Progress in Pediatric Cardiology 36 (2014) 19–26

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Late cardiotoxicity in aging adult survivors of childhood cancer

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ARTICLE INFO

Available online 13 October 2014

Keywords:
Anthracycline
Cardiomyopathy
Cardioprotection
Intervention
Screening

ABSTRACT

The survival rate for childhood cancer is steadily improving, and the current estimate for the prevalence of childhood cancer survivors in the United States is 420,000. With this encouraging trend and the aging of this population, there is an ever-increasing responsibility to identify adult survivors of childhood cancer with adverse health outcomes related to cancer treatment across the span of their lives. To accomplish this, large cohort studies have been developed to follow survivors longitudinally. Compared to siblings, survivors have a higher cumulative incidence of morbidity and mortality, and this gap in incidence only widens with age. One of the most significant late toxicities in survivors is late onset cardiotoxicity, largely due to anthracycline and chest-directed radiation exposure. Survivors also have an increased prevalence of traditional cardiovascular risk factors as they age, which potentiates the risk for major cardiac events. Prevention is essential. Minimizing anthracycline dose exposure in pediatric cancer patients is a primary method of cardioprotection. Dexrazoxane and enalapril have also been studied as primary (pre-exposure) and secondary (post-exposure) cardioprotectant agents, respectively. Additionally, the Children's Oncology Group has published exposure-driven, risk-based screening guidelines for long-term follow-up, which may be a cost-effective way to identify subclinical cardiac disease before progression to clinical presentation. Ongoing research is needed to determine the most effective diagnostic modality for screening (e.g. *echocardiography*), and the most effective intervention strategies to improve long-term outcomes.

1. Introduction

The five-year survival rate for childhood cancer has been improving for decades and recently surpassed 80%, according to data from the Surveillance Epidemiology and End Results program within the United States National Cancer Institute [1]. These data also report the prevalence of childhood cancer in the United States at over 379,100 as of January 2010. Assuming constant rates of incidence and diagnosis of childhood cancers, the current estimate for the prevalence of childhood cancer survivors in the United States is greater than 420,000 [2]. As a greater percentage of children diagnosed with cancer survive into adulthood, there is an ever-increasing responsibility to monitor these survivors for late adverse health outcomes related to their cancer treatment.

To determine the prevalence of, and risk factors for these late effects of cancer treatment, large cohort studies have been developed to follow survivors longitudinally. The largest study of this kind in the United States is the Childhood Cancer Survivor Study, a population of more than 14,000 adults treated for a childhood cancer between 1970 and 1986 [3,4]. Recent expansion of the cohort now includes >10,000 additional survivors diagnosed between 1987 and 1999. Continued follow-up allows for late, treatment-related cardiotoxicities to be identified in this aging survivor population, in which there is often a long latency period prior to the clinical onset of adverse cardiac health outcomes. Similar long-term cohorts have been developed via national population-based healthcare registries in several countries, however, often without the benefit of direct access to specific treatment exposure data. The data from longitudinal cohort studies like the Childhood Cancer Survivor Study and national registries provides the essential data on the incidence of and risk factors for late onset cardiotoxicity as can be used to identify better methods of screening and intervention [5].

2. The Increasing Risk of Treatment-related Cardiac Outcomes in Aging Survivors

Even after children treated for cancer have transitioned into adulthood, the long-term impact of treatment is substantial. Yeh et al. modeled mortality risk among a simulated cohort of five-year survivors, based on a representative Childhood Cancer Survivor Study population, and predicted a loss in life expectancy of greater than ten years, compared to the general population [6]. More recent data in this cohort (14,359 survivors analyzed) showed that this shortened lifespan is coupled with an inflated burden of chronic health outcomes. Compared to siblings, survivors in the Childhood Cancer Survivor Study cohort had a higher cumulative incidence of severe, life threatening, or fatal

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http://dx.doi.org/10.1016/j.ppedcard.2014.09.003
1058-9813/

organ-specific health conditions that continued to increase with age [7]. In this respect, these data showed that a 24 year-old survivor of childhood cancer has the same cumulative incidence of severe and life threatening health events as a 50 year-old sibling.

The disparity in the incidence of severe, life-threatening, or fatal health conditions between survivors and siblings does not resolve with time, even though the general population ages and acquires health problems; on the contrary, the gap between survivors and siblings actually widens with age [7]. Notably, this same study by Armstrong et al. demonstrated that even middle-aged survivors with no previous history of severe, life-threatening, or fatal events move along an escalated trajectory for developing such conditions, compared to siblings. For example, even beyond the age of 35 years survivors had a hazard ratio of 10.9 (95% CI, 4.5 to 26.0) for developing heart failure, compared to siblings [7]. This increased rate of development of negative health outcomes among aging survivors is important for defining risk accurately.

Of all the late toxicities tracked in childhood cancer survivors, major cardiac events and the development of malignant neoplasms are the most common [7]. In addition, there continues to be a striking increase in the cumulative incidence of these health outcomes for survivors beyond age 35 years relative to other health outcomes (Fig. 1). This finding is consistent with previous Childhood Cancer Survivor Study analyses of late mortality, in which subsequent neoplasms and major cardiac events were the most common cause of death after recurrence of primary cancer (standardized mortality ratios of 15.2 [95% confidence interval, 13.9 to 16.6] and 7.0 [95% CI, 5.9 to 8.2] for subsequent malignancies and cardiac events, respectively, compared to an age and sex-matched comparison population) [8].

The longitudinal follow-up of survivorship cohorts has shed light on late major cardiac outcomes, specifically those due to cardiotoxicity from anthracycline and chest-directed radiation exposure. Mulrooney et al. demonstrated that, compared to siblings, survivors in the Childhood Cancer Survivor Study were at a significantly increased risk for congestive heart failure (hazard ratio [HR] 5.9, 95% confidence interval [CI] 3.4 to 9.6), myocardial infarction (HR 5.0, 95% CI, 2.3 to 10.4), pericardial disease (HR 6.3, 95% CI, 3.3 to 11.9), and valvular abnormalities (HR 4.8, 95% CI, 3.0 to 7.6), even after adjustment for demographic characteristics and smoking status (Table 1) [9]. In this analysis, 14,358 survivors and 3899 siblings completed baseline questionnaires that addressed cardiac complications. An adjusted multivariable model evaluated the independent effect of various risk factors on each cardiac outcome (Table 2). A statistically significant association was found between radiotherapy dose and the risk for all

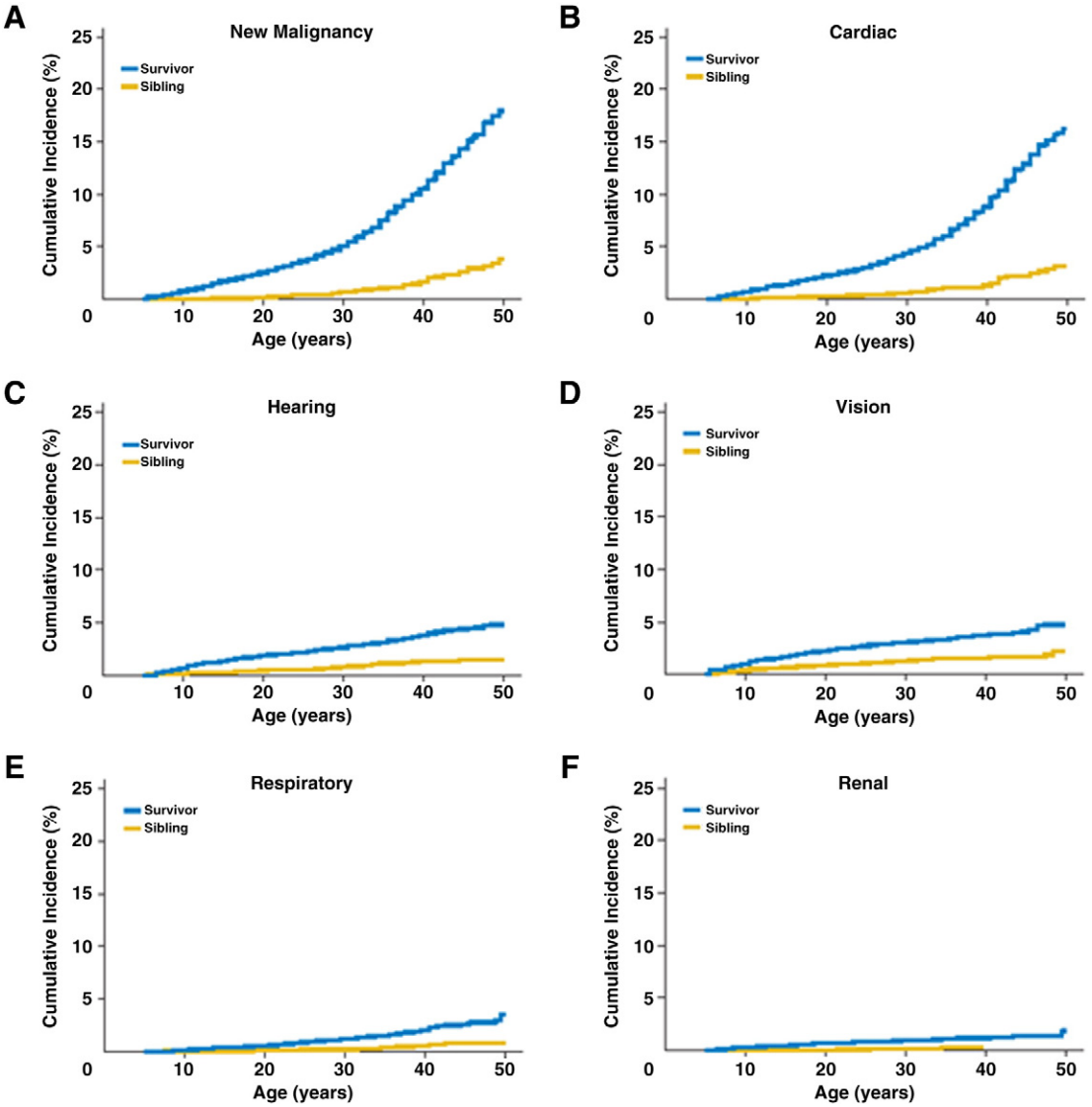

Fig. 1. Cumulative incidence of selected grade 3 to 5 conditions by organ system. (A) New malignancy, (B) cardiac, (C), hearing, (D) vision, (E) respiratory, and (F) renal.