 0.05 suggesting significant model fit improvement with the addition of each subsequent class. A minimum class membership threshold of 5% was established to ensure sufficient power for subsequent analyses. This analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), with odds ratios (ORs) and 95% confidence intervals (CIs) calculated for all predictors and covariates included in the final model.

Main Analyses

In the subsequent phase of analysis, individuals were grouped into latent subgroups based on their class assignment. This new class assignment variable was then utilized to explore associations with covariates and to investigate its relationship with the outcome. The association

between the late effect subgroups and the covariates, including the demographic and clinical attributes of YACCS participants were examined in both univariable and multivariable logistic regression analyses. The covariates included age, sex, treatment intensity, time since diagnosis, and race/ethnicity. For analytical purposes, race/ethnicity was categorically divided, and dummy coded into Non-Hispanic White, Hispanic, Asian, and Other. The categories including Hispanic, Asian, and other races were incorporated into the final model.

4.3 Results

Descriptive Data and Class Selection

Prevalence of Late Effects

The Project Forward Cohort, comprising 1,106 young adult cancer survivors (YACCS), displayed a spectrum of late effects post-treatment. Sensory impairments, including hearing and vision difficulties, were the most prevalent, affecting 222 individuals (20.07%) (Table 4.1). Neurocognitive issues were also notable, impacting 144 survivors (13.02%). Endocrine and reproductive concerns were present in 113 (10.22%) and 119 (10.76%) individuals, respectively. Respiratory conditions were reported by 60 participants (5.42%), while cardiac and digestive late effects were less common, observed in 47 (4.25%) and 22 (1.99%) of the cohort, respectively. Neoplasms and musculoskeletal problems were the least reported, with 21 (1.90%) and 26 (2.35%) individuals affected.

The cohort's psychological well-being, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D), revealed an average score of 13.88 (SD = 10.9), with scores ranging from 0 to 58. A substantial portion of the cohort, constituting 341 survivors (33.66%),

scored at or above the CES-D threshold of 16, suggesting a significant presence of depressive symptoms among the participants.

Table 4.1. Prevalence of Cancer-related Late Effects and Life Milestones among YACCS in the Project Forward Cohort (n=1,106).

	N (Weighted %) Or Mean (SD), range
Late effects	
Cardiac	47 (4.25)
Neoplasm	21 (1.90)
Endocrine	113 (10.22)
Digestive	22 (1.99)
Sensory (Hearing and Vision)	222 (20.07)
Neurocognitive	144 (13.02)
Respiratory	60 (5.42)
Reproductive	119 (10.76)
Musculoskeletal	26 (2.35)
Depressive symptoms (CES-D)*	13.88 (10.9), 0-58
CES-D 16 cut-off	341 (33.66)
Life Milestones	
Married/Partnered	312 (28.21)
Have at least a college degree	316 (28.96)
Living with a parent	568 (52.21)
Full-time	475 (42.95)
Part-time	234 (21.16)
Unemployed	378 (34.18)

* Denotes continuous score, binary cutoff score variable was used in the analysis.

Latent Class Analysis of Cancer-related Late Effects

A Latent Class Analysis (LCA) was conducted to identify underlying subgroups within the Project Forward Cohort based on cancer-related late effects. The model fit indices for one to five latent classes are presented in Table 1.

For the one-class solution, the log-likelihood (LL) was -3134.66. The goodness-of-fit statistic (G^2) was 792.66, with an Akaike Information Criterion (AIC) of 812.66, Bayesian Information Criterion (BIC) of 862.75, Consistent Akaike Information Criterion (CAIC) of

872.75, and sample-size adjusted BIC (ABIC) of 830.99. As expected, this model did not present

a test for the number of classes as it serves as the baseline model.

The two-class model showed a significant improvement in fit, with an LL of -2914.32

and a G^2 of 351.99. The AIC decreased to 393.99, BIC to 499.17, CAIC to 520.17, and ABIC to

432.47. The Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR-LRT) was significant (p

= .003), and the entropy value was 0.72, indicating a clear delineation between classes.

The three-class solution offered a modest improvement in LL to -2901.43 and G^2 to 326.22.

The AIC was 390.22, BIC 550.49, CAIC 582.49, and ABIC 448.85.

Based on the model fit indices, the two-class model appeared to provide the best balance

between fit and parsimony. The BIC, CAIC, and ABIC values were lower for the two-class

model compared to the three-class model, indicating a better fit. The entropy value for the two-

class model was moderate, suggesting distinct and interpretable classes. The VLMR-LRT results

support the selection of a model with more than one class. The LCA revealed distinct subgroups

within the cohort based on the patterns of late effects reported, with the two-class model

emerging as the most informative in describing the latent structure of the data.

Table 4.2 Model Fit Indices for a Latent Class Analysis of Cancer-related Late Effects (n=1,106)

No. of Classes	LL	G^2	AIC	BIC	CAIC	ABIC	VLMR-LRT, P	Entropy
1	-3134.66	792.66	812.66	862.75	872.75	830.99	-	-
2	**-2914.32**	**351.99**	**393.99**	**499.17**	**520.17**	**432.47**	**.003**	**0.72**
3	-2901.43	326.22	390.22	550.49	582.49	448.85	.09	0.70
4	-2878.58	280.51	366.51	581.87	624.87	445.30	.18	0.72
5	-2871.01	265.37	373.37	643.83	697.83	472.32	.24	0.74

NOTE. The two-class model was chosen based on the AIC and BIC values, relative
improvement value, and taking into consideration class interpretation.
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; CAIC,
consistent Akaike's information criterion; VLMR, Vuong-Lo-Mendell Rubin; ABIC, Adjusted
Bayesian information criterion.

Figure 4.1 illustrates the probabilities of endorsement for ten categories of late effects among YACCS grouped into two classes: those with multimorbidity (n=200, 18.1%) and those identified as resilient (n=906, 81.9%). The endorsement probabilities reflect the likelihood that individuals within each class would report experiencing a specific late effect.

For the multimorbidity class, the highest probability of endorsement was observed for sensory effects, with a peak just above 0.60, suggesting that over half of the individuals in this class are likely to report sensory issues. Other late effects with notably higher probabilities in the multimorbidity class include psychological and neurocognitive issues, with probabilities ranging approximately between 0.25 and 0.45. Endocrine and reproductive late effects followed, showing moderate probabilities.

In contrast, the resilient class demonstrated significantly lower probabilities across all late effects, underscoring a clear differentiation between the health status of the two groups. Notably, all late effects in the resilient class are associated with low endorsement probabilities, well below the 0.30 threshold, indicating a low likelihood of reporting any of the late effects listed.

The pattern of endorsement across the late effects categories suggests that YACCS with multimorbidity have a higher probability of experiencing a range of late effects, with neurocognitive issues being the most prevalent. The graphical representation also indicates that YACCS classified as resilient have a low probability of endorsing any late effects, reaffirming the distinction in health outcomes between the two classes.
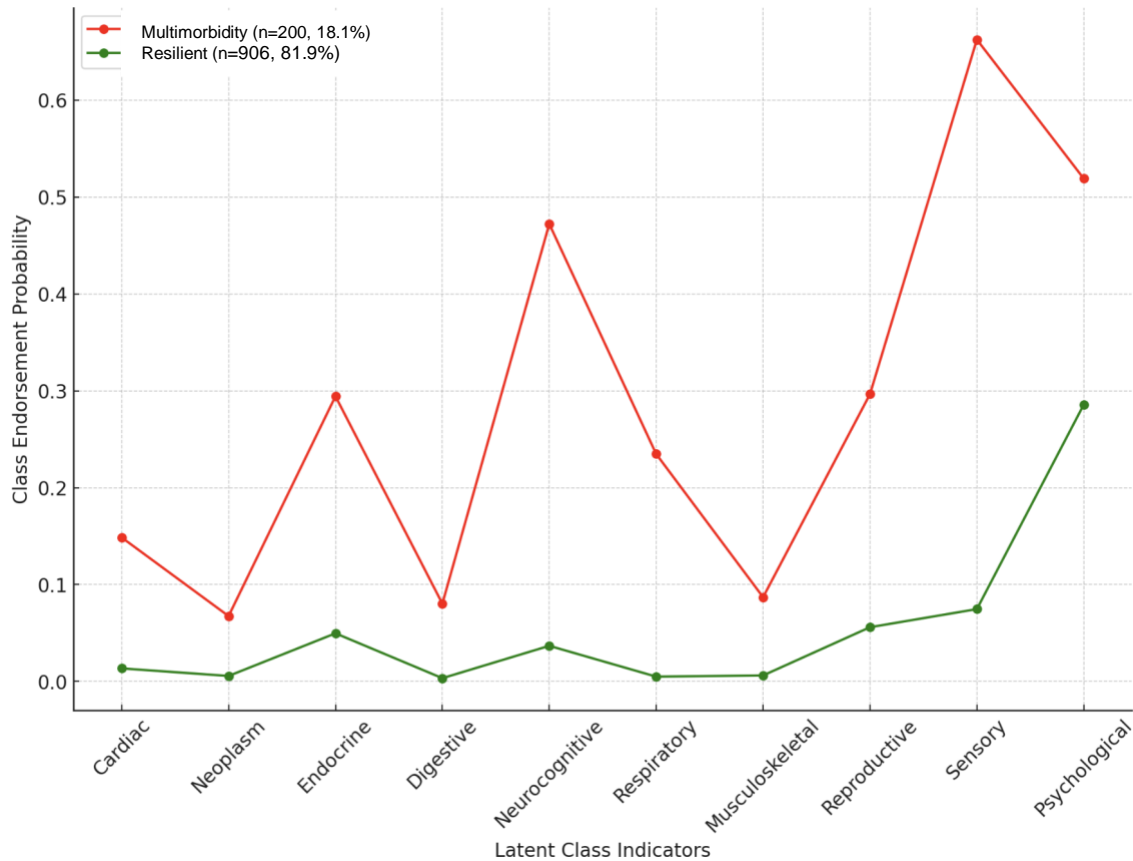
Figure 4.1. Graphical representation of probabilities of latent classes of cancer-related late effects. The class endorsement probabilities are the item-response probabilities for each of the ten late effects categories based on the class they were grouped into. Low item-response probabilities (<0.30) indicate a low probability of endorsing the late effect. High item-response probabilities (>0.70) indicate a high probability of endorsing the late effect.

Table 4.3 summarizes the demographic and clinical characteristics of 1,106 participants, distinguishing between individuals with multimorbidity (n=200, 18.1%) and those classified as resilient (n=906, 81.9%). Significant differences in late effects between the two groups are highlighted, emphasizing the disparities in health outcomes.

Sex distribution between the groups was relatively balanced, with females representing 57% of the multimorbidity group and 49.4% of the resilient group.

Age and years since diagnosis were comparable between the two groups, with an average age of 26.7 years for the multimorbidity class and 26.1 years for the resilient group. The average time since diagnosis was 14.8 and 14.5 years, respectively.

Treatment intensity varied significantly, with the multimorbidity group having a higher proportion of individuals who received the most intensive treatments (23%) compared to the resilient group (11.4%).

Insurance status showed that a higher percentage of individuals with multimorbidity had insurance (95%) compared to the resilient group (89.5%), with private insurance being more common in the multimorbidity group.

Regarding late effects, individuals with multimorbidity reported a higher average number of late effects (4.1) compared to the resilient group (2.1). Specifically, the multimorbidity group showed higher prevalence rates of cardiac (17.5%), endocrine (36.5%), neurocognitive (54.5%), respiratory (28.5%), and sensory (75%) late effects. In contrast, a significant majority of the resilient group reported no late effects (76.05%).

The self-perceived overall health status revealed that individuals with multimorbidity were more likely to rate their health as poor compared to the resilient group. Educational attainment showed that individuals with multimorbidity were less likely to have obtained a college degree (20.1%) than those in the resilient group (31.0%) ($p<001$).

Employment status highlighted a higher unemployment rate in the multimorbidity group (46.5%) as opposed to the resilient group (31.5%). A similar proportion of individuals from both groups were living with a parent, and marital status was also comparable.

Table 4.3 Demographic characteristics by each class membership (N=1,106)

	Multimorbidity (n=200, 18.1%)	Resilient (n=906, 81.9%)
Sex – N (%)		
Male	86 (43%)	458 (50.5)
Female	114 (57%)	448 (49.4)
Race – N (%)		
Non-Hispanic White	59 (29.5)	265 (29.3)
Hispanic	106 (53)	464 (51.2)
Asian	15 (7.5)	92 (10.2)
Other	20 (10.0)	85 (9.4)
Age – N (%)	26.7 (5.4, 19-39)	26.1 (4.8, 18-41)
18-20	26 (13.0)	105 (11.6)
21-25	69 (34.5)	353 (39.0)
26-30	60 (30.0)	279 (30.8)
31-39	45 (22.5)	169 (18.7)
Years since diagnosis Mean (SD), range	14.8 (4.43), 5-22	14.5 (4.3), 5-22
Age at diagnosis Mean (SD), range	11.97 (5.41, 0-19)	11.6 (5.3, 0-19)
Cancer Type – N (%)		
Leukemia	**58 (29.0)**	**334 (36.9)**
Lymphoma	**48 (24.0)**	**192 (21.2)**
Brain CNS	**42 (21.0)**	**127 (14.0)**
Endocrine	**6 (3.0)**	**54 (6.0)**
Skin	**4 (2.0)**	**37 (4.1)**
Other[a]	**42 (21.0)**	**162 (18.9)**
Treatment Intensity – N (%)		
Least Moderate	**48 (24.0)**	**365 (40.3)**
Very Intensive	**53 (53.0)**	**438 (48.3)**
Most intensive	**23 (23.0)**	**103 (11.4)**
Insurance – N (%)		
With insurance	**187 (95.0)**	**782 (89.5)**
Public	**115 (58.4)**	**516 (59.0)**
Private	**71 (36.0)**	**250 (28.6)**
Other	**1 (0.5)**	**16 (1.8)**
None	**10 (5.1)**	**92 (10.5)**
Neighborhood SES – N (%)		
1 Lowest	41 (24.0)	206 (25.3)
2	33 (19.3)	162 (19.9)
3	36 (21.1)	153 (18.8)
4	37 (21.6)	141 (17.3)
5 Highest	24 (14.0)	154 (18.9)
Cancer-related Late effects Mean (SD), range	4.1 (1.1, 2-6)	2.1 (0.6, 1-3)

|		
None – N (%)	0 (0.0)	689 (76.1)
Cardiac	35 (17.5)	12 (1.3)
Neoplasm	15 (7.5)	6 (0.7)
Endocrine	73 (36.5)	40 (4.4)
Digestive	19 (9.5)	3 (0.3)
Neurocognitive	109 (54.5)	35 (3.9)
Respiratory	57 (28.5)	3 (0.3)
Sensory	150 (75)	72 (8.0)
Musculoskeletal	21 (10.5)	5 (0.6)
Reproductive	69 (34.5)	50 (5.5)
Depressive symptoms (>16 points)	94 (50.5)	247 (29.9)
Perceived Overall Health – N (%)		
0 Poor	**14 (7.1)**	**17 (2.0)**
1	**59 (29.8)**	**128 (24.6)**
2	**76 (38.4)**	**317 (36.1)**
3	**38 (19.2)**	**277 (31.6)**
4 Excellent	**11 (5.6)**	**139 (15.9)**
Educational Level – N (%)		
Less than high school	12 (6.0)	46 (5.2)
Graduated high school	40 (20.1)	165 (18.5)
Some college	107 (53.8)	405 (45.4)
Graduated college	40 (20.1)	276 (31.0)
Obtained a college degree	**40 (20.1)**	**276 (31.0)**
Employment – N (%)		
Full time	**68 (34)**	**407 (45.0)**
Part time	46 (18)	198 (21.9)
Unemployed	**93 (46.5)**	**285 (31.5)**
Living with a parent – N (%)	107 (54)	461 (51.8)
Married/Partnered – N (%)	58 (29.0)	254 (28.0)
Single – N (%)	136 (68.3)	615 (69.0)

Note. The percentages are from the total number of participants who provided data for each variable, not from the total number of individuals in each cohort; percentages may not add up to 100 due to rounding. NA denotes not applicable. Bold font indicates statistical significance (*p*<.05)

[a] Oral cavity & pharynx, digestive system, respiratory system, soft tissue including heart, urinary system, eye & orbit, miscellaneous

Figure 4.2 provides a comparative analysis of the prevalence of cancer-related late effects between individuals with multimorbidity (n=200, 18.1%) and those without additional health conditions, referred to as the resilient group (n=906, 81.9%). The data illustrate the percentage of individuals reporting various late effects within these two categories.

In individuals with multimorbidity, sensory late effects (i.e., vision, hearing) were the most reported late effect, with a prevalence of 75%. This was followed by neurocognitive effects and depressive symptoms, which were reported by 54.5% and 50% of individuals in this group respectively. Endocrine and respiratory effects were also notable, with around 36% and 28% prevalence respectively.

In contrast, the healthy group exhibited significantly lower rates of late effects across all categories. The most reported late effect in this group was also sensory-related but was much less prevalent than in the multimorbidity group. All other late effects in the healthy group were reported at rates below 10% except depressive symptoms. The proportion of individuals reporting no late effects was substantially higher in the healthy group, approximately 76%, compared to the multimorbidity group, where it was 0%.
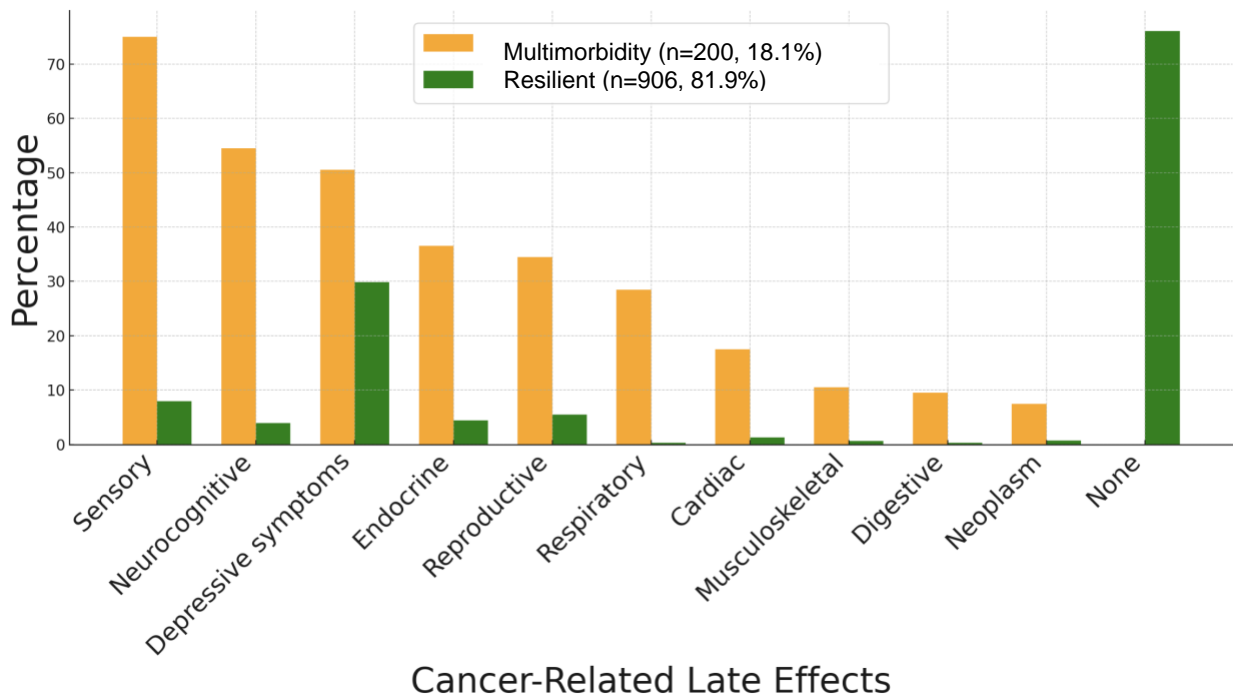
Figure 4.2. Comparison of Late Effects Between Multimorbidity and Healthy Groups (%)

Main Outcome

Table 4.4 presents the associations between various life milestones and the presence of multimorbidity as compared to a healthy state among 1,160 individuals. The odds ratios (OR) and adjusted odds ratios (AOR) with their 95% confidence intervals (CI) and p-values are reported for both univariate and multivariable analyses.

Univariate Analyses

In the univariate analysis, individuals with multimorbidity were less likely to have a college degree (OR = 0.56, 95% CI: 0.39-0.82, p = .003) and less likely to be employed full-time (OR = 0.63, 95% CI: 0.46-0.87, p = .005) compared to healthy individuals. There was no significant association with part-time employment (OR = 0.79, 95% CI: 0.53-1.16, p = .23), being single (OR = 0.96, 95% CI: 0.70-1.35, p = .85), being married/partnered (OR = 1.05, 95% CI: 0.75-1.47, p = .78), or living with a parent (OR = 1.09, 95% CI: 0.80-1.49, p = .57). However, the odds of being unemployed were significantly higher among those with multimorbidity (OR = 1.89, 95% CI: 1.39-2.59, p < .0001).

Multivariable Analyses

After adjusting for sex, current age, years since diagnosis, treatment intensity, and race/ethnicity, the multivariable models showed that individuals with multimorbidity remained significantly less likely to have a college degree (AOR = 0.51, 95% CI: 0.34-0.77, p = .002) and less likely to be employed full-time (AOR = 0.56, 95% CI: 0.39-0.81, p = .002). The odds of being unemployed were even higher in the multivariable analysis (AOR = 1.95, 95% CI: 1.40-2.72, p < .0001). There was no significant multivariable association with part-time employment (AOR = 0.80, 95% CI: 0.53-1.20, p = .27), being single (AOR = 1.17, 95% CI: 0.78-1.74, p

= .45), being married/partnered (AOR = 0.88, 95% CI: 0.59-1.30, p = .52), or living with a

parent (AOR = 1.22, 95% CI: 0.85-1.76, p = .28).

Table 4.4. Univariate Associations and Multivariable Models between Life Milestones and Late Effect Classes (n = 1,160).

	Multimorbidity (vs. Resilient)			
Outcome variables	Univariable Analyses		Multivariable Analyses	
	OR (95% CI)	*p*	AOR (95% CI)	*p*
College degree	**0.56 (0.39-0.82)**	**.003**	**0.48 (0.31-0.76)**	**.002**
Full time	**0.63 (0.46-0.87)**	**.005**	**0.56 (0.38-0.83)**	**.004**
Part time	0.79 (0.53-1.16)	.23	1.02 (0.75-1.39)	.18
Unemployed	**1.89 (1.39-2.59)**	**<.0001**	**2.09 (1.46-3.00)**	**<.0001**
Single	0.96 (0.70-1.35)	.85	1.01 (0.66-1.55)	.97
Married/Partnered	1.05 (0.75-1.47)	.78	1.03 (0.67-1.57)	.89
Living with a parent	1.09 (0.80-1.49)	.57	1.28 (0.86-1.91)	.22

Note. Bold p-values denote statistically significant results (*p*<.05).
The multivariable models controlled for sex, current age, years since diagnosis, treatment intensity, nSES, and race/ethnicity. The analytical sample size varied based on missing responses for covariates of the multivariable regression models. All *p*-values are two-sided.

4.4 Discussion

This study examined the prevalence of cancer-related late effects and their association

with demographic and clinical characteristics among YACCS, distinguishing between

individuals with multimorbidity and a healthy cohort. The findings provide valuable insights into

the prevalence of various late effects in YACCS and highlight the impact of multimorbidity on

the likelihood of experiencing specific social and developmental challenges after cancer

treatment.

The significantly higher prevalence of neurocognitive, sensory, and endocrine late effects

in the multimorbidity group suggests that intensive cancer treatment regimens might have long-

term adverse consequences. Particularly, the neurocognitive late effects observed could be

attributed to both direct neurotoxicity from treatments and the psychological impact of a cancer

diagnosis and its aftermath. This aligns with prior research highlighting neurocognitive

dysfunction as a common late effect in cancer survivors who have undergone aggressive treatment protocols (105).

The predominance of sensory late effects in the multimorbidity group, with 75% reporting such issues, is striking and warrants attention. This may reflect eyesight and/or hearing impairment resulting from certain chemotherapeutic agents or radiation therapy, which often manifest years after treatment completion (106). The fact that these late effects are reported less frequently by the healthy group underscores the potential for targeted interventions that could mitigate these risks.

Endocrine late effects, including thyroid dysfunction and diabetes, were also notably higher in the multimorbidity group. This could be related to the direct impact of certain chemotherapy agents, radiation exposure, and the propensity for lifestyle changes post-treatment that can predispose individuals to metabolic syndromes (105, 106). Higher prevalence of cardiac and respiratory late effects in the multimorbidity group raises concerns about the long-term cardiopulmonary health of these individuals. This finding is consistent with the literature that documents cardiotoxicity and pulmonary fibrosis as potential late effects of treatments such as anthracyclines and chest radiation (106).

The analysis also revealed significant socioeconomic implications. The lower likelihood of obtaining a college degree and higher unemployment rates among individuals with multimorbidity reflect the potential socioeconomic impact of health challenges faced during critical years of career development (44). Ongoing health issues likely interfere with educational attainment and stable employment, leading to long-term socioeconomic disadvantages.

Insurance coverage was higher in the multimorbidity group, reflecting a greater need for ongoing medical care; however, even with insurance, the presence of multimorbidity can lead to

increased medical costs and financial toxicity. The relatively high rates of living with parents and similar marital status across both groups might indicate a need for social support among YACCS, which could be addressed by social services and survivorship care plans.

One of the primary strengths of the study is its population-based design, which leverages data from a broad and representative sample of young adult cancer survivors. Population-based studies are critical in epidemiological research as they provide a comprehensive overview that is more generalizable to the wider population. This design minimizes selection bias and allows for a more accurate estimation of the prevalence of late effects across different demographic groups.

The data collection period of 2015-2017 is another significant strength. It includes a cohort of survivors who received contemporary treatment regimen, reflecting the current landscape of cancer treatment and survivorship. This timeliness ensures that the findings are relevant to current clinical practices and survivorship care plans. It supports the notion that despite improvements in treatment outcomes, survivors are still vulnerable to a range of late effects. This insight is crucial for oncologists, survivorship care planners, and policymakers in adapting strategies that align with the evolving nature of cancer therapies and their long-term impacts.

Furthermore, the study has an ethnic diversity among its participants, with higher representation of Hispanic/Latino and Asian survivors compared to the Childhood Cancer Survivor Study (CCSS) (51% vs 8%). This diversity allows for a more detailed examination of late effects across different ethnicities, providing a richer understanding of how cancer and its treatment outcomes may interact with diverse cultural and genetic backgrounds. The enhanced ethnic representation not only strengthens the validity of our results but also ensures that the study findings are applicable to a broader segment of the survivor population. This is particularly

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important given the disparities in health outcomes that have been documented among different ethnic groups. By including a higher representation of these populations, our study contributes to a more equitable and inclusive understanding of cancer survivorship. The population-based nature of our data, the inclusion of recently treated survivors, and the ethnically diverse makeup of our cohort collectively strengthen the credibility and relevance of our findings, providing a solid foundation for future research and interventions aimed at improving the long-term well-being of cancer survivors.

While our study provides valuable insights into the prevalence of cancer-related late effects among young adult cancer survivors, several limitations must be considered when interpreting the results. The reliance on self-reported data introduces the possibility of recall bias, where participants might inaccurately recall or report their health conditions or treatment experiences. This could potentially lead to underestimation or overestimation of the late effects. The cross-sectional design of the study captures data at a single time point does not observe changes over time. Thus, while associations can be identified, the directionality and evolution of these relationships remain unclear.

The heterogeneity of the cancer types and treatments among participants is another limitation. Various treatments can lead to a wide range of late effects, and without detailed treatment data, pinpointing which specific therapies contribute to late effects is challenging. Additionally, the study did not extensively account for psychosocial variables, which could have a significant impact on the reporting and experience of late effects. For example, factors such as social support, coping mechanisms, and socioeconomic status play critical roles in survivorship and may influence health outcomes.

The rapidly evolving nature of cancer treatments also means that the findings may not reflect the very latest therapeutic approaches. Treatments are continuously advancing, and the late effects experienced by survivors may differ as newer and more targeted therapies are developed.

While the study benefits from an ethnically diverse cohort, cultural differences in health perception and reporting could affect the results. The experiences of health and illness, and the willingness to report them, can vary widely across cultures, potentially influencing the data. Lastly, survivorship bias needs to be considered, as the cohort does not include those who did not survive their cancer or its treatment. This could lead to an underrepresentation of the most severe late effects.

Clinical Implications

The results of this study have several clinical implications for the management and care of young adult cancer survivors. The high prevalence of neurocognitive and sensory late effects among individuals with multimorbidity suggests that these areas require particular attention in post-treatment care. Clinicians should consider implementing routine screening for these late effects as part of standard follow-up protocols to ensure early detection and intervention, potentially improving long-term outcomes.

The diversity of late effects noted in the study emphasizes the necessity of personalized survivorship care plans. These plans should be developed collaboratively with input from a multidisciplinary team, including oncologists, primary care physicians, specialists, and allied health professionals, to address the comprehensive health needs of survivors. Such an approach ensures that the complex and interrelated late effects of cancer treatment are managed effectively, and that care is tailored to each survivor's unique circumstances.

Furthermore, the study's findings highlight the significant impact of cancer and its treatment on psychosocial well-being and economic stability. Survivorship care should therefore extend beyond the medical management of late effects to include psychosocial support and vocational rehabilitation services. These services can assist survivors in coping with the emotional and social challenges that often accompany recovery and reintegration into society.

Additionally, the observed association between multimorbidity and lower educational attainment underlines the importance of advocacy and educational support for survivors. Healthcare providers can play a crucial role in connecting survivors with educational resources and advocating for educational accommodations when needed.

Finally, this study underscores the need for policy changes to support comprehensive long-term survivorship care. This includes advocating for policies that ensure ongoing access to adequate survivorship care, especially as survivors navigate the transition from pediatric to adult care, and developing guidelines that standardize the monitoring for late effects across healthcare systems. The existence of Children's Oncology Group (COG) guidelines is a valuable resource, yet there is a notable gap in awareness among both community physicians and childhood cancer survivors (CCS) regarding these guidelines and the importance of long-term follow-up (LTFU) care (108).

The clinical implications drawn from this study advocate for an integrated approach to survivorship care that is not only responsive and patient-centered but also tailored to meet the changing needs of young adult cancer survivors. The data support a dual model of care, proposing specialized care for survivors with multimorbid conditions and a more general care approach for those without significant health issues. Such stratification could optimize resource

allocation and enhance the practicality of care delivery. Ensuring that high-risk survivors have access to and coverage for specialized care is essential.

By concentrating efforts on these focal points, healthcare providers can significantly improve the quality of life and long-term health outcomes for this at-risk group. Implementing these policy changes and care models will require a concerted effort among healthcare providers, survivors, policymakers, and the healthcare system at large.

CONCLUSION

The three studies provide comprehensive insights into life milestones (e.g., employment, educational attainment, living arrangement, relationship status) and cancer-related late effects among YACCS using a population-based sample from the Los Angeles Cancer Surveillance Program, the SEER Cancer Registry. Study 1 examined the prevalence of life milestones among YACCS and non-cancer population-based cohort controls. The results showed that YACCS were less likely to have a college degree, have a full-time employment, and married/partnered compared to their peers without a cancer history. In contrast, they were more likely to be unemployed, have a part-time employment, and live with a parent.

Study 2 assessed the relationship between delays in achieving life milestones and depressive symptoms over time in YACCS. The study used linear regression model with depressive symptoms as the outcome variable and delay in life milestone as the exposure variable. Delays in educational attainment were significant predictors of depressive symptoms, even when demographic factors and baseline depressive symptoms were controlled.

Study 3 successfully identified the two subgroups of YACCS based on their cancer-related late effects and examined how each subgroup is associated with life milestone achievement. The latent class analysis revealed multimorbidity group and resilient group based on cancer-related late effects reported by the survivors. The multimorbidity group were less likely to have a college degree and be employed full-time compared with the resilient group after adjusting for demographic factors, years since diagnosis, and treatment intensity.

Collectively, these studies illuminate the persistent challenges YACCS face as they navigate through life post-treatment. The findings reveal the multidimensional nature of survivorship, where socioeconomic factors like employment and education intertwine with

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personal growth and psychological well-being. The research underscores the importance of targeted interventions that provide employment assistance, educational support, and mental health care tailored to the diverse needs of survivors.

The implications of these studies support for innovative childhood cancer survivorship care to cover the full spectrum of life experiences and transitions that YACCS encounter. The need for a longitudinal approach in survivorship research is evident, with a call for larger, more diverse samples and the inclusion of various psychosocial measures to capture the long-term and evolving nature of survivors' lives.

The limitations identified across the studies serve as a roadmap for future research endeavors. They stress the need for a definition of unemployment, accounting for educational engagement in young populations, and a longer follow-up period to fully grasp the long-term effects of cancer survivorship on life milestones and mental health.

In conclusion, these studies together contribute significantly to the body of knowledge on YACCS, offering vital evidence to shape effective survivorship programs. The goal moving forward is clear: to facilitate a survivorship journey that is not only about living longer but also about living well, with access to opportunities and support that allow for personal development, stable employment, and overall enhanced quality of life.

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