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Reproductive Problems and Birth Defects in Survivors of Wilms' Tumor and Their Relatives

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In a retrospective cohort study of 47 Wilms' tumor survivors and their 77 sibling controls, female survivors had a fourfold excess risk (risk ratio, 4.1; 95% confidence interval, 1.7–10.1) for any adverse livebirth outcome, including birth defects, compared with their sibling controls. Wives of male survivors had no apparent excess risk for problem pregnancies. The families had a number of severe reproductive problems and major birth defects, such as primary amenorrhea in two survivors, bicornuate uterus in two survivors and one control, and mental retardation in one male survivor and a male control. The son of a female survivor died after bilateral Wilms' tumors. Birth defects in the offspring of female survivors are compatible either with intrauterine constraint, possibly due to radiation-induced fibrosis or with the complex of malformations associated with Wilms' tumor. Female survivors of Wilms' tumor appear to be at increased risk for a variety of reproductive problems, from sterility to fetal loss, early delivery, and birth defects in offspring. Furthermore, relatives of survivors of Wilms' tumor may be at risk of having associated birth defects, with clinically significant consequences.

Key words: low birth weight, late effects, long-term survivors, nephroblastoma, uterine anomalies

INTRODUCTION

Wilms' tumor (nephroblastoma) is a malignant neoplasm of the kidney that occurs annually in about 7 per million U.S. children aged 0 to 14 years [1]. It is associated to varying degrees with aniridia, hemihypertrophy, hypospadias, cryptorchidism, and renal anomalies; some patients with Wilms' tumor and aniridia have a constitutional deletion of the short arm of chromosome 11 [2,3]. The Wilms' tumor–malformation syndrome usually occurs sporadically [4], but some of its features, especially urogenital anomalies, have been seen in otherwise unaffected family members [5,6]. With continued improvements in survival after childhood cancer, questions are being raised about the late effects of therapy and, in particular, about the reproductive potential of survivors [7]. An increased rate of low birth weight and perinatal mortality has been reported in the offspring of female survivors of Wilms' tumor treated with abdominal radiation [8].

We conducted a follow-up study of childhood and adolescent cancer survivors and their sibling controls to answer questions about reproduction, including menstrual history, outcome of pregnancies, and frequency of birth defects in survivors and their children.

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METHODS

Five cancer centers collaborated with the National Cancer Institute: the California State Department of Health, the Connecticut Tumor Registry through the Yale University Epidemiology Unit, the University of Kansas Hospital, the University of Iowa Hospital, and the University of Texas M.D. Anderson Hospital, Houston, Texas. Each center identified those among its patients who met our criteria: a first histologically proven malignant neoplasm, including any intracranial tumor in individuals who were less than 20 years of age at diagnosis; a diagnosis made from 1945 through 1974; survival for at

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TABLE I. Reproductive Histories of Survivors of Wilms' Tumor and Their Sibling Controls

Characteristic	Males[a]		Females	
	Survivors	Controls	Survivors	Control
Subjects, total	21	39	26	38
Subjects with birth defects	3	2	7	4
Ever married	15	28	21	30
Ever pregnant	12	23	15	24
Completed pregnancies[b]	26	59	33	52
Elective abortions	4	1	3	9
Fetal deaths[c]	3	5	12	7
Livebirths	19	53	18	36
Low-birth-weight babies	0	2	3	1
Preterm infants	1	3	5	1
Infants with birth defects	0	2	6	3
Neonatal deaths	0	0	1	1
Livebirth sex ratio, M:F	0.90	1.41	0.80	1.00
Average birth weight of normal liveborn infants, g	3,590	3,440	3,460	3,350

[a]Pregnancies of wives.
[b]Excludes pregnancies in progress and induced abortions.
[c]Includes miscarriages, ectopic pregnancies, and stillbirths.

least 5 years from the date of diagnosis; and attainment of 21 years of age by December 31, 1979. Up to two controls were selected from among the survivors' siblings. They were matched as closely as possible on full sibship, sex, and age. Survivors and controls were interviewed in person or by telephone. Clinical records were abstracted for details of cancer and its treatment, birth defects, and infertility.

In all, 47 survivors (21 males and 26 females) of Wilms' tumor and their 77 sibling controls (39 males and 38 females) met study criteria. Ninety percent of the subjects were interviewed in person; 10% were interviewed by proxy. The survivors, none of whom had bilateral disease, were diagnosed before 1970 and between the ages 3 months and 17 years. All but two were diagnosed before age 12 or before menarche; no pregnancy occurred before diagnosis. Forty-three survivors were treated with surgery and abdominal radiotherapy; 16 also received chemotherapy (actinomycin D, vincristine, vinblastine, nitrogen mustard, bleomycin, Adriamycin, or cyclophosphamide). Some patients also received radiation to other sites such as the lungs. Of the four who received no radiation, three were treated surgically only, and one received nitrogen mustard after surgery.

Pregnancy outcomes were analyzed separately according to whether the reporting parent was a man or woman, because of recall problems commonly attributed to male reporting of reproductive events. Differences in the proportions of adverse reproductive outcomes between pooled survivors and pooled controls were tested for statistical significance ($\alpha = 0.05$, one-sided) using Fisher's exact test [9]. Because problem pregnancies tend to recur in any one couple, the risk ratio was estimated using regression models for prospective binomial data [10] adapted to account for this lack of independence [11]. In these models, the dependent variable was the observed proportion of fetal deaths (miscarriages, ectopic pregnancies, and stillbirths) among the pregnancies of each survivor and control. Pregnancies in progress at the time of interview and those terminated by elective abortion were excluded from analysis.

Initially, pregnancy outcomes for an individual were assumed to be independent and were analyzed using the GLIM computer program [12] with a log link function [10]. The sequence of GLIM directives described by Williams [11] was then used to accommodate extra-binomial variation and to obtain maximum quasi-likelihood estimates of the relative risk. The risks of adverse livebirth outcomes (preterm deliveries, low-birth-weight babies, neonatal deaths, and children with birth defects) among the livebirths of each survivor and control were obtained in a similar fashion. Duration of gestation was coded in months; preterm delivery was defined as gestation less than 9 months; low birthweight was 2,500 g or less.

RESULTS

Reproductive Histories of Male and Female Survivors

Marriage rates among survivors and controls were similar (Table I). Among married subjects, 80% of male survivors fathered a pregnancy compared with 82% of controls; 71% of female survivors became pregnant, compared with 80% of female controls. Although differ-

TABLE II. Risks of Adverse Pregnancy Outcomes Among Survivors and Like-Sexed Controls

Characteristic	Males[a]		Females	
	Survivors	Controls	Survivors	Controls
Fetal deaths[b]				
Subjects ever pregnant	11	20	15	24
Pregnancies[c]	22	58	30	43
Fetal deaths	3	5	12	7
Risk ratios (95% C.I.)[d]	1.5	(0.3–7.4)	1.5	(0.6–4.2)
Adverse livebirth outcomes[e]				
Subjects reporting livebirths	9	19	12	16
Livebirths	19	53	18	36
Adverse livebirth outcomes	1	5	9	3
Risk ratios (95% C.I.)[d]	0.4	(0.0–5.2)	4.1	(1.7–10.1)

[a]Pregnancies of wives of males.
[b]Includes miscarriages, ectopic pregnancies, and stillbirths.
[c]Excludes pregnancies in progress and induced abortions.
[d]Estimated by binomial regression with adjustment for extra-binomial variation (see text).
[e]Includes preterm deliveries, low-birth-weight babies, babies with birth defects, and neonatal deaths.

ences in birth weight between survivors and controls were not statistically significant, it is curious that children of both male and female survivors were heavier at birth than their cousins. One male subject said that he had fathered three of the four elective abortions reported by male survivors. He was separated and had had four marital-type relationships. He reported six pregnancies in all, including a stillbirth and two miscarriages. His recollection of dates and mates was inconsistent, casting doubt on the accuracy of events reported.

Fetal deaths. The number of fetal deaths in wives of male survivors and in wives of male controls was similar (Table I). Of 33 completed (i.e., no longer in progress at time of interview) pregnancies to female survivors, 12 ended in miscarriage. Six of 15 female survivors of proven fertility had at least 1 fetal death compared with 7 of 24 controls. The risk estimates from the binomial regression analysis were 1.5 for both sexes, an excess that did not reach statistical significance (Table II). The apparent excess of fetal deaths in female survivors was due to one woman with a bicornuate uterus whose five pregnancies all ended in miscarriage (case 7; Table III).

Adverse livebirth outcomes. Male survivors did not differ significantly from male controls in reported problems for their liveborn offspring (risk estimate = 0.4; 95% confidence intervals, 0.0–5.2). Nine male survivors reported 19 liveborn offspring, none of whom was said to have a birth defect. Among the 53 liveborn offspring of survivors' brothers were 2 whose fathers said that they had a birth defect; both had inguinal hernias, and one also had a hydrocele. However, more female survivors than controls had a low-birth-weight baby (3/18 or 17% vs. 1/36 or 3%), a preterm delivery (5/18 or 28% vs. 1/36 or 3%), or a baby with a birth defect (6/18 or 33% vs. 3/33 or 10%). The risk estimate for any adverse livebirth outcome to a female survivor was 4.1, a statistically significant elevation of risk (Table II).

Six of 18 liveborn babies born to 12 female survivors were malformed (Table III). These were one case of ventricular septal defect (VSD) (case 9); one case of cryptorchidism and umbilical hernia (case 2); one case of penile anomalies (case 10); two cases of hip dislocation (cases 11 and 12); and one case of umbilical hernia (case 13). All were confirmed by medical records. Among 36 infants of female controls, 2 had clubfoot (unconfirmed) (cases 12 and 14). Dividing the reproductive experiences of female survivors according to whether they were treated with radiotherapy alone (No. = 13) or in combination with chemotherapy (No. = 10) did not reveal any obvious differences related to treatment.

Birth Defects in Survivors and Siblings

Three male subjects reported birth defects. Two were unconfirmed—a hole in the heart at birth and a case of cryptorchidism. The third male was born prematurely with strabismus, inguinal hernia, and numerous dark nevi; he was also mentally retarded. Chromosome studies, done in 1980, were reported to be normal. None of these men's brothers had malformations, but anomalies were reported in two other male controls; one had an unconfirmed inguinal hernia at birth, and the other was mentally retarded.

Seven female survivors had birth defects (Table III, cases 1–7). One woman had hemihypertrophy of the left side of the face and tongue, left arm, and right leg at birth, she developed Wilms' tumor at age 3. The chromosome anomaly noted at age 11 [13] was subsequently shown to be a familial variant of no clinical

TABLE III. Reproductive Histories of 26 Female Wilms' Tumor Survivors

Case No.	Married*	Pregnancies	Live-births	Miscarriages	Elective abortions	Low birth weight	Liveborn <9 months gestation	Disorders in Family[b]
Survivors or controls with birth defects								
1	M	2	1	1	0	1	1	Survivor had hemihypertrophy [13] and Weber-Christian disease; only liveborn child was 3 months premature and died at 1 month. Sister died of leukemia.
2	M	3	2	0	1	2	2	Survivor had horseshoe kidney; son born at 34 weeks had undescended left testis, patent ductus arteriosus and small umbilical hernia; daughter was born at 7 months. Sister had right clubfoot.
3	M	—	—	—	—	—	—	Survivor had finger-tip umbilical hernia diagnosed at birth.
4	S	0	—	—	—	—	—	Survivor had ichthyosis of palms and soles at age 4. Brother had congenital clubfoot.
5	M	1	0	1	0	0	0	Survivor had cleidocranial dysostosis, congenital corneal defect, dysmorphic facies, defective aortic valve, and anomalous right subclavian artery.
6	M	0	—	—	—	—	—	Survivor had bicornuate uterus and double cervix.
7	M	5	0	5	0	0	0	Survivor had polydactyly of left hand and bicornuate uterus.
8	S	0	—	—	—	—	—	Survivor had a double uterus, was born prematurely and had a heart murmur diagnosed at age 24.
Birth defects in offspring								
9	M	4	4	0	0	0	0	Son had a ventricular septal defect and died at 8 months with bilateral Wilms' tumors.
10	M	1	1	0	0	0	1	Survivor had diabetes, onset at age 12. Son, born at 8 months weighing 3,740 g, had hypospadias, rotational anomaly of penis, and meatal stenosis.
11	M	1	1	0	0	0	0	Son had left hip click and asymmetrical thigh. Sister had a heart murmur at birth.
12	M	2	2	0	0	0	0	First daughter had acetabular dysplasia; second daughter was hospitalized for idiopathic thrombocytopenic purpura at age 4. Nephew had bilateral clubfoot.
13	M	7	2	3	2	0	0	Daughter had umbilical hernia.
14	M	1	1	0	0	0	0	Nephew had bilateral clubfoot.

Primary amenorrhea								
15	M	0	—	—	—	—	—	
16	M	0	—	—	—	—	—	
Other cases								
17	M	1	1	0	0	0	1	Mother had umbilical hernia; son was born at 8 months weighing 2,900 g.
18	M	1	1	0	0	0	0	Nephew died from embryonal cell carcinoma of testis at age 19.
19	S	0	—	—	—	—	—	Sister hospitalized for schizophrenia.
20	M	1	1	0	0	0	0	
21	M	2	1	1	0	0	0	
22	M	1	0[c]	1	0	0	0	
23	M	0	—	—	—	—	—	
24	M	0	—	—	—	—	—	
25	S	0	—	—	—	—	—	
26	S	0	—	—	—	—	—	Sister had Stein-Levinthal syndrome.
Total	21 M, 5S	33	18	12	3	3	5	

[a]M = married; S = single.
[b]Family member identified by relationship to survivor.
[c]Pregnancy in progress at time of follow-up.

significance (Dr. Dilys M. Parry, personal communication). Malformations in four other survivors were a finger-tip umbilical hernia on crying; a horseshoe kidney; cleidocranial dysostosis, and icthyosis of the palms of the hands and soles of the feet. Two female survivors had bicornuate uterus; one also had a double cervix (didelphic uterus) diagnosed by laparoscopy after menstrual irregularities; her ovaries had interstitial fibrosis and follicular distortion. She menstruated 1 day a month on taking birth control pills, had never become pregnant, and was presumably infertile. The second woman (a non-Hispanic white) with a bicornuate uterus also had polydactyly. She had a laparoscopy after five successive miscarriages with no liveborn children. She reported no menstrual problems.

Four female controls had birth defects. The sister of a female survivor was diagnosed as having a double uterus after workup for primary infertility of 5 years' duration (case 8). Other birth defects in two sisters were clubfoot (case 2) and a heart murmur (case 11), both unconfirmed. The sister of a male survivor said that she had scoliosis.

Menstrual History

Primary amenorrhea. Two of the 26 female survivors had never menstruated (cases 15 and 16); all of the 38 controls were post-menarcheal. One woman with primary amenorrhea had received 2,250 rads to the kidney and 4,200 rads to the pelvis over an 8-year period, from her diagnosis at age 1 to age 9. The second woman was treated at age 7 with 3,475 rads to the abdomen and a 3-month course of vincristine. At 16 she was diagnosed as having primary ovarian failure, on the basis of abnormal levels of follicle-stimulating hormone and luteinizing hormone, urinary estrogens, 17-ketosteroids, and 17-hydroxycorticosteroids. At that time she had retarded bone growth and had not developed secondary sexual characteristics. When interviewed for this study at age 23, she was 1.5 m tall (5 ft) and weighed 37.2 kg (82 lb).

Menstrual problems. The remaining 24 survivors had all commenced menstruating spontaneously at the same average age as the controls, namely 12.6 years. There were no statistically significant differences between survivors and pooled controls in frequency of menstrual irregularities (29% vs. 25%), skipped menses (17% vs. 11%), or other problems such as cramping or heavy bleeding (17% vs. 17%), although the direction of the differences suggests increased menstrual problems among survivors.

DISCUSSION

In our study women who survive Wilms' tumor and who reach their reproductive years with intact fecundity are four times more likely than female controls to have an adverse livebirth outcome, primarily an early delivery or a child with a birth defect.

Three of 18 babies born to female survivors weighed less than 2,500 g; all were preterm, and 1 died at 1 month (case 1). Two other babies were born before 9 months gestation and weighed more than 2,500 g. Because we asked for duration of gestation in whole months, it was impossible to determine whether these babies were appropriate or small for gestational age. These data support an earlier finding by Li et al. [8] of an excess of low-birth-weight babies and perinatal deaths in infants born to female Wilms' tumor survivors treated with abdominal radiation. Most of their excess neonatal deaths occurred in babies born weighing 2,500 g or less, as did our single neonatal death. Similarily, most of their 34 adverse reproductive outcomes were in infants who were born preterm. Taken together, both series suggest that the likely sequence of events starts with a preterm delivery of a liveborn or, if early enough, of a stillbirth. The low-birth-weight liveborn is then at increased risk for death in the neonatal period.

Abdominal radiation might result in pregnancy problems through its known action on elastic tissue [14]. The radiation-damaged uterus might not expand properly during late pregnancy, which, in some fashion, results in preterm delivery of low-birth-weight babies, as well as babies with deformations due to intrauterine constraint [15]. Uterine fibrosis (if present) may also impair placentation, perhaps leading to abruptio placentae, which can result in early delivery and perinatal death. Other possible explanations for these reproductive problems include positional deformities [16] due to irregular bone growth; internal adhesions resulting from repair of radiation damage, which might prevent the uterus from expanding properly; and genito-urinary malformations associated with Wilms' tumor complex, which may provide mechanical obstacles to successful fetal growth. For instance, in our series one female survivor with bicornuate uterus had had five miscarriages. Thus the reproductive problems seen here and elsewhere [8] might be due to preexisting malformations as well as to the treatment for the malignancy.

Children who develop Wilms' tumor have a higher than expected birth weight [17]. The weight of our respondents at birth was not available. In our study the birth weight of both male and female survivors' offspring was slightly higher than that of controls' offspring. The child with VSD who developed Wilms' tumor at 5 months weighed 2,500 g at delivery, following a full-term pregnancy.

Six female survivors of Wilms' tumor had offspring with major birth defects. Three are compatible with malformations seen as part of the Wilms' tumor com-

plex—cryptorchidism, umbilical hernia, and hypospadias. A fourth was a VSD in the child with Wilms' tumor. The remaining two birth defects—hip dislocation—are compatible with intrauterine constraint. If the excess of birth defects in the offspring of female survivors is associated with Wilms' tumor complex, then the offspring of male survivors also should have more of these types of birth defects; that they do not, in our study, may be due to faulty recollection by the fathers. Alternatively, the difference may be real and would support a role for intrauterine constraint following radiation-induced fibrosis.

The heritability of Wilms' tumor is said to be low [18]; in our series of 37 offspring of 47 affected individuals, 1 child had developed the tumor. However, the pleiotropic effects (i.e., many different clinical manifestations) of the gene(s) are evident, in the form of malformations, in other family members; this effect can be detected in a large survey such as ours, as well as in case reports of individual families [5]. Duplication of the ureters (among other anomalies) is seen frequently in individuals with Wilms' tumor [2,5,18], but there have been no reports of duplication anomalies of the female genital tract, even at autopsy in patients with Wilms' tumor. The frequency of these defects in the general population is unknown; estimates range from 1 to 5 per 1,000 females at delivery [19]. Another anomaly only recently reported to occur in excess in children with Wilms' tumor is septal defects [20]. Our single case of Wilms' tumor in an offspring of a woman with Wilms' tumor had a VSD, which may represent another manifestation of the Wilms' tumor–malformation complex.

It is possible that the association of uterine anomalies in Wilms' tumor families occurs even more often than is indicated here. Their presence or the presence of other types of midline fusion defects might explain some of the reproductive problems in these women. If so, then it may be wise to counsel female Wilms' tumor survivors and other female relatives of both male and female patients who are contemplating pregnancy to undertake non-invasive diagnostic procedures such as ultrasound. Primary amenorrhea in two women seems attributable to their radiotherapy. Ovarian failure, including primary amenorrhea, following abdominal irradiation is known to occur at high frequency—26% in one series [21–23]. We wondered whether the tendency of female survivors to have more menstrual problems could represent ovarian damage too slight to cause primary amenorrhea. Studies of reproductive function [21–23] did not investigate menstrual problems in women who continued to menstruate.

Women who have been treated for Wilms' tumor in the past are at particularly elevated risk for poor reproductive performance and should be followed in a high-risk clinic.

In summary, a variety of fertility problems occurs in female Wilms' tumor survivors. It is not possible at present to determine what proportion can be attributed to direct damage to the uterus from radiation, to indirect effects from other damaged organ systems, or to congenital anomalies of the female reproductive tract. Women who survive Wilms' tumor seem to be at increased risk for all three.

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