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Best Practices in Counseling Young Female Cancer Survivors on Reproductive Health

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Abstract

In the United States, there are more than 400,000 girls and young women of reproductive-age with a history of cancer. Cancer treatments including surgery, chemotherapy, targeted therapy, and radiation can adversely impact their reproductive health. This review discusses infertility, contraception, and adverse pregnancy and child health outcomes in reproductive-aged cancer survivors, in order to increase awareness of these health risks for survivors and their healthcare providers. Infertility rates are modestly higher, while rates of using contraception and using highly effective contraceptive methods are lower in cancer survivors than in women without a history of cancer. During pregnancy, preterm births are also more common in survivors, resulting in more low birth weight offspring. Children of cancer survivors do not have more childhood cancers, birth defects or chromosomal abnormalities than the general population, with the exception of families with hereditary cancer. Reproductive risks in survivors depend on cancer treatment exposures. For example, women with prior abdominal or pelvic radiation have additional risks of small for gestational age offspring and stillbirths, while those with prior chest radiation or anthracycline exposures have higher risks of cardiomyopathy. To help survivors achieve their reproductive goals safely, family planning and preconception counseling are central to survivorship care.

Keywords

cancer survivor; contraception; fertility; pregnancy; child health

Introduction

There are currently more than 8 million female cancer survivors in the United States.¹ Of these, there are 400,000 girls and women who are younger than age 40, and another 610,000

women between ages 40 and 49. For these young women, improvements in cancer surveillance and treatment have resulted in high rates of long-term survival (Table 1). However, cancer treatments, i.e. surgery, chemotherapy, targeted therapy, and radiation, may adversely impact their reproductive health and quality of life.

The objective of this review is to present current data on reproductive health risks in young female cancer survivors and management options for these risks. Cancer survivors refer to individuals with a history of cancer from diagnosis through their life. For this review, we focus on cancer survivors who have completed their initial treatments and have transitioned from primary treatment to extended survival. Specifically, we address infertility, contraception, and adverse pregnancy and child health outcomes. The intention of this review is to increase awareness of reproductive health risks for survivors and their healthcare providers.

Fertility

Cancer treatments pose different threats to fertility, including accelerated ovarian aging, impaired uterine function, and/or disrupting the hypothalamic-pituitary-ovarian axis (Table 2). Ovarian aging refers to the process of oocyte attrition over female reproductive life. Some, but not all chemotherapy can accelerate oocyte attrition, leading to infertility and early menopause.² Oocytes are also sensitive to radiation, incurring dose-dependent risks of ovarian failure following radiotherapy.³ While endocrine therapy including tamoxifen, aromatase inhibitors and gonadotropin releasing hormone (GnRH) agonists does not directly incur oocyte attrition, natural ovarian aging occurs concomitantly during extended time on treatment.⁴ Targeted cancer therapies block cancer growth by interfering with specific molecules; in contrast to chemotherapy and radiation, there is a relative paucity of data on the impact of these treatments on fertility.⁵ Of note, the Food and Drug Administration changed the content of Pregnancy and Lactation Labeling Rule in 2015 to require drug labeling information on risk to fertility for all prescription drugs submitted after June, 2015; drugs approved between 2001 and 2015 will be gradually phased in. Hence, more data on fertility risk in novel agents will be reported and aid healthcare providers in counseling patients.

Following cancer treatment, reproductive-aged survivors are less likely to have live births than their siblings or the general population. Population-based studies in Canada, Norway and Finland and the U.S. have reported lower proportions of survivors achieving births compared to controls,⁶ although there is considerable variability in how much lower these birth rates are after cancer.^{7, 8} 1194 Canadian survivors who were diagnosed as young adults subsequently had a cumulative 10-year live birth rate of 36% compared to 40% in the control group ($p<0.001$).⁷ In contrast, a Norwegian study reported 13% of 16,000 cancer survivors achieved a post-cancer pregnancy following a median observation time of 5 years, compared to 22% of 80,000 controls ($p<0.001$).⁹ In Finland, 2071 female survivors who reached reproductive age were compared to their siblings, and a 50% reduced relative probability of having a first child was observed in cancer survivors (RR 0.5, 95% CI 0.4–0.5).¹⁰ Finally, the Childhood Cancer Survivor Study in the U.S. reported that the likelihood

of having a live birth in female survivors was lower than siblings (HR 0.8, 95% CI 0.8–0.9).¹¹

Infertility rates are also higher in cancer survivors compared to controls, but with more limited data. In the Childhood Cancer Survivors Study, among 3058 survivors queried at a median age of 27, 16% reported no pregnancy following 12 months of attempts or ovarian insufficiency, compared to 11% of siblings (RR 1.5, 95% CI 1.3–1.8).¹² Accordingly, time to pregnancy was significantly longer in survivors compared siblings ($p=0.03$). In a cohort of survivors recruited from the Ontario Cancer Registry, similar proportions reported clinical infertility (15%) or being told of a fertility problem (18%), but no controls were included.¹³

Infertility risk differed by cancer types and treatments. Uterine radiation and alkylating chemotherapy exposures are risk factors for longer time to pregnancy and/or infertility. In the Childhood Cancer Survivor Study, uterine radiation exposure of > 5 Gy increased the risk of infertility by 2- to 2.5-fold.¹² The highest tertile in alkylating chemotherapy exposure increased the risk of infertility by 1.5 fold, 95% CI 1.1–2.0, compared to no alkylating chemotherapy exposure.¹² Brain or head radiation was not associated with increased infertility. Because large-scale data that assess infertility are limited and infertility risk is related not only to cancer treatment exposures but also to age at pregnancy attempt, there are no current tools to predict when infertility will occur in cancer survivors.

The Fertility Window After Cancer Treatment

To prevent infertility, there are standard of care and experimental fertility preservation options that can be considered prior to starting cancer treatment. Accordingly, fertility risk counseling and referral to fertility preservation services prior to the start of cancer treatment have been recommended by the American Society of Clinical Oncology, American Academy of Pediatrics and American Society of Reproductive Medicine.^{14–16}

Post-treatment, survivors frequently raise the question of whether they are fertile, if fertility may be measured, and if there is still an opportunity for fertility preservation. In women without a history of cancer, ovarian reserve biomarkers such as anti-mullerian hormone (AMH), follicle stimulating hormone (FSH) and antral follicle count (AFC) have been associated with reproductive outcomes such as response to ovarian stimulation, time to pregnancy and age at natural menopause.^{17–19} In young women with cancer, biomarkers of ovarian reserve have been followed longitudinally as surrogate measures of ovarian function. The pattern of change from pre-treatment through the first 12–24 months post-treatment has been described and replicated in small cohorts.^{20–22} Using AMH as an example, levels falls with exposure to gonadotoxic therapy; for some, AMH levels rise post-treatment, suggesting ovarian recovery. The pattern of change in FSH levels has been observed to be inverse that of AMH.^{23, 24} There is significant intra- and inter-individual variability in the pattern of change in ovarian reserve measures longitudinally.

There are two clinical implications of the data on ovarian reserve measurements in cancer survivors. First, for many survivors, the rise of AMH, fall of FSH, and resumption of regular menses after completion of gonadotoxic cancer treatment support the concept of a residual window of ovarian function and fertility, which represent an opportunity to conceive.

Unfortunately, data are lacking on when ovarian recovery plateaus and subsequent decline begins. In addition, young cancer survivors seek to achieve social milestones including partnered relationships and cancer milestones such as longer duration of cancer survivorship prior to pregnancy attempt.²⁵ However, these milestones take time to achieve and compete with earlier loss of fertility. Hence, fertility counseling on the residual window of ovarian function should help survivors recognize the importance of not delaying pregnancy and a potential second opportunity to undergo fertility preservation via oocyte or embryo banking in this post-treatment period.

Second, if ovarian reserve biomarkers are to be measured post-treatment, providers and survivors need to be aware the limitations of these measurements. There is a lack of studies in this population on the ability of ovarian reserve biomarkers to predict clinically relevant fertility outcomes like fecundability. Ovarian reserve biomarkers can have significant fluctuations post-treatment. If they are to be measured, serial samples, rather than a single measurement, to track an individual's trajectory over time are likely to be more helpful.

Take home message—Survivors should be counseled that their fertility and likelihood of having births after cancer are lower, but most will have a residual window of ovarian function and fertility after primary cancer treatment. As data estimating the remaining fertility window are lacking, survivors after cancer treatment should consider attempting pregnancy earlier or explore another opportunity for oocyte or embryo banking.

Contraception

Reproductive-aged cancer survivors have complex contraception considerations. Effective methods of contraception need to be used during exposure to teratogenic cancer treatments and cancer type and co-morbidities must be considered in choice of contraceptive method. The American Congress of Obstetricians and Gynecologists (ACOG) recommends that all sexually active women of reproductive age be thoroughly educated on the risks of conceiving during cancer therapy and encouraged to use effective contraception during treatment.²⁶ Further, the National Comprehensive Cancer Network (NCCN) Practice Guidelines for Adolescent and Young Adult Oncology include discussion of contraceptive options prior to the initiation of cancer therapy.²⁷

A consequence of inadequate contraception is unintended pregnancy and pregnancy termination. There are no large-scale data on the rate of unintended pregnancy. Several retrospective cohort studies have described medical abortion in cancer survivors.^{28–32,33} Participants in the Childhood Cancer Survivor Study self-reported 140 pregnancy termination among 1858 pregnancies (7.5%).³¹ More medical abortions occurred in all diagnostic groups (except non-Hodgkin's lymphoma) compared to their siblings, with relative risks from 1.4 to 2.0.³³ A population-based study in Denmark linked survivors to the national registry for induced abortions. In this cohort, pregnancy terminations occurred in 19.7% of pregnancies in survivors, compared to 18.9% in their sisters and 19.7% in the general population.²⁹ Survivors reported predominant reasons for pregnancy termination include social, offspring and maternal health concerns.^{28, 34} For example, 70% of all

terminations among heritable retinoblastoma survivors were due to concerns on child health.
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Contraception utilization rates are low in reproductive-aged cancer survivors

In the U.S., the rate of contraception in the general population of reproductive-aged women (ages 14–44) is ascertained through the National Survey for Family Growth conducted by the Centers for Disease Control and Prevention.³⁵ In the 2011–2013 cycle, 62% of reproductive-aged U.S. women reported current contraceptive use.³⁶ Excluding women who were not at risk of unintended pregnancy, i.e. those who were not sexually active (19%) or pregnant, postpartum or seeking pregnancy (9.5%), 87% of the remaining women reported contraception use. Among women reporting contraception use, the majority (78%) reported using highly effective methods, i.e. World Health Organization (WHO) Tiers I or II methods including surgical sterilization, contraceptive implant, intrauterine device (IUD), combined hormonal contraceptive, injectable progestin, or progestin only pill.³⁷

Several observational studies have demonstrated suboptimal rates of contraception among reproductive-aged cancer survivors. A cross-sectional study of 107 female cancer survivors at a single comprehensive cancer center reported 76% of participants using contraception during primary cancer treatment. Among the subset of 71 who were sexually active after cancer diagnosis, only 27% selected highly effective methods (WHO Tiers I or II).³⁸ A second study recruited survivors from the California Cancer Registry (CCR). Among 918 non-gynecologic cancer survivors who resumed regular menstruation after cancer therapy and had no history of surgical sterilization, 47% reported any contraceptive use, with only 33% of contracepting respondents reporting use of highly effective WHO Tiers I or II methods.³⁹

Compared to the general U.S. population of reproductive-aged women, the rates of contraception and use of highly effective methods are lower. The Fertility Information Research Study recruited 289 survivors from cancer advocacy and fertility preservation programs across the U.S. Following age-adjustment to compare survivors to the general population, 69% of the general population used a method of contraception, compared to only 57% of survivors ($p<0.01$). Moreover, 53% of the general population reported use of Tiers I or II methods, while only 34% survivors reported use of these highly effective contraceptive methods ($p<0.01$).⁴⁰

Family planning counseling in female cancer survivors are associated with higher rates of effective contraception. Qualitative studies of female reproductive-aged cancer survivors consistently report a desire for counseling on contraceptive options and the likelihood of becoming pregnant following cancer therapy.^{41, 42} Contraceptive counseling by a healthcare provider prior to cancer treatment was reported by 65% of sexually-active female cancer survivors at a single comprehensive cancer center in the U.S.³⁸ Among survivors who were on average 2.4 years since their cancer diagnosis, 65% reported family planning counseling within the prior 12 months.⁴⁰ In both studies, women who reported contraceptive counseling were more likely to use Tier I or II methods. The specific discussion of contraception counseling is important, as a survey of California cancer survivors demonstrated no

association between fertility discussions prior to cancer treatment and the survivors' contraception practices after treatment.³⁹

Consideration of cancer type and co-morbidities in contraceptive counseling

In order to provide appropriate counseling on contraceptive options for women after cancer diagnosis and therapy, careful consideration must be given to co-morbidities and their potential interactions with specific contraceptive methods. Summarized in Table 3, the United States Medical Eligibility Criteria for Contraceptive Use (MEC) from the Centers for Disease Control and Prevention offers specific recommendations for the use of contraceptive methods in the setting of medical conditions such as those associated with cancer diagnoses.⁴³

Cancer type and choice of contraceptive methods—There are few medical restrictions for use of barrier contraceptives and intrauterine devices in cancer patients. The exception is the cervical cap, which is contraindicated in untreated cervical cancer. Initiation of IUD use is also contraindicated in endometrial and cervical cancers, but IUDs may be continued in patients who subsequently receive new cancer diagnoses.

On hormonal contraceptives, the MEC cautions against progestin containing and combined hormonal contraceptives (CHC) in women with history of breast cancer. Thus, non-hormonal methods of contraception such as the copper IUD may be considered first-line methods for breast cancer patients.⁴⁴ Several reports have shown that neither movement nor clinically significant heating was associated with MRI and copper IUD.⁴⁵ While the MEC cautions against use of the levonorgestrel IUD, several studies have assessed its efficacy in preventing endometrial polyps, hyperplasia and cancer in breast cancer survivors taking tamoxifen. A Cochrane review of LNG IUD use among women with breast cancer on tamoxifen suggested that the method decreased the incidence of benign endometrial polyps, but available trials were too small to study prevention of hyperplasia, endometrial cancer and breast cancer recurrence.⁴⁶

Thromboembolic risk—Caution is recommended with CHC use in patients diagnosed with thromboembolic disease in the setting of ongoing cancer diagnoses or treatment. The CDC and World Health Organization (WHO) both recommend against CHC use in patients receiving treatment of thromboembolic disease within the prior six months. Exceptions may be considered however, in cases where CHCs are used in a therapeutic capacity to decrease risk of hemorrhagic ovarian cysts and severe menorrhagia in patients receiving therapeutic anti-coagulation.⁴⁷ When avoiding CHCs due to risk of recurrent VTE, barrier methods and IUDs are acceptable alternatives.

Bone loss—Chronic corticosteroid use and certain chemotherapies have been shown to decrease bone density. Given that depot medroxyprogesterone acetate and the etonorgestrel contraceptive implant have been associated with decreased bone mineral density, it has been recommended that these methods be avoided in women who develop osteopenia or osteoporosis following cancer therapy).⁴⁴

Take home message—A limited number of observational studies have identified a gap in care in the contraceptive practices of reproductive-aged cancer survivors. Clinically significant proportions of survivors at risk of unintended pregnancy are not contracepting or using the most effective methods of contraception. Providers need to be aware of MEC and professional society guidelines when counseling this population. While contraception-specific counseling may improve contraceptive practices, further research is needed on how to deliver the most effective contraceptive counseling, when to deliver this information, and what are patient-important factors in contraceptive decision-making.

Maternal and Offspring Health

Reproductive-aged cancer survivors frequently have significant concerns about their personal and offspring health when considering starting a family. These reproductive concerns are associated with depressive symptoms and worse quality of life⁴⁸; for some survivors, these concerns result in choosing to avoid pregnancy.⁴⁹ Primary care providers, including obstetrician gynecologists, oncology providers, and fertility and maternal fetal medicine specialists serve as an important source of information on maternal and offspring health for survivors. In this section we discuss risks of spontaneous abortion (SAB), preterm birth, cardiovascular diseases, and gestational diabetes in reproductive-aged survivors attempting pregnancy, summarized in Table 4. We also include breastfeeding considerations.

Spontaneous abortion

Several large retrospective cohort studies from the U.S., Canada, Denmark, Germany and the United Kingdom have reported similar SAB risk among female childhood cancer survivors when compared to rates in siblings and/or the general population.^{29, 32–34, 50} In these studies, SAB are defined as spontaneous loss of pregnancy before 20–22 weeks of gestation. The Childhood Cancer Survivor Study reported a 15% SAB rate from 4029 pregnancies in 1915 female survivors, comparable to 15% in siblings.³³ From the Danish population, 1688 female cancer survivors had 1479 pregnancies and 7.4% SAB rate. This rate was marginally increased compared to 6.0% in siblings (Proportion Ratio 1.2, 95% CI 1.0–1.5) but no different from 6.1% in the general population.²⁹ Similar proportions of SAB were reported in survivors in the German Childhood Cancer Survivor cohort compared to the general German population (13.2% vs. 15%).³²

While the overall risk of SAB does not appear increased, cranial radiation is associated with higher SAB rates. In the Childhood Cancer Survivor Study, compared to those with no radiation therapy, women exposed to cranial and spinal radiation or cranial radiation alone had a 1.4 to 2.2-fold higher SAB rate; spinal radiation alone did not appear to increase risk.³³ By gestational age, cranial and spinal radiation was associated with significantly increased SAB risk occurring ≥ 12 weeks of gestation (RR 6.1, 95% CI 3.06–12.2), but no increased risk was seen in SAB < 12 weeks gestation.³³ The Danish registry study demonstrated almost a 2-fold increased SAB risk (PR 1.8, 95% CI 1.1–3.0) in survivors who received high-dose radiation treatment to the pituitary gland.²⁹

Abdominal and pelvic radiation is also associated with higher SAB risk. In the British Childhood Cancer Survivor Study, abdominal radiotherapy was associated with a modest

increase in miscarriage (OR 1.4, 95% CI 1.0–1.9), largely attributable to more miscarriages beyond 12 weeks of gestation (OR 1.9, 95% CI, 1.1–3.2) rather than <12 weeks (OR 1.0).³⁴ In the Danish population, survivors exposed to high-dose radiation to the ovary and uterus had an almost 3-fold increased risk of SAB (PR 2.8, 95% CI 1.7–4.7) versus their sisters.²⁹ Radiotherapy in which ovaries were in or near the field may be associated with higher relative risk of SAB (in radiation field RR 1.9, 95% CI 0.8–4.2, near radiation field RR 1.6, 95% CI 0.95–2.8), while SAB did not appear increased if ovaries were shielded (RR 0.9, 95% CI 0.2–3.5).³³ In contrast to the other studies, the Canadian cohort showed that abdominal-pelvic radiation was not related to SAB risk, but this cohort was significantly smaller, limiting power.⁵¹

Similar to women without a history of cancer, smoking appears to increase SAB rate in this population. SAB risk was evaluated with smoking and uterine radiation exposures. Survivors with >5 pack-years smoking history had higher risk for SAB among those with >2.5 Gy uterine radiation (OR=53.9; 95% CI 2.2–1326.1) than those with ≤2.5 Gy of uterine radiation (OR=1.9; 95% CI 1.2–3.0; $P_{\text{interaction}}=0.01$).

There is considerable evidence that radiation to the brain, abdomen or pelvis increases SAB 1.5 to 3 fold, for which survivors need to be counseled. Outside of these exposures, SAB rates did not appear to differ by cancer type or chemotherapy exposure, including alkylating chemotherapy exposure.³³ The mechanisms by which radiation increases miscarriage risk are hypothesized to include direct radiation damage to 1) endometrium causing atrophic changes, 2) myometrium causing fibrosis, decreased elasticity of the muscle and 3) uterine vessels disruption.^{52, 53} More studies are needed to delineate causes of higher rates of loss in the second trimester in order to develop interventions or better assessments of the uterus prior to conception.

Take home message—Radiation exposure to the brain, abdomen or pelvis increases SAB risk 1.5 to 3-fold. Otherwise, miscarriage rates do not appear to be different by cancer type or chemotherapy exposure.

Preterm birth, low birth weight and small for gestational age

Preterm birth prior to 37 weeks gestation poses significant risks to maternal and offspring health. Several large retrospective cohort studies evaluated premature birth among childhood cancer survivors. Compared to siblings and/or the general population, higher rates of preterm birth are observed in cancer survivors.^{33, 34, 50, 54–58} Within the Childhood Cancer Survivor Study, preterm birth occurred in 21% of survivors compared to 13% of siblings (OR 1.9, 95% CI 1.4–2.4).⁵⁷ Linking SEER cancer registries in 4 U.S. regions to birth certificate data, a 15% preterm birth rate was observed in survivors, with an increased relative risk of 1.5 (95% CI 1.3–1.8) compared to matched controls. Importantly, the risk of very early preterm birth < 32 weeks was also increased (RR 1.8, 95% CI 1.2–2.7).⁵⁵ Similar results were observed in Norwegian cohorts, where control women had 5–7% preterm birth rates, compared to approximately 15% in survivors (OR 2.2 to 2.8).^{50, 58}

With increased rates of preterm birth, survivors are also at higher risk of delivering low birth weight (LBW) offspring.^{33, 55, 57, 59} Absolute risks of LBW varied from 7% to 15%.

^{51, 55–57, 60} The Childhood Cancer Survivor Study reported a 2-fold increased risk of having an offspring < 2500 grams compared with siblings (RR 2.1, 95% CI 1.4–3.0). Consistently, a 2- to 3-fold increased risk of LBW offspring was observed in cancer survivors compared to controls.^{34, 50, 55, 57, 58} Importantly, offspring of survivors do not appear to be at greater risk of being small for gestational age (SGA), indicating that the risk of low birth weight is attributable to preterm delivery rather than growth restriction.^{55, 57, 60}

Abdominal radiation is strongly associated with a 2- to 3-fold increase in preterm birth risk. Wilms tumor survivors historically have undergone significant abdominal radiation. The National Wilms Tumor Study reported 10% risk of prematurity in patients with no prior radiation, compared to 22% in patients exposed to >25 Gy of abdominal radiation (P=0.001); among whole abdominal irradiation patients 33% of infants were born prematurely.⁵⁶ The Childhood Cancer Survivor Study and the British Childhood Cancer Survivor Study reported 29 to 41% preterm birth rate in Wilms tumor survivors, compared to 9–28% in other cancer types.^{33, 34} Uterine radiation exposure led to increased prematurity risk in dose-dependent fashion. Importantly, the risks of preterm birth in females who have undergone abdominal radiation did not appear to differ by whether radiation exposure occurred prior to or following menarche.⁵⁷

While the risk for SGA was not higher in the overall cancer survivor population compared to controls, some evidence suggests that abdominal and/or pelvic radiation increase the risk of not only LBW, but also SGA. Across cohorts, abdominal or pelvic radiation increased the risk of LBW offspring 2- to 4- fold.^{33, 34, 51, 59–61} Within the Childhood Cancer Survivor Study cohort, radiation exposure > 5 Gy to the uterus was shown to be associated with increased risk of SGA (> 5 Gy 18% SGA vs. no radiation 7.8%, p=0.003).⁵⁷ Ovarian radiation, pituitary radiation, and alkylator chemotherapy was not associated with SGA.⁵⁷

While the bulk of data on preterm birth focuses on Wilms tumor, most observational studies including the Childhood Cancer Survivor Study and the British Childhood Cancer Survivor Study have reported generally no association between preterm births and other common cancer types or exposure to alkylating chemotherapy.^{34, 57} The exception is the SEER registry linkage study, in which leukemia (RR 2.6, 95% CI 1.8–3.6), lymphoma (RR 1.8, 95% CI 1.3–2.5) and bone cancers (RR 2.2, 95% CI 1.2–3.9) were associated with preterm birth.⁵⁵

The pathophysiology of preterm birth in cancer survivors is not understood, as patient report and registry linkage studies do not ascertain spontaneous versus iatrogenic preterm deliveries. As well, to our knowledge, no interventional studies on preterm birth have been performed in this high-risk population. Further research to delineate causes of preterm birth and test interventions on these causes are needed.

Take home message—Higher rates of preterm birth and LBW neonates are observed among female AYA cancer survivors, particularly in those exposed to abdominal/pelvic radiation (2- to 3-fold increased risks). Abdominal or pelvic radiation also increases the risk of offspring being small for gestational age.

Labor and delivery considerations

Cesarean delivery—Three cohorts of cancer survivors demonstrate increased cesarean deliveries in female cancer survivors. Survivors from a single Norwegian comprehensive cancer center had a 23% cesarean delivery rate, compared with 8% in controls (OR 2.3, 95% CI 1.9–2.7). [Fossa] These estimates were similar in magnitude to the cohort from Western Australia.⁵⁴ U.S. data showed a more modest difference, with 22% cesarean delivery rate in cancer survivors and 17% in controls (RR 1.2, 95% CI 0.99–1.3). Cancer treatments did not appear to be associated with this outcome.⁵⁵

Risks specific to abdominal radiation—In a small cohort of 40 Dutch childhood cancer survivors followed at a single center, increased risks of postpartum hemorrhage (> 1 liter blood loss within 24 hours after delivery) was observed in 2/6 survivors with abdominal radiation exposure, compared to 5% of controls without history of cancer ($p=0.007$). This complication may be related to need for manual placenta extraction (17% in patients exposed to abdominal radiation compared to 3% controls, $p=0.08$).⁶² This finding has not been replicated. In Wilms tumor survivors, fetal malposition, premature rupture of membranes, obstructed labor did not occur more frequently with increased radiation dose.⁵⁶

Take home message—Female childhood cancer survivors are at increased risk of cesarean delivery.

Breastfeeding

Reproductive-aged cancer survivors may face breastfeeding challenges from CNS or chest radiation. A small series reported failure to lactate after delivery in 10/12 females exposed to 24 Gy cranial radiotherapy as CNS prophylaxis for acute lymphoblastic leukemia (ALL), despite normal breast development and regular menstruations prior to conception. Lower CNS radiation doses may not interfere with breastfeeding; a further series of 5 ALL survivors treated with 18 Gy CNS radiation reported normal lactation in all participants.⁶³ An additional risk to lactation is chest radiation. In a retrospective cohort study, Hodgkin lymphoma survivors exposed to chest radiation were less successful at breastfeeding attempts compared to healthy controls (61% vs 79% respectively, $P=0.04$).⁶⁴ Discussion of these challenges with these survivors is important to managing expectations of breastfeeding.

Take home message—Childhood cancer survivors who underwent CNS or chest radiation might experience more problems with breastfeeding comparing to healthy controls.

Cardiovascular concerns

Cancer treatments pose a myriad of cardiovascular risks that can impact maternal health (Table 5). According to the Children's Oncology Group *Long-Term Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (COG LTFU Guidelines) survivors exposed to anthracycline antibiotics or chest radiation are recommended to have screening with ECHO and EKG at entry into long-term follow up, then periodically based on clinical indication, age at treatment, radiation dose, and cumulative anthracycline dose.⁶⁵ While hypertension has been reported to be higher following flank radiation in Wilms tumor

survivors (12% non-radiated vs. 24% in radiated),⁵⁶ pre-eclampsia risks do not appear significantly higher in several cohort studies.^{54, 55, 62} In the SEER Registry linkage study, pre-eclampsia was reported in 5% of birth records of cancer survivors, compared to 4% of the general population (RR 1.0, 95% CI 0.7–1.4). A modestly higher risk was reported in the Western Australia cohort (4% of survivors vs. 3% of controls, adjusted RR 1.4 [95% CI 1.1–1.9]).⁵⁴

Pregnancy-associated cardiomyopathy poses a life-threatening risk in a select population of reproductive-aged cancer survivors. Risk is highest in survivors exposed to anthracyclines, but the absolute risk is low. For example, in a large retrospective cohort study of 847 survivors with 1554 pregnancies, pregnancy-associated cardiomyopathy in survivors was low (0.3%). Survivors who developed cardiomyopathy had higher anthracycline exposure compared to those who did not (321 vs. 164 mg/m², P<0.01). [Hines et al]

There are additional cardiopulmonary risks following some cancer therapies that require consideration prior to pregnancy. According to the COG LTFU Guidelines, cardiology evaluation is recommended for women exposed to 300 mg/m² or cardiotoxic agent (anthracyclines or high-dose cyclophosphamide) plus chest radiation or 30 Gy chest radiation who are pregnant or prior to planned pregnancy. Evaluation should include ECHO before pregnancy, periodically during pregnancy (especially during third trimester) and cardiac monitoring during labor and delivery due to risk of cardiac failure. As new targeted medications are increasingly used and many incur cardiovascular risks, long-term toxicity and its impact on maternal health during pregnancy need to be studied.

Take home message—Female cancer survivors with history of anthracycline and/or chest radiation exposures are at increased risk for developing pregnancy-associated cardiomyopathy. While the absolute risk of this complication is low, the clinical consequence is catastrophic. Pre-conception cardiac evaluations are recommended for survivors who are at risk.

Gestational diabetes

There are limited and inconsistent data on whether gestational diabetes (GDM) risks are increased in cancer survivors. The absolute rates are low. In the Western Australia cohort, 5% of survivors were diagnosed with GDM, compared with 2% of controls (adjusted RR 2.7, 95% CI 2.1–3.6).⁵⁴ In the SEER Registry linkage study, the rate of diabetes was 1.6%, compared to 1.4% in controls (RR 1.0, 95% CI 0.5–2.0).⁵⁵ There are no large-scale data on what cancer types and treatments are related to GDM in cancer survivors.

Take home message—Limited and inconsistent data exists on risk of GDM among female childhood cancer survivors. Several studies demonstrated trend towards increased risk.

Stillbirth

Stillbirth, or the death of a fetus after the 20th week of pregnancy, is a devastating pregnancy outcome. Several large retrospective cohort studies from the U.S., Denmark, Canada,

Norway and the United Kingdom have reported stillbirth risks among female childhood cancer survivors and compared them to risks in siblings and/or the general population.^{29, 33, 34, 50, 51, 61, 66, 67} The absolute risks of stillbirths were low. In the Childhood Cancer Survivor Study, 37 stillbirths occurred in 4029 pregnancies (0.9%). Survivors did not have higher rates of stillbirth compared to their siblings.³³ Similarly the British Childhood Cancer Survivor Study and the Danish registry study reported 0.6 and 0.3% stillbirth rates, respectively.^{29, 34} There was no significant association between history of cancer and stillbirth when comparing survivors to the general population.^{29, 50}

Abdominal and pelvic radiation may be associated with higher stillbirth risk, while chemotherapy exposure does not appear related.^{34, 51, 67} An early study of 65 female Wilms tumor survivors reported 11 stillbirths in 127 pregnancies, all of which occurred in women who received abdominal radiation. Compared to the general U.S. population, this represented an 11-fold increase in risk (RR 11.1, 95% CI 5.4–19.9).⁶¹ In the same study, neonatal mortality was 6% (RR 6.0, 95% CI 2.2–13.1). Subsequent risk estimates have not been significantly elevated, in part due to very low stillbirth rates. Within the British Childhood Cancer Survivor Study, abdominal radiation exposure was associated with an odds ratio of 1.3 (95% CI 0.2–7.2).³⁴ Data from the Ontario Cancer Registry suggest dose-dependent increases in perinatal death risk (Low dose < 2500 cGy OR 2.0, 95% CI 0.3–14.3 vs. high dose > 2500 cGy OR 4.3, 95% CI 0.7–25.4).⁵¹

Take home message—Stillbirth risk is not increased among childhood cancer survivors, except for potentially patients exposed to abdominal and/or pelvic radiation.

Childhood cancer risk in offspring

Reproductive-aged cancer survivors express concern about cancer risk in their offspring.⁶⁸ Several large cohort studies in the U.S. and Nordic countries demonstrated no increase in childhood cancer risk in the offspring of survivors compared to the offspring of controls when hereditary cancer cases were excluded.^{69–72} Linking cancer and birth registries in Denmark, Finland, Iceland, Norway, and Sweden, 44 neoplasms occurred in 5847 offspring of childhood cancer survivors who were followed for 86,780 person-years. Excluding offspring with features of hereditary cancer syndromes, the standardized incidence ratio (SIR) was 1.3 (95% CI 0.8–2.0).⁷¹ Registry data from Finland similarly compared 26,331 children of childhood and young adult onset cancer patients with 58,155 children of siblings and found no increased incidence (SIR 1.0, 95% CI 0.7–1.4).⁶⁹

Of note, discovery of cancer gene risk mutations continues to evolve. Hereditary cancer screening is rapidly expanding beyond traditional BRCA and microsatellite instability testing. As clinical practice evolves, genetic risk assessment (or reassessment) may be indicated in reproductive-aged cancer survivors, as carrier status of a risk mutation would impact both personal health and offspring health risk.

Take home message—No increased risk of childhood cancer has been observed in children of cancer survivors, with the exception of hereditary cancers.

Birth defects and chromosomal abnormalities

Following exposure to cancer therapies, survivors also report concern about risks of major birth defects and chromosomal abnormalities in their offspring. A large number of retrospective cohort studies have reported on birth defect and chromosomal abnormalities in cancer survivors and compared them to the general population or siblings.

28, 51, 55, 58, 59, 61, 62, 66, 70, 72–76 Across studies, congenital malformation rates vary between 3–5% in survivors, while rates of abnormal karyotypes were even lower (0.2 to 0.5%).^{67, 73, 74} Most cohorts showed no higher rates of birth defects in survivors compared to controls. For example, the Danish Cancer Registry demonstrated 2.6% of offspring of cancer survivors exposed to radiation treatment had birth defects versus 2.3% of offspring of the general population (Prevalence Ratio 1.1, 95% CI 0.8–1.5).⁷⁵ In addition, trisomy 21 (RR 1.1, 95% CI 0.2–5.5) and Turner Syndrome (RR 1.3, 95% CI 0.2–8.0) risks were not higher in offspring of cancer survivors than in sibling controls or the general population.^{73, 74} Birth defects and chromosomal abnormalities were also not related to cancer treatments.^{51, 73, 74}

Take home message—Overall, rates of birth defects among childhood cancer survivors are low, do not appear increased comparing to general population, and are not higher in patients exposed to flank/abdominal/pelvic radiation.

Conclusion

The majority of female cancer patients diagnosed at a young age will become long-term survivors and face reproductive health risks related to their cancer treatments. These risks include infertility, inadequate contraception, and pregnancy complications and impact on offspring health. These risks differ by cancer treatments. Family planning counseling is important in this population to discuss both future fertility and effective contraception. Preconception counseling is critical to evaluate and attempt to modify pregnancy-related risks. Equally important to informing survivors of their increased reproductive risks is counseling on which risks they do not face. Currently, this clinical care benefits from expertise of both reproductive and oncology specialists, aided by professional guidelines including the US MEC, Children's Oncology Group Long Term Follow Up Guidelines, National Comprehensive Cancer Network Guidelines for Survivorship, and relevant American Society of Clinical Oncology guidelines. Many clinically important questions remain unanswered, from generating risk estimates by cancer treatment exposures to predicting the window of fertility after cancer. As well, health services research on effective strategies to disseminate information on these modifiable risks to survivors and their healthcare providers is needed.

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Table 1

5-year survival rates by cancer type for the most common cancers diagnosed in girls and young women prior to age 50^{77, 78}

Cancer type	Incidence per 100,000 ^a	Relative 5-year survival ^b
Age < 20 at diagnosis		
Leukemia	4.2	80%
Brain and spinal cord tumors	2.6	73%
Thyroid	2.1	99%
Hodgkin lymphoma	1.2	96%
Non-Hodgkin lymphoma	0.9	83%
Neuroblastoma and ganglioneuroblastoma	0.8 ^c	69% ^d
Bone cancer (includes osteosarcoma, Ewing sarcoma)	0.8	70%
Ovarian germ cell tumors	0.7	93%
Wilms tumor and other renal tumors	0.6	88%
Retinoblastoma and other eye and orbit	0.5	96%
Melanoma of the skin	0.5	96%
Rhabdomyosarcoma	0.4 ^c	65% ^d
Hepatic tumors	0.3	65%
Age 20–49 at diagnosis		
Breast cancer ^d	73.1	88%
Thyroid	27.7	99%
Cancer of the female genital tract	27.5	80%
Melanoma of the skin	15.7	96%
Colorectal cancer	11.2	59%
Non-Hodgkin lymphoma	6.5	80%
Leukemia	4.1	68%
Brain and spinal cord tumors	3.3	58%
Hodgkin lymphoma	3.0	94%
Non-Hodgkin lymphoma	6.5	80%
Sarcomas	1.9	75%
Bone cancer	0.5	79%

^aIncidence rate in 2012, age-adjusted to the 2000 U.S. standard population

^bSurvival relative to people in the general population of the same age, race and sex without a history of cancer

^c2006–2010 incidence rate

^dBreast cancer in situ excluded

Table 2

Impact of cancer treatments on fertility

	Hypothalamic-pituitary-ovarian axis	Ovarian reserve	Uterine function
Chemotherapy	–	+ Some agents	–
Radiation	+ Cranial radiation	+ Abdominal pelvic radiation	+ Abdominal pelvic radiation
Surgery	+ Surgery on hypothalamus/pituitary	+ Bilateral salpingo-oophorectomy	+ Hysterectomy, trachelectomy
Endocrine therapy	–	+ Indirect effect via concomitant aging	–
Targeted therapy	?	?	?

– Evidence suggests no effect; + Evidence suggests adverse effect; ? Unknown effect

Table 3

Select conditions relevant to cancer survivors and guidance from the U.S. Medical Eligibility Criteria for Contraceptive Use, 2016⁴³

	Copper IUD	LNG IUD ^a	Implant ^b	DMPA	POP	CHC ^c	Condom	Spermicide	Diaphragm/Cervical cap
Diagnosis	DVT/PE with active cancer (metastatic cancer, cancer therapy, or cancer within 6 months of cancer remission) excluding non-melanomatous skin cancer	2	2	2	2	4	1	1	1
	Cervical cancer	4/2	2	2	1	2	1	2	1
	Current breast cancer	1	4	4	4	4	1	1	1
	Breast cancer in remission >5 years	1	3	3	3	3	1	1	1
	Endometrial cancer	4/2	1	1	1	1	1	1	1
	Ovarian cancer	1	1	1	1	1	1	1	1
	Malignant Liver Tumor	1	3	3	3	4	1	1	1

Categories of medical eligibility criteria for contraceptive use (9)

- Two categories separated by / indicates categories for initiation/continuation

1 = A condition for which there is no restriction for the use of the contraceptive method.

2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.

3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.

4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

^aLNG = levonorgestrel.

^bImplant = etonogestrel implant (i.e. Implanon, Nexplanon).

^cCHC = combined hormonal contraceptives

Table 4

Maternal and offspring health risks

Health risk	History of cancer	Radiation		Chemotherapy
		Brain	Abdominal/Pelvic	
Maternal	Infertility	↔	↑	↑
	Not using contraception or use of less effective methods	?	?	?
	Pregnancy termination	?	?	?
	Spontaneous abortion	↑	↑	↔
	Preterm birth	↔	↑	↔
	Cesarean delivery	?	?	↔
	Cardiovascular risk	↔ ^a	↔	↑ Anthracyclines
	Gestational diabetes	?	?	?
	Breastfeeding success	↓ ^a	↔	?
	Stillbirth	↔	↑	↔
Offspring	Low birth weight	↔	↑	↔
	Small for gestational age	↔	↑	↔
	Childhood cancer risk	↔	↔	↔
	Birth defects/chromosomal abnormalities	↔	↔	↔

↑ risk increased, ↓ risk decreased, ↔ similar to controls, ? lack of data

^a risk with chest radiation

Table 5Cardiovascular risks associated with chemotherapy, targeted therapy, and radiation^{79, 80}

Arrhythmia	Anthracyclines (Doxorubicin) Chest radiation Anti-metabolites (Capcetabine) Antimicrotubule agents (Paclitaxel)
Congestive heart failure (CHF) and cardiomyopathy	Anthracyclines/antraquinolones (Doxorubicin) Alkylating agents (Cyclophosphomide) HER 2 inhibitors (Trastuzumab) Tyrosine kinase inhibitors (Dasatinib) Proteasome inhibitors (Bortezomib)
Hypertension (HTN)	Platinum agents (Cisplatin) VEGF signaling pathway inhibitors (Bevacizumab) Tyrosine Kinase Inhibitors (Dasatinib)
Myocardial ischemia	Chest radiation Platinum agents (Cisplatin) Anti-metabolites (Fluorouracil)
Pulmonary fibrosis	Antitumor antibiotic (Bleomycin) Antimetabolite agent (Methothrexate) Alkylating agents (Busulfan)
Valvular heart disease	Chest radiation