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Modifiable Risk Factors and Major Cardiac Events Among Adult Survivors of Childhood Cancer

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ABSTRACT

Purpose
To evaluate the relative contribution of modifiable cardiovascular risk factors on the development of major cardiac events in aging adult survivors of childhood cancer.

Patients and Methods
Among 10,724 5-year survivors (median age, 33.7 years) and 3,159 siblings in the Childhood Cancer Survivor Study, the prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity was determined, along with the incidence and severity of major cardiac events such as coronary artery disease, heart failure, valvular disease, and arrhythmia. On longitudinal follow-up, rate ratios (RRs) of subsequent cardiac events associated with cardiovascular risk factors and cardiotoxic therapy were assessed in multivariable Poisson regression models.

Results
Among survivors, the cumulative incidence of coronary artery disease, heart failure, valvular disease, and arrhythmia by 45 years of age was 5.3%, 4.8%, 1.5%, and 1.3%, respectively. Two or more cardiovascular risk factors were reported by 10.3% of survivors and 7.9% of siblings. The risk for each cardiac event increased with increasing number of cardiovascular risk factors (all $P_{trend} < .001$). Hypertension significantly increased risk for coronary artery disease (RR, 6.1), heart failure (RR, 19.4), valvular disease (RR, 13.6), and arrhythmia (RR, 6.0; all P values $< .01$). The combined effect of chest-directed radiotherapy plus hypertension resulted in potentiation of risk for each of the major cardiac events beyond that anticipated on the basis of an additive expectation. Hypertension was independently associated with risk of cardiac death (RR, 5.6; 95% CI, 3.2 to 9.7).

Conclusion
Modifiable cardiovascular risk factors, particularly hypertension, potentiate therapy-associated risk for major cardiac events in this population and should be the focus of future interventional studies.

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INTRODUCTION

Although more than 80% of children diagnosed with a malignancy will become 5-year survivors,[1] therapy-related cardiac disease is established as a primary cause of noncancer morbidity and mortality.[2-5] Chest-directed radiotherapy (RT) is associated with increased risk of myocardial infarction, congestive heart failure, valvular heart disease, and arrhythmias.[6-9] Anthracycline chemotherapy increases risk of heart failure.[9,10] Although clinical trials are attempting to limit exposure, these cardiotoxic therapies remain an important component of curative regimens for many childhood malignancies.

In the general population, hypertension, diabetes, obesity, dyslipidemia, and smoking are primary contributors to the development of coronary artery disease and heart failure.[11,12] Although some cancer therapies increase risk for hypertension,[13,14] diabetes mellitus,[15-17] dyslipidemia,[15] and obesity,[18,19] many long-term survivors will develop traditional, modifiable risk factors related to aging, hereditary predisposition, or unhealthy lifestyle behaviors. To reduce the severity of cardiac disease in this high-risk population, it is imperative to determine the extent to which modifiable cardiovascular risk factors further potentiate cancer therapy–associated cardiac risk. Thus, we used the Childhood Cancer Survivor Study (CCSS) cohort, now with an additional

Table 1. Demographic, Treatment, and Cardiovascular Risk Factor Characteristics of Survivors and Siblings at Last Individual Contact

Characteristic	Survivors (n = 10,724) No.	Survivors (n = 10,724) %*	Siblings (n = 3,159) No.	Siblings (n = 3,159) %*
Sex				
Male	5,623	52.4	1,515	48.0
Female	5,101	47.6	1,644	52.0
Race/ethnicity				
Non-Hispanic white	9,442	88.0	2,786	88.2
Non-Hispanic black	428	4.0	72	2.3
Hispanic	502	4.7	105	3.3
Other	352	3.3	196	6.2
Age at diagnosis, years				
< 5	4,408	41.1		
5-9.9	2,362	22.0		
10-14.9	2,149	20.0		
15-20.9	1,805	16.8		
Age at enrollment, years				
< 20	502	4.7	143	4.5
20-29.9	3,186	29.7	792	25.1
30-39.9	4,360	40.7	1,139	36.1
40-49.9	2,374	22.1	855	27.1
≥ 50	302	2.8	230	7.3
Cancer diagnosis				
Acute lymphoblastic leukemia	3,237	30.2		
Acute myeloid leukemia	280	2.6		
Other leukemia	78	0.7		
Astrocytomas	823	7.7		
Medulloblastoma/PNET	277	2.6		
Other CNS tumors	232	2.2		
Hodgkin lymphoma	1,368	12.8		
Non-Hodgkin lymphoma	835	7.8		
Wilms tumors	1,030	9.6		
Neuroblastoma	762	7.1		
Soft tissue sarcoma	935	8.7		
Ewing sarcoma	269	2.5		
Osteosarcoma	559	5.2		
Other bone tumors	39	0.4		
Chest-directed radiotherapy				
Yes	2,532	26.4		
No	7,058	73.6		
Anthracycline chemotherapy				
Yes	3,779	38.9		
No	5,934	61.1		
Diabetes mellitus				
Yes	397	3.7	75	2.4
No	10,327	96.3	3,084	97.6
Hypertension				
Yes	1,602	14.9	304	9.6
No	9,122	85.1	2,855	90.4
Dyslipidemia				
Yes	959	8.9	190	6.0
No	9,765	91.1	2,969	94.0
Obesity				
Yes	2,308	21.7	727	23.1
No	8,325	78.3	2,425	76.9
Multiple (≥ 2) cardiovascular risk factors				
Yes	1,109	10.3	248	7.9
No	9,611	89.7	2,910	92.1

Abbreviation: PNET, primitive neuroectodermal tumor.
*Percentages for individual characteristics calculated on total number of participants on whom information was available.

decade of follow-up from our initial report,[8] to evaluate the relative contribution of cancer therapy combined with the subsequent development of selected modifiable cardiovascular risk factors in the longitudinal development of major cardiac events.

PATIENTS AND METHODS

Population

The CCSS is a retrospective cohort study, with longitudinal follow-up of survivors of childhood cancer treated at 26 institutions in the United States and Canada. Eligibility for participation in the CCSS includes diagnosis of cancer before age 21; initial treatment between January 1, 1970, and December 31, 1986; and being alive at 5 years after diagnosis of leukemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or a bone tumor. A random sample of siblings of CCSS participants served as a comparison population (n = 4,023). The cohort methodology and study design have been previously described in detail.[20,21] The CCSS was approved by institutional review boards at the 26 participating centers. Participants provided informed consent.

All participants completed a baseline questionnaire (1994 to 1999) that included demographics, personal/family medical history, and history of health conditions including cardiovascular outcomes. A surrogate (parent, spouse, next of kin) completed the baseline questionnaire for survivors who died more than 5 years after diagnosis who were younger than age 18 or unable to complete the questionnaire. In addition, information on cardiovascular outcomes was collected on two subsequent follow-up questionnaires, most recently administered from 2007 to 2009. Siblings similarly participated in the baseline questionnaire and all follow-up questionnaires.

Survivors who completed the baseline questionnaire and at least one of two follow-up questionnaires or were subsequently deceased were considered eligible for longitudinal evaluation of cardiovascular risk factors and subsequent cardiac events (Table 1; Fig 1). Survivors who developed a second

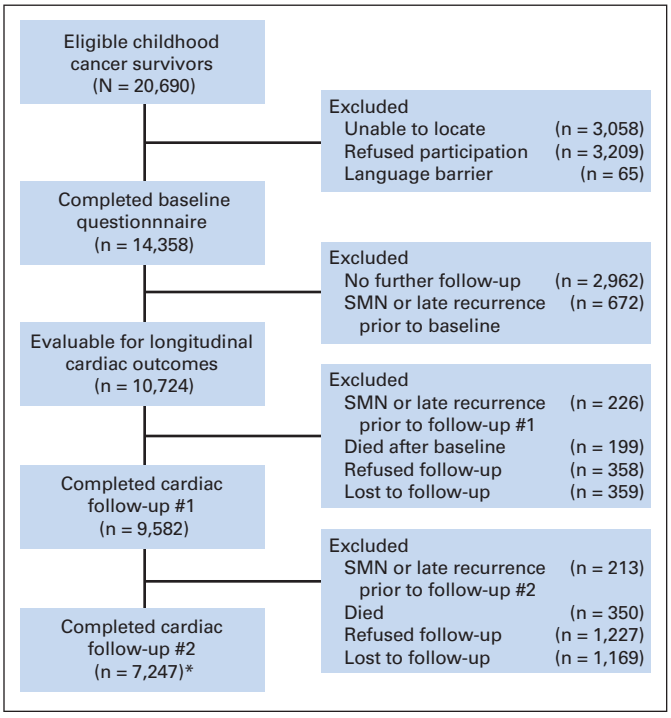

Fig 1. Study population: recruitment and longitudinal participation. SMN, second malignant neoplasm. (*) 624 survivors who did not participate in follow-up #1 subsequently completed follow-up #2.

Table 2. Cardiac Conditions by CTCAE Grade

Grade	Description	Coronary Artery Disease	Heart Failure	Valvular Disease	Arrhythmia
3	Severe	Myocardial infarction, angina, or coronary heart disease not requiring catheterization but on antianginal medication	Cardiomyopathy or congestive heart failure requiring medication	None	Arrhythmia requiring pacemaker
4	Life-threatening	Myocardial infarction requiring catheterization, angioplasty, or coronary artery bypass grafting	Cardiac transplantation	Heart valve replacement	Ventricular fibrillation
5	Death	Death as a result of acute myocardial infarction, ischemic heart disease, or atherosclerosis	Death as a result of heart failure	Death as a result of valvular heart disease	Death as a result of dysrhythmia

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

malignant neoplasm (SMN) or late recurrence (5 or more years from diagnosis) of primary cancer before the baseline questionnaire were excluded from analysis because treatment information for these neoplasms was not uniformly obtained.

Major Cardiac Events

At baseline and subsequent follow-up evaluations, participants completed a multi-item questionnaire that included age at onset of cardiac events. Severity scoring was applied on the basis of the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE, version 4.03), intended for scoring both acute and chronic conditions in patients with and survivors of cancer.[22] We considered four cardiac conditions—coronary artery disease, heart failure, valvular disease, and arrhythmia—and included only conditions graded as severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5; Table 2). If the information needed to distinguish between grades was insufficient, the lower grade was used. For assessment of cardiac mortality, the CCSS cohort was linked with the National Death Index to ascertain cardiac deaths (International Classification of Diseases, 9th revision [ICD-9] codes 390 to 398, 402, 404, and 410 to 429 or ICD-10 codes I00 to I02, I05 to I09, I11, I13, I20 to I28, and I30 to I52).

Cardiovascular Risk Factor Definitions

Study questionnaires included self-report of all prescribed medications taken regularly (consistently for $>$ 1 month or for 30 days or more in 1 year) during the previous 2-year period. Patients with diabetes, hypertension, and dyslipidemia were defined as those who reported being diagnosed by a physician with the condition(s) and who reported taking specific medications prescribed for the treatment of the condition(s). Obesity was defined as a body mass index $\geq$ 30 kg/m^2 calculated from self-report of height and weight. For survivors younger than age 20 years, obesity was defined as a body mass index in the 95th percentile or above for age- and sex-specific distributions for US children. Smoking was not found to be associated with risk of a major cardiac event. Thus, although we adjusted for smoking in the risk factor analyses, specific risks for smoking are not presented.

Cancer Therapeutic Exposures and Additional Factors

Cancer diagnosis and treatment data were abstracted from medical records and included anthracycline exposure[21] and chest-directed RT defined as any RT to the chest field.[23] Sex, race/ethnicity, household income, and education level were available from the questionnaires.

Statistical Methods

Demographic, disease, and treatment characteristics were tabulated at last contact. Cumulative incidences of cardiac events with 95% CIs were calculated for survivors stratified by treatment exposure. Death, SMN, and late recurrence (survivors only) were taken as competing risk events. Prevalence of individual and multiple cardiovascular risk factors were calculated by using reported events from each questionnaire and were tabulated according to age at questionnaire completion to describe the age-specific prevalence. Rates for survivors were compared with rates for the sibling population.

To assess the association of cardiac events with the presence of cardiovascular risk factors after having been exposed to chest-directed RT or anthracyclines, multivariable Poisson regression analysis was performed to calculate the rate ratio (RR) and 95% CI according to the number of cardiovascular risk factors present for each of the four types of cardiac events, conditioned on the chest-directed RT and on anthracycline exposures. Analysis was restricted to the survivor population. Time at risk for cardiac events ended at the first cardiac event of interest, SMN, late recurrence, death, or completion of the last questionnaire. Regression models included age, household income, current smoking status, and education, which were treated as time dependent, and sex, race, chest-directed RT exposure (yes/no), and anthracycline exposure (yes/no). In addition, the relative excess risk due to interaction (RERI) was used to determine whether the interaction effects of treatment with cardiovascular risk factors were more than additive when present together. The bootstrap method was used to calculate the statistical significance for RERI.

Multivariable Poisson regression, adjusted for the same variables as the event analysis, was also used to evaluate potential associations of cardiac-specific mortality with the presence of cardiovascular risk factors. Time at risk for cardiac death started at the completion of the baseline questionnaire when cardiovascular risk factors were first assessed and ended at the earliest of cardiac death, occurrence of SMN, late recurrence, death as a result of other causes, or date of the last mortality ascertainment (ie, National Death Index, December 31, 2007, for US participants and the last questionnaire date for Canadian participants).

RESULTS

Comparisons of Survivors With Siblings

As shown in Figure 1, 10,724 5-year survivors completed the baseline questionnaire and were eligible for evaluation. Demographic and treatment characteristics for survivors and siblings (n = 3,159) at last individual contact are provided in Table 1. Median age at last follow-up of survivors was 33.7 years (range, 11.0 to 58.9 years) at a median of 25.6 years (range, 7.4 to 39.3 years) from cancer diagnosis. The median age at last follow-up of siblings was 36.0 years (range, 7.1 to 62.6 years). Appendix Table A1 (online only) summarizes participation rates at baseline compared with the last follow-up survey.

Among survivors, the cumulative incidence of grade 3 to 5 cardiac events by 45 years of age was 5.3% (95% CI, 4.4% to 6.1%) for coronary artery disease, 4.8% (95% CI, 4.1% to 5.6%) for heart failure, 1.5% (95% CI, 1.0% to 2.0%) for valvular disease, and 1.3% (95% CI, 0.9% to 1.7%) for arrhythmia. The cumulative incidence of cardiac events was associated with exposure to cardiotoxic therapies ($P < .001$; Fig 2). Among siblings, cardiac events were uncommon (Appendix Table A2, online only) with cumulative incidences by age 45 years of 0.9% (95% CI, 0.4% to 1.4%) for coronary artery disease, 0.3% (95% CI, 0.05% to 0.6%) for heart

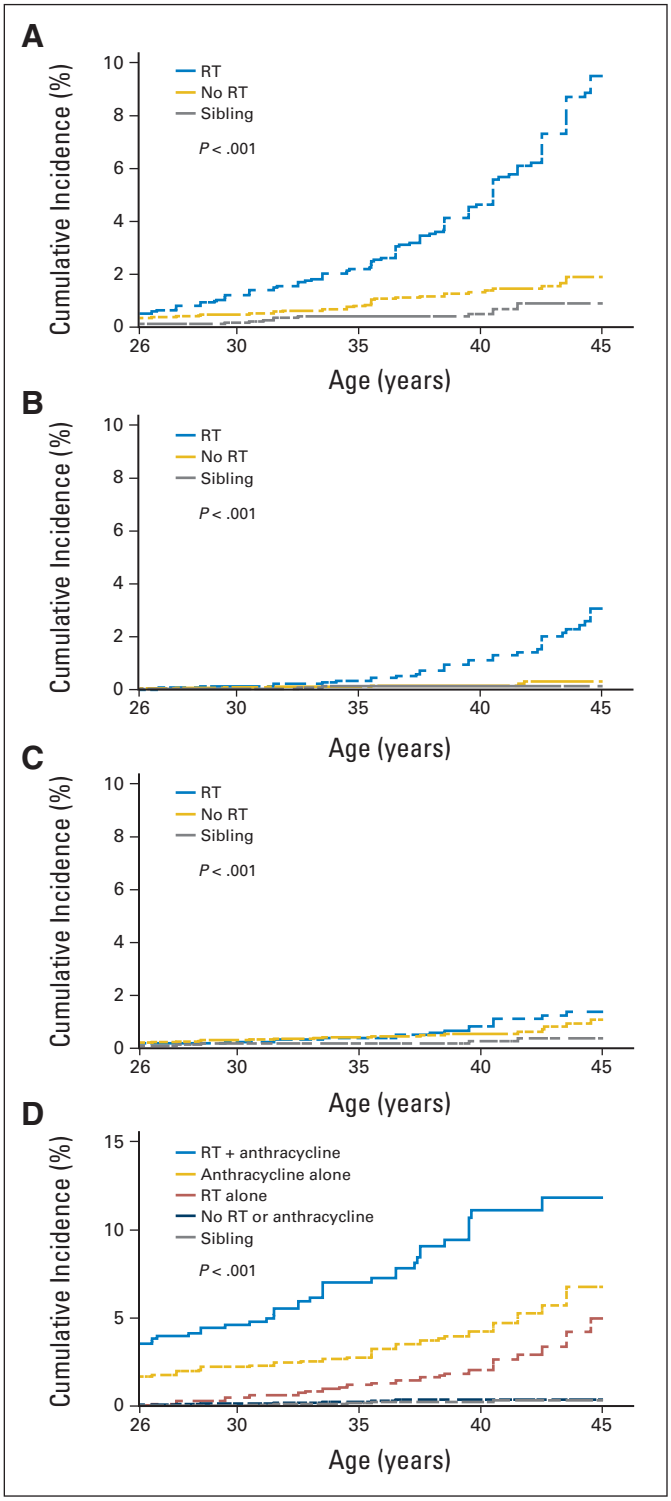

Fig 2. Age-specific cumulative incidence of the four major cardiac events—(A) coronary artery disease, (B) valvular disease, (C) arrhythmia, and (D) heart failure—by therapeutic exposure (survivors) compared with siblings. RT, chest-directed radiotherapy.

failure, 0.1% (95% CI, 0.0% to 0.3%) for valvular disease, and 0.4% (95% CI, 0.06% to 0.7%) for arrhythmia.

Two or more cardiovascular risk factors were reported by 10.3% of survivors and 7.9% of siblings (Table 1). With aging, the prevalence of cardiovascular risk factors increased among survivors and was statistically significantly greater than that for siblings at age 50 years for hypertension (40.2% *v* 25.5%; $P < .001$) and dyslipidemia (23.0% *v* 13.6%; $P = .008$; Appendix Fig A1). The prevalence of obesity was higher among siblings at age 50 (25.2% *v* 31.3%; $P = .02$).

Comparisons Among Survivors

Multivariable models demonstrated that the presence of hypertension alone significantly increased risk for all major cardiac events among survivors exposed to both chest-directed RT and anthracycline (Table 3). However, development of dyslipidemia, diabetes, and obesity each increased risk over therapeutic exposure alone only for certain outcomes. The risk for each cardiac event increased with increasing number of cardiovascular risk factors (P for trend $< .001$ for all cardiac events). However, combinations of risk factors that included hypertension were associated with the highest risk estimates for association with coronary artery disease (hypertension plus diabetes: RR, 23.5; 95% CI, 7.1 to 77.8), heart failure (hypertension plus diabetes: RR, 35.3; 95% CI, 12.1 to 103.3), and valvular disease (hypertension plus obesity: RR, 20.6; 95% CI, 7.2 to 8.7) after exposure to chest-directed RT.

To define the impact of the combination of cardiotoxic therapeutic exposure plus acquired cardiovascular risk factors, we calculated the RERI of these factors. An interaction term statistically significantly greater than zero indicated that interaction between treatment and cardiovascular risk factor is more than additive. Table 4 classifies all survivors on the basis of cardiotoxic exposure and presence of cardiovascular risk factors and provides RRs for comparison with survivors who had no cardiotoxic exposure and no risk factors (referent group) for each major cardiac event. Survivors treated with chest-directed RT who developed two or more cardiovascular risk factors of which one was hypertension, demonstrated a statistically significant increased RERI for development of coronary artery disease (RERI, 27.9; 95% CI, 14.6 to 51.0), heart failure (RERI, 18.3; 95% CI, 7.6 to 37.4), valvular disease (RERI, 60.9; 95% CI, 18.0 to 487.0), and arrhythmia (RERI, 8.6; 95% CI, 1.7 to 21.7; Table 4) suggesting potentiation of risk for major cardiac events. However, when survivors had multiple risk factors that did not include hypertension, statistically significantly increased RERI was not observed (Table 4).

In multivariable models, subsequent development of hypertension (RR, 5.6; 95% CI, 3.2 to 9.7) or two or more cardiovascular risk factors (RR, 2.4; 95% CI, 1.2 to 4.9) was significantly associated with cardiac-specific mortality but not diabetes alone (RR, 2.2; 95% CI, 0.8 to 6.1), dyslipidemia alone (RR, 1.7; 95% CI, 0.7 to 3.8), or obesity alone (RR, 1.2; 95% CI, 0.6 to 2.3).

DISCUSSION

It is well established that long-term survivors of childhood cancer have an increased risk of major cardiac events and cardiac-specific mortality, which is associated with exposure to anthracycline chemotherapy and chest-directed RT in a dose-dependent manner.[2,3,8,24] In this study, we demonstrated in a relatively young survivor population that acquisition of modifiable cardiovascular risk factors, particularly hypertension, increases risk for severe, life-threatening, and fatal (grades 3 to 5) cardiac events, which is independent of cancer therapy–related risk. Moreover, among survivors who received chest-directed RT and

Table 3. Treatment-Specific RRs for Grade 3 to 5 Cardiac Events According to the Number of Reported Cardiovascular Risk Factors and by Individual Risk Factor

	Chest-Directed Radiotherapy												Anthracycline Chemotherapy for Heart Failure		
	Coronary Artery Disease			Heart Failure			Valvular Disease			Arrhythmia					
Variable	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
No. of risk factors*			< .001†			< .001†			< .001†			< .001†			< .001†
4	17.6	5.3 to 58.3	< .001	—	0.0 to 20.1	1.0	25.4	5.3 to 121.3	< .001	39.5	7.5 to 207.4	< .001	—	0.0 to 19.9	1.0
Any 3	13.7	6.7 to 27.8	< .001	16.9	7.2 to 40.1	< .001	8.6	2.3 to 32.6	.002	10.5	2.0 to 53.7	.005	9.3	3.2 to 26.8	< .001
Any 2	10.4	6.1 to 17.7	< .001	10.4	5.6 to 19.3	< .001	12.2	5.0 to 29.8	< .001	5.9	1.6 to 21.4	.007	6.2	3.3 to 11.6	< .001
Any 1	4.0	2.5 to 6.4	< .001	6.0	3.6 to 10.0	< .001	6.5	2.9 to 14.4	< .001	4.1	1.4 to 12.0	.009	4.3	2.8 to 6.7	< .001
None	1.0			1.0			1.0			1.0			1.0		
Individual and combinations of risk factors‡															
Hypertension alone	6.1	3.4 to 11.2	< .001	19.4	11.4 to 33.1	< .001	13.6	5.7 to 32.4	< .001	6.0	1.7 to 21.8	.006	12.4	7.6 to 20.1	< .001
Dyslipidemia alone	4.7	2.0 to 10.7	< .001	1.1	0.2 to 8.5	.90	5.4	1.4 to 20.7	.01	2.9	0.3 to 24.6	.33	1.1	0.1 to 8.0	.93
Diabetes alone	2.7	0.4 to 20.0	.32	5.7	1.3 to 24.3	.02	0.0	0.0 to 21.8	—	14.2	1.7 to 118.9	.01	4.3	1.0 to 17.8	.05
Obesity alone	2.8	1.5 to 5.3	.001	0.9	0.3 to 2.9	.85	2.4	0.6 to 8.9	.19	2.5	0.5 to 12.5	.26	1.6	0.8 to 3.3	.21
Hypertension + dyslipidemia only	20.9	11.1 to 39.4	< .001	7.8	2.6 to 23.1	< .001	11.9	3.8 to 37.8	< .001	10.1	2.4 to 43.3	.002	11.3	4.6 to 27.5	< .001
Hypertension + diabetes	23.5	7.1 to 77.8	< .001	35.3	12.1 to 103	< .001	18.1	2.2 to 146.1	.007	—	—	—	16.9	5.1 to 55.7	< .001
Hypertension + obesity	5.8	2.2 to 14.9	< .001	18.4	8.8 to 38.6	< .001	20.6	7.2 to 58.7	< .001	5.8	0.7 to 48.2	.11	6.5	2.5 to 16.5	< .001
No risk factors	1.0			1.0			1.0			1.0			1.0		

NOTE. All models included age, household income, and education as time-dependent variables and sex, race, smoking, chest-directed radiotherapy, and anthracycline exposure. Grade was determined according to CTCAE version 4.03.[22]

Abbreviation: RR, rate ratio.

*The results were based on a single model that included the entire study population.

†*P* value for trend.

‡The results were based on one model of the entire study population in which survivors with only one risk factor were separated into four groups (hypertension alone, dyslipidemia alone, diabetes alone, obesity alone). Survivors with all other combinations or with no risk factors were included in the model but only selected risk estimates are displayed.

subsequently developed certain individual risk factors or two or more risk factors that included hypertension, the observed risk was greater than what would be expected under an additive assumption. The clinical implications of these findings are of great importance. Early diagnosis and appropriate management of hypertension, diabetes, dyslipidemia, and obesity in at-risk, aging survivors may substantially reduce the risk of premature cardiac disease.

In the general population, the contribution of modifiable risk factors in the development of cardiovascular disease is well defined.[11,12] In addition, specific cancer therapies appear to increase the prevalence of some cardiovascular risk factors. For example, RT is associated with an increased prevalence of obesity,[16] dyslipidemia,[16,18] diabetes,[15] and hypertension.[14,15,25] However, in some childhood cancer survivors, these cardiovascular risk factors may simply result from aging, as in the general population. Regardless of etiology, the relative contribution of these factors to the risk of major cardiac events among childhood cancer survivors is noteworthy.

Although the prevalence of two or more cardiovascular risk factors was relatively similar between childhood cancer survivors and their siblings, the incidence of serious cardiac events was substantially higher among survivors than siblings, despite their young age. Presumably, given a first cardiac insult in childhood initiated by chest-directed RT and/or anthracycline chemotherapy, subsequent development of cardiovascular risk factors accelerates the progression of atherosclerosis, left ventricular dysfunction, and valvular disease, resulting in premature aging of the heart. To the best of our knowledge, the impact of cardiovascular risk factors after cardiotoxic therapy has not previously been demonstrated among a large population of childhood cancer survivors. In a study restricted to 1,474 Hodgkin lymphoma survivors diagnosed before age 41 years, of which only 314 (21.3%) were diagnosed when they were younger than age 21 years, Aleman et al[7] did not find an association of smoking, hypertension, hypercholesterolemia, or diabetes that was independent of the risk for cardiac disease associated with cardiotoxic therapy. Moser et al[26] reported that preexisting hypertension increased the risk of cardiovascular disease in 476 adults (mean age of 49 years) diagnosed with non-Hodgkin lymphoma and treated with anthracycline chemotherapy.

All four cardiovascular risk factors, when evaluated individually, augmented risk for specific cardiac events. However, survivors with hypertension had the most significant increase in risk after chest-directed RT or anthracycline chemotherapy. Greatest risk was observed in survivors with hypertension and one or more additional risk factors. In addition, hypertension was significantly associated with an increased risk of cardiac mortality. Although hypertension has a well-established association with major cardiac events in the general population,[27-29] on the basis of these findings, it is imperative that childhood cancer survivors exposed to chest-directed RT or anthracycline chemotherapy have regular blood pressure monitoring and appropriate management as a high-risk group as outlined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[30] It is interesting

Table 4. Treatment-Specific RRs for Grade 3 to 5 Cardiac Events According to Treatment Exposure and Cardiovascular Disease Risk Factor Status for Hypertension, Dyslipidemia, Diabetes, Obesity, and Multiple (two or more)

Cardiovascular Risk Factor	Treatment Exposure Present	Risk Factor Present	Chest-Directed Radiotherapy								Anthracycline Chemotherapy Heart Failure	
			Coronary Artery Disease		Heart Failure		Valvular Disease		Arrhythmia			
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Hypertension	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	8.7	4.8 to 15.8	12.2	7.4 to 20.2	8.1	1.6 to 40.8	9.3	3.8 to 23.0	34.1	17.7 to 65.6
	Yes	No	5.3	3.2 to 8.7	3.2	1.9 to 5.2	10.1	2.9 to 35.6	2.9	1.2 to 7.0	8.3	4.4 to 15.6
	Yes	Yes	37.2	22.2 to 62.3	55.8	35.1 to 88.7	106.8	31.1 to 366.9	18.5	7.4 to 46.2	85.5	45.2 to 161.8
Relative excess risk due to interaction			**24.2**	**11.8 to 39.7**	**41.4**	**24.1 to 76.8**	**89.6**	**32.6 to 504.9**	7.3	−4.7 to 24.8	**44.5**	**17.2 to 106.1**
Dyslipidemia	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	5.0	2.4 to 10.3	3.5	1.7 to 7.3	2.7	0.3 to 23.6	0.0	0.0 to 1.3	2.3	1.1 to 4.8
	Yes	No	4.6	3.0 to 6.9	4.3	3.0 to 6.1	12.3	4.7 to 32.1	1.8	0.9 to 3.6	4.3	3.0 to 6.2
	Yes	Yes	25.0	15.2 to 41.3	7.0	3.5 to 13.8	33.8	11.3 to 101.0	6.9	2.8 to 17.2	8.9	4.6 to 17.4
Relative excess risk due to interaction			**16.4**	**7.9 to 29.8**	0.1	−4.8 to 5.4	**19.8**	**3.0 to 109.8**	**6.1**	**1.6 to 14.5**	3.3	−2.2 to 10.6
Diabetes	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	5.2	2.2 to 12.5	0.6	0.1 to 4.7	6.4	0.7 to 55.3	1.7	0.2 to 12.8	2.6	1.0 to 7.4
	Yes	No	5.1	3.5 to 7.5	3.6	2.6 to 5.1	14.4	5.6 to 37.0	2.4	1.2 to 4.6	4.2	3.0 to 6.1
	Yes	Yes	20.1	10.6 to 38.4	13.5	6.9 to 26.6	36.4	9.5 to 138.8	9.4	2.7 to 32.4	10.8	4.9 to 23.9
Relative excess risk due to interaction			10.8	0.0 to 28.6	**10.2**	**2.9 to 22.8**	16.6	−19.3 to 123.0	6.3	−3.8 to 21.4	4.9	−2.9 to 17.2
Obesity	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	1.4	0.7 to 2.6	1.4	0.8 to 2.5	0.8	0.1 to 6.6	0.7	0.2 to 2.5	2.0	1.1 to 3.6
	Yes	No	4.6	3.1 to 7.0	4.1	2.8 to 5.9	10.4	4.0 to 27.3	2.0	1.0 to 4.0	5.0	3.3 to 7.4
	Yes	Yes	9.3	5.6 to 15.5	5.7	3.3 to 10.1	23.8	8.3 to 68.3	5.5	2.2 to 13.5	5.4	3.0 to 9.8
Relative excess risk due to interaction			**4.3**	**0.9 to 8.7**	1.3	−1.7 to 4.6	**13.6**	**0.2 to 66.4**	**3.8**	**0.1 to 8.6**	−0.6	−3.9 to 2.6
Multiple risk factors (≥ 2) including hypertension	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	7.9	4.1 to 15.1	5.2	2.7 to 9.9	7.4	1.3 to 41.1	1.5	0.3 to 6.7	8.7	4.8 to 15.5
	Yes	No	5.0	3.3 to 7.7	3.7	2.6 to 5.4	13.4	4.6 to 38.9	2.0	1.0 to 4.0	4.9	3.3 to 7.3
	Yes	Yes	39.8	23.9 to 66.3	26.3	15.7 to 43.9	80.7	25.7 to 253.8	11.1	4.4 to 27.7	24.5	13.7 to 43.6
Relative excess risk due to interaction			**27.9**	**14.6 to 51.0**	**18.3**	**7.6 to 37.4**	**60.9**	**18.0 to 487.0**	**8.6**	**1.7 to 21.7**	**11.9**	**0.3 to 29.6**
Multiple (≥ 2) risk factors excluding hypertension	No	No	1.0		1.0		1.0		1.0		1.0	
	No	Yes	0.0	0.0 to 2.5	0.0	0.0 to 2.6	0.0	0.0 to 22.6	0.0	0.0 to 7.5	0.0	0.0 to 2.3
	Yes	No	4.9	3.4 to 7.0	4.0	2.9 to 5.6	13.0	5.4 to 31.1	2.6	1.4 to 4.8	4.3	3.0 to 6.1
	Yes	Yes	3.0	0.4 to 21.6	0.0	0.0 to 4.6	0.0	0.0 to 36.6	0.0	0.0 to 11.6	0.0	0.0 to 5.2
Relative excess risk due to interaction			−0.9	−5.4 to 5.9	−3.0	−4.5 to 2.0	−12.0	−45.4 to 5.7	−1.6	−3.5 to 0.5	−3.3	−5.1 to 2.1

NOTE. All models adjusted for age, household income, and education, which were all time-dependent variables, and sex, race, smoking, chest-directed radiotherapy, and anthracycline exposure. Bold indicates statistically significant relative excess risk due to interaction; a term statistically significantly greater than zero indicates that interaction between treatment and cardiovascular risk factor is more than additive. The results for all risk factors were based on a single model that included the entire study population.

that in this study, smoking status did not seem to potentiate cardiac risk or modify the risk attributable to other cardiovascular risk factors. It is likely that the length of exposure and follow-up may not have been sufficient to detect adverse effects of smoking in this young population. Nevertheless, the effect of smoking should be monitored as this population ages, given its documented adverse effect on cardiovascular disease in other populations.

The strengths of this study include the large, geographically diverse population of long-term survivors with detailed ascertainment of their cancer therapy, the comparison population of siblings, and the relatively long interval of longitudinal evaluation. When interpreting the findings, study limitations should be also considered. All cardiac events, as well as cardiovascular risk factors, were self-reported, without medical record confirmation. Previous studies suggest that self-report may have reduced sensitivity and specificity for heart failure and coronary artery disease.[31,32] However, for cardiac intervention such as coronary revascularization, agreement between self-report, hospital discharge codes, and physician review of medical records was "substantial to almost perfect" ($\kappa = 0.79$ to 0.92).[32] To improve validity, we restricted these analyses to events in which survivors additionally reported surgical (coronary revascularization, bypass grafting, or cardiac transplantation) or medical intervention for treatment of coronary artery disease or heart failure, surgical therapy for arrhythmia (pacemaker) or valvular disease (valve replacement), or

cardiac death based on linkage with the National Death Index. Thus, we limited this analysis to severe, life-threatening, and fatal (grades 3 to 5) cardiac events substantiated by medical/surgical intervention, so that over-reporting is less likely. Further, only survivors and siblings reporting corroborating pharmacotherapy were considered to have hypertension, diabetes, or dyslipidemia. Therapy for many childhood malignancies has evolved over time and, thus, results may not be directly generalizable to more recently treated populations. Nonetheless, anthracycline chemotherapy and chest-directed RT remain essential therapies for many childhood cancers. Finally, survivors exposed to cardiotoxic therapy may be more likely to be monitored for cardiovascular function, representing a potential for surveillance bias.

In summary, survivors who received chest-directed RT or anthracycline chemothearpy are at high risk for serious cardiac events, and when these therapeutic exposures are combined with cardiovascular risk factors, in particular hypertension, risk is significantly increased for coronary artery disease, heart failure, valvular disease, and arrhythmia. Of note, in individuals treated with chest-directed RT and who have hypertension, the risk is increased above that expected in a simple additive risk model. These findings reinforce the need for careful screening of adult survivors for early detection of cardiovascular risk factors as recommended in the Long-Term Follow-up Guidelines from the Children's Oncology Group.[33] Primary care and subspecialty clinicians who provide clinical care for the majority of survivors[34] should be aware of these increased risks and should monitor the blood pressure, lipid profile, glucose levels, and body mass index of childhood cancer survivors treated with cardiotoxic therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Demographic and Treatment Characteristics of Survivors and Siblings at Baseline and Last Attempted Follow-Up Survey

	Survivors					Siblings				
	Baseline		Last Follow-Up Survey			Baseline		Last Follow-Up Survey		
Characteristic	No.	%	No.	%	*P**	No.	%	No.	%	*P**
Total	10,724		7,247			3,159		2,346		
Sex					< .001					< .001
Male	5,623	52.4	3,688	50.9		1,515	48.0	1,082	46.1	
Female	5,101	47.6	3,559	49.1		1,644	52.0	1,264	53.9	
Race/ethnicity					< .001					< .001
Non-Hispanic white	9,442	88.0	6,509	89.8		2,786	88.2	2,090	89.1	
Non-Hispanic black	428	4.0	229	3.2		72	2.3	54	2.3	
Hispanic	502	4.7	299	4.1		105	3.3	60	2.6	
Other	352	3.3	210	2.9		196	6.2	142	6.1	
Age at diagnosis, years					.01					
< 5	4,408	41.1	2,989	41.2						
5-9.9	2,362	22.0	1,613	22.3						
10-14.9	2,149	20.0	1,440	19.9						
15-20.9	1,805	16.8	1,205	16.6						
Age at enrollment, years					.05					< .001
< 20	3,759	35.1	2,554	35.2		865	27.4	580	24.7	
20-29.9	4,461	41.6	3,085	42.6		1,081	34.2	837	35.7	
30-39.9	2,252	21.0	1,468	20.3		945	29.9	715	30.5	
40-49.9	252	2.3	140	1.9		261	8.3	209	8.9	
≥ 50	0	0.0	0	0.0		7	0.2	5	0.2	
Cancer diagnosis					.11					
Acute lymphoblastic leukemia	3,237	30.2	2,294	31.7						
Acute myeloid leukemia	280	2.6	187	2.6						
Other leukemia	78	0.7	48	0.7						
Astrocytomas	823	7.7	524	7.2						
Medulloblastoma/PNET	277	2.6	191	2.6						
Other CNS tumors	232	2.2	144	2.0						
Hodgkin lymphoma	1,368	12.8	832	11.5						
Non-Hodgkin lymphoma	835	7.8	573	7.9						
Wilms tumors	1,030	9.6	718	9.9						
Neuroblastoma	762	7.1	502	6.9						
Soft tissue sarcoma	935	8.7	646	8.9						
Ewing sarcoma	269	2.5	177	2.4						
Osteosarcoma	559	5.2	386	5.3						
Other bone tumors	39	0.4	25	0.3						
Chest-directed radiotherapy					.008					
Yes	2,532	26.4	1,596	24.2						
No	7,058	73.6	5,003	75.8						
Anthracycline chemotherapy					.75					
Yes	3,779	38.9	2,619	39.1						
No	5,934	61.1	4,072	60.9						

Abbreviation: PNET, primitive neuroectodermal tumor.
*P values are from χ^2 tests comparing survivors who took part in both baseline and 2007 surveys with survivors who took part in the baseline questionnaires but did not complete the most recent surveys.

Table A2. Survivors and Siblings With a Cardiac Condition After Baseline Questionnaire by CTCAE Grade

Cardiac Event	Grade	Siblings		Survivors		ALL		AML		Other Leukemia		Astro-cytoma		Medullo-blastoma PNET		Other CNS Tumors		Hodgkin Lymphoma		Non-Hodgkin Lymphoma		Wilms Tumors		Neuro-blastoma		Soft Tissue Sarcoma		Ewing Sarcoma		Osteo-sarcoma		Other Bone Tumors	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Coronary artery disease	3	5	0.2	72	0.7	10	0.3	0	0.0	1	1.3	2	0.3	2	0.8	0	0.0	39	3.0	3	0.4	1	0.1	3	0.4	5	0.6	2	0.8	4	0.7	0	0.0
	4	11	0.3	87	0.8	6	0.2	3	1.1	1	1.3	0	0.0	2	0.8	1	0.5	54	4.2	6	0.7	2	0.2	2	0.3	3	0.3	3	1.1	3	0.5	1	2.6
	5	0	0.0	25	0.2	2	0.1	0	0.0	1	1.3	1	0.1	0	0.0	1	0.5	16	1.2	1	0.1	2	0.2	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
	Total	16	0.5	184	1.8	18	0.6	3	1.1	3	4.0	3	0.4	4	1.5	2	0.9	109	8.5	10	1.2	5	0.5	5	0.7	8	0.9	5	1.9	8	1.5	1	2.6
Congestive heart failure	3	7	0.2	161	1.6	18	0.6	2	0.8	1	1.4	0	0.0	0	0.0	1	0.5	55	4.3	14	1.7	15	1.5	9	1.2	13	1.4	9	3.5	24	4.5	0	0.0
	4	0	0.0	4	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	1	0.2	0	0.0
	5	1	0.0	12	0.1	1	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	5	0.4	2	0.2	1	0.1	0	0.0	0	0.0	0	0.0	2	0.4	0	0.0
	Total	8	0.3	177	1.7	20	0.6	3	1.1	1	1.4	0	0.0	0	0.0	1	0.5	60	4.7	17	2.1	16	1.6	9	1.2	14	1.6	9	3.5	27	5.0	0	0.0
Valvular disease	4	2	0.1	42	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	35	2.7	2	0.2	1	0.1	1	0.1	1	0.1	1	0.4	1	0.2	0	0.0
	5	0	0.0	12	0.1	1	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	9	0.7	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
	Total	2	0.1	54	0.5	1	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	44	3.4	2	0.2	1	0.1	1	0.1	2	0.2	1	0.4	1	0.2	0	0.0
Arrhythmia	3	2	0.1	47	0.5	4	0.1	2	0.7	0	0.0	0	0.0	0	0.0	0	0.0	18	1.4	7	0.9	1	0.1	0	0.0	4	0.4	4	1.5	6	1.1	1	2.6
	4	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
	5	1	0.0	3	0.0	1	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Total	3	0.1	51	0.5	5	0.2	2	0.7	0	0.0	1	0.1	0	0.0	0	0.0	19	1.5	7	0.9	1	0.1	0	0.0	5	0.6	4	1.5	6	1.1	1	2.6

NOTE. Each person can only have one grade for one specific cardiac event. Second malignant neoplasm, late recurrence, and death are competing risks; thus, events occurring after second malignant neoplasm or late recurrence are not included.
Abbreviations: ALL, acute lymphatic leukemia; AML, acute myelogenous leukemia; CTCAE, Common Terminology Criteria for Adverse Events; PNET, primitive neuroectodermal tumor.

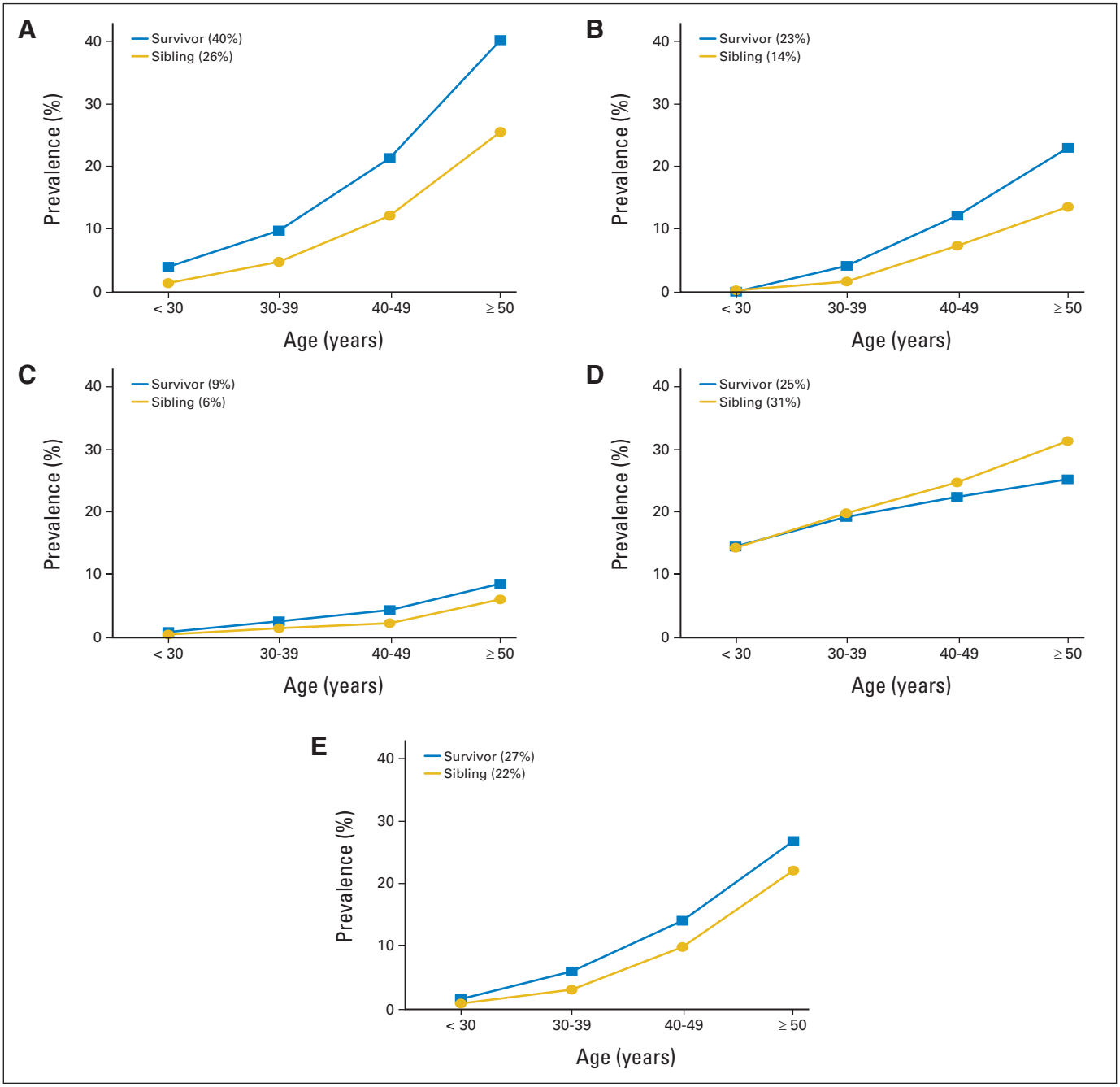

Fig A1. Prevalence of cardiovascular risk factors—(A) hypertension, (B), dyslipidemia, (C), diabetes, (D) obesity, and (E) multiple cardiac risk factors—with increasing age.