EARLY WEIGHT GAIN AND OBESITY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

by

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STATEMENT BY AUTHOR

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Psalms 46:10

"A bear, however hard he tries, grows tubby without exercise." - A.A. Milne, *Winnie-the-Pooh*

DEDICATION

I dedicate this dissertation to all childhood cancer patients and their families. I pray that the cure for all cancer will be found within my lifetime!

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ABSTRACT

Obesity is a recognized problem for children treated for acute lymphoblastic leukemia (ALL) and is present in roughly one fourth of children by the end of therapy. Obesity may lead to immediate health threats, such as an increased risk for cancer relapse, or may cause future heath issues such as diabetes, metabolic syndrome, hypertension, additional cancers, depression or cardiovascular disease.

The purpose of this study was to determine if weight gain during two individual cycles of therapy (Induction or Delayed Intensification Cycle 1) were predictive of obesity (defined as body mass index $\geq 95^{th}$ percentile for age and gender) at the end of treatment. This study retrospectively examined height and weight data from 1,017 childhood leukemia patients treated on Children's Oncology Group (COG) protocol number 1961. This study included patients that had fully completed therapy on protocol 1961 and who were between the ages of 2-20 years. Percentiles and z-scores for age and gender specific body mass index (BMI) were calculated using the height and weight measurements obtained at the beginning of each cycle of chemotherapy.

Univariate and multivariate logistic regression analyses were performed. BMI z-score at the beginning of therapy and difference in BMI z-score during Induction were significant predictors ($p < 0.0001$) of BMI $\geq 95^{th}$ percentile at the end of maintenance in both males and females. A one unit increase in the difference of BMI z-score during Induction resulted in a 3.03 odds ratio (OR) for obesity at the end of therapy for males (95% CI, 1.90 to 4.84) and a 4.15 OR for females (95% CI, 2.32 to 7.43). The change in BMI z-score during Delayed Intensification I was not found to be significant in relationship to obesity at the end of therapy.

Weight gain during Induction consisted of $\geq$ 20% increase in weight for 3.9% of the study participants. Weight gain during Induction therapy of childhood ALL treatment may be useful in predicting patients at increased risk for obesity development during therapy. Early identification of these at risk patients can assist with interventions aimed at normalizing weight gain during therapy.

CHAPTER ONE: INTRODUCTION

Background

Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in children accounting for roughly one third of all newly confirmed cases. Each year in the United States approximately 3,000 new cases of ALL are diagnosed in children and adolescents (Fast Stats, National Cancer Institute, 2012). This once fatal disease is now highly treatable with 5 year survival rates greater than 80% (Pulte, Gondos, & Brenner, 2008). The improved cure rates are due to advances in treatment, but these same treatments carry risks for excessive mortality and adverse health events (Mody et al., 2008). Obesity is one adverse event associated with ALL therapy. Currently there are over 325,000 survivors of childhood cancer living in the United States and the majority of these survivors were treated for ALL (Nathan, Wasilewski-Masker, & Janzen, 2009). As therapy continues to improve, the number of childhood cancer survivors is expected to climb. For this reason, it is increasingly important to better understand and address conditions, such as obesity, which can lead to significant negative health consequences both during and after cancer treatment.

Statement of the Problem

Pediatric cancer patients are considered a vulnerable population as they are a subgroup of society that have increased "risk of poor physical, psychological, or social health" (Aday, 2001, pg. 15). These increased risks can be evidenced by increased morbidity, premature mortality and diminished quality of life when compared to the general population (Flaskerud & Winslow, 1998). The increased risk for morbidity and mortality are due to both the leukemia itself and the medications used to treat the disease.

On COG protocol number 1961 treatment for childhood ALL lasted roughly 2.5 years for girls and 3.5 years for boys. Boys received longer therapy due to the increased risk of testicular relapse. The findings from the original treatment study, COG protocol number 1961, can be located in previous publications (Panosyan et al., 2004; Seibel et al., 2008). Treatment for ALL involves the use of systemic and intrathecal chemotherapy and systemic glucocorticoids. Cranial radiation is employed in a small number of patients, such as those that have leukemia infiltration present in the central nervous system at diagnosis. Due to the many abbreviations used in oncology, a list of abbreviations is included in this paper (Appendix A).

Treatment protocols change every 4-5 years as new research becomes available, but most have utilized a similar line or "backbone" of therapy since the 1960s (Reaman, 1998). This therapy consists of combinations of the following drugs: vincristine, PEG-asparaginase, methotrexate (intrathecal and systemic), cyclophosphamide, cytarabine (intrathecal and systemic), mercaptopurine, doxorubicin, thioguanine, and glucocorticoids (Dexamethasone and/or Prednisone). Daunorubicin is frequently added to the treatment regimen for patients at higher risk for relapse. This multi-drug combination of chemotherapeutic agents has improved survival rates but also places the child at risk for multiple therapy related consequences.

Research shows that 74% of childhood ALL survivors have at least one adverse health condition (Haddy, Mosher, & Reaman, 2009) and that survivors report increased limitations in overall health, activity and functional status when compared to their siblings (Mody et al., 2008). Being overweight or obese can contribute to these adverse health issues. Above and beyond the already existing late effects of cancer therapy, obesity can increase risks for health conditions

such as type 2 diabetes, metabolic syndrome, lipid abnormalities, cardiovascular disease, hypertension, secondary cancers, low self-esteem and depression (Reilly et al., 2003).

Obesity is an important problem to focus on within the childhood ALL population as obesity following therapy has been reported to range from 11% to 57% (Rogers, Meacham, Oeffinger, Henry, & Lange, 2005). Most research has focused on obesity during survivorship (the years post cancer treatment), but increased attention is now being been directed at weight gain during therapy. Excessive weight gain often occurs during therapy and obesity has been reported in 23- 35% of children by the end of treatment (Withycombe et al., 2009; Zee & Chen, 1986).

Obesity during therapy is important as it creates additional health risks for children. For example, increased BMI is associated with higher incidences of osteonecrosis during therapy (Niinimaki et al., 2007). More importantly, obesity during ALL therapy has been linked to an increased risk of relapse in ALL patients who are 10 years of age or older (Butturini et al., 2007). Preventing obesity development during therapy therefore becomes critically important as this can decrease the risk for relapse and other obesity associated diseases.

Significance to Nursing Science

Prevention of chronic illness is a leading health indicator in Healthy People 2020 (U.S. Department of Health and Human Services, 2012). In addition, the National Institute of Nursing Research mandates health promotion and disease prevention as areas of research emphasis (National Institute of Nursing Research, 2011). The objective of identifying obesity related risk factors during childhood ALL therapy will address both of these high priority research areas.

Unlike most other chronic conditions, obesity is considered to be largely preventable. This is one disease where nurses can take the lead with early identification of risk factors, patient education and intervention. As weight trends are known to increase excessively during leukemia therapy, more research needs to be aimed at better understanding the full causal mechanisms as well as developing effective interventions aimed at prevention. The first step in this process is to identify host and treatment-related factors that are associated with in increased risk for developing obesity during therapy for childhood ALL.

Purpose

The purpose of this study was to better understand weight gain associated with childhood ALL therapy. This study explored a clinical event, weight gain during Induction (the first cycle of ALL therapy) or Delayed Intensification 1 (the fourth cycle of chemotherapy), to determine if a change in weight, during either of these cycles, was predictive of obesity at the end of therapy. This study also sought to better understand the frequency of rapid weight gain during individual cycles of chemotherapy.

Specific Aims

The primary aims of this study are:

Aim 1: To determine if weight change (measured by age and gender BMI z score) during ALL Induction therapy is associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of maintenance therapy.

Aim 2: To determine if weight change (measured by age and gender BMI z score) during cycle 1 of Delayed Intensification ALL therapy is associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of maintenance therapy.

The secondary aim of this study is to determine the percent of children, per cycle, who experienced grade 3 weight toxicity (defined as $\geq$ 20% increase in kilograms in one cycle).

Definitions

Definitions important to this study will be explained in this section. The definitions of weight status in children will first be outlined, followed by an explanation of z-scores, treatment acquired obesity, adiposity rebound, and rapid weight gain. In addition, a brief discussion of the 1961 treatment design is included in the definition section as this explanation will assist in understanding how the statistical models were developed.

Childhood Weight Status

It is important to note that no consistent definition has been adopted for use internationally when reporting weight status in children (Cole, Bellizzi, Flegal, & Dietz, 2000). Steps have recently been taken in the United States, however, to clarify terms used to define childhood weight status. The Centers for Disease Control (CDC) and the National Center for Health Statistics (NCHS) changed terminology in 2010 to match the American Medical Association's definitions. Within the United States, the term "obesity" is now consistently used to describe the weight status in children with a BMI $\geq$ the 95^{th} percentile based on the CDC growth charts for age and gender (Ogden & Flegal, 2010). The term "overweight" is used to describe children with a BMI between the 85^{th} – 94^{th} percentiles (CDC, 2011). For adults, obesity and overweight are defined as BMI $\geq$ 30 kg/m^2 and $\geq$25kg/m^2, respectively (Department of Health and Human Services, n.d.). In adults, the same definition of obesity applies to both males and females. The definitions for adult weight status have been provided as a reference when reading literature related to adult childhood cancer survivors.

Z-scores

The use of BMI percentiles to measure weight status in children is common in clinical practice. In research, however, BMI z-scores are considered to be more accurate than BMI percentiles when measuring adiposity in children with wide age spans (Field et al., 2003). BMI z-scores, or standard deviations, utilize the CDC growth charts as a reference point. A BMI percentile of 50% would therefore have a z-score of zero (Must & Anderson, 2006). Positive z-scores represent BMI percentiles above 50%, while negative z-scores represent BMI percentiles below 50%.

Treatment Acquired Obesity

The terminology of "treatment acquired obesity" is a concept developed within this study to define children who begin therapy with a normal BMI but end therapy obese. More specifically, treatment acquired obesity applies to children who begin ALL therapy with a BMI in the 5th to 94^{th} percentile for age and gender, yet end therapy with a BMI $\geq$ the 95^{th} percentile. For this study, examining the BMI percentiles of the study population at the beginning and end of ALL treatment will be useful in understanding the general weight trends for children during therapy.

Adiposity Rebound

Adiposity rebound is a normal phenomenon during early childhood. This term defines the period of time when a child begins to gain weight and have increased adiposity development after a BMI low point or nadir (Reilly, Kelly, et al., 2001). The occurrence of adiposity rebound normally presents during 5-7 years of age in healthy children (Reilly, Kelly, et al., 2001).

Rapid Weight Gain

Rapid weight gain is defined as the change (increase) in weight status during one cycle of chemotherapy (which normally ranges between 4-8 weeks in length). Protocol number 1961 defined an increase $\geq$ 20% of a patient's weight, as a treatment related toxicity. Weight gain of this magnitude ($\geq$ 20%) during one cycle of chemotherapy, was considered a side effect of therapy and was graded (recorded) as a "grade 3 toxicity" if present, per protocol number 1961. The term "weight toxicity" is utilized in this paper to reflect terminology consistent with the original treatment study which utilized the term to imply that an unwanted or adverse side effect had occurred during therapy in relationship to weight gain.

Weight and height were measured at the beginning of each cycle of chemotherapy. As mentioned previously, the length of each treatment cycle varied depending on the arm of therapy the child received. A general guideline for the planned length of each cycle of ALL therapy is presented in Table 8.

Treatment on Protocol 1961

Patients treated on protocol 1961 received multiple different cycles (courses) of chemotherapy. Each cycle of chemo (Induction, Consolidation, Interim Maintenance, Delayed Intensification, and Maintenance) included different combinations of chemotherapeutic agents. Children enrolled on therapy were all newly diagnosed patients with ALL. Initial treatment response was determined by a bone marrow evaluation on day 7. Patients with less than or equal to 25% blasts on day 7 of therapy were classified as Rapid Early Responders (RER), while those with greater than 25% blasts were classified as Slow Early Responders (SER). RER were eligible for randomization to one of four treatment arms: standard intensity post Induction therapy (Arms A and B) or increased intensity therapy (Arms C and D). Additionally, Arms A and C received

one Interim Maintenance and Delayed Intensification phase while Arms B and D received two Interim Maintenance and Delayed Intensification phases. The SER patients were randomized to receive augmented posted Induction therapy consisting of either doxorubicin (Doxo) or idarubicin/cyclophosphamide (Ida/CPM). An outline of the protocol 1961 treatment schema is included (Appendix B).

For treatment on protocol 1961, the cycles (courses) of therapy occurred in the following order: Induction, Consolidation, Interim Maintenance, Delayed Intensification, Interim Maintenance II (for Arm B, Arm D, and SER), Delayed Intensification II (for Arm B, Arm D, and SER), and Maintenance therapy (same 12 week cycle of chemotherapy repeated until the patient reached the end of protocol therapy). Induction is always the first cycle of chemotherapy during ALL treatment. The last cycle, maintenance, is repeated until the patient reaches the time point of two years from the beginning of the Interim Maintenance cycle (for girls) or three years from the beginning of Interim Maintenance cycle (for boys). For protocol number 1961, these time points from the beginning of Interim Maintenance were used to dictate the end of therapy.

Summary

Obesity is a well documented health concern both during and after childhood ALL therapy. Currently there are no standard methods for accurately predicting which childhood ALL patients might be at increased risk for obesity development during therapy. This study will focus on examining one potential cause, early weight gain during two individual cycles of chemotherapy, as a predictor for obesity at the end of Maintenance.

CHAPTER TWO: CONCEPTUAL FRAMEWORK AND REVIEW OF LITERATURE

Theoretical Foundation

The phenomenon of childhood obesity has received increased attention during the last 10 years as obesity rates have continued to escalate (CDC, 2011). As new studies are developed to address the issue of obesity, it is important to consider appropriate theoretical underpinnings. This may be especially important in intervention trials as research shows that studies using theories as the foundation have more powerful effects than intervention studies that lack a theoretical base (Ammerman, Lindquist, Lohr, & Hersey, 2002).

The terms conceptual model or framework are synonymous and are defined as a set of general (relatively abstract) concepts and propositions that broadly address a phenomenon of interest (Fawcett, 2005). The conceptual model that is best suited for informing the on-going research regarding potential associations between genetic polymorphisms and obesity development during childhood ALL therapy is The Center on Injury Mechanisms and Related Responses Framework (University of Arizona College of Nursing, n.d.). This model (Figure 1) explains how understanding biological responses to altered health conditions proves useful in informing nursing science and developing interventions to impact health outcomes.

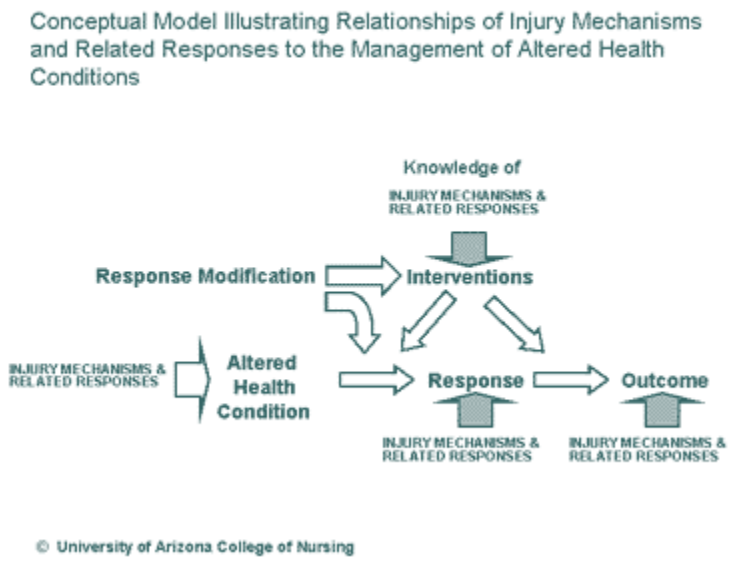


Figure 1: Center on Injury Mechanisms & Related Responses Framework

The concepts identified in this model are "altered health conditions" (to include disease, injuries or other life events with potentially negative effects). These altered health conditions lead to individual "responses" (defined as consequences which are biological, psychological, cultural or sociological in nature). These responses produce "outcomes" which are the end result of the altered health condition. Two factors which may change an individual's response to an altered health condition are labeled "response modification" (defined as factors that may influence the response such as a person's age or genetic makeup) and "interventions" (defined as nursing or other health professional actions to minimize injury and positively impact health outcomes).

This model is useful in guiding knowledge development related to obesity associated with childhood ALL therapy if one considers ALL to be the altered health condition and weight status to be the outcome. Response modifications would encompass factors such as the child's

age or race that may make one more susceptible to treatment effects. Although there are many response modifications that may have a direct impact on the child's weight status during therapy this dissertation will only explore the association between rapid weight change during cycles of therapy which heavily utilize glucocorticoids and weight status at end of therapy. Other events that fall within the response modification category would include variables such as the child's diet during therapy, their age at diagnosis, physical activity, cranial radiation, sleep habits, race, and genetics. Figure 2 shows the conceptual framework for this dissertation research.

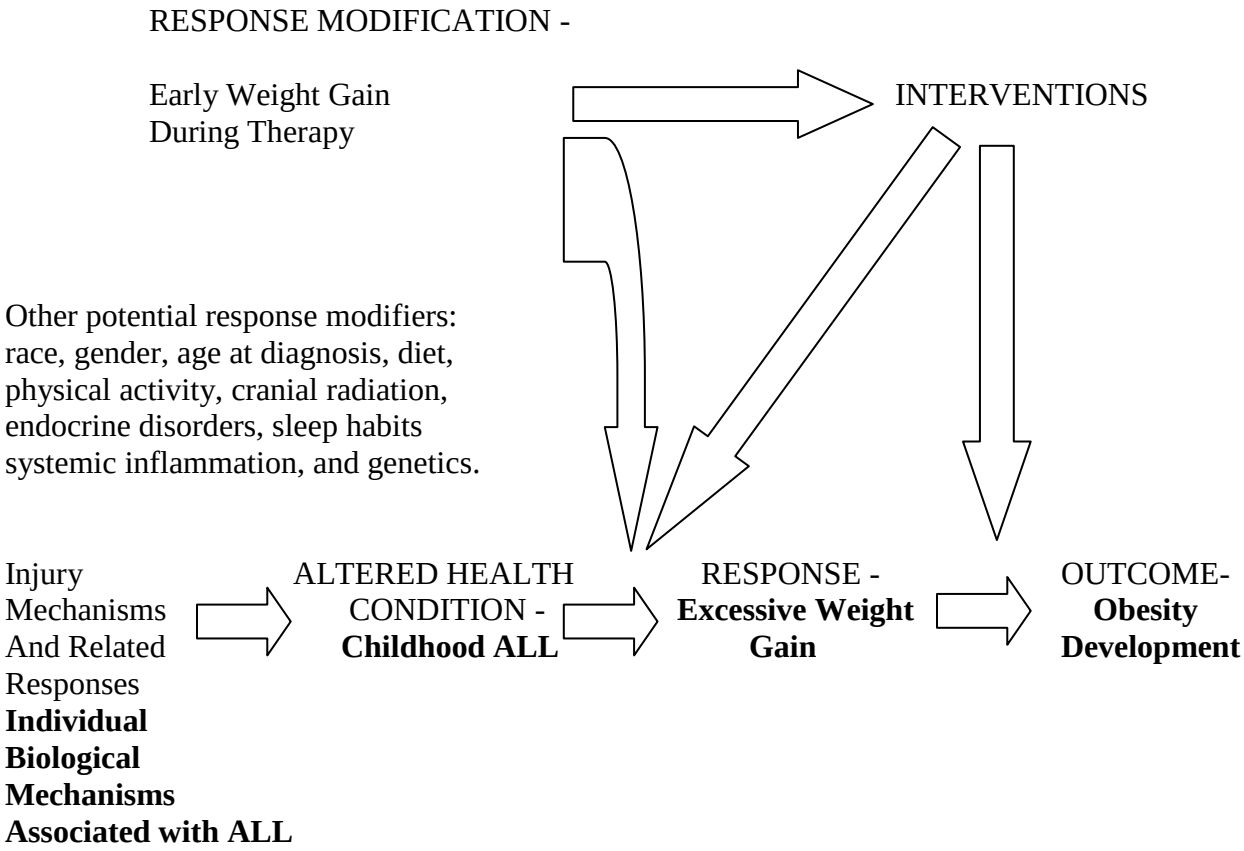


Figure 2: Conceptual Model for ALL Treatment Related Obesity

Literature Review

A literature search was conducted using multiple search databases to include PubMed, Medline and Google Scholar. Key search words were obesity, childhood acute lymphoblastic leukemia, weight gain, pediatric cancer and outcomes. The literature search was not limited by year of publication, type of research or discipline. The search was completed using the University of Arizona Health Science Library and the Palmetto Health Alliance library database during the summer of 2009, and updated during January 2010, July of 2011 and January 2012.

Obesity in the General Population

The issue of obesity has garnered much publicity over the last decade and has been labeled a health epidemic. The prevalence of obesity has increased globally with the United States and England leading the rest of the world in numbers of overweight adults (Wang, McPherson, Marsh, Gortmaker, & Brown, 2011). The obesity epidemic, however, is no longer confined to adults. In the United States, the 2009-2010, National Health and Nutrition Examination Survey (NHANES) reported 16.9% of children aged 2 to 19 years had a BMI at or above the 95th percentile of the 2000 CDC BMI-for-age growth charts, while 31.8% had a BMI at or above the 85^{th} percentile (Ogden, Carroll, Kit, & Flegal, 2012).

Obesity within ALL

The problem of obesity in childhood ALL patients was first raised over 20 years ago (Zee & Chen, 1986). An additional seventeen studies have been published, since this time, which address the issue of excessive weight gain both during and after therapy. In the general pediatric population obesity is felt to occur when “energy intake exceeds energy expenditure” (Dehghan,

Akhtar-Danesh, & Merchant, 2005). The root cause of obesity in pediatric ALL patients is likely more complex and multi-factorial.

The non-standardized definitions for weight status throughout the ALL literature make comparisons between studies, and over time, difficult. With the exception of the Zee and Chin (1986) article which defined obesity as BMI greater than the 95th percentile, most publications between the years 1986-2000, defined obesity as BMI greater than the 85th percentile. Articles published after 2000, have generally adhered to the tighter definitions of obesity meaning that they defined obesity as BMI $\geq$ 95th percentile.

In general literature after the year 2000, show ALL survivors have overweight rates of 20-54% and obesity rates from 10-31%. This means that roughly one-fourth to one- half of ALL survivors are overweight or obese. These rates are slightly higher than the obesity rates reported in the general pediatric population. The latest NHANES data indicated that 12.1% of children ages 2-5 years are obese (defined as BMI $\geq$ 95th percentile) and this number increases to 18% for children 6-11 years and 18.4% for those 12-19 years of age (Ogden et al., 2012).

Based on the review of literature, a few general conclusions can be drawn regarding weight status and childhood ALL patients. Excessive weight is present in childhood leukemia patients both during and after therapy. Another observation is that the number of patients obese at diagnosis seems to be increasing. This finding most likely reflects the growing number of young children who are obese in the general pediatric population. This statistic is important as children who begin ALL therapy obese tend to remain obese throughout treatment (Razzouk et al., 2007; Withycombe et al., 2009).

Obesity and Cancer Connection

Research has now shown that increased BMI is linked to higher risks for cancer as an adult. One meta-analysis showed that as little as a 5 Kg/m^2 increase in BMI was strongly associated with multiple types of cancers, such as thyroid, colon, renal, and oesophageal adenocarcinoma in men and endometrial, gallbladder, renal and oesophageal adenocarcinoma cancers in women (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). Weaker associations were found with increased BMI and cancers such as malignant melanoma, rectal, postmenopausal breast, pancreatic, leukaemia and non-Hodgkin lymphoma (Renehan et al., 2008).

Other researchers have expanded on the connection between obesity and adult leukemia. Compared to normal weight adults (BMI < 25 Kg/m^2), the relative risk for leukemia development (all types) was 1.14 for those overweight and 1.39 for those who were obese (Larsson & Wolk, 2008). Using a continuous scale, this translates to a 13% higher risk for leukemia beginning with a 5 Kg/m^2 increase in BMI (Larsson & Wolk, 2008). This has been referred to as a "dose-response" effect within epidemiological studies that show that cancer risks significantly rise with each increase in BMI from the normal to the overweight and obese categories (Lichtman, 2010).

For children, it still remains to be determined if obesity increases the likelihood of cancer development early in life. There is a known association with higher birth weight (>4,000 g) and increased risk of childhood ALL (Hjalgrim et al., 2003). Possible theories regarding why increased birth weight correlates to ALL development revolve around the increased presence of insulin like growth factor 1 and the fact that larger volumes of bone marrow are present with increased weight therefore increasing the chance for genetic mutations (Hjalgrim et al., 2004).

There also appears to be a dose response effect as increasing weight trends with increasing risk. Regardless of the influence of weight on initial leukemia development during childhood, the evidence for leukemia occurrence later in life is clearly linked to obesity.

Obesity and Cancer Outcomes

The presence of obesity during cancer is important due to the implications on disease outcome. Weight status is known to impact breast cancer survival with higher mortality rates being observed in patients with BMI $\geq$ 30 at the time of diagnosis (Chen et al., 2010). Another large scale study of 900,000 adults in the United States found that the death rate for all combined cancers was significantly associated with increased body weight (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003).

Obesity has also been implicated in reducing the survival of leukemia patients. Adults with BCR-ABL negative ALL who are obese at diagnosis (BMI > 30) have been shown to have a lower event free survival rate than those with normal BMI (Butturini, et al., 2005). Weight status is also important in the survival of children with leukemia. Children with acute myeloid leukemia who begin therapy obese (BMI $\geq$ 95th percentile) are less likely to survive when compared to normal weight patients (Lange et al., 2005). Likewise, children who begin ALL therapy obese have an increased risk of relapse (Butturini et al., 2007; Gelelete et al., 2011). A recent analysis of the CCG 1961 data set, the same patient group as used for this study, found that obesity at diagnosis was associated with increased general (treatment related) toxicity during high risk ALL therapy as well as decreased survival (Orgel, et al., 2011). In addition, Orgel et al. (2011), are expanded the analysis to include evaluating a possible association between survival

and cumulative time in weight extremes, such as obesity or underweight (personal communication, David Freyer, D.O, Children's Hospital of Los Angeles; March 20, 2012).

Risk Factors for Obesity in Childhood ALL

Literature also shows additional risk factors for obesity related to childhood ALL therapy. Younger age at diagnosis for ALL and Hispanic race are associated with an increased risk for excessive weight gain during treatment. Additional mechanisms for obesity development might include leptin insensitivity, corticosteroid effects, growth hormone deficiency (secondary to cranial radiation), and physical inactivity (Reilly et al., 2003). The underlying treatment for childhood ALL may contribute to unique biological factors which influence obesity. The research outlining possible interactions between ALL therapy and weight gain will be discussed. The biological factors of hypothalamic-pituitary-adrenal (HPA) axis disruption; age and adiposity rebound; glucocorticoids; leptin; race and genetics will be discussed first followed by a discussion regarding research on physical activity levels in childhood cancer survivors.

Hypothalamic-Pituitary Adrenal (HPA) Axis Disruption

The HPA axis functions as a neuro-endocrine system that regulates cortisol and an individual's response to stress. As such, the HPA axis plays a major role in energy balance. The cascade of cortisol regulation begins with the hypothalamus producing corticotrophin releasing hormone which stimulates the pituitary to release adrenocortiocotropin (ACTH). In turn, ACTH acts to stimulate the adrenal cortex to produce and release cortisol. Once the cortisol is released into circulation, it may bind to two types of receptors, the glucocorticoid receptor and the mineralocorticoid receptor (Nieuwenhuizen & Rutters, 2008). The hypothalamus has a high

volume of glucocorticoid receptors which act to induce a negative feedback action on the HPA axis pathway.

Administration of glucocorticoids during childhood leukemia treatment causes hypercortisolism. This promotes pre-adipocytes to differentiate into mature adipocytes therefore promoting increased fat tissue (Nieuwenhuizen & Rutters, 2008). A central distribution of body fat is usually associated with hypercortisolism and visceral (abdominal) obesity. Two studies have linked increased visceral fat in ALL survivors to metabolic syndrome (Janiszewski et al., 2007; Jarfelt, Lannering, Bosaeus, Johannsson, & Bjarnason, 2005). Preventing obesity, especially visceral obesity, may prove to be an important factor in preventing other adverse health events such as metabolic syndrome.

Disruption in the HPA axis pathway may also occur in patients receiving cranial radiation. Patients receiving this type of radiation therapy may develop obesity as a result of direct injury to the HPA axis (Rogers et al., 2005). Hypothalamic functions are highly sensitive to radiation and may result in growth hormone deficiency, hypothyroidism, and central adrenal insufficiency (Nandagopal, Laverdiere, Mulrooney, Hudson, & Meacham, 2008).

There is controversy regarding if and when the administration of cranial radiation influences weight gain. Some report no influence (Razzouk et al., 2007; Van Dongen-Melman et al., 1995), while others report that there was no level of significance reached during the course of ALL therapy (Collins, Zarzabal, Nayiager, Pollock, & Barr, 2010; Withycombe et al., 2009). A few studies have shown a relationship between cranial radiation and obesity development prior to ending therapy (Odame, Reilly, Gibson, & Donaldson, 1994; Sklar et al., 2000). Multiple other studies have shown a connection between obesity during survivorship and cranial radiation

during childhood cancer therapy (Green et al., 2012; Groot-Loonen, Otten, van't Hof, Lippens, & Stoelinga, 1996; Oeffinger et al., 2003).

It is also important to note that cranial radiation in children may cause damage to the hypothalamus leading to endocrine issues. Growth hormone deficiency and precocious puberty are reported to be the most common neuroendocrine problems in survivors of childhood ALL (Nathan et al., 2009). The presence of inadequate growth hormone can alter normal growth patterns and lead to shorter statue which in turn can impact BMI.

Association of Race with Obesity Risk

Protocol number 1961 referred to a patient's race instead of ethnicity and that terminology will be reflected in this paper. There is some evidence to support that fact that an individual's race or ethnicity may be associated with obesity development during and after childhood cancer therapy. In a large study of over 9,200 adult survivors of childhood cancer, being Hispanic or black (non-Hispanic) was a risk factor for obesity (Green et al., 2012). Two additional studies found that individuals who were Hispanic were associated with obesity at the end of childhood ALL therapy (Gofman & Ducore, 2009; Withycombe et al., 2009). It has also been reported that pediatric leukemia patients that are Hispanic are more likely to begin therapy obese (Baillargeon et al., 2006). This finding may be secondary to higher rates of pediatric obesity within the Hispanic population in general (Ogden et al., 2012).

Age and Adiposity Rebound

Obesity development in children also appears to be associated with age. Multiple studies report that younger children treated for ALL have an increased risk of obesity development (Razzouk et al., 2007; Sainsbury, Newcombe, & Hughes, 1985; Schell, Ochs, Schriock, &

Carter, 1992; Withycombe et al., 2009). This increased risk associated with age may be partly explained by a phenomenon called adiposity rebound. During normal childhood development there is a period of time when the BMI reaches a nadir. This low point, nadir, of BMI is followed by weight gain and adiposity development. This period of normal childhood growth and development is referred to as adiposity rebound. This occurrence normally happens between 5-7 years of age and is an especially important period for the regulation of energy and prediction of adult obesity (Reilly, Kelly, et al., 2001). Younger children treated for ALL experience adiposity rebound significantly sooner than their peers which pre-disposes them to obesity (Reilly, Kelly, et al., 2001). Early adiposity rebound in children, prior to 5.5 years of age, is significantly related to higher adiposity levels (Rolland-Cachera et al., 1984). The peak incidence of ALL in children occurs prior to the age of 5 years (National Cancer Institute, 2011). These children are then started on ALL Induction therapy which utilizes glucocorticoids. Current COG protocols propose the use of Dexamethasone 6 mg/m^2/day for 28 days for standard disease risk patients and Dexamethasone 10 mg/m^2/day for 14 days for high risk patients. This dose of glucocorticoids, administered early in life, may push children towards early adiposity rebound.

Glucocorticoids

Glucocorticoids are administered on and off throughout the years of childhood ALL therapy. Hypercortisolism results and has been implicated in obesity development (Raber, 1998; Reilly, Brougham, et al., 2001). Glucocorticoids act to promote the differentiation of pre-adipocytes into mature adipocytes (fat cells) (Nieuwenhuizen & Rutters, 2008). Adipose tissue in turn begins to act as an endocrine organ through the production of adipokines. To date, there are more than 50 different molecular entities identified as adipokines which are responsible for a

number of physiological events such as lipid metabolism, insulin sensitivity, hemostasis and angiogenesis (Trayhurn & Wood, 2005). The underlying physiological influences of adipokines may contribute to many adverse events associated with obesity. Perhaps the most concerning findings is that obese individuals are at risk for the development of specific cancers. Adipokines such as TNFα, leptin, PAI 1 and IL-6, are felt to be responsible in part for creating a state of systemic inflammation (Trayhurn & Wood, 2005). Chronic low grade inflammation as well as hyperinsulinemia, hyperglycemia and increased circulating sex steroids are all mechanisms known to contribute to cancer development (Becker, Dossus, & Kaaks, 2009). Obesity, therefore, adds an additional risk factor to the already known risks for developing a secondary cancer following ALL therapy.

Glucocorticoids also trigger increased appetite, sleep disturbances and protein degradation (Sherwood, 2007). Dexamethasone, a corticosteroid commonly used in ALL therapy, has been linked with sleep disturbances and fatigue (Hinds et al., 2007). During the steroid phases of ALL treatment, glucocorticoids are administered two to three times per day. Sleep disturbances develop secondary to the body's natural (diurnal) cortisol rhythm being disrupted. Diminished sleep amounts have also been linked to childhood obesity (Taheri, 2006). In addition, energy imbalances results from glucocorticoids (Reilly, Brougham, et al., 2001) by causing increased appetite and fatigue (triggered through the loss of muscle protein secondary to gluconeogenesis). Prior research has shown a marked increase in energy intake, up to 20%, in childhood ALL patients during phases of glucocorticoid administration (Reilly, Brougham, et al., 2001).

Although there is controversy over which glucocorticoid (Prednisone vs Dexamethasone) has the greatest impact on weight during ALL therapy, there is uniform agreement that both medications independently contribute to weight. Multiple studies have examined obesity development during childhood ALL and found a positive association with glucocorticoids (Chow, Pihoker, Hunt, Wilkinson, & Friedman, 2007; Reilly, Brougham, et al., 2001; Van Dongen-Melman et al., 1995). Studies outside of oncology also confirm the influence on increased weight secondary to glucocorticoids during treatment for diseases such as Crohn's (Sylvester et al., 2009), rheumatoid arthritis (Huscher et al., 2009) and Duchenne muscular dystrophy (Straathof et al., 2009). Glucocorticoids are an important part of ALL therapy and their use is anticipated to continue in future ALL treatment protocols.

Leptin

Leptin is a hormone that plays a major role in energy storage and appetite regulation (Skoczen et al., 2011). This hormone is often referred to as a cytokine and belongs to a group of other hormones such as adiponectin and resistin that are often called adipokines. When leptin binds to cell receptors in the hypothalamus this normally functions to signal the brain to suppress appetite. Leptin levels correlate with fat mass, with higher BMI being associated with increased plasma leptin levels (Skoczen et al., 2011).

Leptin is important in childhood ALL as higher levels have been reported in patients treated with cranial radiation (Skoczen et al., 2011; Tonorezos et al., 2012). Elevated leptin levels have also been reported in children treated for ALL without cranial radiation (Davies et al., 2004). Another study revealed that elevated leptin levels persisted post ALL therapy, without radiation, but only in females (Kohler, Moon, Wright, Willows, & Davies, 2011).

It is known that glucocorticoids stimulate leptin release from the adipocytes. Leptin resistance is felt to develop which may contribute to obesity predisposition in ALL survivors (Davies et al., 2004). The exact mechanism for leptin resistance (outside of cranial radiation) is unknown, but glucocorticoid induced leptin resistance or insensitivity has been demonstrated in animal models (Davies et al., 2004). The biological and clinical role of leptin resistance, especially in the presence of obesity, is still a topic of research interest.

Other findings related to genetics and the leptin / obesity interaction have emerged. A polymorphism in the leptin receptor gene has been associated with obesity development in a select group of childhood ALL patients. In this trial, an increased prevalence for obesity was observed in females who carried the Gln223Arg polymorphism and particularly in those that had received cranial radiation (Ross et al., 2004).

Genetics

New findings of genetic polymorphisms that influence weight status are emerging at a rapid rate. It may be possible that genetic variations exist within pediatric oncology patients that increase their risks of excessive weight gain during therapy. One example may be polymorphisms of the glucocorticoid receptor gene. Glucocorticoid actions are mediated in a large part by glucocorticoid receptors. Individual differences in response to glucocorticoids have been observed and are felt to be related in part to Glucocorticoid Receptor (GR) gene polymorphisms within the receptor genes (van Rossum & Lamberts, 2004). To date, most mutations and polymorphisms present in the GR gene have been studied in leukemia patients in association with glucocorticoid resistance (Zhou & Cidlowski, 2005). No published studies could be located which examined increased GR sensitivity in ALL patients. Within the general

population, however, multiple polymorphisms in the GR gene have been associated with increased BMI and metabolic syndrome (van Rossum & Lamberts, 2004). The BclI polymorphism in the GR gene has been linked to increased body fatness in young adolescents (Voorhoeve et al., 2009). Another interesting study determined that individuals with N363S GR gene variants, who were exposed to glucocorticoids antenatally, displayed increased abdominal adiposity at 19 years of age (Finken et al., 2011).

Other studies have noted an association between obesity in childhood leukemia patients and their parents' weight status. Abnormal maternal BMI has been described as an added risk factor for the presence of obesity in ALL survivors (Asner, Ammann, Ozsahin, Beck-Popovic, & von der Weid, 2008) and particularly in girls (Shaw, Bath, Duff, Kelnar, & Wallace, 2000). Another study described the elevated BMI status of both parents' as been associated with a child's increased BMI status at time of ALL diagnosis (Esbenshade et al., 2011).Whether these correlations in weight between parent and child are genetic in nature or behavioral in nature remains to be determined.

Physical Activity

Lastly, a decrease in physical activity has also been attributed to obesity development in ALL survivors. This is based on evidence that physical fitness activities are lower in ALL survivors when compared to healthy controls (van Brussel, Takken, Lucia, van der Net, & Helders, 2005) or to the general population (Florin et al., 2007). The trend towards decreased physical activity begins during chemotherapy and does not appear to recover post treatment (Keats, Culos-Reed, Courneya, & McBride, 2006). This finding correlates with reports that physical activity patterns of school aged children significantly predicts their adult levels of

physical activity (Telama et al., 2005). The reports of decreased physical activity levels may be secondary to side effects of treatment such as fatigue and neuropathy. Additional, those patients receiving cranial radiation may be an especially high risk population for decreased physical activity (Mayer, Reuter, Dopfer, & Ranke, 2000).

Summary

Obesity is prevalent, but not universal, among children treated for ALL. This finding implies that there are perhaps individual differences that can predispose or protect one from excessive weight gain during therapy. Cranial radiation, Hispanic race and younger age at diagnosis have all be implicated as risk factors for obesity development, but a knowledge gap exists regarding how to accurately predict who is most likely to become obese during therapy.

Literature supports the association between glucocorticoid administration and weight gain. To date, no studies could be located which examined the timing of glucocorticoid administration and weight gain during childhood ALL therapy. This study will examine weight gain during two individual cycles of chemotherapy, in which glucocorticoids are administered, to see if there is an association with obesity at the end of therapy. Early recognition of this patient population may be important as obesity is a disease that is perhaps amenable to preventative measures.

CHAPTER THREE: RESEARCH METHOD

Overview

Leukemia is considered to be a liquid tumor as the cancer cells develop in the bone marrow and spread to the blood stream. ALL is characterized by the unregulated multiplication of immature white blood cells called blasts. These blasts overpopulate the bone marrow which leads to crowding and suppression of normal cell development. In the 1950s it was discovered that glucocorticoids are useful drugs in treating leukemia (Kersey, 1997). Glucocorticoids work primarily through causing apoptosis of the blasts cells and through suppression of the immune system. Because of their usefulness, these drugs are employed throughout the multiple years of childhood ALL therapy. Glucocorticoids, however, have unwanted side effects associated with their use. Excessive weight gain is one of those adverse events. The purposes of this study are to examine two cycles of ALL therapy utilizing glucocorticoids to determine if weight gain during therapy is predictive of obesity at the end of ALL therapy.

Study Design

This study utilizes a retrospective design with secondary data analyses of previously collected information from a COG treatment trial (protocol number 1961). COG is the largest cooperative research group for pediatric oncology (Children's Oncology Group, n.d.). Currently, over 200 facilities have joined forces to utilize the same research protocols and to report data to a central location housed within the COG entity (Children's Oncology Group, n.d.). Utilizing data from research databases, such as those within COG, makes retrospective secondary data analyses feasible due to the larger numbers of pediatric oncology patients accrued to each study.

COG Protocol 1961 was entitled "Treatment of Patients with ALL with Unfavorable Features". Protocol number 1961, was a treatment protocol for children (ages 1-21 years) newly diagnosed with high risk ALL. High risk ALL was defined as children 1-9 years of age with an initial white blood cell (WBC) count $\geq$ 50,000/μl or children between the ages of $\geq$ 10 years and $\leq$ 21 years with any WBC level. This front line treatment study enrolled higher risk ALL patients between September 16, 1996 and May 1, 2002, and accrued 2,078 patients. Of these, 1,746 patients were eligible for randomization into established treatment arms. Patients with CNS leukemia or overt testicular leukemia were eligible for treatment on the 1961 protocol.

Inclusion Criteria

This current, retrospective, study utilized data from patients previously treated on COG protocol number 1961. The total population eligible for randomization in the original treatment study (n=1,746) was further reduced to contain a subset of patients who met the following inclusion criteria. Children who did not complete the full treatment protocol where excluded for analysis in this retrospective study (n=657) as were children who did not have data available for BMI calculations (n=72) at the beginning of therapy, end of Induction therapy (beginning of consolidation), and at the last cycle of maintenance therapy (referred to as end of therapy). This current study only included those age 2 to 20 years as no BMI percentiles could be calculated for younger or older ages. The final number of subjects included in this study was 1,017.

Data Management

The following data items were requested from the COG database for protocol 1961:

Unique patient ID number (COG assigned number)
Age at Diagnosis
Initial Diagnosis Date
Diagnosis (Immunophenotype of Leukemia)

Patient's Race
Sex
Date on Study (Enrollment date)
Deemed eligible for treatment study
CNS disease status at Diagnosis
Treatment assignment (study arm)
Begin and end date for each course of therapy
Height and Weight at the beginning of each course
Induction failure and date
Secondary Malignancy
Radiation therapy received – Yes / No
Date of relapse or death – if occurred
Was the therapy delayed over one week during this phase/course?
Reason delayed
Date off protocol therapy
Reason off-treatment

COG released the above data to Jane Meza, PhD (COG statistician). The data were maintained in a secure computer at the COG statistical center in Omaha, Nebraska, worksite of Dr. Meza. The received data were identified with a unique COG number that could not be used to link the data with additional patient information. No patient names, addresses or phone numbers were received. The data were maintained in a computer secured through user password access. The study principal investigator was involved in discussions related to data analysis, but the actual processing / handling of the data was completed by a COG statistician. A technical report, which listed aggregate data only, was released to the study principal investigator at the conclusion of the final analysis. All data remained in the possession of COG through the analysis and post study completion.

Protection of Human Subjects

All patient data was obtained during prior nationwide treatment trials. Each individual institution participating in the Children's Cancer Group (CCG), now known as COG, research network had the responsibility of obtaining consent / assent for the original treatment study. Data

collection and reporting were integrated parts of these studies. The original treatment consents are stored at the individual facilities which are members of COG. Routine audits are conducted through COG to ensure that individual members are in compliance with all research regulations, including proper consenting of subjects.

This study was submitted to the University of Arizona's Institutional Review Board (IRB) and deemed exempt from review (Appendix D). In addition, a formal protocol was submitted and reviewed by COG which authorized the release and use of the requested data for the purposes of this study. The Principal Investigator for this study is current with all required training for the protection of human subjects.

Data Analysis Plan

Statistical analysis was completed utilizing SAS/STAT software Version 9.2 (SAS Institute, Inc., Cary, NC) housed at the University of Minnesota. A p-value was considered significant when $p \leq 0.05$. Planned statistical procedures include the use of descriptive statistics to summarize demographic and clinical variables. Logistic regression was used to examine the relationship between weight gain during two separate cycles of chemotherapy and obesity at the end of therapy. Logistic regression is an appropriate method of analysis when addressing a dichotomous (yes/no) outcome (Hosmer & Lemeshow, 2002).

The study aims were evaluated as follows:

Primary Aim 1: To determine if weight change (measured by age and gender BMI z score) during ALL Induction therapy is associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of Maintenance therapy.

Primary Aim 2: To determine if weight change (measured by age and gender BMI z score) during cycle 1 of Delayed Intensification ALL therapy is associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of Maintenance therapy.

The US centers for Disease Control and Prevention SASS program was used to calculate BMI age and gender specific percentiles and z scores for all patients between the ages of 2 to 20 years. Boys and girls were examined separately as their planned length of therapy differed by twelve months. The clinical definition of end of protocol therapy was utilized for this study which states that girls complete treatment at two years from the beginning of Interim Maintenance and boys at three years from the beginning of Interim Maintenance. Boys received additional cycles of Maintenance therapy as compared to girls (Table 2). The last BMI information collected on protocol number 1961 occurred at the beginning of the patient's last cycle of Maintenance therapy. This is referred to as end of Maintenance in this study.

BMI was calculated as weight (Kg) / height (m^2). Data on weights and heights were obtained at the beginning of each new cycle of therapy. BMI percentiles and z-scores were based on age and sex, and were calculated using the US Centers for Disease Control SAS macro (http://www.cdc.gov/nccdphp/dnpa/growthcharts/sas.htm).

The change in BMI z-score during Induction was calculated as BMI z-score at beginning of consolidation minus the BMI z-score at the beginning of Induction. The change in BMI z-score during Delayed Intensification (DI) was calculated using one of the following two formulas. For the patients who received Interim Maintenance 2, the change in z-score during DI was calculated as BMI z-score at the beginning of Interim Maintenance 2 minus the BMI z-score at the beginning of DI 1. For patients who did not receive Interim Maintenance 2, the change in

BMI z-score during DI was calculated as BMI z-score at the beginning of Maintenance 1 minus the BMI z-score at the beginning of DI 1. The calculated age and gender-specific BMI z-score values were used as a continuous variable in the testing of the developed statistical models. Univariate and multivariate analyses were examined. Multivariate logistic regression analyses were utilized to determine if weight change during Induction or Delayed Intensification (cycle I) were associated with obesity at the end of Maintenance therapy.

The secondary aim was:

Secondary Aim: To determine the percent of children per cycle who experienced grade 3 weight toxicity (defined as $\geq$ 20% increase in kilograms in one cycle).

The 1961 study utilized a treatment toxicity scale which defined weight gain $\geq$ 20% increase in kilograms in one cycle as a grade 3 toxicity. This aim evaluated the number of patients who experienced this level of weight gain during each cycle of chemotherapy administered according to protocol number 1961. The percent of change in kilograms was measured by the formula 100*(new weight - old weight)/(old weight). This analysis was performed in order to add knowledge regarding the percentage of children on ALL therapy who experience a rapid and excessive weight gain.

Summary

Secondary data analysis, through retrospective review, offers a research method that is useful in examining information that has previously been collected over time. The use of COG data for this study allowed for the examination of BMI information from a large group of previously treated childhood ALL patients. This study utilized BMI data, through the use of z-

scores, to explore weight change during two individual cycles of ALL therapy as a potential predictor for obesity at the end of maintenance therapy.

CHAPTER FOUR: RESULTS

Patient Demographics

A total of 1,089 patients completed therapy with 1,017 of these having the required BMI information available for review. Descriptive statistics were used to summarize patient demographics (Table 1). Of the 1,017 patients included in this study, the majority were white (68%) and a slight majority where males (56%). A larger percentage of patients responded rapidly to the first 7 days of treatment and were therefore randomized on the initial treatment study to either arm A, B, C or D. Patients who responded slower to the first 7 days of therapy were randomized between Augmented Berlin-Frankfurt-Munster (BFM) double delayed intensification (DDI) with Doxorubicin (DOXO) or Augmented BFM DDI utilizing Idarubicin and Cyclophosphamide (IDA/CPM). An overall trend of increasing BMI percentiles was noted during therapy (Table 1). At the beginning of therapy, 27% of the children were overweight (14%) or obese (13%), while at the end of therapy, 42% of children were in the overweight (19%) or obese (23%) categories. The biggest increase was therefore noted within the obese category with an additional 10% of patients obtaining obesity during ALL therapy.

Table 1

Patient Demographics

Characteristic	All patients N=1017	Males N=572	Females N=445
Age, median (range), years	11.3 (2.0 – 17.8)	11.3 (2.0-16.9)	11.4 (2.0-17.8)
Race, N (%)			
White	689 (68%)	429 (75%)	260 (58%)
Black	61 (6%)	31 (5%)	30 (7%)
Hispanic	201 (20%)	78 (14%)	123 (28%)
Other/Unknown	66 (6%)	34 (6%)	32 (7%)
Treatment, N (%)			
Arm A Standard BFM standard duration	198 (19%)	121 (21%)	77 (17%)
Arm B Standard BFM increased duration	186 (18%)	106 (19%)	80 (18%)
Arm C Augmented BFM standard duration	199 (20%)	107 (19%)	92 (21%)
Arm D Augmented BFM increased duration	189 (19%)	104 (18%)	85 (19%)
Augmented BFM DDI Doxo	129 (13%)	69 (12%)	60 (13%)
Augmented BFM DDI IDA/CPM	116 (11%)	65 (11%)	51 (11%)
Radiation Therapy at Consolidation, N (%)	244 (24%)	139 (24%)	105 (24%)
BMI percentile beginning of therapy, N (%)			
Underweight - BMI < 5th percentile	54 (5%)	30 (5%)	24 (5%)
Healthy Weight - BMI 5th - 84th percentile	685 (67%)	383 (67%)	302 (68%)
Overweight - BMI 85th - 94th percentile	146 (14%)	83 (15%)	63 (14%)
Obese - BMI >= 95th percentile	132 (13%)	76 (13%)	56 (13%)
BMI percentile end of therapy, N (%)			
Underweight - BMI < 5th percentile	31 (3%)	21 (4%)	10 (2%)
Healthy Weight - BMI 5th - 84th percentile	562 (55%)	318 (56%)	244 (55%)
Overweight - BMI 85th - 94th percentile	189 (19%)	102 (18%)	87 (20%)
Obese - BMI >= 95th percentile	235 (23%)	131 (23%)	104 (23%)

Note: Due to rounding, not all BMI percentages total 100.

Table 2, listed below, displays the demographics regarding completion of therapy by gender. Males and females were analyzed separately as females generally ended therapy a year sooner than males. The end of protocol therapy for CCG 1961 was defined as two years from the beginning of Interim Maintenance for girls and three years from the beginning of Interim Maintenance for boys. Females completed treatment between Maintenance cycles 4 to 8, with the majority ending therapy after Maintenance cycle 6. Males completed treatment between Maintenance cycles 7 to 12, with the majority ending therapy after Maintenance cycle 10.

Table 2

Completion of Therapy by Gender

Treatment Course	Male (n=572) N (%)	Female (n=445) N (%)
Maintenance #4	0 (0%)	3 (0.7%)
Maintenance #5	0 (0%)	48 (11%)
Maintenance #6	0 (0%)	211 (47%)
Maintenance #7	2 (0.4%)	105 (24%)
Maintenance #8	3 (0.5%)	78 (18%)
Maintenance #9	25 (4%)	0 (0%)
Maintenance #10	253 (44%)	0 (0%)
Maintenance #11	119 (21%)	0 (0%)
Maintenance #12	170 (30%)	0 (0%)

Univariate Analysis

For this study, univariate analysis was used to examine the relationship between obesity (BMI $\geq 95^{th}$ percentile) at the end of therapy and each individual model variable (Table 3). The individual variables that were examined included the difference in BMI z-score during Induction, the difference in BMI z-score during Delayed Intensification 1, the BMI z-score at the beginning of Induction (baseline), age, race and treatment arm. Age was categorized and divided into

ranges so that trends within age groups could be identified. The age groups (ranges of ages) were selected (categorized) based on prior research (Withycombe et al., 2009).

The results of the univariate analysis are provided in Table 3. Of the variants included in the model, only BMI z-score at the beginning of Induction was significant in predicting obesity at the end of Maintenance. The changes in BMI z-score during Induction or Delayed Intensification 1 were not predictive of obesity in a univariate model. Although not statistically significant in females, males demonstrated a significance in the race category ($p = 0.049$) with Hispanics being most likely to be obese at the end of therapy (OR=1.97). Black males also demonstrated an increased risk for obesity at the end of therapy (OR=1.87) as compared to the reference group of white males.

Table 3

Univariate Predictors of BMI Percentile >=95% at the End of Maintenance

		Males		Females	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Diff BMI z-score at induct.	1 unit increase	0.93 (0.75-1.16)	0.53	1.00 (0.79-1.26)	0.98
Diff BMI z-score at DI#1	1 unit increase	0.89 (0.57-1.39)	0.61	1.26 (0.76-2.08)	0.37
BMI z-score at beginning of induct.	1 unit increase	4.84 (3.60-6.50)	<0.0001	7.68 (5.08-11.62)	<0.0001
Age	2 - 4 years	1.46 (0.75-2.87)	0.21	1.42 (0.69-2.91)	0.42
	5 - 9 years	1.97 (1.01-3.86)		0.90 (0.39-2.06)	
	10 - 14 years	1.28 (0.70-2.34)		0.90 (0.47-1.71)	
	15 – 20 years	Ref.		Ref.	
Race	Black	1.87 (0.85-4.12)	0.049	2.32 (1.04-5.17)	0.085
	Hispanic	1.97 (1.16-3.33)		1.59 (0.97-2.61)	
	Other/Unknown	1.21 (0.53-2.77)		0.92 (0.36-2.36)	
	White	Ref.		Ref.	
Treatment	Arm A Standard BFM standard duration	1.00 (0.48-2.08)	0.86	0.81 (0.36-1.81)	0.61
	Arm B Standard BFM increased duration	0.95 (0.45-2.03)		0.56 (0.24-1.30)	
	Arm C Augmented BFM standard duration	1.11 (0.53-2.33)		1.04 (0.46-2.24)	
	Arm D Augmented BFM increased duration	1.09 (0.52-2.31)		0.81 (0.37-1.80)	
	Augmented BFM DDI Doxorubicin	1.49 (0.68-3.27)		0.66 (0.27-1.60)	
	Augmented BFM DDI IDA/CPM	Ref.		Ref.	

Multivariate Analysis

Univariate analysis was followed by multivariate analysis for study aims 1 and 2. Males and females were again examined separately. Scatter plots of the data (Appendix C) show that outlier data points were present within the data set. Outlier cases were detected in both males and females for model 1. Goodness of fit for the logistic regression models was assessed with influence plots and DFBetas plots (SAS Institute, 2004). The regression models were re-run without the outliers and the models did not significantly change (p-values and Odds Ratio were approximately the same as in original model). The decision was therefore made to keep the outliers in the presented models.

Males

The first model examined the change in BMI z-score during Induction in context of other covariates (age, race, treatment arm, course when patient finished therapy and BMI z-score at the beginning of Induction). The interaction between BMI z-score at the beginning of Induction and the change in BMI z-score during Induction was considered but was not statistically significant ($p=0.077$).

The results of the multivariate analysis for the difference in BMI z-score for males during Induction showed that BMI z-score at the beginning of Induction and the change in BMI z-score during Induction were significant predictors of obesity at the end of therapy after adjusting for the other covariates (Table 4). When all other variables are held fixed a one unit increase in the BMI z-score at the beginning of Induction results in a 7.7 increase in the odds ratio for obesity at the end of therapy. When all other variables are held fixed a one unit increase in the difference in

BMI z-score during Induction results in a 3.0 increase in the odds ratio for obesity at the end of therapy.

Table 4

Multivariate Analysis BMI Percentile > 95% at the End of Maintenance in Males (Model 1)

Effect		OR	Lower 95% CI	Upper 95% CI	P-value
Age	2 - 4 years	1.64	0.65	4.18	0.20
	5 - 9 years	2.08	0.85	5.08	
	10 - 14 years	2.35	1.06	5.24	
	15 – 20 years	Ref.	-	-	
Race	Black	1.06	0.37	3.01	0.53
	Hispanic	1.64	0.79	3.40	
	Other/Unknown	0.76	0.26	2.22	
	White	Ref.	-	-	
Treatment	Arm A Standard BFM standard duration	1.64	0.41	6.48	0.85
	Arm B Standard BFM increased duration	1.37	0.51	3.70	
	Arm C Augmented BFM standard duration	1.96	0.49	7.91	
	Arm D Augmented BFM increased duration	1.16	0.43	3.10	
	Augmented BFM DDI Doxo	1.83	0.64	5.24	
	Augmented BFM DDI IDA/CPM	Ref.	-	-	
Complete therapy	Maintenance 10	0.87	0.27	2.76	0.86
	Maintenance 11	0.62	0.17	2.35	
	Maintenance 12	0.74	0.16	3.55	
	Maintenance 7-9	Ref.	-	-	
BMI z-score at beginning of induct.	1 unit increase	7.69	5.23	11.30	<0.0001
Diff BMI z-score at induct.	1 unit increase	3.03	1.90	4.84	<0.0001

Additionally, in males, a second model was utilized to predict BMI percentile >= 95% at the end of therapy in relationship to a change in BMI z-score during cycle 1 of Delayed Intensification, in the context of other covariates (age, race, treatment arm, course when patient completed therapy, and BMI z-score at the beginning of Induction). The interaction between BMI z-score at the beginning of Induction and the difference in BMI z-score during Delayed Intensification cycle 1 was considered but not statistically significant (p=0.22).

BMI z-score at the beginning of Induction was a significant predictor of obesity at the end of therapy after adjusting for all other covariates. When all other variables are held fixed, a one unit increase in the BMI z-score at the beginning of Induction (baseline) resulted in a 5.2 increase in the odds ratio for obesity at the end of therapy. The change in BMI z-score during Delayed Intensification cycle 1 was not significantly associated with obesity at the end of Maintenance. Age demonstrated a trend towards statistical significance (p=0.064) in this model, with younger children displaying increased odds ratio for obesity as compared to older children.

Table 5

Multivariate Analysis BMI percentile >=95th% at the End of Maintenance in Males (Model 2)

Effect		OR	Lower 95% CI	Upper 95% CI	P-value
Age	2 - 4 years	3.11	1.31	7.38	0.064
	5 - 9 years	2.59	1.10	6.08	
	10 - 14 years	2.08	0.98	4.44	
	15 – 20 years	Ref.	-	-	
Race	Black	1.28	0.48	3.43	0.67
	Hispanic	1.49	0.74	2.98	
	Other/Unknown	0.87	0.31	2.48	
	White	Ref.	-	-	
Treatment	Arm A Standard BFM standard duration	1.45	0.38	5.59	0.85
	Arm B Standard BFM increased duration	1.21	0.46	3.21	
	Arm C Augmented BFM standard duration	1.67	0.43	6.47	
	Arm D Augmented BFM increased duration	1.19	0.46	3.08	
	Augmented BFM DDI Doxo	1.64	0.60	4.51	
	Augmented BFM DDI IDA/CPM	Ref.	-	-	
Complete therapy	Maintenance 10	0.85	0.28	2.63	0.69
	Maintenance 11	0.56	0.16	2.02	
	Maintenance 12	0.77	0.17	3.49	
	Maintenance 7-9	Ref.	-	-	
BMI z-score at beginning of induct.	1 unit increase	5.22	3.80	7.17	<0.0001
Diff BMI z-score at DI1	1 unit increase	0.95	0.60	1.50	0.82

Females

Multivariate analyses were used to analyze data from females. The first model examined BMI percentile >=95 % at the end of therapy utilizing change in BMI z-score during Induction as a predictor in the context of other covariates. For model 1, these covariates were age, race, treatment arm, BMI z-score at the beginning of Induction and the difference in BMI z-score

during Induction. The interaction between BMI z-score at the beginning of Induction and the change in BMI z-score during Induction was considered, but not statistically significant (p=0.51).

The results of the multivariate analysis for females, using model 1(Table 6) show that both BMI z-score at the beginning of Induction and the change in BMI z-score during Induction were significant predictors of obesity at the end of therapy after adjusting for other covariates in the model. When all other variables are held fixed a one unit increase in the BMI z-score at the beginning of Induction results in a 15.0 increase in the odds ratio for obesity at the end of therapy. When all other variables are held fixed a one unit increase in the difference in BMI z-score during Induction, results in a 4.1 increase in the odds ratio for obesity in females at the end of Maintenance.

Table 6

Multivariate Analysis BMI percentile >=95% at the End of Maintenance in Females (Model 1)

Effect		OR	Lower 95% CI	Upper 95% CI	P-value
Age	2 - 4 years	0.98	0.33	2.91	0.96
	5 - 9 years	0.93	0.28	3.14	
	10 - 14 years	0.81	0.31	2.12	
	15 – 20 years	Ref.	-	-	
Race	Black	2.13	0.63	7.18	0.13
	Hispanic	2.33	1.13	4.78	
	Other/Unknown	1.39	0.40	4.76	
	White	Ref.	-	-	
Treatment	Arm A Standard BFM standard duration	1.56	0.47	5.17	0.58
	Arm B Standard BFM increased duration	1.29	0.36	4.66	
	Arm C Augmented BFM standard duration	2.79	0.86	9.03	
	Arm D Augmented BFM increased duration	1.67	0.51	5.45	
	Augmented BFM DDI Doxo	1.57	0.44	5.55	
	Augmented BFM DDI IDA/CPM	Ref.	-	-	
BMI z-score at beginning of induct.	1 unit increase	14.62	8.38	25.53	<0.0001
Diff BMI z-score at induct.	1 unit increase	4.15	2.32	7.43	<0.0001

Next, a second multivariate model was used to predict BMI percentile >= 95% at the end of therapy in female patients to determine if the change in BMI z-score during cycle 1 of Delayed Intensification was predictive of obesity in the context of other covariates (Table 7). For model 2, in females, these covariates consisted of age, race, treatment arm, BMI z-score at the beginning of Induction and difference in BMI z-score during Delayed Intensification 1. For females, the course when treatment was completed could not be included in the models because of multicollinearity with treatment regimen. The interaction between BMI z-score at the

beginning of Induction and the change in BMI z-score during Delayed Intensification cycle 1 were also considered, but not statistically significant (p=0.78).

BMI z-score at the beginning of Induction was a significant predictor of obesity at the end of therapy in females after adjusting for the other covariates in the model. When all other variables were held fixed a one unit increase in the BMI z-score at the beginning of Induction, resulted in a 9.0 increase in the risk of being obese at the end of treatment. The change in BMI z-score during cycle 1 of Delayed Intensification was not associated with obesity at the end of therapy.

Table 7

Multivariate Analysis BMI Percentile >=95% at the End of Therapy in Females (Model 2)

Effect		OR	Lower 95% CI	Upper 95% CI	P-value
Age	2 - 4 years	1.35	0.47	3.83	0.64
	5 - 9 years	1.24	0.40	3.82	
	10 - 14 years	0.83	0.34	2.03	
	15 – 20 years	Ref.	-	-	
Race	Black	2.50	0.82	7.61	0.16
	Hispanic	1.94	0.98	3.85	
	Other/Unknown	1.06	0.31	3.58	
	White	Ref.	-	-	
Treatment	Arm A Standard BFM standard duration	1.48	0.47	4.69	0.72
	Arm B Standard BFM increased duration	1.22	0.36	4.13	
	Arm C Augmented BFM standard duration	2.26	0.76	6.76	
	Arm D Augmented BFM increased duration	1.43	0.46	4.39	
	Augmented BFM DDI Doxo	1.31	0.38	4.46	
	Augmented BFM DDI IDA/CPM	Ref.	-	-	
BMI z-score at beginning of induct.	1 unit increase	8.51	5.40	13.42	<0.0001
Diff BMI z-score at DI1	1 unit increase	1.41	0.72	2.76	0.32

Secondary Analysis

Finally, this study examined the number of patients, per treatment cycle, that experienced a weight toxicity of grade 3. Per the 1961 protocol toxicity scale, grade 3 weight toxicity was defined as $\geq$ 20% increase in kilograms in one cycle of therapy. The percent of change in kilograms was measured by 100*(current reporting period weight – previous reporting period weight) / (previous reporting period weight).

The total number of patients included in the analysis for each cycle of therapy is listed as Total N (Table 8). The number of patients with grade 3 toxicity was highest during Induction therapy (n=62). It is important to note that Induction was also the shortest cycle of chemotherapy administered. Of the 62 patients included in the analysis during Induction, 4 were missing BMI percentile information (height values) at the beginning of Induction. For the remaining 58 patients with grade 3 weight toxicity during Induction, only 4 (7%) were obese at the beginning of Induction (baseline).

Table 8

Grade 3 Weight Toxicity

Previous reporting period	Current reporting period	Length of cycle Arms A & B	Length of cycle Arms C, D, SER	Total N	N with Grade 3 Weight Toxicity	%
Induction	Consolidation	4 wks	4 wks	1603	62	3.9
Consolidation	Interim Mtc #1	5 wks	9 wks	1575	14	0.9
Interim Mtc #1	Delayed Intens # 1	8 wks	8wks	1541	12	0.8
Delayed Intens # 1	Interim Mtc #2	7 wks	8 wks	927	8	0.9
Interim Mtc #2 Arms B, D, and SER	Delayed Intens #2	8 wks	8 wks Arm D 6 wks SER	903	6	0.7
Delayed Intens # 1 or #2 DI 2 Arms B, D, & SER	Mtc 1	8 wks	8 wks	1458	21	1.4
Mtc 1	Mtc 2	12 wks	12 wks	1424	25	1.8
Mtc 2	Mtc 3	12 wks	12 wks	1377	5	0.4
Mtc 3	Mtc 4	12 wks	12 wks	1344	8	0.6
Mtc 4	Mtc 5	12 wks	12 wks	1296	4	0.3
Mtc 5	Mtc 6	12 wks	12 wks	1218	3	0.3
Mtc 6	Mtc 7	12 wks	12 wks	954	6	0.6
Mtc 7	Mtc 8	12 wks	12 wks	814	3	0.4
Mtc 8	Mtc 9	12 wks	12 wks	693	0	0
Mtc 9	Mtc 10	12 wks	12 wks	641	1	0.2
Mtc 10	Mtc 11	12 wks	12 wks	336	3	0.9
Mtc 11	Mtc 12	12 wks	12 wks	188	1	0.5

Mtc = Maintenance; Intens = Intensification

Summary

Descriptive statistics were used to detail the study population and to summarize when boys and girls completed protocol therapy (by cycle). Univariate and multivariate logistic regression analysis were utilized to examine the association between weight gain during two individual cycles of chemotherapy (Induction and Delayed Intensification I) and obesity at the end of ALL Maintenance therapy. The covariates for the logistic regression models (age, race, treatment arm, BMI z-score at beginning of therapy, and cycle of therapy completion) were pre-selected, prior to the analysis being performed, and were chosen based on prior research. Lastly, the percent change in kilograms for each patient was calculated through the use of a percentage conversion formula. The percentage of patients experiencing $\geq$ 20% increase in kilograms, in one cycle of therapy, was identified.

CHAPTER FIVE: DISCUSSION

Introduction

In this chapter the major findings from this research study are discussed. Justifications are provided regarding the rationale behind the selected study aims and the chosen methods for data analysis. Lastly, implications of the study findings are outlined along with potential directions for future research projects.

Findings

Study Aim 1

The primary aim of this study was to determine if weight change during ALL Induction therapy was associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of maintenance therapy. Weight change was measured by the difference in age and gender determined BMI z-scores at the beginning and end of Induction (the first four weeks of ALL therapy). Z-score measurements were selected for use in this research study as they have been determined to be more accurate than BMI percentiles when examining body fat percentages in children and adolescents and they are best when examining a population that includes a wide range of ages (Field et al., 2003). BMI z-scores are also more accurate than BMI percentile when comparing weights longitudinally (Must & Anderson, 2006).

The important and new finding from this study is that early weight gain (during the first four weeks of ALL therapy) can predict obesity at the end of therapy. This finding was found for both males and females. Rapid weight gain is often observed clinically during ALL Induction therapy and is most likely related to the glucocorticoids that are administered. For protocol 1961,

this entailed a 27 day course of Prednisone (60 mg/m^2 per day) during Induction, followed by a 10 day taper.

Although there are numerous other studies that describe weight gain during ALL therapy, as discussed in the review of literature, this is the first known study to demonstrate that weight gain during Induction is a predictor for later obesity. Studies, outside of oncology, have previously identified early medication related weight gain as a predictor of weight status later in therapy. For example, early weight gain with Risperidone use in children and adolescents (defined as greater than a 7% increase in body weight during the first two months of therapy) has been shown to be predictive of weight status at six months (Martin et al., 2000). Another study found that adolescents on depot medroxprogesterone acetate with early weight gain (defined as greater than a 5% weight increase in 6 months) was predictive of increased BMI percentile at 18 months (Bonny, Secic, & Cromer, 2011).

The exact mechanisms by which rapid weight gain predisposes to higher BMI status later in life are still unknown. In younger children, this finding may be related to adiposity rebound (Taylor et al., 2011). For older children and adolescents, the underlying mechanism for additional weight gain may be related to genetics or perhaps to systemic changes secondary to adipocyte cytokine production and systemic inflammation (Power, Miller, & Alpert, 2007).

Study Aim 2

A second aim for this study was to determine if weight change (measured by age and gender BMI z-score) during cycle 1 of Delayed Intensification ALL therapy was associated with obesity (BMI $\geq 95^{th}$ percentile for age and gender) at the end of Maintenance therapy. The Delayed Intensification cycle was selected because Dexamethasone was administered for 14

days during this course of therapy (10 mg/m^2 per day on days 0-6 and 14-20). Dexamethasone has been shown, in some studies, to be more strongly associated with weight gain than Prednisone (Ahmed et al., 2002; Van Dongen-Melman et al., 1995).

The hypothesis that weight gain during Delayed Intensification would be predictive of obesity at the end of Maintenance was not supported. Weight gain, secondary to glucocorticoids during Delayed Intensification, may have been offset by the treatment related toxicities (such as gastrointestinal toxicities) observed during Delayed Intensification.

Secondary Analysis

The secondary aim of this study was to determine the percent of children who experienced grade 3 weight toxicity (defined as $\geq$ 20% increase in kilograms in one cycle) by treatment phase (or cycle). An important finding was that excessive weight gain during ALL therapy occurs most frequently during Induction therapy. Of those experiencing $\geq$ 20% increase in weight during Induction, the majority (93%) were not obese at the beginning of therapy. This implies that the change in z-score, in study aim one, may be useful in predicting obesity in those that begin therapy outside of the obese category.

A surprising finding was that a total of 62 patients (3.9 %) experienced a Grade 3 weight toxicity during Induction. COG's final study summary report for protocol 1961 shows that only 17 of these weight toxicities during Induction were reported to COG. This suggests that changes in weight status were not consistently reported, perhaps because they were not viewed as a significant side effect of ALL therapy or perhaps due to the research associate not realizing that this information was requested for central reporting. The reliability of toxicity reporting by practitioners during chemotherapy and radiation therapy, in adult research trials, has previously

been questioned (Bentzen & Trotti, 2007). No literature could be located which discussed underreporting of weight statuses during childhood ALL therapy.

Implications

This is the first known study that identifies early weight gain during childhood ALL therapy as a predictor for obesity at the end of therapy. This finding is beneficial as obesity is known to be associated with poorer patient outcomes, decreased survival, following childhood ALL therapy (Butturini et al., 2007). Obesity has also been linked to increased treatment related toxicity in high risk ALL therapy in addition to decreased overall survival (Orgel, et al., 2011). Communicating the findings from this study to treating practitioners is important as modifying or preventing excessive weight gain may offer additional ways to potentially improve patient outcomes on ALL treatment protocols.

This finding is also beneficial as it only requires the examination of data (heights and weights) that is already routinely collected during therapy. Risk for obesity development may be monitored without additional procedures, lab tests or costs to the patient. The collected height and weight measurements, along with the patient's age and gender, can be entered into a free on line calculators (such as http://stokes.chop.edu/web/zscore/) for easy determination of BMI percentile scores and BMI z-scores. These numbers can then be tracked during therapy to quickly identify changes and weight trends. The calculation of change in BMI z-score during Induction therapy may offer an early indicator for risk of obesity development during therapy.

In addition, this study reinforces findings from previous studies which state that obesity at the beginning of therapy is a strong predictor of obesity at the end of therapy. Obesity that is present at the onset of therapy should be used to initiate early family intervention aimed at

assisting the child to normalize weight gain during therapy. Families should be counseled regarding obesity as a risk factor for worse survival outcomes with ALL treatment.

Family counseling regarding nutrition and physical activity during therapy should be initiated soon after diagnosis, when families might be motivated to promote healthy lifestyles. Some families, however, will be overwhelmed the few weeks of therapy due to the new diagnosis of childhood ALL and the prospect of years of treatment. Family education and support needs to continue throughout therapy in order to reach families when they are best able to process new information. This time frame may differ between families.

Lastly, COG has ceased the requirement for reporting of height and weight measurements during treatment on current ALL protocols. This change will not allow future large scale, retrospective studies related to weight status during treatment on therapeutic trials. Results of weight related studies, including the results from this study, should be shared with COG leadership so that inclusion of height and weight information may be considered in the required reporting for future clinical trials. Height and weight are already being obtained at the local treatment centers and would require minimal effort for data entry and central reporting.

Future Research

As with most research, the findings of one study often lead to multiple indications for future research projects. This study needs additional follow up regarding the patients who experienced $\geq$20% weight increase during Induction. For example, the age, race, gender and treatment arm for the 62 identified patients could be analyzed to see if trends can be identified and future examined.

Additional retrospective studies could be undertaken to verify the findings of this study. COG houses data from every ALL study that it has sponsored. Prospective studies examining the change in BMI z-score during Induction as a predictor for obesity at the end of therapy could be undertaken with newly diagnosed patients, but this approach would be less feasible as it would take years to determine the results. Additional studies are needed to examine early weight gain as a predictor for obesity in other ALL patient populations (such as those with average risk ALL). Research regarding early weight gain as a predictor for later obesity could also be explored in diseases outside of ALL, such as in Hodgkin's disease where glucocorticoids are also administered early in therapy.

Although it is important to be able to predict those most at risk for obesity at the end of therapy, it is essential to gain understanding about the underlying biology and the clinical consequences of the weight gain. Additional explorations of systemic changes with obesity are needed to examine how ALL survival outcomes are impacted by increased weight. Embedding a biological study within a COG ALL treatment trial could be considered as this approach would allow for the attainment of adequate sample sizes within an acceptable time frame. Further study is also warranted to gain knowledge regarding genetic polymorphisms that may be associated with obesity and also how gene expression may change within obese patients.

In addition, future research needs to move beyond understanding the issue, to intervening to change the outcome. More research is needed on interventions directed towards prevention of obesity development and obesity reduction (for those children who are obese at diagnosis). Studies utilizing pharmaceutical products to address obesity may also be considered for those patients who begin therapy obese.

In the childhood ALL setting, the majority of research studies regarding physical activity have taken place near the end of therapy or post therapy (Winter, Muller, Hoffmann, Boos, & Rosenbaum, 2010). One pilot study was located that combined a nutrition and exercise intervention during the maintenance phase of standard risk childhood ALL therapy (Moyer-Mileur, Ransdell, & Bruggers, 2009). Additional research is needed regarding what type of education works best with families as well as additional interventional research aimed at promoting healthy diet and activity. Lastly, research needs to be undertaken to determine if obesity prevention through diet and physical activity, are beneficial in significantly improving treatment related outcomes.

Study Limitations

This study is primarily limited by virtue of being a retrospective data analysis. The inherent limitation with these types of studies is that not all confounding variables can be controlled for, which may weaken internal validity. In this study, the diets and physical activity habits of the child were not captured during therapy. These items may have had an influence on the child's weight gain during therapy. Additionally, the data collection forms used for this study were completed at the end of each cycle of therapy. Personnel responsible for completing these forms were instructed that reported heights and weights should be from the beginning of the cycle of therapy. As a retrospective study, there is no means available to verify that the correct heights and weights were entered or that they were entered from the appropriate time points.

COG collected the height and weight information used in this study, throughout therapy, at the beginning of each new cycle of chemotherapy. This practice limited this study to only having available data up until the patients' final cycle of chemotherapy. There was no true end of

therapy BMI information collected and no reported BMI information during the follow up (post chemotherapy treatment) time period.

Another limitation of this study is analyzing data from only one COG treatment trial which focused on higher risk ALL patients. The findings may not be generalized to standard risk ALL patients. Likewise, the findings may not be applicable to patients treated on other high risk ALL protocols which utilized a different backbone of chemotherapy.

Conclusion

Obesity is a health problem that is common within children treated for ALL (Oeffinger et al., 2003). Within this study, obesity was present in 23% of childhood leukemia patients by the end of therapy while an additional 20% ended therapy overweight. Although prevalent, obesity has not attracted urgent attention in the ALL research community perhaps due to more immediate concerns during cancer therapy such as life threatening toxicities secondary to treatment. Results of studies, such as this, need to be shared with the oncology community so that practitioners may begin to see the benefit of preventing obesity development during ALL therapy.

Most researchers agree that prevention is the best form of treatment for obesity as it is difficult to cure once it is present. This current study offers a new way of monitoring weight trends early in therapy. Identified changes in BMI z-scores during Induction therapy can now be used to guide healthcare practitioners in identifying which patients are most at risk. This finding will not add time or cost to patient care, but may aide in reducing long term healthcare expenses, morbidity and mortality associated with obesity.

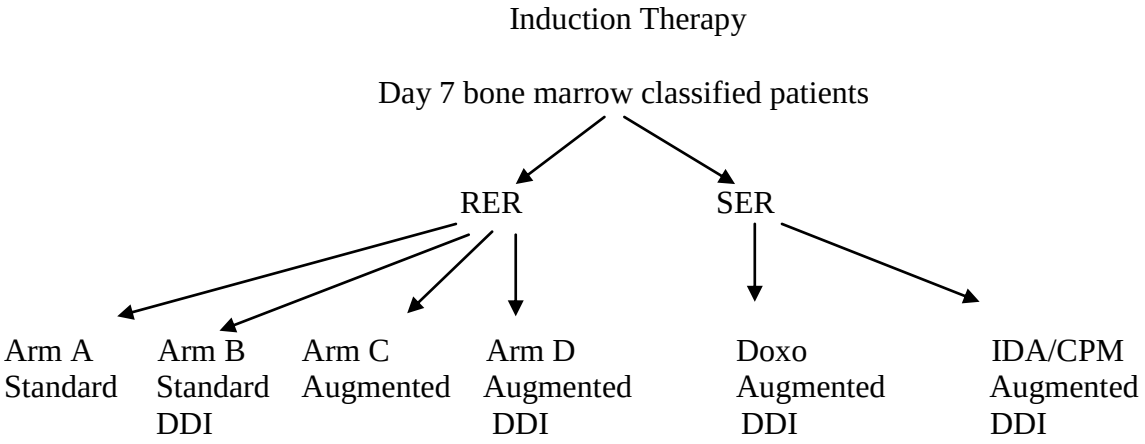
APPENDIX A

ABBREVIATION LIST

ACTH	Adrenocortiocotropin Hormone
ALL	Acute Lymphoblastic Leukemia
BFM	Berlin-Frankfurt-Munster
BMI	Body Mass Index
CDC	Centers for Disease Control
COG	Children's Oncology Group
CPM	Cyclophosphamide
DI	Delayed Intensification
DDI	Double Delayed Intensification
DOXO	Doxorubicin
HPA	Hypothalamic-Pituitary Adrenal
IDA	Idarubicin
NCHS	National Center for Health and Statistics
NINR	National Institute for Nursing Research
RER	Rapid Early Responders
OR	Odds Ratio
SER	Slow Early Responders
WBC	While Blood Cells

APPENDIX B

PROTOCOL 1961 SCHEMA



RER = Rapid Early Responder

SER = Slow Early Responder

Standard = Standard chemotherapy

Augmented = Augmented or intensified chemotherapy

DDI = Double delayed intensification

DOXO = Doxorubicin

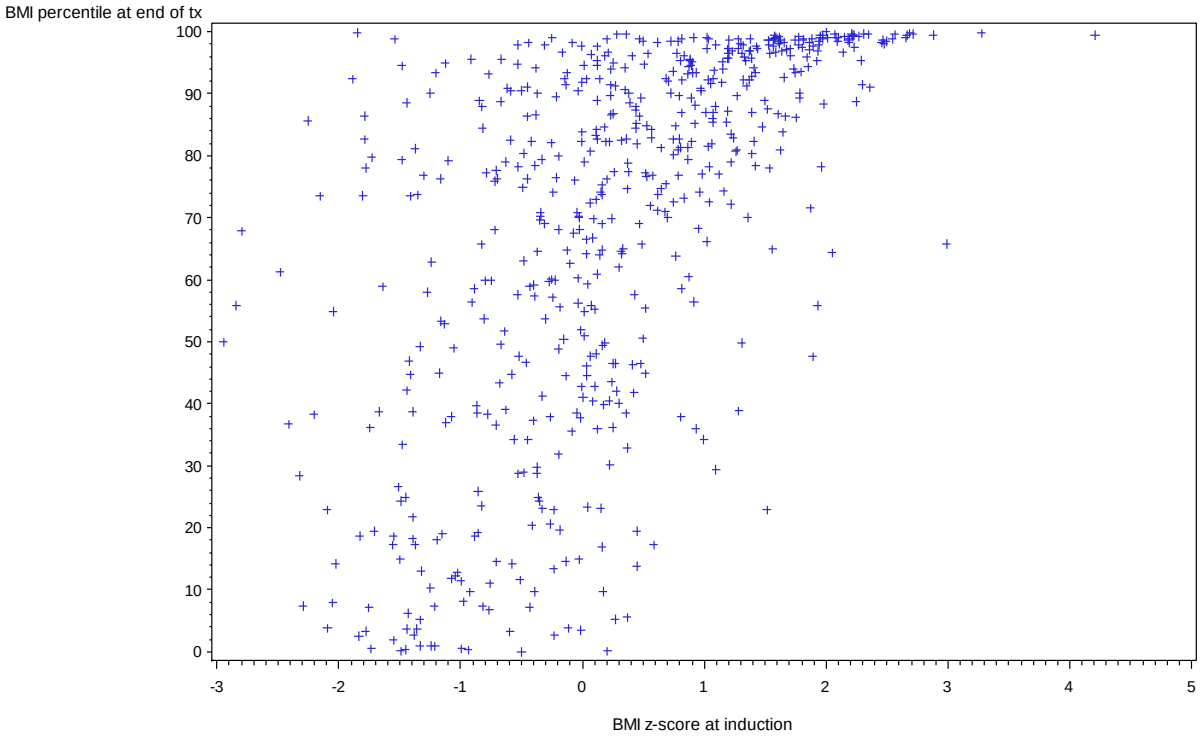
IDA = Idarubicin

CPM = Cyclophosphamide

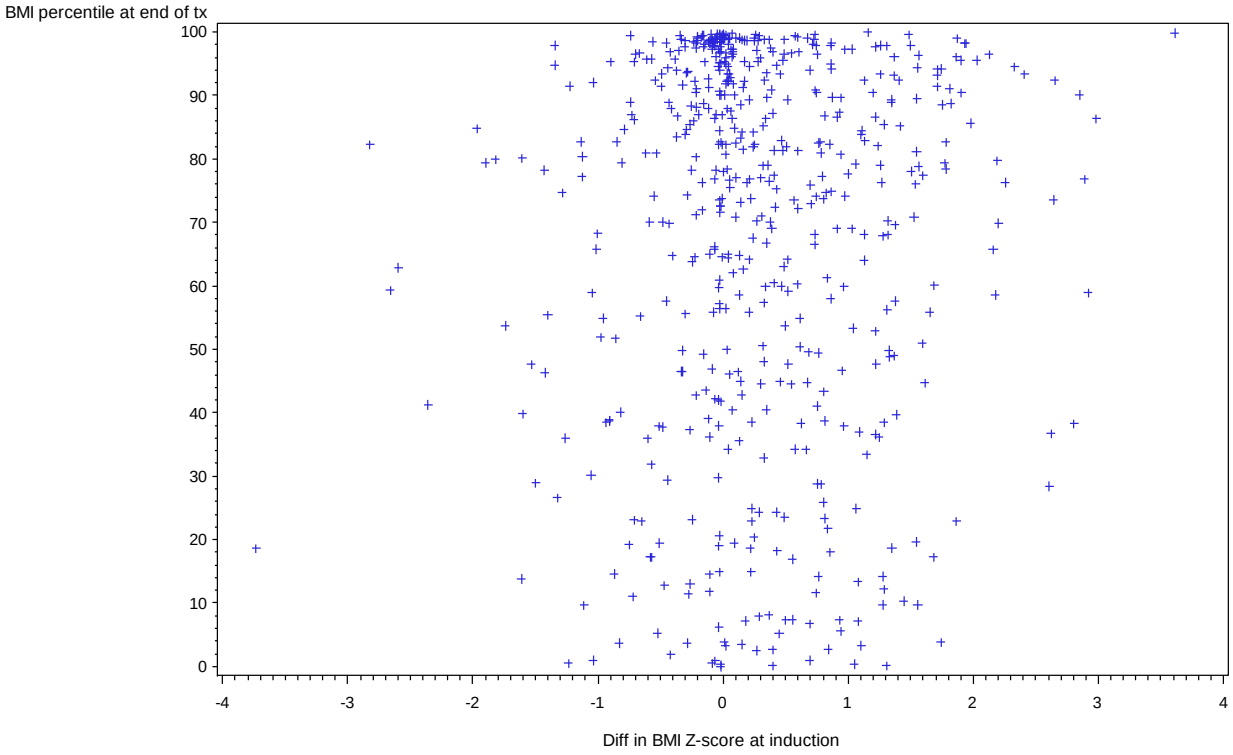
APPENDIX C

SCATTER PLOTS FOR MULTIVARIANT ANALYSES

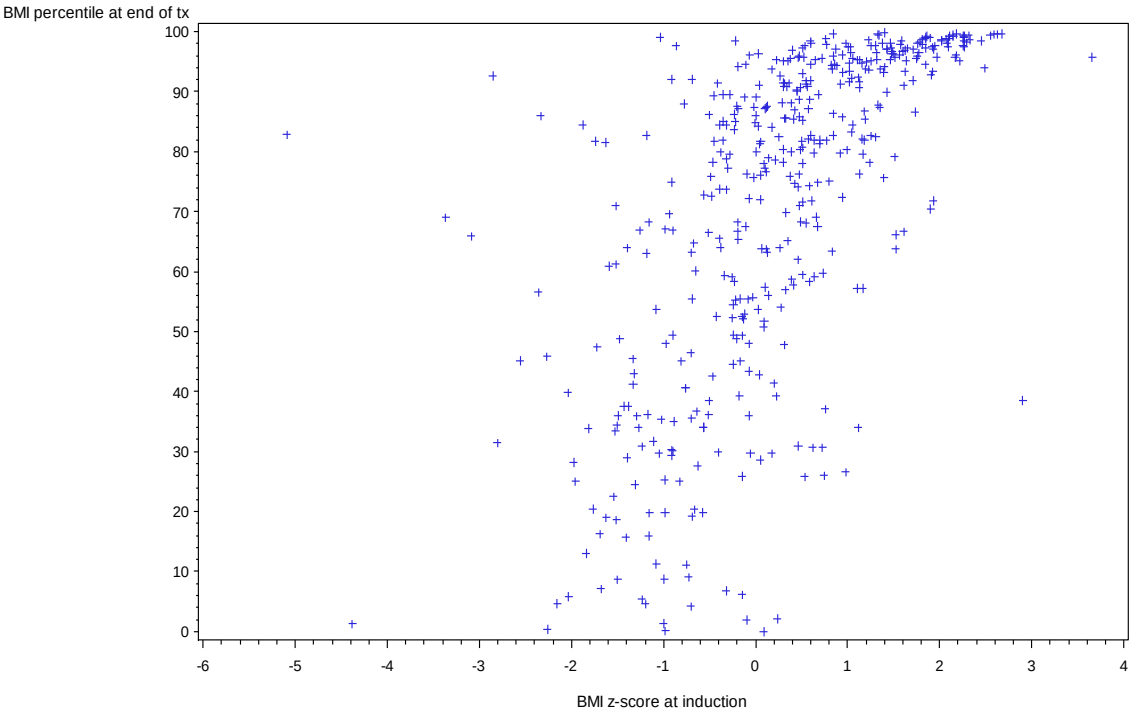
BMI Percentile in Males with z-score at Induction



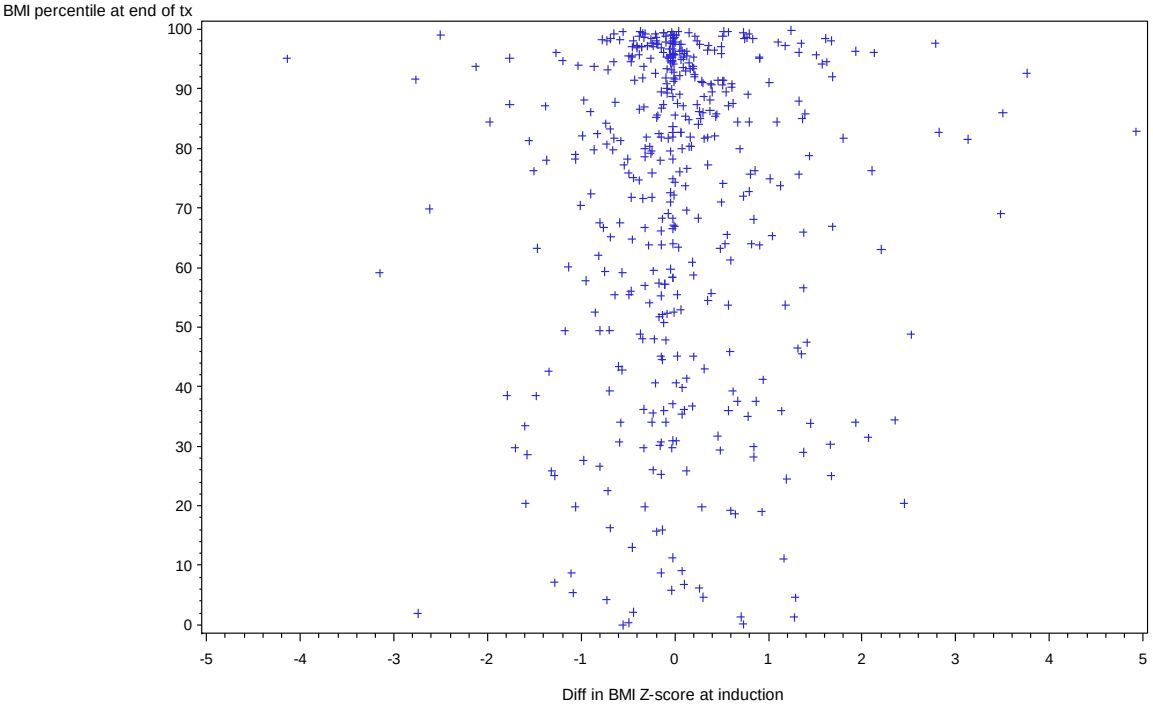
BMI Percentile in Males with Change in z-score during Induction



BMI Percentile in Females with z-score at Induction



BMI Percentile in Females with Change in z-score during Induction



APPENDIX D

IRB REVIEW LETTER

THE UNIVERSITY OF ARIZONA.

Human Subjects
Protection Program

1618 E. Helen St.
P.O. Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://orcr.vpr.arizona.edu/irb

HSPP Correspondence Form

Date: 08/29/11
Investigator: Janice S. Withycombe, RN, MN, CCRP **Department:** Nursing
Project No./Title: 11-0617 Treatment Related Obesity in Childhood Acute Lymphoblastic Leukemia
Current Period of Approval: NA
Submit the "FORM: Continuing Review Progress Report" no later than 45 days prior to the end of the approval period listed above.

IRB Committee Information

Administrative Action **Administrative Review – New Submission**
FWA Number: FWA00004218

Documents Reviewed Concurrently

F200: Application for Human Research (received 08/12/11)
VOTF (version 08/11/11)
AZCC Scientific Review Committee Outcome Report (dated 08/11/11)
American Cancer Society Grant Application

Determination

- **Not Human Subjects Research as defined by 45 CFR 46.102(f):** As presented, the activities described above do not meet the definition of research involving human subjects as cited in the regulations issued by the U.S. Department of Health and Human Services which state that "human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, *or* identifiable private information."

Regulatory Determination(s)

☒ Not Applicable

Sheryl Wurl, PhD
Director, Human Subjects Protection Program
UA Institutional Review Board

08/29/11
Date

SW/md
cc: Scientific/Scholarly Reviewer

Reminder: **No changes to a project may be made prior to IRB approval except to eliminate apparent immediate hazard to subjects.**

REFERENCES

Aday, L. (2001). At *Risk in America: The Health and Health Care Needs of Vulnerable Populations in the United States* (2nd ed.). San Francisco: Jossey-Bass, Inc.

Ahmed, S. F., Tucker, P., Mushtaq, T., Wallace, A. M., Williams, D. M., & Hughes, I. A. (2002). Short-term effects on linear growth and bone turnover in children randomized to receive prednisolone or dexamethasone. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Clinical Endocrinology, 57*(2), 185-191.

Ammerman, A. S., Lindquist, C. H., Lohr, K. N., & Hersey, J. (2002). The efficacy of behavioral interventions to modify dietary fat and fruit and vegetable intake: a review of the evidence. *Preventive Medicine, 35*(1), 25-41. doi: S0091743502910285 [pii]

Asner, S., Ammann, R. A., Ozsahin, H., Beck-Popovic, M., & von der Weid, N. X. (2008). Obesity in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer, 51*(1), 118-122. doi: 10.1002/pbc.21496

Baillargeon, J., Langevin, A. M., Lewis, M., Estrada, J., Mullins, J., Pitney, A., . . . Pollock, B. H. (2006). Obesity and survival in a cohort of predominantly Hispanic children with acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology, 28*(9), 575-578. doi: 10.1097/01.mph.0000212985.33941.d8 00043426-200609000-00006 [pii]

Becker, S., Dossus, L., & Kaaks, R. (2009). Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. *Archives of Physiology and Biochemistry, 115*(2), 86-96. doi: 10.1080/13813450902878054

Bentzen, S. M., & Trotti, A. (2007). Evaluation of early and late toxicities in chemoradiation trials. [Review]. *Journal of Clinical Oncology, 25*(26), 4096-4103. doi: 10.1200/JCO.2007.13.3983

Bonny, A. E., Secic, M., & Cromer, B. (2011). Early weight gain related to later weight gain in adolescents on depot medroxyprogesterone acetate. [Comparative Study Research Support, N.I.H., Extramural]. *Obstetrics and Gynecology, 117*(4), 793-797. doi: 10.1097/AOG.0b013e31820f387c

Butturini, A. M., Dorey, F. J., Lange, B. J., Henry, D. W., Gaynon, P. S., Fu, C., . . . Carroll, W. L. (2007). Obesity and outcome in pediatric acute lymphoblastic leukemia. *Journal of Clinical Oncology, 25*(15), 2063-2069. doi: 25/15/2063 [pii] 10.1200/JCO.2006.07.7792

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine, 348*(17), 1625-1638. doi: 10.1056/NEJMoa021423 348/17/1625 [pii]

Centers for Disease Control and Prevention (September 13, 2011). Healthy Weight – it's not a diet, it's a lifestyle: About BMI for Children and teens. Retrieved on February 11, 2012, from http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

Centers for Disease Control and Prevention. (2011). Obesity and overweight. Retrieved on February 2, 2012, from http://www.cdc.gov/obesity/childhood/data.html

Chen, X., Lu, W., Zheng, W., Gu, K., Chen, Z., Zheng, Y., & Shu, X. O. (2010). Obesity and weight change in relation to breast cancer survival. *Breast Cancer Research and Treatment, 122*(3), 823-833. doi: 10.1007/s10549-009-0708-3

Chow, E. J., Pihoker, C., Hunt, K., Wilkinson, K., & Friedman, D. L. (2007). Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. *Cancer, 110*(10), 2313-2320. doi: 10.1002/cncr.23050

Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. *British Medical Journal, 320*(7244), 1240-1243.

Collins, L., Zarzabal, L. A., Nayiager, T., Pollock, B. H., & Barr, R. D. (2010). Growth in children with acute lymphoblastic leukemia during treatment. *Journal of Pediatric Hematology/Oncology, 32*(8), e304-307. doi: 10.1097/MPH.0b013e3181ece2bb

Children's Oncology Group. (n.d.) The world's childhood cancer experts. Retrieved on April 10, 2012, from http://www.childrensoncologygroup.org/

Davies, J. H., Evans, B. A., Jones, E., Evans, W. D., Jenney, M. E., & Gregory, J. W. (2004). Osteopenia, excess adiposity and hyperleptinaemia during 2 years of treatment for childhood acute lymphoblastic leukaemia without cranial irradiation. *Clinical Endocrinology, 60*(3), 358-365. doi: 1986 [pii]

Dehghan, M., Akhtar-Danesh, N., & Merchant, A. T. (2005). Childhood obesity, prevalence and prevention. *Nutr J, 4*, 24. doi: 1475-2891-4-24 [pii] 10.1186/1475-2891-4-24

Department of Health and Human Services (n.d.) Body mass index: considerations for practitioners. Retrieved on April 10, 2012, from http://www.cdc.gov/obesity/downloads/BMIforPactitioners.pdf

Esbenshade, A. J., Simmons, J. H., Koyama, T., Koehler, E., Whitlock, J. A., & Friedman, D. L. (2011). Body mass index and blood pressure changes over the course of treatment of pediatric acute lymphoblastic leukemia. *Pediatric Blood & Cancer, 56*(3), 372-378. doi: 10.1002/pbc.22782

Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. Retrieved on January 21, 2012 from http://seer.cancer.gov/faststats

Fawcett, J. (2005). *Contemporary nursing knowledge: Analysis and evaluation of nursing models and theories*. Philadelphia: F. A. Davis Company.

Field, A. E., Laird, N., Steinberg, E., Fallon, E., Semega-Janneh, M., & Yanovski, J. A. (2003). Which metric of relative weight best captures body fatness in children? [Research Support, U.S. Gov't, P.H.S.]. *Obesity Research, 11*(11), 1345-1352. doi: 10.1038/oby.2003.182

Finken, M. J., Meulenbelt, I., Dekker, F. W., Frolich, M., Walther, F. J., Romijn, J. A., . . . Wit, J. M. (2011). Abdominal fat accumulation in adults born preterm exposed antenatally to maternal glucocorticoid treatment is dependent on glucocorticoid receptor gene variation. *Journal of Clinical Endocrinology and Metabolism, 96*(10), E1650-1655. doi: jc.2011-0288 [pii] 10.1210/jc.2011-0288

Flaskerud, J. H., & Winslow, B. J. (1998). Conceptualizing vulnerable populations health-related research. *Nursing Research, 47*(2), 69-78.

Florin, T. A., Fryer, G. E., Miyoshi, T., Weitzman, M., Mertens, A. C., Hudson, M. M., . . . Oeffinger, K. C. (2007). Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. *Cancer Epidemiology, Biomarkers and Prevention, 16*(7), 1356-1363. doi: 16/7/1356 [pii] 10.1158/1055-9965.EPI-07-0048

Gelelete, C. B., Pereira, S. H., Azevedo, A. M., Thiago, L. S., Mundim, M., Land, M. G., & Costa, E. S. (2011). Overweight as a prognostic factor in children with acute lymphoblastic leukemia. *Obesity (Silver Spring), 19*(9), 1908-1911. doi: oby2011195 [pii] 10.1038/oby.2011.195

Gofman, I., & Ducore, J. (2009). Risk factors for the development of obesity in children surviving ALL and NHL. *Journal of Pediatric Hematology Oncology, 31*(2), 101-107. doi: 10.1097/MPH.0b013e31818c0120 00043426-200902000-00005 [pii]

Green, D. M., Cox, C. L., Zhu, L., Krull, K. R., Srivastava, D. K., Stovall, M., . . . Robison, L. L. (2012). Risk factors for obesity in adult survivors of childhood cancer: a report from the childhood cancer survivor study. *Journal of Clinical Oncology, 30*(3), 246-255. doi: JCO.2010.34.4267 [pii] 10.1200/JCO.2010.34.4267

Groot-Loonen, J. J., Otten, B. J., van't Hof, M. A., Lippens, R. J., & Stoelinga, G. B. (1996). Influence of treatment modalities on body weight in acute lymphoblastic leukemia. *Medical and Pediatric Oncology, 27*(2), 92-97. doi: 10.1002/(SICI)1096-911X(199608)27:2<92::AID-MPO5>3.0.CO;2-O [pii]

Haddy, T. B., Mosher, R. B., & Reaman, G. H. (2009). Late effects in long-term survivors after treatment for childhood acute leukemia. *Clinical Pediatrics, 48*(6), 601-608. doi: 0009922809332680 [pii] 10.1177/0009922809332680

Hinds, P. S., Hockenberry, M. J., Gattuso, J. S., Srivastava, D. K., Tong, X., Jones, H., . . . Pui, C. H. (2007). Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer, 110*(10), 2321-2330. doi: 10.1002/cncr.23039

Hjalgrim, L. L., Rostgaard, K., Hjalgrim, H., Westergaard, T., Thomassen, H., Forestier, E., . . . Schmiegelow, K. (2004). Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. *Journal of the National Cancer Institute, 96*(20), 1549-1556. doi: 96/20/1549 [pii] 10.1093/jnci/djh287

Hjalgrim, L. L., Westergaard, T., Rostgaard, K., Schmiegelow, K., Melbye, M., Hjalgrim, H., & Engels, E. A. (2003). Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. *American Journal of Epidemiology, 158*(8), 724-735.

Hosmer, D. W. & Lemeshow, S. (2002). *Applied logistic regression (2nd ed.).* Hoboken, NY: John Wiley & Sons, Inc.

Huscher, D., Thiele, K., Gromnica-Ihle, E., Hein, G., Demary, W., Dreher, R., . . . Buttgereit, F. (2009). Dose-related patterns of glucocorticoid-induced side effects. [Multicenter Study Research Support, Non-U.S. Gov't]. *Annals of the Rheumatic Diseases, 68*(7), 1119-1124. doi: 10.1136/ard.2008.092163

Janiszewski, P. M., Oeffinger, K. C., Church, T. S., Dunn, A. L., Eshelman, D. A., Victor, R. G., . . . Ross, R. (2007). Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. *The Journal of Clinical Endocrinology and Metabolism, 92*(10), 3816-3821. doi: jc.2006-2178 [pii] 10.1210/jc.2006-2178

Jarfelt, M., Lannering, B., Bosaeus, I., Johannsson, G., & Bjarnason, R. (2005). Body composition in young adult survivors of childhood acute lymphoblastic leukaemia. *European Journal of Endocrinology / European Federation of Endocrine Societies, 153*(1), 81-89. doi: 153/1/81 [pii] 10.1530/eje.1.01931

Keats, M. R., Culos-Reed, S. N., Courneya, K. S., & McBride, M. (2006). An examination of physical activity behaviors in a sample of adolescent cancer survivors. *Journal of Pediatric Oncology Nursing, 23*(3), 135-142. doi: 23/3/135 [pii] 10.1177/1043454206287304

Kersey, J. H. (1997). Fifty years of studies of the biology and therapy of childhood leukemia. *Blood, 90*(11), 4243-4251.

Kohler, J. A., Moon, R. J., Wright, S., Willows, E., & Davies, J. H. (2011). Increased adiposity and altered adipocyte function in female survivors of childhood acute lymphoblastic leukaemia treated without cranial radiation. *Hormone Research in Paediatrics, 75*(6), 433-440. doi: 000324412 [pii] 10.1159/000324412

Lange, B. J., Gerbing, R. B., Feusner, J., Skolnik, J., Sacks, N., Smith, F. O., & Alonzo, T. A. (2005). Mortality in overweight and underweight children with acute myeloid leukemia. *Journal of the American Medical Association, 293*(2), 203-211. doi: 293/2/203 [pii] 10.1001/jama.293.2.203

Larsson, S. C., & Wolk, A. (2008). Overweight and obesity and incidence of leukemia: a meta-analysis of cohort studies. *International Journal of Cancer, 122*(6), 1418-1421. doi: 10.1002/ijc.23176

Lichtman, M. A. (2010). Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. *The Oncologist, 15*(10), 1083-1101. doi: theoncologist.2010-0206 [pii] 10.1634/theoncologist.2010-0206

Martin, A., Landau, J., Leebens, P., Ulizio, K., Cicchetti, D., Scahill, L., & Leckman, J. F. (2000). Risperidone-associated weight gain in children and adolescents: a retrospective chart review. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Child and Adolescent Psychopharmacology, 10*(4), 259-268.

Mayer, E. I., Reuter, M., Dopfer, R. E., & Ranke, M. B. (2000). Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic leukemia during childhood. *Hormone Research, 53*(4), 193-199. doi: 23566 [pii]

Mody, R., Li, S., Dover, D. C., Sallan, S., Leisenring, W., Oeffinger, K. C., . . . Neglia, J. P. (2008). Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood, 111*(12), 5515-5523. doi: blood-2007-10-117150 [pii] 10.1182/blood-2007-10-117150

Moyer-Mileur, L. J., Ransdell, L., & Bruggers, C. S. (2009). Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy: response to a home-based exercise and nutrition program. *Journal of Pediatric Hematology/Oncology, 31*(4), 259-266. doi: 10.1097/MPH.0b013e3181978fd4 00043426-200904000-00005 [pii]

Must, A., & Anderson, S. E. (2006). Body mass index in children and adolescents: considerations for population-based applications. [Review]. *International Journal of Obesity (Lond), 30*(4), 590-594. doi: 10.1038/sj.ijo.0803300

Nandagopal, R., Laverdiere, C., Mulrooney, D., Hudson, M. M., & Meacham, L. (2008). Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Hormone Research, 69*(2), 65-74. doi: 000111809 [pii] 10.1159/000111809

Nathan, P. C., Wasilewski-Masker, K., & Janzen, L. A. (2009). Long-term outcomes in survivors of childhood acute lymphoblastic leukemia. *Hematology/Oncology Clinics of North America, 23*(5), 1065-1082, vi-vii. doi: S0889-8588(09)00144-0 [pii] 10.1016/j.hoc.2009.07.003

National Cancer Institute (2011). SEER Cancer Statistics Review for Leukemia 1975-2008. Retrieved on March 20, 2012, from http://seer.cancer.gov/csr/1975_2008/results_merged/sect_13_leukemia.pdf

National Institute of Nursing Research (2011). Bringing science to life: NINR strategic plan. Retrieved on April 10, 2012, from http://www.ninr.nih.gov/NR/rdonlyres/8BE21801-0C52-44C2-9EEA-142483657FB1/0/NINR_StratPlan_F2_508.pdf

Nieuwenhuizen, A. G., & Rutters, F. (2008). The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. *Physiology and Behavior, 94*(2), 169-177. doi: S0031-9384(07)00504-5 [pii] 10.1016/j.physbeh.2007.12.011

Niinimaki, R. A., Harila-Saari, A. H., Jartti, A. E., Seuri, R. M., Riikonen, P. V., Paakko, E. L., . . . Lanning, M. (2007). High body mass index increases the risk for osteonecrosis in children with acute lymphoblastic leukemia. *Journal of Clinical Oncology, 25*(12), 1498-1504. doi: 25/12/1498 [pii] 10.1200/JCO.2006.06.2539

Odame, I., Reilly, J. J., Gibson, B. E., & Donaldson, M. D. (1994). Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. *Archives of Disease in Childhood, 71*(2), 147-149.

Oeffinger, K. C., Mertens, A. C., Sklar, C. A., Yasui, Y., Fears, T., Stovall, M., . . . Robison, L. L. (2003). Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 21*(7), 1359-1365.

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2012). Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. [Comparative Study]. *Journal of the American Medical Association, 307*(5), 483-490. doi: 10.1001/jama.2012.40

Ogden, C. L., & Flegal, K. M. (2010). Changes in terminology for childhood overweight and obesity. *National Health Statistics Report*(25), 1-5.

Orgel, E., Sposto, R., Malvar, J., Seibel, N., Ladas, E., Gaynon, P., and Freyer, D. (2011). Extremes of weight are associated with increased treatment related toxicity in high risk acute lymphoblastic leukemia: A report from the Children's Oncology Group. Abstract presented at The American Society of Hematology, San Diego, CA.

Panosyan, E. H., Seibel, N. L., Martin-Aragon, S., Gaynon, P. S., Avramis, I. A., Sather, H., . . . Children's Cancer Group Study, C. C. G. (2004). Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Journal of Pediatric Hematology/Oncology, 26*(4), 217-226.

Power, C., Miller, S. K., & Alpert, P. T. (2007). Promising new causal explanations for obesity and obesity-related diseases. [Review]. *Biological Research for Nursing, 8*(3), 223-233. doi: 10.1177/1099800406292674

Pulte, D., Gondos, A., & Brenner, H. (2008). Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies in the United States, 1990-2004. *Journal of the National Cancer Institute, 100*(18), 1301-1309. doi: djn276 [pii] 10.1093/jnci/djn276

Raber, J. (1998). Detrimental effects of chronic hypothalamic-pituitary-adrenal axis activation. From obesity to memory deficits. *Molecular Neurobiology, 18*(1), 1-22. doi: 10.1007/BF02741457

Razzouk, B. I., Rose, S. R., Hongeng, S., Wallace, D., Smeltzer, M. P., Zacher, M., . . . Hudson, M. M. (2007). Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. *Journal of Clinical Oncology, 25*(10), 1183-1189. doi: 25/10/1183 [pii] 10.1200/JCO.2006.07.8709

Reaman, G. H. (1998). Drug development and chemotherapy in acute lymphoblastic leukemia: of mice to men. *Cancer, 83*(9), 1885-1888. doi: 10.1002/(SICI)1097-0142(19981101)83:9<1885::AID-CNCR1>3.0.CO;2-Z [pii]

Reilly, J. J., Brougham, M., Montgomery, C., Richardson, F., Kelly, A., & Gibson, B. E. (2001). Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. *Journal of Clinical Endocrinology and Metabolism, 86*(8), 3742-3745.

Reilly, J. J., Kelly, A., Ness, P., Dorosty, A. R., Wallace, W. H., Gibson, B. E., & Emmett, P. M. (2001). Premature adiposity rebound in children treated for acute lymphoblastic leukemia. *Journal of Clinical Endocrinology and Metabolism, 86*(6), 2775-2778.

Reilly, J. J., Methven, E., McDowell, Z. C., Hacking, B., Alexander, D., Stewart, L., & Kelnar, C. J. (2003). Health consequences of obesity. *Archives of Disease in Childhood, 88*(9), 748-752.

Renehan, A. G., Tyson, M., Egger, M., Heller, R. F., & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet, 371*(9612), 569-578. doi: S0140-6736(08)60269-X [pii] 10.1016/S0140-6736(08)60269-X

Rogers, P. C., Meacham, L. R., Oeffinger, K. C., Henry, D. W., & Lange, B. J. (2005). Obesity in pediatric oncology. *Pediatr Blood Cancer, 45*(7), 881-891. doi: 10.1002/pbc.20451

Rolland-Cachera, M. F., Deheeger, M., Bellisle, F., Sempe, M., Guilloud-Bataille, M., & Patois, E. (1984). Adiposity rebound in children: a simple indicator for predicting obesity. *American Journal of Clinical Nutrition, 39*(1), 129-135.

Ross, J. A., Oeffinger, K. C., Davies, S. M., Mertens, A. C., Langer, E. K., Kiffmeyer, W. R., . . . Robison, L. L. (2004). Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 22*(17), 3558-3562. doi: 10.1200/JCO.2004.11.152 22/17/3558 [pii]

SAS Institute, Inc. (2004). *SAS/STAT 9.1 User's Guide*. Cary, NC: SAS Institute, Inc.

Sainsbury, C. P., Newcombe, R. G., & Hughes, I. A. (1985). Weight gain and height velocity during prolonged first remission from acute lymphoblastic leukaemia. *Archives of Disease in Childhood, 60*(9), 832-836.

Schell, M. J., Ochs, J. J., Schriock, E. A., & Carter, M. (1992). A method of predicting adult height and obesity in long-term survivors of childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology, 10*(1), 128-133.

Seibel, N. L., Steinherz, P. G., Sather, H. N., Nachman, J. B., Delaat, C., Ettinger, L. J., . . . Gaynon, P. S. (2008). Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. [Randomized Controlled Trial Research Support, N.I.H., Extramural]. *Blood, 111*(5), 2548-2555. doi: 10.1182/blood-2007-02-070342

Shaw, M. P., Bath, L. E., Duff, J., Kelnar, C. J., & Wallace, W. H. (2000). Obesity in leukemia survivors: the familial contribution. *Pediatric Hematology and Oncology, 17*(3), 231-237. doi: 10.1080/088800100276406 P283CY1YB6FYAU6H [pii]

Sherwood, L. (2007). *Human Physiology: From Cells to Systems* (6th ed). Pacific Grove: Brooks/Cole, Thompson Learning.

Sklar, C. A., Mertens, A. C., Walter, A., Mitchell, D., Nesbit, M. E., O'Leary, M., . . . Robison, L. L. (2000). Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. *Medical and Pediatric Oncology, 35*(2), 91-95. doi: 10.1002/1096-911X(200008)35:2<91::AID-MPO1>3.0.CO;2-G [pii]

Skoczen, S., Tomasik, P. J., Bik-Multanowski, M., Surmiak, M., Balwierz, W., Pietrzyk, J. J., . . . Strojny, W. (2011). Plasma levels of leptin and soluble leptin receptor and polymorphisms of leptin gene -18G > A and leptin receptor genes K109R and Q223R, in survivors of childhood acute lymphoblastic leukemia. *Journal of Experimental and Clinical Cancer Research, 30*, 64. doi: 1756-9966-30-64 [pii] 10.1186/1756-9966-30-64

Straathof, C. S., Overweg-Plandsoen, W. C., van den Burg, G. J., van der Kooi, A. J., Verschuuren, J. J., & de Groot, I. J. (2009). Prednisone 10 days on/10 days off in patients with Duchenne muscular dystrophy. *Journal of Neurology, 256*(5), 768-773. doi: 10.1007/s00415-009-5012-y

Sylvester, F. A., Leopold, S., Lincoln, M., Hyams, J. S., Griffiths, A. M., & Lerer, T. (2009). A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Clinical Gastroenterology and Hepatology, 7*(4), 452-455. doi: 10.1016/j.cgh.2008.12.017

Taheri, S. (2006). The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Archives of Disease in Childhood, 91*(11), 881-884. doi: 91/11/881 [pii] 10.1136/adc.2005.093013

Taylor, R. W., Williams, S. M., Carter, P. J., Goulding, A., Gerrard, D. F., & Taylor, B. J. (2011). Changes in fat mass and fat-free mass during the adiposity rebound: FLAME study. [Research Support, Non-U.S. Gov't]. *International Journal of Pediatric Obesity, 6*(2-2), e243-251. doi: 10.3109/17477166.2010.549488

Telama, R., Yang, X., Viikari, J., Valimaki, I., Wanne, O., & Raitakari, O. (2005). Physical activity from childhood to adulthood: a 21-year tracking study. *American Journal of Preventive Medicine, 28*(3), 267-273. doi: S0749-3797(04)00339-3 [pii] 10.1016/j.amepre.2004.12.003

Tonorezos, E. S., Vega, G. L., Sklar, C. A., Chou, J. F., Moskowitz, C. S., Mo, Q., . . . Oeffinger, K. C. (2012). Adipokines, body fatness, and insulin resistance among survivors of childhood leukemia. *Pediatric Blood & Cancer, 58*(1), 31-36. doi: 10.1002/pbc.22964

Trayhurn, P., & Wood, I. S. (2005). Signalling role of adipose tissue: adipokines and inflammation in obesity. *Biochemical Society Transactions, 33*(Pt 5), 1078-1081. doi: BST20051078 [pii] 10.1042/BST20051078

United States Department of Health and Human Services. (2012). Healthy People 2020. Retrieved on February 2, 2012, from www.healthypeople.gov

van Brussel, M., Takken, T., Lucia, A., van der Net, J., & Helders, P. J. (2005). Is physical fitness decreased in survivors of childhood leukemia? A systematic review. *Leukemia, 19*(1), 13-17. doi: 2403547 [pii] 10.1038/sj.leu.2403547

Van Dongen-Melman, J. E., Hokken-Koelega, A. C., Hahlen, K., De Groot, A., Tromp, C. G., & Egeler, R. M. (1995). Obesity after successful treatment of acute lymphoblastic leukemia in childhood. *Pediatric Research, 38*(1), 86-90.

van Rossum, E. F., & Lamberts, S. W. (2004). Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Progress in Hormone Research, 59*, 333-357.

Voorhoeve, P. G., van den Akker, E. L., van Rossum, E. F., Koper, J. W., van Mechelen, W., Lamberts, S. W., & Delemarre-van de Waal, H. A. (2009). Glucocorticoid receptor gene variant is associated with increased body fatness in youngsters. *Clinical Endocrinology, 71*(4), 518-523. doi: CEN3538 [pii] 10.1111/j.1365-2265.2009.03538.x

Wang, Y. C., McPherson, K., Marsh, T., Gortmaker, S. L., & Brown, M. (2011). Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet, 378*(9793), 815-825. doi: S0140-6736(11)60814-3 [pii] 10.1016/S0140-6736(11)60814-3

Winter, C., Muller, C., Hoffmann, C., Boos, J., & Rosenbaum, D. (2010). Physical activity and childhood cancer. [Review]. *Pediatric Blood & Cancer, 54*(4), 501-510. doi: 10.1002/pbc.22271

Withycombe, J. S., Post-White, J. E., Meza, J. L., Hawks, R. G., Smith, L. M., Sacks, N., & Seibel, N. L. (2009). Weight patterns in children with higher risk ALL: A report from the Children's Oncology Group (COG) for CCG 1961. *Pediatric Blood & Cancer, 53*(7), 1249-1254. doi: 10.1002/pbc.22237

Zee, P., & Chen, C. H. (1986). Prevalence of obesity in children after therapy for acute lymphoblastic leukemia. *American Journal of Pediatric Hematology/Oncology, 8*(4), 294-299.

Zhou, J., & Cidlowski, J. A. (2005). The human glucocorticoid receptor: one gene, multiple proteins and diverse responses. *Steroids*, *70*(5-7), 407-417. doi: S0039-128X(05)00037-1 [pii] 10.1016/j.steroids.2005.02.006