Risk of death among the children of the atomic bomb survivors: an update after 62 years of follow-up

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Research in Context

Evidence before this study:

Hereditary effects have been observed in the progeny of many radiation-exposed species, the first publication of such effects appeared in 1927. Concerns that humans would suffer higher rates of deleterious health effects after parental radiation exposure led to the creation of a cohort study of children conceived after the atomic bombs in Hiroshima and Nagasaki.

Added value of this study:

This study is the longest study of children born to parents with significant preconception ionizing radiation exposure. This study contributes an additional 10 years of follow-up to the last report and now totals nearly 63 years of follow-up. More than 20% of the cohort is now 60 or more years old.

Implications of all the available evidence:

Radiation-induced mutations passed to the children of the atomic bomb survivors have not occurred at rates high enough to produce discernible changes to their mortality rates. This is in line with predictions based on the levels of parental radiation doses and induced mutation rates.

Abstract

Background: No clear epidemiological effects among the progeny of radiation-exposed parents have been demonstrated in humans. This report documents the mortality experiences of the children of the atomic bomb survivors after 62 years of follow-up. No previous studies have investigated mortality into mid-adult ages in a population with significant preconception radiation exposures.

Methods: A cohort study of 75,327 children born to atomic bomb survivors and unexposed controls between 1946 and 1984 were followed from birth through 2009. Parental gonadal doses received from the atomic bombings were the primary exposures. The outcomes were deaths due to cancer and non-cancer diseases based on death certificates.

Findings: A total of 5,183 deaths from disease were observed. The average age of the surviving children at the end of follow-up was 53.1 years with 23% older than age 60. For parents who received non-zero gonadal doses, the average dose was 264 mGy. No elevated risks of death due to cancer or non-cancer diseases were observed in relation to parental gonadal exposure. No modifications of radiation risks were observed by attained age or elapsed time between parental exposure and delivery.

Interpretation: Parental radiation exposure is predicted to increase genetic disease rates in progeny, however there were no indications of deleterious health effects in the children of those exposed to the atomic bombs after 62 years of follow-up. Continued studies of epidemiological data complemented by sensitive molecular techniques are needed to understand the overall effects of preconception exposure to ionizing radiation among humans.

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Introduction

Progeny of radiation-exposed parents are predicted to suffer higher rates of Mendelian and multifactorial diseases. However, no clear epidemiological effects have been demonstrated in the first filial (F1) generation of humans after parental radiation exposure.¹⁻³ Concerns of possible deleterious effects among children conceived after parental exposure to the atomic bombs in Hiroshima and Nagasaki led to the creation of the atomic bomb survivors F1 mortality cohort. Previous reports from this cohort have not found increased rates of cancer incidence or cancer mortality.⁴⁻⁸ Despite these findings, continued surveillance remains a priority as scientific interest and public attention have again focused on the health effects of ionizing radiation. Open scientific questions include the dangers of diagnostic x-rays among children, the full effects of the Fukushima nuclear power plant disaster, and germline mutations that could be passed to following generations.

With nearly 63 years of follow-up, the F1 mortality cohort is the longest running study of children born to parents exposed to ionizing radiation and plays an instrumental role in the search for long-term health effects rooted in parental radiation exposure. This report updates the radiation risks of death due to cancer and non-cancer diseases among the children of the survivors of the atomic bombings through 2009 and represents 10 additional years of follow-up since the last report.⁸

Methods

This study uses a prospective cohort design. Children conceived after the atomic bombings and born in Hiroshima and Nagasaki were identified via city birth records or by active recruitment at city offices where pregnant women could apply for supplemental rice allowances. Parents were interviewed or matched to a master list of survivors based on the 1950 Japanese National Census to determine parental exposure status. All singleton-born children with one or more parent within 2,000 m of the hypocenters were selected. Comparison groups consisting of children born to one or both parents in the city but neither closer than 2,500m to the hypocenters, and both parents outside of the cities at the time of the bombing were matched on year of birth, sex, and city. After the Life Span Study (LSS) cohort of atomic bomb survivors was established in 1958,⁹ all singleton children born to an LSS member exposed within 10,000 m were automatically added to the F1 mortality cohort. Thus, the F1 mortality cohort includes a high percentage of all children born to proximally exposed atomic bomb survivors who were born in Hiroshima or Nagasaki. The earliest entry date was May 1946 (10 months after the bombing) and the latest entry year was 1984 when births effectively ceased as the survivors advanced in age.

The F1 mortality cohort consists of 76,814 persons. Persons were excluded from this study if they were not Japanese nationals (763), their residence could not be determined (663), had an unknown date of death (2), they explicitly withdrew from the study (8), or if they did not survive one day (51). The total number of subjects analyzed for this study was 75,327. Date of entry was the child's date of birth and the exit date was the date of death or December 31, 2009 (the last year of complete follow-up data). Vital status was determined using the compulsory Japanese family registry system, which provides virtually complete ascertainment of vital status for all resident Japanese nationals. The primary cause of death was determined from death certificates. Deaths due to non-cancer diseases (ICD-9 codes 1-100; 210-799), and cancers (ICD-9 codes 140-208) including hematopoietic cancers (ICD-9 codes 204-208) were

analyzed.¹⁰ Deaths due to external causes (ICD-9 codes 800-998) or unknown causes (ICD-9 code 999) were censored.

Parental Radiation Exposure Estimates

Data for determining a parent's exposure conditions were generally obtained via one or more interviews. During the active recruitment period, expectant parents were interviewed. In 1950, the Japanese national census included a supplemental attachment to identify atomic bomb survivors. From this master list, survivors still living in Hiroshima or Nagasaki were interviewed to determine their exposure conditions (for a more detailed explanation, please see Ozasa 2013¹¹). Using the collected exposure information, parental radiation doses were calculated using Dosimetry System 2002, which provides gonadal gamma and neutron dose estimates based on distance from the bomb, shielding conditions, body orientation, and age at exposure.¹² Doses derived from the system were adjusted to remove known dose errors.¹³ A weighted gonadal dose (gamma + 10*neutron) was used to account for the greater biological effectiveness of neutrons, which is consistent with current estimates for neutron quality factors and has been traditionally used for the atomic bomb studies. The dosimetry system can calculate arbitrarily small doses; in order to create dose categories, weighted gonadal doses of less than 1 mGy were truncated to 0 mGy for all analyses (n=4,643 mothers and n=2,764 fathers). There were roughly 4,000 mothers and 3,000 fathers for whom a dose could not be assigned, primarily due to complex shielding conditions for which the dosimetry system could not calculate a dose. Many of these persons were at locations where a substantial dose could have been expected; they are included in the study but modeled using special consideration. There were also approximately 8,000 mothers and 8,000 fathers whose whereabouts were unknown ATB and were assumed to be "not in city" (NIC).

Statistical Methods

Hazard ratios (HR) and 95% confidence intervals for cancer and non-cancer disease deaths were estimated using proportional hazards methods.¹⁴ The primary time scale was attained age. Separately modeled father and mother gonadal radiation doses in weighted gray were the primary exposures. The effects of exposure were estimated with categorical dose groups (0, 1-49, 50-149, 150-499, 500+ mGy, and unknown) and a continuous log-linear response model to estimate the HR at 1 gray. Parents NIC at the time of the bombing were assigned 0 Gy dose and an indicator representing this exposure group was included. In many of the included tables, counts of deaths were combined for all groups with 0 dose but the statistical reference group was children born to a parent who was "in city" ATB but with an estimated dose of zero (roughly those located between about 3,500-10,000 m from the hypocenters). Parents with "unknown dose" (i.e. "in city" ATB and close enough to receive a dose but not having an estimated dose due to complex shielding conditions) were represented with an indicator variable and were always included when testing dose effects. A likelihood ratio test for improved model fit was used to test the significance of including radiation exposure in the model. Ninety-five percent confidence intervals (calculated with profile likelihood) and two-sided p-values were reported. Other model covariates were: city of parental exposure, sex of child, year of birth and its squared term (integer values, centered at the average, 1956), mother's age at time of delivery and its squared term (continuous, centered at the average, age 29; those with unknown age were assigned the average), and indicator variables for the study follow-up phases (1946-1948, *post hoc* passive linkage to city records; 1948-1953, active recruitment at city offices; 1953-1958 passive linkage to city records; 1959-1984 passive linkage to city records for children of the LSS cohort exposed within the city). See Table 1. Covariates were selected primarily based on biological relevance for factors related to

neonatal health (i.e. mother's age at time of delivery, sex of child) as well as study design variables (i.e. city, follow-up phase). The squared terms were added to allow for non-linear trends with age and year, and statistically improved the model fit. An alternative model applied to those born prior to 1959, when matching by distance was performed, used the same explanatory variables but tested the HR of children with one or more parents exposed to ≥ 1 mGy compared to those with both parents with assigned doses of 0 mGy. Statistical procedures were performed using the Peanuts module of Epicure.¹⁵

The Radiation Effects Research Foundation's Human Investigation Committee approved the study.

Results

The demographics of the cohort and parents were shown in Table 1. Slightly more than half (51%) of the children were male and 62% were born in Hiroshima. Approximately 50% of the cohort was born prior to 1955. Mothers tended to be slightly younger than fathers at the time of delivery and a complete cross-section of ages ATB were represented.

Table 2 shows the cross-tabulated distribution of parental radiation doses. 31% of mothers were exposed to known doses greater than zero compared to 21% of fathers, reflecting the relative absence of men in the city ATB due to the wartime effort. Approximately 16,000 mothers and 11,000 fathers were "in city" ATB with an estimated dose of 0 mGy. The average weighted dose of exposed parents with non-zero doses was 264 mGy (SD=463).

Over the follow-up period, there were a total of 6,567 deaths. Of the total, 3,937 deaths (60%) were attributed to non-cancer diseases while 1,246 (19%) were attributed to cancer (including hematopoietic cancers). 1,288 deaths were due to external causes and 96 deaths were due to unknown causes. The average age of those still alive at the end of 2009 was 53.1 years (SD=7.9, range: 25.7-63.7) with 23% older than age 60. Among those who died of non-cancer diseases, the timing of the deaths was bimodal. The average age for those who died of non-cancer diseases prior to age 20 was 2.0 years (SD=3.4), while it was 45.8 (SD=11.0) for those dying after age 20. For cancer deaths the average age at death was 47.0 (SD=12.2). Counts, person-years and crude mortality rates are shown in Table 3. Crude mortality rates for those with non-zero parental radiation exposure were not elevated compared to those with 0 mGy exposure.

Crude non-cancer disease death rates by attained age were highest at young ages and were higher for the earliest birth cohort compared to the later birth cohorts (Figure 1). Crude rates for non-cancer disease deaths were elevated at all ages for the earliest birth cohort. Crude rates for cancer deaths were near zero for all birth cohorts until about age 30 when they began to rise.

The upper panel in Table 4 shows the sex-averaged HRs of radiation for non-cancer disease deaths after maternal radiation exposure for children over their full age range, ages <20 , and ages ≥ 20 . For the full age range, no maternal radiation categories indicated elevated risks and there was no overall improvement in model fit after including the five exposure categories (four non-zero categories and the 'unknown' category, $p>0.5$). When modeling risk as a continuous function of maternal gonadal dose, the HR was 0.973 (95% confidence intervals (CI): 0.846, 1.111; $p>0.50$). Roughly two-thirds of the non-cancer disease deaths occurred prior to age 20 but the HR was similar to the full range and again not statistically significant

($p > 0.50$). In a separate analysis starting at age 20, no relationship with maternal radiation exposure was observed. The lower panel of Table 4 shows the risks of paternal gonadal exposure. For the full age range the HR was 1.103 (95% CI: 0.975, 1.236; $p = 0.116$). Similar non-significant results were seen for the periods before and after age 20 ($p = 0.291$ and $p = 0.215$, respectively).

Table 5 shows the sex-averaged HRs of cancer deaths (solid and hematopoietic combined) for maternal gonadal exposure (upper panel) and paternal exposure (lower panel). For the full age range, HR point estimates for cancer deaths were not elevated for any dose category and no improvement in the model fit was detected when including the radiation dose categories compared to the baseline model for either maternal exposure ($p = 0.123$) or paternal exposure ($p = 0.451$). The continuous dose response for maternal exposure was 0.891 (95% CI 0.684, 1.131; $p = 0.356$), while the estimate was 0.815 (95% CI 0.601, 1.062; $p = 0.136$) for paternal exposure. In the period less than age 20, there were only 59 cancer cases, so all known non-zero dose categories were combined. No improvements in model fit were evident when adding two categories to the model (exposed to >0 or unknown dose) for maternal exposure ($p = 0.300$) or paternal exposure ($p = 0.361$). For those aged 20 and beyond, there were sufficient cases to investigate the response by dose categories but the estimates for all categories were consistent with the reference group; the point estimates for the continuous dose responses were also non-significant for both maternal exposure (HR=0.855; 95% CI: 0.646, 1.099; $p = 0.231$) and paternal exposure (HR=0.850; 95% CI: 0.628, 1.105; $p = 0.238$).

Among those born ≤ 1958 , the HR of children born to either parent exposed to ≥ 1 mGy ($n = 22,861$) compared to both parents exposed to 0 mGy ($n = 29,196$) for all disease deaths ($n = 4,596$) was 1.014 (95% CI: 0.957, 1.075; $p > 0.50$).

Analyses indicated no significant interactions between radiation and the elapsed time between exposure and childbirth ($p = 0.307$ for fathers and $p = 0.287$ for mothers). Also, the earliest birth cohort did not show higher radiation effects compared with later birth cohorts for either paternal or maternal exposure. Roughly 21% of deaths were due to external or unknown causes; the radiation risks of deaths due to any cause were tested as an outcome but no elevated risks were observed for either parental exposure. Older age of the mother at the time of delivery was positively and significantly associated with non-cancer disease deaths over the full age range of the child as well as for deaths occurring prior to age 20, while female children had lower risks for cancer and non-cancer disease deaths (data not shown).

Discussion

This study did not detect any associations of parental radiation exposure and death among children of the atomic bombings in Hiroshima and Nagasaki. Analyses were conducted for maternal and paternal exposures, outcomes prior to and after age 20, and for cancer and non-cancer causes of deaths. Non-cancer disease deaths occurred more frequently in the early follow-up period while cancer deaths tended to occur more often in the later period. This cohort of over 75,000 includes a high proportion of all children born to proximally exposed atomic bomb survivors who resided in Hiroshima or Nagasaki at the time of their child's birth. Follow-up began on the child's first full day of life and continued to the end of 2009; approximately 3.8 million person-years and over 5,000 disease-related deaths were recorded. These results corroborate previous findings reported on mortality among the children of the atomic bomb survivors, which have all been negative.^{4,6,8}

Current models predict higher rates of mutations in the progeny of radiation exposed populations leading to higher incidence of Mendelian and multifactorial diseases.^{2,16} An extensive review has recently been published by Little et al describing the current state of evidence for transgenerational effects.¹⁷ Animal studies appear to support findings of somatic cell changes in the offspring irradiated males. Further, there appears to be stronger evidence when conception occurs shortly after irradiation indicating that spermatozoa rather than spermatids may be responsible.

Human studies have attempted to detect molecular changes in the F1 after parental radiation exposure. Livshits et al reported no elevation in the mutation rates in minisatellite alleles comparing children of Chernobyl cleanup workers to unexposed controls but did suggest that children conceived after recent paternal exposure showed higher mutation rates than those with exposures that occurred more than four months prior, although the difference was not statistically significant.¹⁸ Dubrova et al reported higher paternal germline mutation rates in minisatellite loci in families residing near the Techa river compared to families living in non-exposed areas.¹⁹ Among the children of the atomic bomb survivors, Neel and Schull reported no changes in the sex-ratio of births or increases of chromosomal aberrations among children of exposed parents.²⁰ More recent work by Kodaira et al found no increases in minisatellite or microsatellite loci.^{21,22} Tawn et al reported no increases in mutation rates among children born to survivors of childhood cancer who had received radiotherapy.²³

Epidemiological data from human-exposed populations have generally not shown an association with parental exposure. For example, Signorello recently reported no increase in congenital malformations among childhood cancer survivors who were received gonadal radiation doses during treatment.²⁴ Studies among childhood cancer survivors are rich pools from which to draw subjects with high gonadal exposures however, the underlying mechanisms that caused the initial cancer may bias the results and preclude their generalizability.

This study had many strengths. Individual parental exposure data were exceptional for a population-based study and were generally collected prior to the baby's birth, which should eliminate most outcome-dependent recall bias. Parental doses ranged from 0 to more than 1 gray, with an average of more than 250 mGy among the exposed. Mortality data were nearly complete for the cohort and the each cause of death was consistently coded using international standards. Finally, a large percentage of children born to proximal survivors who remained in Hiroshima and Nagasaki are included in the cohort from the years 1946 to 1984. The study also had weaknesses. Mortality data may mask disease course and preclude using date at onset. Not all children of the survivors were included; unknown biases may have been introduced due to migration and selection issues.

Despite the strengths and size of the study, it was still underpowered to detect radiation-induced disease deaths based on current transgenerational models. We were unable to find associations of paternal (or maternal) exposure or interactions of radiation dose and the timing of exposure. Tatsukawa's clinical study of a sub-cohort of this F1 mortality cohort was recently converted to a longitudinal design, which should increase the detection sensitivity and precision of disease onset timing. Also, the availability of biosamples should allow us to combine both phenotype and molecular data. Additional epidemiological follow-up will also be valuable as more than 90% of the cohort is still alive. Together, these data will increase our statistical power in future studies.

In conclusion, the results of this study extend our knowledge of the health effects in the F1 generation of irradiated humans using previously unavailable information. To date, no deleterious effects have been observed in epidemiological studies of the F1 cohort of the atomic bomb survivors. The results, however, do not prove that radiation effects are absent in this cohort. Radiation-induced germline mutations have been observed in other species and, while the mutation rates are clearly low, humans are unlikely to have a fundamentally different radiobiological response. Further epidemiological, clinical, and molecular research using more sensitive techniques should help to clarify the overall effects of preconception exposure to ionizing radiation among humans.

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Figure 1. Sex-averaged crude death rates for non-cancer and cancer deaths by birth cohort and attained age. The birth cohort immediately succeeding the bombs shows higher non-cancer death rates throughout life.

Table 1. Characteristics of the F1 cohort and their parents.

Description	Number of subjects (%)	
Total	75,327	100
Sex		
Male	38,590	51.2
Female	36,737	48.8
City of Birth		
Hiroshima	46,828	62.1
Nagasaki	28,499	37.9
Data Collection Period ^a (birth years)		
Pre Genetics Study (1946-48)	10,154	13.5
Genetics Study (1948-53)	25,268	33.5
Sex Ratio Study (1953-58)	16,635	22.1
LSS Children (1959-84)	23,270	30.9
Age of those alive in 2009 (years)		
Male (average and range)	53.0	25.7-63.7
Female (average and range)	53.2	25.8-63.7
Fathers ^b		
Age at Time of Bombing (years)		
<10	9,540	12.7
10-19	19,960	26.5
20-29	27,218	36.1
30+	18,257	24.2
Unknown	352	0.5
Age at Time of Delivery (years)		
<20	33	0.0
20-24	2,833	3.8
25-29	18,374	24.4
30-34	27,068	35.9
35+	26,667	35.4
Unknown	352	0.5
Mothers ^b		
Age at Time of Bombing (years)		
<10	14,251	18.9
10-19	27,228	36.2
20-29	26,248	34.8
30+	7,088	9.4
Unknown	512	0.7
Age at Time of Delivery (years)		
<20	453	0.6
20-24	13,222	17.6
25-29	30,986	41.1
30-34	19,651	26.1
35+	10,503	13.9
Unknown	512	0.7

^a Assignments are approximate

^b Each parent is listed independently for each child

Table 2. Distribution of parental gonadal radiation exposures by location status and radiation dose categories.

Location at time of bombing		Mothers								Total	
		No Information	NIC ^a	In City	In City	In City	In City	In City	In City		
		0	0	0 ^b	1-49	50-149	150-499	500+	Unknown		
Fathers	No Information	0	3	1	1,976	2,305	1,251	1,514	839	432	8,321
	NIC ^a	0	3	16,731	7,396	3,999	1,949	2,093	1,835	2,488	36,494
	In City	0 ^b	1,981	2,645	3,855	1,122	457	451	330	398	11,239
	In City	1-49	2,348	1,304	1,061	1,294	335	321	194	206	7,063
	In City	50-149	1,083	686	378	344	296	122	52	87	3,048
	In City	150-500	1,359	643	447	315	139	288	57	55	3,303
	In City	500+	881	790	535	295	65	99	195	95	2,955
	In City	Unknown	427	859	702	401	117	148	104	146	2,904
Total			8,085	23,659	16,350	10,075	4,609	5,036	3,606	3,907	75,327

^a NIC: Not in city

^b persons with an estimated dose of <1 mGy were assigned 0 mGy.

Table 3. Subjects, deaths and crude mortality rates by cause of death and parental exposure status.

	Subjects	Person-years ^b	Cause of Death							
			Non-Cancer Disease		Cancer		External Cause ^a		Unknown ^a	
			Count	Crude Rate ^c	Count	Crude Rate ^c	Count	Crude Rate ^c	Count	Crude Rate ^c
All Subjects	75,327	38.12	3,937	103.3	1,246	32.7	1,288	33.8	96	2.5
Father's Exposure Status										
0 mGy ^d	56,054	28.77	3,034	105.4	1,003	34.8	994	34.5	86	3.0
≥1 mGy ^e	19,273	93.5	903	96.6	243	26.0	294	31.4	10	1.1
Mother's Exposure Status										
0 mGy ^d	48,094	24.48	2,525	103.1	806	32.9	863	35.2	69	2.8
≥1 mGy ^e	27,233	13.64	1,412	103.5	440	32.3	425	31.2	27	2.0

^a This category of deaths was not included in the analyses; it is included for completeness

^b x100,000

^c per 100,000 person-years

^d Includes subjects in “not-in-city” and “no information” categories, and those with <1 mGy exposure

^e Includes subjects in ‘unknown dose’ category

Table 4. Non-cancer mortality hazard ratios (HR) after parental radiation exposure to the gonads. Upper panel: maternal radiation exposure; Lower panel: paternal exposure. Results were adjusted for city of parental exposure, sex of child, year of birth and its squared term, mother's age at time of delivery and its squared term, and included indicator variables for the study follow-up phases and not-in-city status.

Mother's Exposure (mGy)	All Ages					Age 0- <20					Age ≥20				
	Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value	
0	2,525 ^a	-				1,692 ^b	-				833 ^c	-			
1-49	548	1.045	0.940	1.161		368	1.038	0.912	1.180		180	1.061	0.881	1.275	
50-149	232	0.969	0.837	1.117		148	0.917	0.764	1.095		84	1.073	0.837	1.361	
150-499	236	0.962	0.832	1.109	>0.50 ^d	157	0.945	0.790	1.123	>0.50 ^d	79	1.001	0.776	1.276	>0.50 ^d
500+	176	0.991	0.840	1.161		119	0.985	0.805	1.194		57	1.007	0.71	1.325	
Unknown	220	1.027	0.884	1.189		146	1.014	0.843	1.212		74	1.053	0.810	1.351	
Continuous (1 Gy)		0.973	0.846	1.111	>0.50 ^e		0.967	0.814	1.136	>0.50 ^e		0.988	0.771	1.237	>0.50 ^e

^a includes 1,600 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^b includes 1,068 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^c includes 532 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^d likelihood test for heterogeneity (5 degrees of freedom)

^e likelihood test for continuous response (1 degree of freedom)

Father's Exposure (mGy)	All Ages					Age 0- <20					Age ≥20				
	Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value	
0	3,034 ^a	-				2,032 ^b	-				1,002 ^c	-			
1-49	315	0.972	0.847	1.113		205	0.906	0.765	1.070		110	1.118	0.881	1.411	
50-149	140	0.986	0.818	1.182		92	0.936	0.742	1.168		48	1.095	0.789	1.491	
150-499	140	0.966	0.800	1.157	>0.50 ^d	92	0.910	0.722	1.135	>0.50 ^d	48	1.095	0.789	1.490	>0.50 ^d
500+	145	1.061	0.882	1.268		95	1.000	0.794	1.241		50	1.203	0.871	1.630	
Unknown	163	0.987	0.827	1.171		114	0.993	0.803	1.218		49	0.968	0.699	1.316	
Continuous (1 Gy)		1.103	0.975	1.236	0.116 ^e		1.084	0.930	1.248	0.291 ^e		1.141	0.922	1.379	0.215 ^e

^a includes 2,424 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^b includes 1,612 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^c includes 812 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^d likelihood test for heterogeneity (5 degrees of freedom)

^e likelihood test for continuous response (1 degree of freedom)

Table 5. Cancer mortality hazard ratios (HR) after parental radiation exposure to the gonads. Upper panel: maternal radiation exposure; Lower panel: paternal exposure. Results were adjusted for city of parental exposure, sex of child, year of birth and its squared term, mother's age at time of delivery and its squared term, and included indicator variables for the study follow-up phases and not-in-city status.

Mother's Exposure (mGy)	All Ages					Age 0- <20					Age ≥20				
	Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value	
0	806 ^a	-				39 ^b	-				767 ^c	-			
1-49	184	1.092	0.907	1.310		7	0.944	0.474	1.926	0.300 ^e	177	1.108	0.917	1.335	
50-149	67	0.883	0.672	1.144		3					64	0.888	0.671	1.157	
150-499	81	1.046	0.813	1.330	0.123 ^d	3					78	1.065	0.824	1.361	0.147 ^d
500+	56	0.970	0.722	1.279		6					50	0.917	0.671	1.227	
Unknown	52	0.721	0.530	0.959		1	0.271	0.015	1.356		51	0.745	0.546	0.995	
Continuous (1 Gy)		0.891	0.684	1.131	0.356 ^f		1.467	0.580	2.805	0.369 ^f		0.855	0.646	1.099	0.231 ^f

^a includes 504 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^b includes 25 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^c includes 479 cases born to mothers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose mothers

^d likelihood test for heterogeneity (5 degrees of freedom)

^e likelihood test for continuous response (2 degrees of freedom)

^f likelihood test (1 degree of freedom)

Father's Exposure (mGy)	All Ages					Age 0- <20					Age ≥20				
	Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value		Cases	HR	95% CI	p-value	
0	1,003 ^a	-				46 ^b	-				957 ^c	-			
1-49	93	0.943	0.732	1.205		5	0.734	0.279	1.965	0.361 ^e	88	0.944	0.728	1.214	
50-149	31	0.735	0.493	1.058		3					28	0.699	0.460	1.023	
150-499	42	0.973	0.688	1.345	0.451 ^d	1					41	1.007	0.708	1.398	0.308 ^d
500+	35	0.830	0.569	1.175		0					35	0.878	0.601	1.245	
Unknown	42	0.782	0.552	1.082		4	1.838	0.487	5.901		38	0.738	0.512	1.036	
Continuous (1 Gy)		0.815	0.601	1.062	0.136 ^f		ND ^g					0.850	0.628	1.105	0.238 ^f

^a includes 813 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^b includes 38 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^c includes 773 cases born to fathers who were not-in-city at the time of the bombing; the reference group is offspring of 0-dose fathers

^d likelihood test for heterogeneity (5 degrees of freedom)

^e likelihood test for heterogeneity (2 degree of freedom)

^f likelihood test for continuous response (1 degree of freedom)

^g Not determined