Published in final edited form as:

*J Cancer Surviv*. 2016 February ; 10(1): 113–121. doi:10.1007/s11764-015-0457-8.

# Pregnancy-Associated Cardiomyopathy in Survivors of Childhood Cancer

**Melissa R. Hines, MD**[1,2], **Daniel A. Mulrooney, MD**[2,3,4], **Melissa M. Hudson, MD**[3,4], **Kirsten K. Ness, PhD**[4], **Daniel M. Green, MD**[3,4], **Scott C. Howard, MD**[2,3], **Matthew Krasin, MD**[5], and **Monika L. Metzger, MD**[2,3]

[1]Department of Pediatric Critical Care, University of North Carolina, 101 Manning Drive, Chapel Hill, NC 27514

[2]Department of Pediatrics, University of Tennessee Health Science Center, 50 N. Dunlap, Rm 461R Memphis, TN 38103

[3]Department of Oncology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678

[4]Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678

[5]Department of Radiological Sciences, St Jude Children's Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678

## Abstract

**Purpose—**Current information regarding pregnancy-associated cardiomyopathy among women treated for childhood cancer is insufficient to appropriately guide counseling and patient management. This study aims to characterize its prevalence within a large cohort of females exposed to cardiotoxic therapy.

**Methods—**Retrospective cohort study of female cancer survivors treated at St. Jude Children's Research Hospital between 1963 and 2006, at least 5 years from diagnosis, ≥ 13 years old at last follow-up, and with at least one successful pregnancy. Pregnancy-associated cardiomyopathy was defined as shortening fraction < 28% or ejection fraction < 50% or treatment for cardiomyopathy during or up to 5 months after completion of pregnancy.

**Results—**Among 847 female cancer survivors with 1554 completed pregnancies only 3 (0.3%) developed pregnancy-associated cardiomyopathy, 40 developed non-pregnancy-associated cardiomyopathy either 5 months post-partum (n=14), or prior to pregnancy (n=26). Among those with cardiomyopathy prior to pregnancy (n=26), cardiac function deteriorated during pregnancy in 8 patients (3 patients with normalization of cardiac function prior to pregnancy, 3 with persistently abnormal cardiac function, and 2 for whom resolution of cardiomyopathy was unknown prior to

**Corresponding Author:** Monika L. Metzger, MD, 262 Danny Thomas Place, MS 260, Memphis, TN 38015-3678 (monika.metzger@stjude.org). Phone: +1-901-595-4974, Fax +1-901-595-8037.

**Conflicts of interest:** The authors report no conflict of interest.

pregnancy). Patients that developed cardiomyopathy recevied a higher median dose of anthracyclines compared to those that did not (321 mg/m$^2$ versus 164 mg/m$^2$; $p < 0.01$).

**Conclusions—**Pregnancy-associated cardiomyopathy in childhood cancer survivors is rare.

**Implications for cancer survivors—**Most female childhood cancer survivors will have no cardiac complications during or after childbirth, however those with a history of cardiotoxic therapies should be followed carefully during pregnancy particularly those with a history of anthracycline exposures and if they had documented previous or current subclinical or symptomatic cardiomyopathy. Female childhood cancer survivors with a history of cardiotoxic therapies should be followed carefully during pregnancy particularly those with a history of anthracycline exposures and if they had documented previous or current subclinical or symptomatic cardiomyopathy.

### Keywords

pregnancy associated cardiomyopathy; cardiac toxicity; childhood cancer survivor; cardiotoxic therapies

## INTRODUCTION

The survival rate for children diagnosed with cancer has increased significantly over the last 50 years and with it an awareness of the long-term effects of therapy. Cardiac sequelae of radiation therapy and anthracycline exposure have been well documented and manifest most commonly as left ventricular dilatation with reduced cardiac output or dilated cardiomyopathy, but also include ischemic heart disease, heart valve dysfunction, and/or conduction disorders [1–9]. Survivors at highest risk are those exposed to both radiation therapy that includes the heart and anthracyclines [2, 6]. Radiation dose and field and the cumulative anthracycline dose are the most important risk factors, but the incidence and severity of cardiac damage may also be influenced by host (e.g., age at treatment, gender, race) and lifestyle factors (tobacco and drug use, diet, weight management). [2, 6, 10–14]. Subclinical cardiac toxicity following anthracycline therapy has also been reported, but its natural history and rate of progression to clinical heart failure is unknown [15]. Physiologic stresses, such as pregnancy, have been hypothesized to precipitate cardiac decompensation among survivors exposed to cardiotoxic therapies who do not have clinical evidence of cardiomyopathy. However, limited data support this claim. Within the general population, peripartum cardiomyopathy, defined as cardiac dysfunction with no identifiable cause during the last month of pregnancy or up to five months postpartum, is rare [16]. Among cancer survivors, pregnancy-associated cardiomyopathy has been anecdotally linked to anthracycline exposure, but formal assessment of left ventricular systolic function before pregnancy was not documented in these reports [17–21]. In small case series of childhood cancer survivors with pre-pregnancy assessment of cardiac function, pregnancy-associated cardiomyopathy did not develop in women with normal left ventricular systolic function [18, 19]. In general, current information regarding pregnancy-associated cardiomyopathy among women treated for childhood cancer is insufficient to appropriately guide counseling and patient management. This study aims to address this knowledge gap by characterizing the

prevalence of and risk factors for pregnancy-associated cardiomyopathy within a large cohort of female childhood cancer survivors exposed to cardiotoxic therapy.

## PATIENTS AND METHODS

### Patient Selection and Data

Patients included in the study were female cancer survivors treated at St. Jude Children's Research Hospital (SJCRH) between May 16, 1963 and May 25, 2006, who were at least 5 years from diagnosis, ≥ 13 years old at last follow-up, and known to have completed at least one pregnancy through delivery. Participants were either patients of the After Completion of Therapy Clinic (ACT Clinic) or enrolled in the St Jude Lifetime Cohort (SJLIFE) Study [22]. These patients are no longer undergoing therapy for their original cancer diagnosis but have continuous follow-up to ascertain health outcomes. ACT Clinic (started in early 1990's) patients are evaluated yearly for at least 10 years after initial cancer diagnosis or until they reach 18 years of age. ACT Clinic patients that have cardiotoxic exposures are screened for cardiac disease as recommended by the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (www.survivorshipguidelines.org) [23]. After 'graduation' from the clinic, they are sent annual questionnaires inquiring about their health status and new health events as well as pregnancies and pregnancy related complications including medications. Those in the SJLIFE Study are ≥ 18 years of age and ≥ 10 years from their cancer diagnosis. Eligibility and recruitment details for this study have been previously published [29]. SJLIFE participants also undergo risk-based health evaluations as recommended by the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (www.survivorshipguidelines.org) [23] including echocardiograms (every year to every 5 years based on risk) if treated with cardiotoxic therapies.

Information extracted from the survivorship database for this analysis included: diagnosis, age at diagnosis, self-identified race, number and dates of pregnancies, previous cyclophosphamide, ifosfamide, and anthracycline exposures including cumulative doses, chest radiation treatment fields, and date of last follow-up. Anthracycline equivalent exposure was calculated by multiplying the cumulative doses of doxorubicin × 1, daunorubicin × 0.833, epirubicin × 0.67, idarubicin × 5 and mitoxantrone × 4 [24, 25]. Radiation exposure was considered if the field included the heart. Records were reviewed for patients who had a history of cardiomyopathy to ascertain a possible association with pregnancy. The results of previous echocardiograms and pregnancy history (self reported) were reviewed. Patients were not followed by our facility during pregnancies and patients were not specifically seen for prenatal or postnatal visits. Echocardiograms were obtained by other facilities by the attending physician following them. Medical records (clinic notes, echocardiogram and electrocardiogram reports) were obtained to validate reports of cardiovascular disease diagnosed at other facilities. The study was approved by the Institutional Review Board.

### Definition of nonpregnancy associated cardiomyopathy and pregnancy associated cardiomyopathy

Nonpregnancy associated cardiomyopathy was defined as shortening fraction (SF) < 28% or ejection fraction (EF) < 50% on echocardiogram or treatment for cardiomyopathy that did not occur during pregnancy or within 5 months of delivery. The cardiomyopathy was considered subclinical if it was asymptomatic and did not require any treatment.

Pregnancy-associated cardiomyopathy was defined as SF < 28% or EF < 50% diagnosed during or within 5 months of delivery or treatment for cardiomyopathy during this interval in a patient with no previous diagnosis of cardiomyopathy.[16, 26]

## RESULTS

### Patient Characteristics

There were a total of 2737 females who survived five years and were at least age 13 and who were treated during the time period specified and were alive at the time of our analysis, while 219 met the eligibility criteria but were expired at the time of our analysis. For this study the patient cohort comprised 847 (31%) female survivors of childhood cancer with 1554 documented completed pregnancies (median=2, range: 1–5 pregnancies). No known therapeutic abortions due to cardiomyopathy were reported. Median age at cancer diagnosis was 10.3 years (range, 1 month – 22.6 years; Table 1). Most patients (83%) were white. Over half of the cohort had been treated for leukemia (38%) or lymphoma (23%). Cardiotoxic treatment exposures included only anthracycline agents in 237 (28%), only radiation therapy with fields involving the heart in 140 (17%), both modalities in 248 patients (29%) and neither in 222 patients (27%). Among 484 women treated with anthracyclines, 376 (44%) received a cumulative dose < 300 mg/m$^2$, 72 (9%) received ≥ 300 and < 400 mg/m$^2$, 26 (3%) received ≥ 400 and < 500 mg/ m$^2$, and 9 (1%) received ≥ 500 mg/ m$^2$ (median 200 mg/m$^2$, range: 39–721 mg/m$^2$), and one patients received an unknown anthracycline dose. In addition, 459 (54%) and 54 (6%) of the survivors received cyclophosphamide (median 7,313 mg/m2, range: 300–38,576 mg/m$^2$) and ifosfamide (median 39,728 mg/m$^2$ range: 6,000–79,606 mg/m$^2$), respectively. Median follow-up time from diagnosis was 26.5 years (range: 6–48.4 years). Most patients were seen or contacted within the last (61%) or 2 years (90%).

### Overall prevalence of cardiomyopathy

We identified 43 women (5%) with development of cardiomyopathy at a median time of 10 years (2 weeks to 37 years) from cancer diagnosis. Forty had non-pregnancy associated cardiomyopathy (26 before pregnancy and 14 > five months postpartum) and 3 had pregnancy associated cardiomyopathy (Figure 1). Cardiotoxic exposures included anthracyclines in 29 (67%), radiation fields involving the heart in 4 (9%), both cardiotoxic modalities in 9 (21%), and neither exposure in 1 patient. Prevalence of cardiomyopathy in patients that had both radiation and anthracycline exposure was 3.6% (9 of 248 patients). Prevalence of cardiomyopathy in patients that received anthracycline alone was 12% (29 of 237). Additionally, 33 (77%) of those with cardiomyopathy received cyclophosphamide and 6 (14%) ifosfamide. Current age, age at diagnosis, and race did not differ among women

who did and did not develop cardiomyopathy (Table 1). Those diagnosed with cardiomyopathy had a higher anthracycline exposure compared to those without cardiomyopathy (median dose 321 mg/m$^2$ vs 164 mg/m$^2$, p< 0.01; t-test).

### Patients with non-pregnancy-associated cardiomyopathy

A total of 40 (4.7% of the whole cohort) women developed non-pregnancy-associated cardiomyopathy (Figure 1 and Table 2). There were 14 of these women who developed a cardiomyopathy more than five months post-partum (subclinical in 1; 13 requiring medication; median time to CMP diagnosis, 24 years after cancer treatment, range, 9–36 years; median time to CMP diagnosis after last pregnancy was 5.5 years, range, 1–26 years). Twenty-six of the 40 women were diagnosed with cardiac dysfunction prior to becoming pregnant (subclinical in 16; 10 on medication). Among those diagnosed prior to becoming pregnant, 16 had documented normalization of function prior to becoming pregnant, 8 had persistent cardiomyopathy, and for 2 patients follow-up of previously diagnosed cardiomyopathy was unavailable prior to becoming pregnant (both of these women had further deterioration of cardiac function during pregnancy). Among the 16 women who had normal function prior to becoming pregnant, 3 had recurrent deterioration of function during their pregnancies. Among the 8 women with persistent cardiomyopathy, 3 deteriorated during pregnancy but 5 remained stable (Table 3 and Supplemental Table). Again after detailed examination of past records for these patients, no therapeutic abortions secondary to cardiomyopathy were reported

In addition we wanted to explore how many of our nonpregnancy associated patients had scheduled echocardiogram prior to their pregnancies. Of the 40 women diagnosed with nonpregnancy-associated cardiomyopathy, 34 patients (85%) had documentation of their cardiac function by echocardiogram prior to their first pregnancy (26 (81%) patients with normal echocardiogram, 8 patients with subclinical cardiomyopathy). Twenty-six patients of this group had a second pregnancy with 13 patients (50%) having echocardiograms prior to second pregnancy (8 patients (66%) with normal heart function and 5 patients with subclinical cardiomyopathy). Six of 9 patients (67%) with third pregnancy in this group had cardiac function documented by echocardiogram with 4 of these patients (83%) with documented normal echocardiogram. Only 4 patients in this group had a fourth pregnancy and only one patient had an echocardiogram documented prior to the fourth pregnancy. Median time of echocardiogram prior to each pregnancy was 1.3 years (range 0.25 to 16 years).

### Patients with pregnancy-associated cardiomyopathy

Only 3 women (0.4% of the cohort) with no prior history of cardiomyopathy developed cardiomyopathy during pregnancy (Tables 2 and 4). Patient 1 is described in a previous case report by Davis et al [20]. The patient received doxorubicin (523 mg/m$^2$) for osteosarcoma diagnosed at 6 years of age. Serial echocardiograms during and after therapy documented normal cardiac function with her last serial echocardiogram performed 5 years after therapy. At 13 years of age she delivered her first baby via Cesarean section that was complicated by significant blood loss requiring large volume fluid resuscitation. Within hours of delivery she developed pulmonary edema and her echocardiogram showed a shortening fraction of

9% with global hypokinesia. Her cardiac function normalized on inotropic and diuretic therapy. There have been no other recorded pregnancies for this patient.

Patient 2 received doxorubicin (cumulative dose 385 mg/m$^2$) for Ewing sarcoma diagnosed at 8 years of age. Serial echocardiograms up to 10 years after completion of therapy confirmed normal left ventricular systolic function. At 31 years of age, she developed cardiomyopathy (ejection fraction 35% to 40% with global hypokinesia) following delivery of her first child by Cesarean section. Her left ventricular function subsequently normalized on a beta-blocker and diuretics, and she remains on a beta blocker. This patient has had no other recorded pregnancies.

Patient 3 received daunorubicin (cumulative dose 84 mg/m$^2$) for acute lymphoblastic leukemia diagnosed at 7 years of age. Echocardiogram performed 8 years after therapy showed normal cardiac function. At age 19, she developed cardiomyopathy (ejection fraction 40% to 45% with mild global hypokinesia) in the 24$^{th}$ week of her first pregnancy. She was treated with beta-blocker therapy for the rest of her pregnancy and had no complications with delivery. Her left ventricular function subsequently normalized 6 months after delivery at which time medication was discontinued. There have been no other pregnancies recorded for this patient.

## COMMENT

In a large and well-characterized cohort of female childhood cancer survivors with prolonged follow-up, we found a low incidence of clinically significant pregnancy-associated cardiomyopathy. As has been previously described our patients are very committed and willing to be in continuos communication providing information about life changing events such as pregnancies and cardiac events, with less than 10% considered lost to follow up. [22] While women exposed to cardiotoxic cancer regimens were at risk for developing cardiomyopathy later in life, only 3 (0.2% of all pregnancies) without any known prior decrease in cardiac function had decompensation during their pregnancies. However, among the cancer survivors with a diagnosis of cardiac dysfunction prior to becoming pregnant, 8 of 26 either had recurrent cardiomyopathy (n=3) or further decrease in function (n=5) during pregnancy, suggesting an increased peripartum risk for survivors with previous evidence of cardiac toxicity [16]. The current recommended mode of delivery in women with pre-existing dilated cardiomyopathies is vaginal if there are no obstetric contraindications. Vaginal deliveries are associated with less blood loss and are overall found to be more hemodynamically stable causing less stress to the cardiocirculatory system. [27]

While low, the incidence of peripartum cardiomyopathy in our cohort is nearly 10-fold higher than what has been reported in the general U.S. population but comparable to other reports among childhood cancer survivors. The National Institutes of Health workshop [16] on peripartum cardiomyopathy reported an incidence of 1 in 3000 to 4000 (0.03%) live births in the general population compared to the 3 in 1514 (0.2%) births (excluding the 40 births complicated by non-pregnancy associated cardiomyopathy) in this cohort of cancer survivors. However, in a study by Van Dalen et al. [18], none of 53 women previously

exposed to anthracycline therapies who delivered one or more children developed pregnancy-associated cardiomyopathy. Patients in the Van Dalen study were diagnosed by symptoms without echocardiograms leading to possible underreporting of subclinical cardiomyopathy. Our study identified patients with subclinical cardiomyopathy because of frequent echocardiograms performed as part of surveillance before and after therapy, and confirms the low incidence of pregnancy associated cardiomyopathy in a much larger cohort. As in our study, Van Dalen et al. considered other therapies including radiation, ifosfamide, and cyclophosphamide, but the risk for cardiomyopathy related to these therapies could not be assessed because none of the exposed patients developed symptomatic pregnancy-associated cardiomyopathy. Bar et al. [19] conducted a longitudinal study of 37 women previously treated with anthracyclines using screening echocardiograms before, during, and after therapy as well as before, during, and after pregnancy. Women with normal function (SF ≥ 30%) prior to pregnancy remained stable, but those (8 of 37; 22%) with a decreased shortening fraction (SF < 30%) prior to pregnancy had further decompensation during pregnancy (19% SF decrease post pregnancy). Our study supports these findings, suggesting an association of pre-pregnancy subclinical impairment of cardiac function with worsening subclinical cardiomyopathy during pregnancy.

Compared to previous reports [12, 18, 19], our study provides more robust data to reassure survivors and health care providers of the low risk of peripartum cardiomyopathy among female childhood cancer survivors, even among women treated with relatively “high-risk” cardiotoxic exposures, particularly those who maintain normal cardiac function during follow up. In our cohort, two of three women who developed pregnancy-associated cardiomyopathy received total anthracycline doses ≥ 250 mg/m$^2$ as well as other concurrent cardiotoxic drugs (including cyclophosphamide). Cyclophosphamide has been associated with acute myocarditis but has not been found to cause chronic cardiomyopathy [13, 28]. Average total anthracycline doses reported in previous studies were > 240 mg/m$^2$ [12, 17, 18, 20]. Higher doses of anthracycline (≥ 250 mg/m$^2$) exposure were also administered to 65% of the non-pregnancy-associated cardiomyopathy patients. Interestingly, none of our patients with pregnancy-associated cardiomyopathy had radiation treatment fields involving the heart. There was no apparent association of increased risk of cardiomyopathy with exposure to both radiation and anthracycline (3%) compared to anthracycline alone (12%). It appears from this study that, while a previous history of cardiomyopathy (including subclinical cardiomyopathy) does not predict cardiomyopathy during pregnancy, there may be an increased risk of worsening heart function even in patients whose heart function had normalized prior to pregnancy as 3 out of 16 patients (19%) had recurrent cardiomyopathy during pregnancy. Furthermore, our data supports that patients without a prior history of cardiomyopathy are at very low risk of developing pregnancy-associated cardiomyopathy. Only 3 out of 804 such patients (0.3%) with no prior history of cardiomyopathy developed cardiomyopathy.

Our study is limited by its retrospective nature and the reliance of self-reporting of successful pregnancies and health problems, including cardiomyopathy, after completion of therapy. There was no prospective systematic ascertainment of pregnancy related cardiomyopathy and, despite best efforts, some inconsistency of echocardiographic screening over the years; therefore, our results are limited and based on last

echocardiographic information that was available and/or self-reporting of any cardiomyopathy the patient which was verified by obtained medical records. Although we initially identified pregnancy-associated cardiomyopathy in some survivors based on self-report, potentially leading to under-reporting, records were obtained and reviewed to verify each case. We also cannot say with absolute certainty that patients that we reported with pregnancy-associated cardiomyopathy had no subclinical cardiomyopathy prior to pregnancy since last echocardiogram in those three cases were obtained 2 years prior to pregnancy. As in previous studies, we were unable to calculate true incidence rates and risk factors for pregnancy-associated cardiomyopathy because of low numbers of patients with the outcome and heterogeneity of the group examined. Given the retrospective nature of this study we were unable to determine if patients had scheduled screening echocardiograms during their pregnancies or had special follow-up with high-risk obstetrics because of their history of previous cardiotoxic treatment.

In conclusion, pregnancy-associated cardiomyopathy in childhood cancer survivors is rare (estimated incidence 3 in 1514 births or 1 in 500 births), but higher than the general population. Female childhood cancer survivors with a history of cardiotoxic therapies should be followed carefully during pregnancy, especially in patients with history of cardiomyopathy in the past. Referral to Maternal-Fetal-Medicine during pregnancy should be considered for those childhood cancer survivors with a history of anthracycline exposures and radiation therapy fields involving the heart, particularly if they have had documented previous or current subclinical or symptomatic cardiomyopathy. Counseling for contraception and preconception counseling is also important for this cohort as their pregnancy could unmask subclinical dysfunction.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Support:** National Institutes of Health Cancer Support Core Grant (CA-21765) and the American Lebanese Syrian Associated Charities (ALSAC).

## References

1. Aleman BM, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007; 109(5): 1878–1886. [PubMed: 17119114]
2. Armstrong GT, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009; 27(14):2328–2338. [PubMed: 19332714]
3. Cosset JM, Henry-Amar M, Meerwaldt JH. Long-term toxicity of early stages of Hodgkin's disease therapy: the EORTC experience. EORTC Lymphoma Cooperative Group. Ann Oncol. 1991; 2(Suppl 2):77–82. [PubMed: 2049323]
4. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol. 1993; 11(7):1208–1215. [PubMed: 8315419]
5. Henry-Amar M, et al. Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. EORTC Lymphoma Cooperative Group. Int J Radiat Oncol Biol Phys. 1990; 19(5):1155–1157. [PubMed: 2254106]

6. Mulrooney DA, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ. 2009; 339:b4606. [PubMed: 19996459]
7. Myrehaug S, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma. 2008; 49(8):1486–1493. [PubMed: 18608873]
8. Swerdlow AJ, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Inst. 2007; 99(3):206–214. [PubMed: 17284715]
9. Wethal T, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer. 2009; 101(4):575–581. [PubMed: 19623176]
10. Kremer LC, et al. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. Ann Oncol. 2002; 13(4):503–512. [PubMed: 12056699]
11. Krischer JP, et al. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. J Clin Oncol. 1997; 15(4):1544–1552. [PubMed: 9193351]
12. Lipshultz SE, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med. 1995; 332(26):1738–1743. [PubMed: 7760889]
13. Simbre VC, et al. Cardiotoxicity of cancer chemotherapy: implications for children. Paediatr Drugs. 2005; 7(3):187–202. [PubMed: 15977964]
14. Abazov VM, et al. Search for R-parity violating supersymmetry in two-muon and four-jet topologies. Phys Rev Lett. 2002; 89(17):171801. [PubMed: 12398658]
15. Kremer LC, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol. 2002; 13(6):819–829. [PubMed: 12123328]
16. Pearson GD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000; 283(9):1183–1188. [PubMed: 10703781]
17. Katz A, et al. Peripartum cardiomyopathy occurring in a patient previously treated with doxorubicin. Am J Med Sci. 1997; 314(6):399–400. [PubMed: 9413345]
18. van Dalen EC, et al. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. Eur J Cancer. 2006; 42(15):2549–2553. [PubMed: 16919450]
19. Bar J, et al. Pregnancy outcome in women treated with doxorubicin for childhood cancer. Am J Obstet Gynecol. 2003; 189(3):853–857. [PubMed: 14526329]
20. Davis LE, Brown CE. Peripartum heart failure in a patient treated previously with doxorubicin. Obstet Gynecol. 1988; 71(3 Pt 2):506–508. [PubMed: 3162299]
21. Pan PH, Moore CH. Doxorubicin-induced cardiomyopathy during pregnancy: three case reports of anesthetic management for cesarean and vaginal delivery in two kyphoscoliotic patients. Anesthesiology. 2002; 97(2):513–515. [PubMed: 12151947]
22. Hudson MM, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. Pediatr Blood Cancer. 2011; 56(5):825–836. [PubMed: 21370418]
23. Landier W, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 2004; 22(24):4979–4990. [PubMed: 15576413]
24. Tolba KA, Deliargyris EN. Cardiotoxicity of cancer therapy. Cancer Invest. 1999; 17(6):408–422. [PubMed: 10434952]
25. Allen A. The cardiotoxicity of chemotherapeutic drugs. Semin Oncol. 1992; 19(5):529–542. [PubMed: 1411651]
26. Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. Circulation. 1971; 44(5):964–968. [PubMed: 4255967]
27. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. J Am Coll Cardiol. 2011; 58(4):337–350. [PubMed: 21757110]

28. Fulbright JM. Review of cardiotoxicity in pediatric cancer patients: during and after therapy. Cardiol Res Pract. 2011; 2011:942090. [PubMed: 21637324]

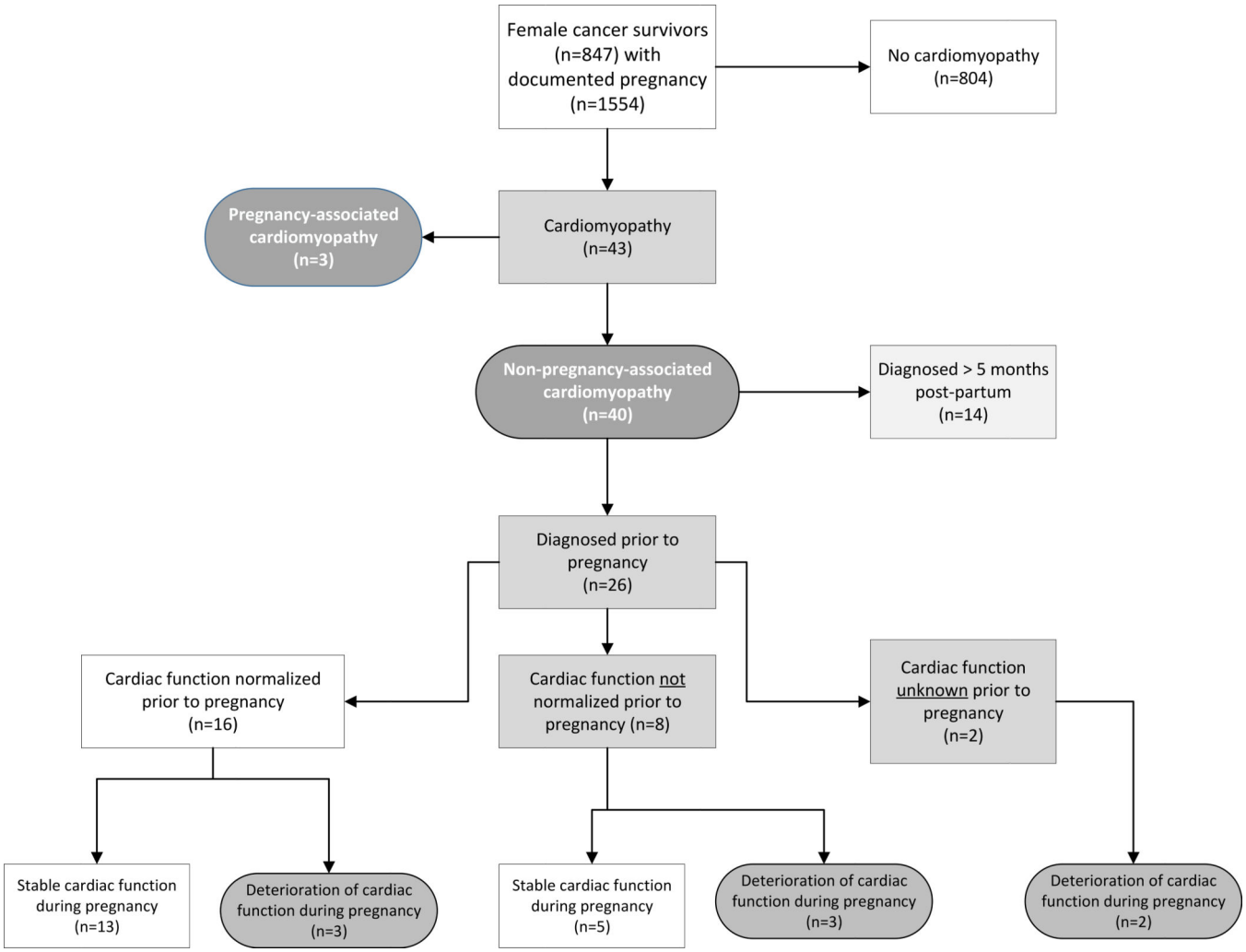


**Figure.**

Flowchart showing the disposition of women with pregnancy-associated cardiomyopathy, as well as those with non-pregnancy associated cardiomyopathy.

*J Cancer Surviv*. Author manuscript; available in PMC 2017 February 01.

**Table 1**

Patient Characteristics

| | All (n=847) | (%) | CMP* (n=43) | (%) | No CMP (n=804) | (%) |
|---|---|---|---|---|---|---|
| **Age at cancer diagnosis** | | | | | | |
| Median (years) | 10.3 | N/A | 12.2 | N/A | 10.1 | N/A |
| Range (years) | 0.02–22.6 | N/A | 0.02–19.9 | N/A | 0.0–22.6 | N/A |
| **Age at first delivery** | | | | | | |
| Median (years) | 22.4 | N/A | 22.4 | N/A | 22.4 | N/A |
| Range (years) | 13.8–40.1 | N/A | 13.9–40.1 | N/A | 10.3–40.1 | N/A |
| **Race** | | | | | | |
| White | 700 | (83) | 35 | (81) | 665 | (83) |
| Black | 134 | (16) | 7 | (17) | 127 | (16) |
| Hispanic | 7 | (<1) | 1 | (2) | 6 | (<1) |
| Other | 6 | (<1) | 0 | (0) | 6 | (<1) |
| **Cancer Diagnosis** | | | | | | |
| Leukemia | 317 | (38) | 9 | (21) | 308 | (38) |
| Lymphoma | 195 | (23) | 11 | (25) | 184 | (23) |
| Sarcoma | 120 | (14) | 20 | (47) | 100 | (13) |
| Embryonal tumors | 86 | (10) | 2 | (5) | 84 | (10) |
| Others | 129 | (15) | 1 | (2) | 128 | (16) |
| **Cumulative Anthracycline dose (mg/m2)** | | | | | | |
| None | 363 | (43) | 5 | (12) | 358 | (45) |
| > 0 and < 300 | 376 | (44) | 15 | (35) | 359 | (45) |
| ≥ 300 and < 400 | 72 | (9) | 14 | (32) | 58 | (7) |
| ≥ 400 and < 500 | 26 | (3) | 8 | (19) | 18 | (2) |
| ≥ 500 | 9 | (1) | 1 | (2) | 8 | (<1) |
| Unknown | 1 | | | | 1 | |
| Median dose for exposed | 200 mg/m$^2$ | | 321 mg/m$^2$** | | | 164 mg/m$^2$** |

| | All (n=847) | (%) | CMP* (n=43) | (%) | No CMP (n=804) | (%) |
|---|---|---|---|---|---|---|
| Range in mg/m$^2$ | (39–721) | | (42–521) | | | (39–721) |
| **Radiation field involving the heart** | | | | | | |
| Yes | 388 | (46) | 13 | (30) | 375 | (47) |
| No | 459 | (54) | 30 | (70) | 429 | (53) |
| **Ifosfamide exposure** | | | | | | |
| Yes | 54 | (6) | 6 | (14) | 48 | (6) |
| No | 793 | (94) | 37 | (86) | 756 | (94) |
| **Cyclophosphamide exposure** | | | | | | |
| Yes | 459 | (54) | 33 | (77) | 426 | (53) |
| No | 388 | (46) | 10 | (23) | 378 | (47) |
| **Follow-up from Diagnosis** | | | | | | |
| Median (years) | 26.5 | NA | 27.1 | NA | 26.4 | NA |
| Range (years) | 6.0–48.4 | NA | 10.5–39.6 | NA | 6.0–48.4 | NA |

CMP, cardiomyopathy, pregnancy and non-pregnancy associated;

* median time to development of CMP 10 years (range, 2 weeks to 37 years) from cancer diagnosis;

** median anthracycline dose for CMP versus no CMP, $p < 0.01$; t-test;

*J Cancer Surviv*. Author manuscript; available in PMC 2017 February 01.

## Table 2

Patient characteristics for non-pregnancy associated cardiomyopathy compared to pregnancy-associated cardiomyopathy

| | Non-pregnancy associated CMP (n=40) | (%) | Pregnancy-associated CMP (n=3) | (%) |
|---|---|---|---|---|
| **Radiation field involving the heart** | | | | |
| Yes | 13 | (32) | 0 | |
| No | 27 | (68) | 3 | (100) |
| **Anthracycline cumulative dose (mg/m2)** | | | | |
| None | 5 | (12) | 0 | (0) |
| ≥ 0 to 300 | 14 | (35) | 1 | (33) |
| ≥ 300 to 400 | 13 | (33) | 1 | (33) |
| ≥ 400 to 500 | 8 | (20) | 0 | (0) |
| ≥ 500 | 0 | (0) | 1 | (33) |
| Median dose for those exposed | 331 mg/m$^2$* | | 172 mg/m$^2$* | |
| Range for those exposed | 42–480 mg/m$^2$ | | 84–521 mg/m$^2$ | |

** median anthracycline dose for non-pregnancy associated CMP versus pregnancy associated CMP, p=0.8; t-test;

*J Cancer Surviv*. Author manuscript; available in PMC 2017 February 01.

**Table 3**

Patients with pre-existing cardiomyopathy and worsening cardiac function during pregnancy

| Patient | Cancer | Age at diagnosis and race | Total Dose anthracyclines (mg/m$^2$) | # of pregnancy at CMP | Time to pregnancy associated CMP | Previous h/o cardiomyopathy | CMP resolved prior to pregnancy? | Outcome** |
|---|---|---|---|---|---|---|---|---|
| 1 | Yolk sac tumor* | 17 mo Caucasian | 380 | 1 | 22 yrs | Yes, severe with ICD placement, 18 yrs after therapy | No | Heart transplant |
| 2 | Osteosarcoma | 17 yrs Caucasian | 380 | 1 | 11 yrs | Yes, on digoxin. 5 yrs after therapy | Unknown | Normalization of EF once on cardiac meds |
| 3 | **1** Non-Hodgkin Lymphoma<br>**2** Fibrohystiocytoma | 11 yo African American | 302 | 1 | 16 yrs | Subclinical CMP, 5 years after therapy | Yes | EF 20% on last ECHO, ICD placed |
| 4 | **1** Neuroblastoma<br>**2** Mucoepidermoid carcinoma | 3 months Caucasian | 151 | 1 | 21 yrs | Yes, Adriamycin toxicity at initiation of therapy | Yes | EF 40%, currently on meds |
| 5 | Synovial sarcoma | 13 yrs Caucasian | 366 | 2 | 23 yrs | Subclinical CMP, 2 yrs after therapy | Yes | EF 30%, currently on meds |
| 6 | Osteosarcoma | 11 yrs Caucasian | 450 | 1 | 15 yrs (became pregnant after dx of CHF) | Clinical CMP, requiring meds 15 yrs after therapy. Also had h/o ASD s/p repair and MVP | No | Heart transplant |
| 7 | Rhabdomyosarcoma | 6 yrs African American | 366 | 1 | 22 yrs | Subclinical CMP, 9 years after diagnosis | Unknown | Normalization of heart function on medication |
| 8 | AML | 2 mo Caucasian | 293 | 1 | 19 yrs | Yes CMP requiring medication, 10 years after therapy | No | EF 45 to 50% on medication |

* Endodermal sinus tumor;

ICD – Intra-cardiac defibrillator; CMP – Cardiomyopathy; mo – months; yrs – years; AML – Acute myelogenous leukemia

** Outcome known at last contact, after pregnancy

**Table 4**

Patients with pregnancy-associated cardiomyopathy

| Patient | Cancer | Age at diagnosis and race/ethnicity | Total Dose anthracyclines (mg/m2) | # of pregnancy at CMP | Time to pregnancy associated CMP | Outcome* |
|---|---|---|---|---|---|---|
| 1 | Osteosarcoma | 6 yrs Hispanic | 523 | 1 | 7 yrs | Resolution |
| 2 | Ewing sarcoma | 8 yrs Caucasian | 385 | 1 | 23 yrs | Normalization of EF on carvedilol |
| 3 | ALL | 7 yrs Caucasian | 84 | 1 | 12 yrs | Resolution |

CMP – Cardiomyopathy; ALL – Acute lymphoblastic leukemia; yrs – Years

*Known outcome at last contact, after pregnancy

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