American Journal of Epidemiology

Vol. 190, No. 11
https://doi.org/10.1093/aje/kwab099
Advance Access publication:
April 13, 2021

Original Contribution

Congenital Malformations and Perinatal Deaths Among the Children of Atomic Bomb Survivors: A Reappraisal

Michiko Yamada*, Kyoji Furukawa, Yoshimi Tatsukawa, Keiko Marumo, Sachiyo Funamoto, Ritsu Sakata, Kotaro Ozasa, Harry M. Cullings, Dale L. Preston, and Paivi Kurttio

* Correspondence to Dr. Michiko Yamada, Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan (e-mail: yamada@rerf.or.jp).

Initially submitted August 20, 2020; accepted for publication February 26, 2021.

From 1948 to 1954, the Atomic Bomb Casualty Commission conducted a study of pregnancy outcomes among births to atomic bomb survivors (Hiroshima and Nagasaki, Japan) who had received radiation doses ranging from 0 Gy to near-lethal levels. Past reports (1956, 1981, and 1990) on the cohort did not identify significant associations of radiation exposure with untoward pregnancy outcomes, such as major congenital malformations, stillbirths, or neonatal deaths, individually or in aggregate. We reexamined the risk of major congenital malformations and perinatal deaths in the children of atomic bomb survivors ($n = 71{,}603$) using fully reconstructed data to minimize the potential for bias, using refined estimates of the gonadal dose from Dosimetry System 2002 and refined analytical methods for characterizing dose-response relationships. The analyses showed that parental exposure to radiation was associated with increased risk of major congenital malformations and perinatal death, but the estimates were imprecise for direct radiation effects, and most were not statistically significant. Nonetheless, the uniformly positive estimates for untoward pregnancy outcomes among children of both maternal and paternal survivors are useful for risk assessment purposes, although extending them to populations other than the atomic bomb survivors comes with uncertainty as to generalizability.

atomic bomb; congenital malformations; genetics; nuclear weapons; perinatal mortality; pregnancy outcomes; radiation effects

Abbreviations: ABCC, Atomic Bomb Casualty Commission; CI, confidence interval; ERR, excess relative risk; RERF, Radiation Effects Research Foundation; UPO, untoward pregnancy outcome.

Editor's note: *An invited commentary on this article appears on page 2334, and the authors' response appears on page 2337.*

From 1948 to 1954, the Atomic Bomb Casualty Commission (ABCC) conducted a large-scale study of pregnancy outcomes among births to survivors of the atomic bombs dropped on Hiroshima and Nagasaki, Japan, who had received radiation doses ranging from 0 Gy to near-lethal levels (1). This research was motivated by already firm experimental findings showing that ionizing radiation causes genetic effects; consequently, examination of pregnancy outcomes in the children of radiation-exposed parents was considered imperative.

The first reported analyses of the data in 1956 considered a nonoverlapping hierarchy of untoward pregnancy outcomes (UPOs) that included major congenital malformations, stillbirths of children without major malformations, and neonatal deaths of children without major malformations (1). Further analyses carried out in 1981 (2) and 1990 (3) used individual parental dose estimates based on the revised tentative 1965 radiation dose estimates and Dosimetry System 1986, respectively, to assess the effects of total (conjoint) parental dose on the risk of UPOs as a group (see Web Table 1, available at https://doi.org/10.1093/aje/kwab099). While the past analyses generally showed a positive trend between

the frequency of UPOs and total parental dose, the effects were not statistically significant (2–4).

Children born to atomic bomb survivors were further studied by researchers of the ABCC and its successor, the Radiation Effects Research Foundation (RERF), for other indicators of genetic effects: sex ratio (4), chromosome aberrations (4), electrophoretic variants of serum and erythrocyte proteins (4), and mutation rate at micro- and minisatellite loci (5). Nonspecific outcomes investigated include mortality (6) and multifactorial diseases in adults (7). To date, these studies have not found associations of the various outcomes with parental radiation exposure.

More recently, RERF has reconstructed and refined the data from the original ABCC genetic study. This reassessment showed that all previous analyses excluded around 700 induced pregnancy terminations with birth weight less than 2,500 g and around 500 terminations with unknown birth weight, although the exclusion criteria differed among the various UPO analyses (Web Table 1) (8). Comparisons of the data set for each previous analysis with the original data indicated that approximately 15% of the total malformations in the original data were not treated as malformations in the 1990 analysis, possibly in error (3). In addition, updated estimates of gonadal dose from Dosimetry System 2002 (9) and refined analytical methods for characterizing dose-response relationships became available.

In view of limitations of the earlier analyses and recently increased concerns about heritable effects of parental exposure to radiation, particularly following the 2011 Fukushima Daiichi accident in Japan (10), we reexamined the risk of major congenital malformations and perinatal deaths in the offspring of the atomic bomb survivors.

METHODS

Subjects

A genetic study of pregnancy outcomes occurring after 20 weeks of pregnancy among atomic bomb survivors was initiated in 1948 (3 years after the bombing) by the ABCC and continued until 1954 (1). In those postwar years, women in the fifth month of pregnancy in Hiroshima and Nagasaki were eligible for a food rationing program upon pregnancy registration. Each mother received an oral explanation and a brief printed description of the study program at the time of pregnancy registration. Based on an agreement made with informed consent, mothers were asked to provide personal identifying information, information on paternal exposure from the blasts, and other data. During the postwar era, most mothers in Japan gave birth at home; the majority of deliveries were attended by midwives and the rest by physicians. Soon after delivery of a baby, midwives and physicians collected information on the pregnancy. A total of 76,614 births were reported to the ABCC.

For each delivery, ABCC physicians and nurses visited the baby's home to conduct a further systemic examination. The examining physicians were required to record all abnormalities, including minor defects. At the examination, detailed information was collected for stillbirths, neonatal deaths, and children with malformations observed at birth and for a randomly selected subset of 10% of all births (8). When the final report on each delivery was coded, a decision was made as to the presence of a major malformation based on the list of major malformations (see "Diagnoses of malformations" in the Web Appendix).

In selecting the study subjects, the exclusion and inclusion criteria differed somewhat from those used in previous studies (Web Appendix). Births after 1953 were excluded from both previous studies and this study. The principal exclusions were for multiple births and induced pregnancy terminations occurring prior to the 30th week; detailed explanations of the exclusions are provided in the Web Appendix. After exclusions, the total number of eligible births was 71,603.

The current reanalysis was approved by the RERF institutional review board. Because RERF restricts the provision of personal data of atomic bomb survivors and their children to third parties, all data and documentation have been permanently archived at RERF.

Radiation dose

The current reanalysis used radiation doses estimated with Dosimetry System 2002 (9), which provides individual gonadal doses for a larger number of parents than the previous systems. For the fraction of neutrons, a radiation weighting factor of 10 was used to account for the greater biological effect (9). We used adjusted dose estimates intended to overcome the regression bias that can arise from random uncertainties in exposure estimation (9).

We analyzed the data on maternal and paternal gonadal doses separately to account for any sex-dependent difference in transgenerational mutability (reported in animals) that might occur in humans (11). The biological rationale for that decision follows. In 1980, the Biological Effects of Ionizing Radiation (BEIR) III Committee noted that the reproductive cells of female mice were much less mutable than those of males (12). In addition, recent murine studies have found that the frequency of radiation-induced germline mutations at a minisatellite locus differed for maternal and paternal exposures (13). Analyses were also carried out with the conjoint dose. Table 1 shows the distribution of parental gonadal doses in the current analysis. Maternal dose was available for 68,533 births, paternal dose for 69,433 births, and conjoint dose for 66,363 births. Approximately 55% of mothers and 77% of fathers were not in Hiroshima or Nagasaki at the time of the bombings (referred to as the "not in city" subjects), and those participants were assigned a dose of 0. The mean maternal, paternal, and conjoint doses were 0.03 Gy, 0.02 Gy, and 0.05 Gy, respectively.

Malformation and perinatal death

In the current reanalysis, outcomes were major congenital malformations observed at birth and also perinatal deaths. Because of the diverse causes associated with each outcome (14, 15), these outcomes were treated separately in the main analyses. Additional analysis based on a hierarchy of outcomes (we analyzed major congenital malformation first, then perinatal death without major congenital malformation)

Table 1. Distribution of Paternal and Maternal Gonadal Doses of Radiation Among Atomic Bomb Survivors With Eligible Births, Hiroshima and Nagasaki, Japan, 1948–1953

Paternal Dose, Gy	Maternal Dose, Gy							
	0	<0.05	0.05–0.49	0.50–0.99	≥1.00	Unknown	Not in City[a]	Total
0	2,565	1,226	265	47	25	244	1,936	6,308
<0.05	871	2,222	320	52	36	304	1,911	5,716
0.05–0.49	166	351	425	31	14	62	537	1,586
0.50–0.99	58	55	47	49	10	15	158	392
≥1.00	58	98	32	11	16	19	144	378
Unknown	376	830	136	31	19	0	778	2,170
Not in city[a]	7,569	8,045	2,161	584	315	2,426	33,953	55,053
Total	11,663	12,827	3,386	805	435	3,070	39,417	71,603

[a] Not present in Hiroshima or Nagasaki at the time of the bombing.

was also conducted. Although stillbirths (i.e., an infant showing no signs of life at birth) and neonatal deaths were treated separately in the first analyses reported in 1956 (Web Table 1), both were considered perinatal deaths in the current analysis because of the difficulties in differentiating between the two. Among the eligible births, there were 3,530 births classified as having 1 or more UPOs: 783 births with a major malformation, 2,667 births with perinatal death occurring within 7 days, and 2,904 births with perinatal death occurring within 14 days.

Although an autopsy was conducted for approximately 30% of perinatal deaths, the main analyses did not include major malformation cases identified only by autopsy, due to potential bias resulting from autopsy sampling with differential selection by dose and city (Web Table 2) and the uneven quality of the autopsies. As a sensitivity analysis, the risks for major malformation cases identified both at birth and at autopsy are provided in Web Table 3.

Statistical analysis

We used binomial regression models to analyze the radiation-associated risk for each of the 3 outcomes of interest (major malformation, perinatal death within 7 days, and perinatal death within 14 days). The primary models were relative risk models of the form $p(x,d) = \pi_0(x)\{1 + \mathrm{ERR}(d)\}$. In the model, π_0 is the baseline (0 dose) probability, described as a log-linear function of baseline risk factors (x) (included risk factors were maternal and paternal ages at birth, parity, consanguinity, year of birth, sex, and city of registration). The excess relative risk (ERR) is the relative risk minus 1, and ERR(d) is a function of parental doses, where children of parents exposed at dose d are compared with children of unexposed parents. The ERRs per unit dose (1 Gy) were estimated for maternal, paternal, and conjoint doses. We calculated maximum likelihood estimates and confidence intervals of the model parameters and conducted hypothesis tests with 2-sided P values via likelihood ratio tests using the "gnm" package of R (16). In addition to 95% confidence intervals, we calculated 90% confidence intervals when the P value was less than 0.1.

RESULTS

Table 1 provides the joint distribution of maternal and paternal gonadal radiation doses, while Table 2 presents demographic characteristics according to paternal and maternal gonadal doses. The mean number of children per parent during the study period was 1.3. Approximately one-quarter (26%) of the parents had no prior children. Mean maternal and paternal ages at the time of delivery were 28 and 33 years, respectively, and 23 and 28 years at the time of the bombings. The most common major malformations found among eligible births were cleft palate and cleft lip ($n = 97$), single cleft palate ($n = 42$), cleft lip ($n = 62$), club foot/hand ($n = 93$), polydactyly ($n = 67$), syndactyly ($n = 35$), and anencephaly ($n = 48$).

Table 3 shows the adjusted rates per 100 births for major malformations and perinatal deaths according to selected characteristics. Background prevalence estimates per 100 births, adjusted to reference categories of nonradiation factors, were 0.95 for major malformations, 3.72 for perinatal deaths within 7 days, and 3.95 for perinatal deaths within 14 days. High parity was associated with higher risk of major malformations. The risk of perinatal death was increased significantly for first pregnancies (parity = 0). Children of closely related parents had a higher risk of adverse outcomes than children born to unrelated parents (about 60% higher for major malformations and 40% higher for perinatal deaths). Maternal age above 40 years was a risk factor for major malformations. Infants of younger fathers and older mothers were at higher risk of perinatal death. Major malformation risks increased significantly ($P < 0.01$) over the course of the study period (1948–1952). While perinatal death rates varied with calendar period, a trend over time was not apparent. In 1948, the risk of perinatal death was approximately 30% higher and the risk of major malformations approximately 30% lower than in other years.

Table 2. Demographic Characteristics of Atomic Bomb Survivors According to Gonadal Dose of Radiation (Paternal or Maternal), Hiroshima and Nagasaki, Japan, 1948–1953

Characteristic	Radiation Dose, Gy													
	0		<0.05		0.05–0.49		0.50–0.99		≥1.00		Unknown		Not in City[a]		Total	
	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%
Paternal Dose																
Total no. of participants[b]	6,308		5,716		1,586		392		378		2,170		55,053		71,603	
No. of major malformations[b]	76		61		17		11		5		21		592		783	
No. of perinatal deaths[b]																
Within ≤7 days	207		231		70		13		17		95		2,034		2,667	
Within ≤14 days	227		251		78		14		21		100		2,213		2,904	
Maternal parity																
0		17.8		18.3		20.2		19.9		24.1		22.1		27.5		25.5
1–3		55.6		55.6		58.3		60.2		60.6		61.8		60.5		59.6
≥4		26.6		26.1		21.4		19.9		15.3		16.1		12.1		14.9
Relative (first cousin) of other parent		4.3		3.6		2.5		3.6		2.6		3.8		4.2		4.1
Paternal age, years	35.2		35.7		35.6		35.1		34.6		33.6		32.4		33.1	
Maternal age, years	29.8		30.0		29.5		29.1		28.9		28.4		27.7		28.1	
Child's year of birth	1950.4		1950.4		1950.3		1950.6		1950.6		1950.5		1950.6		1950.6	
Male child sex		51.0		51.3		50.1		53.1		53.4		51.7		51.9		51.8
City (Hiroshima)[c]		43.2		41.3		78.6		49.7		51.3		39.0				49.1
Distance from hypocenter, km[d]	5,270.5		2,918.1		1,633.2		1,312.3		1,125.1		1,670.8				3,522.0	
% <1.5 km from hypocenter		0.0		0.0		24.7		88.5		100.0		32.3[e]				2.6
% <2.5 km from hypocenter		0.0		25.5		100.0		100.0		100.0		63.9[e]				7.3

Table continues

Table 2. Continued

Characteristic	Radiation Dose, Gy													
	0		<0.05		0.05–0.49		0.50–0.99		≥1.00		Unknown		Not in City[a]		Total	
	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%
								Maternal Dose								
Total no. of participants[b]	11,663		12,827		3,386		805		435		3,070		39,417		71,603	
No. of major malformations[b]	122		127		26		10		8		37		453		783	
No. of perinatal deaths[b]																
Within ≤7 days	435		483		124		44		18		126		1,437		2,667	
Within ≤14 days	470		533		139		47		21		137		1,557		2,904	
Maternal parity																
0		21.8		22.7		22.9		24.3		26.0		30.9		27.3		25.5
1–3		56.8		60.1		61.0		63.2		58.6		59.8		60.1		59.6
≥4		21.4		17.1		16.1		12.4		15.4		9.3		12.6		14.9
Relative (first cousin) of other parent		4.5		3.5		2.2		2.9		2.1		3.0		4.5		4.1
Paternal age, years	33.5		33.3		33.8		32.6		32.5		31.5		32.9		33.1	
Maternal age, years	28.8		28.5		28.4		27.5		27.6		27.0		27.9		28.1	
Child's year of birth	1950.4		1950.5		1950.3		1950.6		1950.5		1950.6		1950.7		1950.6	
Male child sex		51.4		51.9		50.4		48.1		51.3		51.6		52.0		51.8
City (Hiroshima)[c]		36.2		43.0		77.3		56.0		56.3		52.1				49.1
Distance from hypocenter, km[d]	5,205.8		2,872.5		1,596.9		1,255.5		1,079.3		1,705.2				3,432.1	
% <1.5 km from hypocenter		0.0		0.0		32.5		98.1		100.0		35.0[e]				4.8
% <2.5 km from hypocenter		0.0		28.3		100.0		100.0		100.0		77.9[e]				15.0

[a] Not present in Hiroshima or Nagasaki at the time of the bombing.
[b] Values are expressed as number.
[c] Present in Hiroshima at the time of the bombing.
[d] By paternal dose for the father and by maternal dose for the mother.
[e] Among subjects with an unknown dose, distance data were missing for 652 fathers (30.1%) and 454 mothers (14.8%).

Table 3. Background Prevalence of Major Congenital Malformations and Perinatal Deaths (Within ≤7 Days or ≤14 Days) per 100 Births Among Atomic Bomb Survivors, According to Selected Characteristics, Hiroshima and Nagasaki, Japan, 1948–1953

Characteristic	No. of Births	Major Malformations		Perinatal Deaths			
				Within ≤7 Days		Within ≤14 Days	
		No. of Cases	Background Prevalence[a]	No. of Cases	Background Prevalence[a]	No. of Cases	Background Prevalence[a]
Maternal parity							
0[b]	18,255	168	0.95	837	3.72	900	3.95
1	20,111	226	1.16	635	2.66	704	2.93
2–3	22,593	232	1.03	753	2.82	819	3.07
4–5	7,567	114	1.50	280	2.91	303	3.18
≥6	3,077	43	1.21	162	3.67	178	4.09
P for heterogeneity			0.02		<0.01		<0.01
P for trend			0.16		0.32		0.60
Parental consanguinity							
Unrelated[b]	66,511	710	0.95	2,439	3.72	2,649	3.95
First cousin	2,943	51	1.53	145	5.07	164	5.62
Other relative	2,149	22	0.90	83	3.99	91	4.27
P for heterogeneity			0.01		<0.01		<0.01
Paternal age at birth, years							
14–24	5,864	70	1.04	269	5.01	294	5.28
25–29	20,599	184	0.74	833	4.62	906	4.86
30–34[b]	20,357	239	0.95	634	3.72	693	3.95
35–39	14,046	144	0.78	492	3.98	532	4.21
≥40	10,737	146	0.90	439	3.92	479	4.21
P for heterogeneity			0.03		<0.01		<0.01
P for trend			0.42		0.01		0.03
Maternal age at birth, years							
14–24	22,710	231	1.00	901	3.52	992	3.85
25–29[b]	25,979	267	0.95	886	3.72	959	3.95
30–34	14,314	166	1.02	491	3.92	533	4.14
35–39	6,789	82	1.02	290	4.64	313	4.81
≥40	1,811	37	1.69	99	5.57	107	5.73
P for heterogeneity			0.14		0.02		0.04
P for trend			0.21		<0.01		0.01
Child's year of birth							
1948	4,602	38	0.66	220	4.97	240	5.30
1949	16,829	149	0.74	583	3.62	640	3.90
1950[b]	14,644	166	0.95	514	3.72	557	3.95
1951	13,272	161	1.03	491	3.96	534	4.22
1952	12,015	156	1.10	475	4.24	513	4.50
1953	10,241	113	0.94	384	4.03	420	4.34
P for heterogeneity			<0.01		<0.01		<0.01
P for trend			<0.01		0.46		0.48

Table continues

Table 3. Continued

Characteristic	No. of Births	Major Malformations		Perinatal Deaths			
				Within ≤7 Days		Within ≤14 Days	
		No. of Cases	Background Prevalence[a]	No. of Cases	Background Prevalence[a]	No. of Cases	Background Prevalence[a]
Child's sex							
Male[b]	37,064	396	0.95	1,461	3.72	1,593	3.95
Female	34,539	387	1.00	1,206	3.30	1,311	3.49
P for heterogeneity			0.50		<0.01		<0.01
City of registration							
Hiroshima[b]	35,181	397	0.95	1,309	3.72	1,433	3.95
Nagasaki	36,422	386	0.84	1,358	3.76	1,471	3.95
P for heterogeneity			0.08		0.77		0.98

[a] Background prevalence per 100 births estimated from the individual dose model (equations A1 and A2 in the "Statistical analysis" section of the Web Appendix).
[b] Reference category.

Major malformation risks did not vary by sex, but risk for perinatal death tended to be higher for boys than for girls ($P < 0.01$). In Hiroshima, relative to Nagasaki, the risk tended to be higher for major malformations ($P = 0.08$) but not for perinatal deaths.

Table 4 presents the radiation risk estimates for the various UPOs. Considering the effects of parental doses on malformations separately, the ERR per Gy for the maternal dose was 0.28 (95% confidence interval (CI): −0.30, 0.86) and that for paternal dose was 0.40 (95% CI: −0.30, 1.09). When the effects of conjoint doses were considered, the ERR per Gy for malformations was 0.35 (95% CI: −0.11, 0.81; 90% CI: 0.02, 0.80). For risk of perinatal death within 7 days, ERR/Gy estimates were 0.22 (95% CI: −0.08, 0.52) for maternal dose, 0.11 (95% CI: −0.18, 0.41) for paternal dose, and 0.14 (95% CI: −0.07, 0.34) for conjoint dose. The corresponding figures for perinatal death within 14 days were 0.26 (95% CI: −0.04, 0.55; 90% CI: 0.01, 0.50) for maternal dose and 0.21 (95% CI: −0.09, 0.51) for paternal dose. Using conjoint dose, the estimated ERR/Gy for perinatal death within 14 days was 0.21 (95% CI: 0.00, 0.42; 90% CI: 0.05, 0.40), similar to the separate estimates for maternal and paternal dose. The analyses of perinatal deaths excluding major malformations based on a hierarchy of outcomes showed similar results.

Figure 1 shows the fitted maternal and paternal dose-response curves for each of the 3 outcomes with ERR estimates for each dose category. The categorical estimate for the paternal 0.50–0.99 Gy exposure group was significantly ($P < 0.05$) increased for major malformations but not for perinatal death outcomes. For the maternal 0.50–0.99 Gy group, the ERR was increased significantly for both of the perinatal death outcomes but not for major malformations. None of the categorical estimates for the ≥1.00-Gy group were significantly increased.

As described in the "Statistical analysis" section of the Web Appendix, the dose-response models were fitted using all of the data, including births for which either the maternal or paternal dose was unknown. When we conducted sensitivity analyses limiting the data to births for which the dose to both parents was known, the dose-response parameter estimates, the significance test results, and the confidence intervals were essentially unchanged.

DISCUSSION

Shortly after the ABCC was established, a surveillance system was implemented for children born to Hiroshima and Nagasaki atomic bomb survivors and for children of unexposed parents (1, 8). Given the unique nature of the exposed population and the general recognition at the time from experimental studies that radiation causes genetic damage, the ABCC's founders considered that a study of pregnancy outcomes was critical to quantify the extent of genetic injury. That surveillance, which ended in 1954, was the data source used in this and prior analyses directed at the associations between parental radiation exposure and UPOs.

To our knowledge, this is the latest major report on UPOs among children born to the atomic bomb survivors (Web Table 1). The present analysis used an updated and corrected data set with more refined estimates of the relevant dose. The first report (published in 1956) used a distance-based measure, distance from the hypocenter of radiation exposure (1), while later reports used radiation exposure estimated by increasingly sophisticated dosimetry systems (2, 3) (Web Table 1). The present report used estimated gonadal dose from Dosimetry System 2002. The prior reports were based on the original data collected, but with somewhat different exclusion and inclusion criteria and different approaches to

Table 4. Adjusted Excess Relative Risk of Major Congenital Malformations and Perinatal Deaths (Within ≤7 Days or ≤14 Days) According to Radiation Exposure Among Atomic Bomb Survivors, Hiroshima and Nagasaki, Japan, 1948–1953

Outcome	Estimated Risk		*P* Value
	ERR per Gy[a]	95% CI	
Major malformations			
Maternal dose	0.28	−0.30, 0.86	0.28
Paternal dose	0.40	−0.30, 1.09	0.24
Conjoint dose	0.35	−0.11, 0.81	0.08
Perinatal deaths within ≤7 days			
Maternal dose	0.22	−0.08, 0.52	0.15
Paternal dose	0.11	−0.18, 0.41	0.42
Conjoint dose	0.14	−0.07, 0.34	0.18
Perinatal deaths within ≤14 days			
Maternal dose	0.26	−0.04, 0.55	0.08
Paternal dose	0.21	−0.09, 0.51	0.12
Conjoint dose	0.21	0.00, 0.42	0.03

Abbreviations: CI, confidence interval; ERR, excess relative risk.

[a] To estimate the ERR, we adjusted for maternal and paternal ages at birth, maternal parity, consanguinity, child's year of birth, child's sex, and city of registration as covariates.

exposure and dose calculation. On the basis of extensive review of the original data, corrections were made for the present analysis. The population for the present study was selected so as to minimize the potential for bias. Additionally, over time, the analytical methods for characterizing dose-response relationships have been refined. Overall, the prior studies did not find significant associations between radiation exposure or dose and risk of UPOs. In the most recent report (1990), Otake et al. (3) found positive, albeit not statistically significant, associations for UPOs overall.

Given the substantial body of experimental evidence showing that radiation causes genetic changes (11), there has been a strong prior hypothesis that exposure to radiation from the blasts caused genetic changes, with implications for the occurrence of UPOs (1–3). The genetic studies were implemented with the goal of quantifying the magnitude of the additional risk of genetic abnormalities from radiation. For that purpose, multivariate models were used that took into account these other factors; some were associated with the rate of UPO (Table 3).

The adjusted estimates of ERR were uniformly positive, although most estimates were not statistically significant at the 0.05 level (Table 4). Arguably, 1-sided testing might be used based on the prior evidence on radiation and mutation, resulting in smaller *P* values and narrower confidence intervals but leaving the estimates unchanged. Following prior analyses, we used 2-sided testing.

Beyond the precision of estimates, epidemiologic findings need to be interpreted considering the possibility that the results are affected by bias. A possible concern is information bias that might be related to differential ascertainment of the occurrence of a UPO based on exposure status. Consequently, the outcomes identified only by autopsy were excluded from the analyses, except for sensitivity analyses. Another concern is measurement error. Although error in assessment of exposure would affect exposure estimates, Dosimetry System 2002 estimated "true" dose assuming a 35% error in the individual dose estimates and made adjustment for this error (9). Such adjustment increases risk estimates in comparison with unadjusted estimates (9).

Confounding is another concern, particularly given variation in several determinants of some outcomes (e.g., parity) by exposure (Table 2). Diverse maternal and paternal factors affect risk for UPOs (Table 3); to the extent possible, these factors were considered in the analyses to date, as there was awareness of the potential for confounding when the study was designed (1).

Regarding phenotypes in human studies, such as malformation, stillbirth, and neonatal death, the contribution of nongenetic factors is substantial. According to Brent (15), genetic causes account for 15%–25% of congenital malformations observed during the first year of life. Aminu et al. (14) reported that the most frequent causes of stillbirths are associated with maternal factors (such as maternal conditions, infection, and obstetrical factors), which are also related to socioeconomic status, such as poverty and lack of education. Therefore, harsh living conditions and the limited socioeconomic resources available to heavily exposed atomic bomb survivors after the war might have led to an overestimate of genetic effects of radiation. Kato et al. (17) reported that among atomic bomb survivors, the exposed parents had less education than the nonexposed parents. Poverty after the war due to social and human damage cause by the bombings was closely associated with distance from the hypocenters,

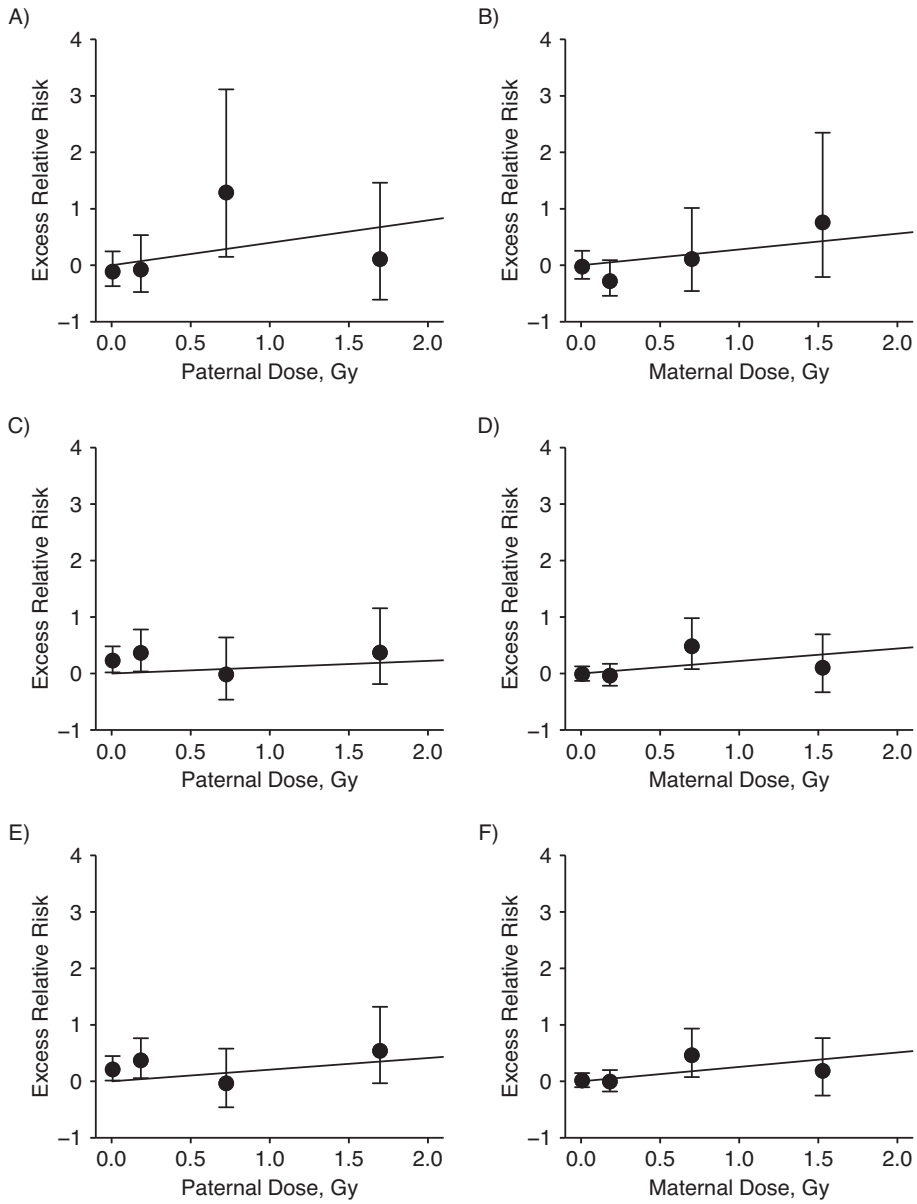

Figure 1. Estimated excess relative risk (•) of major congenital malformations, perinatal death within 7 days, and perinatal death within 14 days among children of atomic bomb survivors, Hiroshima and Nagasaki, Japan, 1948–1953. Solid lines represent the fitted linear dose-response (see Table 4) for the dose-category–specific (<0.05, 0.05–0.49, 0.50–0.99, or ≥1.00 Gy) excess relative risk. A) Major malformations by paternal dose; B) major malformations by maternal dose; C) 7-day perinatal deaths by paternal dose; D) 7-day perinatal deaths by maternal dose; E) 14-day perinatal deaths by paternal dose; F) 14-day perinatal deaths by maternal dose. Bars, 95% confidence intervals.

a surrogate for radiation dose (18). However, information on the full suite of determinants of pregnancy outcome and their consequences for postwar births in the unique circumstances of Hiroshima and Nagasaki was not available.

Other studies have addressed the consequences of preconception radiation exposure among mothers and fathers for pregnancy outcomes. Studies of the children born to cancer survivors who underwent radiation therapy are an important source of information on parental radiation exposure and the risk of UPOs (19, 20). Largely null results have been obtained on risk for UPOs in systematic reviews of studies comparing offspring of cancer, leukemia, and lymphoma survivors with those of cancer-free controls (including siblings) (19–21). Although only a limited number of studies assessed exact doses to the target organ (20), a statistically significant excess of congenital malformations was not detected even among children born to parents with a high gonadal dose (22, 23), and dose-response relationships were

not suggested (22, 23). Studies of preconceptional radiation exposure and pregnancy outcomes in various occupationally and environmentally exposed groups have had limited statistical power because of small sample size, low gonadal dose, lack of dosimetry information, or inadequate comparison groups (19). Although some of the individual malformations showed a positive association with radiation exposure, such as an increased risk of neural tube defects among offspring of male workers at the Hanford plutonium processing site (Richland, Washington), the findings may reflect type I error (24, 25). There was no evidence of an increased risk when congenital malformations were analyzed in aggregate (24–27).

In the Childhood Cancer Survival Study, adverse effects of radiotherapy on stillbirths and neonatal deaths were reported for maternal exposure before menarche, but not for maternal exposure after menarche or for paternal exposure (28). This result was interpreted as reflecting uterine damage induced by high-dose pelvic irradiation prior to puberty (28). Parker et al. (29) reported an excess risk of stillbirths among children of male workers at the Sellafield nuclear facilities (Seascale, Cumbria, United Kingdom). Abrahamson and Tawn (30) examined the findings of Parker et al. and found them to be too high when considered in the context of the foundation of evidence on radiation and mutations. They suggested that inadequate control of background maternal risk factors for adverse outcomes may have led to Parker et al.'s findings (30). In a larger study involving workers in the British nuclear industry, Doyle et al. (27) found no increase in stillbirths among newborns of the males. While they reported that the number of stillbirths increased among children of female workers, this result was considered equivocal because of the small number of female workers (27). A case-control study of children born to childhood and adolescent cancer survivors in Denmark (31) showed no significant association between risk of UPOs (congenital malformation and perinatal death combined) and parental gonadal radiation doses (ovarian dose: median, 0.10 Gy; mean = 1.16 Gy; maximum = 40 Gy; uterine dose: median, 0.10 Gy; mean = 2.30 Gy; maximum = 100 Gy; testicular dose: median, 0.039 Gy; mean = 0.41 Gy; maximum = 8 Gy). Overall, other studies on radiation exposure of parents prior to conception provide mixed evidence on UPOs.

This analysis was based on a study that was implemented more than 70 years ago; the population is unique and represents the most extensive data set on parental radiation exposure and subsequent birth outcomes available to date. The findings show that radiation is associated with increased risk of UPO, but the estimates are imprecise for direct radiation effects, and most are not statistically significant. Nonetheless, the estimates are useful for risk assessment purposes, although extending them to current circumstances comes with uncertainty as to the generalizability of the experience in Hiroshima and Nagasaki. With this report, an effort begun shortly after the atomic bombings of World War II comes to a close. We suggest that additional insights on radiation and reproduction might be gained by using contemporary genomic methods to compare the DNA of parents irradiated by the bombings with that of their children.

ACKNOWLEDGMENTS

Author affiliations: Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan (Michiko Yamada, Yoshimi Tatsukawa); Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan (Kyoji Furukawa, Sachiyo Funamoto, Harry M. Cullings); Department of Information Technology, Radiation Effects Research Foundation, Hiroshima, Japan (Keiko Marumo); Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan (Ritsu Sakata, Kotaro Ozasa); HiroSoft International Corporation, Eureka, California, United States (Dale L. Preston); and Natural Radiation Regulation and Health Environmental Radiation Surveillance Section, Radiation and Nuclear Safety Authority, Helsinki, Finland (Paivi Kurttio).

The advice and guidance provided by Drs. Jonathan M. Samet (Radiation Effects Research Foundation (RERF) Councilor), Robert L. Ullrich (RERF Chief of Research), Roy E. Shore (RERF former Chief of Research), Nori Nakamura (RERF Department of Genetics), Richard Sposto (RERF Department of Statistics; verification for the statistical methodology), and Fumiyoshi Kasagi (RERF Department of Epidemiology) are gratefully acknowledged.

The Radiation Effects Research Foundation (Hiroshima and Nagasaki, Japan) is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare and the US Department of Energy. The views of the authors do not necessarily reflect those of the 2 governments.

Conflict of interest: none declared.

REFERENCES

1. Neel JV, Schull WJ. Studies on the potential genetic effects of the atomic bombs. *Acta Genet Stat Med*. 1956–1957;6(2):183–196.
2. Schull WJ, Otake M, Neel JV. Genetic effects of the atomic bombs: a reappraisal. *Science*. 1981;213(4513):1220–1227.
3. Otake M, Schull WJ, Neel JV. Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: a reanalysis. *Radiat Res*. 1990;122(1):1–11.
4. Neel JV, Schull WJ, Awa AA, et al. The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans. *Am J Hum Genet*. 1990;46(6):1053–1072.
5. Nakamura N. Genetic effects of radiation in atomic-bomb survivors and their children: past, present and future. *J Radiat Res*. 2006;47(suppl B):B67–B73.
6. Grant EJ, Furukawa K, Sakata R, et al. Risk of death among children of atomic bomb survivors after 62 years of follow-up: a cohort study. *Lancet Oncol*. 2015;16(13):1316–1323.
7. Tatsukawa Y, Cologne JB, Hsu WL, et al. Radiation risk of individual multifactorial diseases in offspring of the atomic-bomb survivors: a clinical health study. *J Radiol Prot*. 2013;33(2):281–293.
8. Neel JV, Schull WJ. *The Children of Atomic Bomb Survivors: A Genetic Study*. Washington, DC: National Academy Press; 1991.

9. Cullings HM, Fujita S, Funamoto S, et al. Dose estimation for atomic bomb survivor studies: its evolution and present status. *Radiat Res*. 2006;166(1):219–254.
10. Suzuki Y, Takebayashi Y, Yasumura S, et al. Changes in risk perception of the health effects of radiation and mental health status: the Fukushima Health Management Survey. *Int J Environ Res Public Health*. 2018;15(6): Article 1219.
11. Russell WL. Mutation frequencies in female mice and the estimation of genetic hazards of radiation in women. *Proc Natl Acad Sci U S A*. 1977;74(8):3523–3527.
12. Committee on the Biological Effects of Ionizing Radiation, National Academy of Sciences–National Research Council. *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. Washington, DC: National Academy of Sciences; 1980.
13. Abouzeid Ali HE, Barber RC, Dubrova YE. The effects of maternal irradiation during adulthood on mutation induction and transgenerational instability in mice. *Mutat Res*. 2012; 732(1-2):21–25.
14. Aminu M, Unkels R, Mdegela M, et al. Causes of and factors associated with stillbirth in low- and middle-income countries: a systematic literature review. *BJOG*. 2014; 121(suppl 4):141–153.
15. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics*. 2004; 113(4 suppl):957–968.
16. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014.
17. Kato H, Schull WJ, Neel JV. A cohort-type study of survival in the children of parents exposed to atomic bombings. *Am J Hum Genet*. 1966;18(4):339–373.
18. Lebow RN, Committee for the Compilation of Material on Damage Caused by the Atomic Bombs in Hiroshima and Nagasaki, Ishikawa E, et al. *Hiroshima and Nagasaki: The Physical, Medical, and Social Effects of the Atomic Bombings*. London, United Kingdom: Hutchinson & Co. Ltd.; 1981.
19. Boice JD Jr, Tawn EJ, Winther JF, et al. Genetic effects of radiotherapy for childhood cancer. *Health Phys*. 2003;85(1): 65–80.
20. Little MP, Goodhead DT, Bridges BA, et al. Evidence relevant to untargeted and transgenerational effects in the offspring of irradiated parents. *Mutat Res*. 2013;753(1): 50–67.
21. Shliakhtsitsava K, Romero SAD, Dewald SR, et al. Pregnancy and child health outcomes in pediatric and young adult leukemia and lymphoma survivors: a systematic review. *Leuk Lymphoma*. 2018;59(2):381–397.
22. Signorello LB, Mulvihill JJ, Green DM, et al. Congenital anomalies in the children of cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2012; 30(3):239–245.
23. Winther JF, Boice JD Jr, Frederiksen K, et al. Radiotherapy for childhood cancer and risk for congenital malformations in offspring: a population-based cohort study. *Clin Genet*. 2009; 75(1):50–56.
24. Sever LE, Gilbert ES, Hessol NA, et al. A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. *Am J Epidemiol*. 1988;127(2): 226–242.
25. Lim H, Agopian AJ, Whitehead LW, et al. Maternal occupational exposure to ionizing radiation and major structural birth defects. *Birth Defects Res A Clin Mol Teratol*. 2015;103(4):243–254.
26. Roman E, Doyle P, Ansell P, et al. Health of children born to medical radiographers. *Occup Environ Med*. 1996;53(2): 73–79.
27. Doyle P, Maconochie N, Roman E, et al. Fetal death and congenital malformation in babies born to nuclear industry employees: report from the Nuclear Industry Family Study. *Lancet*. 2000;356(9238):1293–1299.
28. Signorello LB, Mulvihill JJ, Green DM, et al. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. *Lancet*. 2010; 376(9741):624–630.
29. Parker L, Pearce MS, Dickinson HO, et al. Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant. *Lancet*. 1999;354(9188):1407–1414.
30. Abrahamson S, Tawn EJ. Risk of stillbirth in offspring of men exposed to ionising radiation. *J Radiol Prot*. 2001;21(2): 133–144.
31. Winther JF, Olsen JH, Wu H, et al. Genetic disease in the children of Danish survivors of childhood and adolescent cancer. *J Clin Oncol*. 2012;30(1):27–33.