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Genetic and clinical factors associated with obesity among adult survivors of childhood cancer: a report from the St. Jude Lifetime cohort

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Abstract

Purpose—We aimed to identify treatment and genetic factors associated with obesity among childhood cancer survivors.

Methods—Participants included 1996 survivors previously treated for cancer at St. Jude Children's Research Hospital who survived 10 years from diagnosis (median age at diagnosis 7.2 years, median age at follow-up 32.4 years). Obesity was defined as a body mass index $\geq 30\text{kg/m}^2$. Factors associated with adult obesity were identified by subgroup-specific (cranial radiation (CRT) exposure status) multivariable logistic regression. Single nucleotide polymorphisms (SNPs) associated with obesity were identified by subgroup-specific exploratory genome-wide association analyses (two-stage resampling approach with type I error rate $= 5 \times 10^{-6}$).

Results—Forty-seven percent and 29.4% of survivors treated with or without receive CRT were obese at evaluation, respectively. In multivariable analyses, abdominal/pelvic radiation exposure was associated with decreased prevalence of obesity among survivors regardless of cranial radiation ($p < 0.0001$). The odds of obesity were increased among survivors treated with CRT who had also received glucocorticoids ($p = 0.014$), or who were younger at diagnosis ($p = 0.013$). Among survivors treated with CRT, 166 SNPs were associated with obesity. The strongest association was observed with rs35669975 ($p = 3.3 \times 10^{-8}$) on 13q33.3, approximately 30kb downstream of *FAM155A*. SNPs within *GLRA3*, and near *SOX11* and *CDH18* were also identified. These genes have been implicated in neural growth, repair, and connectivity.

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Conclusion—Obesity in childhood cancer survivors remains associated with previous CRT and glucocorticoid exposures. Genetic variants related to neural connectivity may modify the risk of obesity among survivors treated with cranial radiation. Validation of our findings in independent cohorts is required.

Keywords

childhood cancer survivor; polymorphism; obesity; late effects

INTRODUCTION

Survivors of childhood cancer (CCS) who were exposed to cranial radiation during therapy (CRT) curative therapy are at high risk for obesity¹. Obesity is problematic because it increases susceptibility to chronic diseases² and premature mortality. Among survivors exposed to CRT, the highest risk of obesity is generally observed among females and those diagnosed at a younger age^{3–5}. Weight gain accelerates with age⁶, and is hypothesized to be associated with radiation-induced damage to the hypothalamic-pituitary axis (HPA), leading to alterations in leptin sensitivity or growth hormone production^{3, 4, 7}. Additional factors suggested to influence obesity risk among survivors include exposure to corticosteroids^{8, 9}, sub-optimal physical activity¹⁰, and reduced energy expenditure during exercise¹¹.

Tissue injury following radiotherapy results from a complex integrated cellular and intracellular response involving the production of reactive oxygen species, initiation of inflammatory pathways, and cell death¹². Germline variation in genes controlling individual response to radiotherapy may modify the risk of toxicity to normal tissues, and over time, the development of organ dysfunction. Accordingly, previous studies conducted in survivors of adult cancers suggest that radiation-induced toxicities are influenced by common genetic variants^{13, 14}. Further, an association has been reported between a leptin receptor polymorphism (*LEPR* Gln223Arg) and obesity among survivors of childhood leukemia¹⁵. Given the high risk of obesity among CCS, particularly those exposed to CRT, and evidence that suggests genetic variation can modify the risk of radiation-induced toxicities, we hypothesized a potential role for gene-environment (therapy) interactions on adult obesity among CCS. Therefore, the first aim of this study was to estimate the prevalence of obesity among CCS, and identify clinical and treatment-related risks for obesity. The second aim of this study was to conduct an exploratory analysis to investigate genetic factors associated with obesity among CCS several decades following treatment.

METHODS

Study population

Participants included individuals enrolled in the Institutional Review Board approved St. Jude Lifetime Cohort (SJLIFE) Study¹⁶. Eligibility for the current analysis included: diagnosis and treatment of cancer at St. Jude Children's Research Hospital (SJCRH); 10 years from diagnosis; and 18 years of age at follow-up as of February 2012 (see Supplementary Figure 1 and Supplementary Methods). Informed consent was obtained from each study participant.

Diagnosis, Treatment, and Anthropometrics

Diagnosis and treatment information were obtained from medical records by trained abstractors. Height, weight and body mass index (BMI) were assessed at SJLIFE clinical evaluation; adult BMI was categorized as underweight ($<18.5\text{kg/m}^2$), normal ($18.5\text{--}24.9\text{kg/m}^2$), overweight ($25\text{--}29.9\text{kg/m}^2$), and obese ($\geq 30\text{kg/m}^2$). BMI at diagnosis was also calculated. Among individuals who were diagnosed ≥ 2 years of age, BMI was assessed by age- and sex-specific percentiles with those individuals with a BMI $\geq 95^{\text{th}}$ percentile classified as obese¹⁷. For individual diagnosed at less than 2 years of age, obesity was assessed based on sex-specific length-for-age¹⁸.

Genotyping and imputation

DNA was genotyped using the Affymetrix® Genome-Wide Human SNP Array 6.0. Individual SNPs with minor allele frequencies (MAF) $<1\%$ or $<95\%$ call rates across all samples were excluded from analyses. Samples with $<95\%$ call rates across markers were also excluded. SNPs were screened for deviations from Hardy-Weinberg equilibrium and discarded where $p < 1 \times 10^{-6}$. Imputation of SNPs not represented on the array was conducted using minimac with reference data from the 1000 Genomes Project (RELEASE STAMP 2012-10-09)^{19, 20}. Imputed SNP markers with imputation quality scores $r^2 < 0.3$ or $\text{MAF} < 1\%$ were excluded from analyses.

Associations between clinical and treatment-related characteristics and obesity

Logistic regression was used to evaluate associations between diagnostic and treatment characteristics and obesity. Sex, age at diagnosis, age at follow-up, race/ethnicity, obesity at diagnosis, glucocorticoid, anthracycline and alkylating agent exposures, and radiation to the head, chest, abdomen, or pelvis were considered in initial models. Because of the high risk of obesity observed among survivors treated with CRT^{3, 4}, participants were stratified on CRT exposure, and associations between diagnostic and treatment characteristics reexamined.

Genome-wide association analysis

To identify and prioritize Affymetrix Array SNPs associated with obesity, a two-step iterative resampling approach²¹ was used comparing genotype frequencies between obese and non-obese survivors. These additive models were stratified by cranial radiation. Participants were randomly divided into discovery (70%) and validation (30%) cohorts, balanced by diagnosis. Within the discovery cohort, SNPs were individually tested for associations with obesity and all SNPs with $p < 1 \times 10^{-4}$ were carried forward to the second step where a SNP was considered to be validated if associated with obesity at $p < 0.05$. This two-step process was repeated 100 times for CRT and non-CRT groups separately. SNPs that were associated with obesity ≥ 20 times using the resampling approach were considered internally validated. Imputed SNPs located within one megabase of internally validated Affymetrix Array SNPs were then tested for associations with obesity using the same approach. All models were adjusted for ancestry using STRUCTURE²² Mach2dat and PLINK, version 1.07 was used for analyses^{19, 20, 23}. The results of our simulation study suggest that this two-step iterative approach preserved the type I error rate below 5×10^{-6} .

and provided adequate power for reasonable effect sizes for a wide range of minor allele frequencies (see Supplementary Table 3). An overview of the study design is provided in Figure 1.

Finally, we used logistic regression to evaluate the odds of obesity associated with clinical risk factors alone, and for clinical and genetic predictors combined. Genetic risk factors included a single SNP marker for each genomic region of interest identified in GWA analyses. Model fits were assessed using pseudo- R^2 (RN^2), likelihood ratio tests, and Akaike information criterion (AIC) values.

RESULTS

The study cohort comprised 1996 (51% male) CCS (Table 1). Median age at diagnosis was 7.2 years (range: 0.1–24.8) and median age at follow-up was 32.4 years (range: 18.9–63.8). Median length of follow-up from diagnosis was 24.6 years (range: 10.7–48.3). At SJLIFE evaluation, 645 survivors (32.3%) were of normal weight, 71 (3.6%) underweight, 556 (27.9%) overweight, and 723 (36.2%) obese.

The highest prevalence of obesity was observed among male survivors of leukemia (42.5%) and other tumors (38.8%; Table 2). The highest prevalence of obesity among female survivors was in neuroblastoma (43.6%) and leukemia (43.1%). The prevalence of obesity was highest among male (40.4%) and female (39.5%) survivors diagnosed before five years of age, and those more than 30 years from diagnosis (45%; Supplementary Table 1).

Multivariable models demonstrated that older age at evaluation (≥ 30 years vs. <30 years, $p<0.001$), CRT ($p<0.001$), and glucocorticoid exposures ($p=0.004$) were independently associated with obesity (Table 3). Chest, abdominal or pelvic radiation exposure were associated with a decreased prevalence of obesity ($p<0.001$). Survivors exposed to CRT had a higher prevalence of obesity when compared to those unexposed (47% vs. 29.4%, $p<0.001$). In the model limited to survivors treated with CRT, older age at follow-up (≥ 30 years vs. <30 years, $p=0.003$), younger age at diagnosis (0–4 years vs. ≥ 15 years, $p=0.013$), and treatment with glucocorticoids ($p=0.014$) were associated with obesity (Table 4). Among survivors not exposed to CRT, older age at follow-up ($p<0.001$) was associated with obesity, whereas abdominal or pelvic radiation was inversely associated with obesity ($p<0.001$).

Supplementary Table 2 summarizes the 166 SNPs internally validated as being associated with obesity among survivors treated with CRT using the iterative resampling approach. The most significant SNP, rs35669975 ($p\text{-value}=3.3\times 10^{-8}$), is located approximately 30kb downstream of family with sequence similarity 155, member A (*FAM155A*) gene on chromosome 13 (Supplementary Figure 2A). Regions on chromosomes 2, 4, and 5 were also identified. The region on chromosome 2 was located approximately 908kb upstream of sex determining region Y box 11 gene (*SOX11*; Supplementary Figure 2B). On chromosome 4, 17 SNPs located within glycine receptor $\alpha 3$ (*GLRA3*) gene were identified, of which one SNP, rs12648678, located in exon 7, codes for a synonymous amino-acid substitution (Supplementary Figure 3A). The region of interest on chromosome 5 was located between

cadherin 18 type 2 (*CDH18*) and brain abundant membrane attached signal protein 1 (*BASPI*) genes (Supplementary Figure 3B). Among non-CRT survivors, only one SNP (rs12073359) located on chromosome 1 was internally validated as being associated with increased odds of obesity (OR=1.7, 95% CI=1.4–2.1, $p=5\times 10^{-6}$). This SNP is located upstream of vacuolar protein sorting 45 homolog (*S. cerevisiae*) gene (*VPS45*).

Among survivors exposed to CRT (Table 4), we obtained values of RN^2 for a multivariable model that included only clinical risk factors, and a model including both clinical and genetic risk factors. The values were $RN^2=0.174$ for the clinical risk factors model, and $RN^2=0.303$ for the clinical risk factors and SNPs model. An improvement of 0.129 in RN^2 represented a statistically significant improvement in model fit among survivors previously treated with CRT. The likelihood ratio test comparing both models ($p<0.001$) combined with an improvement in the AIC value (866.35 vs. 1005.67) provided further evidence that the addition of genotype data to clinical risk factors significantly improved model fit. Among patients not exposed to CRT, the value of RN^2 increased from 0.129 to 0.143 indicating a marginal improvement following the addition of rs12073359 to the clinical model (Table 4).

DISCUSSION

We estimated the prevalence of obesity among CCS and examined the potential roles of clinical and genetic risk factors on prevalent obesity. Over one third of our cohort was obese after a median follow-up of 25 years from childhood cancer diagnosis. Our results confirm the increased odds of adult obesity following corticosteroids^{8,9} and obesity in childhood²⁴, and decreased odds of obesity following abdominal radiation identified in previous studies¹. We also identified genetic polymorphisms in regions near, or within, *FAM155A*, *SOX11*, *CDH18*, and *GLRA3*, that may increase the odds of obesity among survivors who received CRT.

The prevalence of obesity was 36% in our population, which is 14% higher than the expected prevalence of 31.6% (standardized morbidity ratio [SMR]=1.14, 95% CI= 1.06–1.22) when age-, sex-, and race-matched National Health and Nutrition Examination Survey data (2007–2012) were used to estimate the expected prevalence²⁵. With the exception of female survivors of renal cancers, greater than 25% lymphoma or solid tumors survivors were obese, while 43% of lymphoblastic leukemia survivors were obese. Previous studies of adult survivors of leukemia reported obesity in 19–32% (a median of 15–25 years after diagnosis)^{5,6}. Although studies of body composition among survivors of non-hematological cancers are limited, one report found that survivors of select solid tumors are less likely to be obese¹. The high prevalence of obesity among survivors is concerning given the association with morbidity²⁶ and premature mortality²⁷ in the general population. These findings further highlight the need for effective weight loss interventions for CCS, a population at high-risk of chronic disease.

We identified four genomic regions associated with obesity in CCS treated with CRT. Among these, the strongest observed was located near *FAM155A*. *FAM155A* polymorphisms have been previously associated with increased percent fat mass in children

of Hispanic descent²⁸, and anorexia nervosa²⁹. Although little is known about the function of *FAM155A*, it is expressed in the hypothalamus and pituitary^{30, 31}, consistent with the hypothesis that CRT may modify risk of obesity among survivors by disrupting the HPA. SNPs within *GLRA3*, which codes for a membrane-bound receptor protein involved in signaling by the neurotransmitter glycine, were identified³², as were genetic variations in regions near *CDH18* and *SOX11*. *CDH18* is a classical cadherin expressed in the brain and has been implicated in synapse formation and neuroplasticity³³. SNPs within *CDH18* have been previously associated with increased BMI^{34, 35} and waist circumference³⁵. *SOX11* is a transcription factor involved in embryonic³⁶ and adult neurogenesis³⁷ and is expressed in proliferating progenitor and immature neurons during migration, during dendritic and axonal growth, and is up-regulated following peripheral nerve injury³⁸. As both *CDH18* and *SOX11* appear to influence neuronal growth, repair and connectivity, these genes may be important regulators of neuronal response to radiation-induced damage among CCS. The significance of associations between these genes and obesity among CCS exposed to cranial radiation require further study.

Previous studies have indicated potential associations between female sex^{4, 5, 9, 39}, younger age at diagnosis^{3, 4}, or *LEPR* Gln223Arg¹⁵, and obesity. Additionally, in some studies, associations between obesity and young age at diagnosis^{3, 4} or homozygosity for the leptin receptor Arg allele¹⁵ were strongest among females who were exposed to more than 20Gy of CRT. In the current study, we did not observe a significant difference in the odds of obesity among survivors based on sex or leptin receptor genotype. However, we were unable to investigate whether radiation dose could alter associations between these factors and obesity, as our sample size prohibited further stratification radiation dose to the HPA. It is possible that females, and survivors homozygous for leptin Arg allele, may represent sub-populations at higher risk for early-onset obesity. Among SJLIFE participants, who represent an older population than many previous survivor cohorts, the cumulative effect of insufficient physical activity and poor dietary choices over time may have contributed substantially to the proportion of survivors who were obese, thus, obscuring associations with risk factors for adult obesity.

A strength of this study is the use of the SJLIFE cohort, which is a large, well characterized cohort of adult survivors, over half of whom are more than 25 years from diagnosis of their childhood cancer. Nevertheless, this study also had several limitations. First, BMI may not be an accurate measure of adiposity among cancer survivors, as lean mass may be abnormally low for height, thus allowing survivors to maintain normal BMI despite high adiposity³⁹. Accordingly, we may have misclassified some participants with high percent body fat as non-obese by using BMI as the outcome measure, although for germline polymorphisms participants would be unaware of polymorphism status. Outcome misclassification in this scenario is likely to be non-differential. Second, we did not have data on obesity status following the completion of therapy, nor were data on lifestyle factors, such as physical activity and diet available, which may be important risk factors for obesity in the study cohort²⁴. Third, our small sample size combined with stringent criteria for statistical significance may have restricted our ability to identify genetic factors associated with small to moderate increases in obesity risk. Our ability to detect true genotype-

phenotype associations may also have been obscured by the variety of treatments received by participants, which may have modified the risk of obesity among sub-populations of survivors via alternative pathways. Finally, we did not externally validate our genotype-phenotype associations.

In summary, our findings confirm that the high prevalence of obesity among CCS persists decades following cancer treatment and appears to be influenced by therapies received during childhood and obesity status at diagnosis. We also observed that among survivors who receive CRT, polymorphisms in genes responsible for neural growth, repair and connectivity potentially may modify the risk of obesity, but validation of these SNP-phenotype associations in independent cohorts is necessary. The ability to identify patients at increased risk of obesity on the basis of genetic susceptibility may improve early detection of high-risk sub-groups. The high prevalence of obesity among survivors underscores the need for immediate focus on research directed at developing effective interventions for weight management to optimize health outcomes among survivors of childhood cancer as they age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Iterative resampling approach to identify SNPs associated with obesity among survivors treated with or without cranial radiation.

Table 1

Descriptive characteristics of study participants

Characteristic	Number	%
Sex		
Male	1018	51.0
Female	978	49.0
Race		
White	1726	86.5
Black	250	12.5
Other	20	1.0
Age at diagnosis (years)		
0–4	761	38.1
5–9	474	23.7
10–14	448	22.4
15	313	15.7
Age at follow-up (years)		
18–29	755	37.8
30–39	807	40.4
40	434	21.7
Diagnosis		
Leukemia	838	42.0
CNS	158	7.9
HL	276	13.8
NHL	123	6.2
Renal	129	6.5
NB	80	4.0
STS	96	4.8
Bone	141	7.1
Other	155	7.8
Household income		
\$19,999	334	16.7
\$20,000–\$39,999	438	21.9
\$40,000–\$59,999	312	15.6
\$60,000	633	31.7
Unknown	279	14.0
Education		
<High school diploma/general equivalency diploma	186	9.3
High school graduate	973	48.8
College graduate	691	34.6
Unknown	146	7.3
	Median	Range

Characteristic	Number	%
Height ^a (cm)		
Male	174.7	134.1–213.0
Female	161.9	128.6–183.7
Weight ^a (kg)		
Male	84.7	36.7–220.0
Female	70.0	31.7–174.0
BMI ^a (kg/m ²)		
Male	27.6	14.3–67.7
Female	26.7	13.9–66.5

CNS, central nervous system malignancy; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; NB, neuroblastoma; STS, soft tissue sarcoma.

^aHeight, weight and BMI were assessed at SJLIFE clinical evaluation

Table 2

Distribution of BMI by diagnosis^a

Characteristic	BMI<18.5 (%)	18.5	BMI <25 (%)	25	BMI <30 (%)	BMI 30 (%)
Male						
All males	27 (2.7)		294 (28.9)		327 (32.1)	370 (36.4)
Leukemia	6 (1.5)		101 (24.7)		128 (31.8)	174 (42.5)
CNS	1 (1.1)		27 (28.4)		31 (32.6)	36 (37.9)
HL	5 (3.6)		45 (32.1)		48 (34.3)	42 (30.0)
NHL	1 (1.6)		20 (25.6)		29 (37.2)	28 (35.9)
Renal	1 (2.0)		22 (44.0)		14 (28.0)	13 (26.0)
NB	1 (2.4)		16 (39.0)		13 (31.7)	11 (26.8)
STS	6 (11.3)		16 (30.2)		14 (26.4)	17 (32.1)
Bone	3 (3.5)		29 (34.1)		30 (35.3)	23 (27.1)
Other	3 (4.5)		18 (26.9)		20 (29.9)	26 (38.8)
Female						
All females	44 (4.5)		351 (35.9)		229 (23.4)	354 (36.2)
Leukemia	12 (2.8)		131 (30.5)		101 (23.5)	185 (43.1)
CNS	1 (1.6)		24 (38.1)		17 (27.0)	21 (33.3)
HL	3 (2.2)		51 (37.5)		43 (31.6)	39 (28.7)
NHL	2 (4.4)		19 (42.2)		9 (20.0)	15 (33.3)
Renal	8 (10.1)		37 (46.8)		20 (25.3)	14 (17.7)
NB	1 (2.6)		16 (41.0)		5 (12.8)	17 (43.6)
STS	4 (9.3)		20 (46.5)		7 (16.3)	12 (27.9)
Bone	8 (14.3)		28 (50.0)		2 (3.6)	18 (32.1)
Other	5 (5.7)		25 (28.4)		25 (28.4)	33 (37.5)

CNS, central nervous system malignancy; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; NB, neuroblastoma; STS, soft tissue sarcoma.

^aBMI was determined at SJLIFE clinical evaluation

Table 3

Association between clinical and treatment characteristics with adult obesity in childhood cancer survivors from multivariable analyses^a

Characteristic	BMI>30 (%)	OR ^b	95% CI ^b	p-value
Sex				
Male	36.5	1.0		
Female	36.3	1.07	0.88–1.31	0.49
Age at follow-up (years)				
18–29	28.5	1.0		
30–39	41.1	1.88	1.49–2.38	
40	41.3	2.13	1.59–2.86	<0.001
Age diagnosis (years)				
0–4	40.0	1.28	0.92–1.78	
5–9	33.6	0.88	0.62–1.24	
10–14	33.8	0.94	0.67–1.32	0.025
15	35.7	1.0		
Cranial Radiation				
No	29.3	1.0		
Yes	47.8	1.66	1.33–2.07	<0.001
Chest/Abdominal/Pelvic Radiation				
No	40.7	1.0		
Yes	22.4	0.48	0.36–0.63	<0.001
Glucocorticoid				
No	29.9	1.0		
Yes	42.5	1.37	1.11–1.70	0.004
Obese at diagnosis				
No	33.3	1.0		
Yes	68.8	4.95	3.47–7.06	<0.001

^aParticipants with BMI 30kg/m² were defined as obese

^bOdds Ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression. All ORs are adjusted for race/ethnicity

Table 4

Association between clinical and treatment characteristics with adult obesity in survivors of childhood cancer from multivariable analyses

	Patients treated with cranial radiation					Patients treated without cranial radiation				
	Clinical factors only			Clinical and genetic factors		Clinical factors only			Clinical and genetic factors	
	OR ^a	95%CI ^a	p-value ^b	OR ^a	95%CI ^a	p-value ^b	OR ^a	95%CI ^a	p-value ^c	p-value ^c
Age at follow-up (years)										
18–29	1.0			1.0			1.0		1.0	
30–39	1.76	1.20–2.58		2.01	1.33–3.04		1.83	1.33–2.51	1.85	1.35–2.55
40	1.98	1.24–3.16	0.003	2.11	1.29–3.47	0.001	2.07	1.37–3.13	2.08	1.37–3.16
Age diagnosis (years)										0.002
0–4	2.50	1.30–4.79		2.63	1.32–5.25		1.0	0.67–1.50	1.04	0.69–1.56
5–9	1.74	0.90–3.36		1.94	0.97–3.91		0.73	0.48–1.13	0.78	0.51–1.20
10–14	2.05	1.04–4.03		1.98	0.97–4.07		0.77	0.51–1.15	0.81	0.54–1.21
15	1.0		0.013	1.0		0.043	1.0			0.34
Chest/Abdominal/Pelvic Radiation										
No	1.0			1.0			1.0		1.0	
Yes	0.20	0.09–0.46	<0.001	0.15	0.06–0.38	<0.001	0.54	0.40–0.73	0.54	0.40–0.74
Glucocorticoid										
No	1.0			1.0			1.0		1.0	
Yes	1.75	1.19–2.58	0.014	1.63	1.08–2.47	0.021	1.29	0.97–1.70	1.24	0.94–1.65
Alkylating agent										0.13
No	1.0			1.0			1.0		1.0	
Yes	0.56	0.39–0.79	<0.001	0.61	0.42–0.89	0.010	0.96	0.73–1.27	0.98	0.74–1.29
Obesity at diagnosis										0.87
No	1.0			1.0			1.0		1.0	
Yes	0.56	1.89–6.16	<0.001	3.75	1.99–7.04	<0.001	5.74	3.69–8.93	5.73	3.68–8.92
SNP										<0.001
rs4971486 ^d				2.01	1.50–2.71	3.5×10 ⁻⁶				
rs4530610 ^e				0.55	0.40–0.76	0.0004				
rs2923762 ^d				1.78	1.40–2.26	2.6×10 ⁻⁶				

	Patients treated with cranial radiation					Patients treated without cranial radiation				
	Clinical factors only			Clinical and genetic factors		Clinical factors only			Clinical and genetic factors	
	OR ^a	95%CI ^a	p-value ^b	OR ^a	95%CI ^a	p-value ^b	OR ^a	95%CI ^a	OR ^a	p-value ^c
rs3566975 ^d				0.57	0.44–0.74	2.8×10 ^{−5}			1.56	1.24–1.96
rs12073359 ^e										0.0008
AIC ^f		1005.67			866.35			1342.32		1445.57
−2 Log L ^g		919.75			832.35			1316.32		1419.57
RN ² ^h		0.174			0.303			0.129		0.143

^a Odds Ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression. All ORs are adjusted for race/ethnicity

^b Data on BMI at diagnosis was unavailable for 36 survivors treated with cranial radiation. P-values were obtained using logistic regression models that included 740 survivors exposed to cranial radiation, of who 353 (47.8%) were obese

^c Data on BMI at diagnosis was unavailable for 38 survivors treated without cranial radiation. P-values were obtained using logistic regression models that included 1182 survivors not exposed to cranial radiation, of who 346 (29.3%) were obese

^d The effect allele is G.

^e The effect allele is C.

^f Akaike information criterion

^g −2 Log Likelihood statistic

^h Pseudo R²