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Fertility of Long-Term Male Survivors of Acute Lymphoblastic Leukemia Diagnosed During Childhood†

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Fertility impairments among men treated during childhood for cancer are known to occur after some, but not all, types of anti-cancer therapy. This is the first study to evaluate proven fertility among adult male survivors of childhood acute lymphoblastic leukemia (ALL). In a retrospective cohort study, proven fertility (ever fathered a pregnancy) was evaluated by self-report among 213 men treated for ALL before age 18 on protocols of the Children's Cancer Group (CCG). Controls (N = 145) were drawn from among male siblings. Overall, with a proportional hazards analysis, proven fertility of male survivors was not different from that of controls (relative fertility (RF) = 0.95, 95% CI 0.63–1.43). However, married men treated before age 10 with high dose (24 cGy) cranial radiotherapy (RT), without spinal RT, had only 9% of the fertility of controls (Relative risk, RR = 0.09, 95% CI 0.01–0.82). High dose cranial RT at older ages was not associated with a statistically significant fertility deficit (RR = 0.56, 95% CI 0.25–1.28). In this first study of proven fertility among men treated for childhood leukemia, the majority of survivors showed no evidence of fertility impairment compared to controls. However, men treated at a young age with high dose cranial RT may have impaired fertility. These results suggest that further investigation of men with these treatments is needed to confirm and extend these findings. Pediatr Blood Cancer 2004;42:364–372. © 2003 Wiley-Liss, Inc.

Key words: cohort study; fertility; male childhood leukemia survivors; radiotherapy

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. In the United States during the years 1990–1995, ALL constituted 18.5% of all newly diagnosed cancers in young people aged less than 20 [1]. As the continuing success of modern cancer treatment has raised 5-year relative survival for ALL to 77% [1], the lasting consequences of therapy on the everyday life of survivors become more important.

Among the chief concerns of cancer survivors are the maintenance of fertility and the possibility of starting a family. There is growing realization that fertility impairments arise from certain specific types of therapies and are present only in subgroups of survivors. Leukemia typically occurs early in childhood; long-term effects of current therapies on fertility cannot be evaluated for many years until survivors reach their reproductive years. As newer and more aggressive therapies come into use, continued long-term follow-up studies of large numbers of survivors are needed to tease out the effects of specific therapies on subgroups.

Treatment-related fertility deficits have been shown in retrospective cohort studies of survivors of the most common types of childhood cancer [2], but because of their young age at diagnosis leukemia survivors were not represented in large numbers in these studies. Thus, little is known of the effects on their fertility of treatments received by ALL survivors. In order to evaluate proven fertility among men who had survived leukemia diagnosed during childhood or adolescence, the National Institutes of Health collaborated with the Children's Cancer Group (CCG, since subsumed into the Children's Oncology

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Group), a US national collaborative oncology group, to interview a cohort of leukemia survivors diagnosed during childhood and adolescence and their sibling controls (CCG L891). This report is the first time that fertility among male ALL survivors has been evaluated.

PATIENTS AND METHODS

Eligibility Requirements

A list of all children newly diagnosed with ALL and treated on clinical trials was obtained from the CCG. Survivors were treated on the following CCG protocols: 101, 105, 106, 123, 139, 141, 141A, 162, 162A, 163, 903, 9998. To be eligible for the study, each participant had to be at least age 18, in continuous remission, and to have survived at least 2 years since diagnosis by October 15, 1990. Men were diagnosed from 1970 until 1987. Controls had to be at least 18 years of age within the 9 months following the survivor's interview. Telephone interviews (conducted between 1990 and 1991) were carried out with the survivors and controls only; no proxies were interviewed. The proportion of survivors who could not be located was 9.3%, and the refusal rate was 7.2%. The corresponding proportions for controls were 8.8 and 7.5%. Details of institutional and individual participation were previously published [3,4], and are provided in the companion paper concerning female fertility [5]. Institutional review boards at each participating institution approved the study and informed consent was obtained from all subjects. Among the 1,002 subjects who participated in this study 302 were male survivors and 189 were male controls.

Data Collection

Telephone interviews covered basic demographic information, education of parents and respondent, dates and duration of special schooling, marital status, including live-in relationships, their number and duration, history of sexual intercourse, including age at first sexual intercourse, number of sexual partners and frequency of intercourse in the past month, as well as pregnancy history, family plans, health, and risk-taking behavior. A series of questions asked about male health conditions, including testicular biopsy or radiation, serious injury to the testis, a sexually transmitted disease, varicocele, vasectomy, or cryptorchidism, and for partners, tubal ligation, hysterectomy, or oophorectomy. In order to determine attitudes towards pregnancy we asked a series of questions about family plans, including doctors' advice about having children and fertility tests, intentions about having children, attitudes towards the health of children, history of trying to become pregnant and frequency of intercourse, history of clinical infertility (''did you ever have sexual intercourse for one year or more without using contraception and not become pregnant?''), ever seek medical assistance with fertility issues, reasons, any diagnosis and any treatment for infertility. Due to time restrictions, we did not seek contraceptive history.

Proven fertility was defined as ever having fathered a pregnancy, whether that pregnancy ended in miscarriage or induced abortion, stillbirth, ectopic pregnancy, or a liveborn child. Since pregnancy can be a matter of choice as well as biology, respondents also completed a measure of affective state or mood, the Profile of Mood States (POMS). This is a 65-item self-report questionnaire designed to measure six mood states (tension/anxiety, depression, anger, confusion, vigor, and fatigue). Use of a total score to summarize the strong correlations between the subscales has proved to be a valid and useful way to report on the findings [4].

Data concerning treatment with radiotherapy (RT) and chemotherapy, relapse, and bone marrow transplant was abstracted from the survivors' charts maintained by the CCG. Doses of cranial RT specified by CCG clinical trials were either none, 18, or 24 Gy. However, clinical records indicated that some individuals received slightly different doses. For this reason, cranial RT was categorized as either none, 1–18 Gy, or more than 18 Gy, which was mostly 24 Gy. Among the male survivors in this study, 91.3% had been treated with any RT, 90.4% received cranial RT and of these, 16.1% were treated with cranio-spinal RT; most (82%) males treated with spinal RT received the higher cranial dose (24 Gy). All men treated with spinal RT also received cranial RT ($N = 34$). Alkylating agent chemotherapy was administered to 33.5% of males; cyclophosphamide (CY) was the most frequently administered alkylator. Men (31.4%) received a mean CY dose of 6 g/m^2 with a range from 0.9 to 28 g/m^2. Ten men received 15 g/m^2 or more of CY. Intrathecal methotrexate was administered to 84.5% of survivors.

STATISTICAL METHODS

This analysis included only men (both survivors and controls) who reported ever having had sexual intercourse. Person-years analyses and proportional hazards models were used to evaluate treatment-related effects on fertility and the influence of potentially confounding variables. For this analysis of rates of fathering a pregnancy, we used a time (years) to first pregnancy approach, considering the first pregnancy as an event; person-years were counted from age 18 or 2 years from diagnosis (for survivors) whichever was later. We excluded subjects whose first pregnancy was fathered before cohort entry, subjects with unknown age of first pregnancy, and males diagnosed at ages 18 or older. Thus, men who were eligible for this cohort analysis comprised 213 male survivors and 145 male controls. Table I lists their characteristics.

The probability of fathering a first pregnancy was defined as an event; event rates were calculated as the

TABLE I. Characteristics of Male Leukemia Survivors and Male Sibling Controls

	Survivors (N = 213)		Sibling controls (N = 145)	
	N	%	N	%
Age at leukemia diagnosis (years)				
<4	30	14.1	—	—
5–9	68	31.9		
10–14	63	29.6		
15–17	52	24.4		
Year of diagnosis				
1970–1974	66	31.0	—	—
1975–1979	73	34.3		
1980–1984	52	24.4		
1985–1986	22	10.3		
Age at interview (years)				
18–19	45	21.1	13	9.0
20–24	128	60.1	63	43.5
25–29	36	16.9	48	33.1
30–34	4	1.9	17	11.7
35–41	0	0	4	2.8
Ever married, or had a live-in relationship				
Yes	71/213	33.3	71/145	49.0
Age at first marriage (years)				
18–19	21	29.6	12	16.9
20–24	43	60.6	44	62.0
25–29	7	9.9	15	21.1
Ever fathered a pregnancy?				
Yes	46/213	21.6	49/145	33.8
Age when first fathered a pregnancy (years)				
18–19	14	30.4	11	22.5
20–24	26	56.5	26	56.1
25–29	6	13.0	12	24.5

number of events divided by person-years accrued within the time period. In order to control for age differences between survivors and controls and potential confounding arising from age at diagnosis and follow-up, age since cohort entry was divided into two intervals, 18–21 and 22+ years old. Thus, men could have contributed person-years to the first interval and, if they had not fathered a pregnancy, also contributed person-years to the second interval, depending on their age at interview.

Standard methods for analysis of continuous (*t*-test) and categorical (chi-square) data were used to compare characteristics of survivors and controls. The relative risk was used to define the difference between survivors and controls and was calculated as the event rate among survivors divided by the rate among controls. Associated hypothesis tests and confidence intervals were obtained under the assumption that the rates were constant over each age interval and that the observed number of events followed a Poisson distribution [5,6]. When methods appropriate to the proportional hazards model were used to estimate factors affecting the pregnancy rates [7], the proportional hazard assumption was evaluated by testing whether the relative risks varied with time.

Because the study design enrolled siblings as controls, we attempted to carry out the main analyses on only those survivors who had a same-sex match, i.e., a brother. There were 82 pairs where a male survivor had a male sibling control. Matching within families was done with logistic regression, conditioning on families. Analysis of data and statistical calculations were carried out with SAS (SAS Institute, Inc., Cary, NC).

On average, male survivors were diagnosed at age 10.9 years (Table I). At interview, survivors averaged 22.8 years of age, and controls were 24.0 years old. Only 33.3% of male survivors had married or had a live-in relationship compared to 49.0% of male controls. The ages at first fathering a pregnancy of each group were similar, but survivors had become fathers less often than controls.

RESULTS

Fertility and Family Plans

Table II compares survivors to controls on a series of questions related to fertility and family plans. Male survivors were significantly more likely than controls to be told by a doctor that they might have trouble having children ($P < 0.001$), and they were more likely than controls to be concerned about their children's health ($P = 0.006$) and their own fertility ($P < 0.0001$).

TABLE II. Comparison of Male Leukemia Survivors and Male Sibling Controls on Questions Related to Fertility

	Male leukemia survivors	Male sibling controls	
	N = 213	N = 145	
Fertility questions	% Yes	% Yes	*P*
Has a doctor ever said that you might have trouble having children?	32.9	1.4	<0.0001
Do you intend to have (more) children biologically?	68.9	70.4	0.7
Do you intend to have (more) children by adoption	3.3	1.3	0.4
Do you intend to have (no/more) children?	7.6	15.1	0.02
Are you concerned that your biological children might not be healthy?	37.0	23.2	0.006
Are you concerned that you might not be healthy enough to have children?	26.9	10.5	0.0001
Are you concerned that your partner isn't healthy enough?	10.6	7.1	0.3
Is either of you biologically unable to have children?	6.6	6.4	0.9
Did you ever have intercourse with the intention of starting a pregnancy?	14.1	20.0	0.4
If YES to previous question:			
Number of times you tried to father a pregnancy: once	70.0	62.1	0.5
Number of time had sexual intercourse while trying to get pregnant: once weekly	69.0	65.4	0.8
Ever have intercourse for more than one year without using contraception and not father a pregnancy	30.0	24.2	0.6

Notwithstanding, survivors seemed to be similar to controls on expectations of having a family, since they were equally likely to say that they would have (more) children biologically; and that they would adopt and to have intercourse with the intention of starting a pregnancy. Survivors were as likely as controls to know that they were unable to have children. More controls than survivors said that they wanted no (more) children.

Among the small number of subjects who were asked about pregnancy difficulties (N = 30 and 26, respectively), survivors were as likely as controls to say that they had trouble fathering a pregnancy after more than 1 year of trying (the standard definition of infertility). Three survivors and four controls saw the doctor about fertility issues. Of these, one survivor and three controls reported a pregnancy.

Male Health Conditions

Table III presents the proportions of male survivors and controls with a number of male health conditions related to fertility. Survivors were significantly more likely than controls to say that they had a testicular biopsy or testicular radiation or surgical removal of the testis, conditions that are associated with leukemia and its treatment. There were no differences between the two groups in the proportions with a serious testicular injury, or a sexually transmitted disease. More survivors than controls had cryptorchidism ($P = 0.04$).

In this analysis, among males, we could not detect any relationship between mood disturbances and having fathered a pregnancy, either overall, or among any of the treatment-related subgroups described below. Relapses occurred in 14 males, four were in the bone marrow, four in the central nervous system, and six were testicular relapses. All 14 received RT and only one reported a pregnancy. Four men had a second cancer and two of them reported fathering a pregnancy. Male survivors who had testicular biopsies (N = 109, reported on clinical records) were more likely to have fathered a pregnancy than survivors who did not (23.9 vs. 18.1%, $P > 0.05$).

Person-Years Analyses

Initially, pregnancy event rates among male survivors were compared to those among male controls by stratified analyses (Table IV). Overall fertility of male survivors was

TABLE III. Health Conditions Reported by Male Leukemia Survivors and Male Sibling Controls

	Male leukemia survivors	Male sibling controls	
Male health conditions	N = 213 (% yes)	N = 145 (% yes)	*P*
Did you ever have a testicular biopsy?	51.2	0	<0.001
Ever have irradiation of the testis?	6.2	0	<0.002
Ever have a serious injury to the testis?	3.3	4.1	0.7
Ever have a sexually-transmitted disease?	4.2	6.2	0.4
Ever have surgical removal of the testis?	1.9	0	0.06
Ever have cryptorchidism?	2.8	0	0.04

TABLE IV. Age-Specific First Pregnancy Rates of Male Leukemia Survivors and Male Sibling Controls According to Survivors' Treatment, per 1,000 Person-Years

	First pregnancies occurring between 18 and 21 years of age					First pregnancies occurring after age 21				
	Number of events	Number of PY	Rate ×1,000	RR	*P*	Number of events	Number of PY	Rate ×1,000	RR	*P*
Sibling controls	21	452.8	46.4			28	355.2	78.8		
Survivors, overall	23	621.7	37.0	0.80	0.47	25	312.0	80.1	1.02	0.93
Survivors by treatment										
Cranial radiotherapy by dose										
None	2	60.3	33.2	0.81	0.65	2	6.6	301.9	3.83	0.07
1–18 Gy	16	292.9	54.6	1.18	0.59	14	144.0	97.3	1.24	0.53
>18 Gy	5	268.5	18.6	0.40	0.08	9	161.4	55.8	0.71	0.37
Radiotherapy by site										
No spinal RT	22	517.7	42.5	0.92	0.82	22	244.7	89.9	1.14	0.65
Spinal RT	1	104.0	9.6	0.21	0.14	3	67.2	44.6	0.57	0.35
Alkylating agent chemotherapy										
With alkylators	10	436.5	29.8	0.64	0.27	9	87.6	102.7	1.30	0.49
No alkylators	13	185.2	54.0	1.16	0.65	16	224.3	71.3	0.91	0.73
Intrathecal methotrexate										
Ever	0	100.3	0	—	—	4	59.4	78.8	1.00	0.82
Never	23	521.4	44.1	0.56	0.88	21	252.6	83.1	1.05	0.86
Age at diagnosis										
0–9	3	251.5	11.9	0.26	0.03	4	57.4	69.9	0.85	0.82
10+	20	366.6	54.6	1.18	0.57	21	254.5	82.5	1.05	0.86

RT, radiotherapy. Event rate is the number of events, i.e., fathered a first pregnancy, per 1,000 person-years (PY), for men during these ages. Follow-up time is in person-years (PY). RR, relative risk, i.e., the probability of fathering a first pregnancy for survivors divided by the probability for controls.

TABLE V. Hazard Ratios and 95% Confidence Intervals for Association of Fertility Among Male Survivors Treated With 24 cGY Cranial Radiotherapy Under Various Analytic Models

Model restrictions	Hazard ratio	95% confidence interval	*P*
None (married and unmarried, all ages at diagnosis)	0.47	0.24–0.89	0.02
Married subjects only, all ages at diagnosis	0.44	0.21–0.91	0.03
Married and unmarried subjects, survivors diagnosed 0–9	0.40	0.12–1.32	0.13
Married subjects only, and survivors diagnosed 0–9	0.09	0.01–0.82	0.03
Married and unmarried subjects, survivors diagnosed age 10+	0.54	0.24–1.20	0.13
Married subjects only, survivors diagnosed age 10+	0.56	0.25–1.28	0.17

Proportional hazards models controlling for spinal radiotherapy; hazard ratios describe fertility of male survivors treated with 24 cGY cranial radiotherapy compared to those treated with lower doses, including no cranial radiotherapy.

lower than that of male controls during the ages 18–21 years (relative fertility, RF = 0.80), but the difference did not reach statistical significance. At ages older than 21, male fertility was closely similar to that of controls (RF = 1.02). However, there were differences among subgroups. Men treated before age 10 and whose first fatherhood occurred before age 22 had significantly depressed fertility (RF = 0.26, $P = 0.03$). Further, men treated with more than 18 GY cranial RT had depressed fertility (RF = 0.40, $P = 0.08$). RF of men treated with spinal RT was only 0.21, but was not statistically significant ($P = 0.14$). Among men whose first fatherhood occurred after age 21, there were no suggestions of treatment effects.

Potential confounding variables emerging from earlier analyses (Tables I–III) included marital status, concern about the health of children and their own health, low expectations of fertility based on physician advice, and age at interview. We constructed a series of proportional hazards models to evaluate RF differences and treatment effects while controlling for the effects of spinal RT. The effect of marital status was evaluated in a model restricted to married subjects, and effects of early age at diagnosis by restricting the model to those survivors diagnosed before 9 years (Table V). In the first model, without these restrictions, male survivors had only 47% of the fertility of male controls (RF = 0.47, $P = 0.02$). Restricting the model to married subjects did not affect RF. Married survivors who were diagnosed before age 9 had only 9% of the fertility of male controls ($P = 0.03$). Survivors diagnosed at older ages whether married or unmarried, did not have a statistically significant fertility deficit. A further series of models evaluated the influence of factors such as intention to have children biologically or by adoption, unable to have children, concern about the health of self, partner or children, frequency of intercourse, trouble fathering children, and ever have a sexually transmitted disease. In all cases, the RF deficit associated with 24 Gy cranial RT remained statistically significant, suggesting little or no effect of these factors (data not shown). As the most frequently administered alkylating agent, we evaluated the influence of cyclophosphamide (CY) on RF. Whether analyzed as ever/never taken, or by dose (split at 15 mg/m^2), CY had no independent effect on fertility, nor did inclusion of a term for CY change the hazard estimate for RF with high-dose CRT.

Survival curves (Fig. 1) show that, despite the short length of follow-up, the proportion of men who never fathered a pregnancy remained very high during the entire follow-up period for men treated at early ages with high dose CRT compared to other survivors or to controls.

A matched analysis on the 82 pairs (survivor and brother) confirmed the main finding of this study, that high-dose cranial RT is associated with a significant fertility deficit (hazard ratio = 0.33; 95% CI 0.1–1.0) compared to controls. We were unable to evaluate these results further with a matched analysis due to small numbers of survivors.

DISCUSSION

This is the first study to evaluate attained fertility in men who were long-term survivors of ALL diagnosed during childhood or adolescence. Overall, our results can provide reassurance to men who have had ALL. However, as with female ALL survivors [5] men who received certain therapies did show evidence of decreased fertility. In this study, men treated with cranial RT, without spinal RT, at a younger age—before age 9—were less likely to become fathers than controls; their fertility was only 9% (RF = 0.09, 95% CI 0.01–0.82) of the fertility of controls. Craniospinal RT was associated with a RF of 0.46, which was not statistically significant in these data ($P = 0.14$). Men treated at older ages showed no significant fertility deficit in this study.

This study also attempted to assess and rule out the effects of choice on fertility of male survivors. We found, not surprisingly, that male survivors had more concerns than controls on a number of factors related to family planning and male health conditions. A large fraction, one-third, had been told that they might have trouble having children; and many were concerned about their own health and that of their children. However, most wished to have children normally and only a small proportion were

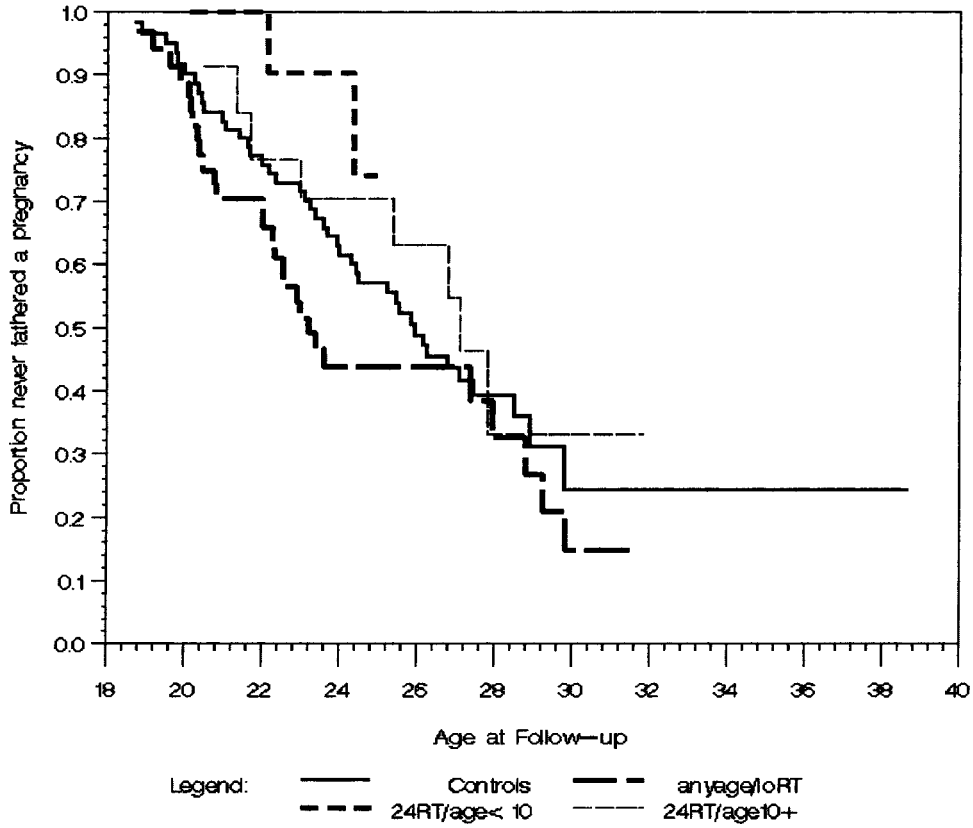

Fig. 1. Survival curves describing fertility experience of male survivors of childhood cancer and controls.

planning to adopt. When we adjusted for all these pregnancy risk factors, the fertility deficit of survivors was maintained, suggesting that survivors' cancer history may not have influenced their decisions to become fathers. We did not seek medical documentation of fertility tests, and, unfortunately, subjects' level of information about the nature and results of any fertility tests they might have undergone was too limited for this analysis. By application of a standardized inventory, the Profile of Moods States (POMS) we were able to evaluate survivors' mood at the time of interview compared to controls, and use these measures to control for possible fertility differences. We found that mood did not affect fertility for survivors.

The results of this study suggest that high dose cranial RT for childhood leukemia administered at a young age is associated with lowered fertility in men, independent of spinal RT. One possible explanation for this observation is that the hypothalamic-pituitary region of the developing brain is susceptible to the harmful effects of high-dose (>18 Gy) RT in a way that the brain of older boys is not, and demonstrates this in the form of reduced fertility. Although functioning of the hypothalamic-pituitary–testicular axis has been evaluated in patients treated for brain tumors as well as ALL, there have been no studies known to us that evaluated the effects of cranial RT alone, controlling for chemotherapy and testicular RT, and its effects on fertility. In a number of studies that documented testicular damage following chemotherapy high-dose cranial RT was also given [9]. In contrast, those studies that evaluated the effect of cranial RT without alkylating agent chemotherapy on gonadal functioning could not find evidence of impairment of testicular functioning [10,11]. It may be that more subtle endocrine measures are needed to detect damage [12].

However, data supporting our result is provided by studies of growth and growth hormone. Younger age at cranial RT adversely affected final height in ALL survivors [13]. Radiation-induced growth hormone deficiency appears to develop following cranial RT at doses greater than 18 Gy; prepubertal patients may be more at risk [14,15]. Further supporting information on sex hormone damage comes from a study that found subtle ovulatory disorders in girls with ALL who were treated before puberty with cranial RT [12].

Some earlier studies of gonadal functioning after treatment for childhood ALL did not clearly distinguish cranial RT from craniospinal RT and chemotherapy effects. Thus Quigley et al. [9] report elevated gonadotropins in both pre- and post-pubertal boys treated for ALL, but all received 24 Gy cranial RT and alkylating

agent chemotherapy. Testicular biopsies in this study were all abnormal. In a study from the Nordic countries, Siimes et al. [16] reported reduced testicular size and elevated gonadotropins in men treated for childhood ALL with alkylating agent chemotherapy and 24 Gy cranial RT. In this study, treatment before age 12 with cranial RT led to significantly reduced testicular size ($P = 0.05$).

Although we did not find evidence that high doses of CY were associated with reduced fertility, others have noted that other measures of testicular damage, such as abnormal sperm counts, damaged germinal epithelium, and altered gonadotropins can follow CY treatment, even before puberty [17–19].

Autopsy findings lend support to other clinical evidence for gonadal damage in males following treatment for leukemia. Both spermatogenic activity and tubular fertility index (TFI, a measure of the proportion of seminiferous tubules containing spermatogonia) were significantly reduced in male leukemia patients at autopsy, more so in adult males than in children [11,20].

The clinical pathway from potentially damaging exposures to clinical evidence of dysfunction to ultimately achieved (or not) fertility is complicated by the potential for recovery of gonadal function among men treated during childhood for leukemia. In a longitudinal evaluation of testicular biopsies, Wallace et al. [21] showed a return to normal morphology in a proportion of males followed up 10 years after treatment for ALL with alkylating agents without RT. There is little information on the factors that affect the sequence linking loss of function to recovery. It seems that alkylating agent chemotherapy offers some recovery potential. Direct testicular radiation exposure may not. However, in our study, attained fertility was less than expected even 10 years after treatment. More research into this aspect of cancer survival is surely needed.

We hypothesized at the outset that body image and psychosocial impairment might adversely impact on fertility. By the instruments used in our study, any impairment of mood at the time of interview could not account for the reduced fertility of survivors compared to controls.

A curious finding in this study was that 2.7% of survivors and no controls said that they had cryptorchidism (risk ratio: 1.67, 95% CI 1.53–1.81). Birth defects, most notably Down syndrome are more frequent in children with ALL, but no study suggests that cryptorchidism is more common [22–24]. Our observation may be a chance finding.

This study has a number of strengths and limitations. Among its strengths is the large size of the cohort, representing a single type of childhood cancer. Subgroups with specific therapy combinations were big enough to enable us to evaluate their effects on fertility. Use of a person-years approach allowed detection of strong effects based on relatively small numbers of events. One of the weaknesses was the lack of clinical documentation of fertility outcomes. This would have exceeded the resources available for the project, and is perhaps best done in a clinical setting. Our goal in designing this study was to enroll a complete cohort of children treated for ALL on CCG clinical protocols. We estimate that enrollment was about half that expected. We have no information on those survivors who did not participate, so cannot claim non-participation did not produce bias. It is possible that survivors treated at non-participating institutions received different treatments with different late consequences for fertility. Future studies of leukemia survivors should investigate this possibility. These risk estimates from this group of male survivors of ALL may be subject to bias since men are reporting to pregnancies to their wives/partners. Men may underreport pregnancies, especially those that do not come to term. Paternity was not determined for this study.

These results apply to about one-quarter (22.1%) of the men in this study; thus, three-quarters of the men treated for ALL showed little evidence of fertility impairment by the methods used here. Although these treatments are no longer used for childhood ALL, and RT has been replaced by other, safer and more efficacious treatments, nevertheless these survivors are the oldest survivors of ALL, and are now in their peak reproductive years. Detailed clinical assessments should be undertaken to confirm and extend these results.

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