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Genetic Disease in Offspring of Long-Term Survivors of Childhood and Adolescent Cancer

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Summary

Numerous case series have addressed the concern that cancer therapy may damage germ cells, leading to clinical disease in offspring of survivors. None has documented an increased risk. However, the methodological problems of small series make it difficult to draw firm conclusions regarding the potential of cancer treatments to damage the health of future offspring. We conducted a large interview study of adult survivors of childhood cancer treated before 1976. Genetic disease occurred in 3.4% of 2,198 offspring of survivors, compared with 3.1% of 4,544 offspring of controls ($P = .33$; not significant); there were no statistically significant differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations. A comparison of survivors treated with potentially mutagenic therapy with survivors not so treated showed no association with sporadic genetic disease ($P = .49$). The present study provides reassurance that cancer treatment using older protocols does not carry a large risk for genetic disease in offspring conceived many years after treatment. With 80% power to detect an increase as small as 40% in the rate of genetic disease in offspring, this study did not do so. However, we cannot rule out the possibility that new therapeutic agents or specific combinations of agents at high doses may damage germ cells.

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Introduction

Survival in children and adolescents with cancer has increased significantly in recent decades, owing to advances in therapy. Although childhood cancer is still a life-threatening disease (Ries et al. 1994), overall survival of >70% has increased concerns for long-term adverse consequences of therapy, including effects on intellectual functioning and on fertility, as well as on genetic disease in offspring.

Concerns for the effects that cancer treatment may have on the health of an unconceived child are well founded. The high doses of radiation and chemotherapeutic agents used to treat childhood cancer cause alterations in DNA and are mutagenic in animal models and in in-vitro assays (Epstein 1990; Russell et al. 1981; Hales et al. 1992; DeMarini et al. 1989). Previous studies typically enrolled small numbers of survivors of many types of childhood cancer, and surveillance bias and reporting bias were not adequately controlled. Although these studies showed little or no increase in the risk of genetic disease in offspring, their methodological problems, including small sample size, make it difficult to draw reassuring conclusions (earlier studies have been summarized in Mulvihill and Byrne 1985; Mulvihill et al. 1987*a;* Hawkins 1991; Aisner et al. 1993; Dodds et al. 1993; Kenney et al. 1996; Green et al. 1989, 1997).

The issue of genetic disease in offspring of cancer survivors is important not only for counseling of cancer survivors but also for the larger question of induction of human germ-cell mutation by environmental agents such as radiation or toxic emissions. Elsewhere we examined the risk of cancer in the offspring of cancer survivors and found no significantly increased risk attributable to cancer therapy (Mulvihill et al. 1987*a*). In the present report we evaluate the hypothesis that cancer therapy causes no clinically detectable increased risk of genetic disease (defined as a birth defect, a cytogenetic

abnormality, a single-gene defect, or altered sex ratio) in cancer survivors' offspring conceived after their parents' treatment had ceased. Information on the presence of genetic disease in the offspring of cancer survivors and in the offspring of controls was obtained by interview; medical-record documentation was obtained where possible. To refine the exposures and outcomes, we restricted the final analyses to survivors with potentially mutagenic exposures and to offspring with sporadic genetic disease.

Although this is the first large study of childhood cancer survivors that evaluates the issue of germ-cell mutagenesis, and although our results are generally reassuring, nevertheless the older therapies received by this cohort may not predict the effects of newer protocols. However, the totality of late effects experienced by even older cancer survivors is still not known. Early mortality, even decades after treatment, is among the problems coming to light only now (Nicholson et al. 1994). More-recent cohorts, in their turn, must wait decades for their experiences to be described.

Subjects and Methods

Subjects

The National Cancer Institute collaborated with three hospital-based cancer registries (University of Iowa, University of Kansas, and University of Texas–M. D. Anderson Hospital) and two population-based registries (California Department of Health Services and Yale University for the Connecticut Tumor Registry) in the Five Center Study. Eligible cancer survivors must have met the following requirements: (1) histologically diagnosed malignant neoplasm or any CNS neoplasm in a person <20 years of age at diagnosis (basal- and squamous-cell skin cancers excluded), (2) diagnosis during 1945–75, (3) survival for $\geqslant 5$ years after diagnosis, and (4) attainment of 21 years of age by December 31, 1979. At the time of interview, survivors were asked for permission to review hospital and physician records and to contact siblings. When possible, as many as two controls were selected from among survivors' siblings. To be included, siblings had to have reached 19 years of age by December 31, 1979, and they were matched as closely as possible with regard to full sibship, sex, and date of birth, in that order.

Interviews were completed with 91% of eligible survivors and 91% of eligible controls. Reasons for not interviewing included failure to locate the subject or refusal by the subject, physician, or subject's next of kin. Proxy interviews were obtained for 10% of survivors and 4% of controls. No statistically significant differences were observed between survivors and controls, with respect to center, sex, or race. Interviews were conducted between August 1980 and April 1983 by trained interviewers. Both survivors and controls were asked about demographic characteristics, family history, and medical history. Details about tumors and therapy were abstracted from tumor-registry and hospital records. We defined "potentially mutagenic therapy" as either radiotherapy given below the diaphragm and above the knees or chemotherapy with an alkylating agent. Alkylating agents used were chlorambucil, cyclophosphamide, mechlorethamine, procarbazine, triethylenethiophosphoramide, busulfan, and melphalan. All other therapies were defined as "nonmutagenic."

Offspring

To be eligible for this analysis, a child of a *survivor* had to be born not less than 9 mo after the parent's cancer diagnosis, ensuring that the survivor had been exposed to some therapy before the child was conceived. Offspring of *controls* had to be born after their parent had reached the same age as the cutoff for the matched survivor sibling. These requirements yielded 2,198 offspring of survivors and 4,544 offspring of controls (table 1). At follow-up, the mean age of offspring of survivors and the mean age of offspring of controls were 10.6 years (SD = 7.2 years) and 11.4 years (SD = 8.0 years), respectively.

At interview, subjects were asked specifically about each conception and live-born child. One question inquired about "conditions sometimes present at or soon after birth" and referred the subject to two printed lists of conditions. The list entitled "Health Conditions at Birth" included the following: crossed eyes (strabismus); stomach blockage (pyloric stenosis); hole in roof of mouth (cleft palate); hare lip (cleft lip); rupture in groin (inguinal hernia); clubfoot; absent, fused, or extra fingers or toes; hole in the heart; hip displacement; diverted urinary stream (hypospadias); mongolism (Down syndrome); open spine (spina bifida); water on the brain (hydrocephalus); exposed brain (anencephaly); undescended testicle (cryptorchidism); prematurity; hyaline-membrane disease; and other conditions. The second list, entitled "Other Conditions," included achondroplasia, acrocephalosyndactyly, aniridia, Apert syndrome, cancer, dystrophia myotonica, Gardner syndrome, Marfan syndrome, multiple polyposis, neurofibromatosis, osteogenesis imperfecta, polycystic disease of the kidney, Recklinghausen disease, retinoblastoma, and Steinert syndrome. Efforts to verify the reported condition through review of hospital records, death certificates, and cancer-treatment records were made for each reported event. All disorders were included in the analysis unless records specifically denied the report.

"Genetic disease" was defined as a syndrome of malformations known to have an associated cytogenetic ab-

Table 1

Numbers of Cancer Survivors, Sibling Controls, and Offspring, by Sex

Group	No. of Survivors	No. of Controls
Subjects:		
Males	436	912
Females	626	1,120
Subtotal	1,062	2,032
Offspring:		
Of male subjects:		
Male offspring	468	1,022
Female offspring	448	1,021
Subtotal	916	2,043
Of female subjects:		
Male offspring	644	1,278
Female offspring	638	1,223
Subtotal	1,282	2,501
Total	2,198	4,544

normality (regardless of whether karyotypes were available), a single-gene (i.e., Mendelian) disorder, or any one of 15 common simple birth defects. A condition was described as "sporadic" if, in the opinion of two reviewing physicians, no relative had the same or related genetic disease. All recessive disorders were called "familial" (nonsporadic), since both parents were gene carriers. If a child had both a familial condition and a sporadic condition, then the child was classified as sporadic; when the number of genetic conditions was tabulated, only the condition determined to be sporadic was counted. χ^2 Analysis and Fisher's exact test were used to test statistical significance.

Results

Among the 1,062 eligible survivors, the most frequently observed type of neoplasm was Hodgkin disease, which accounted for 18% of survivors. Next in frequency were soft-tissue sarcomas (14%), thyroid-gland cancers (14%), and brain and other CNS neoplasms (12%). All other cancers accounted for the remainder. Mean age at diagnosis of cancer was 13.5 years and 14.0 years, for male and female survivors, respectively.

Table 2 classifies the treatment received by survivors, into potentially mutagenic and nonmutagenic therapies. The majority (72.8%) of survivors received nonmutagenic therapy, whereas 22.1% received therapy that could be classified as potentially mutagenic. The likelihood of being treated with potentially mutagenic therapy increased with time: 16% of survivors in this study who were diagnosed with cancer during 1945–54 received potentially mutagenic therapy, compared with 32% for the years 1965–74.

The rate of genetic disease in the offspring of survivors was 3.4%, compared with 3.1% in the offspring of controls (table 3); this difference was not statistically significant. The rate of genetic disease was also examined separately for male and female subjects; again, no significant difference between survivors and controls was observed. However, female survivors were more likely than male survivors to report children with a birth defect (4.0% vs. 2.5%, $\chi^2 = 3.1$; $P = .08$ [two-tailed test]). There was no difference between female controls and male controls.

When types of genetic disease (cytogenetic syndromes, single-gene defects, and simple malformations) were examined individually, the differences, in rates of these defects, between offspring of survivors and offspring of controls were not statistically significant (table 4), either overall or for each type. Down syndrome occurred at approximately the same rate in both groups—1.3/1,000 in survivors' offspring and 0.88/1,000 in controls' offspring. Neither rate was different from the expected rate of 0.8/1,000 (James 1993; table 5). Individual single-gene defects did not occur more frequently among survivors' offspring (data not shown). To see whether overall rates concealed differences in specific types of malformations, we compared rates of occurrence of 15 types of simple malformations in the two groups; no single type of malformation occurred to excess among offspring of survivors compared with offspring of controls (table 6). However, although the rates of heart defects were not different between survivors' offspring and controls' offspring, both rates were higher than expected (55/10,000 and 46/10,000, respectively, for septal defects), compared with the reported 1-year prevalence of all heart defects, which is 37/10,000 (Ferencz et al. 1985). But many heart defects are not diagnosed until later in childhood (Correa-Villasenor et al. 1991). Since offspring in the present study were 11 years of age at the time of the interview, it is likely that length of ascertainment explains the relatively high rate of heart defects.

Finally, we constructed a nested case-control study within this cohort study, to determine the odds of sporadic genetic disease in offspring of survivors only, comparing those who had received potentially mutagenic therapy versus those who had received nonmutagenic therapy. The odds ratio was virtually at unity (OR = .99; 95% confidence interval 0.48–2.01), indicating no association (table 7).

Survivor pregnancies and control pregnancies were analyzed with regard to possible confounding factors, including both parental age at birth of the offspring and exposures, during each pregnancy, to cigarettes, alcohol, rubella, herpes, and x-rays. These factors did not differ significantly between survivors and controls, with the exception of x-ray exposure during pregnancy; 20.8% of survivors' pregnancies were exposed to radiation,

Table 2

Anticancer Therapy Received by Survivors

Type of Therapy	No. (%)
Potentially mutagenic:	
Radiotherapy below diaphragm only	87 (8.2)
Radiotherapy below diaphragm/ chemotherapy with alkylating agent	49 (4.6)
Chemotherapy with alkylating agent only	46 (4.3)
Radiotherapy above diaphragm/ chemotherapy with alkylating agent	34 (3.2)
Radiotherapy below diaphragm/ chemotherapy (no alkylating agent)	14 (1.3)
Radiotherapy of unknown site/ chemotherapy with alkylating agent	5 (.5)
Subtotal	235 (22.1)
Nonmutagenic:	
No radiotherapy or chemotherapy	550 (51.8)
Radiotherapy above diaphragm only	193 (18.2)
Chemotherapy only (no alkylating agent)	18 (1.7)
Radiotherapy above diaphragm/ chemotherapy (no alkylating agent)	12 (1.1)
Subtotal	773 (72.8)
Unclassifiable:	
Radiotherapy only of unknown site	51 (4.8)
Radiotherapy of unknown site/ chemotherapy (no alkylating agent)	3 (.3)
Subtotal	54 (5.1)
Total	1,062 (100)

compared with 17.2% of controls' pregnancies ($\chi^2 = 12.8$; $P = .0003$).

To follow up on the unexpected finding in table 3—that is, that female survivors had more children with birth defects than did male survivors—we evaluated the percentage of offspring with genetic disease, both according to their parents' cancer and according to whether the genetic disease was sporadic or familial. None of these strata demonstrated a statistically significant difference ($P < .05$) between male survivors and female survivors, suggesting that this is a possibly spurious finding.

Alterations in the sex ratio of offspring of survivors may indicate genetic damage. We evaluated the sex ratio of offspring born to male survivors and to female survivors, compared with that of offspring born to controls (1.05 vs. 1.00, respectively, for males, and 1.01 vs. 1.05, respectively, for females; table 1). Neither difference reached statistical significance. Next, we restricted the comparisons to survivors only, comparing survivors treated with potentially mutagenic therapy versus those without this treatment. The sex ratio of offspring of male survivors receiving potentially mutagenic therapy was 1.06, versus 1.01 for offspring of male survivors treated with other therapies ($\chi^2 = 0.10$; $P = .8$). For offspring of female survivors, the respective sex ratios were 0.84 and 1.03, again not statistically significantly different ($\chi^2 = 1.7$; $P = .2$).

Discussion

Our study demonstrates no statistically significant difference in the risk of genetic disease among offspring of childhood-cancer survivors, compared with that in offspring of sibling controls. As the largest study to date with results consistent with findings from earlier reports, the present study provides reassurance that cancer therapy in use during 1945–75 did not carry a large risk for clinically detectable genetic disease in offspring conceived many years after their parents' therapy was finished. Although the relatively old age of participants means that relatively out-of-date therapies were being evaluated, it must be borne in mind that this situation will always apply. Studies of fertility and offspring in people exposed as children must always wait decades to be done. The mutagenic potential of today's therapies cannot be evaluated for perhaps decades, as we wait for these patients to become adults. Very large studies of patients treated for cancer with new drugs are needed to evaluate the potential for mutagenicity of new therapies. Two new studies of patient cohorts treated during the 1980s and early 1990s are currently being implemented.

The strength of this study lies in its statistical power and ability to control potential biases. The study's power to detect a doubling in the risk of genetic disease in offspring is >90% ($\alpha = .05$ [two-tailed test]); a nested case-control study with a power of 80% failed to find an increase in germ-cell damage unless such increase was >40% (table 7). Inclusion of controls meant reduced potential for surveillance bias. Increased medical sophistication of survivors would mean greater awareness of their children's health, leading to surveillance bias; inclusion of sibling controls who would share some of their siblings' health concerns would tend to equalize this bias. Offspring of both groups were similar in age,

Table 3

Genetic Disease in Offspring of Cancer Survivors and in Offspring of Sibling Controls, by Sex of Subject's Parent

	No. of Offspring with Genetic Disease/Total No. of Offspring, of[a]	
	Survivors	Controls
Females[b]	51/1,282 (4.0%)	75/2,501 (3.0%)
Males[b]	23/916 (2.5%)	67/2,043 (3.3%)
Total	74/2,198 (3.4%)	142/4,544 (3.1%)

[a] Comparison of survivors to controls yields $\chi^2 = 0.3$ and $P = .3$ (one-tailed test).

[b] Comparison of female to male survivors yields $\chi^2 = 3.1$ and $P = .08$ (two-tailed test).

Table 4

Genetic Disease in Offspring of Cancer Survivors and in Offspring of Sibling Controls

Type of Genetic Disease	No. (%) of Offspring with Genetic Disease, of	
	Survivors ($n = 2,198$)	Controls ($n = 4,544$)
Cytogenetic syndrome	4 (0.2)	6 (0.1)
Single-gene disorder	14 (0.6)	10 (0.2)
Simple malformation	59 (2.7)	127 (2.8)
Total[a]	74 (3.4)	142 (3.1)

[a] The totals are less than the sums of the categories because offspring may have more than one type of genetic disease.

making the potential for late ascertainment of birth defects comparable.

We found, as did Hawkins (1991), no significant differences in the sex ratio of offspring, whether overall, by the sex of the survivor parent, or between subgroups of survivors who did or who did not receive potentially mutagenic therapy. The theory is that exposed mothers could give birth to fewer male offspring because of an increase in X-linked lethal mutations, whereas exposed fathers could show an increased sex ratio because of X-linked dominant mutations (Scholte and Sobel 1964). In this study the sex ratio of offspring of females exposed to mutagenic therapy was decreased (0.84; not significant), compared with that in offspring of unexposed survivors, which would be expected if an effect were present.

There were no differences in rates of cytogenetic diseases, single-gene defects, or simple malformations in offspring when survivors were compared with sibling controls. However, compared with rates derived from registries and special studies, both groups in this study had higher rates of heart defects, possibly because of surveillance bias and/or a longer period of observation (Ferencz et al. 1985; James 1993). Many heart defects are diagnosed late in the 1st year of life and even into the 2d year of life (Ferencz et al. 1985). We and others have evaluated the suggestion that treatment with dactinomycin might be associated with heart defects, and, in the present study, we found no children with heart defects who were born to mothers exposed to dactinomycin (Green et al. 1991; Byrne et al. 1992). Investigators who evaluate the potential of cancer treatment to produce heart defects in offspring ascertained throughout childhood may find a spuriously raised rate if controls are not comparable.

Individuals with cancer-susceptibility syndromes whose cancer treatment includes mutagenic agents may produce excess offspring with either cancer or birth defects. Although theoretically this is possible, the excess would be small and, except in a special study, hard to detect. We did not see any suggestion of such an excess when we evaluated genetic disease on the basis of type of tumor.

The presence of germ-line mutations may be indicated by other outcomes, such as either cancer in the offspring or early spontaneous abortions. At least three studies have evaluated a potential raised risk of cancer in the offspring of survivors; none found a significantly greater risk than expected, after exclusion of known familial cancers (Mulvihill et al. 1987*b*; Dodds et al. 1993; Hawkins et al. 1995).

Recognized miscarriages have not been convincingly linked to cancer treatment considered as a mutagenic exposure. However, excess miscarriages occur among the pregnancies of women treated with radiotherapy below the diaphragm, possibly as a result of direct radiation of the uterus (Li et al. 1987; Byrne et al. 1988; Hawkins and Smith 1989;Hawkins 1994). Uterine anomalies also occur to excess in girls with Wilms tumor and may result in miscarriages independently of therapy (Nicholson et al. 1996).

Early unrecognized miscarriages may be observed as infertility, which is a common result both of treatment with high-dose abdominal radiotherapy and of alkylating agents. A previous report from this study showed that radiation therapy below the diaphragm depressed fertility in both sexes and that chemotherapy with al-

Table 5

Cytogenetic Syndromes in Offspring of Cancer Survivors and in Offspring of Sibling Controls

Cytogenetic Syndrome	No. of Offspring of	
	Survivors	Controls
Down	3	4
Turner	1	1[a]
Cri-du-chat	0	1
Total	4	6

[a] Parent stated that there were a "chromosome defect and no ovaries at birth."

Table 6

Simple Malformations in Offspring of Cancer Survivors and in Offspring of Sibling Controls, and Rate/10,000 Live Births

Malformation	No. of Offspring with Malformations (Rate/10,000 Live Births), of		P[a]
	Survivors	Controls	
Anencephaly	0 (0)	2 (1)	NS
Spina bifida	9 (2)	9 (4)	NS
Hydrocephalus	9 (2)	0 (0)	NS
Transposition of the great vessels	0 (0)	4 (2)	NS
Septal defects	55 (12)	46 (21)	NS
Patent ductus	23 (5)	13 (6)	NS
Cleft lip without cleft palate	14 (3)	7 (3)	NS
Cleft lip with or without cleft palate	9 (2)	9 (4)	NS
Tracheo-esophageal fistula	5 (1)	0 (0)	NS
Rectal atresia/stenosis	5 (1)	2 (1)	NS
Hypospadias	23 (5)	18 (8)	NS
Clubfoot	73 (16)	106 (48)	NS
Limb-reduction deformity	5 (1)	20 (9)	NS
Hip dislocation	55 (12)	66 (30)	NS
Renal agenesis	0 (0)	4 (2)	NS

[a] NS = not significant.

kylating agents was associated with decreased fertility in male survivors (Byrne et al. 1987). Although it may represent genetic damage, infertility is a complicated outcome, with many causes. A genetic etiology for infertility has not been studied.

Another possible reason for the lack of clinically observable genetic damage in our study may be that the mutant phenotype is below the threshold of detection for clinical events (Crow and Denniston 1984). More detailed biological studies of abnormalities in electrophoretic mobilities of proteins or alterations in DNA in future cohorts of cancer survivors may reveal more subtle damage (Mohrenweiser et al. 1989).

Despite the large sample size of our study, fewer than one quarter of the survivors were exposed to potentially mutagenic therapy. Furthermore, this study is limited in its power to detect small changes in either (*a*) the risk of new (spontaneous) mutations or (*b*) risks due to individual agents or specific combinations of agents. One study of 69,277 infants found, in the first 5 d of life, only 11 detectable malformations that could be attributed to new (spontaneous) mutations (Nelson and Holmes 1989). A much larger sample size than our study would be necessary to detect a doubling of this very low rate, and that would require international collaboration.

Quantification of the dosages of radiation and chemotherapeutic agents was not attempted in our survivors because of the complex nature of this estimation. As a result, we are unable to consider dose-response relationships. Similarly, we have not considered separately patients who received combinations of chemotherapeutic agents. Cancer treatments are continually being modified in the search for more effective, less toxic therapies. Although radiation doses have fallen, newer chemotherapeutic agents and higher doses of potentially mutagenic drugs are commonplace.

As new chemotherapeutic agents are introduced, concern over their potential for germ-cell damage will continue. Some drugs, such as diethylstilbestrol, are carcinogenic and teratogenic if administered during pregnancy (Mittendorf 1995). Although animal studies have limited ability to provide reassurance for human therapies, such studies nevertheless have provided much of the basis for the concern about germ-cell mutagenesis. For instance, cyclophosphamide in high doses causes heritable damage in F2 generations after exposure of male rats (Hales et al. 1992). After irradiation and treatment with urethane, a potent mutagen, male and female mice produced more offspring with tumors and congenital anomalies (Nomura 1982).

Several other types of studies have addressed the question of germ-cell mutation in humans exposed to radiation before conception. Extrapolation from animal models may be limited if, as is suggested, humans are less sensitive to the mutagenic effects of radiation (Neel et al. 1990). Other studies have associated radiation exposure of parents with a raised risk, in offspring, of leukemia, lymphoma, and Down syndrome (Gardner et al. 1990; Shu et al. 1994; Bound et al. 1995). The major study addressing this issue is the follow-up of offspring of atomic-bomb survivors in Hiroshima and Nagasaki. The indicators of genetic damage that were used were sex ratio, birth weight, anthropometric data, and frequencies of stillbirths, neonatal deaths, and gross malformations. Further studies include cytogenetic evaluation of individuals who had reached 13 years of age, examination of survival of offspring, and alteration of the electrophoretic patterns of proteins. None of these measures has shown any statistically significant association with parental exposure (Neel and Schull 1991). However, the authors point out that their findings are

Table 7

Risk of Sporadic Genetic Disease in Offspring of Cancer Survivors, by Type of Treatment Received

Sporadic Genetic Disease Status	No. (%) Administered Therapy Type	
	Potentially Mutagenic	Nonmutagenic
Positive	11 (2.7)	46 (2.7)
Negative	397 (97.3)	1,647 (97.3)

Note.—$\chi^2 = 0.0004$; $P = .49$ (one-tailed test).

in the direction expected if the hypothesis of genetic damage is correct. More recently, reports of germ-cell mutagenesis in animals after the Chernobyl disaster provide evidence for inherited mutations in this context (Ellergren et al. 1997).

Some difficulties inherent in the method used to collect information in this study must be recognized. The ascertainment of birth defects in survivor offspring and in control offspring relied on interviews with parents, with documentation sought for positive reports, a method that may underestimate the true rate (Rasmussen et al. 1990). However, if a difference exists, then one would expect to overestimate birth defects in offspring of survivors, because of their heightened knowledge of medical conditions, a bias in the direction of our hypothesis, a result that, again, tends to strengthen our negative findings. The use of interview data has an advantage, however, over either examination of newborns or review of medical records, in that conditions that may manifest themselves later in life are more likely to be ascertained. We were careful to exclude the possibility of teratogenic exposures, which might have led to a spurious association.

In conclusion, our study demonstrates no increased risk of genetic disease, as defined herein, in offspring of cancer survivors treated before 1976, compared with the risk in offspring of sibling controls. This information is important for clinical counseling of individuals who have survived childhood or adolescent cancer; patients can be reassured that their risk of a child with a birth defect is not likely to be greater than that in the general population. However, this study cannot rule out a small increase in risk(s) associated with exposure to specific agents delivered at high doses. Furthermore, the issue of biological changes associated with cancer treatment that do not result in functional or anatomic problems has not been addressed here and therefore remains an open question. The numbers of patients needed to satisfactorily answer questions about the potential mutagenicity of either single-agent therapies or specific combinations of therapies are considerable, and this problem must be addressed in a multi-institutional and/or international setting. The causes of most birth defects and childhood cancer are not at all understood. In a time of increasing rates of many cancers, including those of childhood (Gurney et al. 1996), comprehensive studies such as these become increasingly important and must be undertaken.

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