

# Diabetes Mellitus in Long-term Survivors of Childhood Cancer

## *Increased Risk Associated With Radiation Therapy: A Report for the Childhood Cancer Survivor Study*

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**Background:** Childhood cancer survivors are at increased risk of morbidity and mortality. To further characterize this risk, this study aimed to compare the prevalence of diabetes mellitus (DM) in childhood cancer survivors and their siblings.

**Methods:** Participants included 8599 survivors in the Childhood Cancer Survivor Study (CCSS), a retrospectively ascertained North American cohort of long-term survivors who were diagnosed between 1970 and 1986 as well as 2936 randomly selected siblings of the survivors. The main outcome was self-reported DM.

**Results:** The mean ages of the survivors and the siblings were 31.5 years (age range, 17.0-54.1 years) and 33.4 years (age range, 9.6-58.4 years), respectively. Diabetes mellitus was reported in 2.5% of the survivors and 1.7% of the siblings. After adjustment for body mass index, age, sex, race/ethnicity, household income, and insurance, the survivors were 1.8 times more likely than

the siblings to report DM (95% confidence interval [CI], 1.3-2.5;  $P < .001$ ), with survivors who received total body irradiation (odds ratio [OR], 12.6; 95% CI, 6.2-25.3;  $P < .001$ ), abdominal irradiation (OR, 3.4; 95% CI, 2.3-5.0;  $P < .001$ ), and cranial irradiation (OR, 1.6; 95% CI 1.0-2.3;  $P = .03$ ) at increased risk. In adjusted models, an increased risk of DM was associated with total body irradiation (OR, 7.2; 95% CI, 3.4-15.0;  $P < .001$ ), abdominal irradiation (OR, 2.7; 95% CI, 1.9-3.8;  $P < .001$ ), use of alkylating agents (OR, 1.7; 95% CI, 1.2-2.3;  $P < .01$ ), and younger age at diagnosis (0-4 years; OR, 2.4; 95% CI, 1.3-4.6;  $P < .01$ ).

**Conclusion:** Childhood cancer survivors treated with total body or abdominal irradiation have an increased risk of diabetes that appears unrelated to body mass index or physical inactivity.

*Arch Intern Med.* 2009;169(15):1381-1388

**A**S A RESULT OF THEIR CURATIVE therapies, childhood cancer survivors face an increased risk of morbidity and mortality. We recently reported that by 30 years after diagnosis, almost three-fourths of survivors will have a chronic health condition, including 42.4% with a severe, disabling, or life-threatening condition or death due to a chronic condition.<sup>1</sup> Furthermore, survivors frequently suffer from multiple conditions. Among long-term childhood cancer survivors, Mertens et al<sup>2</sup> reported a standardized mortality ratio of 7.0 for deaths due to cardiovascular disease. Importantly, most childhood cancer survivors worldwide are still relatively young, with only a small percentage beyond their fifth decade of life.

In the general population, diabetes mellitus (DM) is strongly associated with an increased risk of cardiovascular dis-

ease and all-cause death.<sup>3</sup> We can anticipate that DM in long-term survivors of childhood cancer will further increase their risk of adverse health outcomes. Importantly, the risk of type 2 DM is potentially modifiable. Therefore, it is important to determine whether childhood cancer survivors are at increased risk of DM, to identify treatment exposures or other factors that may affect risk, and to alert clinicians and survivors regarding these risks.

Recent studies suggest that cancer survivors whose treatment included bone marrow transplantation may have an increased prevalence of DM, particularly those who were treated with total body irradiation (TBI).<sup>4-9</sup> Two small studies suggested a possible increased risk of DM after abdominal irradiation for Wilms tumor.<sup>10,11</sup> Also, survivors of acute lymphoblastic leukemia (ALL) and brain tumors who were treated with cranial irra-

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diation, particularly females treated at a young age, have an increased risk of obesity in adulthood.<sup>12,13</sup> Obesity is a strong predictor of insulin resistance and type 2 DM; therefore, it can be anticipated that these subpopulations of childhood cancer survivors may develop type 2 DM at an increased rate.

The purpose of this cross-sectional study was to further elucidate the risk of DM in long-term survivors of childhood cancer using a large, diverse, and well-characterized cohort of survivors and a comparison group of siblings. Also, we sought to identify treatment exposures and other factors that modify the risk of DM.

## METHODS

### CANCER SURVIVORS AND SIBLINGS

The methodology of the Childhood Cancer Survivor Study (CCSS) and a description of participants have previously been published in detail.<sup>14</sup> Briefly, the CCSS cohort consists of survivors of specific childhood cancers (leukemia, central nervous system tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft-tissue sarcomas, or bone tumors) who were diagnosed before the age of 21 years at 1 of 26 participating centers between 1970 and 1986 and who were alive at least 5 years after their original diagnosis. The eligible cohort consisted of 20 720 patients, 14.6% of whom were deemed unavailable for follow-up after intensive tracing. Of the 17 703 who were successfully contacted, 14 366 (81.2%) enrolled in the study. Comparisons of demographic and cancer-related characteristics of participants and nonparticipants did not demonstrate significant differences with regard to sex, cancer type, age at diagnosis, age when the cohort was assembled (eg, 1993-1994), and type of cancer treatment.<sup>14,15</sup> To allow comparisons with a representative of the general population without cancer, a random sample of participating survivors were asked to identify their nearest-age living sibling. Of 4782 eligible siblings, 3846 (80.4%) participated.

Since the time of enrollment (1995-1996 for most participants), a series of questionnaires have been administered. Eligibility for this analysis was limited to participants who completed the CCSS 2003 Follow-up Survey, which included questions about medication use for DM (<http://www.stjude.org/ccss>). The study was approved by the institutional review board of all 26 participating institutions, and written informed consent was obtained from all participants or their parents or guardians. Participating CCSS institutions are listed in the eAppendix (<http://www.archinternmed.com>).

### CANCER TREATMENT INFORMATION

Information regarding original cancer diagnoses was obtained for eligible cases from treating institutions. For all CCSS participants returning signed medical releases, information regarding primary cancer therapies was collected, including initial treatment, treatment for relapse, and (where applicable) preparatory regimens for bone marrow transplantation. Qualitative information was abstracted from medical records for 42 specific chemotherapeutic agents, 22 of which also had quantitative dose information. Copies of radiation therapy records were obtained and centrally reviewed, including doses of cranial and craniospinal radiotherapy and TBI. The treatment abstraction forms used in data collection are available at <http://www.stjude.org/ccss>.

## OUTCOME MEASURE

In the CCSS 2003 Follow-up Survey, participants were asked if they had taken insulin or an oral medication for DM for more than 1 month in the preceding 2 years. To prompt participants, common examples of oral DM medications and forms of insulin were provided. Participants were asked to specify the name of the medications. They were considered to have DM if they listed an oral DM medication and/or a form of insulin.

## POTENTIAL RISK FACTORS

Sociodemographic characteristics of the participants included sex, race/ethnicity, highest level of educational attainment, household income, and health insurance status. Race/ethnicity was included to account for racial and ethnic disparities in the prevalence of DM.<sup>16,17</sup> Body mass index (BMI) was calculated from self-reported heights and weights. Based on questions in the 2003 Behavioral Risk Factor Surveillance System, conducted through the Centers for Disease Control and Prevention (CDC), 2 measures of physical activity were included in the CCSS 2003 Follow-up Survey.<sup>18</sup> First, participants who reported either 30 minutes or more of moderate-intensity physical activity on 5 days or more per week or 20 minutes or more of vigorous-intensity physical activity on 3 days or more per week were classified as meeting the CDC recommendation for physical activity.<sup>19</sup> Second, participants were considered inactive if they reported no leisure-time physical activity in the month preceding the survey. Additional risk factors assessed among survivors included cancer diagnosis, age at diagnosis, interval from diagnosis to study, and cancer therapy.

## STATISTICAL ANALYSIS

Characteristics of survivors and siblings (age, sex, race/ethnicity, education, household income, health insurance, physical activity, and BMI [calculated as weight in kilograms divided by height in meters squared]) were compared using nonparametric bootstrap by resampling families 1000 times so that the potential within-family correlation was taken into account in the comparison.<sup>20</sup> The prevalence of DM was estimated for survivors and siblings. Logistic regression analysis was conducted to estimate the odds ratios (ORs) and associated 95% confidence intervals (CIs) for DM developing in survivors compared with siblings, with adjustment for age at interview, sex, race/ethnicity, household income, and health insurance. Because of the influence of BMI on the risk of DM, a second model was fitted, with adjustment for BMI in addition to the above-mentioned variables. Similarly, models adjusted for the participants being inactive or for not meeting the CDC recommendations for physical activity were assessed. Specific subgroups of survivors, depending on cancer type or therapy, were compared with siblings with respect to the prevalence of DM. Generalized estimating equations with nonindependent working correlations were used to modify the logistic regression after the potential within-family correlation was accounted for.<sup>21</sup> Note that there is only 1 possible nonindependent working correlation, as there is at most 1 sibling per family.

To further assess the independent effects of different cancer therapies on DM, a logistic regression analysis was performed among survivors only, after adjustment for BMI, physical activity, age at interview, sex, race/ethnicity, household income, and health insurance. Treatment exposures within the first 5 years from the original cancer diagnosis were considered. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), and 2-sided statistical inferences were used throughout the analyses.

## CHARACTERISTICS OF THE COHORT

At the time of the CCSS 2003 Follow-up Survey, there were 11 465 survivors who were alive and eligible for medical records abstraction. Of the 11 465 survivors, 1751 (15.3%) were passive or active nonrespondents, and 406 (3.5%) could not be located. Furthermore, 709 patients with a second malignant neoplasm (SMN) and/or a recurrence after 5 years since diagnosis were excluded from the analysis (32 had an SMN and a recurrence, 391 had an SMN only, and 286 had a late recurrence only). Participants did not differ from nonparticipants by diagnosis, original cancer treatment, or age at diagnosis. However, participants were slightly more likely than nonparticipants to be female (48.5% vs 43.4%;  $P < .001$ ) and slightly younger at the first contact (mean age at baseline contact, 23.7 years vs 24.3 years;  $P < .001$ ). There were 3599 siblings in the cohort who were alive when the CCSS 2003 Follow-up Survey was administered; 597 (16.6%) were active or passive nonrespondents, and 51 (1.4%) could not be located. Also, 12 siblings who developed cancer were excluded. Therefore, there were 8599 survivors and 2936 siblings available for analysis.

## COMPARISONS OF SURVIVORS WITH SIBLINGS

**Table 1** shows the characteristics of survivors and siblings. The mean age of survivors was 31.5 years (age range, 17.0-54.1), and the mean interval from cancer diagnosis to the CCSS 2003 Follow-up Survey was 23.5 years (range, 16.0-35.2). The mean age of siblings was 33.4 years (age range, 9.6-58.4). In comparison with survivors, siblings were slightly more likely to be female (53.6% vs 48.5%;  $P < .001$ ), white, and non-Hispanic (91.8% vs 85.3%;  $P < .001$ ), to have a household income of \$20 000 or more (92.6% vs 86.7%;  $P < .001$ ), and to have health insurance (90.6% vs 87.4%;  $P < .001$ ).

Of the 8599 survivors, 218 (2.5%) reported taking a medication for DM; of the 2936 siblings, 49 (1.7%) reported taking a medication for DM. Fifty-seven percent of the survivors with DM were younger than 35 years, in contrast to only 35% of the siblings (**Figure 1** and **Figure 2**). Of the 218 survivors with DM, 45 (20.6%) were using insulin only; the rest were taking oral medications with or without insulin. Similarly, 20.4% of the siblings (10/49) were using insulin alone. Therefore, at least 79% of survivors and 80% of siblings with DM had type 2 DM.

Compared with siblings and after adjustment for age at interview, sex, race/ethnicity, household income, and health insurance, survivors were 1.6 times as likely to have DM (95% CI, 1.2-2.2;  $P < .01$ ) (**Table 2**). This estimate was slightly higher when also adjusted for BMI (OR, 1.8; 95% CI, 1.3-2.5;  $P < .001$ ). Findings were not significantly different after adjustment for either not meeting the CDC recommendation for physical activity or for being inactive. Compared with siblings, the adjusted ORs (including BMI) were significantly increased for the following cancer groups: acute myeloid leukemia (AML) (OR,

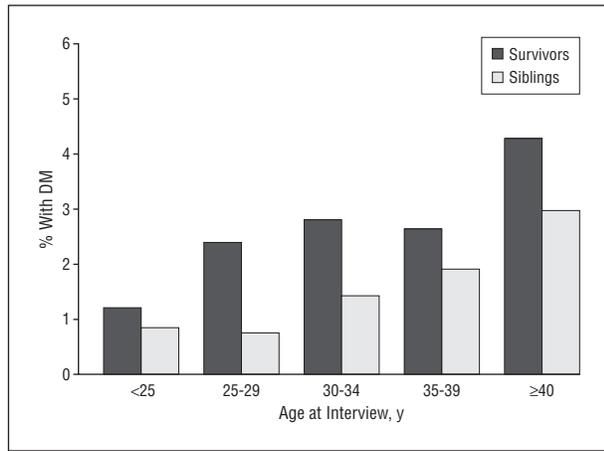
Table 1. Characteristics of the Study Participants

Variable	Survivors, % (n=8599)	Siblings, % (n=2936)	P Value
Age at interview, y			<.001
≤24	23.0	20.2	
25-29	21.8	18.0	
30-34	23.2	18.9	
35-39	17.6	17.8	
≥40	14.4	25.1	
Sex			<.001
Male	51.5	46.4	
Female	48.5	53.6	
Race/ethnicity			<.001
White, non-Hispanic	85.3	91.8	
Black, non-Hispanic	3.8	2.3	
Hispanic/Latino	4.1	3.0	
Other	6.8	2.9	
Education			.84
High school graduate or less	5.3	5.0	
High school plus some college or other training	94.7	95.0	
Household income, \$			<.001
<20 000	13.3	7.4	
≥20 000	86.7	92.6	
Health insurance			<.001
Yes or Canadian	87.4	90.6	
None	12.6	9.4	
PA measures			
Did not meet CDC recommendation for PA <sup>a</sup>	53.9	48.1	<.001
Inactive <sup>b</sup>	22.8	13.9	<.001
BMI at interview			<.001
<18.5	4.3	2.6	
18.5-24.9	44.8	45.5	
25.0-29.9	30.3	31.1	
≥30.0	20.6	20.8	
Cancer diagnosis			
Acute lymphoblastic leukemia	30.0		
Acute myeloid leukemia	2.5		
Other leukemia	2.0		
Central nervous system tumor	12.2		
Hodgkin lymphoma	11.7		
Non-Hodgkin lymphoma	7.8		
Wilms tumor	9.9		
Neuroblastoma	6.9		
Soft-tissue sarcoma	8.8		
Bone tumor	8.2		
Age at cancer diagnosis, y			
0-4	41.6		
5-9	22.6		
10-14	19.7		
15-20	16.2		
Radiation therapy			
Cranial irradiation	35.4		
Abdominal irradiation	17.0		
Total body irradiation	1.3		
Chemotherapy			
Alkylating agents	50.0		
Corticosteroids	49.1		
Anthracyclines	39.1		

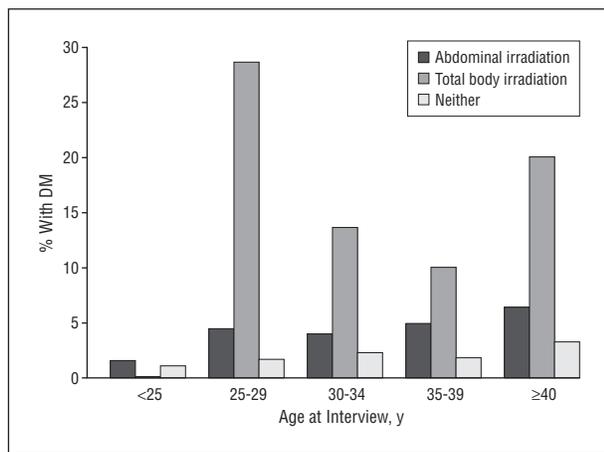
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDC, Centers for Disease Control and Prevention; PA, physical activity.

<sup>a</sup>Either 30 minutes or more of moderate-intensity PA on 5 or more days per week or 20 minutes or more of vigorous-intensity PA on 3 or more days per week.

<sup>b</sup>No leisure-time PA in preceding month.



**Figure 1.** Percentage of childhood cancer survivors and siblings with diabetes mellitus (DM) by age at interview.



**Figure 2.** Percentage of childhood cancer survivors and siblings with diabetes mellitus (DM) by age at interview for 3 treatment groups. Twenty-six patients younger than 25 years underwent total body irradiation, and none of them had DM, which is why the middle bar is absent in the “<25” category.

5.7; 95% CI, 3.1-10.6;  $P < .001$ ), neuroblastoma (OR, 2.9; 95% CI, 1.5-5.6;  $P < .01$ ), Wilms tumor (OR, 2.2; 95% CI, 1.2-3.9;  $P = .01$ ), and ALL (OR, 1.8; 95% CI, 1.2-2.6;  $P < .01$ ).

The relationship of different chemotherapy and radiation therapy exposures was assessed after adjustment for age at interview, sex, race/ethnicity, household income, and health insurance status. Treatment with an alkylating agent, corticosteroid, or anthracycline was associated with an increased prevalence of DM (Table 2). For both alkylating agents and anthracyclines, survivors with higher cumulative doses were not more likely to have DM than those with lower doses, so these treatment exposures were collapsed into yes/no variables. In survivors who were not treated with radiation therapy, there was no association between the use of alkylating agents and DM. There was no difference in the association of individual corticosteroids (dexamethasone, hydrocortisone, or prednisone) and DM, so these agents were grouped into a single corticosteroid category. Other chemotherapeutic agents, including asparaginase, were not associated with DM. Three types of radiation therapy were

**Table 2. Adjusted Odds Ratio (OR) Estimates of Diabetes Mellitus in Childhood Cancer Survivors, by Diagnosis and Therapy, Compared With Siblings<sup>a</sup>**

Variable	Not Adjusted for BMI		Adjusted for BMI	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Siblings	1 [Reference]		1 [Reference]	
All survivors	1.6 (1.2-2.2)	<.01	1.8 (1.3-2.5)	<.001
Cancer groups				
Neuroblastoma	2.5 (1.3-4.8)	<.01	2.9 (1.5-5.6)	<.01
Leukemia				
ALL	2.0 (1.4-3.0)	<.001	1.8 (1.2-2.6)	<.01
AML	5.7 (3.2-10.2)	<.001	5.7 (3.1-10.6)	<.001
Wilms tumor	1.7 (1.0-3.1)	.07	2.2 (1.2-3.9)	.01
Hodgkin lymphoma	1.3 (0.8-2.1)	.21	1.6 (1.0-2.5)	.06
Non-Hodgkin lymphoma	1.6 (0.9-2.7)	.12	1.7 (0.9-3.1)	.08
CNS tumor	1.4 (0.8-2.3)	.24	1.3 (0.8-2.3)	.34
Soft-tissue sarcoma	1.2 (0.7-2.1)	.54	1.4 (0.8-2.6)	.25
Bone tumor	1.2 (0.7-2.1)	.46	1.5 (0.9-2.7)	.14
Chemotherapy				
Any chemotherapy	1.7 (1.3-2.4)	<.001	1.9 (1.4-2.7)	<.001
Alkylating agents	1.9 (1.3-2.6)	<.001	2.1 (1.5-3.1)	<.001
Corticosteroids	1.6 (1.1-2.3)	<.01	1.7 (1.1-2.4)	<.01
Anthracyclines	1.8 (1.3-2.7)	<.01	2.1 (1.4-3.1)	<.001
Radiation therapy				
Any radiation therapy	1.8 (1.3-2.5)	<.001	1.9 (1.4-2.7)	<.001
Cranial irradiation <sup>b</sup>	1.6 (1.1-2.4)	.02	1.6 (1.0-2.3)	.03
Abdominal irradiation <sup>b</sup>	2.6 (1.8-3.8)	<.001	3.4 (2.3-5.0)	<.001
TBI	9.7 (4.9-19.1)	<.001	12.6 (6.2-25.3)	<.001

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CNS, central nervous system; TBI, total body irradiation.

<sup>a</sup>Adjusted for age at interview, sex, race/ethnicity, household income, health insurance, with and without BMI adjustment.

<sup>b</sup>Cranial and abdominal irradiation do not include TBI.

associated with DM: TBI, abdominal irradiation, and cranial irradiation.

To further investigate the relationship between radiation and DM, we compared survivors with siblings, stratified by diagnosis (neuroblastoma, Wilms tumor, Hodgkin lymphoma, AML, ALL, and central nervous system tumor) and type of radiation therapy (Table 3). Survivors who were treated with abdominal irradiation (neuroblastoma: OR, 6.9; 95% CI, 3.5-13.9;  $P < .001$ ; Wilms tumor: OR, 2.1; 95% CI, 1.1-4.0;  $P = .03$ ; and Hodgkin lymphoma: OR, 2.1; 95% CI, 1.2-3.5;  $P < .01$ ) were significantly more likely to be diabetic than siblings. After adjustment for BMI, these point estimates were further increased. In contrast, survivors of these 3 cancer groups who were not treated with abdominal irradiation were not more likely than siblings to have DM. Survivors of AML treated with and without TBI were more likely to be diabetic than siblings (with TBI: OR, 17.7, 95% CI, 6.4-49.4;  $P < .001$ ; without TBI: OR, 2.8; 1.2-6.3;  $P = .01$ ). Adjustment for BMI increased both of these estimates. Survivors of ALL who were treated with cranial irradiation were 1.8 times as likely as the siblings to report DM (95% CI, 1.2-2.8;  $P < .01$ ), with a decrease in the estimate to 1.6 (95% CI, 1.0-2.5;  $P = .06$ ) after adjustment for BMI.

**Table 3. Adjusted Odds Ratio (OR) Estimates of Diabetes Mellitus in Childhood Cancer Survivors Compared With Siblings<sup>a</sup>**

Variable	Not Adjusted for BMI		Adjusted for BMI	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Siblings	1 [Reference]		1 [Reference]	
Cancer survivors				
Neuroblastoma				
Without abdominal irradiation	0.7 (0.2-2.3)	.55	0.8 (0.2-2.7)	.73
With abdominal irradiation	6.9 (3.5-13.9)	<.001	9.2 (4.5-18.9)	<.001
Wilms tumor				
Without abdominal irradiation	0.6 (0.1-2.6)	.52	0.8 (0.2-3.3)	.72
With abdominal irradiation	2.1 (1.1-4.0)	.03	2.7 (1.4-5.3)	<.01
Hodgkin lymphoma				
Without abdominal irradiation	0.5 (0.2-1.4)	.20	0.5 (0.2-1.5)	.26
With abdominal irradiation	2.1 (1.2-3.5)	<.01	2.7 (1.6-4.5)	<.001
AML				
Without total body irradiation	2.8 (1.2-6.3)	.01	3.0 (1.3-6.8)	.01
With total body irradiation	17.7 (6.4-49.4)	<.001	23.8 (8.2-69.5)	<.001
ALL				
Without cranial irradiation	1.4 (0.7-2.6)	.34	1.3 (0.7-2.6)	.39
With cranial irradiation	1.8 (1.2-2.8)	<.01	1.6 (1.0-2.5)	.06
CNS tumor				
Without cranial irradiation	0.8 (0.3-2.2)	.64	0.9 (0.3-2.5)	.84
With cranial irradiation	1.0 (0.5-2.0)	.98	1.0 (0.5-2.1)	.94

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CNS, central nervous system.

<sup>a</sup>Adjusted for age at interview, sex, race/ethnicity, household income, health insurance, with and without BMI adjustment. Cranial and abdominal irradiation do not include total body irradiation.

As noted above, we could not ascertain whether patients who were using insulin had type 1 or 2 DM. When the above analyses were repeated, excluding all survivors and siblings who were using insulin only, the findings were not different (data not shown).

#### COMPARISONS AMONG SURVIVORS (WITHOUT SIBLINGS)

A multivariate logistic regression model (**Table 4**) was used to estimate the odds of the survivors having DM and included sociodemographic factors that are associated with DM in the general population (age, sex, race/ethnicity, household income, insurance, physical inactivity, and BMI category). Survivors who were treated with abdominal irradiation were 2.7 times as likely to report DM (95% CI, 1.9-3.8;  $P < .001$ ) as those who were not treated with abdominal irradiation or TBI; those treated with TBI were 7.2 times as likely to report DM (95% CI, 3.4-15.0;

**Table 4. Results of a Multivariate Logistic Regression Analysis for Diabetes Mellitus in Childhood Cancer Survivors**

Variable	OR (95% CI)	P Value
Radiation therapy		
Abdominal irradiation <sup>a</sup>	2.7 (1.9-3.8)	<.001
Total body irradiation	7.2 (3.4-15.0)	<.001
No abdominal RT or TBI	1 [Reference]	
Chemotherapy		
Alkylating agents	1.7 (1.2-2.3)	<.01
No alkylating agents	1 [Reference]	
Age at cancer diagnosis, y		
0-4	2.4 (1.3-4.6)	<.01
5-9	1.5 (0.8-2.7)	.70
10-14	1.1 (0.7-1.8)	.09
15-20 (referent)	1 [Reference]	
Age at interview, y		
≤24	1 [Reference]	
25-29	2.7 (1.4-4.9)	<.01
30-34	3.4 (1.8-6.4)	<.001
35-39	3.8 (1.8-8.0)	<.001
≥40	8.0 (3.6-17.6)	<.001
Sex		
Female	1.3 (1.0-1.8)	.07
Male	1 [Reference]	
Race/ethnicity		
White, non-Hispanic	1 [Reference]	
Black, non-Hispanic	1.7 (0.8-3.5)	.18
Hispanic/Latino	2.1 (1.1-3.8)	.02
Other/unknown	0.9 (0.5-1.8)	.79
Household income, \$		
<20 000	1.5 (0.9-2.4)	.09
≥20 000	1 [Reference]	
Income unknown	1.0 (0.6-1.7)	.95
Health insurance		
Yes or Canadian	0.7 (0.4-1.2)	.23
None	1 [Reference]	
Met the CDC recommendation for PA <sup>b</sup>		
No	1.5 (1.1-2.1)	.02
Yes	1 [Reference]	
BMI at interview		
<18.5	0.8 (0.3-2.2)	.63
18.5-24.9	1 [Reference]	
25.0-29.9	2.0 (1.3-3.0)	.001
≥30	4.3 (2.9-6.4)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDC, Centers for Disease Control and Prevention; CI, confidence interval; OR, odds ratio; PA, physical activity.

<sup>a</sup>Abdominal irradiation does not include total body irradiation.

<sup>b</sup>Either 30 minutes or more of moderate-intensity PA on 5 or more days per week or 20 minutes or more of vigorous-intensity PA on 3 or more days per week.

$P < .001$ ). In this final model, cranial irradiation was not associated with DM.

After adjustment for radiation therapy, previous treatment with an alkylating agent also increased the risk of DM (OR, 1.7; 95% CI, 1.2-2.3;  $P < .01$ ). However, there was not a significant interaction between alkylating agent exposure and either abdominal irradiation ( $P = .32$ ) or TBI ( $P = .97$ ). In the adjusted multivariate model with different treatment exposures, previous therapy with corticosteroids or asparaginase was not associated with DM.

Age at cancer diagnosis modified the risk of DM, with survivors who were diagnosed before the age of 5 years being 2.4 times as likely to report DM (95% CI, 1.3-4.6;

$P < .01$ ) as those who were diagnosed in late adolescence (age range, 15-20 years). As in the general population, older age, black or Hispanic/Latino background, lower household income, physical inactivity, and increased BMI were associated with an increased risk of DM. The final model was not significantly different when survivors who were using insulin only were excluded (data not shown).

## COMMENT

Among this large and diverse cohort of young adult survivors of childhood cancer, we found an almost 2-fold increased risk of self-reported DM, primarily of probable type 2, in comparison with their siblings. This risk was most evident for survivors of AML, neuroblastoma, Wilms tumor, and Hodgkin lymphoma who were treated with TBI or abdominal irradiation. Importantly, this risk was independent of obesity and physical inactivity. Survivors of ALL who were treated with cranial irradiation were also more likely than the siblings to be diabetic, but this finding was in part related to increased BMI and physical inactivity. The relationship between cranial irradiation and insulin resistance has been well described<sup>7,22-24</sup> and is an expected outcome of the increased prevalence of obesity after cranial radiation therapy in this population.<sup>13,25</sup> Furthermore, Mohn et al<sup>26</sup> suggest that impaired  $\beta$ -cell function may persist after chemotherapy for ALL. Therefore, the following discussion focuses on the less well-characterized association between DM and abdominal irradiation and TBI. Indeed, the diabetes observed among this irradiated cancer population may represent a form of therapy-induced DM and may be the result of an impairment of insulin release and specific  $\beta$ -cell lesions.<sup>27</sup>

To our knowledge, DM after abdominal irradiation for neuroblastoma has not previously been reported. Neuroblastoma survivors who were treated with abdominal irradiation had a 9-fold increased likelihood of being diabetic in comparison with siblings, after adjustment for BMI. In contrast, those who were not treated with abdominal irradiation did not have an increased risk of DM. This pattern was also seen in the 2 other groups of survivors who were commonly exposed to abdominal irradiation. For both Wilms tumor and Hodgkin lymphoma survivors, a significantly increased risk of DM in comparison with siblings was observed only in those who were treated with abdominal irradiation. To date, there are a few studies that have assessed the risk of DM after abdominal irradiation. In a small retrospective chart review of 121 Wilms tumor survivors, 8 (6.6%) developed DM, which was controlled with either diet or treatment with an oral medication in 6 of them.<sup>11</sup> Conversely, among 4387 childhood cancer survivors who had a median age of 29.8 years, Hawkins et al<sup>28</sup> did not find an increased prevalence of DM associated with abdominal irradiation.

There are several mechanisms by which abdominal irradiation may lead to DM. The pancreas is in the field of left-sided (or bilateral) abdominal irradiation. Small studies of animals suggest that, after radiation therapy, the pancreatic islet cells show evidence of degranulation, vacu-

olization, mitochondrial destruction, and impaired insulin secretion.<sup>29,30</sup> Pancreatic insufficiency, relative or absolute, may result after irradiation. It is of interest, however, that most survivors in our study who developed DM after abdominal irradiation were either taking an oral medication or receiving combination therapy, suggesting that, if they have  $\beta$ -cell dysfunction, it is not absolute. Therefore, there are likely other mechanisms by which abdominal irradiation leads to DM. Alterations in adipose-derived hormones after radiation therapy may lead to insulin resistance. Adipose tissue, which was originally thought to have only an energy storage function, is now recognized as an endocrine organ, producing and secreting a variety of factors, including leptin, resistin, and adiponectin.<sup>31,32</sup> Perhaps the production of adiponectin or other adipose-derived hormones is a radiosensitive process, and decreased levels may be a late effect of therapeutic abdominal irradiation.

Our finding of an association between TBI and DM confirms the findings of other recent studies.<sup>4-9</sup> Generally, the studies suggest that DM after TBI is due to hyperinsulinemia rather than to  $\beta$ -cell insufficiency.<sup>6,7,9</sup> It is likely that the development of DM after TBI is multifactorial. Needless to say, the mechanisms described above with abdominal irradiation may also apply to patients who have been treated with TBI. Notably, though, the radiation dose to the abdomen is lower with TBI (12-15 Gy [1200-1500 rad]) than with abdominal irradiation (20-30 Gy [2000-3000 rad]) for the treatment of neuroblastoma or Wilms tumor. Growth hormone deficiency (GHD) is common among childhood cancer survivors who are treated with TBI, particularly those who are treated at a young age.<sup>33,34</sup> In noncancer populations, GHD is associated with insulin resistance<sup>35,36</sup> and is likely one of the primary pathways by which ALL survivors become insulin resistant.<sup>22,37</sup> Neville et al<sup>7</sup> did not find an association between GHD and insulin resistance. Rather, they found that untreated hypogonadism and abdominal obesity were predictive of insulin resistance or hyperinsulinemia. The relationship of hypogonadism and insulin resistance among childhood cancer survivors has been reported by others.<sup>6,9</sup> In the general population, men with androgen insufficiency have an increased prevalence of insulin resistance and metabolic syndrome.<sup>38-40</sup> However, this increase has not been reported in women with ovarian failure.

Interestingly, both GHD and androgen deficiency contribute to abdominal obesity.<sup>38,40</sup> Abdominal obesity, particularly an increase in visceral adipose tissue, is strongly associated with the development of insulin resistance.<sup>41-43</sup> It is thought that visceral fat is the more metabolically active fat, and its ability to challenge the liver directly with free fatty acids may play a crucial role in insulin resistance.<sup>41,44</sup> Elevated levels of intrahepatic free fatty acids delivered directly through the portal system can lead to increased hepatic glucose production and reduced insulin sensitivity. Of note, recent studies within the human immunodeficiency-infected population reported redistribution of adipose tissue in patients who were taking a protease inhibitor. In these patients with human immunodeficiency-associated adipose redistribution syndrome, there is an increase in visceral adi-

pose tissue that is strongly correlated with insulin resistance and dyslipidemia.<sup>45</sup>

When interpreting the findings of this study, there are several limitations that need to be recognized. Diabetes was attributed to participants who stated that they were taking a medication commonly used to treat DM or hyperinsulinemia. Misclassification resulting from reporting medications for DM is likely low. There is, however, a greater probability of misclassification resulting from undiagnosed DM. Also, survivors who are aware of their increased risk for chronic health problems might be more likely to seek medical care than their siblings and therefore more likely to be diagnosed as having a condition such as DM, leading to potential ascertainment bias and overestimates of risk. The sibling cohort is intended to represent a general, noncancer population. While some outcomes may be different between siblings and the general population, we previously did not find any difference between the siblings and age- and sex-matched participants in national surveys with respect to BMI or meeting the CDC recommendations for physical activity.<sup>46-48</sup> Nonparticipation may have introduced a selection bias in the study; 19% of the eligible survivors did not participate in this survey. Notably, participants did not differ from nonparticipants by diagnosis, original cancer treatment, or age at cancer diagnosis. Lastly, the cross-sectional design of this study precludes inferences of temporality, causality, and risk.

In summary, the prevalence of DM was almost twice as high in childhood cancer survivors than in their siblings, with the risk being markedly increased in those who were treated with either TBI or abdominal irradiation. It is likely that this additional chronic disease in childhood cancer survivors, who frequently also sustain damage to the heart, kidneys, and endocrine system,<sup>1</sup> will lead to further morbidity and premature mortality. Therefore, it is imperative that clinicians recognize this risk, screen for diabetes and prediabetes when appropriate, and approach survivors with aggressive risk-reducing strategies. Moreover, further research is warranted to understand the pathways by which these 2 modes of radiation therapy lead to diabetes.

**Accepted for Publication:** April 24, 2009.

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**Author Contributions:** Drs Oeffinger and Robison had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Meacham, Sklar, Robison, and Oeffinger. *Acquisition of data:* Meacham, Sklar, Whitton, Stovall, and Robison. *Analysis and interpretation of data:* Meacham, Sklar, Li, Liu, Gimpel, Yasui, Stovall, and Oeffinger. *Drafting of the manuscript:* Meacham and Oeffinger. *Critical revision of the manuscript for important intellectual content:* Meacham, Sklar, Li, Liu, Gimpel, Yasui, Whitton, Stovall, Robison, and Oeffinger. *Statistical analysis:* Li, Liu, Gimpel, and Yasui. *Obtained funding:* Robison. *Administrative, technical, and material support:* Whitton and Stovall. *Study supervision:* Robison and Oeffinger.

**Financial Disclosure:** None reported.

**Funding/Support:** This work was supported by grant U24-CA-55727 (Dr Robison, Principal Investigator) from the Department of Health and Human Services, by funding to the University of Minnesota from the Children's Cancer Research Fund, and by funding to St Jude Children's Research Hospital from the American Lebanese Syrian Associated Charities (ALSAC).

**Role of the Sponsors:** The funding organizations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

**Additional Information:** The eAppendix is available at <http://www.archinternmed.com>.

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