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Malignant Tumors during the First 2 Decades of Life in the Offspring of Atomic Bomb Survivors

Y. Yoshimoto,* J. V. Neel,† W. J. Schull,‡ H. Kato,* M. Soda,* R. Eto,* and K. Mabuchi*

*Radiation Effects Research Foundation, Hiroshima and Nagasaki; †Department of Human Genetics, University of Michigan Medical School, Ann Arbor; and ‡Center for Demographic and Population Genetics, University of Texas, Houston

Summary

The risk of cancer (incidence) prior to age 20 years has been determined for children born to atomic bomb survivors and to a suitable comparison group. Tumor ascertainment was through death certificates and the tumor registries maintained in Hiroshima and Nagasaki. The rationale for the study stemmed from the evidence that a significant proportion of such childhood tumors as retinoblastoma and Wilms tumor arise on the basis of a mutant gene inherited from one parent plus a second somatic cell mutation involving the allele of this gene. Gonadal radiation doses were calculated by the recently established DS86 system, supplemented by an ad hoc system for those children for one or both of whose parents a DS86 dose could not be computed but for whom an ad hoc dose could be developed on the basis of the available information. The total data set consisted of (1) a cohort of 31,150 live-born children one or both of whose parents received >0.01 Sv of radiation at the time of the atomic bombings (average conjoint gonad exposure 0.43 Sv) and (2) two suitable comparison groups totaling 41,066 children. Altogether, 43 malignant tumors were ascertained in the children of exposed parents, and 49 malignant tumors were ascertained in the two control groups. A multiple linear regression analysis revealed no increase in malignancy in the children of exposed parents. However, examination of the data suggested that only 3.0–5.0% of the tumors of childhood that were observed in the comparison groups are associated with an inherited genetic predisposition that would be expected to exhibit an altered frequency if the parental mutation rate were increased. There is thus far no confirmation of the positive findings that Nomura found in a mouse system.

Introduction

This paper will report on the occurrence of malignant tumors prior to age 20 years both in the children born between the years 1946 and 1982 to survivors of the atomic bombings and in a suitable control group. The justifications for having employed the finding as an indicator of the potential genetic effects of the atomic bombs are as follows: For many years certain of the tumors of childhood, of which retinoblastoma serves as the prototype, have been known to be occasionally familial—and, when familial, usually in the pattern of dominant inheritance (reviewed in Vogel 1979). In 1971, Knudson suggested that children with retinoblastoma result from either of two mechanisms (Knudson 1971). On the one hand, the child may inherit from one of its parents an altered gene or a deletion at the retinoblastoma locus. A second somatic cell event in the child results in a change in or loss of the normal allele of this gene in a retinoblast, in consequence of which this cell is now homozygous (or hemizygous) for an abnormality at this locus, and a clonally derived retinoblastoma results (and, as was suggested later, there sometimes also result, by the same mechanism, osteosarcoma [Kitchin and Ellsworth 1974], other mesenchymal tumors [Friend et al. 1987], and breast cancer [Lee et al. 1988]). Multiple such somatic cell events result in multiple foci of retinoblastoma or sarcoma. Cytological and molecular evidence for the nature of both the first and second events has been forthcoming from sev-

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Address for correspondence and reprints: James V. Neel, Department of Human Genetics, University of Michigan Medical School, M4708 Medical Sciences II, Ann Arbor, MI 48109–0618.

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eral laboratories (Cavenee et al. 1983; Friend et al. 1986; Lee et al. 1987; Bookstein et al. 1988). Technically, then, inherited retinoblastoma is a recessive trait. In some affected children (in fact, the majority), on the other hand, both of the necessary events occur in a somatic cell (e.g., retinoblast, osteocyte), as a consequence of which the child is now homozygous for an abnormality at this locus in this cell; but, although the child develops a malignant tumor, he or she does not transmit an altered allele to the next generation because the germ line is not affected. Parental radiation would not be expected to increase the frequency of this type of retinoblastoma.

Wilms tumor also rather clearly meets the specifications of this model (reviewed in Matsunaga 1981; Dao et al. 1987), as, probably, does neuroblastoma (Knudson and Meadows 1978; Bundey and Evans 1982). Although the evidence is less extensive, childhood gonadal dysgerminoma, pheochromocytoma, hepatoblastoma, and, more problematically, rhabdomyosarcoma and the central nervous system tumors may have a similar but less pronounced genetic basis (reviewed in Knudson and Meadows 1978; Koufos et al. 1985; Schimke 1985; Knudson 1986). A further argument for the genetic basis of some of these tumors is the reportedly more frequent occurrence of *other* malignancies in the parents of affected children (Hartley et al. 1986; Li et al. 1988).

The leukemias and the malignant lymphomas of childhood have not yet been shown to exhibit a pattern comparable to retinoblastoma or Wilms tumor (Videbaek 1947; Steinberg 1960), but, because of the poor survival of affected children in the past, the appropriate systematic genetic data to support an opinion concerning the proportion of the leukemias consistent with the above-described model are not yet available. There are, however, anecdotal data concerning familial clusterings of childhood leukemia (see Gunz et al. 1978), and the risk of leukemia in siblings of children with leukemia is increased about two- to fourfold (Miller 1971; Draper et al. 1977). Furthermore, concordance rates in identical twins are about 20% (MacMahon and Levy 1964). The observation that in more than half the concordant twin pairs described in the literature the leukemia was diagnosed during the first year of life, whereas overall the peak incidence is between 3 and 5 years of age (Zuelzer and Cox 1969), is consistent with (but does not demand) the hypothesis that the very-early-onset cases reflect a mutational event in one of the parents.

In recent years a variety of approaches has led to the recognition of a second class of genes concerned with carcinogenesis, generically termed proto-oncogenes, which as a result of a mutational event in a somatic cell become the basis for a clonally derived malignancy. A related phenomenon is the implication of precise chromosomal regions, including fragile sites, in the chromosomal breakpoint associated with various clonally derived leukemias, lymphomas, and other malignancies. The number of such proto-oncogenes is thought to be of the order of 50 (reviewed in Bishop 1987; Human Gene Mapping 9 1987), and the list continues to grow, although hard data relating many of those proto-oncogenes to the malignant transformation are still lacking, and there is evidence that, with respect to the childhood malignancies, the number could be relatively limited (Koufos et al. 1985). We are not aware of any clear evidence that a transmitted (germ-line) mutation in a proto-oncogene can be the basis for a childhood malignancy, but, if there are such mutations, in principle they should be no less responsive to radiation than are mutations in tumor-suppressor genes.

Finally, Batra and Sridharan (1964) reported an increase in leukemia persisting over 4 generations in the offspring of radiated mice, but Kohn et al. (1965) saw no increase in leukemia or other tumors under comparable experimental circumstances. More recently, Nomura (1982, 1983, 1986) has reported an increase in the frequency of a variety of adult-onset-type tumors in the offspring of irradiated male mice, an increased frequency which persisted for the several subsequent generations during which the strain was observed. This latter observation created an experimental precedent which in part motivated the present study. Moreover, Shiono et al. (1980) have reported a relative risk of childhood malignancy of 2.61 in the offspring of women who received preconception diagnostic X-ray exposures to the ovaries, the risk being computed from a comparison with matched controls ($P = .021$). An estimated mean ovarian exposure was not given for these women, but it may be presumed to be <0.01 gray (Gy).

Our hypothesis in investigating the possibility of an increase in malignancy in the children of survivors of the atomic bombings was that the proto-oncogenes and tumor-suppressor genes collectively constitute a sufficient target such that the frequency of cancer of relatively early onset might be a suitable indicator of the genetic effects of the atomic bombs, a thesis reinforced by the experimental findings just cited.

Design of Study

Definition of Sample and Sources of Data

The Radiation Effects Research Foundation (RERF), under whose aegis this study was conducted, maintains two sources of information concerning malignant disease in childhood. The first is a study of the survival of the children live born to the survivors of the bombings and to suitable control groups: the F_1 Mortality Study (see Kato et al. 1966; Neel et al. 1974; Schull et al. 1982). For the purposes of this study, three cohorts were identified in 1959, namely, (1) all children live born between 1946 and 1958 to survivors residing in Hiroshima or Nagasaki, one or both of whom were <2,000 m from the hypocenter at the time of the bombing (ATB), i.e., proximally exposed; (2) an equal number of age-, sex-, and city-matched children born either to survivors residing in either city ATB, both of whom were >2,500 m from the hypocenter, or to parents one of whom was >2,500 m (i.e., distally exposed) ATB and the other of whom was not in the city (NIC) ATB; and (3) an equal number of age-, sex-, and city-matched children born in either city to parents who ATB were NIC. Children born prior to May 1, 1946 (i.e., in utero ATB) were excluded from the cohorts. The radiation received by the more distally exposed ATB is generally assumed, on the basis of the current data on the atomic bomb explosions, to have been negligible. Children born to parents whose exposures occurred within the 2,001–2,500-m radius from the hypocenter have not been followed up because, although the gonadal doses are thought to be quite small at this distance, they are difficult to estimate and because the considerable number of children born to such parents would not be very informative with respect to the genetic effects of radiation. The original cohorts have been periodically enlarged by the inclusion of (*a*) all additional children born to proximally exposed parents between 1959 and 1984 and, again, (*b*) suitably matched controls.

The three cohorts combined consisted of 76,817 entries. However, for the purposes of this analysis, it was necessary to exclude 799 individuals either because they did not have Japanese citizenship (and so were not entered in the Japanese family record [*koseki*] which was the basis for follow-up) or, if Japanese, because their survival was uncertain. An additional 3,790 individuals were excluded because of inadequate data on parental exposure, and 12 individuals were excluded because they were born after the cutoff date of 1982 (see below). These deletions plus the repositioning of the hypocenter in Nagasaki, the introduction of new data on radiation exposure, and various other technical factors have considerably altered the originally envisioned 1:1:1 ratio of the three cohorts. The viability of the children in the cohorts is determined on an approximately 3-year cycle by a search of the *koseki* record to determine whether an individual is alive or dead; if the individual was listed as dead, the cause of death was transcribed from schedules based on death certificates kept in health centers throughout Japan. The last complete and verified cycle of checking death certificates terminated in 1985.

The second source of information is the tumor registries maintained (with assistance from RERF) by the Medical Association of Hiroshima and the Medical Association of Nagasaki, registries dating from 1957 and 1958, respectively (Ikeda et al. 1986; Monzen and Wakabayashi 1986). These registries overlap with the F_1 Mortality Study with respect to children who die of cancer, but the tumor registries are the only source of information on living children with malignancies. It is difficult to estimate the completeness of the tumor registries with respect to cancer morbidity, but, given the various procedures that have been adopted, we believe reporting of recognized malignant tumors in childhood is at least at the 90% level. Because of the cycle on which the registries are maintained, the data on morbidity are thought to be as complete as possible only through 1982. Accordingly, in order to bring the data from death certificates and the data from the tumor registry into temporal concurrence, we have included in this analysis only the registry cases ascertained through 1982 that occurred prior to age 20 years.

Diagnostic Standards

In both the F_1 Mortality Study and the tumor registries, diagnoses have been coded in keeping with successive publications of the World Health Organization's International Classification of Diseases (editions 7–9 plus the International Classification for Cancer of 1976). These coded entries were reviewed independently by two of the authors, and, for all possible or probable diagnoses of malignant tumor, the death certificates and the verifying medical information contained in the files were reexamined. Diagnoses of benign tumors, such as meningiomas, papillomas, lipomas, skeletal exostoses, polyps, or neurofibromas, were specifically excluded from consideration. For 73 individuals there was

histological verification of the diagnosis, but eight of the diagnoses in individuals still alive rest on clinical/operative findings without tissue studies, and another 11 diagnoses in deceased individuals rest only on clinical evidence/death certificates.

De Novo Origin of the Potentially Inherited Malignancies in the Study

Because of the extensive literature on inherited forms of retinoblastoma and Wilms tumor, we have conducted studies of the occurrence of cancer in the 19 nuclear families of individuals with these tumors, as well as with osteosarcoma, renal sarcoma, embryonal carcinoma of the testes, and neuroblastoma. Data are available on 38 parents, 57 siblings, and eight children. There have been seven diagnoses of cancer among the parents (one each of the urinary bladder, maxillary sinus, thyroid, pancreas, esophagus, colon, and liver). No cancer deaths were reported among siblings and children. The possibility of cancer occurring in the living members of these nuclear families was also explored through inquiries to the tumor registries of Hiroshima and Nagasaki, the Japanese National Retinoblastoma Registry, and the Japanese Childhood Malignancy Registry, with no additional reports of malignancies being encountered. Thus all the children in this series who have the above-enumerated malignancies can be considered to result either from mutation in the germ line of the preceding generation plus a somatic cell mutation or from a double somatic cell mutation in their generation.

Dosimetry

The procedures for assigning organ radiation doses to the individual survivors who are the parents of the children in the present study have recently been revised (Roesch 1987), resulting in the Dosimetry System 1986 (DS86). This replaces the previous tentative dosimetry system known as "T65D" and "T65DR" (Milton and Shohoji 1968). DS86 doses have been assigned to both parents of each of 67,574 of the children included in the study. For the parents of the remaining 4,642 children, the recently developed DS86 system cannot be used to assign gonadal doses, either because in the early years of the study the radiation histories were not sufficiently detailed to supply all the parameters necessary for the assignment of a DS86 dose or because of the present inability of the DS86 system to cope with the complex shielding ATB of some of the survivors. These individuals have been assigned gonadal doses on the basis of an empirical conversion from the previously assigned T65DR doses, the conversion factors being derived from persons for whom both T65DR and DS86 doses were available (for detailed description, see Otake et al. 1990). Individuals not in city ATB have, of course, been assigned zero doses. Resorting to this procedure added to the sample a total of 4,265 children whose parents were estimated to have received $\geq$0.01 Sv (a 15.9% increase in the sample of proximally exposed) but only 377 children (0.9%) whose parents sustained exposures less than this. The discrepancy is of course due to the greater ease in determining dose for distally exposed parents. We will use the term "extended data set" to refer to the sample of children whose parents were assigned either a DS86 dose or an ad hoc dose.

The unit of ionizing radiation is the gray (1 Gy = 100 rad), but, because of the mixed gamma-neutron exposure, gonadal doses will be expressed in sieverts (1 Sv = 100 rem). In calculating sieverts, the relatively small neutron component of the radiation exposure has been assigned an RBE of 20. In accordance with past RERF policy, surface doses (kerma) estimated to be >6 Gy were truncated at that value. Jablon (1971) has placed the total error involved in assigning individual doses based on the previous T65R schedule at $\pm$30%; we assume a similar error for the DS86-assigned doses.

Statistical Procedures

The data were analyzed on the basis of a linear multiple regression model. We treat cancer in an individual as a binary observation, so $Y = 1$ if we observe a cancer in an individual and 0 otherwise. We assumed that Y had an expected function of the following form:

$$E(Y_{ij} \text{ given } x,d) = P_{ij}(x,d) = g_{ij}(x) + b_4\, d,$$

where $P_{ij}(x,d)$ is the probability ($0 < P < 1$) of Y_{ij} in an individual with parental dose d and having background characteristics city i ATB, sex j, and x years between the bombing and the birth of the subject. This simple linear model is a first approximation to an exponential curve of the kind described as a "one-hit" model.

It is assumed that the three background characteristics (city, sex, and years between bombing and birth) act additively on the background rate $g_{ij}(x)$. $g_{ij}(x)$ can then be expressed by the function

$$g_{ij}(b_0, b_1, b_2, b_3, x) = b_0 + b_1\, I(i) + b_2\, I(j) + b_3(x - \bar{x}),$$

where $I(i) = 1$ if i is Hiroshima and $I(j) = 1$ if j is male but both are zero otherwise and where x is equal to the years between bombing and birth ($\bar{x}$) is the sample

mean of x, 10.5 years). The parameters of the model have been calculated by two different methods, namely, (1) the method of least squares and (2) the method of maximum likelihood for binary observations, where P ranges from 1 to 0 and where combined parental gonad dose is truncated at 7 Sv.

Results of Analysis

The estimated gonadal radiation exposures of the parents of the 67,574 children for whom parental DS86 doses are available are shown in table 1. Among the children of those parents receiving increased amounts of radiation (≥0.01 Gy), the conjoint parental gonad exposure for the cities combined averaged 0.002 Gy of neutron radiation and 0.358 Gy of gamma radiation, or 0.405 Sv; but there was marked skewing of the dose curve to the right. There were a total of 83 diagnoses of malignant tumors in the children. Because of the organization of the Japanese family-records system, all deaths from cancer in the children in the present study will have a very high probability of being identified, even if the family concerned has left Hiroshima or Nagasaki subsequent to enrollment in the study. This does not hold true for the registry data, since the cancer registries are limited to persons residing within the limits of the two cities at the time of diagnosis. If out-migration from the two cities during the period of this study were related to radiation exposure, this fact could introduce bias into the study. We have examined this possibility by a comparison of the parental exposures for the children ascertained through death certificates with the exposures when the child was ascertained through registry notification only, by using the radiation exposure categories of table 1 but combining the two highest dose categories (data not shown). There were 49 of the former children and 34 of the latter. The heterogeneity χ^2 with respect to parental gonad doses is 2.481, df = 4, and P = .648. Thus there is no suggestion of a biased ascertainment in children with malignancies known only through the tumor registries.

Table 2 lists the 83 tumors accepted as malignant, categorized by the exposure status of the parents and their city of birth. Among the children of the control (zero-dose) parents, the total incidence of all types of childhood cancer was 1.2/1,000 (6.6/100,000 person-years). Those malignancies that seem to conform most

Table 1

Distribution of Combined Parental Gonad Doses for the Subset of Children Both of Whose Parents Have Been Assigned DS86 Gonadal Doses

City and Parameter	Total	Joint Parental Dose (Sv, RBE = 20)					
		0	.01–.09	.10–.49	.50–.99	1.00–2.49	2.50+
Hiroshima:							
No. of children	43,181	25,920	6,597	7,143	1,847	1,273	401
Mean neutron	.001	.0	.000	.001	.004	.013	.049
Mean gamma	.132	.0	.041	.214	.604	1.283	2.847
Total (Sv)	.155	.0	.041	.233	.690	1.546	3.824
Nagasaki:							
No. of children	24,393	14,769	4,045	2,719	1,645	1,022	193
Mean neutron	.001	.0	.000	.000	.002	.005	.018
Mean gamma	.161	.0	.030	.243	.691	1.327	3.425
Total (Sv)	.172	.0	.030	.250	.729	1.423	3.793
Combined:							
No. of children	67,574	40,689	10,642	9,862	3,492	2,295	594
Mean neutron	.001	.0	.000	.001	.003	.009	.039
Mean gamma	.142	.0	.037	.222	.645	1.303	3.035
Total (Sv)	.161	.0	.037	.238	.708	1.491	3.814

Note.—We have assigned zero value as a parental dose for those parents who ATB were NIC. Parents whose joint gonadal exposure was estimated to be <4 mSv have been assigned to the zero-dose group. Neutron and gamma doses are expressed in grays, but total mean dose is expressed in sieverts, with the neutron component assigned an RBE of 20. An explanation of the distinction between this sample and the full sample can be found in the text.

Table 2

Number of Malignant Tumors prior to Age 20 Years in Hiroshima and Nagasaki in Children Born in 1946–82, in Relation to Gonadal Dose (DS86) Received by Parents (Sv, RBE = 20)

Site and Tumor	Dose								
	Hiroshima				Nagasaki				
	0	.01–.09	.10–.49	.50+	0	.01–.09	.10–.49	.50+	Total
Lip, oral cavity, and pharynx:									
Skin sarcoma, sublingual[a]					1				1
Carcinoma, lip					1				1
Basal cell carcinoma, skin	1								1
Digestive organs:									
Adenocarcinoma, stomach					1				1
Leiomyosarcoma, stomach[a]		1							1
Bone and connective tissue:									
Osteosarcoma[b]	1		1						2
Fibrosarcoma[a]	1			1					2
Hemangiopericytoma	1								1
Genitourinary organs:									
Wilms tumor[b]		1		1	1	1	1		5
Sarcoma, kidney[b]			1						1
Embryonal carcinoma, testis[b]			1		1				2
Lymphatic and hematopoietic tissue:									
Leukemia	13	6	3		4	1		4	31
Malignant lymphoma	3	1			1	1			6
Endocrine organs:									
Adenocarcinoma, thyroid	1								1
Nervous system:									
Retinoblastoma[b]	1				3			1	5
Neuroblastoma[b]	2				1				3
Brain									
Unspecified[a]	1								1
Ependymoma[a]	1								1
Meningiosarcoma[a]	1								1
Germinoma[a]						2			2
Medulloblastoma[a]				1			1		2
Astrocytoma[a]	2								2
Glioma[a]		1							1
Glioblastoma multiforme[a]				1					1
Miscellaneous:									
Metastatic malignancy, type and primary site unknown	—	—	–	–	1	–	–	–	1
Total	29	10	6	4	15	5	2	5	76
Total showing strong evidence for heritability (see text)	4	1	3	1	6	1	1	1	18
Total showing less evidence for heritability (see text)	6	2	0	3	1	2	1	0	15

[a] Less evidence for heritability.
[b] Strong evidence for heritability.

strongly to the retinoblastoma–Wilms tumor model are indicated by a superscript "b" and are termed "heritable"; a superscript "a" indicates those for which the evidence is less convincing. There is probably a continuum in the role to be assigned to inherited factors in the etiology of these various tumors; arbitrarily, however, for the purposes of certain analyses to come, we will, following the earlier discussion, apply the rubric "herita-

ble" only to those indicated by a superscript "b," a conservative procedure. The family studies mentioned earlier were restricted to the latter group.

Table 3 presents the findings based on the application of the multiple regression model to the 67,574 children both of whose parents have been assigned DS86 gonadal exposures; the parameters given are shown both as estimated by the method of least squares and as estimated by the method of maximum likelihood. The data were analyzed both as a whole and after subdivision into three categories, namely, leukemia, heritable (as defined earlier), and others. With neither procedure are there significant findings with respect to radiation dose in either the total or subdivided data. The results of the analyses of the three convenient subsets (leukemia, heritable, and other) are consistent except for the reversal of sign of the regression on dose of "other" in the two analyses, reflecting how very close the regressions are to zero. As table 2 shows, these negative regressions on dose were due primarily to the disproportionate clustering of tumors in children whose parents, although exposed, received less than the average amount of radiation experienced by all exposed parents.

The results of an analysis of the extended data set (see Dosimetry section above) are given in table 4. The tabulations on which this analysis is based are presented by Yoshimoto et al. (in press). In this analysis, although the number of children born to parents receiving no increased radiation remained almost unchanged, the extended set includes 4,265 additional children whose parents received significant amounts of radiation, an increase of 15.9% in the data base. There are nine additional tumors in the extended data set, bringing the total to 92. Now the conjoint parental exposure is 0.435 Sv, again with marked skewing of the dose to the right. Only the results based on the method of least squares are given; the method of maximum likelihood yielded similar results. The results of this analysis are so similar to the results of the earlier analysis that no specific discussion seems indicated; we note only the slightly greater precision of the analysis of the extended sample. For this extended sample, the mean age (if alive) of the members of the sample was 26.1 years; 79.7% of the children in the sample had completed their nineteenth year, the diagnostic cutoff point.

With regard to the other variables, the regression on

Table 3

Results of Linear Multiple Regression Analysis of the Incidence of Cancer Below the Age of 20 Years by Conjoint Parental Dose (DS86, Sv, RBE = 20), City, Sex, and Birth Year

Method and Category	Joint Dose	Hiroshima	Maleness	Years since Birth	Intercept[a]
Least squares:					
Leukemia	−.000033	.000126	.000301	−.000007	.000229
	(.000170)	(.000172)	(.000165)	(.000011)	(.000163)
Heritable[b]	−.000053	−.000153	−.000013	.000005	.000380
	(.000130)	(.000131)	(.000126)	(.000008)	(.000124)
Other	.000005	−.000052	.000270	−.000002	.000397
	(.000178)	(.000180)	(.000173)	(.000011)	(.000171)
All cases	−.000081	−.000079	.000558*	−.000003	.001006
	(.000278)	(.000282)	(.000270)	(.000017)	(.000267)
Maximum likelihood:[c]					
Leukemia[d]			No convergence		
Heritable[b,d]			No convergence		
Other	.000049	−.000021	.000266	−.000002	.000372
	(.000174)	(.000176)	(.000171)	(.000010)	(.000160)
All cases	−.000098	−.000004	.000538*	−.000001	.000971
	(.000230)	(.000276)	(.000268)	(.000017)	(.000251)

NOTE.—Values in parentheses are standard errors for the estimated parameter.

[a] Adjusted for the averaged years between bombing and birth.

[b] As defined in the text.

[c] Within P = 1–0 range (dose is 7 Sv truncated for convergence).

[d] Convergence cannot be obtained with this model with the use of maximum likelihood.

* $.01 < p < .05$.

Table 4

Results of Linear Multiple Regression Analysis on the Full Sample of the Incidence of Cancer Below the Age of 20 Years, by Conjoint Parental Dose (Sv, RBE = 20), City, Sex, and Birth Year

Category	Joint Dose	Hiroshima	Maleness	Years since Birth	Intercept[a]
Leukemia	−.0000003	−.000075	.000281	−.000007	.000266
	(.000151)	(.000165)	(.000159)	(.000010)	(.000156)
Heritable[b]	−.000073	−.000156	−.000040	.000007	.000395
	(.000114)	(.000125)	(.000121)	(.000008)	(.000118)
Other	−.000009	−.000165	.000361*	.000004	.000473
	(.000166)	(.000181)	(.000175)	(.000011)	(.000171)
All cases	−.000081	−.000247	.000602*	.000004	.001134
	(.000252)	(.000275)	(.000266)	(.000017)	(.000260)

NOTE.—The method of least squares was used. Values in parentheses are standard errors for the estimated parameter.

[a] Adjusted for the number of years between bombing and birth.

[b] As defined in the text.

* $.01 < p < .05$.

city was negative, in keeping with the slightly greater frequency of childhood tumors encountered in Nagasaki. The regression on sex was significantly positive (more males involved), in keeping with other Japanese data (Children's Cancer Association of Japan 1989). None of the analyses of subsets with respect to city, sex, or years between bombing and birth was noteworthy, with the possible exception of both the reversal of sign for the regression on maleness of heritable tumors and a similar reversal, for leukemias (leukemias of earlier onset), for the regression of years between bombing and birth.

Discussion

This failure to demonstrate a statistically significant increase in malignant tumors prior to age 20 years in children born to the survivors of the atomic bombings confirms an earlier, less detailed report by Schull et al. (1982), as well as a still earlier report, restricted to leukemia, by Ishimaru et al. (1981). The mechanism to follow these children into their adult years is now in place, and we anticipate in due time a follow-up to this report, directed at determining whether the pattern of adult-onset tumors is altered among the children of exposed parents.

Inasmuch as ionizing radiation has produced mutations in every properly studied plant and animal species, we accept the premise that there was genetic damage in the parents who were proximally exposed to the atomic bomb explosions. In our various studies of the children of survivors, our ultimate objective has been to take at face value the observed results, statistically significant or not, and to develop an estimate of the sensitivity of the human genome to radiation. An insignificant negative regression of indicator on dose, as in this study, is viewed as a random deviation from some small positive effect. In order to refine the present analysis, we must next deal with the fact that the frequency of only a fraction of the malignancies indicated as heritable should, according to current concepts, be altered by an increased mutation rate in the parents. This fraction provides an improved baseline against which to view the observed regressions.

To return to the retinoblastoma paradigm, we note that on a worldwide basis about 60% of such tumors are now thought to result from somatic cell events only (see Vogel 1979; Knudson 1986); Matsunaga and Minoda (1988) have recently endorsed this figure with reference to the Japanese population. The frequency of tumors due only to somatic cell mutations would not be altered in children by parental radiation. Furthermore, in as many as 5%–10% of the carriers of the appropriate germinal mutation the tumor is not diagnosed. For Wilms tumor the original estimate of the percent associated with a germ-line mutation was 38% (Knudson and Strong 1972), an estimate that was subsequently reduced to ≤10% by Matsunaga and Minoda (1988). However, Li et al. (1987) found no cases of either Wilms tumor or any other cancer among the 155

offspring surviving the neonatal period who were born to 99 patients who had been successfully treated for Wilms tumor, most of which patients had received abdominal radiotherapy in addition to surgery. Since these patients had unilateral disease, it may be presumed that, in the great preponderance, the malignancy was not associated with a germ-line mutation. The median age of the children was 6 years. Recently it has been suggested that two or three different genetic loci are involved in the Wilms tumor phenotype (Grundy et al. 1988; Huff et al. 1988). Data on genetic transmission are still quite scanty for the other heritable tumors. Familial cases of neuroblastoma are very rare, and only two have been reported from Japan (Kaneko and Sawaguchi 1988). Then, although some 20% of the tumors in this series may conform in the most general sense to the retinoblastoma model (our "b"-superscripted tumors in table 2), only a minority of those conforming to this model have a genetic basis that should reflect, in the next generation, any change in the parental mutation rate. That the transmissibility of the tumors indicated by a superscript "a" in table 2 is even less (<1%) is indicated both by the literature survey of Mulvihill and Byrne (1985) and by the multicenter study of Mulvihill et al. (1987).

Any attempt to generalize from these studies must, however, consider that these survivors may not be typical of the spectrum of the childhood malignancies. For instance, familial retinoblastoma and Wilms tumor are much more often bilateral (i.e., multifocal) than are sporadic cases and confer a greater risk of death (or failure to marry and reproduce) than do their nonfamilial counterparts. Nevertheless, although many of the children in the Mulvihill series were still quite young at the time of the reports, so that the ultimate estimate of cancer incidence below the age of 20 years will undoubtedly be greater, these empirical data suggest that a transmissible germinal mutation is involved in a fraction of the childhood tumors that is much smaller than the figures mentioned above for retinoblastoma and Wilms tumor. The sib recurrence risks lead to a similar conclusion (see Leck 1977).

Among the children of unexposed parents, the representation of tumors designated as heritable and indicated by a superscript "b" in table 2 is 21.6%. An additional 18.1% (indicated by a superscript "a") may ultimately be shown to conform to this model, but, as noted, the fraction of these that is associated with a germ-line mutation does not appear to be nearly as high as that for retinoblastoma and Wilms tumor. This is admittedly a small sample on which to base such a breakdown, but it is the only Japanese sample of "early-onset" cancers known to us that is based on both the morbidity and mortality data of defined cohorts. On the basis of the foregoing review, we conclude that approximately 20% of the tumors in this series conform to the retinoblastoma model, of which only 10%–20% are associated with a germ-line mutation in the parents. The corresponding percentage for the "less heritable" tumors cannot be >5%. This suggests that, in the control series, 3%–5% of all tumors are associated with a germ-line mutation. The approximate character of this calculation is clear, but it provides a rough perspective.

Returning now to the previous analysis, we can express the findings somewhat more concretely. The estimate of 3%–5% developed in the preceding paragraph suggests that, of the cancers observed in the control series in this study, roughly one or two are heritable in the sense of involving a germ-line mutation in a "tumor suppressor" gene and that, in the children of the exposed, the expectation in the absence of a radiation effect is very similar. Even if the additional 18.1% of tumors indicated by a superscript "a" in table 2 were clearly shown to conform to the retinoblastoma model, this demonstration would add only one or two tumors to the germ-line-associated baseline. Only two or three additional heritable tumors of the germ-line type in the children of proximally exposed would constitute a doubling. Given the role of the stochastic process in such small expectations, where the chance occurrence (placement) of one or two malignancies can alter the sign of the regression in either direction, the regression's closeness to zero is noteworthy. As noted earlier, the importance of *germ-line* mutations in proto-oncogenes in childhood cancer remains unclear, but, whatever that role, the impact that oncogene response to radiation has on live-born children was also implicitly examined in the foregoing analysis.

In view of these findings, it seems appropriate to return to a more detailed consideration of the murine data that were one of the compelling factors in this examination of tumor mortality and morbidity in these children. From Nomura's (1982) data, derived from acutely administered X-ray exposures of 36–504 rad, it can be estimated that, in the offspring of male mice receiving 150–200 rad to germ cells in the spermatogonial stage, the frequency of *all* tumors was approximately twofold greater than "normal." (Traditional radiation units are retained if they appear in the work being cited. In all current RERF reports, the International System of Units is employed.) From the results of enhancing the fre-

quency of tumors by postnatal treatment of the F_1 with urethane, Nomura (1983) has suggested that for this endpoint the "genetic doubling dose" of spermatogonial radiation should be placed at 50 rad. Different tumors appear to exhibit different doubling doses. These tumors in mice occurred over a period of 8 mo, a period which, in terms of life cycle, is proportionately longer than the restricted (human) age span in the present study. A precise comparison of the results of the two studies is therefore inappropriate, but it does appear that, if the totality of the human tumors encompassed by this study responded as the totality of the mouse tumors, we might already expect an effect greater than that observed, since the average conjoint gonadal exposure in the proximally exposed parents can be estimated to be 0.435 Sv. Given, however, that most of the tumors reported by Nomura are adult-onset tumors in humans, a definitive comparison of the present findings with the murine data will not be possible for some years to come.

There are, however, aspects of the Nomura data which render their relevance to the human situation moot. In his experiments with the ICR strain of mice, 87% of the tumors in the offspring of treated mice were scored as papillary adenomas of the lung. In the experiments with LT and N5 mice, 16.0% and 21.0%, respectively, of tumors were pulmonary, 25.3% and 22.8%, respectively, were ovarian tumors, and 5.3% and 3.9%, respectively, were leukemias. These endpoints had a relatively high frequency in the controls. Transplantation experiments involving 26 tumors suggested that 88% of the tumors were malignant (Nomura 1986). As Nomura points out, the predominance of a single or several tumor types in his data leads to the suspicion of a strain-specific effect which, given our previous analysis of the genetic basis of human childhood malignancies, in our opinion necessitates great caution in extrapolation from the mouse paradigm to the human situation.

Finally, we point out that the base for Nomura's doubling-dose calculations appears to be *all* the tumors of any specific type in the control animals. To the extent that some of the tumors in the mouse model are due to somatic mutation only, this biases the estimate of the doubling dose, i.e., if, as seems likely, some of the spontaneous tumors in the F_1 mice are entirely due to somatic cell events, their inclusion in a doubling-dose estimate tends to bias it to a higher absolute value. The correct calculation of the mouse doubling dose should yield a figure lower than that quoted above, thus further intensifying the discrepancy at this point between the mouse and the human data.

Our results are incompatible with the previously mentioned findings of Shiono et al. (1980) on 40 malignant tumors of childhood, especially when we consider that the relative risk of 2.61 that they derived applied to *all* tumors and not just to the fraction presumed to be related to a germ-line mutation in the mother. A correct treatment of their data would imply a genetic doubling dose for this indicator <0.01 Gy, far below any other genetic doubling-dose estimate based on either human or murine data.

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