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STATE-OF-THE-ART REVIEW

Modifiable Cardiometabolic Risk Factors in Survivors of Childhood Cancer

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

The growing community of childhood cancer survivors faces a heavy burden of late onset morbidities and mortality, with cardiovascular diseases being the leading noncancer cause. In addition to demographics and cancer treatment exposures, which cannot be altered, cardiometabolic risk factors (obesity, hypertension, diabetes, and dyslipidemia) and frailty potentiate the risk of morbidity and mortality associated with chronic health conditions. Important opportunities exist to target these risk factors and improve late health outcomes for survivors. Unfortunately, limited evidence exists on the optimal methods to prevent, screen, and treat cardiometabolic risk factors among survivors, resulting in significant underdiagnosis and undertreatment. In this review, we discuss the prevalence of, risk factors for, current survivor-specific recommendations, and gaps in knowledge to mitigate potentially modifiable cardiometabolic risk factors and frailty among survivors of childhood cancer. (J Am Coll Cardiol CardioOnc 2024;6:16-32) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Survivors of childhood cancer, expected to exceed 580,000 by 2040 in the United States,[1] have an increased burden of treatment-related chronic health conditions and reduced life span.[2,3] Cardiovascular disease is the leading noncancer cause of morbidity and mortality in survivors.[2-4] Fortunately, efforts to reduce treatment intensity have significantly decreased the risk of late cardiovascular disease for survivors diagnosed and treated in more recent eras.[5] Nevertheless, survivors remain at a 4-fold increased risk of cardiac-related mortality compared to the general population, with the rate of excess deaths attributable to cardiovascular disease increasing throughout survivorship and accelerating beyond 30 years from diagnosis (**Figure 1A**).[3,4]

As survivors of childhood cancer age into adulthood, cardiometabolic risk factors (CMRFs), including obesity, hypertension, diabetes, and dyslipidemia, increase the risk of health-related mortality[3,4] and potentiate treatment-related cardiotoxicity beyond the risk associated with childhood cancer and its

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HIGHLIGHTS

- Cardiometabolic risk factors and frailty increase the risk of morbidity and health-related mortality among survivors of childhood cancer.
- These conditions are important targets for interventions but remain underdiagnosed and/or undertreated in this population.
- Survivorship research should focus on determining the optimal prevention, screening, and treatment modalities for cardiometabolic disease.

ABBREVIATIONS AND ACRONYMS

ALL = acute lymphoblastic leukemia

ASCVD = atherosclerotic cardiovascular disease

BMI = body mass index

CMRF = cardiometabolic risk factor

COG LTFU = Children's Oncology Group Long-Term Follow-Up

DXA = dual X-ray absorptiometry

RR = rate ratio

TBI = total body irradiation

treatment (**Figures 1B, 1C, and 2**).[6] However, survivors are often underdiagnosed and undertreated for these conditions.[7] Additionally, physiologic frailty, a phenotype characterized by the presence of at least 3 of the following: low lean mass, physical exhaustion, low energy expenditure, slowness, and weakness, has been observed among middle-aged survivors at a rate comparable to older adult populations.[4,8,9] Fortunately, both CMRFs and frailty in adult survivors are potentially modifiable, unlike the cardiotoxic chemotherapy and radiotherapy received for treatment of their childhood cancer, making them important targets for interventions that reduce the long-term burden of cardiovascular disease and mortality in survivors (**Central Illustration**).

In this State-of-the-Art review, we aim to provide a comprehensive summary of the existing evidence of the health consequences associated with CMRFs and frailty in survivors of childhood cancer and outline current recommendations for facilitating early detection, prevention, and treatment while identifying knowledge gaps and opportunities to mitigate risks associated with CMRFs. Studies were identified by a MEDLINE search of Medical Subject Heading terms and key words and supplemented by a search of ClinicalTrials.gov (additional details presented in Supplemental Methods).

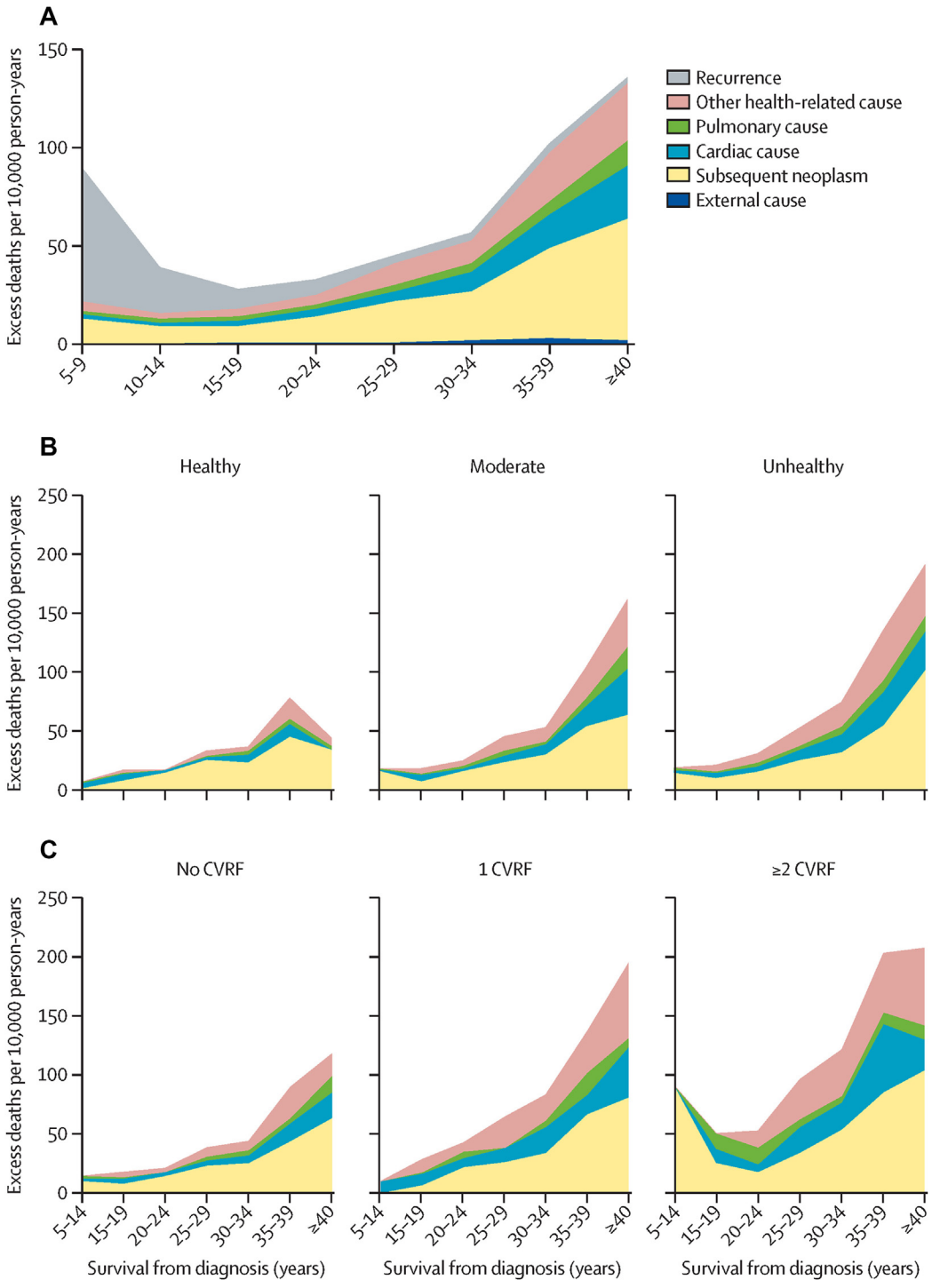
OBESITY

DEFINITION AND EPIDEMIOLOGY. Obesity is defined as a body mass index (BMI) ≥30 kg/m² in adults or ≥95th percentile for age and sex in children.[10] The prevalence of clinically ascertained obesity among survivors of childhood cancer in their 30s ranges from 13.5% in a Dutch cohort compared to 15.1% in the general Dutch population to 36% in a North American cohort compared to 31.6% in the age-, sex-, and race-matched general U.S. population.[11,12] Importantly, BMI does not account for the imbalance between lean and fat mass distribution, and a number of studies have highlighted treatment-related changes in body composition among survivors. They observed that 42% to 46% of male and >50% of female survivors were misclassified as nonobese based on BMI compared to body fat percentage (obesity defined as body fat percentage ≥25% for males and ≥30% for females) by dual X-ray absorptiometry (DXA) measurements.[13,14] Consequently, BMI alone underestimates overall body fat mass and the associated metabolic risk for adiposity-based chronic disease.

RISK FACTORS. When stratified by primary cancer diagnosis, survivors of acute lymphoblastic leukemia (ALL) and central nervous system tumors, including craniopharyngioma, have the highest risk for obesity.[15,16] Cranial radiation therapy exposure has been linked to obesity[11,17] and fat mass ascertained by DXA.[18] Total body irradiation (TBI) and abdominal irradiation are associated with a high relative fat mass, which when occurring in combination with low muscle mass is termed sarcopenic obesity.[13,19] Although some studies have reported a dose-response relationship between glucocorticoid exposure and therapy-related weight gain[20] or obesity in survivors,[11,21] these findings have not been consistent across other studies.[15,22] Other risk factors include hypothalamic injury,[23] younger age at treatment, female sex, unfavorable health behaviors (low-quality diet and physical inactivity), and use of mood stabilizing medications.[24] Furthermore, although genetic and epigenetic risks and their interaction with cancer treatment are not fully elucidated, studies have identified genetic risk factors in survivors including sequence variations associated with obesity risk in those exposed to cranial radiation[11] and a 53-fold increase in risk for class III obesity (BMI ≥40 kg/m²) among survivors with high compared to low polygenic risk for obesity independent of clinical and lifestyle factors.[25]

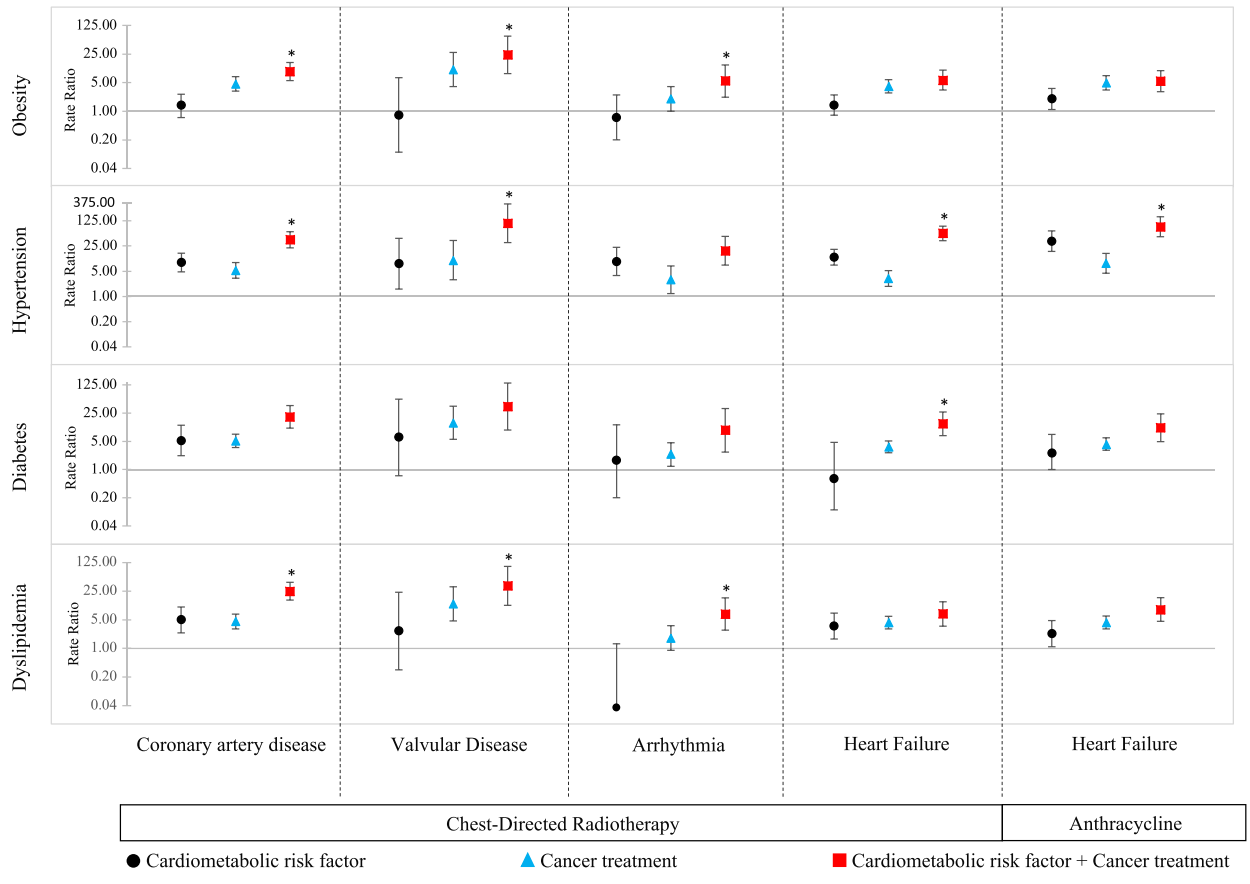
ASSOCIATED COMORBIDITIES. Obesity in survivors of childhood cancer exacerbates the baseline treatment-related risk for cardiovascular morbidity and mortality. Self-reported obesity interacts in a near multiplicative fashion with cardiotoxic therapies to potentiate the risk of coronary artery disease, valvular disease, and arrhythmia (**Figure 2**).[6] Independent of treatment exposure, obesity has been linked to diastolic dysfunction,[26] cardiac autonomic

FIGURE 1 **Absolute Excess Risk of Death per 10,000 Person-Years by Survival Time**



(A) Among all eligible survivors including recurrence, external and accidental, and health-related causes of death. (B and C) Among 20,051 adult survivors included in the modifiable risk analysis* as health-related causes of death by lifestyle score ([B] healthy, moderately healthy, or unhealthy and the number of cardiovascular risk factors [CVRFs] [C] 0, 1, or ≥2). *Modifiable risk analysis adjusted for sex, age at diagnosis, attained age during follow-up, race and ethnicity, treatment exposures, educational attainment, income, and insurance status. Reproduced with permission from Dixon et al.[3]

FIGURE 2 **Relative Risk for Serious Cardiac Events by Treatment Exposure and Cardiometabolic Risk Factor**



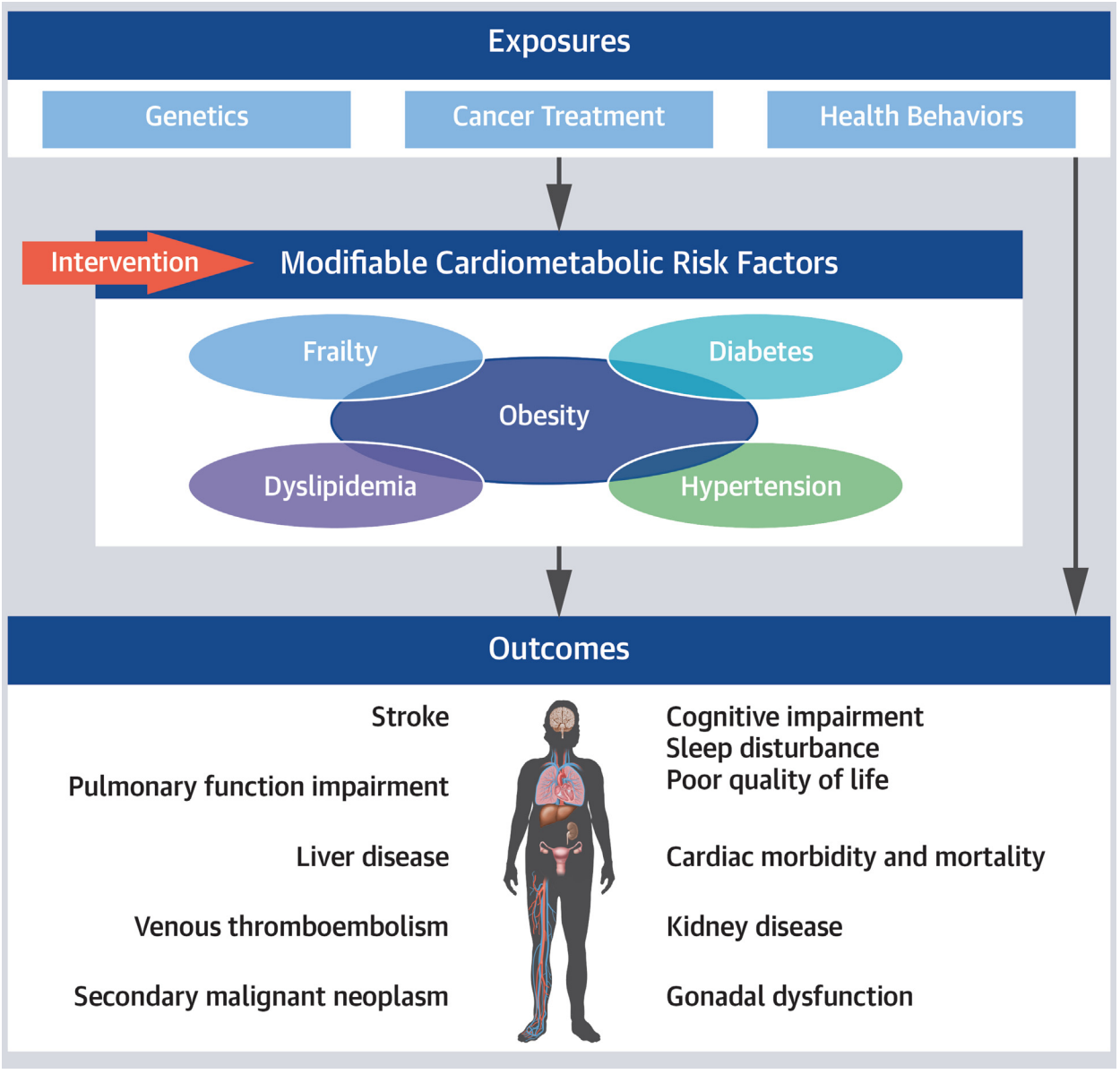
y-Axis is on a log scale. RR for arrhythmia with dyslipidemia: 0.0 (95% CI: 0.0-1.3). *Indicates statistically significant relative excess risk for cardiac outcome because of interaction between treatment and cardiometabolic risk factor. Results obtained from Armstrong et al.[6]

dysfunction,[27] and late venous thromboembolism in survivors.[28] It also serves as a central driver of morbidity by doubling the risk of hypertension and dyslipidemia[29] and increasing the risk of diabetes by 5- to 7-fold.[30,31]

Obesity extends its risk beyond the cardiovascular system, contributing to late liver,[32,33] lung,[34] and reproductive organ dysfunction.[35,36] Moreover, it impacts survivors' physical function,[37] is associated with accelerated epigenetic aging,[38] and contributes to the frailty phenotype.[8,9] Strong evidence supports the negative impact of obesity on psychosocial well-being[37,39] and neurocognitive function in survivors.[40] Moreover, overweight or obesity at the time of primary cancer diagnosis as well as abnormal weight gain during treatment have been associated with an increased risk of long-term metabolic syndrome;[41,42] central precocious puberty;[43] and, in a single study, a 4-fold increased risk of secondary malignant neoplasms within the first 25 years from primary cancer diagnosis among those who remained obese at the end of therapy.[44]

CURRENT MANAGEMENT AND FUTURE DIRECTIONS. **General population.** Guidelines for individuals with overweight (BMI 25-<30 kg/m^2) or obesity in the general population recommend lifestyle changes as the initial approach. Such interventions have been well described across different age groups, with health benefits, including reduced risks of diabetes and other chronic diseases, observed with even modest weight loss of 5%.[45] However, it is important to note that even in highly effective lifestyle change studies, fewer than 50% of participants achieved the 5% weight loss goal, many patients required a higher weight loss target, and sustainability over time was challenging with most patients experiencing weight regain.[46,47]

CENTRAL ILLUSTRATION **Long-Term Health Consequences of the Modifiable Cardiometabolic Risk Factors**



Hammoud RA, et al. J Am Coll Cardiol CardioOnc. 2024;6(1):16–32.

Cardiometabolic risk factors (obesity, hypertension, diabetes, and dyslipidemia) and frailty increase the risk of chronic health conditions and health-related mortality. These conditions are modifiable and important targets for interventions but remain underdiagnosed and undertreated in this population.

Pharmacotherapy can be considered as a secondary approach. Recent pharmacologic interventions have shown promising results, with once-weekly injectable incretin mimetic agents (semaglutide and tirzepatide) leading to a mean percent weight loss of 15% to 20% in noncancer adult populations.[48,49] In adolescents aged 12 years and older, oral phentermine/topiramate and subcutaneous weekly semaglutide have demonstrated a clinically significant average change in BMI of −8% and −16%, respectively.[50,51] Bariatric surgery, a highly effective and safe treatment option for sustained weight loss and reduction of obesity-related comorbidities, may be considered in adolescence[10] and has

TABLE 1 Summary of Evidence on the Current Screening Practices for Each Cardiometabolic Risk Factor

	Obesity	Hypertension	Diabetes	Dyslipidemia
General population screening recommendations	BMI at each well-child or adult visit beginning at age 2 years (U.S.)[10,55] and at the age of 6 (Europe)[139]	U.S.: annually for those ≥40 years or at high risk (Black race, overweight BMI, SBP 120-129 mm Hg) Every 3 to 5 years for adults aged <40 years[140] Europe: every 5 years for blood pressure <120/80 mm Hg, every 3 years for blood pressure = 120-129/80-84 mm Hg, annually for blood pressure = 130-139/85-89 mm Hg[141]	U.S.: American Diabetes Association recommends inclusion of healthy weight adults ≥35 years and any individual <35 years with overweight and at least 1 additional risk factor Every 3 years, with more frequent screening depending on risk status[92,93] United Kingdom: screen using risk assessment tool for adults ≥40 years or ≥25 years from high-risk ethnic groups or with other cardiovascular risk factors. Every 5 years for low risk to yearly in high-risk[142]	Adults without risk enhancing factors for ASCVD with blood cholesterol at age 20 should be screened every 4 to 6 years from the joint ACC/AHA Guideline on Management of Blood Cholesterol[106,108] Europe: men >40 years and women >50 years or postmenopausal. Frequency is risk dependent.[143]
Cancer treatment-related risk factors	Head/brain radiation[23] Neurosurgery involving the hypothalamic-pituitary axis, hypothalamic injury[23] Higher cranial radiation (≥18 Gy)[17] Corticosteroids[11,20,21]	Alkylating agent (particularly ifosfamide)[23] Heavy metals (carboplatin, cisplatin)[23] Hematopoietic cell transplant[23] Abdominal radiotherapy ≥20 Gy and TBI[69] Nephrectomy[68]	Abdomen/TBI radiation,[23] including radiation affecting pancreatic tail in dose-dependent fashion[30]	Abdomen/TBI radiation[23] Chest or craniospinal field radiation[101] Platinum-based chemotherapy[104] Anthracycline doses ≥200 mg/m^2[103]
Other risk factors to consider				
Patient factors	Younger age at treatment Female sex Unfavorable health behaviors Genetic predisposition	Family history and genetic predisposition	Younger age at radiation exposure Family history	Family history
Comorbid conditions	Growth hormone deficiency Hypothyroidism Hypogonadism Inability to exercise Pretreatment obesity	Obesity Pre-existing renal impairment Congenital absence of kidney	Obesity	Growth hormone deficiency Hypogonadism Hypothyroidism
Screening recommendations for survivors				
Modality	BMI 3 skinfold Waist-to-height ratio	Office blood pressure measurement	Fasting blood glucose Hemoglobin A1C	Fasting lipid profile
Frequency	Yearly	<40 y: 3-5 y ≥40 y or exposed to nephrotoxic or cardiotoxic treatment: yearly	2 y 3 y in general population	2 y
Management	1. Evaluate for presence of other comorbid cardiometabolic risk factors 2. Lifestyle modification (diet, exercise, and health behavior modification) with planned, frequent, reassessment at 3-6 months so escalation of intervention including pharmacologic therapy is not delayed 3. Referral to provider with cancer-specific expertise when available in high-risk patients (ie, cardio-oncology for aggressive CMRF management and screening in survivors with cardiotoxic therapy exposure or known cardiomyopathy) 4. Pharmacotherapy if indicated by general population recommendations and consideration for shared decision making when gaps of evidence exist (ie, statin consideration with high treatment-specific ASCVD risk)			
Gaps	1. Efficacy of behavioral or pharmacologic interventions for prevention of CMRF in survivors at high-risk based on treatment exposure 2. Optimal timing and frequency of screening for CMRF in survivors with exposure-based risk and not meeting eligibility for general population-based screening recommendations 3. Optimal timing and modality of treatment in survivors as well as goals of treatment/definitions of control and whether these differ from the general population based on survivor-specific cardiovascular disease risk 4. Dissemination and implementation strategies to improve receipt of recommended screening and management			

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CMRF = cardiometabolic risk factor; SBP = systolic blood pressure; TBI = total body irradiation.

demonstrated a reduction in the risk of all-cause and obesity-associated mortality.[52,53]

Survivor-specific considerations. Weight gain and obesity often begin during treatment of childhood cancer and persist into survivorship.[20,54] However, studies focusing on optimal preventive and treatment strategies tailored to survivors are limited,[3] with no recommendations on what represents a concerning amount of weight gain or how to effectively intervene in a population receiving weight-promoting medications such as high-dose glucocorticoids. Although no guidelines for the measurement of body composition in survivors exist, the assessment of anthropometrics (3 skinfold method and waist-to-height ratio) or DXA

may be considered.[13,19] Notably, DXA (the gold standard) may have limitations because of cost, availability, and associated low-dose radiation exposure.[13] Currently, the Children's Oncology Group Long-Term Follow-Up (COG LTFU) Guidelines recommend screening for obesity by evaluating BMI annually and following general population guidelines (**Table 1**).[10,23,55]

Research on weight management in childhood cancer survivors is limited and has primarily focused on lifestyle interventions, both during and after cancer treatment (Supplemental Table 1). Small-scale studies have suggested that tailored strategies targeting diet and physical activity are safe and feasible but minimally effective in this population. Four interventions focusing on diet and physical activity modifications implemented during ALL treatment demonstrated varying degrees of success in managing weight gain, ranging from slowing the rate of fat mass increase to small reductions in BMI.[56-59] Successful interventions in survivors were personalized[60] and targeted either caregivers as role models for health behaviors[61] or survivors ≥14 years of age.[62] Pharmacologic interventions have been restricted to cases of hypothalamic obesity and have rarely achieved 5% weight loss.[63-65] Ongoing research is investigating setmelanotide, a targeted melanocortin-4 receptor agonist developed to treat rare monogenic or syndromic obesity, as a therapy for acquired hypothalamic obesity (including craniopharyngioma) in a randomized controlled trial (NCT05774756) after a promising phase 2 trial achieved 10% reduction in BMI in 80% of participants.[66] Bariatric surgery has demonstrated weight changes for survivors with hypothalamic obesity comparable to those in the general population using sleeve gastrectomy,[67] but knowledge of efficacy and safety in other survivor populations is lacking. Future trials must not only evaluate how interventions for obesity differentially impact survivors with specific therapy-associated risks (TBI, abdominal radiation, and hypothalamic injury) but also how they may differentially change body composition and cardiometabolic risk in this group compared to the general population.

HYPERTENSION

DEFINITION AND EPIDEMIOLOGY. The prevalence of hypertension, defined as ≥130/≥80 mm Hg according to the 2017 American College of Cardiology/American Heart Association guideline, has been reported to reach 45% at a median age of 37 years among survivors in North America.[7] However, studies characterizing the risk factors and consequences of hypertension in survivors of childhood cancer used the cutpoint of 140/90 mm Hg or self-reported pharmacologic treatment of hypertension. Adult survivors of childhood cancer from the St. Jude Lifetime cohort had a 2.6-fold higher prevalence of hypertension than age-, sex-, race-, and BMI-matched individuals from the general population.[68] In contrast, the prevalence of hypertension was similar between adult survivors (16.3%) and controls (18.2%) in the Dutch Childhood Cancer Survivor Study.[69]

RISK FACTORS. Although therapy-related risk factors have not been consistently identified across studies, independent associations have been observed between hypertension and nephrectomy, moderate-dose alkylating agents,[68] abdominal radiotherapy ≥20 Gy, and TBI, suggesting a link to nephrotoxic therapy.[69] No associations were noted with steroid exposure.[68] Cardiotoxic treatments interact with an individual's genetic risk for hypertension, together accounting for 40.2% of cases among survivors.[70] This leaves approximately 60% of the risk unaccounted for, with obesity and other lifestyle factors being the primary nongenetic contributors to hypertension risk in noncancer populations.[29,70,71]

ASSOCIATED COMORBIDITIES. Survivors with hypertension, compared to those without, and independent of cardiotoxic treatment, have an increased risk for cardiomyopathy (HR: 4.9; 95% CI: 3.6-6.7), valvular heart disease (HR: 3.1; 95% CI: 1.1-8.9), arrhythmia (HR: 2.6; 95% CI: 1.3-5.3), coronary artery disease (HR: 4.7; 95% CI: 3.4-6.7), pericardial disease (HR: 6.3; 95% CI: 1.6-25.8),[5] all-cause mortality (standardized mortality ratio: 5.3; 95% CI: 4.8-5.9), and cardiac mortality (standardized mortality ratio: 5.9; 95% CI: 4.6-7.4).[3] The risk for cardiovascular disease is further amplified by the interaction between hypertension and exposure to anthracycline chemotherapy and chest-directed radiotherapy (**Figure 2**).[6] Additionally, hypertension has been associated with a 4- and 2-fold risk for stroke and stroke recurrence independent of cranial radiation[72,73] and has been linked to decreased kidney function[69,74] and accelerated epigenetic age.[38]

CURRENT MANAGEMENT AND FUTURE DIRECTIONS.

General population. In the general population, normotensive adults under 40 years of age without known risk factors should have blood pressure evaluated every 3 to 5 years; this is increased to annual screening for those at high risk or above 40 years. The recommended first-line treatment is management of lifestyle, including diet and exercise.[75] Consideration for pharmacologic management is based on

cardiovascular disease risk, age, and severity of hypertension. The 2017 American Heart Association and 2022 European Society of Cardiology guidelines recommend the initiation of pharmacologic antihypertensive treatment for all adults with blood pressure >140/90 mm Hg or ≥130/80 mm Hg in high-risk groups based on atherosclerotic cardiovascular disease (ASCVD) risk.[75,76]

Survivor-specific considerations. The COG LTFU Guidelines recommend yearly screening for survivors exposed to nephrotoxic chemotherapy (eg, ifosfamide and platinum agents), abdominal radiation, TBI, hematopoietic cell transplantation, or a history of nephrectomy. Annual screening should be considered in survivors at increased risk for cardiac late effects after exposure to any cardiotoxic therapy (**Table 1**).[23]

As for management, failure to demonstrate improvement in blood pressure among childhood cancer survivors participating in 2 lifestyle interventions adapted from the general population emphasizes the need for tailored treatments for this group.[77,78] Because obesity is an important contributor to hypertension in survivors,[29] evidence regarding the impact of adapted lifestyle changes on hypertension primarily comes from trials targeting weight loss. Yet, survivors following a 1-year personalized physical activity program did not observe improvement in their blood pressure despite a decrease in total body fat proportion.[60] In survivors of ALL, a tailored counseling-based weight management intervention (Supplemental Table 1) was successful in preventing weight gain but did not affect blood pressure measurements,[62] whereas a home-based unsupervised resistance training program (Supplemental Table 1) resulted in improved blood pressure despite a lack of significant change in BMI.[79] In survivors with hypothalamic obesity, weight loss achieved with Tesomet (a combination of triple monoamine reuptake inhibitor and beta-blocker)[63] but not diazoxide (nondiuretic thiazide drug)[80] was associated with improved systolic blood pressure.

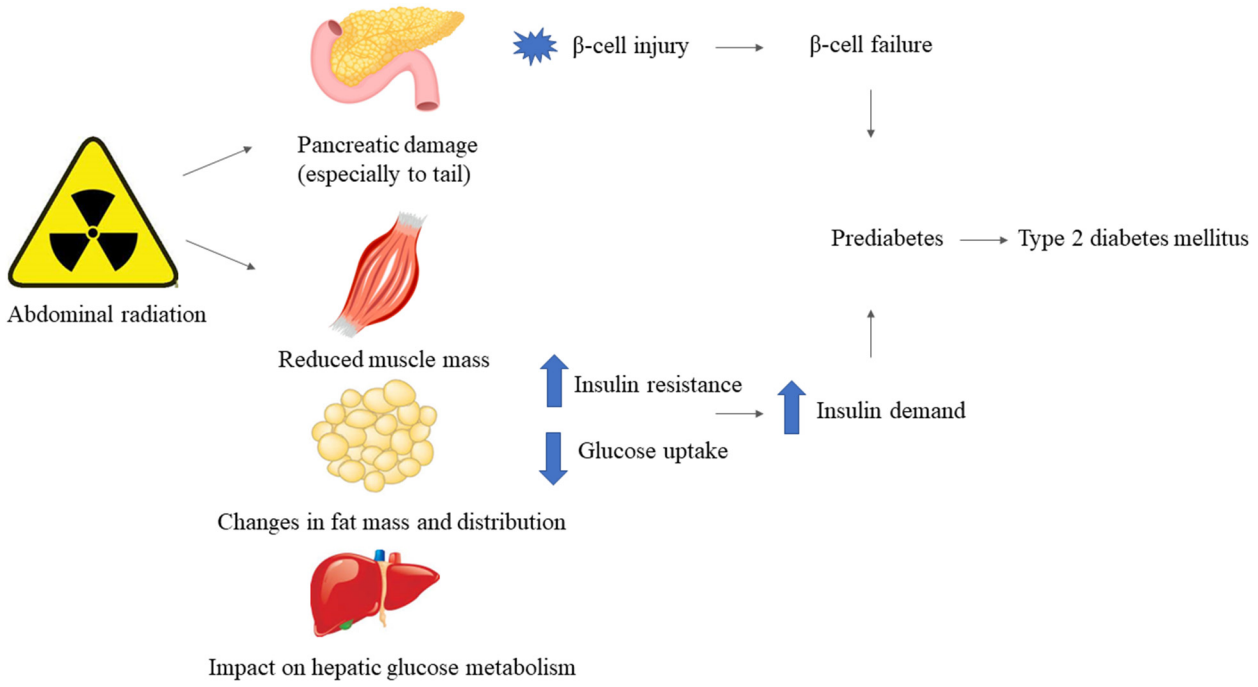
The use of pharmacotherapy for survivors follows the general population guidelines[75,76,81] and should consider survivor-specific factors including cancer diagnosis, treatment exposures, and survivor-specific ASCVD risk calculation.[81-84] Considering the strong evidence for the synergistic relationship between hypertension and cancer treatment on cardiovascular health[6] and the potential for differential efficacy because of the effects of cancer treatment,[68] research is needed to investigate survivor-specific thresholds for the initiation of treatment and corresponding therapeutic blood pressure goals. Additionally, studies are essential to optimize the choice of treatment agents, taking into consideration the multifactorial mechanisms underlying the development of hypertension in survivors and the impact of therapeutic selection on the risks for late renal or cardiotoxicity (eg, preferencing angiotensin-converting enzyme inhibitors or angiotensin receptor blocker or considering beta-blocking agents with indications in heart failure in those with prior cardiotoxic treatment exposure).[85]

DIABETES MELLITUS

DEFINITION AND EPIDEMIOLOGY. Diabetes mellitus is clinically diagnosed by either 2 measurements of an elevated hemoglobin A1C (≥6.5%) or fasting blood glucose (≥126 mg/dL) or a random glucose ≥200 mg/dL associated with symptoms of hyperglycemia. In the research setting, a single measurement of glucose control at a given time point has been used for diabetes assessment in many survivor cohorts. The prevalence of diabetes in clinically ascertained cohorts of adult survivors ranges between 4% and 6% in European (median age 28 years) and U.S. (median age 32 years) cohorts.[86,87] Compared to community or sibling controls, survivors in high-income countries have a 50% to 80% greater risk of developing diabetes[17,88,89] and a younger age at onset (mean of 22.1 years in survivors vs 26.9 years in controls).[88] Moreover, the prevalence of prediabetes among survivors in the United States is 29% at a median age of 30 years.[87]

RISK FACTORS. The risk of diabetes is highest among survivors exposed to abdominal irradiation, especially if affecting the pancreatic tail, or TBI.[30] Importantly, survivors with exposures to pancreatic tail radiation or TBI have an increased risk for developing prediabetes and progressing from prediabetes to diabetes.[87] Hyperglycemia during ALL treatment and survivorship has been associated with the use of corticosteroids, through effects on obesity and metabolic dysregulation,[11] and asparaginase, through potential for direct damage to pancreatic tissue.[31] The exact mechanism underlying the development of diabetes in survivors remains unknown but may include decreased insulin production because of damage to pancreatic tissue leading to beta-cell dysfunction;[30] increased insulin resistance;[90] and/or the possibility of altered glucose and insulin regulation from liver, adipose tissue, and skeletal muscle irradiation (**Figure 3**). Independent of treatment exposure, family history is associated with the development of diabetes among survivors.[71]

FIGURE 3 Theoretical Model for the Increased Risk of Diabetes Mellitus



Although the exact pathophysiology for the development of diabetes after exposure to abdominal radiation remains unknown, longitudinal studies suggest a multitude of effects on the pancreas, liver, adipose tissues, and skeletal muscles.

Associated comorbidities. Survivors with prediabetes have a more than 2-fold increased risk for myocardial infarction and chronic kidney disease.[87] With progression to diabetes, survivors are at a 3-fold increased risk for all cardiovascular diseases, including heart failure, arrythmia, diastolic dysfunction, ischemic heart disease, and cerebrovascular disease.[5,6,26,91] Diabetes is also an independent risk factor for late onset kidney failure[87] and all-cause and cardiac-related mortality in survivors.[3,4]

CURRENT MANAGEMENT AND FUTURE DIRECTION.

General population. Screening recommendations include fasting plasma glucose or hemoglobin A1c every 3 years for adults 35 to 70 years of age with at least 1 of the following risk factors for diabetes: family history, obesity, known cardiovascular disease, hypertension, dyslipidemia, polycystic ovary syndrome, history of gestational diabetes, and high-risk race/ethnicity (American Indian/Alaska Native, Hispanic, non-Hispanic Asian, or non-Hispanic Black).[92,93]

The initial treatment primarily focuses on weight reduction through lifestyle modifications and has a hemoglobin A1C target of <7%. When pharmacotherapy is initiated, metformin is typically first line for both children and adults, with alternative or additional medications considered based on comorbidities, response, and severity of the disease.[94]

Survivor-specific considerations. The COG LTFU Guidelines recommend diabetes screening in survivors exposed to abdominal radiation or TBI every other year using hemoglobin A1C or fasting blood glucose.[23] Outside of these guidelines, it has been proposed that oral glucose tolerance testing may identify earlier impairments in glucose metabolism for survivors at highest risk.[95] Survivors without the aforementioned treatment exposures but with an increased risk for diabetes because of traditional risk factors should be screened following guidelines for adults without a history of cancer (**Table 1**).[92,93]

Similar to other CMRFs, there are no survivor-specific recommendations for diabetes management.[3] For survivors with treatment-related diabetes risk, including abdominal radiation, it is essential to consider differences in pathophysiology and potential treatment efficacy of lifestyle or pharmacologic management. Among the completed trials listed in Supplemental Table 1, limited analyses included glucose metabolism as a secondary outcome, and results for the impact on insulin sensitivity after a reduction in fat mass were mixed.[56,60,62,63,79]

Furthermore, because one-half of the survivors with diabetes do not achieve the general population goals for hemoglobin A1C control,[7] investigations on additional therapeutic interventions and targeted delivery methods to this population are needed. An ongoing trial (NCT05023993) is studying the effect of home exercise with or without the dietary supplement nicotinamide riboside, a vitamin B3 derivative that enhances oxidative metabolism, on hyperglycemia in survivors with prediabetes. Another open-label trial (NCT04742751) is investigating the feasibility of combining a digitally delivered lifestyle intervention with metformin in prediabetic survivors. Moreover, there is strong rationale to support synergistic therapy selection because newer Food and Drug Administration–approved agents for diabetes have a favorable cardiovascular risk profile.[96] For example, among individuals from the general population with diabetes treated with semaglutide, a 25% reduction in the risk of major adverse cardiovascular events was observed in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term-Outcomes with Semaglutide in Subjects with Type 2 Diabetes), whereas empagliflozin and dapagliflozin have each been successful at reducing heart failure hospitalization or cardiovascular death in patients with both reduced and preserved ejection fraction.[96-99] The development of survivor-specific trials for diabetes prevention or management should consider these agents in a population in which many participants are at high risk for heart failure or ischemic heart disease.

DYSLIPIDEMIA

DEFINITION AND EPIDEMIOLOGY. Dyslipidemia is a metabolic disorder characterized by an imbalance in lipid levels. With various classifications currently in use, the reported prevalence of dyslipidemia in survivors of childhood cancer varies widely between cohorts. Based on fasting lipid profiles, the prevalence in North American survivors has been noted to be as high as 50% at a median age of 38 years.[7] A German childhood cancer survivor cohort study reported a prevalence of 28.3% at a mean age of 34 years.[100] In multiple settings, survivors have been reported to have an increased risk of developing dyslipidemia compared to siblings with an odds ratio of 1.6 in a Childhood Cancer Survivor Study of 8599 survivors[101] and a HR of 4.3 among 2530 Finnish survivors.[102] A recent study of survivors with a history of cardiotoxic therapy exposure who underwent in-home assessment identified that 1 in 5 survivors without a known history of dyslipidemia may be underdiagnosed, and nearly 50% of those diagnosed may be suboptimally managed.[7]

RISK FACTORS. A number of treatment-related risk factors for dyslipidemia have been reported including exposure to platinum-based chemotherapy; anthracycline doses ≥200 mg/m^2; and radiation to the chest, abdomen, craniospinal field, or TBI.[101,103,104] However, the only consistent associations, independent of BMI, were exposure to abdominal irradiation or TBI.[101,104] Primary hypothyroidism, growth hormone deficiency, and hypogonadism, which each occur as late effects of cancer therapy, have been independently associated with dyslipidemia.[104,105]

ASSOCIATED COMORBIDITIES. Self-reported dyslipidemia in association with a history of cardiotoxic treatment exposure has been shown to increase the risk for coronary artery disease (rate ratio [RR]: 4.7; 95% CI: 2.0-10.7) and valvular diseases (RR: 5.4; 95% CI: 1.4-20.7) in an additive manner.[6] Independent of treatment, dyslipidemia has been linked to an increased risk for diastolic dysfunction (RR: 1.4; 95% CI: 1.2-1.8),[26] cardiomyopathy (HR: 2.3; 95% CI: 1.5-3.5), and arrhythmia (HR: 3.5; 95% CI: 1.8-6.9).[5]

CURRENT MANAGEMENT AND FUTURE DIRECTIONS.

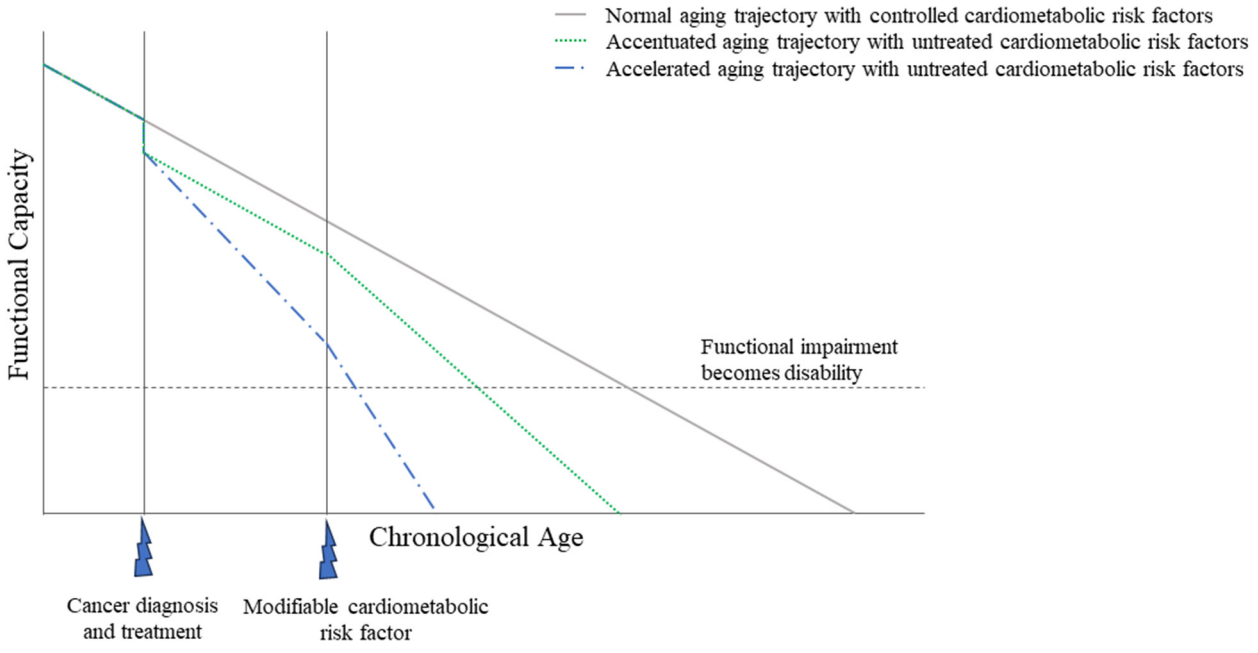
General population. Screening for dyslipidemia is recommended for asymptomatic individuals beginning at the age of 40 years (>50 years for females in Europe) and earlier in the presence of high cardiovascular risk (obesity, hypertension, diabetes, or family history of cardiovascular disease).[106] First-line management is lifestyle changes.[107] Statin therapy is recommended based on lipid levels and ASCVD risk calculation.[106]

Survivor-specific considerations. The COG LTFU Guidelines recommend screening survivors exposed to abdominal irradiation or TBI for lipid disorders every other year (**Table 1**).[23] For all other survivors, following the general population guidelines is advised.[106] Notably, this does not account for other cancer treatment exposure–related cardiovascular risk that may increase survivor-specific ASCVD.[108]

For managing dyslipidemia in survivors, a retrospective study observed improved triglyceride levels in survivors in response to adopting lifestyle modifications guidelines from the general pediatric population.[77] However, among the trials listed in Supplemental Table 1, those measuring lipid levels as a secondary outcome did not report significant changes regardless of the effect on weight.[60,62,63,65,78,79]

For statin initiation, it is important to note that the population-based ASCVD risk calculator is valid starting at the age of 40 years,[106] decades after the

FIGURE 4 Hypothesized Trajectories of Aging-Related Consequence of Cancer Treatment and Untreated Cardiometabolic Risk Factors



Childhood cancer and its treatments can disturb the biological system leading to either a trajectory parallel to normal aging but with a lower reserve (accentuated aging hypothesis) or a different trajectory with a more rapid decline in functional state (accelerated aging hypothesis). As survivors age and accumulate untreated modifiable cardiometabolic risk factors, this decline is further accentuated, resulting in earlier functional impairment.

treatment of childhood cancer, which precludes the opportunity to detect a considerable number of survivors who may develop dyslipidemia at a younger age.[7] Furthermore, it fails to capture the increased risk for premature ASCVD associated with treatment in survivors, which has motivated the development of survivor-specific risk calculators for heart failure, ischemic heart disease, and stroke.[82-84] For example, the calculated risk for a survivor of Hodgkin lymphoma in their early 30s with moderate (15-34 Gy) mantle field radiation exposure without cardiovascular risk factors is estimated at >10% for ischemic heart disease by age 50 years (and 3% risk of stroke).[82-84] Future studies are important to explore the potential utility and optimal timing of statin initiation in specific high-risk groups of survivors, including those who develop diabetes and dyslipidemia at a young age. To date, a small pilot study demonstrated preliminary feasibility and safety of early statin initiation in survivors but did not demonstrate significant improvement in vascular function,[109] whereas a recent large randomized study in adult patients receiving anthracycline chemotherapy for lymphoma suggested an early cardioprotective effect.[110] More work is needed to determine if early initiation of statin therapy in survivors at high treatment-related risk of ischemic heart disease or stroke can reduce cardiovascular morbidity and mortality to a similar degree as that noted in the general population at high risk because of traditional cardiovascular risk factors.[107] Finally, it is essential to consider that survivors may find benefit from correcting underlying endocrine conditions that contribute to dyslipidemia, particularly those with insulin resistance, hypothyroidism, growth hormone deficiency, or hypogonadism.[111,112]

FRAILTY

DEFINITION AND EPIDEMIOLOGY. The increased risk for morbidity and mortality at a young age in survivors has suggested an acceleration of disease, including cardiometabolic risk, similar to that associated with general aging.[2,38] Frailty, a measure of aging defined in survivor-specific studies as having 3 of the following criteria: low lean mass, physical exhaustion, low energy expenditure, slow walking speed, and weakness, has a prevalence of 6% to 7%, consistent across multiple cohorts of survivors.[8,9,113] Notably, survivors in their 30s have a similar

prevalence of frailty as general population controls in their 60s[8] and 3× the prevalence as similar-aged sibling controls in the Childhood Cancer Survivor Study.[9]

RISK FACTORS. Treatment exposures associated with this phenotype include radiation to the brain and abdominopelvic region,[8,9,113] exposure to platinating or alkylating agents,[9,113] and lung surgery.[9] Independent of treatment exposures, prefrailty (only 2 of the frailty criteria are fulfilled) or frailty have been associated with the presence of modifiable factors such as obesity, sedentary lifestyle, and smoking.[8,9,113] These exposures may augment the risk for frailty directly through DNA damage or indirectly through endocrine disturbances including growth hormone deficiency, hypogonadism, and hyperthyroidism.[113,114] It is important to note that even among survivors without high-risk exposures, frailty remains prevalent, suggesting a role for cancer-specific disease processes.[4] On a molecular level, multiple mechanisms have been proposed to interact with genotoxic treatment and contribute to the process of aging in survivors, including premature telomere attrition,[115,116] epigenetic age acceleration,[38] and persistent treatment-related DNA methylation (**Figure 4**).[117]

ASSOCIATED COMORBIDITIES. Frailty has been associated with a 2-fold increase in the risk for new onset chronic diseases and all-cause mortality.[4,8]

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General population. Two approaches have been suggested to prevent or mitigate the hallmarks of aging: behavioral interventions focusing on nutrition and physical activity[118] and pharmacologic interventions using senolytic agents.[119] Studies in animal models and noncancer populations suggest that calorie restriction can slow biological aging.[119] Additionally, modulation of specific micronutrition or macronutrition (restriction of methionine and carbohydrate and protein supplementation) in rodent models improved health outcomes, including symptoms of frailty.[119,120]

Survivor-specific considerations. Recent work has identified several biomarkers associated with the accelerated aging phenotype in survivors. These include serum levels of high-sensitivity C-reactive protein;[121,122] plasma Th1, Th2, and Th17 cytokines;[115] $p16^{INK4a}$;[122,123] and advanced glycation end products.[124] Further investigation is needed to better characterize aging-associated biomarkers within this population and establish associations with components of frailty to provide understanding of the underlying physiologic mechanisms of dysregulations and stratify high-risk survivors in order to identify targets for intervention.

TABLE 2 The 2022 IGHG Cardiomyopathy Surveillance Recommendations for Survivors With Cardiotoxic Treatment Exposure

	Exposure to Cardiotoxic Cancer Treatment			
Risk Group	Anthracycline Only (mg/m²)[a]	Chest-Directed Radiotherapy Only (Gy)	Both Anthracycline (mg/m²) and Chest-Directed Radiotherapy (Gy)	Recommendation for Screening
High	≥250	≥30	≥100 and ≥15	Yes, every 2 years
Moderate	100 to <250	15 to <30	–	Yes, every 5 years
Low	>0 to <100	>0 to <15	–	No screening

Changes from the 2015 version of the guideline are as follows: threshold for high-risk chest-directed radiotherapy lowered from 35 to 30 Gy; change in screening recommendations for low-risk groups (<100 mg/m² anthracyclines or <15 Gy chest-directed radiotherapy) from 5 years intervals to none. Reproduced with permission from Ehrhardt et al.[129] [a]Anthracycline dose reported as doxorubicin-equivalent dose in which conversions are idarubicin × 5, daunorubicin × 0.5, mitoxantrone × 10, and epirubicin × 0.67.

IGHG = International Late Effects of Childhood Cancer Guideline Harmonization Group.

Physical activity interventions have shown promise in improving physical function parameters in children and young adults with active or treated cancer.[59,125,126] A randomized trial of 67 survivors observed a significant increase in lean mass with resistance training over a period of 24 weeks regardless of protein supplementation.[127] Although more research is needed to determine the most effective exercise prescription for this population, limited trials have demonstrated the effectiveness of digital health interventions in promoting and sustaining behavioral changes.[126] Ongoing trials include those leveraging mobile health technologies to administer tailored interventions to improve physical activity, exercise capacity, and diet in survivors (NCT04765241, NCT05075759, and NCT04714840) and interventions testing the effects of nicotinamide riboside on skeletal muscle health and insulin resistance in survivors (NCT05023993 and NCT05194397). Moreover, an ongoing clinical trial is evaluating 2 senolytic regimens, dasatinib plus quercetin and fisetin, in survivors (NCT04733534) to determine the safety and efficacy for improving markers of cellular senescence and components of frailty. If successful, future research will be needed to optimize the role of exercise interventions and senolytic agents during survivorship, including optimal timing and duration of intervention, to improve long-term cardiometabolic health and reduce morbidity and mortality caused by chronic disease in survivors. Additional considerations for this work include the role of hormone

replacement for treatment-related endocrinopathies in mitigating frailty.[113]

CONCLUSIONS

Survivors of childhood cancer face an increased risk for cardiovascular disease and mortality extending beyond the first 5 years of cancer survivorship, highlighting the essential need for lifelong risk reduction strategies. The high prevalence of CMRFs in this population and their established independent associations with late cardiovascular events emphasize the importance of targeted interventions (**Central Illustration**). The International Late Effects of Childhood Cancer Guideline Harmonization Group has recognized the importance of these CMRFs and incorporated recommendations for their screening and management in specific surveillance guidelines for treatment-associated coronary artery disease[128] and the recently updated cardiomyopathy guidelines (**Table 2**).[129] However, further research is necessary to identify optimal screening methods, identify high-risk individuals, and assess preventive and treatment interventions.

Early detection through screening may provide opportunities for interventions to reduce the burden of cardiovascular morbidities and mortality.[7] The American Heart Association released a scientific statement recommending category-specific cutpoints for diagnosis and management of these CMRFs in the pediatric population based on the individual risk for cardiovascular diseases, including childhood cancer survivor at-risk (cardiotoxic chemotherapy), moderate-risk (chest irradiation), and high-risk (hematopoietic stem cell transplant) categories.[130] However, aging survivors, those with high-risk exposures in the absence of traditional CMRFs, or those 20 to 39 years of age fall into a gap where neither evidenced-based guidelines or consensus-based recommendations exist regarding screening, diagnosis, and initiation of treatment. Intervention trials and continued observational work using large cohort and population-based data in survivors are necessary to determine the effectiveness of survivor-specific treatment. With recent work identifying racial disparities in the burden of CMRFs, independent of sociodemographic and treatment-related factors,[131] future studies must include diverse populations and capitalize on the use of available genetic and epigenetic data to optimize risk assessment and understand therapeutic response.

Despite the available guidelines, many cases of CMRFs remain underdiagnosed and/or undertreated among survivors,[7] partly because of limited familiarity of primary care providers with cancer-specific screening guidelines.[132,133] To bridge the gap between survivorship and primary care, the Institute of Medicine recommends a survivorship care plan, a shared patient-specific follow-up plan between oncologists and primary care providers.[134] Various models for such plans have been developed,[135] and efforts are ongoing to identify the most effective model that supports long-term health in different risk groups of survivors.[136-138]

Many questions remain unanswered regarding the optimal timing, duration, and goals of interventions, as well as the persistence of effect. Addressing these gaps requires large, multisite collaborative studies that simultaneously incorporate nutrition, physical activity, and behavioral change strategies while accounting for the heterogeneity of treatment effects and the impact of survivorship on the individual's physical abilities. Generalizability of any intervention to a primary care setting must consider regional, cultural, and socioeconomic factors and draw on expertise from dissemination and implementation science. Moreover, evidence on the importance of tailoring lifestyle interventions to survivorship[77] brings into question the translation of pharmacotherapy guidelines from the general population to survivors, necessitating survivor-specific trials with novel study designs to evaluate the safety and effectiveness of available treatments in this unique patient population.

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KEY WORDS **cardiometabolic risk factors, cardiomyopathy, cardiovascular diseases, childhood cancer survivors, frailty, prevention, risk prediction**

APPENDIX **For an expanded Methods section and supplemental table, please see the online version of this paper.**