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Treatment factors rather than genetic variation determine metabolic syndrome in childhood cancer survivors

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Abstract ***Background:*** Genetic variation that regulates insulin resistance, blood pressure and adiposity in the normal population might determine differential vulnerability for metabolic syndrome after treatment for childhood cancer.
Objective: To evaluate the contribution of candidate single nucleotide polymorphisms (SNPs) relevant for metabolic syndrome in our single centre cohort of adult long-term childhood cancer survivors.
Methods: In this retrospective study 532 survivors were analysed. Median age at diagnosis was 5.7 years (range 0.0–17.8 years), median follow-up time was 17.9 years (range 5.0–48.8) and median age at follow-up was 25.6 years (range 18.0–50.8). *JAZF1* gene rs864745, *THADA* gene rs7578597, *IRS1* gene rs2943641, *TFAP2B* gene rs987237, *MSRA* gene rs7826222, *ATP2B1* gene rs2681472 and rs2681492 were genotyped. The association of genotypes with total cholesterol levels, blood pressure, body mass index, waist circumference and frequency of diabetes were assessed.
Results: Metabolic syndrome was more frequent in cranially (23.3%, $P = 0.002$) and abdominally (23.4%, $P = 0.009$) irradiated survivors as compared with non-irradiated survivors (10.0%). Association of allelic variants in rs2681472 and rs2681492 with hypertension, rs987237 and rs7826222 with waist circumference and rs864745, rs7578597 and rs2943641 with diabetes were not significant. None of the SNPs was associated with the metabolic syndrome. Adjusting for age, sex, follow-up time, cranial irradiation and abdominal irradiation did not change these results.

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Conclusions: Treatment factors and not genetic variation determine hypertension, waist circumference, diabetes and metabolic syndrome in adult long-term survivors of childhood cancer.

1. Introduction

Hypertension, adiposity, dyslipidemia and insulin resistance, when occurring together and referred to as the metabolic syndrome, have been reported frequently in childhood cancer survivors.[1–6] Metabolic syndrome (MetS) is known to increase the risk for cardiovascular diseases and type 2 diabetes mellitus.[7] Especially survivors treated with cranial irradiation, total body irradiation or abdominal irradiation seem to be at risk for developing (components of) the MetS.[4–6]

Variation of long-term toxicity in equally treated childhood cancer survivors suggests that genetic variation and environmental factors may influence the occurrence and the level/impact of late effects. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. SNPs determine about 90% of all human genetic variation. Large-scale genome-wide association studies (GWAS), in which hundreds of thousands of common genetic variants are genotyped, identified genes associated with common diseases and traits.[8,9] The *ATP2B1* gene appeared to be associated with systolic and diastolic blood pressure and hypertension.[10] This gene encodes PMCA1, a plasma membrane calcium/calmodulin dependent ATP-ase that is expressed in vascular endothelium and is involved in calcium pumping from the cytosol to the extracellular component.[11] Two loci near *TFAP2B* and *MRSA* influence adiposity and fat distribution through an effect on overall obesity or fat mass.[12] A SNP located adjacent to the insulin receptor substrate 1 gene (*IRS1*) is associated with insulin resistance, hyperinsulinemia and reduced IRS1 protein levels and decreased insulin induction of *IRS1*-associated phosphatidylinositol-3-OH kinase activity in human skeletal muscle.[13] Furthermore, loci at the *JAZF1* and *THADA* gene regions have been associated with diabetes.[14,15]

The aim of the current study was to evaluate whether SNPs that have been associated with blood pressure, adiposity and diabetes influence the occurrence of the MetS in adult long-term childhood cancer survivors.

2. Methods

2.1. Patients

This retrospective study was performed in a single centre cohort of adult long-term childhood cancer survivors treated at the Erasmus MC-Sophia Children's Hospital from October 1960 to June 2004. Survivors were younger than 18 years at the time of diagnosis and were at least 5 years after cessation of treatment when they visited the outpatient clinic for long-term side effects of cancer treatment.

To minimise ethnic influences on the study outcome, only Caucasian subjects were included in this study. Full details on cancer treatment were previously recorded: type and cumulative dose of chemotherapy, site, field and cumulative dose of radiotherapy, extent of surgery, conditioning regimen prior to stem cell transplantation (SCT), complications and relapses. During their regular visit at the outpatient clinic general health screening, extensive history and physical examination were performed. Education level was scored as high (i.e. university or college), medium (i.e. secondary education or vocational education) and low (primary school). Written informed consent was obtained from all participants.

2.2. Components of the metabolic syndrome

Height was measured to the nearest millimetre using a Harpenden Stadiometer and weight was assessed but in underwear only to the nearest 0.1 kg with a standard clinical balance. Body mass index (BMI) was calculated as weight in kilograms divided by the squared length in metres. Waist circumference was measured to the nearest 1 cm, midway between last rib and the iliac crest, hip circumference was measured at the maximum circumference of the buttocks to the nearest 1 cm and waist-hip-ratio was calculated. Blood pressure was measured on the right arm of the patient with the Dinamap® Procare. Medication use was routinely asked for during visits and was abstracted from the medical records. Medication was categorised in treatment for diabetes, anti-hypertensive treatment and lipid-lowering treatment.

Non-fasting blood samples were taken to assess total cholesterol levels using an enzymatic in vitro assay (Roche Diagnostics, Mannheim, Germany).

Due to the unavailability of fasting lipid spectrum and fasting glucose in our patients, the modified definition of the MetS as proposed by Haugnes et al.[16] was used, as previously described.[17] Subjects with at least two of the following components were diagnosed with MetS: Blood pressure $\geqslant$ 140/90 mmHg; body mass index $\geqslant$ 30 kg/m^2; self reported prevalence of diabetes or medication; serum total cholesterol $\geqslant$ 5.2 mmol/l or medication.

Prevalence of the MetS was assessed in the total group and in diagnosis subgroups containing at least