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REVIEW ARTICLE

Reproductive Function and Outcomes in Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Review

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ABSTRACT

Some survivors of childhood, adolescent, and young adult cancer are at increased risk of gonadal dysfunction and adverse pregnancy outcomes. We reviewed currently available literature that evaluated reproductive function and pregnancy outcomes of female cancer survivors diagnosed before the age of 25 years. High-dose alkylating agent chemotherapy and abdominal/pelvic radiotherapy adversely affect gonadal function in a dose-related fashion, with older age at exposure conferring greater risk as a result of the age-related decline in ovarian reserve. Gonadal injury clinically manifests as ovarian hormone insufficiency (delayed or arrested puberty, premature ovarian insufficiency, or premature menopause) and infertility. The effect of molecular-targeted agents on ovarian function has not been established. For female cancer survivors who maintain fertility, overall pregnancy (relative risk, 0.67 to 0.81) and live birth rates (hazard ratio, 0.79 to 0.82) are lower than those in the general public. Pregnancy in cancer survivors also may be associated with risks to both the mother and the fetus related to miscarriage; preterm birth; and, rarely, cardiomyopathy. Women at risk for these complications require preconception assessment and counseling from both obstetricians and oncology providers. The risk for inherited genetic disease in offspring conceived after cancer treatment exposure is not increased. The optimization of reproductive outcomes and minimization of risks of pregnancy complications in survivors requires informed, risk-based assessment and monitoring.

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INTRODUCTION

The childhood cancer survivor population has been growing rapidly over the past four decades, with 5-year survival rates now approximately 80% in the developed world. Despite increasing survival, the majority of these survivors will experience at least one and often several chronic health conditions by age 40 years that will significantly affect their overall quality of life.[1,2] Among the health consequences of cancer, gonadal dysfunction and infertility are major concerns of survivors and their parents, which results in distress, fear, anxiety, and interference with intimate relationships.[3] The identification of risk factors that affect reproductive function and fertility is important to facilitate accurate counseling and timely referral for established (eg, oocyte, embryo cryopreservation) and experimental (eg, ovarian tissue cryopreservation) interventions that may help to restore future fertility in high-risk populations.[4] In this review, we assess currently available literature on reproductive function and pregnancy outcomes of female childhood, adolescent, and young adult cancer survivors diagnosed before the age of 25 years.

CANCER THERAPY AND GONADAL FUNCTION

Some cancer survivors are at increased risk of damage to reproductive function, which may manifest as ovarian hormone insufficiency (absent or arrested puberty, premature ovarian insufficiency [POI; also referred to as early menopause]), and infertility.[4] POI is a clinical condition that develops in any adult female at an age younger than 40 years and is characterized by the absence of menstrual cycles for ≥ 4 months and two elevated serum follicle-stimulating hormone levels in the menopausal range.[5] Compared with siblings, the risk of nonsurgical POI is increased, with a cumulative incidence of approximately 8% to 10% by age 40 years.[6-8] These manifestations generally reflect direct or indirect

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adverse effects of cancer treatment on the nonrenewable pool of primordial follicles within the ovary.[9]

The body of evidence that describes adverse effects of multimodal cancer therapies on female reproductive function largely is based on retrospective cohort studies.[10] A dissection of the contribution of individual therapeutic components in these studies often is difficult, but increasingly data have elucidated predisposing treatments. These studies confirm that among chemotherapeutic agents, the alkylating agents impart a higher risk in a dose-related manner when both individual agents and a combination of alkylating agents are used.[11] Of note, no consistent threshold seems to exist for a safe alkylating agent dose.

The ovaries also may be damaged by radiation to a field that potentially exposes them (eg, total body, abdominal, pelvic, spinal irradiation). The magnitude of the effect is related to dose, fractionation schedule, and age at the time of treatment. The oocyte is extremely sensitive to radiation, with < 2 Gy representing the estimated dose required to destroy 50% of primordial follicles[12]; nomograms that identify the dose likely to cause POI across a range of ages have been produced.[4]

Molecular-targeted agents, such as monoclonal antibodies and kinase inhibitors, increasingly have been used in the treatment of female cancer. At present, the effects of such agents on female reproductive function are largely unknown, but reports have proposed a likely transient effect of bevacizumab (an anti–vascular endothelial growth factor agent) on ovarian function.[13] Because follicle growth depends on angiogenesis, normal folliculogenesis may be impaired by this agent; effects on the nongrowing ovarian follicle pool remain unknown. Other agents may have effects on the nongrowing primordial follicle pool through activity on pathways of physiologic relevance to the control of follicle dormancy and growth activation. One potential example of this is imatinib, which has adverse effects on ovarian function[14] but also may have protective effects against the gonadotoxicity of cisplatin.[15] The effect of ^{131}I-metaiodobenzylguanidine for neuroblastoma is unclear because only two cases have been reported to result in damage to the female gonads, but because of the localization of the tumors (pelvis), the ovaries might have received some scattered irradiation.[16]

DIAGNOSIS OF POI

In addition to compromising fertility, POI is associated with osteoporosis, cardiovascular disease, impaired well-being, and compromised sexual health.[5,17] Therefore, surveillance of at-risk survivors may facilitate early detection and access to interventions that preserve health and improve quality of life.[18,19]

Several initiatives have developed national guidelines for POI surveillance in survivors.[20-23] However, many differences were observed, which result in difficulties in implementing guidelines in clinical practice. As part of a larger international effort to harmonize existing late-effects screening recommendations for survivors of childhood cancer, POI surveillance recommendations for female survivors were reviewed[19] (Fig 1). Gaps in knowledge also were identified, including the lack of information on safe treatment dosages and the role of genetic susceptibility on subsequent POI risk, to lead future directions in research.

Assessment for POI should begin, as appropriate for age, with documentation of pubertal, menstrual, and pregnancy history and symptoms (eg, hot flashes) and physical findings of ovarian hormone insufficiency (eg, delayed/stalled puberty). Among useful biomarkers, follicle-stimulating hormone remains the key hormone of diagnostic value for POI, but now, increasing data show the value of anti-Müllerian hormone (AMH) in identifying women with low ovarian reserve after cancer therapy.[24] The value of AMH in predicting early menopause remains uncertain, and a very low AMH does not preclude natural conception. Thus, although this biomarker is of great value in a research context, its value in routine clinical practice is less clear. Antral follicle count by transvaginal ultrasound also is an established method for assessing ovarian reserve in adult women, but it is not part of the definition of POI.

TREATMENT OF OVARIAN HORMONE INSUFFICIENCY

Sex steroid replacement therapy (SSRT) can remediate or prevent the consequences of estrogen deprivation in survivors with POI. SSRT differs for survivors who are prepubertal and those who experience POI after secondary sexual characteristics have developed. Timing and tempo of estrogen substitution in the prepubertal patient are crucial to ensure normal pubertal development (especially breast development) and an acceptable final height and ideally should be managed by a provider with expertise in pediatric pubertal development. In postpubertal females, SSRT promotes bone and cardiovascular health.[25] Progesterone therapy also is needed to avoid endometrial hyperplasia and cancer in women with a uterus once breast development is complete.

In noncancer survivors, POI is treated with SSRT to remediate symptoms of low estrogen. Moreover, women should be advised that SSRT may play a role in primary prevention of cardiovascular disease and in bone protection.[5] In these women, SSRT use before the age of natural menopause has not been found to increase the risk of breast cancer.[5] Literature on the effects of SSRT in female cancer survivors, however, is scarce. Similarly, limited data exist on oral versus transdermal SSRT administration. A crossover study of oral versus transdermal SSRT in young women with POI related to Turner syndrome and childhood cancer treatment showed that transdermal treatment is more effective than standard oral treatment in terms of bone and cardiovascular health.[26-28] Participant numbers were limited and the study groups heterogeneous, which emphasizes the importance of pursuing randomized studies on SSRT in survivors.

Although most providers uniformly would recommend SSRT to support pubertal development and growth, use of SSRT in older patients is variable partly because of concerns about induction of second malignant neoplasms, especially breast cancer. In this regard, recent research from the Childhood Cancer Survivor Study reported that survivors with POI treated with SSRT have a lower risk of breast cancer than those who continue to menstruate naturally. These data suggest that SSRT does not affect breast cancer risk to the same degree as endogenous hormones.[29]

PREGNANCY RATES

For survivors of reproductive age, concerns about achieving pregnancy, maternal health during pregnancy, and pregnancy

Fig 1. Harmonized recommendations for premature ovarian insufficiency (POI) surveillance in survivors of childhood, adolescent, and young adult cancer. POI is a clinical condition that develops in any adult female before age 40 years that is characterized by the absence of menses for > 4 months and two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (on the basis of the maximum threshold of the laboratory assay used). (*) Treatments with evidence of causing POI include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy to a field that includes the ovaries (level A evidence). (†) At least annually, with increasing frequency as clinically indicated on the basis of growth and pubertal progression. (‡) At least for girls of ≥ 11 years of age and for girls with primary amenorrhea (age 16 years). (§) If amenorrhea, measured FSH and estradiol randomly; if oligomenorrhea, measured during early follicular phase (days 2 to 5). (‖) This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after 2 months without oral contraceptive pills. (¶) The absence of initiation of puberty (Tanner stage 2 breast development) in girls ≥ 13 years of age or failure to progress in pubertal stage for ≥ 12 months. AMH, anti-Müllerian hormone; level A, high level of evidence; level B, moderate/low level of evidence; level C, very low level of evidence. Reprinted with permission.[19]

outcomes represent priority health concerns. Large cohort studies have demonstrated that overall, female cancer survivors have lower rates of pregnancy[30-32] and live births[32-35] than their siblings and general population controls (Table 1). Risks for lowest rates occur after exposure to cranial and abdominal radiation. Abdominal radiotherapy also is associated with delayed time to pregnancy,[36] and in a large German cohort of survivors of Hodgkin lymphoma, pelvic radiotherapy was the key determinant of not achieving parenthood.[37] Pelvic radiotherapy also may affect the uterus, with consequences for early and late pregnancy loss and pregnancy complications (see Pregnancy Outcomes).

Chow et al[32] demonstrated that survivors who received chemotherapy alone had lower live birth rates (hazard ratio, 0.82; 95% CI, 0.76 to 0.89). Cyclophosphamide equivalent dose was associated at the highest doses with lower live birth rates (upper quartile *v* no exposure: hazard ratio, 0.85; 95% CI, 0.74 to 0.98). Detailed information on treatment revealed that only busulfan and lomustine are specific agents associated with a reduced chance of pregnancy. This study also highlighted the effect of delaying pregnancy such that the effect of chemotherapy was magnified in women whose first pregnancy was after 30 years of age; thus, there seems to be some evidence of age-related loss of fertility. These findings have clear implications for advising young women about the timing of pregnancy after cancer treatment. Higher pregnancy rates have been reported in more-recent treatment eras, which likely reflects the risk-adapted use of gonadotoxic treatment modalities.[35]

Pregnancy rates are not synonymous with either fertility or infertility. In the former, factors other than treatment exposure can affect pregnancy, such as having a partner and the desire for having children. In addition, the presence of clinical infertility does not necessarily preclude pregnancy, especially with the use of assisted reproduction.[36]

PREGNANCY OUTCOMES

As in the general population, live birth rates in cancer survivors are lower than pregnancy rates, which reflects losses during pregnancy.[32] Cohort and national registry data show that spontaneous pregnancy loss at < 22 weeks of gestation occurs with limited frequency (7% to 15%) in survivors, which is a comparable rate to siblings and population controls.[38-40] However, higher spontaneous pregnancy loss rates have been reported in women exposed to cranial radiation (1.4- to 6.1-fold increase) and abdominopelvic radiation (1.4- to 2.8-fold increase).[33,38,39] Of particular concern is the observation that second trimester losses are significantly increased in women with these exposures.[33,39] Abdominopelvic radiation is hypothesized to damage the endometrium, myometrium, or uterine vessels.[41-43]

Preterm birth at < 37 weeks gestation poses significant risks to offspring and occurs in 13% to 21% of pregnancies in cancer survivors.[44,45] Compared with siblings or the general population, these rates are 1.5- to twofold higher in survivors, including similarly elevated relative risks for early preterm births before 32 weeks.[44-47] Preterm birth risk is related to abdominopelvic radiation in a dose-dependent fashion but does not seem to vary by radiation before or after menarche.[33,39,44] Most reported data have shown no association between preterm birth and exposure to alkylating chemotherapy.[33,44] A dearth of data exists on risks of

Table 1. Pregnancy and Live Birth Rates in Childhood Cancer Survivors

First Author	Study Cohort (no. of patients)	Treatment Period	Age at Diagnosis, Years	Control Group	Pregnancy Rates (95% CI)	Live Birth Rates (95% CI)	Risk Estimate
Green[30]	CCSS (5,149)	1970-1986	0-21	Sibling controls	RR, 0.81 (0.73-0.90)	Not reported	Patients with hypothalamic/pituitary radiation dose ≥ 30 Gy (RR, 0.61; 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose > 5 Gy were less likely to have ever been pregnant
Reulen[33]	BCCSS (10,483)	1940-1991	0-14	General population England and Wales	Not reported	O/E, 0.64 (0.62-0.66)	Brain and abdominal RT
Stensheim[31]	Cancer Registry of Norway (16,105)	1967-2004	16-25 (subset of total study)	General population	HR, 0.67 (0.63-0.73)	Not reported	Not applicable because risks reported for total cohort (age 16-45 years)
Pivetta[34]	Italian AIEOP Off-Therapy Registry (2,670)	1960-1998	0-14	General Population	Not reported	O/E, 0.57 (95th, 0.53-0.62)	Malignancy of the CNS
Chow[32]	CCSS: chemotherapy only (5,298)	1970-1986	0-21	Siblings	HR, 0.87 (0.81-0.94; $P < .001$)	HR, 0.82, (0.76-0.89; $P < .001$)	Busulfan and higher doses of lomustine (≥ 411 mg/m^2) and cyclophosphamide equivalent doses in the upper quartile (≥ 11,295 mg/m^2).
Armuand[35]	Swedish National Patient Register (552)	Born between 1973 and 1977	0-21	Age-matched controls from the general population	Not reported	HR, 0.79 Before 1988 HR, 0.71 After 1988 HR, 0.90	Malignancy of the eye or CNS or leukemia

Abbreviations: AIEOP, Italian Pediatric Ematology and Oncology Association; BCCSS, British Childhood Cancer Survivor Study; CCSS, Childhood Cancer Survivor Study; HR, hazard ratio; O/E, observed/expected; RR, relative risk; RT, radiotherapy.

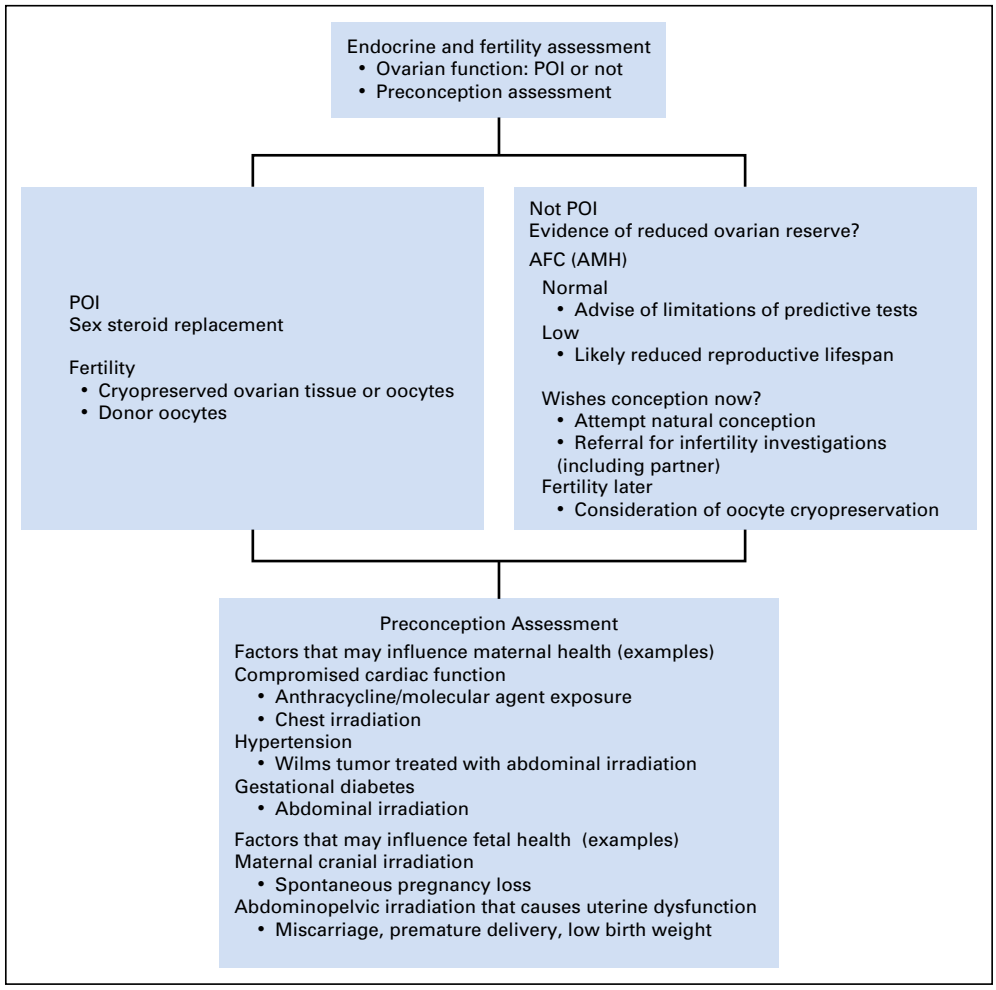

Fig 2. Assessment of the postpubertal survivor. AFC, antral follicle count; AMH, anti-Müllerian hormone; POI, premature ovarian insufficiency.

very early preterm birth (< 28 weeks) as well as on causes of preterm birth (ie, spontaneous *v* iatrogenic). Hence, a lack of studies remains on how to prevent this adverse late effect.

Concordant with higher rates of preterm birth, low-birth-weight babies (< 2,500 g) occur in 7% to 15% of offspring of cancer survivors, which is two- to threefold more frequent than in the offspring of controls.[39,44,45,48] With the exception of abdominopelvic radiation, higher rates of offspring being small for gestational age are not observed, which suggests that most of the low-birth-weight risk is attributable to preterm birth rather than to intrauterine growth restriction.[44,45,49] Overall, cancer survivors do not seem to be at a higher risk for stillbirth versus the general population.[38,47] However, similar to other pregnancy outcomes, abdominopelvic radiation exposure may be associated with a higher risk of perinatal death, but studies are limited in power because of overall low incidence.[33,50-52]

Cancer treatment exposures, including anthracyclines, chest radiation, and molecular-targeted agents, pose cardiovascular risks that can affect pregnancy outcomes. Several cohort studies reported an approximately 5% absolute risk of preeclampsia during pregnancy in cancer survivors, but rates are not higher or only modestly (1.4-fold) higher than in controls.[45,53,54] In the British Childhood Cancer Survivor Study, survivors of Wilms tumor treated with abdominal radiotherapy were at a threefold risk for the development of hypertension during pregnancy. Pregnancy-associated cardiomyopathy occurred rarely (0.3%) in a retrospective cohort study of 847 survivors, but increased risk was observed with anthracycline exposure.[55] Hence, the International Late Effects of Childhood Cancer Guideline Harmonization Group has recommended that cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines or chest radiation.[56] With the increased use of targeted therapy, long-term and pregnancy-related cardiotoxicity of these agents requires additional study.

During pregnancy, overall rates of gestational diabetes are low (< 5%) and not consistently higher in cancer survivors than in controls.[45,54] However, abdominal radiation has been associated with a 2.7- to 4.7-fold higher risk in one study.[33] Cesarean deliveries are consistently 1.2- to 2.3-fold higher in survivors than in controls.[45,54]

Because of these potential pregnancy-related complications, survivors would benefit from preconception counseling to estimate the magnitude of risk, establish a surveillance plan, and discuss interventions to reduce risk; obstetricians and oncology providers must be aware of these complications to comanage survivors accordingly (Fig 2). A dearth of intervention studies has focused on improving these adverse perinatal outcomes. Moreover, these data were derived from cohorts treated with regimens

Table 2. Health Risk Outcomes in Cancer Survivor Offspring

First Author	Study Cohort	No. of Offspring	Outcome Assessment	Comparison	Cancer (treatment)	Health Risk Outcomes Measures	Risk Estimate
Chiarelli[51]	Female CCS: Ontario Cancer Registry, diagnosis < 20 years of age (1964-1988)	594 singleton pregnancies born to 340 CS	Questionnaire	Internal comparison: patients treated with nonsterilizing surgery only or no treatment	Medical records Five treatment groups: nonsterilizing surgery, AA, AP irradiation (low [≤ 25 Gy], high [> 25 Gy]), AA + AP irradiation, and all other treatments	Congenital malformations (n = 22)	CS with AP irradiation (OR, 0.45; 95% CI, 0.12 to 1.70) General: decreased risk of having an infant with a congenital anomaly compared with those having surgery only No effect of high- *v* low-dose AP radiation (small number)
Winther[58]	CCS: Danish Cancer Registry, diagnosis < 20 years of age (1943-1996)	2,130 born to 550 female and 550 male CS	Registry linkage	General Danish population Internal comparisons	Registry-based information on RT (yes/no) Five categories of estimated radiation dose to gonads: low, low-medium, medium, medium-high, and high	Sex ratio alterations (2,130 offspring)	Male (0.99):female (1.00) ratio *v* Danish population (1.06) No effect of RT on the male:female ratio *P* for trend with ovarian dose = .51
Winther[61]	CCS: Danish Cancer Registry, diagnosis < 20 years age (1943-1996)	2,630 born to 4,676 female and male CS	Registry linkage	Offspring of siblings	Registry-based information on RT (yes/no) Information on CT abstracted from medical records (for survivors with affected outcomes only)	Chromosomal abnormalities (eight survivors with one or more children/ fetuses with an abnormal karyotype)	Proportion of live-born children with abnormal karyotypes born to CS was 0.21% and for siblings, 0.21% Direct comparison with siblings' offspring: Down syndrome (RR, 1.07; 95% CI, 0.16 to 5.47), Turner syndrome (RR, 1.32; 95% CI, 0.17 to 7.96)
Reulen[64]	BCCSS: National Registry of Childhood Tumors, diagnosis < 15 years of age (1940-1991)	6,232 born to 3,218 female and male CS	Questionnaire obtained from general practitioners	General population of England and Wales Internal comparisons among female CCS (CCS without CT/RT; high *v* low gonadal dose)	Registry-based information on RT (yes/no) and CT (yes/no) High *v* low estimated RT dose to gonads	Sex ratio alterations (6,232 offspring)	Male:female ratio CCS offspring *v* general population: 1.08 (range, 1.01-1.15) *v* 1.05 RT only *v* no RT and CT (OR, 0.97; 95% CI, 0.81 to 1.16) CT only *v* no RT and CT (OR, 1.00; 95% CI, 0.77 to 1.30) High- *v* low-dose gonadal RT (OR, 0.95; 95% CI, 0.77 to 1.18)
Magelssen[46]	CS: Norway, diagnosis 15-35 years of age (1980-1997)	First born (number not stated) to 251 female and 487 male CS	Registry information	First-born offspring in the general population of Norway	Hospital-based information on cancer treatment Four categories: surgery alone, RT (± surgery), CT (± surgery), and RT and CT (± surgery); not included in analyses for malformation outcome)	Congenital malformations (n = 7)	OR of 0.7 (95% CI 0.4 to 1.6) in female CS

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Table 2. Health Risk Outcomes in Cancer Survivor Offspring (continued)

First Author	Study Cohort	No. of Offspring	Outcome Assessment	Comparison	Cancer (treatment)	Health Risk Outcomes Measures	Risk Estimate
Winther[59]	CCS: Danish Cancer Registry, diagnosis < 20 years of age (1950-1996)	1,715 born to 970 CS	Registry linkage	Offspring of siblings	Registry-based information on RT (yes/no) Four categories of estimated RT dose to ovary and uterus: low, low-medium, medium-high, and high	Congenital malformations (n = 44 at birth; n = 96 later in life)	PPR at birth, survivors' *v* siblings' offspring: 1.1 (95% CI, 0.8 to 1.5) *v* general Danish population (O/E, 1.2; 95% CI, 0.9 to 1.6) Offspring of irradiated *v* nonirradiated parents (PPR, 1.2 *v* 1.0 at birth), including malformations diagnosed later in life, no ratio change
Mueller[45]	CS: Seattle, WA; Utah; Detroit, MI; and Atlanta, GA, diagnosis < 20 years of age (1973-2000)	1,898 first live births born to 898 CS, 892 CCS, and 1,006 adolescent cervical and genital CS	Registry linkage	Comparison offspring selected from birth records	Registry-based information on cancer therapy Four categories: CT, surgery, RT, and combinations	Congenital malformations (n = 10) Sex ratio alterations (1,898 offspring)	RR, 0.92 (95% CI, 0.48 to 1.75) Male:female ratio among offspring in the two cohorts and comparisons similar (range, 0.98-1.02) CCS: RR, 1.00 (95% CI, 0.93 to 1.07) Adolescent cervical and genital CS: RR, 0.97 (95% CI, 0.90 to 1.03) No significant increased RRs for malformations across groups
Madanat-Harjuoja[63]	CS: Finnish Cancer Registry, diagnosis < 35 years of age (1953-2004)	26,331 born to 12,735 CS 9,877 born after parent diagnosis (4,764 female and 5,113 male CS)	Registry linkage	Population expectations on the basis of cancer incidence rates in Finland (SIR) Indirect comparison with offspring of siblings	Registry-based information on RT (yes/no)	Cancer (n = 65 in children born after their parent's diagnosis)	Offspring of CS: SIR, 1.67 (95% CI, 1.29 to 2.12) Offspring of CS, excluding hereditary cases: SIR, 1.03 (95% CI, 0.74 to 1.40) Offspring of siblings: SIR, 1.07 (95% CI, 0.94 to 1.21) RT no effect on the risk: SIR, 0.91 (95% CI, 0.51 to 1.49)
Green[70]	National Wilms Tumor LTFUS: female CCS (and partners of male CS of Wilms tumor; earlier than January 2007)	1,021 pregnancies of ≥ 20 weeks duration, including 955 live born singletons; 677 included in analyses of 2,369 female CS and partners of 2,060 male CS	Self-administered questionnaire	Internal comparison	RT doses estimated on the basis of RT treatment protocols and each patient assigned a flank irradiation dose category except for those who received whole-abdomen irradiation Five dose categories in Grays	Congenital malformations (n = 44)	*P* for trend with radiation dose = .94

(continued on following page)

Table 2. Health Risk Outcomes in Cancer Survivor Offspring (continued)

First Author	Study Cohort	No. of Offspring	Outcome Assessment	Comparison	Cancer (treatment)	Health Risk Outcomes Measures	Risk Estimate
Winther[62]	CCS: Danish Cancer Registry, diagnosis < 20 years of age (1950-1996)	1,920 born to 527 female and 539 male CS	Registry linkage	Offspring of siblings. Population-based comparisons	Registry-based information on RT (yes/no) Four categories of estimated RT dose to ovary, uterus and pituitary gland: low, low-medium, medium-high, and high	Untoward disorders measured as hospitalization in childhood with the assumption that hospitalization is an indicator of multifactorial genetic disease (1,053 discharge diagnoses in CS offspring)	HR ratios compared with population: CS's offspring: (HRR, 1.05; 95% CI, 0.98 to 1.12), siblings' offspring (HHR, 1.01; 95% CI, 0.97 to 1.05) HRR irradiated parents *v* nonirradiated parents on the basis of population comparisons (1.1 *v* 1.0) but unrelated to estimated radiation dose to gonads A sixfold excess risk for hospitalization for malignant tumors in the offspring of survivors largely explained by hereditary cancer syndromes
Winther[66]	CS: Danish Cancer Registry, diagnosis < 20 years of age (1943-1996)	472 CS; 145 case CS (with affected child or stillbirth) and 372 subcohort members (including 45 patients) (one third of a fertility cohort consisted of 1,474 CS with 2,767 pregnancies included in Winther[62])	Registry linkage	Internal comparison: nonirradiated survivors (for association with RT overall and with ovarian and uterine and testicular dose) Nonexposed to CT (for association with CT overall)	Medical records, including detailed information on CT and individual preconception RT doses to ovaries, uterus, and pituitary gland	Genetic diseases defined as chromosomal abnormalities, congenital malformations, stillbirths, and neonatal deaths (181 presumed genetic diseases in offspring)	Dose-response findings: RRs for ovarian RT dose categories > 0 to < 0.50 Gy and ≥ 0.50 Gy (with nonirradiated being reference): 1.12 and 1.04, respectively (P = .96) Risk of genetic disease among children of CS: Irradiated *v* nonirradiated CS: RR, 1.02 (95% CI, 0.59 to 1.44; P = .94) AA *v* no AA agents in CS: RR, 0.82 (95% CI, 0.53 to 1.28; P = .51) An association between uterine dose and congenital malformations, stillbirths, and neonatal death, taken together, was of borderline statistical significance (P = .07), with the highest uterine doses associated with a 2.3-fold increased risk (not significant).

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Table 2. Health Risk Outcomes in Cancer Survivor Offspring (continued)

First Author	Study Cohort	No. of Offspring	Outcome Assessment	Comparison	Cancer (treatment)	Health Risk Outcomes Measures	Risk Estimate
Signorello[65]	CCSS: Canada/United States, diagnosis < 21 years of age (1970-1986)	4,699 born to 1,627 female and 1,128 male CS	Self-administered questionnaire	Internal comparison Nonirradiated CS (for association with RT dose) Nonexposed to CT (for association with CT)	Medical records, including AAD score: 1-3 (lowest, middle, and top tertile exposure) and individual preconception RT doses to the gonads	Congenital anomalies defined as cytogenetic abnormalities, single-gene defects, and congenital malformations (129 offspring with congenital anomalies)	Dose-response findings: ORs for ovarian RT dose categories low, medium, and high, 0.87, 0.80, and 0.59 respectively (*P* for trend with radiation dose = .53) ORs for AAD score categories lowest, middle, and top tertile exposure, 0.63, 1.00, and 1.13, respectively (*P* for trend with AAD score = .69) For congenital malformations, ORs for ovarian radiation dose categories ranged from 0.84 to 1.14, which suggested no adverse effect. AAD score analysis showed a nonsignificant decreased risk for the lowest and nonsignificant increased risks for the middle and top tertile exposure.
Haggar[54]	CS: Western Australia Cancer Registry, diagnosis 15-39 years of age (1982-2007)	1,894 first completed pregnancies of 1,894 female CS	Registry linkage	Population-based comparisons without cancer	Five treatment groups: surgery only, CT only, RT only, CT and RT, and all other types and therapy combinations (not included in analyses for malformation outcome)	Congenital malformations (n = 12) Sex ratio alterations (1,894 offspring)	RR, 0.78 (95% CI, 0.41 to 1.37) Male:female ratio: RR, 1.05 (95% CI, 0.98 to 1.10)
Seppanen[60]	CS: Finnish Cancer Registry, diagnosis < 35 years of age (1953-2004)	6,862 born to 3,929 CS (2,197 female and 1,732 male) 2,412 born to CCS 4,450 born to young adult CS	Registry linkage	Offspring of siblings	Registry-based information on RT (yes/no)	Congenital malformations (n = 220)	PRs for CS's *v* siblings' offspring: Any anomaly: 1.17 (95% CI, 0.92 to 1.49) Lip and palate anomalies: 2.09 (95% CI, 1.06 to 4.12) Any anomaly in offspring of retinoblastoma: 3.15 (95% CI, 1.37 to 7.23) Renal tumors: 2.13 (95% CI, 1.07 to 4.26; small number) No association with RT of the parent: 1.12 (95% CI, 0.86 to 1.45)

NOTE. The health risk outcome measures miscarriage, stillbirth, and perinatal death are evaluated in the Pregnancy Outcomes section.

Abbreviations: AA, alkylating agents; AAD, alkylating agent dose; AP, abdominopelvic; BCCSS, British Childhood Cancer Survivor Study; CCS, childhood cancer survivors; CCSS, Childhood Cancer Survivor Study; CS, cancer survivors; CT, chemotherapy; HR, hospitalization rate; HRR, hospitalization rate ratio; LTFUS, long-term follow-up study; O/E, observed/expected; OR, odds ratio; PPR, prevalence proportion ratio; PR, prevalence ratio; RR, risk ratio; RT, radiotherapy; SIR, standardized incidence rate.

that may no longer be in practice and may be less applicable for counseling patients treated with more-contemporary treatment strategies.

HEALTH RISKS IN OFFSPRING

Childhood cancer survivors represent one of the largest groups of people exposed to well-documented high doses of potent mutagens in the form of chemotherapy and radiation therapy that might affect human germ cells and cause potential transmissibility of germline damage to offspring.[57] Health indicators of a possible mutagenic effect of cancer therapy that have been considered include single-gene disorders and chromosomal abnormalities (rare but purely genetic diseases); the relatively common congenital malformations (which although to some extent genetically determined, are multifactorial); and miscarriage, stillbirths, and perinatal death. The occurrence of cancer and sex ratio alterations also have been considered as appropriate measures of germ cell mutations in the next generation. Although most early studies lacked sufficient statistical power, their findings have suggested a low risk of treatment-induced heritable genetic effects. Findings of more-recent, larger, and refined studies are listed in Table 2.

Five population-based Nordic studies on the risk of sex ratio,[58] congenital malformations,[59,60] chromosomal abnormalities,[61] and hospitalizations[62] in offspring of survivors did not observe a significantly increased risk. In the largest population-based study to date that evaluated cancer risk in the next generation, 9,877 children born to survivors showed no increased risk of cancer except in the rare event of a familial cancer syndrome.[63] A population-based cohort study from the British Childhood Cancer Survivor Study that reported on sex ratio alterations[64] maximized the statistical power by pooling its data with those from previous large-scale studies.[58] The sex ratio of the offspring of survivors treated with potentially high-dose gonadal irradiation was not significantly different from that of survivors treated with presumably low-dose gonadal irradiation (odds ratio, 0.92; 95% CI, 0.78 to 1.08). These findings were confirmed by more-recent studies in the United States[45] and Western Australia.[54]

Although the design and methodology differed among the more recently published studies on the risk of congenital malformations in offspring, no significantly increased risks have been reported.[45,46,51,54,59,60] Two comprehensive studies evaluated the risk of genetic disease in children of childhood cancer survivors.[65,66] and provided strong evidence that potentially mutagenic chemotherapy and radiotherapy doses to the ovaries are not associated with genetic defects in the children. Consistent with the epidemiologic studies, no evidence for an increased rate of germline minisatellite mutations at hypervariable loci, markers for radiation-induced human germline mutation, was identified in parents who had received radiotherapy.[67]

To date, no environmental exposure, including cancer therapy, has been proven to cause human germline mutations that manifest as heritable disease in offspring.[57] Inadequate study size has been suggested, and failure to measure the appropriate outcome might explain the reassuring results reported in the majority of studies on health risks in offspring.[57] Total genomic sequencing that directly evaluates the presence of genetic damage in germ cells and epigenomic analysis might be ways to address this issue in the future, particularly in the era of targeted cancer therapies that include epigenetic modifiers.[68]

In conclusion, over the past decades, the adverse effects of cancer and its therapy on reproductive outcomes have become clear, especially after specific treatment, yet significant gaps in knowledge continue to limit the ability to assess risk for gonadal failure in individual patients who receive these therapies. Little is known about how host factors, such as genetic risks for infertility or differences in drug metabolism, affect risk from treatment. The effect of newer (molecular-targeted) agents is virtually unknown, and after therapy is delivered and a gonadotoxic insult has occurred, we know little about whether there is compensation in the rate of decline of ovarian reserve. Furthermore, the methods by which we assess impending ovarian insufficiency and loss of the reproductive window still remain inexact, which limits the ability to counsel survivors about making reproductive decisions.

We recommend that all clinical trials and treatment strategies for patients with cancer include surveillance for adverse effects on reproductive health, which in female patients should include assessment of ovarian function, pregnancy outcomes, and fertility (Fig 2). Detailed information about chemotherapy and radiotherapy exposures should be collected routinely to correlate with reproductive outcomes because treatment exposures rather than the nature of the cancer largely determine risks for chronic health conditions, including gonadal function and fertility in cancer survivors. Survivors should receive personalized counseling about type and magnitude of reproductive health risks on the basis of their specific treatment exposure, and studies should be established to determine the efficacy of fertility preservation procedures undertaken in this population.

Although oncofertility options have expanded globally, a need still exists to identify the specific fertility threats related to the primary cancer and treatment patterns by country. De Roo et al[69] proposed a global oncofertility index to permit experts to determine the scale of the problem and facilitate the development of educational tools that define access to reproductive technologies. As identified in the International Late Effects of Childhood Cancer Guideline Harmonization Group POI guideline, major gaps exist in information about safe treatment dosages, safety of novel therapies, and the role of genetic susceptibility on subsequent POI risk in survivors.[19]

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Reproductive Function and Outcomes in Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Review

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