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Reproductive Outcomes for Survivors of Childhood Cancer

Melissa M. Hudson, MD

St. Jude Children's Research Hospital, Department of Oncology, Division of Cancer Survivorship,
262 Danny Thomas Place; Mailstop 735

Abstract

Due to remarkable progress in therapy for pediatric cancer, long-term survival is expected for 80% of children and adolescents diagnosed with cancer. Infertility remains one of the most common and life-altering complications experienced by adults treated for cancer during childhood. Surgery, radiation, or chemotherapy that negatively affects any component of the hypothalamic-pituitary-gonadal axis may compromise reproductive outcomes in childhood cancer survivors. The risk of infertility is generally related to the tissues or organs involved in cancer and the specific type, dose, and combination of cytotoxic therapy. In addition to anticancer therapy, age at treatment, sex, and likely genetic factors influence the risk of permanent infertility. When possible, contemporary protocols limit cumulative doses of cytotoxic therapy in an effort to optimize reproductive potential. If sterilizing therapy is required for cancer control, fertility preservation measures should be explored before initiation of therapy. For childhood cancer survivors who maintain fertility, health risks to offspring resulting from their cancer treatment are major concerns. Radiation affecting ovarian and uterine function has been linked to pregnancy complications including spontaneous abortion, preterm labor, fetal malposition and low birth weight. The risk of congenital malformations, genetic disorders, and cancer appears to be low, with the exception of cancer risk in offspring born to survivors with germline cancer-predisposing mutations. This review will summarize research about cancer treatment factors impacting fertility and pregnancy outcomes of childhood cancer survivors. The data presented should facilitate the delivery of preventive counseling and age- and gender-appropriate interventions to optimize reproductive outcomes in childhood cancer survivors.

Introduction

Each year, over 12,000 children and adolescents are diagnosed with cancer.¹ Thanks to advances in pediatric cancer therapeutics achieved over the last 40 years, long-term survival is expected for 80% of this population.² In the United States, the prevalence of survivors of childhood cancer in January 2005 was estimated to be 328,652. Twenty-four percent were more than 30 years from diagnosis.³ Concurrent with the improvement in survival achieved during this period, a significant increase in age-adjusted incidence trends (rates per 100,000) has occurred for many histological subtypes of childhood cancer including acute lymphoblastic leukemia, acute myeloid leukemia, non-Hodgkin lymphoma, neuroblastoma, soft tissue, and germ cell tumors.³ Because of the steady increase in pediatric cancer

incidence and long-term survival rates, larger numbers of childhood cancer survivors can be anticipated.³ Consequently, clinicians caring for adults treated for cancer during childhood should be aware of the unique health risks resulting from the cancer experience and the need to provide appropriate health surveillance and interventions to reduce morbidity and mortality.

Research has established that a significant number of childhood cancer survivors experience chronic health sequelae resulting from cancer and/or its treatment.⁴ Late effects, or cancer-related complications that persist or develop five or more years after completion of cancer therapy, represent the ultimate “cost of cure” for long-term survivors.⁵ Late effects include a spectrum of clinical conditions that can adversely impact growth and development, organ function, fertility and reproduction, risk of secondary carcinogenesis, and psychosocial functioning.⁶ Moreover, late effects are commonly reported in adults who have survived childhood cancer and demonstrate an increasing prevalence associated with longer time elapsed from cancer diagnosis.⁴ Investigators from the Childhood Cancer Survivor Study (CCSS), a retrospective multi-institutional cohort investigation that has been monitoring health outcomes of over 20,000 long-term childhood cancer survivors for over 15 years, estimated a cumulative incidence of 73.4% for at least one chronic health problem by 40 years of age among the 10,397 adults participants (mean age, 26.6 years); over 40% will experience a chronic condition that is severe, life-threatening or fatal.).⁴

In an effort to improve survival and reduce late effects, pediatric cancer treatment protocols have changed significantly over the last several decades. Recognition of excess morbidity and mortality associated with specific treatment modalities, coupled with increased knowledge of cancer biology and advances in therapeutics, radiological sciences, and supportive care, have resulted in a change in the prevalence and spectrum of treatment effects. With the exception of survivors requiring intensive multimodal therapy for aggressive or refractory/relapsed malignancies, severe and life-threatening treatment effects are relatively uncommon after contemporary therapy. However, survivors still frequently experience morbidity related to effects of cancer treatment affecting endocrine, reproductive, musculoskeletal and neurologic function. For example, women treated with chest radiation for childhood cancer have a substantially elevated risk for breast cancer at a young age that does not seem to plateau with prolonged follow-up of long-term survivor cohorts.⁷ Breast cancer surveillance offers potential benefits associated with early detection. Awareness by providers of breast cancer and other health risks predisposed by childhood cancer and its treatment can increase opportunities for interventions that reduce morbidity.⁸

Detailed information about the cancer treatment modalities including specific surgical procedures, the type and cumulative doses of chemotherapeutic agents, and radiation treatment volumes and doses are needed to estimate health risks associated with childhood cancer. Ideally, the pediatric cancer center will provide a summary of this information which permits subsequent providers to anticipate cancer-related health risks based on the wealth of research data linking specific therapeutic exposures with late effects. A comprehensive treatment summary is often referred to as a survivorship care plan as it provides information about date of cancer diagnosis, cancer histology, sites involved by cancer, treatment

modalities and cumulative doses, potential cancer-related health risks and health surveillance recommendations.

A risk-based care approach, recommended for all childhood cancer survivors, should include a systematic plan for lifelong screening, surveillance, and prevention that incorporates risk estimates based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and co-morbid health conditions.⁵ The Children's Oncology Group (COG) has developed and periodically updates a resource to facilitate risk-based survivor care,⁹ The *COG Guidelines Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* and their accompanying patient education materials called "Health Links" are available for downloading free of charge at <http://www.survivorshipguidelines.org>.

Infertility remains one of the most common life-altering treatment effects experienced by long-term childhood survivors.¹⁰ Recent reports from the CCSS observed that, compared to a sibling cohort, female participants were less likely to become pregnant (relative risk of ever pregnant 0.81; 95% Confidence Interval [CI], 0.73-0.90)¹¹ and male participants were less likely to sire a pregnancy (hazard ratio, 0.56; 95% CI, 0.49-0.63).¹² These data are not surprising as gonadal injury is a well-established consequence of cytotoxic chemotherapy and radiation therapy. However, ascertainment of fertility potential in a given patient relative to treatment with specific anti-cancer modalities and dose exposures may be challenging. Preservation, recovery of function, or both of these are possible for some individuals treated with contemporary therapy that limits cumulative doses of cytotoxic therapy. In addition to anti-cancer therapy, age at treatment, sex, and likely genetic factors influence the risk of permanent infertility. Consequently, many health outcomes investigations have been undertaken to identify individual and cancer-related factors that characterize groups at risk for permanent gonadal injury who may benefit from fertility preservation interventions before initiation of therapy.

For many children and adolescents diagnosed with cancer, fertility preservation is not feasible due to its expense or investigational nature. In some cases, fertility preservation may be relegated to a lower priority because of the desire or necessity to initiate cancer treatment urgently. Many childhood cancer survivors who maintain fertility have concerns about the potential effects of cancer treatment on their health during pregnancy and their offspring's health.¹⁰ Specific therapeutic interventions such as abdominal/pelvic radiation have been associated with increased risks of adverse pregnancy outcomes.¹³ In addition, offspring born to survivors with germline cancer-predisposing mutations have a substantial risk of developing cancer.¹⁴ The objective of this review is to summarize the research regarding clinical and cancer treatment factors that impact fertility and pregnancy outcomes of childhood cancer survivors to facilitate the delivery of preventive counseling and age- and gender-appropriate interventions to optimize reproductive outcomes in childhood cancer survivors.

Adverse Effects of Cancer Treatment on Reproductive Function

Surgery, radiation, or chemotherapy that negatively affects any component of the hypothalamic-pituitary-gonadal axis may compromise reproductive outcomes in childhood cancer survivors (Table 1).⁶ Pediatric cancer treatment protocols often prescribe combined modality therapy; thus the additive effects of gonadotoxic exposures may need to be considered in assessing reproductive potential.

Surgery Affecting Reproduction

Gonadal and extragonadal germ cell tumors account for only 1% of primary tumors in children younger than 15 years and 10% of primary cancer sites in adolescents and young adults 15 to 29 years.¹⁵ Orchiectomy or oophorectomy performed for the management of these relatively rare pediatric cancers may reduce germ cell numbers. Contemporary treatment regimens for pediatric germ cell tumors utilize fertility- and organ-sparing surgical procedures combined with systemic chemotherapy.^{16, 17} Notably, the addition of chemotherapy may preclude the need for more radical surgical resection, but may also increase the risk of infertility, especially if alkylating agents are components of the regimen.¹⁶ Classical alkylating agents include anticancer drugs like mechlorethamine (nitrogen mustard), the oxazaphosphorines (cyclophosphamide and ifosfamide), chlorambucil, melphalan, the nitrosoureas (lomustine and carmustine), busulfan and procarbazine (Box 1). These drugs are used to treat a variety of pediatric hematological and solid malignancies. Fertility may also be adversely impacted in survivors with autonomic nerve damage and/or vascular injury resulting from pelvic or spinal surgery. Sexual dysfunction associated with these procedures may be exacerbated in survivors with androgen or estrogen insufficiency.

Chemotherapy Affecting Reproduction

Alkylating agents are the primary chemotherapeutic agents associated with a high risk of infertility that are used in the treatment of pediatric cancers. These agents, which damage DNA and induce apoptosis through covalent binding of alkyl groups to cellular macromolecules, have a well-established dose-related risk of carcinogenesis and gonadotoxicity. Current pediatric cancer treatment protocols proactively restrict the cumulative doses of these agents and preferentially incorporate alkylating agents that have more favorable toxicity profiles. It should be noted that combinations of alkylating agents may be routinely prescribed for advanced stage or unfavorable risk pediatric cancers, e.g., the COPP (cyclophosphamide, Oncovin [vincristine], procarbazine, prednisone) regimen used in the treatment of Hodgkin lymphoma.

The literature evaluating toxicity associated with alkylating agents (e.g., secondary leukemia or infertility) often analyzes outcomes in the context of an alkylating agent dose score that is derived from the distribution of doses based on the summation of an individual's cumulative dose per square meter for each alkylating agent.¹⁸ Generally, alkylating agent dose distributions are divided into tertiles with higher scores reflecting higher total alkylating agent exposure and higher risk for potential alkylating agent toxicity.^{11, 12} When using published data to counsel patients, clinicians should be aware that investigators have used

variable methods to calculate alkylating agent dose scores; correlating an individual patient's cumulative dose exposure with the cumulative dose exposure per tertile of a published study is recommended to accurately assess risk.^{11, 12, 19, 20} Because combinations of alkylating agents are associated with larger alkylating agent dose scores, they would be expected to be more gonadotoxic than treatment with single alkylating agents.

Factors influencing the risk of gonadal injury in children treated with alkylating agent chemotherapy include cumulative dose, the specific alkylating agent, the length of treatment, age at treatment, and sex.^{21, 22} Results from investigations evaluating cumulative dose effects in men treated for cancer during childhood, adolescence or young adulthood are limited due to the fact that studies report outcomes of relatively small cohorts and have not consistently correlated clinical and laboratory measures with the results of semen analyses.²³⁻²⁸ In general, Leydig cell function is preserved, but germ cell failure is very common in men treated with high cumulative doses of cyclophosphamide (7500 mg/m^2)^{25, 26} and more than 3 months of combination alkylating agent therapy.^{23, 24, 28} Prepubertal status does not provide protection from gonadal injury.^{29, 30} Treatment with combined modality therapy that includes alkylating agents and pelvic/gonadal radiation may produce subclinical Leydig cell dysfunction characterized by borderline low testosterone, elevated luteinizing hormone, altered body composition and bone mineral density deficits.^{25, 27, 31, 32} Germ cell and Leydig cell failure are common after specific therapies including conditioning for hematopoietic cell transplantation, testicular irradiation, and combined modality therapy that includes alkylating agent chemotherapy and hypothalamic-pituitary or gonadal irradiation.²¹

Because ovarian hormone production is linked to the maturation of primordial follicles, depletion of follicles by alkylating agent chemotherapy can potentially impact both fertility and ovarian hormone production.³³ In general, girls maintain ovarian function at higher cumulative alkylating agent doses compared to boys. Because of their greater complement of primordial follicles, the ovarian reserve of prepubertal and adolescent girls is more robust than that of adults.³³ Retention or recovery of ovarian function is the norm for most female childhood cancer patients who are treated initially with risk-adapted combination chemotherapy. However, the risk of acute ovarian failure and premature menopause is substantial if treatment includes combined modality therapy with alkylating agent chemotherapy and abdominal/pelvic radiation or dose-intensive alkylating agents for myeloablative conditioning before hematopoietic cell transplantation.^{19, 20, 34, 35} Among 3390 eligible women (median age, 31 years) participating in a CCSS investigation of female health outcomes, 6.3% reported that they developed acute ovarian failure, defined as loss of ovarian function with 5 years from diagnosis.¹⁹ Significant risk factors for acute ovarian failure included high-dose radiation (especially over 10 Gy) exposure of the ovaries, treatment with procarbazine, and, among those who were 13 to 20 years of age at diagnosis, treatment with cyclophosphamide. Premature non-surgical menopause, defined as cessation of menses before age 40 years, occurred in 8% of eligible participants compared to 0.8% of a sibling control group.²⁰ Risk factors for premature menopause included older attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent score, and a primary diagnosis of Hodgkin lymphoma. Figure 1 illustrates the cumulative incidence of nonsurgical premature menopause among female survivors in the CCSS cohort according

to treatment with alkylating agents, abdominal.-pelvic radiation or combined modality therapy including both exposures. The cumulative incidence of nonsurgical premature menopause among survivors treated with alkylating agents and abdominal/pelvic radiation approached 30% in this cohort.

Radiation Affecting Reproduction

The risk of radiation injury to the hypothalamic-pituitary (HPT) gonadal axis is related to the treatment volume, total dose, fractionation schedule and age at treatment. Cranial radiation impairs HPT function in a dose-related fashion.^{36, 37} Altered pubertal timing (early, precocious or rapid tempo) has been observed after 18 to 24 Gy (doses historically used to treat or prevent central nervous system leukemia).³⁷ Delayed puberty related to gonadotropin insufficiency/deficiency may develop when doses exceed 30 Gy (doses used for treatment of central nervous system malignancies). Deficiencies of follicle stimulating hormone and luteinizing hormone secretion may result in a significant reduction in circulating sex hormone levels that can impact fertility.^{36, 38} Delayed effects of low-dose cranial radiation (18-24 Gy) in females include decreased luteinizing hormone secretion, an attenuated luteinizing hormone surge, and shorter luteal phases. Short luteal phases have been linked to incipient ovarian failure and early pregnancy loss.³⁶

Among men treated for childhood cancer, the potential for primary gonadal injury exists if radiation treatment fields include the pelvis, gonads or total body. Similar to chemotherapy-induced toxicity, Leydig cells are more resistant to radiation damage than the germinal epithelium. Sperm production is reduced in a dose-dependent fashion following radiation. Azoospermia may be reversible at doses of 1 to 3 Gy, but doses in excess of 3 Gy typically produce irreversible azoospermia.³⁹ Radiation injury to Leydig cells is related to the dose delivered and age at treatment.³² Testosterone production may be normal in prepubertal boys treated with < 12 Gy fractionated testicular radiation, but elevated plasma concentrations of luteinizing hormone observed in this group suggest subclinical injury. Gonadal failure typically results when prepubertal boys are treated with > 20 Gy radiation to the testes; androgen therapy is required for masculinization. Leydig cell function is usually preserved in sexually mature males if radiation doses do not exceed 30 Gy.⁴⁰

In women treated for childhood cancer, the potential for primary gonadal injury exists if treatment fields involve the lumbo-sacral spine, abdomen, pelvis, or total body. As with chemotherapy-induced gonadal injury, the ovaries of younger patients are more resistant to radiation damage than are those of older women. Permanent ovarian failure uniformly occurs in childhood cancer patients treated with ovarian radiation doses > 20 Gy.²² Combined modality therapy with alkylating agent chemotherapy and radiation treatment volumes that include the ovaries increases the risk for both acute ovarian failure and premature menopause.^{19, 20} Prepubertal girls treated with 20 to 30 Gy abdominal radiation may fail to undergo or complete pubertal development. Ovarian transposition to a region that is lateral or medial to the planned radiation volume may preserve ovarian function in young girls and adolescents who require pelvic radiation therapy for lymphoma.⁴¹

Reproduction after Hematopoietic Cell Transplantation

Individuals treated with hematopoietic cell transplantation generally have a substantial risk of gonadal dysfunction and infertility related to conditioning with total body irradiation (TBI) and/or high-dose alkylating agent chemotherapy. Since transplantation is often undertaken for relapsed/refractory cancer, previous treatment with alkylating agent chemotherapy or HPT-gonadal radiation may confer additional risks. Age at treatment also influences the risk of gonadal injury. Young boys and adolescents conditioned with high-dose cyclophosphamide (200 mg/kg) will generally maintain Leydig cell function and testosterone production, but germ cell failure is common.⁴²⁻⁴⁴ Following TBI conditioning, most males retain their ability to produce testosterone, but will experience germ cell failure.⁴⁴ Women conditioned with high-dose alkylating agents are at increased risk of acute ovarian failure and premature menopause.^{19, 20, 45} The risk of ovarian failure is very high after conditioning with busulfan and cyclophosphamide regardless of pubertal status, with the majority requiring long-term hormonal replacement therapy.^{42, 46} Ovarian function may be retained in 50% of prepubertal girls conditioned with TBI, in contrast to girls older than 10 years who uniformly experience acute ovarian failure.⁴⁷⁻⁴⁹

Pregnancy Outcomes in Childhood Cancer Survivors

Pregnancy Complications in Childhood Cancer Survivors

Childhood cancer survivors who maintain fertility often experience considerable anxiety about the potential impact of radiation and chemotherapy on their health during pregnancy and the health of their offspring. Numerous investigations have evaluated the prevalence of and risk factors for pregnancy complications in adults treated for cancer during childhood. Pregnancy complications including hypertension, fetal malposition, fetal loss/spontaneous abortion, preterm labor, and low birth weight have been observed in association with specific diagnostic and treatment groups.^{13, 34, 50-62} Many early studies focused on the offspring of female survivors of Wilms tumor and speculated that the excess risk of preterm and low-birth weight offspring was related to uterine dysfunction associated with abdominal radiation and a high prevalence of congenital uterine abnormalities.^{50, 53, 58} Subsequent studies of larger cohorts provided compelling data that flank irradiation increased the risk of early or threatened labor, fetal malposition, and low birth weight.^{51, 55} A recent report from the National Wilms Tumor Long-Term Follow-Up Study evaluating 1,021 pregnancies (955 live-born singletons), again observed that the percentages of low birth weight (< 2500 g) and preterm (< 37 weeks gestation) offspring born to women in the cohort increased with flank radiation dose. In addition, women treated with flank radiation therapy for unilateral Wilms tumor had a higher risk of hypertension complicating pregnancy, fetal malposition, and premature labor.⁵⁴ Table 2 summarizes the incidence rates of these complications in relation to radiation dose.

Critchley and colleagues have undertaken studies to evaluate the pathophysiology of radiation injury that predispose to pregnancy complications.^{13, 63, 64} They demonstrated that pelvic radiation may affect reproductive function by impairing uterine growth and development and blood flow. Higher radiation dose, treatment fields including larger uterine volumes, and prepubertal age at treatment increased the risk of uterine damage. Reduced

uterine volume, lack of endometrial response to estrogen therapy, and absence of uterine artery blood flow by Doppler ultrasound have been observed in women treated during childhood with pelvic radiation doses between 14 and 30 Gy.¹³ Adverse pregnancy outcomes including early pregnancy loss, preterm birth, and delivery of low or very low birth weight infants have been attributed to radiation-induced uterine dysfunction and vascular insufficiency in women treated with TBI and pelvic radiation for childhood cancer.^{63, 65}

Women conditioned with TBI for hematopoietic cell transplantation also have an increased risk of early pregnancy loss, preterm birth and delivery of low birth weight infants.⁶⁶ Sanders et al.⁶⁶ reported recovery of normal ovarian function in only 110 of 708 postpubertal women who underwent hematopoietic cell transplantation for a childhood cancer. Among these, 32 became pregnant and 9 formerly prepubertal girls with normal gonadal function became pregnant. Spontaneous abortion terminating the pregnancy was significantly higher in females conditioned with TBI compared to rates occurring in those conditioned with cyclophosphamide (37% v. 7%, $P=0.02$). Preterm delivery was also higher than the expected population incidence of 8% to 10% ($P=0.001$) and occurred at significantly higher rates in females conditioned with TBI compared to those conditioned with cyclophosphamide (63% versus 18%, $P=.01$) All preterm deliveries resulted low or very low birth weight infants with an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population ($P = .0001$).

The risk of pregnancy complications among other more diverse groups of female childhood cancer survivors has been evaluated through registry and cohort studies,^{56, 60-62, 67, 68} all of which implicate pelvic, uterine or ovarian radiation as a significant predictive factor for excess risk of spontaneous abortion, preterm birth, low birth weight and small for gestational age offspring. A CCSS report that compared 2201 singleton births of 1264 survivors to 1175 births of 601 siblings, observed a higher likelihood of preterm birth among survivors' compared to siblings' children (21.1% versus 12.6%; OR = 1.9, 95% CI = 1.4 to 2.4; $P<.001$). Preterm birth (50.0% versus 19.6%; OR = 3.5, 95% CI = 1.5 to 8.0; $P = .003$), low birth weight (36.2% versus 7.6%; OR = 6.8, 95% CI = 2.1 to 22.2; $P = .001$), and small for gestational age offspring (18.2% versus 7.8%; OR = 4.0, 95% CI = 1.6 to 9.8; $P = .003$) were more likely to be born to women treated with high dose (> 500 Gy) uterine radiation, compared to those born to women who did not receive radiation.⁶⁸

Several large studies have determined that chemotherapeutic agents do not adversely affect fetal growth and development or uterine function during pregnancy.^{55, 61} However, obstetrical providers should be aware that anecdotal reports indicate that pregnancy may precipitate cardiac decompensation in women treated with anthracycline antibiotics (e.g., doxorubicin, daunorubicin) for childhood cancer.⁶⁹ Anthracyclines have a well established risk of cardiotoxicity that may manifest as asymptomatic left ventricular dysfunction, cardiomyopathy, congestive heart failure and death.⁷⁰⁻⁷⁴ Anthracycline cardiotoxicity is characterized by impaired myocardial growth that leads to progressive left ventricular dysfunction over time.⁷⁰ As many as 5% of at-risk survivors will develop congestive heart failure 15 years after treatment.⁷¹ Cardiotoxicity has been reported at all dose levels, but the risk of anthracycline-induced cardiomyopathy increases significantly when cumulative

doses exceed 300 mg/m².⁷² Notably, the effects of anthracyclines may be asymptomatic in up almost 60% of survivors, becoming apparent only with other physiologic stressors such as infection or pregnancy.⁷² A Dutch study did not observe any cases of peripartum anthracycline-related congestive heart failure in 53 childhood cancer survivors who had delivered one or more children (20.3 years mean follow-up time after first administration of anthracycline therapy), but the mean cumulative anthracycline dose received by the study cohort was only 267 mg/m².⁷⁵ These investigators emphasized the need for further studies with adequate power and long-term follow-up to reliably evaluate the cumulative incidence of peripartum anthracycline-induced cardiotoxicity and associated risk factors. Because of the high prevalence of subclinical toxicity and the potential for pregnancy-induced exacerbation of cardiac dysfunction, a baseline evaluation left ventricular systolic function by echocardiogram or comparable cardiac imaging modality is advised for women exposed to anthracycline chemotherapy who are planning pregnancy or who become pregnant with periodic follow-up especially during the third trimester.

Several studies have evaluated the prevalence of pregnancy complications among partners of male survivors of childhood cancer, which collectively have provided no evidence of an excess risk of adverse pregnancy outcomes.^{54, 57, 61, 76} An earlier CCSS investigation observed a significant difference in the male-to-female ratio of 2323 offspring born to 1227 survivors.⁵⁷ These investigators speculated that the deficit of male infants born to survivors in the cohort resulted from a lower testosterone level. A follow-up investigation from the British CCSS tested this hypothesis by evaluating the impact of gonadal radiation on sex ratio in 9685 offspring born to childhood cancer survivors. Study results demonstrated no difference in the sex ratio for offspring born to male and female survivors. Exposure to high-dose versus low-dose gonadal radiation was not associated with a significant alteration in sex ratio. Moreover, there was no evidence that the sex ratio varied in relation to time from cancer diagnosis in survivors treated with radiation compared to those who did not receive radiation.

Health Risks to Offspring of Childhood Cancer Survivors

A number of investigations have addressed the issue of offspring risk of cancer, chromosomal disorders and congenital malformations associated with cancer treatment-related germ cell mutations.⁷⁷⁻⁸² The Five Center Study, which evaluated offspring born to adult survivors treated for childhood cancer before 1976, observed no statistically significant differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations.⁷⁸ Genetic disease occurred in 3.4% of 2,198 offspring of survivors, compared with 3.1% of 4,544 offspring of controls ($P=.33$). A population-based study through the Danish Cancer Registry compared the prevalence of abnormal karyotypes diagnosed in 2630 offspring born to 4,676 children treated for cancer to that of 5504 born to 6,441 siblings. The proportion of children with abnormal karyotypes born to survivors (5.5/2,631.5 [0.21%]) and siblings (11.8/5,505.8 [0.21%]) was similar.⁸² The prevalence of Down syndrome (relative risk [RR]=1.07; 95% CI 0.16-5.47) and Turner syndrome (RR=1.32; 95% CI 0.17-7.96) was also not different among the children of cancer survivors and siblings.

Another Danish Cancer Registry based study evaluated the relationship of gonadal radiation and congenital malformations in offspring of childhood cancer survivors. Gonadal and uterine radiation doses were estimated from the standard radiation treatment regimens. The prevalence of congenital malformations among 1715 offspring of 3963 childhood cancer survivors was compared to that observed in 6009 offspring of 5657 siblings. At birth, the prevalence of congenital malformations in survivors' offspring (44 cases, 2.6%) did not differ significantly from that of siblings' offspring (140 cases, 2.3%) [prevalence proportion ratio (PPR), 1.1; 95% confidence interval, 0.8-1.5] or of the general population (observed-to-expected ratio, 1.2; 0.9-1.6).⁸¹ The ratios did not change when malformations diagnosed later in life were included. Offspring of irradiated parents did have a slightly higher risk of malformations compared to those born to non-irradiated parents (PPR 1.2 vs 1.0), but there was no association with increasing gonadal radiation dose.

Another population-based study using nationwide registry data in Finland evaluated the potential of cancer treatment to cause germline mutations that might increase the risk of cancer in their offspring. The prevalence of cancer among children born to 26,331 cancer survivors (diagnosed under age 35 between 1953 and 2004) was compared to 58,155 children of siblings.⁸⁰ Cancer risk was increased (SIR 1.67; 95% CI 1.29-2.12) among the 9,877 children born after their parent's diagnosis, but this increase disappeared (SIR 1.03; 95% CI 0.74-1.40) after exclusion of cases of hereditary cancer. The risk of cancer among the offspring of siblings was not different from offspring of patients with non-hereditary cancer (SIR 1.07; 95% CI 0.94-1.21). Collectively, these studies do not support an excess risk of major congenital malformations, single gene disorders or chromosomal syndromes in children born to survivors of childhood cancer. Offspring of childhood cancer survivors are also not at an increased risk of cancer except in the rare event of a cancer-predisposing germline mutation.¹⁴ Common hereditary cancer syndromes presenting in childhood cancer patients are summarized in Table 3.⁸³

Summary

Due to extensive research evaluating the relationship of therapeutic exposures to specific treatment complications, the adverse effects of pediatric cancer and its therapy on reproductive outcomes can be anticipated and proactively addressed to reduce cancer-related morbidity. Surgical removal of reproductive organs and treatment with HPT-gonadal radiation and alkylating agent chemotherapy place a survivor at risk of infertility. When at all possible, fertility preservation measures should be considered if treatment planned for childhood cancer is anticipated to confer a risk of significant risk of irreversible infertility. Women treated with radiation impacting ovarian and uterine function are at high risk of acute ovarian failure, premature menopause and pregnancy complications including spontaneous abortion, preterm labor, fetal malposition, and low birth weight offspring. These data are important for family planning and obstetrical management. Survivors should be reassured that research to date does not support an excess risk of congenital malformations, genetic disorders, or chromosomal syndromes in offspring born to childhood cancer survivors. The incidence of cancer in offspring is also not increased except in survivors with cancer-predisposing germline mutations. For a concise summary of potential late reproductive and other cancer-related effects, clinicians are directed to the COG Long-

Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers available at <http://www.survivorshipguidelines.org>.

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Box 1**Alkylating Agents Used for Treatment of Childhood Cancer**Classical Alkylators

Busulfan
Carmustine (BCNU)
Chlorambucil
Cyclophosphamide
Ifosfamide
Lomustine (CCNU)
Mechlorethamine
Melphalan
Procarbazine

ThiotepaHeavy Metal Alkylators

Carboplatin

CisplatinNon-Classical Alkylators

Dacarbazine (DTIC)
Temozolomide

Figure 1.

Cumulative incidence curves of nonsurgical premature menopause in survivors according to treatment exposures. (A) Survivors treated with alkylating agents (AA) but not with abdominal-pelvic radiation therapy (A-P RT). (B) Survivors treated with A-P RT but not AA. (C) Survivors treated with AA and A-P RT. Green DM et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 27(14), 2009:2374-81. Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved.

Table 1**Childhood Cancer Therapy Affecting Reproductive Tissues**

	Reproductive effect	Predisposing therapy	Modifying factors
Both Sexes	Altered pubertal timing (precocious, early, rapid tempo) Delayed puberty Gonadotropin insufficiency/deficiency	Hypothalamic-pituitary radiation	Altered pubertal timing more common after low dose radiation 18-24 Gy Gonadotropin insufficiency more common after radiation > 30 Gy
Females	Acute ovarian failure (ovarian failure within 5 years of diagnosis) Premature menopause (cessation of menses before age 40 years)	Alkylating agent chemotherapy Radiation impacting female reproductive system (whole abdomen, pelvis, lumbosacral spine, total body) Oophorectomy	Older age at treatment due at higher risk
	Uterine vascular insufficiency Uterine growth impairment	Radiation impacting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)	History of Wilms tumor and associated Müllerian anomalies
	Vaginal fibrosis/stenosis	Radiation impacting the vagina	History of hypogonadism (estrogen insufficiency) History of chronic graft versus host disease
	Sexual dysfunction Dyspareunia	Pelvic surgery, hysterectomy Radiation impacting uterus or vagina	History of hypogonadism (estrogen insufficiency)
	Spontaneous abortion Neonatal death Premature labor Low birth weight infant Fetal malposition	Radiation impacting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)	History of Wilms tumor and associated Müllerian anomalies
Males	Azoospermia Oligospermia	Alkylating agent chemotherapy Radiation impacting the male reproductive system (pelvic, testicular, total body) Orchiectomy (bilateral)	Prepubertal status at treatment does not reduce risk
	Retrograde ejaculation Anejaculation Erectile dysfunction	Pelvic surgery (retroperitoneal node or tumor dissection, cystectomy, radical prostatectomy) Radiation to pelvis, bladder or spine	History of hypogonadism (androgen insufficiency)

Modified from Hudson MM. Survivors of childhood cancer: coming of age. *Hematol Oncol Clin North Am* 2008;22:211–231, with permission from Elsevier.

See www.survivorshipguidelines.org for health risks to other organs and tissues resulting from treatment for childhood cancer.

Table 2
Relationship Between Flank Radiation and Pregnancy Outcomes in Female Survivors of Wilms Tumor

Radiation dose (Gy)	No. of offspring	Proportion (%) with Adverse Pregnancy Outcome			
		Low birth weight infant (< 2500 gm)	Preterm infant (20-36 weeks gestation)	Early or threatened labor	Hypertension complicating pregnancy
None	187	9.1	10.2	15.0	12.3
0.01-15.00	49	8.2	6.1	12.2	18.4
15.01-25.00	111	12.6	20.7	25.2	20.7
5.01-35.00	84	21.4	22.6	26.2	35.7
> 35	50	16.0	22.0	30.0	24.0
Whole abdomen	18	33.3	33.3	44.4	0
					Malposition of fetus
					4.3
					12.2
					6.3
					13.1
					10.0
					11.1

Data from Green DM, Lange JM, Peabody EM, Grigorjeva NN, Peterson SM, Kalapurakal JA et al. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study . J Clin Oncol 2010 Jun 10;28:2824-30. Epub 2010 May 10.

Table 3

Syndromes of Inherited Cancer Predisposition

Syndrome	Major tumor types	Mode of inheritance
Hereditary gastrointestinal malignancies		
Adenomatous polyposis of the colon	Colon, stomach, intestinal cancers Thyroid cancer Hepatoblastoma	Dominant
Juvenile polyposis	Gastrointestinal	Dominant
Peutz-Jeghers syndrome	Intestinal cancers Ovarian carcinoma Pancreatic carcinoma	Dominant
Genodermatoses with cancer predisposition		
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma Medulloblastoma	Dominant
Neurofibromatosis type 1	Neurofibroma Optic pathway glioma Peripheral nerve sheath tumor	Dominant
Neurofibromatosis type 2	Vestibular schwannoma	Dominant
Tuberous sclerosis	Hamartoma Renal angiomyolipoma Renal cell carcinoma	Dominant
Xeroderma pigmentosum	Melanoma Leukemia	Recessive
Rothmund Thomson syndrome	Skin, bone	Recessive
Leukemia/lymphoma predisposition syndromes		
Bloom syndrome	Leukemia Lymphoma Skin cancer	Recessive
Fanconi anemia	Leukemia Squamous cell carcinoma Gynecological tumors	Recessive
Nijmegen breakage syndrome	Lymphoma Medulloblastoma Glioma	Recessive
Ataxia telangiectasia	Leukemia Lymphoma	Recessive

Syndrome	Major tumor types	Mode of inheritance
Genitourinary cancer predisposition syndromes		
Simpson-Golabi-Behmel Syndrome	Embryonal tumors Wilms tumor	X-linked
Von Hippel-Lindau syndrome	Retinal and central nervous tumors Hemangioblastoma Pheochromocytoma Renal cell carcinoma	Dominant
Beckwith-Wiedemann syndrome	Wilms tumor Hepatoblastoma Adrenal carcinoma Rhabdomyosarcoma	Dominant
Wilms tumor syndrome	Wilms tumor	Dominant
WAGR syndrome	Wilms tumor Gonadoblastoma	Dominant
Retinoblastoma	Retinoblastoma Osteosarcoma	Dominant
Rhabdoid predisposition syndrome	Rhabdoid tumor Medulloblastoma Choroid plexus tumor	Dominant
Medulloblastoma predisposition	Medulloblastoma	Dominant
Sarcoma/bone cancer predisposition syndromes		
Li-Fraumeni syndrome	Soft tissue sarcoma Osteosarcoma Breast carcinoma Adrenocortical carcinoma Leukemia Brain tumor	Dominant
Multiple exostosis	Chondrosarcoma	Dominant
Werner syndrome	Osteosarcoma Meningioma	Recessive
Endocrine cancer predisposition syndrome		
Multiple endocrine neoplasia (MEN) 1	Pancreatic islet cell tumor Pituitary adenoma Parathyroid adenoma	Dominant

Syndrome	Major tumor types	Mode of inheritance
Multiple endocrine neoplasia (MEN) 2	Medullary thyroid carcinoma Pheochromocytoma	Dominant

Modified from Strahm B, Malkin D. Hereditary cancer predisposition in children: genetic basis and clinical implications. Int J Cancer 2006; 119:2001–2006.