Letter to the Editor

Am. J. Hum. Genet. 70:1069, 2002

Genetic Disease in Offspring of Long-Term Survivors of Childhood and Adolescent Cancer Treated with Potentially Mutagenic Therapies

To the Editor:

With increasing survival to reproductive age among individuals treated during childhood or adolescence by anticancer regimens that included mutagenic agents—and, in many cases, with recovery of fertility—there is concern that germ cells may carry mutations that could lead to genetic disease in offspring. A large body of evidence suggests that radiation and alkylating agents are mutagenic toward germ cells (Witt and Bishop 1996). However, numerous studies evaluating genetic disease among offspring of individuals who previously received therapy for cancer with radiation or chemotherapy have not found evidence of significant increases in such genetic disease in the offspring (Byrne et al. 1998).

Nevertheless, the following questions remain: What is the upper confidence limit of the level of genetic disease that might have been induced but remained undetected? How can the information available be used in combination with future studies, with the goals of either detecting genetic disease or further lowering this upper confidence limit?

In the largest study of genetic disease among offspring of cancer survivors (Byrne et al. 1998), 2,198 offspring of 1,062 long-term survivors of childhood cancer and 4,544 offspring of 2,032 sibling controls were studied. Most of the data were analyzed to compare the 2,198 offspring of the overall group of cancer survivors with those of the sibling control group. However, only 235 of the 1,062 cancer survivors received "potentially mutagenic therapy," defined as either radiotherapy below the diaphragm and above the knee or chemotherapy with an alkylating agent. The 408 offspring of these 235 survivors constitute the group most likely to be at risk for genetic disease, since the other 1,790 offspring were born to parents who received treatment that would be expected either to be nonmutagenic or to have a low mutagenic potential. We thought it essential for proper interpretation of the results of this study, as well as for combining these data with the results of other studies, to separately report all of the data on genetic disease in the offspring, according to the mutagenic potential of the therapy received by their parents, which was not done in the original report (Byrne et al. 1998). Further-

Table 1

Sex of Offspring of Cancer Survivors (Stratified by Type of Treatment Received) and of Sibling Controls

Sex of Offspring Stratified by Sex of Subjects	No. of Offspring of Survivors Who Received[a,b]		No. of Offspring of Sibling Controls[b]	No. of Offspring of Survivors Who Received[c]	
	Potentially Mutagenic Therapy	Less- or Nonmutagenic Therapy		Potentially Mutagenic Therapy	Less- or Nonmutagenic Therapy
Male subjects:					
Male offspring	100	344	1,022	137	529
Female offspring	94	340	1,021	141	522
Subtotal (sex ratio)	194 (1.06)	684 (1.01)	2,043 (1.00)	278 (0.97)	1,051 (1.01)
Female subjects:					
Male offspring	98	513	1,278	140	794
Female offspring	116	498	1,223	165	731
Subtotal (sex ratio)	214 (0.84)	1,011 (1.03)	2,501 (1.04)	305 (0.85)	1,525 (1.09)
Total	408	1,695	4,544	583	2,576

[a] The sum of offspring of survivors treated with potentially mutagenic therapy and those treated with less- or nonmutagenic therapy is slightly less than the total number of offspring of the survivors, because the site of radiotherapy, in some patients, was not known.

[b] Data on offspring of subjects from original study (Byrne et al. 1998).

[c] Combined data (Hawkins 1991; Byrne et al. 1998).

more, since mechanisms of mutation induction differ by sex—because different germ cells are at risk—we have also stratified the data by the sex of the exposed survivor, which was not done consistently in the original study.

Table 1 presents the numbers of survivors and their offspring, stratified as described above. There were no significant differences between the male-to-female sex ratios among the offspring of the group treated with potentially mutagenic therapy and any of the control groups (the survivors treated with nonmutagenic therapy, the siblings of the survivors, or the combination of these two groups). However, when these data are combined with the second largest study of offspring of survivors of childhood cancer, which involved 161 offspring of survivors who had received potentially mutagenic therapy (Hawkins 1991), the male-to-female sex ratio among offspring of female survivors who had received potentially mutagenic therapy (0.85) was significantly lower than that for survivors exposed to nonmutagenic therapy (1.09) and, in further support of the result, was lower than that for the general population (1.06) (both $P = .05$, two-tailed χ^2 test). Although this shift is in the expected direction for induction of mutations, since sex-linked lethal mutations on the X chromosomes would selectively reduce the number of male offspring, the statistical significance of the result is marginal; future studies are needed to confirm or refute this observation.

Analysis of the incidence of all genetic disease among the offspring (table 2) showed no significant difference between the survivors who had received potentially mutagenic therapy and any of the control groups for male parents, female parents, or both sexes combined ($P > .4$). The frequency of genetic disease among offspring of women treated with nonmutagenic therapy was marginally higher ($P = .045$, two-tailed χ^2 test) than that among the offspring of sibling controls. Although the marginal statistical significance may be a result of chance, possible biological explanations for this unexpected finding are that some of the nonalkylating agents may be mutagenic or may cause uterine damage, or the higher frequency of uterine anomalies in girls with Wilms tumor (Nicholson et al. 1996) may result in deformations that mimic genetically caused birth defects.

The data in table 2 were used to determine the minimum percentage increase in incidence of genetic disease among the offspring of survivors treated with potentially mutagenic therapy that, if present, could have been detected with 95% confidence (one-tailed test for comparison of two proportions), because these treatments produce mutations in many other systems), with a power of 80% (Fleiss 1991). This increase was 85% when the control group comprised only the offspring of the siblings and 82% when the control group comprised the offspring of siblings and those exposed to nonmutagenic treatment. Note that these incidences are higher than the 40% increase reported in the original study, because we limited the group at risk to the offspring of survivors who had received potentially mutagenic therapy. Furthermore, when these data are combined with those of the Hawkins study (Hawkins 1991), there is still no evidence of an increase in genetic disease in the offspring of survivors treated with potentially mutagenic therapy, but the upper limit of the possible increase in genetic disease that would have remained undetected is slightly reduced, to 76%.

In table 3, the specific types of genetic disease are stratified according to the type of treatment received. There were no significant differences in the frequencies of the individual types of genetic disease between the offspring of survivors treated with potentially mutagenic therapy and those of any of the control groups ($P > .3$), whether the data were analyzed for the offspring of male and female survivors individually (see footnotes, table 3) or after grouping the offspring of male and female survivors.

Thus, this reexamination of the original report (Byrne et al. 1998) failed to detect any significant induction of genetic disease in offspring of survivors treated with potentially mutagenic therapy for childhood cancer, but it raised the upper limit on the percentage increase that can be ruled out. Further studies must be pursued to determine whether there are low levels of induced genetic

Table 2

Genetic Disease among Offspring of Cancer Survivors Treated with Potentially Mutagenic Therapy or with Less- or Nonmutagenic Therapy and among Controls, Stratified by Sex of Parent Who Was a Subject

	No. of Offspring with Genetic Disease/Total Offspring (%)		
Sex of Subject	Offspring of Survivors Treated with Potentially Mutagenic Therapy	Offspring of Survivors Treated with Less- or Nonmutagenic Therapy	Offspring of Sibling Controls
Male	6/194 (3.1%)	17/684 (2.5%)	67/2,043 (3.3%)
Female	7/214 (3.3%)	44/1,011 (4.4%)	75/2,501 (3.0%)
Total	13/408 (3.2%)	61/1,695 (3.6%)	142/4,544 (3.1%)

Note.—Data on offspring of subjects from original study (Byrne et al. 1998).

Table 3

Genetic Disease among Offspring of Cancer Survivors Treated with Potentially Mutagenic Therapy, or with Less- or Nonmutagenic Therapy and among Control Subjects, by Type of Genetic Disease

	No. (%) of Offspring with Genetic Disease		
Type of Genetic Disease	Offspring of Survivors Treated with Potentially Mutagenic Therapy	Offspring of Survivors Treated with Less- or Nonmutagenic Therapy	Offspring of Control Subjects
Cytogenetic syndrome	0 (0.0%)	4 (.2%)[a]	6 (.1%)
Single-gene disorder	1 (.2%)[b]	13 (.8%)[c]	10 (.2%)
Simple malformation only	12 (2.9%)[d]	44 (2.6%)[e]	127 (2.8%)
Total	13/408 (3.2%)	61/1,695 (3.6%)	142/4,544 (3.1%)[f]

Note.—Data on offspring of subjects from original study (Byrne et al. 1998).

[a] All cases (one in the offspring of a male survivor and three in offspring of female survivors) were sporadic.

[b] The single-gene disorder occurred in the offspring of a female subject and was familial.

[c] All but one of these cases (in an offspring of a male survivor) were familial.

[d] Six of the simple malformations (all sporadic) occurred in the offspring of male subjects, and six (five of which were sporadic) occurred in the offspring of female subjects.

[e] Twelve cases (11 of which were sporadic) occurred in offspring of male subjects and 32 (27 of which were sporadic) in offspring of female subjects.

[f] One of the offspring had both a single-gene (familial) disorder and simple malformations.

disease among offspring of patients treated with potentially mutagenic anticancer agents and, if no increases are found, to provide data for meta-analyses to further reduce the level of increase in genetic disease that can be excluded.

Marvin L. Meistrich[1] and Julianne Byrne[2]
[1]*Department of Experimental Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston; and* [2]*Children's National Medical Center, Washington, DC*

References

Byrne J, Rasmussen SA, Steinhorn SC, Connelly RR, Myers MH, Lynch CF, Flannery J, Austin DF, Holmes FF, Holmes GE, Strong LC, Mulvihill JJ (1998) Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. Am J Hum Genet 62:45–52

Fleiss JL (1991) Statistical methods for rates and proportions. Wiley and Sons, New York, pp 38–49

Hawkins MM (1991) Is there evidence of a therapy-related increase in germ cell mutation among childhood cancer survivors? J Natl Cancer Inst 83:1643–1650

Nicholson HS, Blask AN, Markle BM, Reaman GH, Byrne J (1996) Uterine anomalies in Wilms' tumor survivors. Cancer 78:887–891

Witt KL, Bishop JB (1996) Mutagenicity of anticancer drugs in mammalian germ cells. Mutat Res 355:209–234

Address for correspondence and reprints: Dr. M. L. Meistrich, Department of Experimental Radiation Oncology, Box 66, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. E-mail: meistrich@mdanderson.org

The authors would like to thank Louise Strong for discussions regarding this analysis.

0002-9297/2002/7004-0030$15.00