Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study

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Summary

Background **The reproductive implications of mutagenic treatments given to children with cancer are not clear. By studying the risk of untoward pregnancy outcomes, we indirectly assessed the risk of transmission of germline damage to the offspring of survivors of childhood cancer who were given radiotherapy and chemotherapy.**

Methods **We did a retrospective cohort analysis, within the Childhood Cancer Survivor Study (CCSS), of the risk of stillbirth and neonatal death among the offspring of men and women who had survived childhood cancer. Patients in CCSS were younger than 21 years at initial diagnosis of an eligible cancer, were treated at 25 US institutions and one Canadian institution, and had survived for at least 5 years after diagnosis. We quantified the chemotherapy given to patients, and the preconception radiation doses to the testes, ovaries, uterus, and pituitary gland, and related these to the risk of stillbirth or neonatal death using Poisson regression analysis.**

Findings **Among 1148 men and 1657 women who had survived childhood cancer, there were 4946 pregnancies. Irradiation of the testes (16 [1%] of 1270; adjusted relative risk 0·8 [95% CI 0·4–1·6]; mean dose 0·53 Gy [SD 1·40]) and pituitary gland (17 [3%] of 510, 1·1 [0·5–2·4] for more than 20·00 Gy; mean dose 10·20 Gy [13·0] for women), and chemotherapy with alkylating drugs (26 [2%] of 1195 women, 0·9 [0·5–1·5]; ten [1%] of 732 men, 1·2 [0·5–2·5]) were not associated with an increased risk of stillbirth or neonatal death. Uterine and ovarian irradiation significantly increased risk of stillbirth and neonatal death at doses greater than 10·00 Gy (five [18%] of 28, 9·1 [3·4–24·6]). For girls treated before menarche, irradiation of the uterus and ovaries at doses as low as 1·00–2·49 Gy significantly increased the risk of stillbirth or neonatal death (three [4%] of 69, 4·7 [1·2–19·0]).**

Interpretation **Our findings do not support concern about heritable genetic changes affecting the risk of stillbirth and neonatal death in the offspring of men exposed to gonadal irradiation. However, uterine and ovarian irradiation had serious adverse effects on the offspring that were probably related to uterine damage. Careful management is warranted of pregnancies in women given high doses of pelvic irradiation before puberty.**

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Introduction

Aggressive treatments given to children with cancers in the past decades have substantially improved survival rates. Some of these treatments are mutagenic—eg, radiotherapy causes somatic mutations in human beings and germline mutations in animals.[1] Although unproven, radiation-induced damage of human germ cells might be transmitted to the offspring of patients, which could have adverse effects on reproduction and the health of offspring. This damage could also have implications for those who are exposed to radiation and chemicals in occupational or other settings.[1–3] For example, in the UK, an association between stillbirth and paternal exposure to ionising radiation was reported in a study of workers at a nuclear fuel reprocessing plant.[4–10] This finding was not confirmed in a subsequent study, although a doubling of stillbirth risk associated with maternal radiation monitoring was noted.[11]

Analysis of the offspring of individuals who have survived cancer provides a unique opportunity to assess whether quantifiable, preconception gonadal exposure to radiation or chemotherapy results in an increased risk of stillbirth or neonatal death—ie, a marker of potential damage to germ cells. It could also provide important data to inform clinical follow-up of survivors of cancer for late effects since increasing numbers of patients attain reproductive age with intact fertility. We report the risk of stillbirth and neonatal death among children of a well defined cohort of individuals who survived childhood cancer.

Methods

Study population

Details about the Childhood Cancer Survivor Study (CCSS) have been reported.[12,13] Cohort members of CCSS were younger than 21 years at initial diagnosis of an eligible cancer between Jan 1, 1970, and Dec 31, 1986, at 25 US institutions and one Canadian institution, and had survived for at least 5 years after diagnosis. The study was approved by the institutional review board at the participating institution. For CCSS, the parents or survivors older than 18 years were asked to provide separate written consent for self-report (questionnaire) and medical record abstraction. The institutional review board allowed verbal consent for the questionnaire data

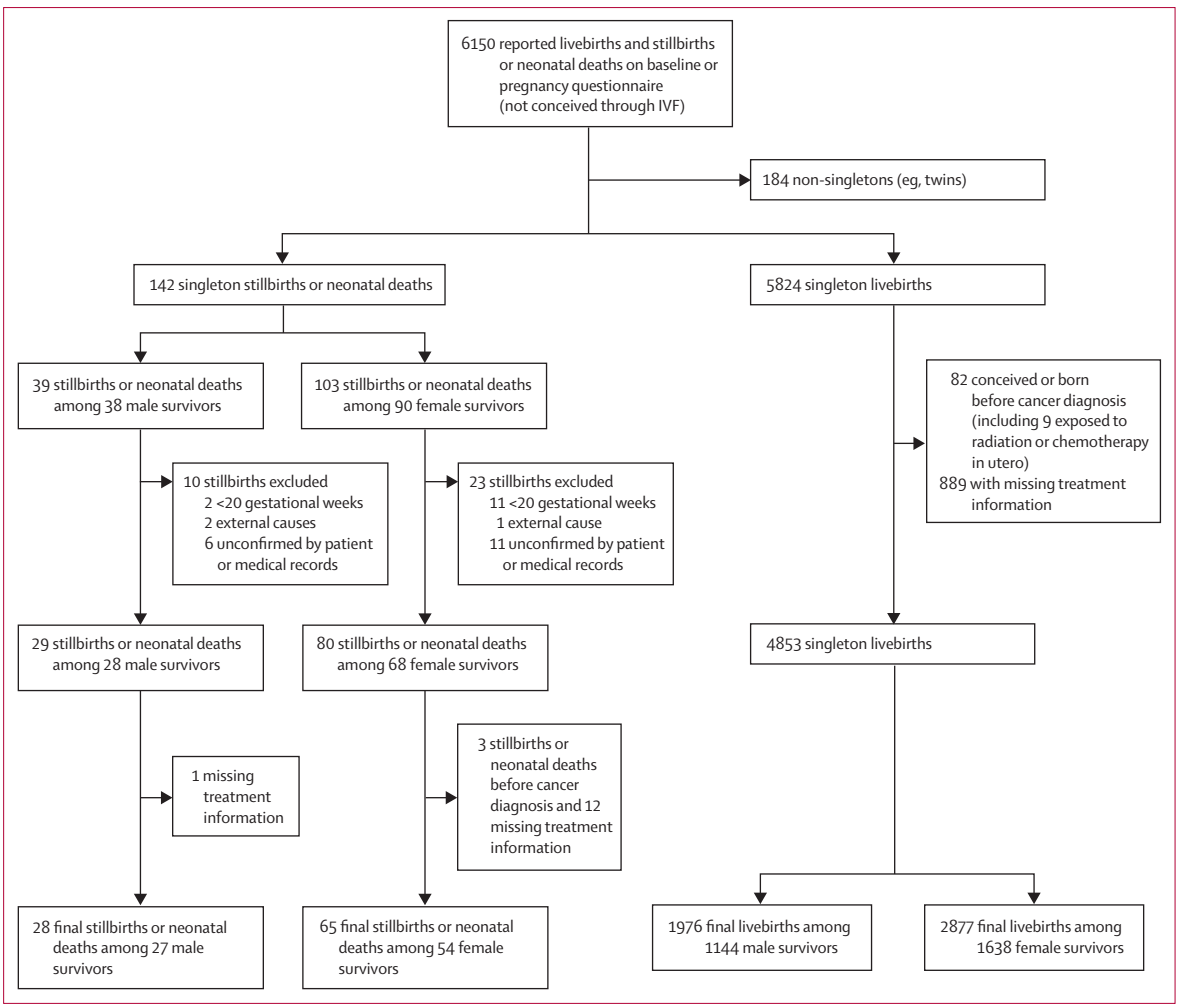

Figure: **Study profile**
Survivors with livebirths were not mutually exclusive from those with stillbirths or neonatal deaths because some patients had both adverse and non-adverse outcomes. Thus, numbers of survivors in the two groups cannot be added up. There were 1657 female survivors and 1148 unique male survivors included in the study. IVF=in-vitro fertilisation.

if the respondent (age ≥18 years) completed the questionnaire but did not return the questionnaire consent (which involved several reminders).

Data were gathered from participants in CCSS by use of a baseline questionnaire, starting in 1994, and from follow-up questionnaires completed periodically thereafter. These surveys elicited reports of pregnancies (their own for women, or sired for men) and their outcomes. If pregnancies were reported, participants received a detailed questionnaire to obtain further information about the pregnancy, including maternal and paternal exposures, and details about any children, including health problems or deaths. For the present study, we identified all livebirths or stillbirths reported by participants for 1971–2002.

Children conceived through in-vitro fertilisation were not eligible for this study because the use of donor eggs or sperm could not be conclusively established. Non-singleton pregnancies were excluded because this group was too small to assess separately. Pregnancies were also excluded if the cancer diagnosis came after or during the pregnancy, or if the details of the cancer treatment were unavailable or incomplete.

Validation of self-reported pregnancy outcomes

In the USA, a fetal death arising before the 20th gestational week is classified as a miscarriage and after week 20 as a stillbirth. Death immediately after birth or within the first 28 days of life is classified as a neonatal death. Because of uncertainties about self report, additional information was often sought to establish the correct classification.[13] For self-reported stillbirths, the validation approach began with an initial review of the questionnaires by a physician and cancer geneticist (JJM)—eg, a self-report of a stillbirth at 16 weeks' gestation would be rejected. CCSS staff telephoned participants if a clear gestational week was not reported or if other medical

details were required, with the purpose of obtaining clarification of the self report and permission to obtain copies of relevant medical records. All available information about the self-reported outcome and data gathered during the validation process were reviewed by a panel of individuals (JJM, DMG, JDB) to achieve a consensus decision.

Radiation dosimetry

The medical records of individuals who survived cancer were abstracted (by the data management staff at each participating clinical institution who were unaware of pregnancy outcome) to obtain data for the treatment of the index cancer and recurrences, including the dates and types of treatment and anatomical sites exposed during radiotherapy. Photocopied records of radiotherapy were obtained from the treating institutions and forwarded to the medical physicists (MS, REW). For every individual, doses absorbed by the testes, ovaries, uterus, and pituitary gland, including the contribution of radiation scatter, were estimated on the basis of measurements in water and applied to age-specific three-dimensional mathematical phantoms.[14] Gonadal shielding, oophoropexy, and field blocking were taken into account. The total dose was the sum of all doses from all radiation treatments. Doses to the two ovaries were estimated separately. We used the minimum dose to either ovary as the treatment exposure in our analyses, because the less exposed ovary was more likely to be the functioning one. Use of the maximum ovarian dose led to similar results, which are also presented.

Every patient was assigned a gonadal dose uncertainty score on the basis of completeness of radiotherapy records and whether the gonads were in a region near the edge of the treatment field in which the dose gradient was large. 1508 (85%) of 1774 patients had dose scores that indicated minimum uncertainty. Only 18 (1%) patient records were inadequate for dosimetry on the basis of uncertainty scores and were excluded from analysis. Radiation dose to the pituitary gland was also assessed as a potential risk factor for stillbirths and neonatal deaths among female survivors (mean dose 10·20 Gy), because it might lead to a permanent disruption of the hypothalamic-pituitary-gonadal axis.[15]

Statistical analysis

Stillbirths and neonatal deaths were combined into one outcome category similar to previous approaches.[16–18] We also reported stillbirths separately. Poisson regression was used to estimate relative risks (RR) associated with radiation dose to various organs. The offspring of survivors who were not given radiotherapy was the reference group. Calendar year of birth was included as a covariate in all adjusted models, with maternal age (in female models) and paternal age (in male models). Adjustment for other potential confounders was possible for only 3035 (61%) of 4946 pregnancies because these data were gathered by use of a specialised pregnancy follow-up questionnaire that was not completed by all individuals. These covariates were age of the partner, maternal smoking status, alcohol drinking status, vitamin supplement, and antibiotic use during pregnancy, birth order, time since diagnosis of cancer, pregnancy complications (diabetes, hypertension, toxaemia, bladder or other infections), and maternal and paternal use of medications to aid conception. In the subpopulation of

	Women (n=1657)	Men (n=1148)
Index cancer diagnosis		
Leukaemia	442 (27%)	314 (27%)
Hodgkin's lymphoma	364 (22%)	200 (17%)
Non-Hodgkin lymphoma	121 (7%)	159 (14%)
Bone sarcoma	238 (14%)	155 (14%)
Soft tissue sarcoma	186 (11%)	127 (11%)
CNS cancer	119 (7%)	98 (9%)
Kidney cancer or Wilms' tumour	104 (6%)	64 (6%)
Neuroblastoma	83 (5%)	31 (3%)
Age at diagnosis of cancer (years)		
0–4	314 (19%)	193 (17%)
5–9	315 (19%)	217 (19%)
10–14	528 (32%)	326 (28%)
15–20	495 (30%)	409 (36%)
Missing	5 (<1%)	3 (<1%)
Age at birth of first child (years)		
<20	356 (21%)	95 (8%)
20–24	624 (38%)	374 (33%)
25–29	469 (28%)	418 (36%)
≥30	205 (12%)	256 (22%)
Missing	3 (<1%)	5 (<1%)
Number of children included in study born after diagnosis		
1	717 (43%)	538 (47%)
2	667 (40%)	428 (37%)
3	219 (13%)	137 (12%)
≥4	54 (3%)	45 (4%)
Sex of children included in study born after diagnosis*		
Male	1508 (51%)	1018 (51%)
Female	1419 (48%)	975 (49%)
Unknown	15 (<1%)	11 (<1%)
Treated with†		
Radiation and alkylating drugs	529 (32%)	310 (27%)
Radiation but no alkylating drugs	485 (29%)	397 (35%)
No radiation but alkylating drugs used	275 (17%)	176 (15%)
No radiation and no alkylating drugs	321 (19%)	229 (20%)
Number of survivors reporting at least one stillbirth or neonatal death	54 (3%)	27 (2%)

Data are number (%). *For women, the denominator was 2942 children; for men, the denominator was 2004 children. †Percentages add up to 97% because information about treatment with alkylating drugs was missing for 3% of individuals. χ^2 p value for the association between treatment with radiation and treatment with alkylating drugs was 0·02 for women and 0·90 for men.

Table 1: **Characteristics of survivors of childhood cancer**

61% with full covariate data, these factors did not result in noticeable changes to the effect estimates. Accordingly, the final analyses were based on the entire study population without the inclusion of these additional covariates. Treatment with alkylating drugs (mutagenic chemotherapy drugs) was thought to be a confounder of the association of radiation with stillbirths or neonatal deaths (and a potential independent risk factor for stillbirths and neonatal deaths) and was assessed by use of an alkylating drug score developed as previously described.[13,19] With the wide variety of alkylating drugs used, a summary variable of cumulative exposure was created. The dose for each drug was abstracted for each patient, and then for all patients in the CCSS the dose (standardised according to body-surface area) was divided into tertiles for each drug. Each patient was assigned an exposure code of 0 (not administered), 1, 2, or 3 per alkylating drug. These exposure codes for all drugs given per patient were added, and then the cumulative scores for the cohort were divided into tertiles: treatment scores for alkylating drugs were from 0 to 3 per patient in the cohort (0=no treatment with an alkylating drug). Alkylating drugs were busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, chlormethine, melphalan, semustine, mitomycin, prednimustine, procarbazine, thiotepa, and uramustine. The platinum compounds are not thought to be alkylating drugs, but because of their DNA damaging capability they were included in the alkylating drug score.[13]

Multiple pregnancies per person were included. To account for dependency between children born to the same individual, we used generalised estimating equations to produce effect estimates and SEs with an exchangeable working correlation structure. Analyses at the parent level, with an ever or never approach to the outcome (stillbirth or neonatal death) were also done with adjustment for the number of pregnancies (singleton, >20 week), but this approach did not result in noticeably different results compared with the models by use of generalised estimating equations.

	Uterine radiation dose (Gy)				No radiation
	0·01–0·99	1·00–2·49	2·50–9·99	≥10·00	
Ovarian radiation dose (Gy)					
0·01–0·99	24/1404 (2%)*	0/12	0/6	..	..
1·00–2·49	0/32	5/155 (3%)*	0/24	0/1	..
2·50–9·99	..	3/54 (6%)	5/126 (4%)*	2/16 (13%)	..
≥10·00	..	0/6	0/3	5/28 (18%)*	..
No radiation	..	..	..	..	21/1075 (2%)*

Data are n/N (%), and are for pregnancies lasting at least 20 weeks that ended in stillbirth or neonatal death. *Diagonal categories.

Table 2: **Cross-tabulation of radiation doses to uterus and ovaries for survivors of childhood cancer**

	All pregnancies lasting at least 20 weeks*	Stillbirth or neonatal death	Relative risk (95% CI) of stillbirth or neonatal death		Relative risk (95% CI) of stillbirth
			Crude	Adjusted†	Adjusted†
Women					
Not treated with radiation	1075	21 (2%)	Reference	Reference	Reference
Radiation dose to uterus and ovaries (Gy)					
0·01–0·99	1404	24 (2%)	0·8 (0·4–1·4)	0·7‡ (0·4–1·4)	0·7§ (0·3–1·5)
1·00–2·49	155	5 (3%)	2·1 (0·8–5·7)	1·9‡ (0·7–5·4)	2·4§ (0·8–7·3)
2·50–9·99	126	5 (4%)	1·6 (0·4–6·0)	1·6‡ (0·4–6·5)	1·9§ (0·5–7·6)
≥10·00	28	5 (18%)	9·2 (3·3–25·4)	9·1‡ (3·4–24·6)	7·3§ (2·3–23·0)
Men					
Not treated with radiation	734	12 (2%)	Reference	Reference	Reference
Radiation dose to testes (Gy)					
0·01–0·09	692	8 (1%)	0·7 (0·3–1·8)	0·8 (0·3–2·0)	1·1 (0·4–3·0)
0·10–0·49	337	5 (1%)	0·9 (0·3–2·7)	0·8 (0·3–2·3)	0·7 (0·2–2·8)
≥0·50	241	3 (1%)	0·8 (0·2–2·8)	0·6 (0·2–1·9)	0·9 (0·2–3·2)

Data are number or number (%), unless otherwise indicated. *Stillbirths and livebirths. †Adjusted for calendar year of birth and maternal age (for analyses of uterus or ovaries), and paternal age (for analyses of testes). ‡Adjusted relative risks, with exposure defined as uterine and maximum ovarian radiation dose, were 0·7 (95% CI 0·4–1·4) for 0·01–0·99 Gy, 1·5 (0·5–4·6) for 1·00–2·49 Gy, 1·3 (0·3–6·4) for 2·50–9·99 Gy, and 7·8 (3·1–19·4) for 10·00 Gy or more with outcomes noted in 24 (2%), four (3%), four (3%), and six (14%) offspring, respectively. §Adjusted relative risks, with exposure defined as uterine and maximum ovarian radiation dose, were 0·7 (0·3–1·5) for 0·01–0·99 Gy, 1·9 (0·6–6·2) for 1·00–2·49 Gy; 1·6 (0·3–7·5) for 2·50–9·99 Gy, and 6·9 (2·5–19·5) for 10·00 Gy or more with outcomes noted in 16 (1%), four (3%), three (2%), and four (10%) offspring, respectively.

Table 3: **Association between organ-specific radiotherapy doses and risk of stillbirth or neonatal death in offspring of survivors of childhood cancer**

Role of the funding source

The study sponsors had no role in the study design, collection, analysis, or interpretation of data, or the preparation of the report. LBS and JDB had full access to all study data and had final responsibility to submit the report for publication.

Results

The figure shows the study profile. 23 (22%) of 103 stillbirths reported by female participants and ten (26%) of 39 reported by male participants were excluded because review of the medical records or further participant-provided information indicated a miscarriage before 20 gestational weeks (n=13), did not confirm the original self report (n=17), or because non-genetic causes were implicated (eg, car accident; n=3). The final study population consisted of 93 cases of stillbirths and neonatal deaths, and 4853 livebirths among 2805 survivors of cancer. The 1774 survivors who were given radiotherapy reported 60 stillbirths or neonatal deaths, and 3077 livebirths.

Table 1 shows the characteristics of the study population. The most common diagnoses were leukaemias and lymphomas (1600 [57%] of 2805). Survivors had a wide age range at the time of diagnosis of cancer and age at first birth. 1042 (63%) of 1657 of female survivors and 732 (64%) of 1148 male survivors had radiotherapy.

Because of the proximity of the uterus and the ovaries, radiation doses to these organs were highly correlated

	Treatment before menarche		Treatment after menarche	
	Risk of stillbirth or neonatal death	Relative risk*† (95% CI)	Risk of stillbirth or neonatal death	Relative risk*‡ (95% CI)
No radiation	5/494 (1%)	Reference	13/447 (3%)	Reference
0·01–0·99 Gy	11/636 (2%)	1·3 (0·5–3·9)	7/599 (1%)	0·3 (0·1–1·0)
1·00–2·49 Gy	3/69 (4%)	4·7 (1·2–19·0)	2/70 (3%)	1·2 (0·2–6·4)
≥2·50 Gy	11/82 (13%)	12·3 (4·2–36·0)	1/85 (1%)	0·2 (0·0–1·4)

Data are n/N (%), unless otherwise indicated. Data are for the offspring of only 1481 (89%) of 1657 female survivors for whom timing of treatment in relation to menarche could be established. For the 160 women in whom age at menarche was missing and needed to be estimated, we assumed they were treated before menarche if they were treated at age 9 years or younger, and after menarche if they were treated at age 18 years or older. *Adjusted for calendar year of birth and maternal age. †p value for trend was 0·006. ‡p value for trend was 0·32.

Table 4: **Association between radiotherapy doses to uterus and ovaries and risk of stillbirth or neonatal death in offspring of survivors of childhood cancer**

	All pregnancies lasting at least 20 weeks*	Stillbirth or neonatal death	Relative risk (95% CI) of stillbirth or neonatal death		Relative risk (95% CI) of stillbirth
			Crude	Adjusted†	Adjusted†
Women					
Alkylating drug score					
0	1449	36 (2%)	Reference	Reference	Reference
1	529	14 (3%)	1·2 (0·6–2·3)	1·4 (0·7–2·7)	1·1 (0·5–2·5)
2	378	8 (2%)	0·8 (0·3–2·1)	0·7 (0·3–1·9)	0·8 (0·3–2·4)
3	288	4 (1%)	0·5 (0·1–1·7)	0·6 (0·2–2·1)	0·7 (0·2–2·8)
Men					
Alkylating drug score					
0	1097	15 (1%)	Reference	Reference	Reference
1	411	6 (1%)	1·1 (0·4–2·8)	1·3 (0·5–3·2)	1·4 (0·6–3·7)
2	170	2 (1%)	0·9 (0·2–3·9)	1·0 (0·2–4·3)	0·6 (0·1–4·8)
3	151	2 (1%)	1·0 (0·2–4·4)	1·0 (0·2–4·2)	0·6 (0·1–4·6)

Data are number or number (%), unless otherwise indicated. Data are for offspring of only 4473 (90%) of 4946 survivors for whom alkylating score could be established. *Stillbirths and livebirths. †Adjusted for calendar year of birth, maternal age, and radiation dose to uterus and ovaries (for analyses in women); and for calendar year of birth and paternal age (for analyses in men).

Table 5: **Association between chemotherapy with alkylating drugs and risk of stillbirth or neonatal death in offspring of female and male survivors of childhood cancer**

(table 2). For 1713 (92%) of 1867 radiation-exposed data points, doses to the uterus and ovaries were exactly concordant within categories, reducing our ability to distinguish independent effects. RRs for stillbirths or neonatal deaths associated with doses of radiation to the uterus and ovaries separately were nearly identical (data not shown). We thus created dose categories corresponding to the left-to-right diagonal of table 2 (ie, doses to both the uterus and ovaries of 0·01–0·99 Gy, 1·00–2·49 Gy, 2·50–9·99 Gy, and ≥10·00 Gy). (Note, because the few data that arose outside of these diagonal categories were unused in most analyses of uterine and ovarian radiation doses, totals shown in the tables do not match those in the figure). The adjusted RRs of stillbirth or neonatal death for these categories were similar to those of stillbirth only (table 3). For the dose group with the highest risk (≥10·00 Gy), the mean preconception dose to the uterus was 17·52 Gy (SD 12·03) and the mean dose to the ovaries was 18·08 Gy (9·75).

A positive association between testicular irradiation and risk of stillbirth or neonatal death was not noted (table 3). The adjusted RR for receipt of any testicular irradiation was 0·8 (95% CI 0·4–1·6) in 16 (1%) of 1270 men, and no increased risk was noted for those in the highest exposure category. The association with stillbirth alone also was not raised in relation to testicular dose of radiation.

Age at menarche was known (1321 [80%] of 1657) or could be estimated (160 [10%] of 1657]) for 90% of female survivors, which allowed analyses that were stratified by whether the survivors were treated before or after menarche (table 4). The adverse association between irradiation of the uterus and ovaries and stillbirth or neonatal deaths was restricted to cases treated before menarche (table 4). Few girls in the group treated after menarche were given high doses of radiation to the uterus and ovaries, so exposure categories could not be extended beyond 2·50 Gy. For mothers treated before menarche with 2·50–9·99 Gy, the risk of stillbirth or neonatal death was four (8%) per 49 offspring (RR 5·8, 95% CI 1·2–28·2); and for 10·00 Gy or more, the risk was five (22%) per 23 offspring (19·0, 5·6–65·2). Although women given more than 2·50 Gy before menarche had a variety of index cancer diagnoses (leukaemia, CNS cancer, Hodgkin's lymphoma, non-Hodgkin lymphoma, Wilms' tumour, neuroblastoma, and soft tissue sarcoma), three women with leukaemia and five with Wilms' tumour (given uterine doses of 2·70–21·00 Gy and ovarian doses of 4·40–21·00 Gy) had all 11 stillbirths or neonatal deaths.

After adjustment for maternal age, calendar year of birth, and radiation dose to the uterus, we did not note an effect of high-dose pituitary irradiation among female survivors (17 [3%] of 510 survivors, RR 1·1, 95% CI 0·5–2·4 for ≥20·00 Gy *vs* no irradiation).

Treatment with any alkylating drugs did not increase the risk of stillbirths or neonatal deaths among the children of female survivors (26 [2%] of 1195 survivors, adjusted RR 0·9, 95% CI 0·5–1·5) or among the children of male survivors (ten [1%] of 732 survivors, 1·2, 0·5–2·5]. An assessment of the dose response by use of alkylating drug scores, representing tertiles of cumulative dose in CCSS, also did not show any pattern of increasing risk with increasing exposure (table 5).

Discussion

We did not note an association between testicular (for men) or pituitary (for women) radiation exposure before conception and the risk of stillbirth or neonatal death. By contrast, uterine or ovarian irradiation greatly increased the risk of stillbirth or neonatal death, with high doses (≥2·50 Gy) associated with a greater than 12-fold risk for women treated before menarche. We previously showed that pelvic irradiation increased the risk of preterm birth for female childhood survivors of cancer.[19] As such, an

association with neonatal death was not unexpected on the basis of the association of the risk of preterm birth with infant mortality. The robust association we noted with stillbirth alone is, however, an important independent finding because it indicates that radiotherapy has a role in the cause of late fetal death.

We could not directly assess whether uterine damage (eg, to the musculature, vasculature, or endometrium) or oocyte damage was the cause of the association with stillbirth or neonatal death, although we believe a uterine effect was most likely. High-dose pelvic irradiation can permanently impair growth and blood flow to the uterus and results in a reduced uterine volume,[15] and these effects of radiation are likely to be dependent on age.[20] Whether these types of effects on the uterus increase the risk of placental or umbilical-cord anomalies or other factors already linked to stillbirth, or whether they operate through different mechanisms needs clarification.[21] A small proportion of patients with Wilms' tumours might also have uterine anomalies that could contribute to the increased risk of stillbirth or neonatal death, independently of radiation effects.[22]

Evidence to support that irradiation of human germ cells results in genetic damage to the offspring is lacking.[1,16–18,23–26] Our ability to fully assess mutagenesis of human germ cells is likely to improve as genomic technologies improve,[3] and we cannot entirely rule out the possibility that irradiation of the ovaries resulted in transmissible mutations that increased the risk of stillbirth or neonatal death in our study population. Stillbirth or neonatal death is only one marker of germline damage, and other more direct outcomes such as cytogenetic or single-gene disorders have been studied in radiation-exposed women with largely null results.[18,24,25] These with our null findings for male gonadal exposure and for the mutagenic alkylating drugs suggests a non-genetic explanation. We attempted to document chromosomal or congenital abnormalities in the cases of stillbirths and neonatal deaths, but available information was sparse and incomplete. The four recorded cases of these abnormalities were Ivemark's syndrome (female survivor was not irradiated), lung hypoplasia with several other malformations (female survivor with a dose of less than 0·50 Gy to the uterus and ovaries), Edwards' syndrome (male survivor given 0·10–0·50 Gy testicular dose), and anencephalocele (male survivor given less than 0·10 Gy testicular dose).

Our null findings with testicular irradiation corroborate results from previous studies of survivors of the atomic bomb,[16–18] and the results of a study of UK nuclear industry workers[11] in which men exposed to radiation did not have an increased rate of untoward sired pregnancy outcomes, including stillbirth. In the only study of nuclear workers in which an association was noted,[4] the odds of stillbirth was estimated to increase by 24% per 100 mSv (roughly 0·10 Gy) increase in cumulative preconception dose (not specific to the testes). Such an effect should have been notable within our study population, with testicular doses of 0–15·40 Gy (mean 0·53 Gy [SD 1·40]). A difference between our study and Parker and colleagues' study[4] is that some workers were exposed near the time of conception when gamete mutations could have arisen (although an association with radiation film badge measurements for the 90 days preceding conception was not noted). In our study, the children were born an average of 15·0 years after paternal irradiation, thus any potential effects would be emanating from damage to the sperm stem cells (spermatogonia). So far, results from studies of animals, but not human beings, have shown transmissible germline damage in response to paternal irradiation.[27,28] If this damage arises in human beings, then it would be difficult to detect in all but the largest and most heavily exposed populations because paternal influences on the risk of stillbirth are outweighed by maternal and external (eg, prenatal care) factors. However, no effect was noted in this cohort of men exposed to testicular irradiation at levels far higher than would be expected from background exposure, diagnostic medical, or occupational settings.

Chromosomally abnormal fetuses might not complete 20 weeks' gestation or they might be selectively aborted in response to prenatal testing. Thus, we might have missed these outcomes in our study of only late pregnancy losses. Higher miscarriage rates have been noted among survivors of cancer, particularly those treated with abdominal radiation.[29,30] As for induced abortions, we checked within the data for the current study to assess whether induced abortions were more frequently reported by survivors exposed to high gonadal irradiation, and they were not. 8·0% of non-miscarried pregnancies that were sired by men given testicular doses of radiotherapy greater than 0·50 Gy were electively aborted versus 11·5% of those sired by men not given any radiotherapy. Similarly, in women given ovarian doses greater than 2·50 Gy and greater than 10·00 Gy, 8·4% and 8·2% of non-miscarried pregnancies, respectively, were electively aborted versus 18·7% of those in women not given any radiotherapy. These results confirm those reported by Winther and colleagues,[30] showing that Danish female survivors of cancer were not more likely than were their siblings or other controls to have elective abortions, including second-trimester abortions for fetal abnormalities.

The strengths of this study included the ability to assess radiotherapy dose response and the ability to temporally relate treatments to each pregnancy, accounting for potential confounders that were generally not available in previous studies. We also rigorously validated the self-reported outcomes, and attempted to remove cases that resulted from unrelated causes. Although unlikely to have any effect on our dose-response findings, one limitation of our study is the possibility that cohort members who had an adverse pregnancy outcome (stillbirth or neonatal death) were more likely to report their pregnancies on the CCSS questionnaires, which could affect the interpretation of the absolute risks that we noted for these outcomes. Another limitation is the requisite exclusion of 15% of the

potential cohort because treatment information was missing, mostly because participants did not sign medical record release forms during the CCSS study.

In conclusion, for men exposed to gonadal irradiation, there does not seem to be an increased risk of stillbirth or neonatal death among their offspring, which is reassuring not only for male survivors of childhood cancer but also for men exposed to ionising radiation in occupational or other settings. For women, however, high-dose uterine or ovarian radiation does seem to have important adverse effects, which are most likely to be attributable to uterine damage. Therefore, careful management is warranted for pregnant women treated with high-doses of pelvic irradiation before they have reached puberty.

Contributors

JDB, JJM, and DMG initiated the study and did the validation of self-reported pregnancy outcomes. LBS and JDB drafted the report. HMM did the main statistical analyses with input from LBS and JDB, and also participated in the validation study. MS and REW reconstructed radiation dose measurements for the cohort. LLR supervised the recruitment of participants and the gathering of data. ACM and JAW participated in data gathering, data cleaning, and dataset generation, assisted coordination with the CCSS, participated in the validation study, and aided in the interpretation of study variables. All authors contributed to the interpretation of the final results and editing of the report for scientific content. All authors saw and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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