# Cardiovascular Risk and Insulin Resistance in Childhood Cancer Survivors

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**Objective** Increased cardiovascular (CV) risk has been reported in adults who are childhood cancer survivors (CCS). We sought to determine the emergence of CV risk factors in CCS while still children.

**Study design** CCS in remission ≥5 years from cancer diagnosis (n = 319, age = 14.5 years) and their siblings (control subjects, n = 208, age = 13.6 years) participated in this cross-sectional study of CV risk, which included physiologic assessment of insulin sensitivity/resistance (hyperinsulinemic euglycemic clamp). Adjusted comparisons between CCS major diagnoses (leukemia [n = 110], central nervous system tumors [n = 82], solid tumors [n = 127]) and control subjects were performed with linear regression for CV risk factors and insulin sensitivity.

**Results** Despite no significant differences in weight and body mass index, CCS had greater adiposity (waist [73.1 versus 71.1 cm, $P = .02$]; percent fat [28.1 versus 25.9%, $P = .007$]), lower lean body mass (38.4 versus 39.9 kg, $P = .01$) than control subjects. After adjustment for adiposity, CCS had higher total cholesterol level (154.7 versus148.3 mg/dL, $P = .004$), low-density lipoprotein cholesterol level (89.4 versus 83.7 mg/dL, $P = .002$), and triglyceride level (91.8 versus 84 mg/dL, $P = .03$) and were less insulin sensitive (insulin stimulated glucose uptake, measure of insulin resistance, adjusted for lean body mass 12.1 versus 13.4 mg/kg/min, $P = .002$) than control subjects.

**Conclusions** CCS have greater CV risk than healthy children. Because CV risk factors track from childhood to adulthood, early development of altered body composition and decreased insulin sensitivity in CCS may contribute significantly to their risk of early CV morbidity and mortality. *(J Pediatr 2012;160:494-9)*.

Effective therapies for childhood cancer have led to dramatic improvements in survival rates.[1,2] As childhood cancer survivors (CCS) progress to adulthood, clinical and epidemiological research is focusing on long-term adverse medical effects from cancer treatment to characterize and understand the "consequences of cure."[3] Among these are the metabolic syndrome (MetS) or combinations of cardiovascular (CV) risk factors (eg, obesity, dyslipidemia, hypertension, insulin resistance), all known to be potent risk factors for premature CV disease in adults[4] and leading causes of non-relapse deaths in CCS.[5-7]

Although most studies relating CCS to CV risk have been performed in adults,[8-10] studies in smaller cohorts of CCS have shown increased prevalence of CV risk factors in late adolescence and young adulthood,[11,12] and an increased incidence of obesity and hypertension were reported in a sample of children who survived leukemia.[13] These studies were limited by small numbers of subjects, lack of concurrent control subjects, and use of surrogate markers for insulin resistance, which are less sensitive estimates of insulin resistance in youth.[14]

This study is focused on the early development of CV risk and its relation to insulin sensitivity/resistance. We undertook a comprehensive assessment in a large population of CCS while they are still children and compared the CV risk profile and euglycemic hyperinsulinemic clamp, the "gold standard" for measurement of insulin sensitivity/resistance, between a cohort of children who survived a variety of childhood cancers and a control group of healthy sibling children.

## Methods

This study was approved by the institutional review board: human subjects committee at the University of Minnesota Medical Center and Children's Hospitals and Clinics of Minnesota. Consent (and assent as appropriate) was

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| BMI | Body mass index | LBM | Lean body mass |
| CCS | Childhood cancer survivors | LDL | Low-density lipoprotein |
| CNS | Central nervous system | $M_{lbm}$ | Insulin stimulated glucose uptake, measure of insulin resistance, adjusted for lean body mass |
| CV | Cardiovascular | | |
| DXA | Dual-energy X-ray absorptiometry | | |
| HDL | High-density lipoprotein | MetS | Metabolic syndrome |
| HOMA-IR | Homeostasis model assessment-insulin resistance | PFM | Percent of fat mass |

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obtained from children and their parent/guardian(s). The participants were CCS, age 9 to 18 years at examination, who were in remission at least 5 years from cancer diagnosis and who had received treatment at the University of Minnesota Medical Center or the Children's Hospitals and Clinics of Minnesota. Recipients of hematopoietic cell transplant were excluded from the study. A control group consisted of eligible healthy siblings who were 9 to 18 years old and had never had cancer.

Of 723 eligible CCS, 66 could not be located. The remaining 657 were contacted, and consent for participation was obtained from 319 CCS (49%) and 208 of their siblings (control subjects). There were no significant differences in age, sex, race, diagnosis, age at diagnosis, and length of follow-up (time from diagnosis to study evaluation) between the 319 CCS participants and the 338 CCS non-participants.

Participants underwent a 2-day examination at the University of Minnesota Clinical Research Center. Body mass index (BMI) was calculated as weight (kg) divided by height ($m^2$). Waist circumference was measured in duplicate midway between the anterior superior iliac spine and the lower rib margin directly over the skin, the method used in all earlier studies from our group designed to measure the site of natural waist and the level of minimal abdominal width, considered the level of the smallest circumference around the waist. Tanner stage was assigned according to pubic hair development in boys and breast and pubic hair development in girls. Dual-energy X-ray absorptiometry (DXA) measurements were obtained with a Lunar Prodigy scanner (software version 9.3; General Electric Medical Systems, Madison, Wisconsin). Fat mass was expressed as a percent of fat mass (PFM), and lean body mass (LBM) was expressed in kilograms. Visceral fat and subcutaneous fat were determined with volumetrics from a limited abdominal computed tomography scan without contrast, with a Siemens Somaton Sensation 40 slice (Siemens AG, Munich, Germany). The average of two blood pressure measurements from the right arm of rested, seated subjects was used in analyses.

Hyperinsulinemic euglycemic clamps were conducted after a 10- to 12-hour overnight fast as previously described.[15] Intravenous catheters were inserted in an arm vein for infusion of potassium phosphate, insulin, and glucose and in a contralateral vein for blood sampling. Baseline insulin and-glucose levels were determined from samples drawn at −5 and 0 minutes before beginning the insulin and glucose infusions. Insulin infusion was started at time 0 at a rate of 1 mU/kg/min for 3 hours. An infusion of 20% glucose was given and adjusted to maintain euglycemia (serum glucose level of 100 mg/dL [5.6 mmol/L]) with plasma glucose determined every 10 minutes. Insulin sensitivity (M) was determined by the amount of glucose required to maintain euglycemia in the final 40 minutes of the clamp study and expressed as mg/kg/min of glucose with adjustment for lean body mass ($M_{lbm}$) obtained from LBM. Lower $M_{lbm}$ values are indicative of lower insulin sensitivity (ie, greater insulin resistance).

Plasma glucose was analyzed at the bedside with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, California). Serum insulin was determined with a chemoluminescence immunoassay (Immulite Insulin DPC, Los Angeles, California). Homeostasis model assessment insulin resistance (HOMA-IR) was calculated with fasting insulin and glucose values on the basis of the equation HOMA-IR = [(fasting glucose units of mmol/L * insulin units in $\mu$U/mL)/22.5].[16] Serum lipid levels were analyzed from fasting blood samples obtained at the time catheters were placed for the clamp, with a Vitros 5600 (Ortho-Clinical Diagnostics, Inc, Rochester, New York). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation.

The criteria for MetS were based on pediatric modification[17,18] of the adult MetS criteria[19] and consisted of 3 or more of these criteria: (1) waist circumference >90th percentile for age and sex; (2) triglyceride level >110 mg/dL (1.24 mmol/L); (3) high-density lipoprotein (HDL) cholesterol ≤40 mg/mL (1.03 mmol/L); (4) blood pressure ≥90th percentile for age and sex; and (5) fasting glucose level ≥100 mg/dL (5.6 mmol/L).

Descriptive statistics are expressed as frequencies and percents or mean plus or minus SE, as appropriate. Multivariable linear regression models were used to compare mean outcome measures between groups, with adjustments for age, sex, race, and Tanner stage (unless noted otherwise). All analyses including data from both CCS and sibling control subjects used robust variance estimates from generalized estimating equations to account for intra-family correlation. Adjusted means were evaluated at the mean levels of co-variates included in the models. Additional models were fit adjusting for adiposity with BMI and PFM. Duration of time elapsed since diagnosis was examined as a risk factor in a linear and non-linear fashion on $M_{lbm}$ levels. Logistic regression models were fit to evaluate differences between groups in prevalence of MetS and its components (as defined previously). ORs and associated 95% CIs are reported. Partial correlation co-efficients, also adjusted for the same factors, were calculated to evaluate the associations between CV risk factors in CCS and control subjects separately. A two-sided $P$ value ≤.05 was considered to be statistically significant, although because of the high number of statistical tests carried out, those between .01 and .05 should be viewed with caution.

## Results

The characteristics of the study population are described in **Table I**. There were no significant differences in sex distribution between CCS and control subjects. The length of follow-up (time from diagnosis to study evaluation) was not different in the cancer groups ($P = .50$). CCS were slightly older, but similar to control subjects in degree of sexual maturation. A higher prevalence of white, non-Hispanic participants was present in the control subjects compared with CCS. Further analyses were adjusted for age at study, sex, race, and Tanner stage. On the basis of overall