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Diabetes Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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DIABETES AMONG ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract

Over half of childhood Acute Lymphoblastic Leukemia (ALL) survivors will suffer from one or more treatment-related medical conditions in their lifetime, many of which are known risk factors for diabetes. This study aims to determine the prevalence and potential risk factors of diabetes among ALL survivors from the St. Jude Lifetime Cohort (SJLIFE). We performed a retrospective-cohort analysis of 1041 SJLIFE 10-year survivors of ALL compared to 368 controls. Risk factors associated with increased risk of type 2 diabetes (T2DM) in survivors included: drug-induced diabetes (OR 4.98, 95% CI 2.59-9.58), obese/overweight BMI (OR 7.02, 95% CI 2.45-20.07; OR 3.26, 95% CI 1.03-10.23), and increasing age (OR 1.04, 95% CI 1.01-1.08). Survivors were also more likely to suffer from pre-diabetes (OR 1.33, 95% CI 1.06-1.67) and T2DM (OR 2.03 95% CI 1.09-2.83) compared to controls, highlighting the importance of surveillance and early interventions in SJLIFE survivors of childhood ALL.

Table of Contents

Chapter	Page #
Introduction	**1**
Literature Review	**3**
Acute Lymphoblastic Leukemia	3
Diabetes Mellitus	4
Diabetes among ALL survivors	7
Methods	**9**
St. Jude Lifetime Study	9
Study Participants.	9
Non-Participants.	9
SJLIFE Controls.	9
Data Collection.	10
Study Variables	10
Cancer Treatment Exposures.	10
Outcome Measurements.	11
Covariates.	11
Results	**13**
Cohort Characteristics	13
Comparisons of Survivors and Controls	14
Risk Factors	14
Type 2 Diabetes Mellitus.	14
Gestational Diabetes Mellitus.	15
Drug Induced Diabetes Mellitus.	16
Discussion	**17**
Limitations	20
Conclusion	20
References	**22**
Tables	**25**
Appendices	**31**
Appendix A: IRB approval letter from University of Memphis	31
Appendix B: IRB approval letter for St. Jude Lifetime Cohort (SJLIFE) Study	32

List of Tables

Tables **Page #**

1. CHARACTERISTICS OF SJLIFE PARTICIPANTS AND NON-PARTICIPANTS 25

2. CHARACTERISTICS OF SJLIFE SURVIVORS AND CONTROLS 26

3. COMPARING THE PREVALENCE OF PRE-DIABETES AND TYPE 2 DIABETES BETWEEN SJLIFE ALL SURVIVORS AND CONTROLS 27

4. RISK FACTORS FOR TYPE 2 DIABETES IN ADULT SURVIVORS OF CHILDHOOD ALL 28

5. RISK FACTORS FOR GESTATIONAL DIABETES IN FEMALE ADULT SURVIVORS OF CHILDHOOD ALL 29

6. RISK FACTORS FOR DRUG-INDUCED DIABETES WHILE UNDERGOING TREATMENT FOR CHILDHOOD ALL 30

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common form of childhood cancer, with over 3000 new cases occurring each year in the United States.[1] Current survival rates for childhood ALL have reached 90%, presenting a new challenge for the medical community: the surveillance and treatment of childhood ALL survivors.[1] The Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE) are both long-term follow up studies, designed to evaluate health outcomes among aging survivors of childhood cancer.[2] Research from these studies has found that comorbidities and secondary cancers are common in childhood cancer survivors, with over half of childhood ALL survivors suffering from one or more chronic medical conditions in their lifetime.[3] Data from the SJLIFE study has shown that survivors of childhood ALL have an increased risk of obesity, metabolic syndrome, and hypertension, all of which are known risk factors for diabetes.[4]

In the United States, the overall prevalence of diabetes has been increasing, and is estimated to be between 12%-14% among adults.[5] Individuals who suffer from diabetes are at an increased risk for a multitude of co-existing conditions and complications, including an increased risk of cardiovascular disease and all-cause mortality.[5] The high prevalence of known diabetes risk factors among ALL survivors potentially puts this population at an increased risk for developing diabetes and other adverse health outcomes in the future.

Recent studies have produced conflicting information regarding an increased risk of diabetes among ALL survivors. Reports from the SJLIFE study have shown that the prevalence of diabetes among SJLIFE survivors is similar to that of is similar to that of age-, sex- and race-matched controls.[4] In contrast, ALL survivors from CCSS were found to be almost twice as likely to be diagnosed with diabetes compared to their healthy siblings.[6]

Determining whether ALL survivors are at an increased risk for developing diabetes could allow for early interventions aimed to reduce risk and improve health outcomes within this population. In an effort to better understand the epidemiology of diabetes within the SJLIFE ALL survivor population, this study aims to evaluate and enumerate the prevalence of potential risk factors for diabetes among ALL survivors enrolled in SJLIFE.

Study Aims

The primary aim of this study is to determine the prevalence of diabetes in adult survivors of childhood ALL compared to age, gender and race matched controls from SJLIFE. Secondary aims for this study are as follows:

1. Describe the types of diabetes experienced by ALL survivors in the SJLIFE cohort, including: Type I Diabetes, Type II Diabetes, Pre-diabetes, Gestational Diabetes Mellitus, and Drug-Induced Diabetes Mellitus (while undergoing treatment).
2. Evaluate the associations between treatment exposures, demographic characteristics, health behaviors (smoking, alcohol intake, caloric/micronutrient intake, physical activity), body habitus (percent lean mass/relative lean mass, waist to hip ratio, waist to height ratio) and diabetes.

Literature Review

Acute Lymphoblastic Leukemia

Acute Lymphoblastic Leukemia (ALL) is a form of blood cancer that affects lymphoid cell development, resulting in the proliferation and accumulation of immature lymphoid cells. In healthy individuals, lymphoid stem cells differentiate into lymphoblast cells in the bone marrow before becoming mature lymphocytes. In individuals with ALL, immature lymphocytes (lymphoblast cells) proliferate and spread from the bone marrow to extramedullary sites where they compete successfully with normal hematopoietic cells. As the name suggests, "acute" lymphoblastic leukemia progresses quickly and requires immediate treatment; if left untreated the disease can be fatal within several months. Children with ALL typically present with increased bruising, fatigue and bleeding due to thrombocytopenia and anemia.[7,8] Neutropenia is also common at ALL diagnosis, and can lead to an increased risk of infection.[7,8]

There are approximately 6000 new cases of ALL each year in the United States, with over half being diagnosed in children under the age of 20 years old.[7] ALL is the most common form of childhood cancer, and accounts for 26% of all pediatric cancer cases in children less than 14 years old.[9] Risk factors associated with childhood ALL include age, sex, race/ethnicity, genetics and environmental exposures. In the United States, the incidence of ALL is highest in children between the ages of 3 and 5 years old.[7] While there is strong evidence of acquired genetic changes leading to the development of ALL, less than 5% of cases are due to inherited genetic syndromes.[8] Males are more likely to develop childhood ALL than females, with males accounting for 55% of all cases.[7] Incidence of childhood ALL varies by race/ethnicity, with Hispanic children having the highest incidence rates (44.9 cases per million), followed by white children (34.2 cases per million), then black children (18.3 cases per million).[9]

Treatment for childhood ALL typically begins with 4-6 weeks of remission induction therapy, during which time glucocorticoids, vincristine, anthracyclines, and/or asparaginase are administered.[10,11] The goal of remission induction therapy is to achieve remission, at which point the patient will begin several months of consolidation/intensification therapy followed by 2-3 years of maintenance therapy.[10,12] Radiation therapy and allogeneic bone marrow transplants are typically reserved for patients with high risk ALL or in children who have relapsed.[12] Improvements in risk-directed therapy for childhood ALL has been widely successful, with the current 5-year survival rate estimated to be 90%.[9,13]

While survivorship for childhood ALL is impressive, comorbidities and secondary cancers are common among adult survivors. Chemotherapy and radiation therapy received during ALL treatment puts survivors of childhood ALL at an increased risk for various adverse health outcomes later in life.[3] In the United States, over half of childhood ALL survivors will suffer from one or more chronic medical conditions in their lifetime due to treatment-related exposures [3]. Data from the CCSS has shown that adult survivors of childhood ALL are at an increased risk for muscoskeletal (OR 7.7, 95% CI, 2.8-21.3), cardiac (OR 6.9, 95% CI, 4.1-12.9), neurological (OR 5.3, 95% CI, 3.1-11.4) and endocrine (OR 3.1, 95% CI, 2.1-4.5) conditions, among others compared to their non-survivor siblings.[3] Within the SJLIFE cohort, it has been shown that survivors of ALL are at an increased risk for several known risk factors of diabetes, including obesity (RR 1.47, 95%CI 1.29-1.68); metabolic syndrome (MetS) (RR 1.43, 95%CI 1.22-1.69); and hypertension (RR 2.43, 95%CI 2.06–2.86) compared to non-survivor controls.[4]

Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disease characterized by the body's inability to regulate blood glucose levels. Individuals suffering from diabetes are at an increased risk for

numerous health complications, including acute myocardial infarction (RR 1.8, 95% CI 1.3-2.3), stroke (RR 1.5, 95% CI 1.1-2.0), amputation (RR 10.5, 95% CI 6.2-15), end-stage renal disease (RR 6.1, 95% CI 5.7-6.3), and death from hyperglycemic crisis compared to non-diabetic individuals.[14] Other common diabetes-related complications include retinopathy/loss of vision, hypertension, Charcot joints, and nerve disease, among others.[15]

In the United States, the overall prevalence of diabetes among adults has been increasing, with an average of 1.7 million new cases being diagnosed each year.[16] In 2014, an estimated 29 million Americans (9.3% of US population) suffered from diabetes; of those with diabetes, approximately 8.1 million individuals were undiagnosed.[16] Diabetes is the 7th leading cause of mortality in the United States, and accounts for more deaths than AIDS and breast cancer combined.[16,17] Most diabetes diagnoses fall into one of two etiopathogenetic categories: absolute insulin deficiency (Type 1) or a combination of insulin resistance and decreased insulin production (Type 2).[15]

Type I Diabetes Mellitus (T1DM) is an autoimmune disorder that is also known as "insulin dependent diabetes." It is caused by the autoimmune destruction of pancreatic β-cells, and eventually results in absolute insulin deficiency. The exact cause of T1DM is unknown; however, environmental factors and genetics are considered to play a large role. T1DM accounts for approximately 5% of all diagnosed diabetes cases in the United States, and has a prevalence of 1 in 300 in adolescents under 18 years old.[16,18] T1DM is more common in youth and accounts for 85% of diabetes cases in those > 20 years old; however it can develop at any age.[18]

Type II Diabetes Mellitus (T2DM) is the most common form of diabetes, accounting for 90-95% of all diabetes cases in the United States.[16] It is defined by the American Diabetes Association (ADA) as individuals suffering from both relative insulin deficiency and peripheral

insulin resistance. Risk factors associated with T2DM include: increasing age, obesity, a family history of diabetes, and lack of physical activity. In the US, 85.2% of individuals diagnosed with T2DM are overweight or obese, both of which can lead to insulin resistance.[16] T2DM is also more common among certain racial/ethnic groups, with American Indians, African Americans and Hispanics, having the highest rates of diabetes, followed by Asian Americans and Non-Hispanic Whites.

Pre-diabetes, also known as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), is a modifiable condition that occurs before T2DM. It is estimated that approximately 86 million Americans suffer from pre-diabetes. Individuals diagnosed with pre-diabetes have elevated glucose levels (fasting blood glucose of 100 – 125 mg/dl), however their levels are not high enough to be classified as T2DM. Pre-diabetes strong predictor of T2DM, with approximately 15-30% of pre-diabetic individuals progressing to T2DM within five years.[16] Lifestyle changes leading to weight loss are highly effective in patients with pre-diabetes, and have been shown to reduce risk of T2DM by over 50%.[16]

Gestational Diabetes Mellitus (GDM) is a type of diabetes that occurs in women during pregnancy and resolves post-partum. The ADA defines GDM as women diagnosed with diabetes in the second or third trimester of pregnancy, who did not have overt diabetes prior to pregnancy. The prevalence of GDM has been increasing in the United States and is currently estimated to be around 14%.[19] Uncontrolled GDM is dangerous for both the mother and fetus, and can result in spontaneous abortion, fetal anomalies, preeclampsia, macrosomia, neonatal hypoglycemia, among other risks. Post-partum women diagnosed with GDM during pregnancy are at an increased risk of developing GDM in subsequent pregnancies, as well as developing T2DM later in life.[19]

Drug induced Diabetes Mellitus (DIDM) is a transient form of diabetes that manifests as the result of some pharmacological treatment. DIDM has been reported in approximately 10-20% of children receiving treatment for ALL; and typically occurs during the remission induction phase of therapy when high doses of glucocorticoids and L-asparaginase are administered.[20] Age has been shown to be a strong predictor for developing DIDM, with children ≥ 10 years old being 9.6 times more likely (95% CI 5.1-17.8; *P*=<.001) to experience DIDM compared to their younger counterparts.[21] Trisomy 21 and central nervous system (CNS) involvement at ALL diagnosis are also both known risk factors for DIDM in children with ALL.[21] Studies have shown no difference in remission, survival or relapse rates between children who developed DIDM versus children who did not; however, few studies have looked at differences in metabolic outcomes later in life.[20,22,23] When comparing metabolic disturbances of children who developed DIDM while on therapy to children who did not, it was shown that children with a history of DIDM were more likely to develop impaired glucose tolerance (4/30 vs. 1/90, *P*=0.07) and other metabolic syndromes later in life, though these findings were not statistically significant.[23] Therefore, it is possible that development of DIDM during remission induction therapy identifies individuals at risk of developing metabolic disorders later in life.

Diabetes among ALL survivors

In survivors of childhood ALL, cranial radiotherapy (CRT) has been shown to be associated with a greater rate of increasing BMI.[24] Glucocorticoids, which are prominent during ALL treatment, are also known to produce diabetogenic effects leading to insulin resistance and impaired β-cell function in genetically susceptible individuals.[25] Both obesity and insulin resistance are known risk factors for diabetes in the general population.[16] Therefore, it is possible

that treatment exposures during ALL therapy could lead to an increased risk of diabetes in survivors of childhood ALL.

Recent studies have produced conflicting information regarding the risk of diabetes among adult survivors of childhood ALL. In 2014, Nottage et al reported that the prevalence of overt diabetes mellitus among 784 SJLIFE ALL survivors [median age of 31.7 years, range = 18.9-59.1] was similar to that among age, sex, race matched controls. In contrast, Meacham et al reported that childhood ALL survivors from CCSS were 1.8 times more likely (95% CI 1.2-2.6; *P*=<.01) to be diagnosed with diabetes compared to their siblings. Among the CCSS cohort, 2.5% of ALL survivors suffered from DM compared to 1.7% of healthy siblings.[6] However, this increased risk was found to be primarily due to treatment exposures, specifically total body irradiation.[6]

With current survival rates for childhood ALL reaching 90%, many survivors are either approaching or well into their adulthood. Survivors of childhood ALL are known to be at an increased risk for various treatment-related adverse health outcomes later in life, highlighting the importance of surveillance in these survivors. It is possible that some exposures occurring during ALL treatment lead to an increased risk of diabetes among survivors compared to the general population. Due to the increasing number of ALL survivors and potentially modifiable risk of diabetes, it is important to investigate both treatment-related and environmental etiologic factors that contribute to diabetes risk within the ALL survivor population. Determining whether survivors are at an increased risk for developing diabetes could allow for early interventions aimed to reduce risk and improve health outcomes among survivors of childhood ALL.

Methods

St. Jude Lifetime Study

Study Participants. The St. Jude Lifetime Cohort (SJLIFE) is an institutional review board-approved study designed to establish a lifetime cohort of childhood cancer survivors. Study design and details for SJLIFE have been previously published.[2] Eligible participants were survivors of childhood Acute Lymphoblastic Leukemia (ALL) who were diagnosed and treated at SJCRH, had survived ≥10 years since diagnosis, and are currently ≥18 years of age at time of study participation. All participants completed detailed health questionnaires as well as an on-campus visit at SJCRH, consisting of risk-based screening and diagnostic evaluations per the recommendations of the *Children's Oncology Group Long Term Follow-Up Guidelines*.[26] A total of 1041 SJLIFE study participants met the eligibility criteria for this analysis. All participants provided written informed consent.

Non-Participants. Survivors of childhood ALL who had not completed an on-campus evaluation were included in this analysis as non-participants. The inclusion of non-participants in our study was to provide a comparison cohort and to elucidate any participation bias. A total of 602 non-participants were included in this analysis.

SJLIFE Controls. Control participants were recruited on SJLIFE to serve as a comparison cohort to SJLIFE survivors. Eligible SJLIFE control participants were individuals ≥ 18 years old, not currently pregnant or lactating, and either a non-first degree relative or friend of current or past SJCRH patients. All SJLLIFE controls completed health questionnaires and an on-campus visit that consisted of core laboratory assessments and clinical evaluations. A total of 368 SJLIFE controls were eligible for this analysis. All participants provided written informed consent.

Data Collection. The data used for this analysis were collected and abstracted as part of the SJLIFE study. Medical records were abstracted for SJLIFE participants by trained abstractors. Data abstracted from medical records included: age at ALL diagnosis, chemotherapy treatment and dose, radiation therapy and dose, key health events, toxicities, and any secondary malignancies. Participants also completed health questionnaires, including a total of 883 items, assessing the following: health history, behavior and status; social and demographic factors; psychosocial functioning; and psychosexual health. Results from baseline laboratory and physical examinations were collected for study participants and SJLIFE controls, and included: complete blood cell count with differential, comprehensive metabolic panel, fasting lipid panel, measurement of insulin and hemoglobin A1c levels, and body composition measures.

Study Variables

Cancer Treatment Exposures. Participants in our study were treated with conventional chemotherapy or hematopoietic stem cell transplant, per TOTAL therapy protocols.[27] Mercaptopurine and Methotrexate treatment was evaluated categorically, as having received treatment or having not received treatment. Cumulative doses were abstracted for the following chemotherapeutic drugs: vincristine, Cytarabine, Aspraginase, glucocorticoids, and Anthracycline. Dose equivalents were calculate for Asparaginase treatment (L-Asparaginase, Pegylated Asparaginase and Erwinase Asparaginase) as the type and dose of Asparaginase administered varied by treatment protocol.[27] Dose equivalents were also calculated for glucocorticoids, which were converted to prednisone-equivalents.[28] Radiation therapy was evaluated categorically as having received any spinal radiation or having received no spinal radiation. Cranial Radiation Treatment (CRT) dose was evaluated as having received no CRT (0 Gy), having received 1-23 Gy or having received 24+ Gy therapy.

Outcome Measurements. Pre-diabetes was defined per the American Diabetes Association (ADA), as having a fasting plasma glucose level between 100 mg/dL to 125 mg/dL, and/or HgBA1C between 5.7-6.4%. Type 2 diabetes (T2DM) was defined per the ADA, as having a fasting plasma glucose level of ≥ 126 mg/dL (7.0 mmol/L) on two separate tests, or HgbAlc ≥ 6.5%, or random glucose ≥ 200 mg/dL. Participants currently receiving medication for diabetes were also classified as having T2DM. Type 1 diabetes (T1DM) was defined as participants diagnosed with insulin-dependent diabetes. Gestational Diabetes Mellitus (GDM) was defined per ADA guidelines, and included female participants diagnosed with diabetes during pregnancy that was not clearly overt diabetes prior to gestation, and whose symptoms resolved postpartum. Participants were classified as having Drug-Induced diabetes (DIDM) if they experienced treatment-induced hyperglycemia requiring brief insulin therapy while undergoing treatment for ALL. Classification of diabetes type for participants without a clear diagnosis was determined by reviewing medical charts and evaluating fasting laboratory results.

Covariates. Demographic and health behavior data were collected from participant health questionnaires and medical records by trained abstractors. Demographic factors used in our analysis included: sex, ethnicity, marital status, household income, insurance access, and highest level of educational attainment. Self-reported health behaviors used in our analysis included: tobacco use, alcohol intake and level of physical activity (calculated as total Met-minutes per week). Additional risk factors included in our analysis included: Body Mass Index (BMI), categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30 kg/m^2), relative lean mass, and percent body fat. Relative lean mass and percent body fat were determined by Dual energy x-ray absorptiometry (DXA) studies, which were performed on Hologic Discovery-A unit and analyzed using APEX 3.3 software.

Statistical Analysis

Demographic and treatment variables were characterized and compared between participant and non-participant survivors using Chi-square tests and Fishers exact test for categorical variables, and t-tests for continuous variables. These same methods were used to compare demographic variables and diabetes prevalence (pre-diabetes, T2DM, GDM, T1DM, and DIDM) between survivors and SJLIFE controls.

Generalized linear models adjusting for age, race, gender, and level of educational attainment, were used to compare the prevalence of pre-diabetes and T2DM between survivors and SJLIFE controls. Results were reported as odds ratios (OR) or prevalence ratios (PR), with 95% confidence intervals (95% CI). For rare outcomes, logistic regression models were used to estimate odds ratios as an approximation to prevalence ratio estimates. For non-rare outcomes, log binomial models were used with a log link and Poisson error structure to estimate prevalence ratios.

Logistic regression models adjusting for age, race, gender, and level of educational attainment, were used to evaluate associations between potential risk factors and diabetes (T2DM, GDM, DIDM) within our study population. Potential risk factors were assessed by bivariate analysis; those included in our analysis were determined *a priori* and by backwards selection. CRT was not included in our final model for T2DM due to the fact that CRT and BMI are on the same causal pathway for T2DM risk.[29] A second logistic regression model adjusting for BMI, in addition to the above-mentioned variables, was used to evaluate potential risk factors associated with T2DM risk. Analyses were performed using SAS v9.4.

Results

Cohort Characteristics

At the time of this analysis, a total of 1798 ALL survivors were potentially eligible for enrollment on SJLIFE. Of those, 1041 individuals were eligible as participants for our analysis. Of the remaining 757 individuals, 155 individuals died prior to participation, the remaining 602 individuals were included in our analysis as non-participants (Figure 1).

Table 1 compares demographic and treatment exposures between participants and non-participant survivors. There was a slightly greater proportion of males among both participant (51%) and non-participant (57%) groups. Median age at ALL diagnosis was similar between participant (5 years, IQR 3, 9) and non-participant (5 years, IQR 3, 9) groups. Both participant and non-participant groups were primarily Non-Hispanic White. However, a greater proportion of non-participants were of non-Caucasian ethnicity compared to participants (20% non-participants vs 13% participants).

Participants were more likely to have received cranial radiation therapy (CRT) (n=540, 53% of participants vs. n=222, 36% of non-participants) and/or spinal radiation therapy (n=84, 8% of participants vs. n=46, 8% of non-participants). Common treatment exposures between both groups included: vincristine, cyclophosphamide, glucocorticoids, 6-mercaptopurine, antracycline, cytarabine, methotrexate, and asparaginase. The mean cumulative dose administered for asparaginase, anthracylines, glucocorticoids, and vincristine, was higher in non-participants compared to participants; with the exception of cytarabine where the mean cumulative dose was higher in participants. There was a similar proportion of bone marrow transplants between both participant (2%) and non-participant (3%) groups.

Comparisons of Survivors and Controls

Characteristics and diabetes diagnoses of survivors and controls are shown in Table 2. The median age at time of most recent interview was slightly higher in controls (34 years; IQR 28, 42) compared to survivors (33 years; IQR 27, 41). The median survival time in survivors was 28 (IQR 20, 34) years since diagnosis. Survivors were significantly more likely to be obese or overweight compared to controls, with 73% of survivors being obese or overweight compared to 63% of controls. Compared to survivors, controls were more likely to be college graduates (53% in controls vs. 33% in survivors, *P*=<0.0001) and to be female (54% in controls vs. 49% in survivors, *P*=0.0857).

The prevalence for all types of diabetes (pre-diabetes, T2DM, GDM) was higher in survivors compared to controls with the exception of T1DM. Among survivors, 27% had pre-diabetes and 7% had T2DM, compared to 19% and 4% of controls, respectively. Of females who had been pregnant, the prevalence of GDM was similar between survivors (6.4%) and controls (3.4%). The prevalence of T1DM was less than 1% in both survivor and control groups.

Compared to controls, and adjusting for age, sex, race, education and BMI, survivors were 1.33 times more likely to have pre-diabetes (95% CI 1.06-1.67, *P*=0.02) and 2.03 times more likely to have T2DM (95% CI 1.09-3.82, *P*=0.03; Table 3).

Risk Factors

Type 2 Diabetes Mellitus. A total of 78 (7%) survivors had been diagnosed with T2DM (Table 2). Multivariable modeling, adjusting for sex, race, education, and BMI, identified age at most recent interview, overweight or obese BMI, cumulative anthracyline dose and the development of DIDM while on-therapy as predictors for T2DM among survivors (Table 4).

Age at most recent interview was associated with a slight elevated risk of T2DM in survivors (OR=1.04, 95% CI, 1.01-1.08; *P*=0.0056). Survivors who were overweight were 3.3 times more likely to have T2DM, compared to survivors who were normal/underweight (95% CI 1.03-10.23; *P*=0.0436). Obese survivors had the highest risk of T2DM, and were 7.02 times more likely to have T2DM compared to survivors who were normal/underweight (95% CI 2.45-20.07; *P*=0.0003). Neither total Met-minutes (per week/100), nor level of educational attainment were associated with increased T2DM risk in survivors.

On treatment exposures evaluated included cumulative glucocorticoid dose (dose per 1000 mg/m^2) and antrhacycline dose (per 100 mg/ m^2) as well having developed DIDM. Increased cumulative glucocorticoid dose (1000 mg/m^2) was not associated with an increased risk of T2DM in survivors (OR=0.95, 95% CI 0.906-1.004; *P*=0.0701). Cumulative anthracycline dose (per 100 mg/m^2) was associated with an elevated risk of T2DM (OR=1.29, 95% CI 1.04-1.61). Of the 83 survivors who developed DIDM while undergoing treatment for ALL, 21 (25%) survivors developed T2DM later in life. Survivors who developed DIDM while undergoing treatment for ALL were 4.98 times more likely to develop T2DM later in life, compared to survivors who had not developed DIDM (95% CI 2.59 – 9.58; *P*= <.0001).

Gestational Diabetes Mellitus. Of the 514 female survivors, a total of 249 (48%) had been pregnant at least once, of those, 16 (6%) developed GDM during pregnancy. Adjusting for race, none of the treatment exposures included in our analysis (glucocorticoids (*P*=0.1211), asparaginase (*P*=0.8026), anthracycline (*P*=0.1674)) were associated with an increased risk of GDM (Table 5). Age at ALL diagnosis (P=0.2378) and race/ethnicity (P=0.5656), were also not associated with an increased risk of GDM (Table 5). Participant BMI during pregnancy was not available; therefore we could not include BMI in our model.

Drug Induced Diabetes Mellitus. A total of 82 (8%) survivors developed DIDM while undergoing treatment for ALL. Multivariable modeling, adjusting for sex and race, identified age at diagnosis as a predictor for developing DIDM while on-treatment (Table 6). Age at diagnosis of ALL was associated with an elevated risk of DIDM in survivors (OR=1.24, 95% CI 1.18-1.31; P=<.0001). Gender, race and treatment exposures (glucocorticoids, asparaginase, anthracycline) were not associated with an increased risk of developing DIDM.

Discussion

In this study we evaluate the prevalence and risk factors associated with diabetes among 10-year SJLIFE ALL survivors, in an effort to better understand the epidemiology of diabetes among this population. Of 1041 SJLIFE ALL survivors, three hundred and ninety-eight (38%) had experienced some form of diabetes within their lifetime, compared to 23% of non-cancer survivor controls.

To our knowledge, the prevalence of pre-diabetes among survivors of childhood ALL has not been previously reported. Of 1041 SJLIFE ALL survivors, two hundred and seventy-seven (27%) survivors suffered from pre-diabetes. This was significantly higher than the prevalence of pre-diabetes reported in SJLIFE controls (19%). Survivors of childhood ALL were 1.33 times more likely (95% CI 1.06-1.67, P=0.02) to suffer from pre-diabetes compared to SJLIFE controls.

In contrast to previous reports from SJLIFE, we found the overt prevalence of T2DM among SJLIFE ALL survivors to be significantly higher compared to controls.[4] A total of 79 (7%) SJLIFE ALL survivors suffered from T2DM, compared to 14 (4%) SJLIFE controls (P=0.01). Survivors were 2.03 times more likely (95% CI 1.09 – 3.82) to develop T2DM compared to controls. These findings are similar to those reported by Meacham et al. (OR 1.8, 95% CI 1.2-1.6). Both age at interview and overweight/obese BMI were associated with an increased risk of T2DM among survivors in our cohort. It is possible that the higher overt prevalence of T2DM in our analysis was due increasing age, with the median age in our analysis being 33.2 years (range= 18.43.- 62.15) compared to 31.7 (range= 18.9-59.1) at the time of the Nottage et al. analysis.

Anthropometric risk factors associated with an increased risk of T2DM in survivors included age at most recent interview (OR 1.04, 95% CI 1.01-1.08), overweight BMI (OR 3.26, 95% CI 1.03-10.23) or obese BMI (OR 7.02, 95% CI 2.45-20.07). These findings are to be expected, as age and overweight/obese BMI are well known risk factors for T2DM.[16]

Of exposures that occurred during ALL treatment, cumulative anthracycline dose and the development of DIDM were associated with an increased risk of T2DM. Cumulative glucocorticoid dose (per 1000 mg/m^2) was found to have a slightly protective effect against T2DM (OR 0.95, 95% CI 0.90-1.00; *P*=0.0451); however this association was lost after adjusting for BMI (*P*=0.0701). This finding is similar to what was reported by Nottage et al, where cumulative glucocorticoid dose (per 1000 mg/m^2) was found to be slightly protective (RR 0.99, 95% CI 0.97-1.01) against Metabolic Syndrome in SJLIFE survivors of ALL.[4] Cumulative anthracycline dose (per 100 mg/m2) was associated with an elevated risk of T2DM (OR 1.29, 95% CI 1.04-1.61). While the association between anthracyclines and diabetes has not been previously evaluated, anthracyclines have been shown to increase risk of elevated glucose levels (RR 1.24, 95% CI 0.95-1.61) within this cohort.[4]

Few studies have investigated the association between DIDM and T2DM risk among survivors of childhood ALL. Yeshayahu et al. reported the rate of impaired glucose tolerance among survivors of childhood ALL as being four times higher in those who developed DIDM compared to those who did not, however this findings did not reach statistical significance.[23] Our analysis found that SJLIFE ALL survivors who developed DIDM while on-therapy were 4.98 times more likely (95% CI 2.59-9.58) to be diagnosed with T2DM compared to survivors who did not develop DIDM. This increased risk remained the same both when adjusting and not adjusting for BMI. To our knowledge, this finding is unique to our study and potentially

identifies a subgroup of individuals who have an elevated risk of developing diabetes and other adverse health outcomes later in life.

Previous studies have reported the prevalence of DIDM in children undergoing treatment for ALL to be between 10 to 20%.[20,30] Among SJLIFE ALL survivors, 83 (8%) survivors developed DIDM while undergoing treatment for ALL. It is possible that the lower prevalence of DIDM in our cohort is due to our study consisting of 10-year survivors, whereas the prevalence reported in other studies was determined in patients undergoing ALL treatment. It is also important to note that our definition of DIDM may have resulted in milder cases, where treatment was not administered, being excluded in our analysis, whereas other studies may have included these cases. As a result, our analysis captured individuals who experienced more serious DIDM where brief insulin therapy was required, as opposed to all individuals who developed any level of DIDM. Age at ALL diagnoses was associated with an elevated risk of developing DIDM during treatment (OR 1.24, 95% CI 1.18-1.31) in SJLIFE ALL survivors. This finding is consistent with reports from previous studies.[20,23,30]

While our findings show an increased risk of T2DM in survivors who experienced DIDM, further studies are needed to evaluate the cause of this increased risk. It is possible that the development of DIDM in some patients unmasks an underlying predisposition leading to an increased risk of T2DM, similar to the increased risk of T2DM in women who develop GDM while pregnant. Since diabetes is highly associated with obesity, it would be beneficial to evaluate the association between BMI during treatment and DIDM risk.

The prevalence of GDM among females who had experienced one or more pregnancies was similar between control and survivor groups (3% controls vs. 6% survivors). Of the

demographic and treatment exposures included in our analysis, none were significantly associated with an increased risk of GDM in female survivors who had been pregnant.

Limitations

It is worth noting the findings from this study should be considered within the context of study limitations. It is possible the results of our analysis were influenced by selection bias due to the 36% participation rate. It is possible that survivors who participated in on-campus evaluations may have differed in health status compared to non-participants; however, the demographic differences between participants and non-participants have been previously investigated and were found to be unsubstantial.[31] Survivors were only recruited from one institution, St. Jude Children's Research Hospital, which limits the widespread applicability of our findings. In our model for GDM we were unable to include patient BMI at time of GDM diagnosis, as this information was not available at the time of our analysis. Due to the relationship between high BMI and insulin resistance, it would be of interest to include patient BMI at GDM diagnosis in a future analysis. It is also possible that our sample size of survivors who developed GDM (n=16) was too small to detect any associations between exposures and GDM risk. The use of standardized follow-up medical assessments in SJLIFE has allowed for the continued collection of objective measures such as height, weight, percent body fat, among others, in SJLIFE ALL survivors. However, some self-reported measures such as smoking, alcohol intake, total met-minutes per week, are known risk factors for diabetes; as a result, these measures may have been over- or under- estimated in our population.

Conclusion

Adults diagnosed with diabetes are at an increased risk for numerous chronic health conditions, ranging from metabolic syndrome to cardiovascular disease.[5] Among SJLIFE

survivors of childhood ALL, there is a high prevalence of both pre-diabetes and T2DM, 27% and 7%, compared to controls, 19% and 4%, respectively. Survivors are also at a 33% increased risk for pre-diabetes and over 100% increased risk of developing T2DM compared to controls. Our findings show that age, obese/overweight BMI and a diagnosis of DIDM while on treatment, are all predictors of T2DM in survivors of childhood ALL. As the survival rate for childhood ALL continues to improve, it is important to investigate late-effect health outcomes in this aging population. The high prevalence and increased risk of diabetes among SJLIFE ALL survivors, combined with the potentially modifiable risk of diabetes, underscores the importance of surveillance and early interventions among survivors. Therefore, it is important to continue investigating treatment-related factors and other factors associated with an increased risk of adverse health outcomes, in a continued effort to improve the treatment of childhood ALL.

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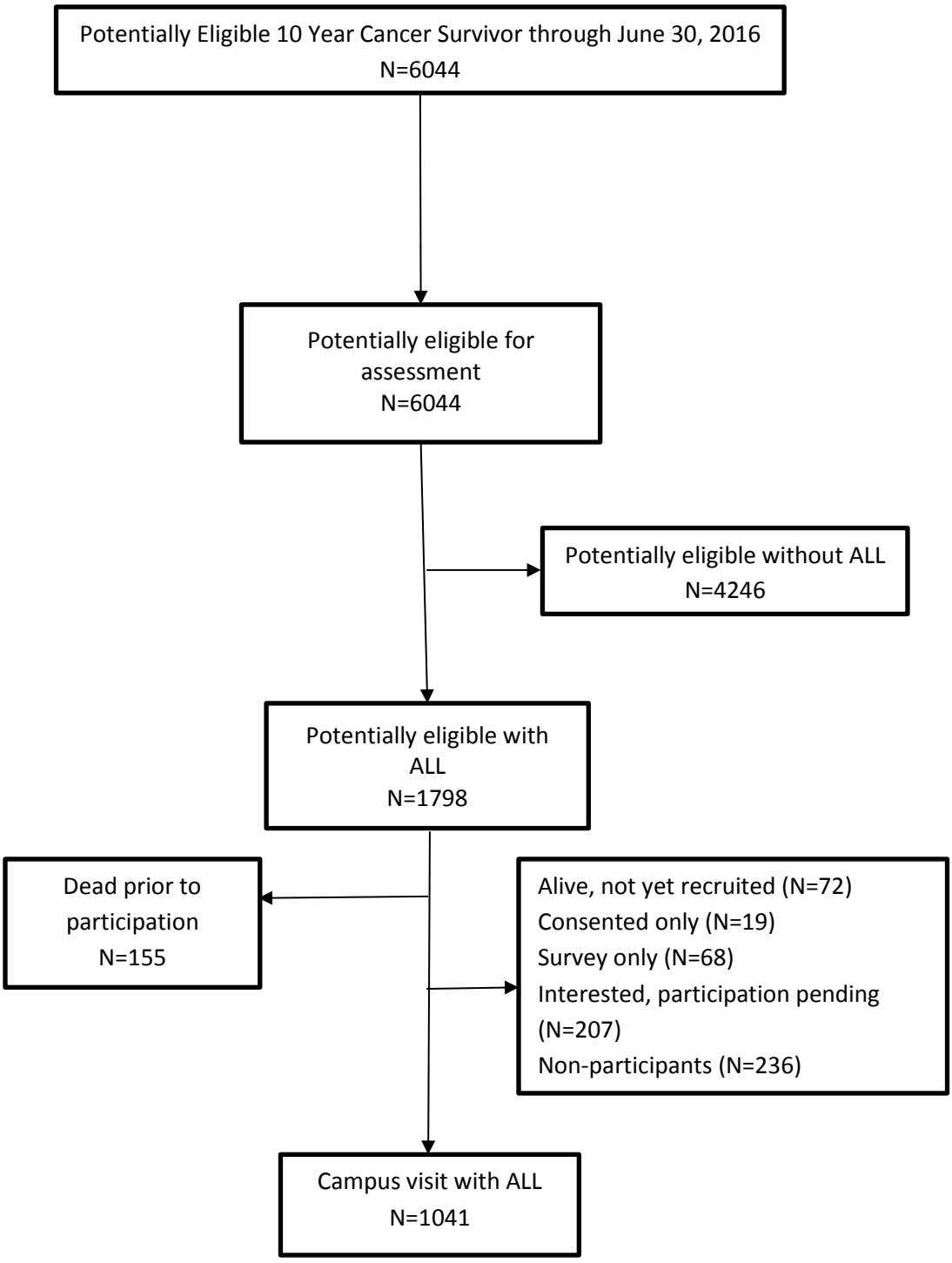

Figure 1. Consort diagram of 10 year survivors of Acute Lymphoblastic Leukemia (ALL) eligible as participants in our analysis

Table 1. Characteristics of SJLIFE participants and non-participants

Characteristics	Participants	Non-Participants	
	N (%)	N (%)	P-value
Sex			
Female	510 (49)	260 (43)	0.0232
Male	531 (51)	342 (57)	
Race			
Non-Hispanic White	903 (87)	482 (80)	0.0004
Non-Hispanic Black	94 (9)	66 (11)	
Hispanic	23 (2)	20 (3)	
Asian	3 (0)	4 (1)	
Other	18 (2)	30 (5)	
Spinal radiation			
No	957 (92)	556 (92)	0.7568
Yes	84 (8)	46 (8)	
Cranial Radiation Dose			
0 Gy	476 (47)	350 (58)	<.0001
1-23 Gy	234 (23)	95 (15)	
24+ Gy	306 (30)	127 (21)	
Bone Marrow Transplant			
No	1016 (98)	583 (97)	0.3613
Yes	25 (2)	19 (3)	
6-Mercaptopurine			
No	8 (1)	5 (1)	1.0000**
Yes	1033 (99)	597 (99)	
Methotrexate: IT or Oral			
No	1 (0)	2 (0)	0.5583**
Yes	1049 (100)	600 (100)	
At ALL diagnosis (years)			
Mean (SD)	7 (4)	7 (5)	0.8700*
Median (IQR)	5 (3, 9)	5 (3, 9)	
Survival Time (years since diagnosis)			
Mean (SD)	27	.	.
Median (IQR)	28 (20, 34)	.	
Cumulative Vincrinstine dose (mg/m^2)			
Mean (SD)	37 (28)	39 (27)	0.2066
Median (IQR)	44 (6, 58)	46 (7, 59)	
Cumulative Cytarabine dose (mg/m^2)			
Mean (SD)	6492 (5030)	6134 (4923)	0.2113*
Median (IQR)	5254 (2094, 10662)	4915 (1899, 10102)	
Cumulative Glucocorticoids dose (mg/m^2)			
Mean (SD)	7436 (5692)	7637 (5438)	0.4859*
Median (IQR)	9520 (1120, 10830)	9560 (1160, 11925)	
Cumulative Anthracycline dose (mg/m^2)			
Mean (SD)	124 (89)	127 (79)	0.5913*
Median (IQR)	102 (55, 151)	103 (77, 156)	
Cumulative Asparaginase dose (mg/m^2)			
Mean (SD)	5879 (6505)	8158 (9761)	<.0001*
Median (IQR)	3534 (2060, 6265)	4553 (2497, 10304)	

Notes: Differences between participants and non-participants were examined using Chi-Square tests. T-tests were used to examine continuous variables, marked with '*'. Fishers exact tests were used to compare variables with small sample size, marked with '**'. SD, standard deviation, IQR; interquartile range; Gy, Gray; IT, intrathecal

Table 2. Characteristics of SJLIFE survivors and controls

Characteristics	SJLIFE ALL Survivors	SJLIFE controls	
	N (%)	N (%)	P-value
Age At most recent interview			
Mean (SD)	34 (9)	35 (10)	0.0223*
Median (IQR)	33 (27, 41)	34 (28, 42)	
Sex			
Female	510 (49)	200 (54)	0.0773
Male	531 (51)	168 (46)	
Race			
0: Non-Hispanic White	903 (87)	310 (84)	0.0002
1: Non-Hispanic Black	94 (9)	23 (6)	
2: Hispanic	23 (2)	10 (3)	
3: Asian	3 (1)	3 (1)	
4: Other	18 (2)	22 (6)	
Education			
1: <College Graduate	670 (64)	167 (45)	<.0001
2: College Graduate	340 (33)	195 (53)	
3: Other	31 (3)	4 (1)	
Body Mass Index (BMI)			
1: Underweight	17 (2)	12 (3)	0.0003
2: Normal	264 (25)	126 (34)	
3: Over weight	287 (28)	102 (28)	
4: Obese	473 (45)	128 (35)	
No Diabetes			
0: No	396 (38)	85 (23)	<.0001
1: Yes	645 (62)	283 (77)	
Pre-Diabetes			
0: No	765 (73)	300 (81)	0.0020
1: Yes	276 (27)	68 (19)	
Type I Diabetes			
0: No	1038 (100)	365 (99)	0.1871**
1: Yes	3 (0)	3 (1)	
Type 2 Diabetes			
0: No	963 (93)	354 (96)	0.0138
1: Yes	78 (7)	14 (4)	
Gestational Diabetes Mellitus			
0: No	233 (94)	115 (97)	0.2837
1: Yes	16 (6)	4 (3)	
Drug Induced Diabetes Mellitus			.
0: No	959 (92)	.	
1: Yes	82 (8)	.	

Notes: Differences between participants and controls were examined using Chi-Square tests. T-tests were used to examine continuous variables, marked with '*'. Fishers exact tests were used to compare variables with small sample size, marked with '**'. SD, standard deviation, IQR; interquartile range

Table 3. Comparing the Prevalence of Pre-diabetes and Type 2 Diabetes between SJLIFE ALL survivors and controls

	Pre-diabetes (N=344)							**Type 2 Diabetes*** (N=92)						
		Adjusted for BMI			**Not adjusted for BMI**				**Adjusted for BMI**			**Not adjusted for BMI**		
	%	**PR**	**95% CI**	**P-value**	**PR**	**95% CI**	**P-value**	**%**	**PR**	**95% CI**	**P-value**	**PR**	**95% CI**	**P-value**
Survivors (N=1041)	27	1.33	1.05-1.67	0.02	1.41	1.12-1.78	0.004	7	2.03	1.09-3.81	0.03	2.34	1.26-4.36	0.007
Controls (N=368)	19	Ref	.	.	.	.	.	4	Ref	.	.	.	.	.

Notes: Logistic regression model was used to estimate odds ratio as an approximation to PR for rare outcomes (<10%), marked with '*'. PR, Prevalence Ratio; 95% CI, 95% confidence interval; BMI, Body Mass Index; P, P-value; %, % of those with outcome; Ref; referent group

Table 4. Risk Factors for Type 2 Diabetes in adult survivors of childhood ALL

Characteristics	Adjusted for BMI			Not Adjusted for BMI		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age						
Age at most recent interview	1.04	1.01 - 1.08	0.0056	1.05	1.02 - 1.08	0.0005
Gender						
Male (referent)	1.00	.	.	1.00	.	.
Female	1.11	0.67 - 1.85	0.6904	1.07	0.65 - 1.77	0.7904
Race						
Non-Hispanic White (referent)	1.00	.	.	1.00	.	.
Other	1.88	0.91 - 3.89	0.0881	1.82	0.90 – 3.68	0.0968
Education						
< College Graduate (referent)	1.00	.	.	1.00	.	.
College Graduate	0.66	0.37 - 1.18	0.1577	0.60	0.33 – 1.06	0.0795
Other	2.81	0.99 - 7.96	0.0523	2.65	0.96 – 7.29	0.0590
BMI						
Underweight/Normal (referent)	1.00	.	.	.	.	.
Overweight	3.26	1.03 - 10.23	0.0436	.	.	.
Obese	7.02	2.45 - 20.07	0.0003	.	.	.
Physical Activity						
Total Met-minutes per week per 100	0.99	0.97 - 1.00	0.1088	0.99	0.97 -1.00	0.0760
On Treatment Exposures						
Glucocorticoid dose per 1000 mg/m^2	0.95	0.91 - 1.00	0.0701	0.95	0.90 – 1.00	0.0451
Anthracycline dose per 100 mg/m^2	1.29	1.04 - 1.61	0.0217	1.25	1.01 - 1.55	0.0403
Drug Induced Diabetes Mellitus	4.98	2.59 - 9.58	<.0001	4.98	2.64 – 9.39	<.0001

Notes: OR, Odds Ratio; 95% CI, 95% confidence interval; BMI, Body Mass Index; ALL, Acute Lymphoblastic Leukemia

Table 5. Risk Factors for Gestational Diabetes in female adult survivors of childhood ALL

Characteristics	OR	95% CI	P-value
Age			
Age at ALL diagnosis	1.06	0.94 - 1.21	0.3580
Race			
Non-Hispanic White (referent)	1.00	.	.
Other	0.51	0.06 - 4.45	0.5436
Chemotherapy			
Glucocorticoid dose per 1000 mg/m^2	0.91	0.80 - 1.03	0.1253
Anthracycline dose per 100 mg/m^2	1.36	0.77 - 2.41	0.2924
Asparaginase dose per 1000 mg/m^2	1.02	0.88 - 1.19	0.8026

Notes: OR, Odds Ratio; 95% CI, 95% confidence interval; ALL, Acute Lymphoblastic Leukemia

Table 6. Risk Factors for Drug-Induced Diabetes while undergoing treatment for childhood ALL

Characteristics	OR	95% CI	P-value
Age			
Age at ALL diagnosis	1.24	1.18 - 1.31	<.0001
Gender			
Male (referent)	1.00	.	.
Female	0.79	0.49 - 1.29	0.3454
Race			
Non-Hispanic White (referent)	1.00	.	.
Other	1.69	0.91 - 3.11	0.0944
Chemotherapy			
Glucocorticoid dose per 1000 mg/ m^2	1.03	0.98 - 1.08	0.2388
Anthracycline dose per 100 mg/m^2	0.72	0.49 - 1.07	0.1025
Asparaginase dose per 1000 mg/ m^2	1.02	0.98 - 1.07	0.2538

Notes: OR, Odds Ratio; 95% CI, 95% confidence interval; ALL, Acute Lymphoblastic Leukemia

Appendices

Appendix A: IRB approval letter from University of Memphis

Institutional Review Board
Office of Sponsored Programs
University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

Mar 31, 2017

PI Name: Hannah Williams
Co-Investigators: Matthew Smeltzer
Advisor and/or Co-PI: Vikki Nolan
Submission Type: Initial
Title: Diabetes among adult survivors of childhood Acute Lymphoblastic Leukemia
IRB ID: #PRO-FY2017-272

Expedited Approval: Mar 31, 2017
Expiration: Mar 31, 2018

Approval of this project is given with the following obligations:

1. This IRB approval has an expiration date, an approved renewal must be in effect to continue the project prior to that date. If approval is not obtained, the human consent form(s) and recruiting material(s) are no longer valid and any research activities involving human subjects must stop.

2. When the project is finished or terminated, a completion form must be submitted.

3. No change may be made in the approved protocol without prior board approval.

Thank you,
James P. Whelan, Ph.D.
Institutional Review Board Chair
The University of Memphis.

Appendix B: IRB approval letter for St. Jude Lifetime Cohort (SJLIFE) Study

Institutional Review Board #29
FWA00004775

3/28/2016

Melissa Hudson, MD
ONCOLOGY

RE: **SJLIFE** - Establishment of a Lifetime Cohort of Adults Surviving Childhood Cancer

Dear Dr. Hudson:

This is to certify that, on 3/24/2016, the

Response Memo dated 3/22/2016 to the 3/8/2016 convened IRB review of 2016 Continuing Review Report; Amendment 8.0 protocol document dated 5/13/2015; Amendment 8.0 informed consent document dated 6/10/2015; Cardiopulmonary Testing Adverse Event Log SJLIFE Continuing Review 2016; Cardiopulmonary Testing Deviation Log SJLIFE Continuing Review 2016; SJLIFE Deviation Log Continuing Review 2016; SJLIFE Adverse Event Log Continuing Review 2016; SJLIFE Data Tables 20150630; NIH grants FP00005506 Lawson #110242320, FP00006327 Lawson #111725050, FP00005868 Lawson #112203010, FP00005390 Lawson #112123010, FP00006092 Lawson #111951360, FP00006392 Lawson #111178375; Amendment 8.1 (main and control) informed consent document dated 3/22/2016; Updated Control SJLIFE (Men's and Women's) Health Questionnaires both dated 2/24/2016; Updated SJLIFE (Men's and Women's) Health questionnaires both dated 3/1/2016; Updated SJLIFE HomeSurvey_Under18 document not dated; Updated SJLIFE Home Survey (control) dated 5/7/2014; and Updated SJLIFE Home Survey (patient) dated 3/2/2016

submitted to the Institutional Review Board for consideration was reviewed by an IRB member using expedited procedures with respect to the adequacy of protecting the rights and welfare of participants, the use of appropriate methods of securing informed consent, the measures to be taken to minimize risk and the degree of risk relative to the potential benefits of the proposed research.

Appendix B: IRB approval letter for St. Jude Lifetime Cohort (SJLIFE) Study

The St. Jude IRB is the primary IRB of Record for this project under the Memorandum of Agreement (Cooperative Agreement) between St. Jude Children's Research Hospital and the University of Tennessee, dated November 22, 2003. In this capacity the St. Jude IRB will have full responsibility for the oversight of the research. It is your responsibility to comply with all Federal and St. Jude IRB regulations concerning the conduct of the study. Under the cooperative agreement mentioned above, the St. Jude IRB will maintain correspondence with the University of Tennessee Health Science Center (UTHSC) IRB in regard to the performance of the research.

IRB Review Status: Approved

The continuing review report is approved and the research is re-approved for a period of one year under children's research categories 45CFR46.404 and 21CFR50.51. The IRB determined the research to be greater than minimal risk with one parent's permission and signature was appropriate for consent. The IRB determined the study to be greater than minimal risk for adults.The study remains open to participant accrual.

IRB Approval Date: 03/24/2016
IRB Expiration Date: 04/10/2017

For further assistance, please contact the Office of Human Subjects' Protection at 901-595-4357 or
email hsp-1@stjude.org.

(Submission Link: CR00006063)

Reminder of Principal Investigator's Responsibilities:
As previously signed and certified, approval of this research involving human subjects is contingent upon your agreement:
1. To report to the Institutional Review Board for Human Research (IRB) any adverse effect or research related injuries which might occur in relation to the human experimentation. To read and comply with IRB reporting guidelines.
2. To submit in writing for prior IRB approval any alterations to the plan of human research.
3. To submit timely continuing review reports of this research as requested by the IRB.
4. To maintain copies of all pertinent information related to the research activities in this project, including copies of informed consent agreements obtained from all participants.
5. To notify the IRB immediately upon the termination of this project, and/or the departure of the principal investigator from this institution and the project.