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Family Life Events In The First Year Of Acute Lymphoblastic Leukemia Therapy

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FAMILY LIFE EVENTS IN THE FIRST YEAR OF ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY.

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Abstract

Despite remarkable advances in cure rates, childhood acute lymphoblastic leukemia (ALL) may continue to result in considerable family strain. We sought to 1) measure incidence of divorce, reduced career opportunities, changes to work hours, home relocation, and changes to family planning at one year after ALL diagnosis 2) identify family and patient factors associated with these events. We conducted a prospective cohort study of 159 children with average risk-ALL enrolled and treated on COG protocol AALL0331 at 31 selected sites. In the first year of ALL treatment, 46% of parents lost a job, 13% divorced/separated, 22% decided not to have more children, 51% declined occupational opportunities, 68% decreased work hours, and 27% of families relocated homes. In adjusted analyses, no unifying factors were associated with all family events. Relocation correlated with less maternal education (OR: 4.27 [95% CI: 1.43-12.82]). Declining parental opportunities associated with family income <$50,000 (OR: 4.25 [95% CI: 1.50-12.02]) and child <5 years old (OR: 4.21 [95% CI: 1.73-10.25]). Deciding not to have more children correlated with smaller family size 2-3 vs.4-5 (OR: 3.62 [95% CI: 1.10-11.96]). In summary, childhood ALL still confers a substantial family burden, especially in the earlier stages of treatment.

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Introduction

Currently, over ninety percent of children diagnosed with standard-risk acute lymphoblastic leukemia become long-term survivors. In a study utilizing multiple Children's Oncology Group national leukemia trials over a few decades, Hunger et al. found improved survival among all age, gender, racial, and disease risk stratification subgroups, excluding infants less than or equal to one years old (1). This study encompassed more than fifty percent of estimated cases of acute lymphoblastic leukemia in children and young adults in the United States. Compared to the five-year survival rate of 83.7% in the early 1990s, the survival rate in the early 2000s was reported as 90.4%. Improved survival was attributed to decreased incidence of death secondary to relapse or progression of leukemia. Hunger credited enhanced treatment regimens based on patient-specific genotype and molecular targets, such as inclusion of imatinib for patients with Philadelphia chromosome positive acute lymphoblastic leukemia, with the overall increased rate of survival.

However, even with high cure rates, the cancer experience can be overwhelming. The duration of therapy for standard-risk leukemia is two to three years, involving frequent clinic visits, unanticipated hospitalizations, and other therapy-related complications. Children suffer fatigue, nausea, prolonged absence from school, and behavioral changes as side effects of chemotherapy.

The challenging experience of cancer has psychological repercussions for the family. At the Children's Hospital of Philadelphia, Kazak et al. studied posttraumatic stress in one hundred and twenty-five families of children diagnosed with a pediatric cancer, most of whom were diagnosed with leukemia. Based on the Posttraumatic Stress

Disorder Reaction Index self-report survey, the majority of parents (68% of mothers and 57% of fathers) scored in the moderate to severe range for posttraumatic stress symptoms during active treatment. Similarly, a prior study by Kazak et al. found more posttraumatic stress symptoms in parents of childhood leukemia survivors than in parents of healthy children, though these symptoms manifested to a lesser degree in parents of survivors than in parents with children actively undergoing treatment (2,3).

In addition to the psychological stresses, families experience many financial, social, and family-management burdens, which have not yet been well-quantified. Prior studies on the family burden of pediatric cancer tend to be qualitative and measure broad domains of family stress. For example, Patterson et al. utilized focus groups of parents of childhood cancer survivors to assess family strain. Twenty-six families were represented in total, and their recorded responses were transcribed and categorized into various domains of relational or financial strain. Instead of quantifying specific, discrete family life events, Patterson reported such outcomes as "Strong parental emotions during treatment (feeling numb, devastated, overwhelmed; helpless, loss of control; fear child would die; grief re pain, losses; guilt)" or "Parent-child relationship strains (being overprotective of child; uncertainty re child's independence; telling child diagnosis; conflict over taking meds)" (4).

Studies of family burden, specifically in childhood acute lymphoblastic leukemia, are limited. Instead, past studies used cohorts that included patients with heterogeneous cancers that varied in therapy intensity, hospitalization rates, and need for radiation therapy. The impact on the family may have differed based on the type of malignancy. Certain cancers, such as central nervous system or bone malignancies, are associated with

more severe symptom manifestations and intensive treatment regimens. These studies were also performed in earlier treatment eras, relied on retrospective data, and yielded conflicting results (2-4).

With respect to childhood cancer's impact on parental marriages, past studies found differing results, showing both increased and decreased divorce/separation rates compared to population norms. In a national registry-based study in Denmark, Grant et al. compared the risk of termination of parental cohabitation between parents of two thousand four hundred and fifty children with cancer and parents of forty-four thousand eight hundred and fifty-three age and gender matched controls. Of the cohort of children with cancer, nine hundred and eighteen were diagnosed with leukemia or lymphoma. Grant assessed cohabitation, rather than formal marriage, to reflect modern family structures since 60% of first-born children in Denmark are born to cohabitating, non-married parents. Utilizing the substantial registry data, Grant et al. were able to assess the state of certain families up to twenty years post-cancer diagnosis. They found no association between a child's cancer diagnosis and parental separation with similar risk of dissolution of cohabitation in both the study and control cohorts. Furthermore, parents of children who survived a cancer diagnosis did not have significantly different rates of separation than parents of children who did not survive. In both the study and control groups, factors that associated with increased risk of parental separation included low family income, unemployment, young parental age, living in more urban settings, and increased length of time since entry into the study (5).

Grant's results were similar to an earlier national registry-based study in the Netherlands by Syse et al. Syse compared four thousand five hundred and ninety married

couples with a child with cancer and over nine hundred and seventy thousand married couples with a child without cancer. Syse found no association between a child's cancer diagnosis and increased risk of parental divorce. Time since diagnosis, child's age, and survival also did not significantly affect divorce rates. Interestingly, Syse found that maternal education greater than high school level correlated with increased rates of divorce in parents of children with cancer. The authors noted that, in Norway, shared parental responsibility after separation occurs more commonly when mothers have attained higher education. However, they were unable to conclude whether this fact contributed to the increase in divorce rates amongst higher maternal education parents of children with cancer in their study (6).

In contrast to these two large population studies, in 1976, Kaplan et al. found increased rates of divorce/separation (23%) three months after the death of a child with leukemia (7). It is important to note that the survival rate in the 1970s is not reflective of current therapy and that Kaplan's use of a population that suffers such extreme emotional distress, such as loss of a child, may not accurately portray the experience of the majority of parents of current children diagnosed with leukemia.

Like past studies regarding childhood cancer's impact on parental marriage, available studies concerning changes in parental employment showed mixed results, were limited in their sample size and distribution, and/or were performed in former treatment eras (8-13). Available studies concerning changes in parental employment in the United States are over two decades old (8-10). In the early 1980s, Bloom et al. studied five hundred and sixty-nine children with cancer and the medical costs of treatment, out-of-pocket disease-related costs, and loss of parental wages to their families. Of the children

in Bloom's study, slightly less than 30% were diagnosed with acute lymphoblastic leukemia. Bloom found families spent an average of 38% of gross annual income on disease-related care, which encompassed medical expenses (hospitalizations, medications, physicians, etc.), nonmedical, but disease-related, expenses (transportation to and from the hospital, costs for child home services, etc.), and indirect expenses such as lost parental wages. Lost wages accounted for a large proportion of the costs (8). Bloom noted that costs were particularly high in the first year of diagnosis and tapered off as treatment progressed; costs rose again if a child did not respond well to treatment.

Two earlier studies by Lansky et al. likewise attempted to quantify medical and non-medical costs to families of children with cancer (9,14). Lansky qualified nonmedical costs as expenses related to transportation to and from treatment sites, lodging for out-of-town patients and their families, meals, and family care. For non-medical expenses, seventy families with children undergoing treatment for cancer at the University of Kansas Medical Center completed weekly expense journals. A subgroup of parents also completed a log regarding loss of wages. About half of the families sampled reported loss of pay. Like Bloom, Lansky noted that the bulk of costs were bimodal in distribution, peaking at the earlier stages of treatment as well as terminal stages.

Researchers in countries with public health insurance have published more recent studies regarding pediatric cancer and financial burden (11-13). A Canadian pilot study in British Columbia in the 1990s evaluated child's cancer diagnosis's financial impact on the family. In this study, Limburg et al. used a retrospective questionnaire to sample over one hundred patients and their families to assess how parental employment was affected by a child's cancer diagnosis and what, if any, alternative sources of income were

utilized. This cohort included heterogeneous cancers with less than a quarter of patients diagnosed with leukemia. Children had to be at least two years post-diagnosis to facilitate capturing changes to parental employment over the entire treatment course. Limburg concluded that most families suffered considerable, albeit short-term, economic losses during their child's cancer treatment (12). Limburg conceded that this conclusion may not be generalizable to countries with different health insurance policies. For example, in the United States, private health insurance predominates, and coverage of children is often tied to their parents' employment. The need to maintain health insurance coverage may limit a parent's ability to take extended leave from work. Furthermore, the results of Limburg's study may suffer from selection bias, as the final response rate was merely 41%. Families who were unable or unwilling to return questionnaires may be the families with less financial resources or less employment stability.

In a larger Norwegian population-based study by Syse et al., a child's cancer diagnosis was not associated with parental loss of employment. Syse utilized national census data to compare parents of over three thousand children with cancer with parents of healthy children. When analyzed by particularly type of cancer, there was no significant association between type of cancer and loss of parental employment. Contrary to the expectation of increased family management strains associated with more children, no association between loss of employment and increased family size was found. However, younger age of child at diagnosis (less than 10 years old) was associated with about a ten percent decrease in maternal earnings. Interestingly, in families of children diagnosed with cancer, lower maternal education correlated with decreased cessation of employment (OR 1.31) (13).

In contrast, Heath et al. reported great financial hardship among families newly diagnosed with childhood cancer in 2002 in Australia (15). Heath analyzed self-report questionnaires regarding economic burden from fifty-six parents of children newly diagnosed with cancer. Of families studied, greater than seventy percent of parents reported great or moderate financial hardship after their child's diagnosis. Financial hardship included disruption of employment, loss of income, use of sick leave and other employee benefits, and costs of relocation to areas closer to treatment centers. Families who experienced greater economic burden had lower household income, lived a greater distance from the treatment center, and were single-parent households. Over ninety percent of parents reported that these economic difficulties greatly added to their emotional distress, and sixty percent of couples reported that these financial burdens negatively affected their spousal relations to a large degree. These findings are surprising given the availability of government funds for assisting families with children with cancer in Australia. Heath et al. report that, given public health insurance, the out-of-pocket costs paid by a family of a child undergoing cancer treatment in Australia is roughly half the total cost in the United States. The authors conclude that available resources are not being delivered effectively to families with the greatest need since families not in the lowest income bracket, who also did not self-report financial need, also received financial assistance.

Despite the range of studies completed in geographically and temporally varied settings and the use of assorted research methodologies, at present, there are no studies regarding objective family life events, after a childhood acute lymphoblastic leukemia diagnosis, in an ethnically diverse patient population, in the modern era of therapy.

Measuring the family burden of average risk B-precursor acute lymphoblastic leukemia and its treatment is particularly important because it is among the most common and curable of childhood cancers (1). Pediatric cancer centers already recognize the need for multidisciplinary, family-centered care that encompasses the psychosocial needs of the family. The well-being of the family unit has repercussions for the child's health. As noted by Patterson et al., past studies note a bidirectional effect between parental psychological well-being and psychosocial difficulties in survivors of childhood cancer. This includes posttraumatic stress disorder symptoms in survivors of childhood cancer whose parents suffered posttraumatic stress disorder symptoms (4). Positive parental responses had a protective effect on children during their cancer treatment (16). Prospective and representative data, in the current era of therapy, regarding critical family outcomes are needed to inform further support interventions and to empower healthcare providers to offer anticipatory guidance to families.

In this prospective, longitudinal study, our aim was to measure the relational, financial, and psychosocial burdens to families of children treated for newly diagnosed average risk acute lymphoblastic leukemia. We hypothesized that, despite advances in treatment, a childhood diagnosis of acute lymphoblastic leukemia still placed a significant burden to families in the form of an increased incidence of adverse family life events. We recruited patients enrolled on Children's Oncology Group therapeutic protocol AALL0331 from a predominantly United States subset of all Children's Oncology Group clinical trials sites. We selected patients with average risk features as this risk stratification group represents the majority of pediatric acute lymphoblastic leukemia. Families were surveyed regarding the incidence of discrete family life events at

three time points during the first year of therapy. We sought to 1) measure the incidence of changes in marital status, parental occupational and educational opportunities, parental work hours, location of home, and family planning and 2) identify family and patient factors associated with a greater likelihood of these major family life events.

Methods

Study population

We conducted a prospective, longitudinal study of major life events in families of children with average risk acute lymphoblastic leukemia who were enrolled and treated on Children's Oncology Group protocol AALL0331 between April 2005 and March 2009 at thirty-one sites (thirty American sites and one Australian site) selected from approximately two hundred sites at which this trial was open to patient enrollment. Participating institutions were selected to represent a broad geographic distribution and both community care and tertiary care centers. The thirty-one sites are as follows: Children's Hospital Medical Center (Akron, OH), Children's Hospital at the Cleveland Clinic (Cleveland, OH), Children's Hospital Colorado (Aurora, CO), Children's Hospital of Central California (Madera, CA), Children's Hospital and Clinics of Minnesota (Minneapolis and St. Paul, MN), Children's Hospital (New Orleans, LA), Children's Hospital of Pittsburgh (Pittsburgh, PA), Seattle Children's Hospital (Seattle, WA), Helen DeVos Children's Hospital (Grand Rapids, MI), Doernbecher Children's Hospital (Portland, OR), Nemours/Alfred I. DuPont Hospital for Children (Wilmington, DE), East Tennessee Children's Hospital (Knoxville, TN), Hackensack University Medical Center (Hackensack, NJ), Randall Children's Hospital at Legacy Emanuel (Portland, OR), Loma

Linda University Medical Center (Loma Linda, CA), Midwest Children's Cancer Center (Milwaukee, WI), Nevada Cancer Research Foundation, Princess Margaret Hospital for Children (Perth, Australia), St. Vincent Hospital Regional Cancer Center (Green Bay, WI), Packard Children's Hospital at Stanford (Stanford, CA), SUNY Upstate Medical University (Syracuse, NY), St. Joseph's Children's Hospital of Tampa (Tampa, FL), University of Alabama at Birmingham Hospital (Birmingham, AL), University of Florida Academic Health Center (Gainesville, FL), University of Minnesota Medical Center, Fairview (Minneapolis, MN), Children's Hospital University of Mississippi Medical Center (Jackson, Mississippi), University of New Mexico Children's Hospital (Albuquerque, New Mexico), University of Texas Southwestern Medical Center (Dallas, TX), American Family Children's Hospital University of Wisconsin Children's Hospital (Madison, WI), Children's Hospital at Vanderbilt (Nashville, TN). Additional eligibility criteria included age ≥2 years old at diagnosis and at least one parent with English or Spanish literacy, the languages for which validated surveys were available. Average risk acute lymphoblastic leukemia is defined as standard risk acute lymphoblastic leukemia by National Cancer Institute criteria (peripheral white blood count <50,000 and age between 1.0 and 9.99 years) (17) with no central nervous system or testicular leukemia, and bone marrow minimal residual disease <0.1% at the end of four weeks of Induction therapy. Patients with Down syndrome and/or certain molecular features such as favorable cytogenetics (trisomies of 4, 10, and 17 or TEL-AML translocation) were also eligible for enrollment in this trial. Patients with prior steroid therapy were eligible for enrollment while patients with prior cytotoxic chemotherapy exposure, excepting intrathecal cytarabine, were excluded. Patients who relapsed during the duration of the

trial were also excluded. (See http://www.cancer.gov/clinicaltrials/search/view?cdrid=409589&version=HealthProfessional for more details).

At the end of Induction therapy, average risk acute lymphoblastic leukemia patients who consented to continue on the AALL0331 trial were randomized in a 2x2 therapeutic trial design to: 1) standard Consolidation (SC) vs. intensified Consolidation (IC) therapy that added two doses of cyclophosphamide and peg-asparaginase and 2) standard Interim Maintenance (SIM) with oral methotrexate vs. augmented Interim Maintenance (AIM) with escalating intravenous (IV) methotrexate as post-Consolidation therapy. Maturation of protocol CCG-1991 data showed that IV methotrexate was superior to oral methotrexate (18). Therefore, all patients enrolled subsequent to 09/29/2008 received IV methotrexate, and the study randomization regarding post-Consolidation was closed.

Of the patients enrolled in AALL0331 at the thirty-one participating institutions, 194 patients met the eligibility criteria for this health-related quality of life ancillary study. Of these, twenty-four declined participation. Of the one hundred and seventy who consented, four patients withdrew prior to administration of the first set of surveys, and seven did not receive the first set of evaluations due to administrative errors. The thirty-five eligible non-participants were similar to the one hundred and fifty-nine patients who participated (82% of eligible) with regards to gender and age at diagnosis. Participants, compared to non-participants, were more likely to be White ($p=0.01$). Compared to the greater therapeutic AALL0331 study population, participants were similar with regards to gender distribution, but more likely to be ≥ 5 years old at diagnosis, White, and randomized to Standard (not Augmented) Interim Maintenance (Table 1).

Based on a 7.4% divorce rate nationally (per 2011 maternal age-matched census data), which results in an expected proportion of approximately 0.10, and a 95% confidence interval with a total width of confidence interval of 0.10, our study would require a sample size of 138 (Appendix 6E of Designing Clinical Research (19)). As such, our study was sufficiently powered with a sample size of 159.

Procedures

In addition to the Yale University Human Investigation Committee, institutional review boards of each participating center approved the current study. Informed consent and assent, when indicated, were obtained for all participants. Each participating family in the study was assigned a Children's Oncology Group participant code to protect patient privacy and comply with Health Insurance Portability and Accountability Act standards.

The self-identified primary caregiver (the child's mother in 84% of instances) completed surveys during regular clinic visits at three selected time points within the first year of therapy: day 1 of Consolidation phase (~1 month after diagnosis), end of Delayed Intensification phase (~6 months after diagnosis), and six months after starting Maintenance phase (~12 months after diagnosis).

Measures

Socioeconomic data were obtained using a parent demographic survey, which included questions about race/ethnicity, household income, marital status, maternal education, and family size. In this study, marital status responses of "married" or "living with someone in a marriage-like relationship" were consolidated due to their presumed similar impact on social and financial support and to reflect current family structures.

Incidence of major family life events was quantified by line item responses to the Family Inventory of Life Events and Changes Subset (FILE-S; adapted from McCubbin, Patterson, and Wilson 1991 (20)). Parents were specifically asked whether the following life events occurred since their child's diagnosis of leukemia. For changes in marital status, "Husband and wife separated or divorced." For increased work hours, "Took a second job or worked more hours." For decreased work hours, "Quit or lost my job." or "Worked part-time instead of full-time." For decreased occupational/educational opportunities, "Did not start a job but wanted to." "Did not accept a job promotion or transfer." or "Quit or did not start further education/training." For change in residence, "Moved to different home or community." For changes to family planning, "Changed plan and decided not to have more children."

Family coping was assessed using the Coping Health Inventory for Parents (21), which has been validated for children with a variety of chronic illnesses. In this forty-five-item checklist, parents rate how helpful a particular coping behavior is (e.g. "talking over personal feelings and concerns with spouse" and "talking with other parents in the same type of situation and learning about their experiences") on a four point scale ranging from "not helpful" to "extremely helpful". Responses to these questions are then consolidated to determine scores for three subscales of coping behaviors. The three subscales, (1) Maintaining family integration and optimism, (2) Maintaining social support and self-esteem, and (3) Understanding the medical situation, have α reliabilities of 0.79, 0.79, and 0.71. A higher score on each subscale indicates a greater reliance on that coping pattern, but there are no normative scores.

Parental perception of cancer's impact on a child's quality of life was measured using the PedsQL 3.0 Cancer Module Parent Proxy-Report (22). In this twenty-seven-item questionnaire, parents rate each item on a five point scale ranging from "never a problem" to "almost always a problem". Of the eight subscales, "Nausea" (α reliability of 0.85) and "Pain and Hurt" (α reliability of 0.89) subscales were analyzed as these physical symptoms are typical acute lymphoblastic leukemia treatment complications. A higher score indicates fewer problems or symptoms.

Data analyses

The family and patient factors of age at diagnosis, gender, and race/ethnicity were summarized and compared between participants and eligible nonparticipants using an exact chi-square test to evaluate the potential for response bias. Data regarding eligible nonparticipants were obtained from the AALL0331 therapeutic study database.

The primary outcomes of interest were changes in marital status, parental working hours, parental work and educational opportunities, moving of residence, and family planning at the three time points after diagnosis. The cumulative incidences of loss of employment, home relocation, and divorce/separation among married couples at one year after diagnosis were calculated after excluding the eight Australian participants to enable comparison with available United States Census data. However, the data from the eight Australian participants were included in the final logistic regression analyses. Logistic regression was used for univariate and multivariate analyses for each outcome. Potential predictors that were nominally significant at p value of <0.1 in the univariate analyses were included in the multivariate model. In addition, we determined, based on the longitudinal model with repeated measures, whether the incidence of events changed

significantly between the three time points. All analyses were performed using SAS® software, Version 9.2 (SAS Institute Inc., Cary, NC, USA; 2008).

Samantha Lau composed the analysis plan to determine the impact to families of a new diagnosis of standard risk acute lymphoblastic leukemia in children, corresponded with site-based clinical research associates to facilitate timely collection of data, coded and entered collected data into a central system, conceptualized the data analysis, interpreted the data results, and wrote this manuscript. Regina Myers and Moira Whitley entered data and communicated with site investigators to coordinate timely data collection. Xiaomin Lu, PhD. and Meenakshi Devidas, PhD. carried out completed data analysis and advised on best methods of analysis given the research aims and available data. Lyn Balsamo, PhD., Naomi Winick, MD., Stephen Hunger, MD., Linda Stork, MD., Kelly Maloney, MD., and William Carroll, MD. interpreted the data results and provided suggestions for revisions upon reviewing the completed manuscript. Nina Kadan-Lottick, MD., MSPH designed the original ancillary study as part of the greater Children's Oncology Group therapeutic trial, successfully applied for NCI research funding, helped to formulate the aims, hypotheses, and study analysis plan, interpreted the data results, and reviewed and revised the manuscript.

Results

Characteristics of study population

Table 1 displays characteristics of the one hundred and fifty-nine enrolled patients and their families. The study population was mostly White (68%) with 16% Hispanic and 7% Black. The majority of parents were married or living in a marriage-like relationship

(75%) at the time of diagnosis. The majority of families consisted of four to five individuals (59%). The average maternal age at diagnosis was 34 years old with the majority of mothers achieving less than a college education (58%).

Cumulative incidence of major family life events

Table 2 displays the cumulative incidence of major family life events in the first year after diagnosis. Among the one hundred and twenty sets of parents initially married or living together in a marriage-like relationship, 13% divorced or separated by approximately twelve months after acute lymphoblastic leukemia diagnosis. Of those married, 10% divorced or separated (vs. 7.4% annually for married women 20-34 years old from the 2011 U.S. Census American Community Survey (23)). The incidence of moving to a different home was somewhat higher (27% vs. 21% annually) when compared to a group matched for average age of child at diagnosis (persons 1-4 years old from 2009 Census data (24)). After their child's acute lymphoblastic leukemia diagnosis, 22% of parents changed their plans and decided not to have additional children.

Overall, the economic and occupational impact on families was substantial. Among parents, 51% declined work or educational opportunities, 18% increased work hours, and 68% decreased work hours (including 46% who reported loss of employment vs. 9.1% from 2010 Census data (25,26)). As seen in Figure 1, the increase in frequency of major family life events is greatest earlier in treatment but continues to steadily rise. This is most notable in outcomes involving parental employment. Forty-two percent of parents decreased work hours from the time of diagnosis to time point 1; at subsequent time points, the additional number of parents decreasing work hours was substantially less. The increases in frequencies of outcomes between time points are statistically

significant for all events at a significance level of $p<0.05$, except for the change in frequencies from time point 2 to 3 for divorce/separation, increased work hours, and decreased work hours.

Patient and family factors associated with major family life events

Table 3 displays the univariate analysis of factors associated with major family life events. Moving was strongly associated with maternal education less than college (OR=4.63, p=0.004) and non-White race/ethnicity (OR=2.88, p=0.008). Deciding not to have more children was associated with smaller family size (two to three vs. four to five members; OR=3.44, p=0.02). Declining occupational or educational opportunities was associated with lower family income (OR=3.21, p=0.003), child younger than 5 years at diagnosis (OR=2.48, p=0.008), and less than a college level education in the mother (OR=2.05, p=0.05). Less maternal education was also associated with divorce/separation (OR=4.61, p=0.05). A decrease in work hours was predicted by more intensive treatment (IC/AIM vs. SC/SIM; OR= 3.75, p= 0.04). Parental perception of the child's pain and nausea and endorsement of parental coping behaviors were generally not associated with the studied outcomes.

In multivariate analysis (Table 4), moving was substantially associated with lower maternal education (OR=4.27, p=0.009) but no longer associated with race/ethnicity. The strong association between deciding not to have more children and smaller family size (two to three vs. four to five; OR=3.62, p=0.04) remained. Declining occupational or educational opportunities was still associated with lower family income (<$50,000; OR=4.25, p=0.006) and younger age of child at diagnosis (<5 years old; OR=4.21, p=0.002). Randomization to IV methotrexate significantly ($p<0.05$) reduced the

likelihood of parents having to increase work hours or decline work/educational opportunities (OR=0.18 and 0.25, respectively). No unifying patient or family factor correlated with all six studied major family life events.

Discussion

Our multi-site, prospective study of one hundred and fifty-nine children undergoing contemporary therapy for childhood average risk acute lymphoblastic leukemia demonstrates that families experience considerable psychosocial, economic, and relational stresses despite the high probability of cure and mostly outpatient chemotherapy. These findings are consistent with our a priori hypothesis. By one year after diagnosis, 46% of the 68% of parents who decreased work hours either quit or lost their jobs, 18% increased work hours, 51% declined educational/occupational opportunities, 27% relocated residences, and 22% changed their family planning regarding additional children. In addition, 13% of parents, who were initially married or living-as-married, divorced or separated. In general, families of all socioeconomic backgrounds were vulnerable to economic stresses, ranging from increases and reductions in work hours to quitting or losing a job. Parental perception of a child's physical symptoms, such as pain and nausea, as well as parental coping behaviors were not associated with studied outcomes, though nausea did limit continued study participation. While the burden is considerable, no common patient or family factor was identified that increased the likelihood of all these major life events.

This is the first study to quantify the family burden of newly diagnosed childhood acute lymphoblastic leukemia in a large, racially and regionally diverse sample in the era

of modern therapy. The substantial percentage of patients from previously underrepresented groups (16% Hispanic and 7% Black) and the thirty designated sites from across the United States enable fair representation of the diversity of children who develop average risk acute lymphoblastic leukemia. Our high participation rate of 82% also mitigates major selection bias, although there was some bias given the requirement of parental English or Spanish literacy. In contrast to prior studies that mainly used measures of parental strain, coping measures, or qualitative interviews (11,27-32) to measure family burden, our study measured distinct family life events. Furthermore, the prospective cohort design of this study decreases the likelihood of recall bias as compared to prior retrospective questionnaire-based studies (4,12). In addition, our use of three time points within the first year of diagnosis, allows the results to reflect short-term changes in employment. This is a strength of our study as previous research has shown that the steepest changes in parental employment occur within the first year (8,12,14).

In this study, the incidence of divorce/separation in married parents of children with acute lymphoblastic leukemia in the first year after diagnosis was only slightly higher than the United States national annual rate for women of a similar age range (10% vs. 7.4%). It is difficult to determine to what degree the child's acute lymphoblastic leukemia diagnosis had affected parental marriage as the baseline state of the parents' marriage was not assessed. Even so, our results concur with previous studies, which likewise report no impact on divorce rates. In 1978, Lansky et al. (33) found a similar divorce rate among parents during their child's cancer treatment and a control group of parents of children with hemophilia. Lansky's study differed from ours in the use of a control group that also experiences a high family burden due to childhood disease, a

single region sample that only included patients in Kansas and Missouri, and an older treatment era.

More recent population studies from Norway and Denmark likewise concluded no significant increase in divorce rates (5,6) amongst parents with a child diagnosed with cancer. Similar to the study in Denmark by Grant et al., our results did not show a correlation between higher maternal education and divorce although this association between maternal education and divorce was noted by Syse in Norway. A strength of both the Danish and Norwegian national registry-based studies is the enormous sample size and subsequent power of their studies. Furthermore, given detailed reporting of data in multiple government-run registries and linking of individuals across various databases by government-issued identification numbers, Syse and Grant were able to follow accurately the progression of both childhood cancer diagnosis and outcome and parental marital relationships over an extended period of time. Potential weaknesses of both these registry-based studies, when attempting to generalize their results to pediatric leukemia, are their inclusion of all types of cancer as well as their use of a broad timeframe. The selection of patients diagnosed with cancer in the 1970s through the early 2000s results in a mixed study population that experienced vastly different treatment regimens and outcomes based on the time of a child's diagnosis. However, the results were adjusted for time since diagnosis, which should assist in delineating treatment eras, and showed insignificant differences in divorce rates between parents of children with and without cancer. Another potential weakness of these studies is the inability to evaluate potentially confounding factors that may contribute to a couple's decision to divorce, such as

baseline satisfaction with the marriage prior to a child's cancer diagnosis or whether a couple had considered divorce prior to their child's illness.

Our results, like those of Syse and Grant, contrast with the increased rate of divorce/separation in parents whose children died from cancer that was reported by Kaplan et al. in 1976 (7). This difference may be attributed to newer therapy regimens and the resultant improved five-year acute lymphoblastic leukemia survival rates above 90%.

While the literature supporting increased divorce rates following a child's cancer diagnosis is sparse, other studies took a more subjective approach, measuring marital dissatisfaction and stress rather than divorce/separation. Past studies concur that the experience of childhood cancer possesses the potential to substantially impact the marital relationship, either in a positive or negative manner. For example, Patistea et al. utilized open-ended interviews to assess the self-reported impact of an initial diagnosis of childhood leukemia on the parental marital relationship in twenty-nine Greek couples. They found that over a third of parents felt their child's diagnosis of leukemia caused significant marital strain, particularly with regards to communication, while over forty percent of parents actually reported that their marital relationship strengthened as a result of their child's diagnosis (32).

Likewise, a study of thirty-five Israeli couples by Lavee et al. showed that a child's cancer diagnosis and treatment simultaneously strengthened and weakened certain aspects of the marital relationship. Over forty percent of parents reported decreased marital satisfaction, specifically with respect to sexual intimacy, while slightly less than thirty percent actually reported improved communication between spouses. Couples

reported decreased satisfaction with their marriage with lengthening time of a child's illness (greater than four years). Lavee et al. noted that the retrospective nature of their study may have led to averaging of changes to the marital relationship contributing to a perceived minimal net change in the marriage at the time of completion of the questionnaires (34).

In Finland, Lahteenmaki et al. studied twenty-one families in the first year after a child's cancer diagnosis to determine subjectively the impact on parental wellness in social, occupational, and health domains. When compared to forty-six maternal education-matched controls, parents of children with cancer reported no statistically different levels of marital satisfaction. Lahteenmaki suggests that the short follow-up of one year may have contributed to the lack of change in quality of parental marriage (11).

A review performed by da Silva et al. included fourteen articles published between 1997 and 2009 and sought to comprehensively assess the effects of a child's diagnosis of cancer on marital relationships. Da Silva noted similar temporal trends across multiple studies showing initial negative changes in marital relationships at diagnosis, minimal changes at one year of diagnosis, improvement in spousal relations in the first two to three years of treatment, and a mix of deterioration and maintenance of marital relationships for extended child illness. Nine of the fourteen articles noted that difficulties in communication played an important role in marital stress, especially in families where parents were geographically separated due to child's hospitalization or distance of treatment site from home (35). Factors contributing to marital distress include balancing care of other children, difficulties in communication between spouses, negative mood that subsequently limits a spouse's ability to be emotionally supportive, limitations

to previous work or social life, and shifting of roles (6,35). While our study did not show increased divorce rates following a child's cancer diagnosis, further research in this area is needed given the qualitative impact of a cancer diagnosis on the marital relationship and the importance of the family unit to a child's experience of cancer.

By one year after diagnosis, about 20% of parents had decided to change family planning and not to have more children. Our study concurs with a 1995 retrospective Netherlands study by Van Dongen-Melman et al (36) wherein 20% of parents decided not to have more children after a child's leukemia diagnosis. Family planning is pertinent to families of children with average risk acute lymphoblastic leukemia since the peak age at diagnosis is approximately 4 years old. Many parents of young children may be in the midst of building their families. Our study found that smaller family size (two to three vs. four to five) was predictive of changing family planning. This association may reflect that larger families have completed family building or decided not to have more children prior to a child's cancer diagnosis. However, interpretation of these results is limited by lack of knowledge of parental rationale for changes to family planning. Furthermore, family planning is a dynamic decision process and may change subsequent to completion of a child's treatment.

The economic impact of a child's diagnosis of average risk acute lymphoblastic leukemia is likewise substantial during the first year of therapy: 68% of parents decreased work hours, 18% increased work hours, and 51% declined occupational/educational opportunities. From our study, in the first year of treatment, 46% of families reported that one or more parents resigned from or lost their jobs. This is over five times the national annual incidence of unemployment among previously employed individuals. Our data

also indicated that more than half of parents decreased work hours and that the economic impact was felt most acutely at the onset of treatment.

Prior studies, using prospective family expense journals (8,9) and population data analysis, (13) similarly recognized the economic impact of a cancer diagnosis and its treatment on families, noting 25-60% decreases in weekly income. In the 1980's, Bloom's study quantified expenses over a six-month period utilizing hospital billing records to calculate medical costs. A subset of patients was selected to complete week-long expense diaries to account for out-of-pocket, nonmedical expenses. While Bloom accounted for certain aspects of indirect expenses by including lost parental wages, he accedes that the indirect costs were likely underestimated. This study did not account for loss of employment, decreased work productivity, or opportunity costs, such as not accepting a promotion that may require a parent to relocate (8).

Lansky et al. similarly had families complete expense diaries and found that medical costs contributed less to total expenses than non-medical costs. While medical costs consumed 5.8% of a family's weekly budget, nonmedical costs used up 26% of the weekly budget. Lansky reported associations between increased family size, decreased patient functioning, and distance from the hospital with increased nonmedical costs. In addition to devouring a larger portion of a family's weekly expenses, nonmedical costs may prove even more stressful as they lack a system of reimbursement and require immediate payment (9,14).

In Limburg's study in Canada, the majority of parents, 65% of mothers and 78% of fathers, took leave from work during the first year of their child's treatment, and the majority of parents, 80% of mothers and 89% of fathers, were able to return to their prior

employment after their initial leave of absence. By diagnosis, mothers of children diagnosed with leukemia had the greatest loss of work at 92%. While on employment leave at the time of diagnosis, a third of families relied on both salary and non-salary sources of income (employment insurance, social assistance, and other forms of financial support), and over ten percent of families solely relied on non-salary sources of income. By the time of the survey, after the vast majority of parents had resumed employment, the percentages of families utilizing both salary and non-salary income decreased to 13% while families using non-salary income sources decreased to 7%. Limburg concluded that a child's cancer diagnosis induced a considerable, yet short-lived, loss of parental employment and shift in sources of family income (12).

In the Norwegian study by Syse et al., parental loss of employment did not associate with a child's cancer diagnosis. However, as noted in both national registry-based publications by Syse et al., studies done in social welfare states where public health care is provided to all citizens free of charge may not be generalizable to other countries (6,13). Therefore, their finding no association between a child's cancer diagnosis and loss of parental employment may only be applicable to other countries with similar welfare options such as Canada and certain Western European countries. Furthermore, this study by Syse et al., like their registry-based study on parental marriage, once again encompassed patients diagnosed over more than a decade. Syse noted some inconclusive variations in parental employment and earnings by time period that were not discussed further. It is possible that these variations were secondary to national economic shifts or adjustments in intensity of treatment regimens over time. In addition, the use of census data provides only one time point per year. As such, a potential limitation is the inability

to assess short-term employment changes within the first year of diagnosis. This is particularly noteworthy because previous studies have found most parental employment changes occur within that initial year of treatment (8,12,14). Strengths of this study include its large sample size as well as the use of government-collected census data, which minimizes the recall bias inherent to questionnaire-based studies.

While other studies noted that parental losses of income had a more short-lived effect on a family's financial well-being, this may not be the case in our studies as government-funded resources are more limited in the United States. As such, these results warrant further follow-up in the later stages of treatment to determine whether parents are as readily able to return to work or find alternative sources of income. Our results showed lower age of child (age <5) at diagnosis and lower family income (<$50,000) were associated with decreased occupational/educational opportunities. These associations may reflect the greater amount of supervision required for younger children and the greater burden of unexpected medical costs to lower income families. Families with lower income may have less money in savings, which limits their abilities to pay for extra expenses, such as a parent returning to college, when faced with the unexpected expense of a child's illness. Furthermore, as noted by Syse (13), parents may be unable to take leave from work as lower paying jobs tend to be less flexible with regards to re-hiring employees after extended absences. Families with lower income likewise may be more dependent on a parent's current employment, which forces a parent to maintain his or her job rather than explore other occupational or educational opportunities that may have less immediate financial security.

Intravenous methotrexate, compared to oral methotrexate, was associated with a lower likelihood of parents declining work/educational opportunities or increasing work hours. This may be due to possible differences in toxicities between the treatment arms. From a the CCG 1991 trial in which there was also an oral vs. escalating IV methotrexate randomization, more hepatic toxicity was observed in the oral methotrexate arm (18). This was attributed to the combination of the oral methotrexate with 6-mercaptopurine. In that study, patients on the oral methotrexate arms that immediately preceded the delayed intensification phases of therapy also had a higher number of mean hospital days during the delayed intensification. Toxicity outcomes have not yet been reported for the therapeutic arm of the current study (AALL0331) so we cannot confirm if toxicity differences were observed in our sample with regards to methotrexate randomization.

This study should be understood in the setting of potential limitations. Because families were enrolled only after the diagnosis of acute lymphoblastic leukemia, data regarding baseline inter-family member dynamics and relationships as well as economic/occupational, family building, and housing relocation plans, prior to a child's acute lymphoblastic leukemia diagnosis, are not available. For example, the quality of the parents' marriage prior to the child's diagnosis was not determined. While the burden of a new cancer diagnosis likely has major ramifications for a marital relationship, it is also plausible that financial, emotional, and interpersonal strains existed prior to the diagnosis. As such, it is impossible to determine whether the child's diagnosis and treatment of acute lymphoblastic leukemia was the impetus for separation, an additional source of conflict, or non-contributory. Similarly, we did not ascertain the reason for home relocation. This would be helpful in clarifying whether families moved for work, for

treatment, to be closer to extended family for psychosocial or financial reasons, or for reasons unrelated to the leukemia.

Participants with missing data at time point 3 reported higher scores on the Peds QL nausea subscale at time point 1. While this may be more correlative than causative, it would be interesting to further examine whether a child's physical symptoms affect parental participation. It may be plausible that nausea caused a family to either be late or re-schedule a clinic appointment hence leading to confusion with regards to administration of the survey and a subsequently missed data point.

Given the dynamic nature of family planning, it is possible that families, who decided not to have more children, will choose to have more children upon completion of average risk acute lymphoblastic leukemia treatment. As such, analysis of later time points is needed to clarify whether changes to family planning were temporary or permanent decisions.

For most participating families, the surveys for all three time points were completed by the same primary caregiver. However, at some time points, a caregiver other than the one who completed the initial survey was present and completed the study survey. The occasional difference in reporter is a potential limitation; nonetheless, the majority of survey questions, especially those related to the six study outcomes of interest (divorce, moving, loss of employment/opportunities, increased work hours, decreased work hours, and changes to family planning), were worded in such a way as to elicit reporting of objective, discrete life events, rather than subjective feelings thereby limiting inter-reporter variability. Furthermore, parent self-report was used to limit social desirability bias that may occur with an interview format as some parents may not wish to

discuss in-person difficulties regarding sensitive topics, such as finances and marital satisfaction.

For a comparison group, we gathered United States Census data for populations that were age-matched for our study cohort; however, not all of the potentially contributing demographic factors were available in the Census data. As such, our use of Census data can only provide a rough comparison group. The impact of including one Australian site in our results is limited as this site enrolled only 8 patients. Furthermore, we controlled for potential cultural and economic differences by excluding these eight participants in our calculations of annual incidences of family life event outcomes, which were then subsequently compared to United States Census data. Given that our study included thirty United States sites, the results predominantly represent the family situation in the United States, and we believe the use of national census data for rough comparison is accurate.

Of the 194 families eligible for study enrollment, 169 chose to participate and were enrolled in the study. We recognize that there is a potential selection bias as families experiencing the greatest burden may be least inclined to participate in this study and to take the time to complete multiple surveys. Follow-up to determine the cause of withdrawal is needed. However, the eligible participants who withdrew possessed demographic features/characteristics that were no different than those who remained and continued in the study.

A potential confounder is the recession in 2008, which overlapped with our period of enrollment and likely influenced the financial stability and choices of participating families. It would be relevant to delineate a parent's reason for not starting a new job to

determine whether it was a decision made secondary to his or her child's cancer diagnosis versus due to lack of employment opportunities. Given that such decisions are often multi-factorial, it would be difficult to clearly separate the two reasons. For example, a parent may have chosen not to take a new job because the opportunity was in a location that made it more difficult for the family to access a preferred pediatric oncology treatment center. Regardless of the lack of information with respect to parental motivation for refusing employment opportunities, our observed frequency of job loss was about five-fold higher than national figures, suggesting that the child's diagnosis of leukemia did indeed play some role in the decision process.

While there have been considerable advances in the treatment of childhood acute lymphoblastic leukemia, this study emphasizes the great burdens that the disease places on the family in the first year after a child's diagnosis. The burden may be even greater for families of children with other cancers that have lower cure rates and more intensive therapy. As such, similar studies in other cancers are needed to fully understand the impact of childhood cancer on family functioning. Understanding the impact on the entire family is essential as a family's adaptation impacts a child's adjustment to cancer (4,37). Discussion of anticipated family burdens as well as expected treatment and disease-related symptoms allows physicians to prepare parents for their role as caretakers.

In our study, a child's acute symptoms and parental coping strategies did not substantially correlate with any of the six major family life event outcomes. As such, our results suggest that more clinically modifiable factors, such as a child's pain and nausea or parental coping strategies, do not contribute to family burden in the first year after diagnosis as much as the family's greater socioeconomic context. Therefore, improved

access to financial resources, such as gifts and scholarships from private organizations or physician letters requesting medical leave benefits, may be needed, especially in the first few months of treatment. As noted by Lansky et al., social workers can only offer families resources if they are available (9). While many wonderful organization, such as Ronald McDonald House, the Make a Wish Foundation, and Leukemia and Lymphoma Society, provide financial assistance, low-cost housing options, and other gifts to patients and families, the cost of cancer treatment is still substantial. Thus, it may be necessary for new legislation to be considered that would enable greater access to economic resources to families with financial need.

Historically, greater awareness of issues surrounding delivery of healthcare has been leveraged to encourage policy change, such as with the Affordable Care Act (ACA). For example, in the area of cancer survivorship, the ACA's provision of no lifetime caps on coverage may promote greater access to necessary survivorship screening and care (38). With regards to children actively undergoing treatment, the ACA's policy regarding insurance coverage despite pre-existing conditions may allow for more parental employment flexibility, enabling parents to switch employment without fear of losing coverage for their child. Since the closing of enrollment for our study in 2009, the Affordable Care Act has been passed and implemented. It remains to be seen how these policy changes will affect our study cohort in the later time points, up to two years after completion of therapy. Although the provisions in the ACA are a step forward, there remains room for growth in the delivery of comprehensive and affordable cancer care.

Our findings, as well as results from previous studies, suggest the steepest incidence of family burdens occur at diagnosis and the initiation of treatment (8,12). For

that reason, social workers and other members of the multidisciplinary oncology team should help families anticipate these challenges, access financial and social resources, and develop coping strategies soon after diagnosis. Additional studies, with more detailed questionnaires that elicit baseline states of parental marriage and employment, are needed to elicit the degree to which a child's new cancer diagnosis impacts dynamic, multi-factorial decisions, such as parental divorce, increasing work hours, and moving during a child's treatment. Our study is ongoing and will prospectively follow children and their families until two years after the end of therapy. Results at later time points will be essential to determine the persistence of certain family life outcomes seen in the first year after diagnosis. These results will also be valuable in determining the family impact through the later stages of acute lymphoblastic leukemia treatment and survivorship.

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Table 1: Characteristics of participants, eligible nonparticipants, and therapeutic study cohort

	Participants (n = 159)	Eligible nonparticipants (n = 35)	P-value	Therapeutic AALL0331	P-value
Age at diagnosis: n (%)			0.13		0.002
2.0-4.99 years	86 (54%)	24 (69%)		3294 (66%)	
5.0-9.99years	73 (46%)	11 (31%)		1666 (34%)	
Gender: n (%)			0.58		0.63
Female	76 (48%)	19 (54%)		2299 (46%)	
Male	83 (52%)	16 (46%)		2661 (54%)	
Race/Ethnicity: n (%)			0.01		0.03
White, non-Hispanic	108 (68%)	16 (46%)		2917 (59%)	
Black, non-Hispanic	11 (7%)	1 (3%)		262 (5%)	
Hispanic	26 (16%)	9 (26%)		1005 (20%)	
Other	14 (9%)	9 (25%)		776 (16%)	
Average maternal age	34				
Marital status: n (%)					
Married	105 (66%)				
Living as married	15 (9%)				
Not married (separated, divorced, widowed, never married, refused)	30 (19%)				
Missing	9 (6%)				
Maternal education: n (%)					
Less than college (training school, high school grad, some HS, grade school)	92 (58%)				
At least some college (some college, college grad, post-grad)	55 (35%)				
Missing	12 (7%)				
Family size: n (%)					
2 – 3 individuals	26 (16%)				
4 – 5 individuals	93 (58%)				
6 or more individuals	31 (20%)				
Missing	9 (6%)				
Family income: n (%)					
Less than $50,000	72 (45%)				
$50,000-$79,000	25 (16%)				
$80,000 or more	30 (19%)				
Missing	32 (20%)				
Treatment: n (%)					<0.001
Standard Consolidation, Standard Interim Maintenance	37 (23%)			198 (15%)	
Standard Consolidation, Augmented Interim Maintenance	42 (26%)			445 (34%)	
Intensified Consolidation,	41 (26%)			201 (16%)	

Standard Interim Maintenance Intensified Consolidation, Augmented Interim Maintenance	39 (25%)	446 (35%)
Peds QL: score (SD) *Pain and Hurt**	49.4 (25.76)	
*Nausea***	81.3 (17.24)	
CHIP: score (SD) *CHIP subscale 1*: Maintaining Family Integration, Cooperation, and an Optimistic Definition of the Situation	42.9 (9.37)	
CHIP subscale 2: Maintaining Social Support, Self Esteem, and Psychological Stability	25.6(10.39)	
CHIP subscale 3: Understanding the Health Care Situation through Communication with Other Parents and Consultation with the Health Care Team	17.3 (4.90)	

* Normative Pain and Hurt subscale score is 74.7, and **Nausea subscale normative score is 77.8, based on the responses of 333 patients with all types of cancer. Higher scores indicate better functioning.

Table 2: Cumulative incidence of major family life events

Time point*	Total Number Respondents	Number with Outcome	Frequency of Outcome (%)
Parents divorced or separated among married/living together			
1	120	3	3
2	110	7	6
3	106	14	13
Parents divorced or separated among married			
1	105	3	3
2	97	5	5
3	91	9	10
Parents decreased work hours			
1	151	63	42
2	148	90	61
3	144	98	68
Parents increased work hours			
1	156	11	7
2	144	18	13
3	138	25	18
Declined occupational and/or educational opportunities			
1	154	31	20
2	144	56	39
3	144	73	51
Moved residence			
1	156	14	9
2	144	26	18
3	139	38	27
Changed family planning by deciding not to have more children			
1	157	13	8
2	146	21	14
3	138	30	22

*Time point 1, 2, and 3 are approximately 1, 6, and 12 months after diagnosis. The increases in frequencies of outcomes between time points are statistically significant for all events at a significance level of $p<0.05$, except for frequency changes from time point 2 to 3 for divorce/separation, increased work hours, and decreased work hours.

Table 3: Univariate association of patient and family factors with the six outcomes at time point 3 (~12 months after diagnosis)

	Divorced Separated OR(95% CI)	**Decreased Work Hours** OR(95% CI)	**Increased Work Hours** OR(95% CI)	**Declined Opportunities** OR(95% CI)	**Relocated Home** OR(95% CI)	**Changed Family Planning** OR(95% CI)
***Age at diagnosis*:** Pre-school (2-4 years old) vs. School-age (5-9.99 years old)	1.47 (0.50-4.28)	0.70 (0.34-1.42)	0.49 (0.20-1.19)	2.48 (1.26-4.86)	1.03 (0.49-2.19)	2.17 (0.91-5.16)
***Race/Ethnicity*:** Other vs. White, non-Hispanic	2.40 (0.84-6.90)	2.28 (0.99-5.29)	1.25 (0.51-3.12)	1.83 (0.90-3.73)	2.88 (1.33-6.29)	1.14 (0.48-2.70)
***Family Income*:** Less than $50,000 vs.$50,000 or more	4.33 (0.91-20.1)	0.95 (0.43-2.07)	0.97 (0.36-2.63)	3.21 (1.49-6.94)	1.57(0.65-3.76)	0.80 (0.32-1.98)
***Maternal Education*:** No college vs. At least some college	4.61 (1.00-21.28)	1.64 (0.78-3.43)	1.25 (0.49-3.19)	2.05 (1.00-4.20)	4.63(1.65-12.99)	1.17 (0.48-2.88)
***Marital Status*:** Other vs. Married or live together		0.83 (0.33-2.06)	2.01 (0.73-5.56)	1.66 (0.71-3.88)	0.72 (0.25-2.12)	0.33 (0.07-1.49)
***Family size*:** 2-3 vs.4-5	0.71 (0.14-3.51)	2.13 (0.66-6.90)	1.20 (0.35-4.13)	1.40 (0.56-3.48)	1.61 (0.57-4.57)	3.44(1.17-10.10)
6 or more vs.4-5	1.05 (0.30-3.64)	0.58 (0.25-1.38)	1.85 (0.68-5.05)	1.94 (0.82-4.61)	1.38 (0.54-3.51)	1.46 (0.49-4.33)
Pain and Hurt subscale	0.97 (0.95-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.02)	1.01 (0.99-1.02)	1.00 (0.98-1.01)	1.01 (0.99-1.03)
Nausea subscale	1.00 (0.97-1.04)	0.98 (0.95-1.00)	1.00 (0.97-1.03)	0.99 (0.97-1.01)	0.97 (0.95-1.00)	1.01 (0.98-1.04)
Maintaining family integration coping behaviors (CHIP subscale 1)	0.95 (0.90-1.00)	0.96 (0.92-1.01)	0.97 (0.93-1.02)	0.98 (0.94-1.02)	0.99 (0.95-1.04)	0.95 (0.91-1.00)
Maintaining social support coping behaviors (CHIP subscale 2)	0.99 (0.94-1.05)	0.99 (0.95-1.02)	1.06 (1.01-1.11)	1.00 (0.97-1.03)	1.03 (0.98-1.07)	0.97 (0.93-1.01)
Understanding the medical situation coping behaviors (CHIP subscale 3)	0.90 (0.82-1.00)	0.99 (0.91-1.06)	0.98 (0.89-1.07)	1.02 (0.95-1.09)	1.03 (0.95-1.11)	0.96 (0.89-1.05)
***Treatment**:* IC/AIM vs. SC/SIM	0.54 (0.12-2.48)	3.75(1.05-13.34)	0.58(0.18-1.84)	0.74 (0.28-1.98)	1.56 (0.52-4.69)	1.65(0.56-4.89)
SC/AIM vs. SC/SIM	0.48 (0.11-2.18)	0.83 (0.32-2.19)	0.20 (0.05-0.79)	0.34 (0.13-0.89)	1.08 (0.37-3.15)	0.35(0.10-1.31)
IC/SIM vs. SC/SIM	0.88 (0.23-3.34)	0.66 (0.25-1.74)	0.45 (0.14-1.40)	0.44 (0.17-1.14)	1.16 (0.39-3.40)	0.70(0.22-2.21)

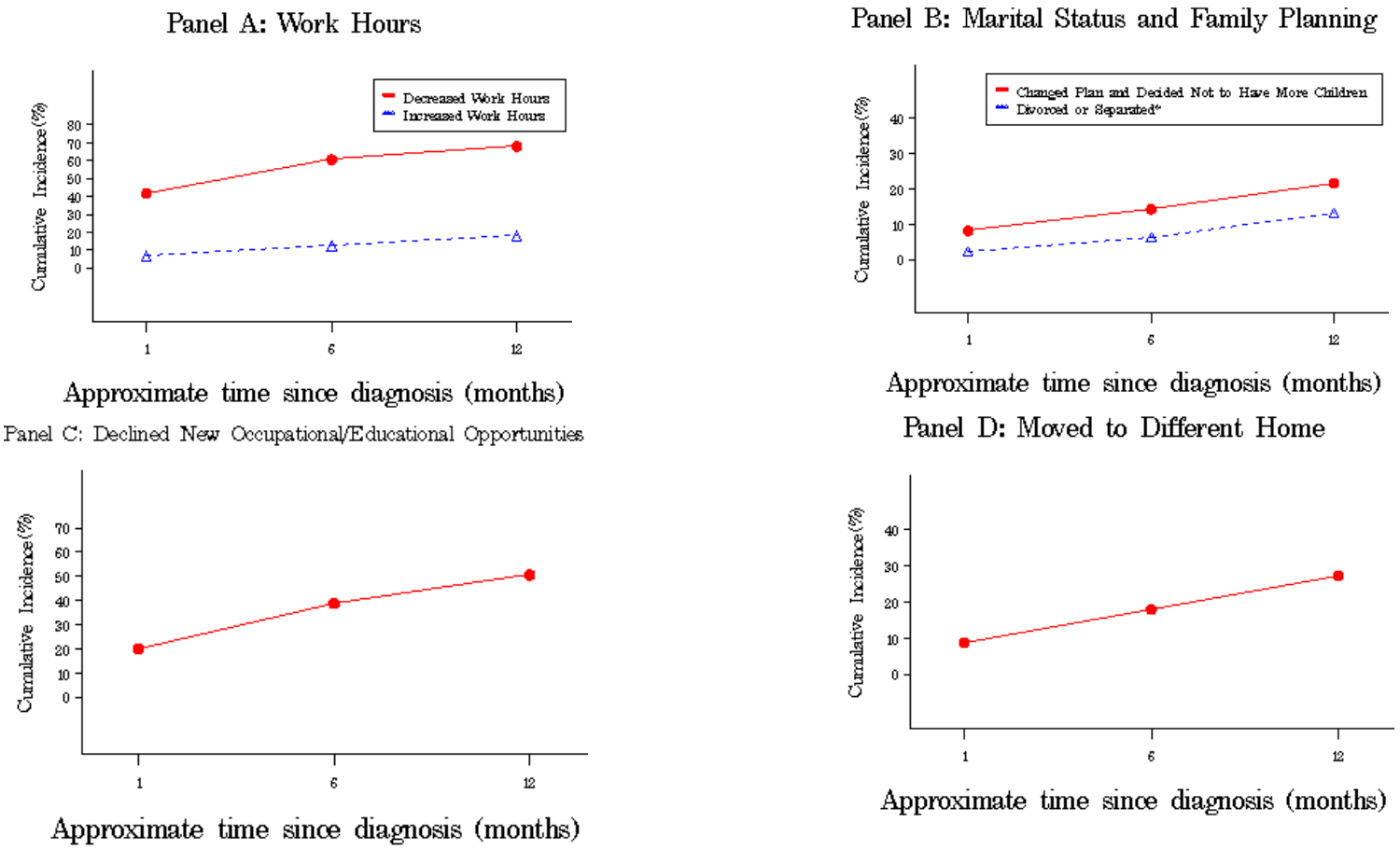
*SC-standard consolidation; IC-intensified consolidation (additional cyclophosphamide and peg-asparaginase); SIM- standard interim maintenance (oral methotrexate); AIM-augmented interim maintenance (escalating intravenous methotrexate)

Table 4: Multivariate analyses for the association of patient and family factors with the six outcomes at time point 3 (~12 months after diagnosis)

	Divorced Separated OR(95% CI)	**Decreased Work Hours** OR(95% CI)	**Increased Work Hours** OR(95% CI)	**Declined Opportunities** OR(95% CI)	**Relocated Home** OR(95% CI)	**Changed Family Planning** OR(95% CI)
***Age at diagnosis*:** Pre-school (2-4 years old) vs. School-age (5-9.99 years old)				4.21(1.73-10.25)		1.72 (0.63-4.66)
***Race/Ethnicity*:** Other vs. White, non-Hispanic		2.40 (0.93-6.24)		0.71 (0.26- 1.97)	1.93 (0.79-4.74)	
***Family Income*:** Less than $50,000 vs.$50,000 or more	3.16(0.52-19.23)			4.25(1.50-12.02)		
***Maternal Education*:** No college vs. At least some college	1.72(0.28-10.64)			1.52 (0.57-4.05)	4.27 (1.43-12.82)	
***Family size*:** 2-3 vs.4-5		1.82(0.52-6.37)				3.62 (1.10- 11.96)
6 or more vs.4-5		0.44(0.16-1.18)				1.54 (0.44- 5.36)
Pain and Hurt subscale	0.97(0.95-1.00)					
Nausea subscale		0.98(0.95-1.00)			0.97 (0.94-0.99)	
Maintaining family integration coping behaviors (CHIP subscale 1)	1.02(0.93-1.11)					0.95 (0.90- 1.00)
Maintaining social support coping behaviors (CHIP subscale 2)			1.06(1.01-1.12)			
Understanding the medical situation coping behaviors (CHIP subscale 3)	0.90 (0.75- 1.07)					
***Treatment**:** IC/AIM vs. SC/SIM		3.45(0.89-13.30)	0.40(0.10-1.59)	0.84 (0.24-2.86)		1.18 (0.32- 4.35)
SC/AIM vs. SC/SIM		1.44(0.48-4.26)	0.18(0.04-0.80)	0.30 (0.09-1.02)		0.34 (0.08- 1.42)
IC/SIM vs. SC/SIM		0.99(0.33-2.93)	0.48(0.14-1.69)	0.25 (0.07-0.87)		0.46 (0.12- 1.81)

*SC-standard consolidation; IC-intensified consolidation (additional cyclophosphamide and peg-asparaginase); SIM- standard interim maintenance (oral methotrexate); AIM-augmented interim maintenance (escalating intravenous methotrexate)

Figure 1: Cumulative Incidence of Family Life Events in the First Year of Treatment of Acute Lymphoblastic Leukemia



*Among those married or living together as married prior at diagnosis.

The increases in frequencies of outcomes between time points are statistically significant for all events at a significance level of $p<0.05$, except for frequency changes from time point 2 to 3 for divorce/separation, increased work hours, and decreased work hours.