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Radiotherapy for childhood cancer and risk for congenital malformations in offspring: a population-based cohort study

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Abstract

Offspring of childhood cancer survivors may be at risk of genetic disease due to the mutagenic cancer treatments received by their parents. Congenital malformations were evaluated in a population-based cohort study of 1715 offspring of 3963 childhood cancer survivors and 6009 offspring of 5657 survivors' siblings. The Danish Central Population Register, Cancer Registry and Hospital Register were used to identify study subjects and congenital malformations. Gonadal and uterine radiation doses were characterized based on standard radiation-treatment regimens. The prevalence of congenital malformations at birth in offspring of survivors (44 cases, 2.6%) was slightly higher but not statistically different from that of offspring of siblings (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). Including malformations diagnosed later in life did not change the ratios appreciably. The risk for malformations was slightly higher in the offspring of irradiated parents than in that of non-irradiated parents (PPR 1.2 vs 1.0) but was unrelated to gonadal dose. This study provides evidence that cancer therapy of children does not increase the risk for malformations in their offspring. Continued monitoring of genetic risks among their offspring, however, is warranted.

Keywords

cancer survivor; childhood cancer; germ-cell mutation; malformation; pregnancy outcome; radiation

High doses of ionizing radiation and chemotherapeutic agents used to treat childhood cancer cause somatic cell mutations that elevate the risk of second malignant neoplasms among survivors (1). Little is known, however, about the effect of such exposure on human germ cells. Childhood cancer survivors form one of the largest groups of people exposed to high doses of potent mutagens before reproductive age and thus offer a special opportunity for studying any trans-generational health hazards. To date, few studies (2,3) have been carried out on the

reproductive hazards associated with these curative treatments. In a nationwide population-based cohort study, we obtained quantitative information on the risks for congenital malformations among the offspring of childhood cancer survivors and compared these risks with those seen among the offspring of their siblings and of the general Danish population. By characterizing the radiation treatments received by each survivor, we were able to evaluate whether the occurrence of malformation was related to gonadal dose.

Materials and methods

Study groups

From the Danish Cancer Registry, we identified 5508 patients born 1950–1984 and alive on 1 April 1968, when the Central Population Register was established, in whom cancer was diagnosed sometime between 1950 and 1996, when they were younger than 20 years of age. The cancer registry records contain information on the diagnosis and the personal identification number of the patient, which permits accurate linkage to the Central Population Register containing up-to-date information on vital status, migration and first-degree relatives. The Cancer Registry also records whether radiotherapy is given (yes/no) (4). Of these patients, 3963 (72%) survived until the assumed onset of fertility (15 years) and formed the survivor cohort. We identified 5745 non-affected siblings of the cancer patients from the Central Population Register, using inclusion criteria similar to those for the patients. The 5657 siblings, who survived until the age of 15 (98% of identified siblings), formed the sibling cohort. Only survivors and their siblings born 1950 or later were included as sibling identification before 1950 was incomplete.

All liveborn children were identified by linking the survivor and sibling cohorts to the Central Population Register. Only children born between 1 January 1977 and 31 December 2001 were included (the former date being the start of the Danish National Hospital Register, from which information on congenital malformations was derived; see *Congenital malformations*).

Congenital malformations

The National Hospital Register, which keeps information on nearly 99% of all admissions and outpatient visits to non-psychiatric hospitals in Denmark (5), was used to identify offspring diagnosed with a congenital malformation. Birth defects recorded at birth as well as those reported later in life are registered. Each admission record includes the personal identification number, the date of visit and up to 20 discharge diagnoses coded according to a Danish version of ICD-8 until 1993 (6) and thereafter to ICD-10 (7). The respective malformation codes are 740–759 and Q00–Q99.

Malformations were grouped into 12 main diagnostic groups, each with several subgroups defined by the ICD-8 classification. Malformation diagnoses were validated against information in hospital medical records collected on 70% of the children who were enrolled in another ongoing study. As no discrepancies were found, the register-based codes for the main diagnostic categories were used in the analysis.

Radiation dose characterization

For survivors treated with radiotherapy, an estimate was made of the dose to the ovary and uterus or testis. Four categories of radiation dose were developed (low, low or medium, medium or high, and high). Dose categories were assigned to the gonads and the uterus by a highly experienced medical physics team (M. S.) based on the type and topography of the childhood cancer being treated, knowledge of treatment procedures for specific tumors during the study period and assumptions of the gonadal proximity to the radiation field.

The categories 'low or medium' and 'medium or high' were used for grouping of cases when a more accurate organ exposure could not be determined without additional treatment detail. For primary cancer treatment extending below the diaphragm, dose to ovary and uterus was estimated to be medium to high with a dose ranging between 100 and 4000 cGy and the dose to testis between 20 and 2500 cGy. For primary cancer treatment above the diaphragm, including treatment for retinoblastoma or brain tumors, the dose to ovary and uterus was between 1 and 100 cGy and the dose to testis less than 20 cGy.

Special attention was given to four female parents who gave birth to children with club feet. Accurate estimates of radiation dose to the ovary and uterus were obtained using actual radiotherapy records, and experimental simulations were performed using tissue-equivalent and three-dimensional mathematical phantoms (8).

Statistical analysis

The prevalence of congenital malformations among offspring of persons previously treated for childhood cancer was compared with that among offspring of siblings. Congenital malformations are by definition present at birth. Nonetheless, only about 60% of all malformations are noticed and recorded in the National Hospital Register within the first year of life. Therefore, the prevalence of congenital malformations was estimated for those registered only at birth and at any age after birth. Prevalences were estimated for all malformations combined and for each of the 12 main diagnostic groups. Adjustment was made for maternal age, year of birth and sex of offspring. Separate estimates were calculated according to the sex of the survivor, the type of cancer within the main diagnostic groups of the International Classification Scheme for Childhood Cancer (9) and the estimated radiation dose to gonads.

The prevalence of congenital malformations at birth among offspring of survivors was compared with that of offspring of siblings by a log-linear model for proportions and relative risks were given as adjusted prevalence proportion ratios (PPRs). The observed prevalences of congenital malformations in offspring in the survivor and the sibling cohorts at birth were compared with those expected, based on sex- and birth cohort-specific prevalence proportions in the general population. The ratio between the observed and the expected numbers of prevalent cases was estimated, and 95% confidence intervals (CIs) were calculated, on the assumption of a Poisson distribution of the observed cases (10).

To include malformations recorded in the National Hospital Register at any time after birth, Cox proportional hazards regression was used to model the time to first registration for a congenital malformation in offspring of survivors compared with offspring of siblings. Children were followed from birth until age at first registration for a congenital malformation, emigration, death or end of follow-up (31 December 2001), whichever occurred first, and relative risks were given as adjusted hazard ratios (HRs).

Results

Of the 3963 childhood cancer survivors and the 5657 siblings who met the inclusion criteria, 970 (24%) and 3042 (54%), respectively, became parents between 1977 and 2001. After exclusion of 15 children born before or up to 9 months after their parent's cancer diagnosis, 1715 offspring of survivors of childhood cancer and 6009 offspring of their siblings remained for analysis. The main diagnoses of the parents who survived a cancer were central nervous system neoplasm (18%), carcinoma or other malignant epithelial neoplasm (17%) mainly malignant melanoma and thyroid cancer, malignant lymphoma (17%), germ-cell, trophoblastic or other gonadal tumor (11%) and leukemia (9%). The survivor parents of 559 offspring (33%) had undergone radiotherapy (Table 1).

The prevalence of congenital malformations at birth in the offspring of cancer survivors (44 cases, 2.6%) was slightly higher but not statistically different from that of the offspring of siblings (140 cases, 2.3%) (PPR, 1.1; 95% CI, 0.8–1.5) (Table 1) or to that of the general Danish population (observed-to-expected ratio, 1.2; 95% CI, 0.9–1.6) (data not shown). Expanding the registration period to include malformations diagnosed later in life (median follow-up of 8.2 years; range, 0–25) more than doubled the number of malformations but did not change the risk estimates appreciably. The risk of malformations in the offspring of cancer survivors (96 cases, 5.6%) was slightly higher but not statistically different from that of the offspring of siblings (301 cases, 5.0%) (HR, 1.1; 95% CI, 0.9–1.4) (Table 1).

We were able to characterize the level of radiation to gonads and uterus in the parents of 436 offspring. An accurate characterization could not be made for the parents of 123 offspring because the location of the tumor was not adequately specified, as was often the case for Hodgkin and other lymphomas. The prevalence ratio for malformations was slightly higher in the offspring of irradiated parents than in offspring of non-irradiated parents compared with siblings (PPR 1.2 vs 1.0 at birth) and similarly for registrations at any time after birth but was unrelated to estimated radiation dose to gonads (Table 1). Slightly higher prevalence ratios were seen among female compared with male cancer survivors. No deviation in risk was observed according to the main category of cancer in the survivor (not shown). No significant association was seen for any of the main groups of malformations in offspring of survivors when compared with the prevalence of malformations in offspring of siblings registered at birth or registered at any age (Table 2) or with that of newborns in the general population (data not shown); however, the numbers of persons in most subgroups were small.

A non-significantly 1.5-fold increased risk for malformations of the extremities was mainly due to an increased risk of foot malformations, which was of borderline significance (13 cases of club foot among survivors' offspring registered at any time after birth; HR, 2.0; 95% CI, 1.0–3.9) (data not shown). According to the medical records, one child was born with infantile spastic paraplegia and psychomotor retardation and developed malalignment of the feet as a neurological late effect (mother had been treated for retinoblastoma; see below). The remaining 12 children had been diagnosed with typical club foot at birth (four bilateral and eight unilateral malalignment). One of these children was also born with pyloric stenosis (as also recorded among several family members). All children were cephalic presentations. The excess prevalence of club foot was seen in children of irradiated (HR 4.7; 95% CI, 2.2–9.8; 10 cases) rather than in children of non-irradiated parents (HR 0.7; 95% CI, 0.2–2.3; 3 cases), but there was no trend of increasing risk with increment of presumed dose to the gonads. Six of the irradiated parents were male and four female survivors. Three female parents had low uterine dose, i.e. 0.8, 2.4 and 11 cGy, received during treatment for leukemia, retinoblastoma and non-Hodgkin lymphoma, respectively, whereas one received an estimated uterine dose of 230 cGy during treatment for mixed papillary and follicular carcinoma of the thyroid with regional metastasis and spread to lymph nodes in the superior mediastinum.

Discussion

In this nationwide population-based cohort study of the offspring of childhood cancer survivors, the prevalence of all congenital malformations at birth in the offspring of cancer survivors was slightly higher but not statistically different from that of the offspring of siblings or to that of the general Danish population. Expanding the registration period to include malformations diagnosed later in life did not change the risk estimates appreciably. In this first study to attempt a quantification of gonadal and uterine doses and not just whether the survivor patient received radiotherapy (yes/no), the risk for malformations was slightly higher in the offspring of irradiated parents than in offspring of non-irradiated parents but was unrelated to radiation dose to the gonads.

The excess risk for foot anomalies noticed in the offspring of irradiated parents may be a chance finding associated with multiple testing as no clear relationship was found with gonadal dose. None of the cases occurred among the offspring of mothers with Wilms' tumor, who would have received high doses of radiation to the pelvis, with an associated risk of deformities due to atrophic damage to the uterine musculature (11–13).

Our observation of no significant overall increase in the prevalence of congenital malformations in the offspring of childhood cancer survivors accords with the finding of the Five Center Cancer Study (14) and with the preliminary finding of the Childhood Cancer Survivor Study (15), both conducted in the USA and based on self-reports of affected offspring at anytime after birth. The prevalences in offspring of survivors and siblings were 2.6% vs 2.3% at birth and 5.6% vs 5.0% at all ages in our study compared with 3.4% vs 3.1% and 3.5% vs 3.9% in the two US studies. Our study included a total of 184 affected offspring at birth increasing to a total of 397 affected at any age, while 216 and 238 (offspring with cancer excluded), respectively, were included in the two US studies. The results of a recent report from the National Wilms Tumor Study Group, however, suggested that prior flank radiation (renal fossa/tumor bed) as part of initial treatment may increase the risk of fetal malposition and associated malformations. The prevalence of malformations among offspring increased from 3.2% among non-irradiated females to over 10.0% for the more heavily irradiated mothers (16).

The largest and most comprehensive study of malformations following radiation exposure is that of the children of the Japanese atomic bomb survivors. Among 55,303 children born to survivors of the atomic bombings in Hiroshima and Nagasaki examined for congenital malformations, there was no significant increase over categories of parental gonadal dose (17).

The Eighth Report of the Committee on Medical Aspects of Radiation in the Environment (COMARE) provided a recent review of pregnancy outcomes following pre-conceptional exposure to radiation (18). The committee concluded that if an association of congenital malformations and pre-conceptional exposure to radiation exists, it is likely to be concentrated in the specific sub-grouping of neural tube defects. We observed no congenital malformations of the nervous system among liveborn offspring of cancer survivors at birth and six at any time after birth. None of the six malformations of the nervous system recorded later in life, however, were neural tube defects.

Abnormal zygotes or fetuses might end up as spontaneous abortions or stillbirths. A slight excess risk for being hospitalized with a spontaneous abortion was found in a Danish population-based cohort of female childhood cancer survivors when compared with sisters and population comparisons (19). This excess risk may have resulted from uterine damage after high-dose pelvic radiotherapy, consistent with previous studies, although radiation-induced germinal mutations could not be ruled out. The risk of early abortions among women examined as outpatients only was lower than in comparison groups. No increased risk for stillbirths was reported, and only two induced abortions were found to be related to fetal abnormality (one neural tube defect and one abdominal wall defect).

Chromosomal abnormalities, such as Down or Turner syndromes, might be more likely to occur following parental irradiation of the gonads than other malformations, yet no increase was observed in the Danish population, even when pregnancy terminations were included (20). Malformations and deformations can result because of growth restrictions within the uterus, secondary to high-dose radiotherapy effects, but there was no evidence in the current study for such a relationship (although numbers were small).

The mouse studies at Oak Ridge National Laboratory showed that the genetic response to radiation was lower in mice than in *Drosophila*, that the dose–response relationship was linear over a wide range of gonadal doses (up to 6 to 9 Gy), that lowering the rate at which the gonadal dose was delivered could reduce response by a factor of three and that males might be more radiosensitive than female mice (21–23). It is not straightforward on how to extrapolate these and other murine data to humans, but previous attempts to do so suggest that the doubling dose for genetic outcomes, i.e. the amount of radiation that will produce the same mutational impact on a population as occurs spontaneously each generation, might be of the order of 2–4 Gy (22). If so, then the associated scatter gonadal doses for patients in our study (most doses to gonads were estimated to be low to medium with a range between 0.01 and 1 Gy) may have been too low to result in a detectable increase, despite being much higher than reported in other human studies (18). However, more recent estimates based on human data on spontaneous mutation rates and mouse data on radiation-induced mutation rates suggest a doubling dose of only 0.82 ($\pm$ 0.29) Gy, which while still high indicates that more accurate estimates of gonadal dose coupled perhaps with larger studies of cancer survivors will have adequate statistical power to detect genetic diseases had they occurred (23). Also, based on the mouse data, females may be less susceptible than males for trans-generational effects related to irradiation of the germline which would lower the combined power to detect effects since female survivors represent 42.5% of the study population.

The strengths of our nationwide, population-based study include identification of cancer survivors from a national cancer registry, unbiased identification of siblings and offspring through population registry linkage, unbiased ascertainment of congenital malformations well beyond the neonatal period through linkage to the National Hospital Register, virtually complete follow-up of the study populations and categorization of individual doses to the gonads for those survivors who received radiotherapy. We were, however, unable to examine the risk for congenital malformations due to precise estimates of radiation dose to gonads and uterus, but the approximate gonadal dose categories have been validated against more accurate doses estimated based on the actual radiotherapy schemes (8) in a previous study (19) and were found to be of sufficient validity that we believe that our results have not been distorted by the absence of complete dosimetry information. Risks associated with chemotherapeutic agents could not be examined because cancer registry records were incomplete. However, no significant risk of malformation was observed among survivors of leukemia, who likely received intense chemotherapy administrations, and only two affected children were observed among non-irradiated survivors of leukemia. Furthermore, previous studies have found no association between chemotherapy and adverse pregnancy outcomes (11,24–27). Fatal germ-cell mutations might lead to pregnancy losses as early as in the very first gestational weeks. As such, extremely early pregnancy losses will not be noticed by the women themselves and, therefore, never reported or registered, we might have missed some important fetal abnormalities. Another weakness is lack of clinical details on potential confounders, such as familial history of malformations and associated syndromes. Despite the large number of cancer survivors and pregnancies evaluated, the main study limitation, similar to that of previous studies is the small number of children born with congenital malformations. The relative small number of outcomes to evaluate results in low precision in risk estimates, especially for subgroups of malformations. This fact indicates a need for greater international collaboration in the study of trans-generational effects of cancer treatment in children and adolescents as is currently underway in the USA, Denmark and Finland (2,3) (www.gcct.org).

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Table 1
Adjusted prevalence proportion ratios (PPRs) and hazard ratios (HRs) of congenital malformations registered at birth and at any age, respectively, among offspring of childhood cancer survivors in comparison with offspring of siblings

Offspring of childhood cancer survivors	No.	At birth		At any age		
		Obs ^a	PPR ^b	95% CI	Obs ^c	HR ^d 95% CI
Total offspring	1715	44	1.09	0.78–1.52	96	1.10 0.88–1.39
Sex						
Offspring of male survivors	819	18	0.9	0.6–1.5	38	0.9 0.7–1.3
Offspring of female survivors	896	26	1.2	0.8–1.9	58	1.3 1.0–1.7
Radiotherapy exposure ^e						
Offspring of non-irradiated parents:	1143	28	1.0	0.7–1.6	60	1.0 0.8–1.4
Non-irradiated father	532	9	0.7	0.4–1.4	23	0.9 0.6–1.3
Non-irradiated mother	611	19	1.3	0.8–2.1	37	1.2 0.9–1.7
Offspring of irradiated parents:	559	16	1.2	0.7–2.0	36	1.2 0.9–1.8
Irradiated father	284	9	1.3	0.7–2.6	15	1.0 0.6–1.8
Irradiated mother	275	7	1.1	0.5–2.2	21	1.4 0.9–2.2
Gonadal radiation dose of survivor parent ^f						
Low	185	5	1.1	0.5–2.8	16	1.7 1.1–2.9
Low-medium	118	5	1.9	0.8–4.5	8	1.5 0.7–2.9
Medium-high	71	2	1.2	0.3–4.8	3	0.9 0.3–2.7
High	62	1	0.6	0.1–4.5	3	0.8 0.3–2.5

^aObserved number of survivors' offspring with malformations at birth.

^bThe prevalence of congenital malformations at birth in the offspring of cancer survivors divided by the prevalence of congenital malformations at birth in the offspring of siblings (140 observed cases among siblings), adjusted for maternal age, birth year and sex of offspring.

^cObserved number of survivors' offspring with malformations registered in the observation period.

^dHR of being diagnosed with a congenital malformation for offspring of cancer survivors compared with offspring of siblings (301 observed cases among siblings), adjusted for maternal age, birth year and sex of offspring.

^eAccording to information in the Danish Cancer Registry. 13 offspring had parents with radiation exposure unknown.

^fRadiation dose to ovary and uterus (females) and testis (males).

Table 2

Adjusted prevalence proportion ratios (PPRs) and hazard ratios (HRs) of diagnostic groups of congenital malformations^a registered at birth and at any age, respectively, among offspring of childhood cancer survivors in comparison with offspring of siblings

Diagnostic group of congenital malformation (ICD-8; ICD-10) ^b	At birth		At any age					
	Obs (S) ^c	Obs (C) ^d	PPR ^e	95% CI	Obs (S) ^f	Obs (C) ^g	HR ^h	95% CI
Nervous system (740–743; Q00–07, Q85.0)	0	5	—	—	6	13	1.7	0.6–4.4
Eye, ear, face and neck (744–745; Q10–18)	2	1	6.5	0.6–73	9	33	0.9	0.4–1.9
Heart and blood vessels (746–747; Q20–28)	10	34	1.0	0.5–2.0	18	64	1.0	0.6–1.6
Respiratory organs (748; Q30–34)	0	7	—	—	0	9	—	—
Lip and palate (749; Q35–37)	4	11	1.2	0.4–3.9	6	14	1.5	0.6–3.9
Digestive system (750–751; Q38–45, Q79.2–.5)	2	9	0.7	0.1–3.1	8	23	1.2	0.5–2.7
Genitalia (752; Q50–56)	5	21	0.8	0.3–2.2	18	68	0.9	0.6–1.6
Urinary organs (753; Q60–64)	1	3	1.2	0.1–11	2	12	0.6	0.1–2.6
Extremities (754–755; Q65–66, Q69–74)	17	40	1.4	0.8–2.5	24	56	1.5	0.9–2.3
Musculoskeletal system (756; Q67–68, Q75–78, Q79.0,1,.8,.9)	1	3	1.2	0.1–12	4	13	1.1	0.4–3.3
Skin, hair, nails (757; Q79.6, Q80–84)	2	3	2.2	0.4–13	5	7	2.4	0.8–7.6
Malformations in multiple organ systems ^d (759; Q85.1,.8,.9, Q87, Q90–99)	1	6	0.5	0.1–4.6	4	13	1.0	0.3–3.2

^a All malformations in different main diagnostic groups for children with more than one malformation were included in the analysis in the respective diagnostic categories. Within each main group, however, only the first malformation was counted.

^b ICD-8 and ICD-10 codes according to the International Classification of Diseases, 8th and 10th revision (6,7).

^c Observed number of survivors' offspring with malformations at birth (S).

^d Observed number of siblings' offspring with malformations at birth (C).

^e Prevalence of the congenital malformation at birth in the offspring of cancer survivors divided by the prevalence of the congenital malformation at birth in the offspring of siblings, adjusted for maternal age, birth year and sex of offspring.

^f Observed number of survivors' offspring with malformations registered in the observation period (S).

- ^g Observed number of siblings' offspring with malformations registered in the observation period (C).
- ^h HR of being diagnosed with a congenital malformation for offspring of cancer survivors compared with offspring of siblings, adjusted for maternal age, birth year and sex of offspring.
- ⁱ Primarily chromosomal abnormalities involving multiple malformations such as Down, Edward, Patau and Turner syndromes.