

RESEARCH ARTICLE

Initial Report for the Radiation Effects Research Foundation F1 Mail Survey

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Abstract

To study the full health effects of parental radiation exposure on the children of the atomic bomb survivors, the Radiation Effects Research Foundation developed a cohort of 76,814 children born to atomic bomb survivors (F1 generation) to assess cancer incidence and mortality from common adult diseases. In analyzing radiation-associated health information, it is important to be able to adjust for sociodemographic and lifestyle variations that may affect health. In order to gain this and other background information on the F1 cohort and to determine willingness to participate in a related clinical study, the F1 Mail Survey Questionnaire was designed with questions corresponding to relevant health, sociodemographic, and lifestyle indicators. Between the years 2000 and 2006, the survey was sent to a subset of the F1 Mortality Cohort. A total of 16,183 surveys were completed and returned: 10,980 surveys from Hiroshima residents and 5,203 from Nagasaki residents. The response rate was 65.6%, varying somewhat across parental exposure category, city, gender, and year of birth. Differences in health and lifestyle were noted in several variables on comparison across city and gender. No major differences in health, lifestyle, sociodemographics, or disease were seen across parental exposure categories, though statistically significant tests for heterogeneity and linear trend revealed some possible changes with dose. The data described herein provide a foundation for studies in the future.

Keywords: Radiation - epidemiology - children of atomic bomb survivors, disease prevalence, lifestyle, mail survey

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Introduction

One of the primary foci of the Radiation Effects Research Foundation (RERF) is to monitor the offspring of the atomic bomb survivors and determine whether there are any radiation-related health effects in the first generation after the bombings (F1 generation). To that end, the F1 mortality cohort was established, consisting of offspring born between 1946 and 1984 to atomic bomb survivors and a comparison group of children born during the same time frame to non-exposed parents who were not in the city at the time of the bombing (Kato and Schull, 1960).

To this date, there have been no observable effects of parental atomic bomb radiation exposure on their first generation offspring, including effects on childhood and adult cancers (Yoshimoto et al., 1990; Izumi et al., 2003), chromosome aberration frequency (Kodaira et al., 2010), enzymatic activity (Neel et al., 1988), mortality (Kato et al., 1966; Neel et al., 1974; Yoshimoto et al., 1991; Little et al., 1994; Grant et al., 2015), pregnancy outcome (Neel and Schull, 1956; Otake et al., 1990), and prevalence of multifactorial (that is, lifestyle-related) diseases (Fujiwara

et al., 2008; Tatsukawa et al., 2013). As animal studies have confirmed, it is possible for irradiation of parents pre-conception to induce mutations in the F1 generation (Rinchik et al., 1986; Barber et al., 2002; Shiraishi et al., 2002; Barber et al., 2006; Barber et al., 2009; Abouzeid Ali, et al., 2012), and as the F1 Mortality Cohort is just now entering the stages of life where more cancers and lifestyle-related diseases are to be expected, further studies are warranted.

An F1 Clinical Studies Cohort was conceived for the purpose of more closely monitoring morbidities due to parental radiation exposure. In order to both inquire into F1 Mortality Cohort subject willingness to participate in such a study and to determine baseline epidemiological information for mortality and cancer/non-cancer incidence studies, the F1 Mail Survey was undertaken (Koyama et al., 2002; Fujiwara et al., 2008; Tatsukawa et al., 2013).

This report was drafted to record the initial results of this mail survey in terms of prevalence of self-reported health indices and differences in subjects' sociodemographics and lifestyles, and to perform a cursory analysis of health factors by parental radiation dose.

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Materials and Methods

Study population

The F1 Mortality Cohort is composed of 76,814 subjects born between May 1, 1946 (nine months after the bombings) and December 31, 1984 to survivors of the atomic bombings (both proximal and distal to the hypocenter) as well as children born in the same years to parents who were not in either city (NIC) at the time of the bombings (ATB) (Kato and Schull, 1960).

Initial candidates for the F1 Mail Survey cohort were selected from the F1 Mortality Cohort using the following criteria:

A. Matched exposed: Subject must have met at least one of the following conditions: 1) Dosimetry System 1986 (DS86) dose estimates were available for both parents, and at least one parent received a dose greater than 5 mGy, 2) Either parent received a dose greater than 1000 mGy regardless of the other parent, 3) Both parents were exposed but did not have available DS86 doses.

B. Matched controls: Subject must have met the condition that both parents received doses of less than 5 mGy or were not in the city at the time of the bombing. These subjects were matched to exposed subjects (A) on city, sex, and age.

C. Unmatched controls: Subject met the parental exposure conditions required for B, but was not matched to A.

D. Reserve exposed: Subject did not meet any of the above conditions, but at least one parent was exposed to 5-999 mGy of radiation.

A total of 17,698 eligible subjects met the inclusion criteria (n=7,774 from group A, 5,222 from group B, and 4,702 from group C). To increase the overall mailing contact numbers, mail survey expansions were endorsed. Another 6,975 subjects from groups A and D were selected for this expansion, provided they lived in or near Hiroshima or Nagasaki according to the respective municipality offices. In total, 24,673 subjects were selected to receive the mail survey, making up the F1 Mail Survey recipients sample.

The cohort was designed to ensure males and females were evenly represented and that Hiroshima had twice the representation as Nagasaki to adequately reflect the demographics existing in the F1 Mortality Cohort.

Mailing

A pilot study (Koyama et al., 2002) was conducted to determine expected response rate, completeness of the returned questionnaire, cost of processing, and problems within the questionnaire. Questionnaires were sent to 300 members of the F1 Mail Survey recipients sample in May and June 2000. The overall response rate for the pilot study was 72.0%. The questionnaire was modified according to the responses and comments received from the pilot study. The final form for use in the full study contained questions relating to demographics, height, weight, general health, medical history, mental health status, smoking and drinking habits, eating habits, activity levels, women's health, and whether subjects would be willing to participate in clinical examinations. Surveys

were mailed to the addresses of F1 Mail Survey sample subjects. If the questionnaire was not returned, up to three reminders were sent to subjects. Subjects who returned and answered at least one question on the questionnaire were included in the analysis, excepting subjects who only answered the question regarding whether they would be willing to visit the RERF clinic.

Analysis

Parental data regarding ground distance from the hypocenter and testicular/ovarian dose as estimated by the Dosimetry System 2002 (DS02) was linked to the respondents (Joint US- Japan Working Group, 2005). As doses in this system and the previous DS86 (used for selecting the study population) are highly correlated, these newer, more accurate doses were used for analysis (Cullings et al., 2006). As per RERF's methodology, adjustments were made for dose error (Cullings et al., 2006) and a weighted dose (the gamma dose plus ten times the neutron dose) was used. In-city paternal and maternal gonadal doses were divided into three exposure categories for summary analyses: <1 mGy, 1-99 mGy, and 100+ mGy. The choice of 1mGy as the lowest cutoff stems from the most recent paper published describing the F1 Mortality Cohort

(Grant et al., 2015); as low-dose studies have recently been of interest to the epidemiological community, this paper intends to contribute to providing low dose information. Those subjects with either a mother or father exposed within either city but for whom a dose could not be estimated (typically due to complex shielding scenarios) were classified as "dose unknown" for that parent. A fifth category included subjects with parents who were NIC at the time of the bombing and assigned 0 mGy exposure. A "no information" group, which includes subjects with a parent for whom neither dose nor distance information was available, exists in this cohort for both paternal and maternal dose. The likely reason no information was available for these parents is that they were not in the city at the time of the bombing and were only connected to the database after the birth of their child with an individual who was in the city during the bombing. These parents were therefore considered NIC. Subjects with a parent in this group invariably also had an exposed parent (i.e., not NIC). Thus, paternal and maternal dose were divided into the three gonadal dose groups and the NIC group. A conjoint dose was used, as well, which combined the doses of both parents. In the conjoint dose groups, a subject was classified as NIC if both parents were NIC, exposed to <1 mGy if at least one parent was in city and both parents were exposed to a total of less than 1 mGy at the time of the bombing, and either 1-99 mGy or 100+ mGy if either parent or both parents were exposed to at least 1 mGy, depending on the total summed dose.

Tabulations and summary statistics were used to calculate numbers (and percentages) of study subjects for categorical variables and means (and standard deviations) for continuous variables across subjects' city and sex. Tabulations were conducted with chi-squared tests and t- tests (where appropriate) to ensure the mail survey respondents were representative of both a) all intended

recipients of the mail survey and b) the full F1 Mortality Cohort in terms of gender, year of birth, father's exposure, and mother's exposure.

To infer predicted percentages and means across paternal, maternal, and combined parental dose categories, logistic and linear regression were used for categorical and continuous variables, respectively. These models were used to conduct separate tests for both heterogeneity and linear trend to determine the potential impact of parental dose on any diseases, physical or mental. Unfortunately, due to unfounded concern about potential risk heterogeneity stemming from differences in demographics and lifestyle between the exposed and NIC populations, no children were added to the F1 Mortality Cohort if both parents were NIC after 1959, resulting in a skewed NIC age distribution. Furthermore, matching procedures changed after 1959, resulting in the <1 mGy group having a greater proportion of individuals born before 1959 than did the other dose groups. Logistic and linear regressions therefore adjusted for age; the models also adjusted for city. Rather than adjusting for gender, regressions were run separately for each sex. The four categorical dose categories described above were used in all models, but unknown dose and NIC groups were controlled for in each regression analysis. Thus, heterogeneity and linear trend tests only took into account the three exposed dose groups. All tabulations consider missing data, though missing data are not reported; therefore, tabulations do not sum to 100%. Variables were clustered by category for analysis; the major categories were demographics, general health, disease history, mental health, lifestyle, and women's health.

All analyses were performed with STATA Data Analysis and Statistical Software (StataCorp LP, 2013).

Review and approval

All methods were approved by the external committee known as the Scientific and Ethical Committees for the Health Effects Study of the Children of A-bomb Survivors,

which consists of ethicists, lawyers, psychiatrists, and scientists, to ensure the integrity of its studies.

Results

Response

Table 1 details the construction of the mail survey respondents cohort in comparison to the mail survey recipients and the full F1 Mortality Cohort; it also provides final response rates from those who received the survey.

After the pilot mailing and the first mailing, 12.9% of recipients responded; after the second and third mailings, 30.6% and 48.2% of the recipients responded, respectively. Finally, after the fourth mailing, 65.6% of prospective participants had returned the questionnaire (not shown). Of the 16,386 subjects who returned a questionnaire, 61 (0.56%) in Hiroshima and 142 (2.73%) in Nagasaki declined to answer the questions or only answered the question regarding whether they would be willing to visit the RERF clinic. These individuals were classified as non-respondents; they made up 1.14% of total non-respondents in Hiroshima and 4.55% in Nagasaki. Final response rates appeared higher in Hiroshima than Nagasaki, higher among older subjects, and lower among subjects with NIC mothers in both cities. The final mail survey respondents cohort had variable-specific response rates that resulted in a distribution similar to that of both the mail survey recipients and the full F1 Mortality Cohort.

Among the respondents, response rates for the individual questions were excellent. The question regarding whether participants would be willing to come for clinical checkups had the poorest response rate (~96%) across gender, city, and parental dose groups. None of the other questions had response rates lower than 98%.

Population characteristics

In total, 16,183 (65.6%) recipients both returned and answered at least one of the questions on the questionnaire (not including the question regarding willingness to come

Table 1. Comparison of Full F1 Mortality Cohort, Mail Survey Recipients, and Mail Survey Cohort

		Full Mortality Cohort		Mail Survey Sample (Survey Recipients)		Final F1 Mail Survey Cohort		Final Response %
		N	%	N	%	N	%	%
Total		76,814	100.0	24,673	100.0	16,183	100.0	65.6
City	Hiroshima	48,014	62.5	16,348	66.3	10,980	67.8	67.2
	Nagasaki	28,800	37.5	8,325	33.7	5,203	32.2	62.5
Gender	Male	39,398	51.3	13,389	54.3	8,101	50.1	60.5
	Female	37,416	48.7	11,284	45.7	8,082	49.9	71.6
Father's Exposure Status	NIC	45,632	59.4	13,235	53.6	8,537	52.8	64.5
	<1 mGy	11,492	15.0	3,284	13.3	2,255	13.9	68.7
	1-99 mGy	8,967	11.7	3,662	14.8	2,390	14.8	65.3
	100+ mGy	7,741	10.1	4,084	16.6	2,719	16.8	66.6
Mother's Exposure Status	Dose unknown	2,982	3.88	408	1.65	282	1.74	69.1
	NIC	32,409	42.2	8,662	35.1	5,309	32.8	61.3
	<1 mGy	16,647	21.7	4,879	19.8	3,355	20.7	68.8
	1-99 mGy	13,175	17.2	5,361	21.7	3,546	21.9	66.1
Dose unknown	100+ mGy	10,631	13.8	5,471	22.2	3,759	23.2	68.7
		3,952	5.14	300	1.22	214	1.32	71.3

Table 2. Counts and Percentages of Demographics, General Health, Lifestyle by Gender and City

		Male		Female		Hiroshima		Nagasaki		
		N	%*	N	%*	N	%*	N	%*	
Demographics	Education	Junior high school	677	8.36	443	5.48	618	5.63	502	9.65
		High school	3470	42.8	4250	52.6	4767	43.4	2953	56.8
		Junior college	312	3.85	1995	24.7	1670	15.2	637	12.2
		University	3241	40.0	865	10.7	3296	30.0	810	15.6
		Graduate school	143	1.77	24	0.30	132	1.20	35	0.67
	Currently Employed	Other (technical school)	219	2.70	462	5.72	446	4.06	235	4.52
		Yes	7544	93.1	5404	66.9	8876	80.8	4072	78.3
		Never married	1109	13.7	1285	15.9	1541	14.0	853	16.4
	Marital Status	Married	6444	79.6	5777	71.5	8431	76.8	3790	72.8
		Divorced	409	5.05	729	9.02	734	6.68	404	7.76
Widowed		52	0.64	234	2.90	189	1.72	97	1.86	
Other		18	0.22	11	0.14	21	0.19	8	0.15	
General Health	Current Medical Condition	Good	1874	23.1	2058	25.5	2727	24.8	1205	23.2
		Not Bad	4731	58.4	4671	57.8	6382	58.1	3020	58.0
		Not Good	714	8.81	633	7.83	881	8.02	466	8.96
		Don't Know What to Say	674	8.32	642	7.94	851	7.75	465	8.94
	Hours of Sleep per Night	≥9 hrs	135	1.67	99	1.22	157	1.43	77	1.48
		7-8 hrs	3740	46.2	3102	38.4	4743	43.2	2099	40.3
		5-6 hrs	3953	48.8	4538	56.2	5677	51.7	2814	54.1
	Smoking	<5 hrs	251	3.10	318	3.93	368	3.35	201	3.86
		Non-smoker	1517	18.7	6085	75.3	5081	46.3	2521	48.5
		Current smoker	4143	51.1	1343	16.6	3687	33.6	1799	34.6
Drinking	Former Smoker	2435	30.1	635	7.86	2196	20.0	874	16.8	
	Never drinker	1605	19.8	4146	51.3	3736	34.0	2015	38.7	
	Current drinker	6262	77.3	3753	46.4	6955	63.3	3060	58.8	
Lifestyle	Exercise per Week (Leisure)	Former drinker	225	2.78	172	2.13	277	2.52	120	2.31
		Everyday	335	4.14	341	4.22	444	4.04	232	4.46
	Activity Level at Work	4-6 times a week	410	5.06	410	5.07	544	4.95	276	5.30
		2-3 times a week	1081	13.3	1092	13.5	1453	13.2	720	13.8
		Once a week	1902	23.5	1433	17.7	2300	21.0	1035	19.9
	Activity Level at Work	<once a week	4335	53.5	4777	59.1	6198	56.5	2914	56.0
		Relatively heavily	1642	20.3	1529	18.9	2014	18.3	1157	22.2
Activity Level at Work	Moderate	2955	36.5	4002	49.5	4640	42.3	2317	44.5	
	Light	3488	43.1	2540	31.4	4305	39.2	1723	33.1	

*Percentages do not total to 100% as missing answers are not included

to the RERF clinic) and were considered respondents. Of the respondents, 8,101 (50.1%) were male, 8,082 (49.9%) were female; 10,980 (67.8%) were from Hiroshima, and 5,203 (32.2%) were from Nagasaki.

Counts of subjects in each parental dose group appeared largely consistent across city, though they differed by birth year. Sex distribution changed over birth year and city (not shown in tables). Age did not seem to vary substantially by gender or city. Among men and women, the respective mean ages were 48.4 and 47.6, with a standard deviation of 7.26 for men and 7.77 for women. Ranges for men and women were 17-60 and 21-59, respectively. Within Hiroshima and Nagasaki, the mean ages were 48.3 and 47.3, respectively, with a standard deviation of 7.61 in Hiroshima and 7.34 in Nagasaki. The age range for Hiroshima was 17-60; that for Nagasaki was 21-59. The average age across dose groups was 48.0; however, age differed by parental dose

group. Subject age in all parental dose groups except NIC appeared to decrease with increasing dose, with NIC showing a different distribution. As described in the methods section, the NIC distribution was skewed by design in the original cohort. A comparative analysis of birth year by dose groups revealed that subjects born in 1958 or earlier with parental doses of less than 1 Gy were selected more often than subjects in the same dose group born in later years. After 1958, subject selection by age group was more even across doses. The total effect was to skew the ages of those in the <1Gy dose toward an older group average. This finding suggests that the decreasing age with dose group is the result of the early matching scheme that was no longer used after 1958, as described in the methods section. Age, height, and weight descriptively show few differences across city, and height and weight appeared consistent across parental dose groups (not shown). Height and weight did vary across gender (not

Table 3. Predicted Probabilities of Subjects Self-Reporting Medical Conditions Among Parental Dose Categories by Gender*

		Paternal Dose**											
		Males					Females						
		“% NIC”	% <1 mGy	% 1-99 mGy	% 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value	“% NIC”	% <1 mGy	% 1-99 mGy	% 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value
All Disease***	All Disease Prevalence	71	73	71.5	73.2	0.581	0.878	69.7	69.6	71.3	70.8	0.685	0.59
	All Cancer Prevalence	1.46	1.82	1.73	1.83	0.976	0.997	3.55	3.52	3.22	2.61	0.386	0.178
	Hypertension	16.1	18.3	18.5	15.5	0.094	0.072	8.24	7.72	8.34	8.95	0.5	0.239
	Diabetes	7.73	7.98	8.14	7.3	0.691	0.51	2.75	2.83	2.55	2.49	0.832	0.565
	Hyperlipidemia	18	17.5	18.2	16.6	0.591	0.551	10.4	10.8	13.2	12.1	0.166	0.285
	Myocardial Infarction	0.56	0.57	0.56	0.48	0.926	0.725	Model does not converge					
	Stroke	0.75	0.66	0.85	1.1	0.389	0.17	0.55	0.3	0.41	0.62	0.379	0.1646
	Liver Cirrhosis	0.39	0.8	0.43	0.24	0.12	0.041	0.16	0.24	0.21	0.06	0.38	0.219
	Pollinitis/Allergic Rhinitis	15.2	15.5	14.8	17.2	0.228	0.218	23	21.5	25	21.8	0.071	0.972
	Asthma	2.6	3.06	2.03	3.29	0.1	0.632	3.71	5.02	4.12	4.34	0.58	0.467
Mental Health	Feeling Depressed	5.32	7.31	6.57	4.91	0.035	0.012	4.74	6.44	6.44	4.9	0.159	0.098
	Recently Lost Weight	5.33	5.7	5.75	7.06	0.289	0.157	3.69	3.02	4.55	4.3	0.105	0.111
	Recently Gained Weight	17.8	17.9	17.2	17.1	0.841	0.583	22.6	23.6	20.4	21.3	0.172	0.207
	Insomnia	16.4	19	16.7	17.4	0.316	0.312	16.5	19.8	18.5	16.2	0.066	0.022
	Exhaustion	24.4	25.7	25.6	24.9	0.866	0.615	26.2	27.6	29.6	28	0.51	0.916
			Maternal Dose**										
		Males					Females						
		“% NIC”	% <1 mGy	% 1-99 mGy	% 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value	“% NIC”	% <1 mGy	% 1-99 mGy	% 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value
All Disease***	All Disease Prevalence	71.8	70.9	74	70.2	0.034	0.641	69.5	69.6	69.3	72	0.153	0.11
	All Cancer Prevalence	1.36	1.67	1.66	1.82	0.91	0.715	3.6	3.05	2.93	3.66	0.366	0.267
	Hypertension	16.9	16.4	16.5	16.8	0.952	0.763	8.24	9.06	7.81	8.07	0.288	0.237
	Diabetes	7.5	7.35	7.89	8.57	0.338	0.141	2.7	2.68	2.62	2.8	0.937	0.814
	Hyperlipidemia	17.1	17.3	18.7	17.5	0.479	0.826	10.7	12	10.8	11.2	0.432	0.376
	Myocardial Infarction	0.47	0.69	0.62	0.39	0.327	0.162	0.26	0.03	0.17	0.03	0.13	0.993
	Stroke	0.86	0.69	1.01	0.76	0.418	0.731	0.5	0.64	0.61	0.31	0.161	0.096
	Liver Cirrhosis	0.49	0.36	0.15	0.67	0.024	0.131	0.15	0.07	0.18	0.29	0.15	0.054
	Pollinitis/Allergic Rhinitis	15.7	16.2	15.6	14.5	0.339	0.147	22.2	23.7	21.4	24.1	0.101	0.644
	Asthma	2.61	2.66	1.78	3.4	0.008	0.146	4.23	3.54	3.77	4.66	0.207	0.089
Mental Health	Feeling Depressed	5.67	4.6	6.79	6.01	0.018	0.076	5.28	5.48	5.27	5.02	0.82	0.536
	Recently Lost Weight	6	5.64	5.24	5.9	0.693	0.74	3.94	3.69	3.48	4.02	0.656	0.567
	Recently Gained Weight	17.5	17.2	17.6	18.7	0.504	0.251	21.2	23.3	22.8	22.6	0.902	0.661
	Insomnia	17.2	18	16.2	16.6	0.312	0.247	16.5	16.4	17.5	18.8	0.166	0.058
	Exhaustion	24.1	25.2	25.9	24.8	0.742	0.74	25.9	26.2	28.4	28.3	0.283	0.19

*All predicted probabilities are adjusted for city and average age at time of survey (48 years old); **Logistic and linear regression tests adjusted for NIC, unknown dose, city, and age at time of survey; ***Not including mental health-related diseases

shown). Among the F1 Mail Survey respondents, at the time of survey completion, an average man was 48.4 years old, 169.2 cm tall, and weighed 67.6 kg, while an average woman was 47.6 years old, 156.2 cm tall, and weighed 54.4 kg.

Results by questionnaire section4

Due to the length of the questionnaire and the relevance of some questions solely to future studies, only select indicator variables in each overarching category are discussed herein.

The demographics section of the survey is presented

Table 5. Predicted Probabilities and Means of Women’s Health Characteristics by Parental Dose*

		Paternal Dose***						Maternal Dose***					
		%** / Mean NIC	%** / Mean <1 mGy	%** / Mean 1-99 mGy	%** / Mean 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value	%** / Mean NIC	%** / Mean <1 mGy	%** / Mean 1-99 mGy	%** / Mean 100+ mGy	Test for heterogeneity p-value	Linear trend test p-value
Current Menstruation	Yes	68.6	66.2	57.4	65.3	0.01	0.75	67.1	68.3	66.3	63.0	0.04	0.01
	No	30.7	33.0	41.7	34.0	0.01	0.69	32.1	31.0	33.3	36.0	0.05	0.02
	Regular	27.7	25.8	24.3	27.4	0.24	0.32	28.3	26.8	28.1	23.1	<0.01	0.02
Regularity of Cycle	Slightly regular	15.4	14.5	11.4	12.5	0.09	0.24	14.2	16.4	12.5	14.1	0.01	0.10
	Irregular	7.49	8.20	6.70	7.37	0.41	0.51	7.66	7.45	7.07	7.40	0.90	0.98
Number of Pregnancies		2.33	2.28	2.26	2.24	0.83	0.54	2.28	2.31	2.25	2.35	0.15	0.41
Number of Deliveries		1.73	1.68	1.70	1.70	0.87	0.69	1.70	1.74	1.70	1.75	0.29	0.68
Age at Menarche		12.8	12.8	12.8	12.9	0.07	0.05	12.8	12.8	12.8	12.8	0.99	0.96
Age at First Delivery		26.2	26.1	26.2	26.3	0.41	0.18	26.4	26.1	26.1	26.3	0.37	0.18
Age of Spontaneous Menopause****		49.9	49.8	49.7	49.9	0.55	0.69	50.0	49.9	49.9	49.8	0.86	0.83

*Predicted probabilities and means are adjusted for city and average age at time of survey (48 years old); **Percentages do not total to 100% as missing answers are not included; ***Logistic and linear regression tests adjusted for NIC, unknown dose, city, and age at time of survey; ****Adjusted for average age of respondents who reported this outcome at time of survey (54 years old)

in Table 2 for city and sex (parental dose not shown). Men were descriptively more likely to report higher education and current employment than women, with 43.9% of men and 35.4% of women reporting completion of college or junior college and 93.1% of men and 66.9% of women reporting current employment. Men were also seemingly more likely to report being married. Hiroshima citizens claimed better education than Nagasaki citizens (45.2% and 27.8%, respectively, reporting graduation from college or junior college) as well as a slightly higher proportion of respondents currently married. Paternal and maternal dose showed few apparent differences in any of the demographic categories, though there were indications that children of NIC parents were more likely to have received a higher education and that females with mothers or fathers exposed to 100+ mGy were more likely to be married.

In general health (Table 2), men and women were each most likely to report 5-6 hours of sleep per night, with 48.8% of men and 56.2% of women selecting this option. However, seemingly more men (46.2%) than women (38.4%) reported getting 7-8 hours of sleep. No substantial differences in general health were seen between residents of different cities or between subjects with parents in different exposure categories.

Among lifestyle variables (Table 2), men and women differed considerably. Men reported current or former smoking and drinking much more often than did women; 51.1% of men and 16.6% of women reported current smoking, and 77.3% of men and 46.4% of women reported current drinking. Among smokers, the average number of cigarettes smoked per day was 24.0 for males and 15.2 for females (not shown). Men reported slightly higher levels of exercise during leisure than did women. Women, however, appeared more likely to report moderate amounts of activity at work, while men more often reported only light activity at work. Hiroshima citizens reported current drinking slightly more often than did Nagasaki citizens

(63.3% and 58.8%, respectively). Hiroshima residents also seemed more likely to report only light activity at work than Nagasaki residents. Women whose mothers were exposed to 100+ mGy appeared slightly less likely to be current drinkers. No other substantial differences were seen across parental dose groups.

Tabulations over disease categories are not presented in the tables by city or sex; they are briefly discussed here. Overall, 5,855 (72.3%) men and 5,630 (69.7%) women reported having been diagnosed with one or more non-mental health diseases (“all disease”) from the complete list recorded on the survey; 7,952 (72.4%) Hiroshima subjects and 3,533 (67.9%) Nagasaki subjects reported having been diagnosed with at least one of these diseases. Differences across specific disease prevalence are evident among male and female subjects, with men seemingly more prone to diseases often associated with lifestyle such as hypertension, diabetes, and hyperlipidemia, and women more at risk of cancer. In mental health, women were seemingly more likely to have recently gained weight than men. Residents of Hiroshima reported hyperlipidemia and allergies slightly more than did residents of Nagasaki; no apparent differences were seen in prevalence of any other illnesses or mental health variables.

Table 3 shows estimated percentages, tests for heterogeneity, and tests for linear trend of individuals in disease categories by paternal and maternal dose. Estimates are derived from a logistic regression model with age centered at 48.0, reflecting the mean age across dose groups; all estimates also adjust for NIC, unknown dose, and city. Estimated prevalence for NIC is reported, but NIC is controlled for in tests for heterogeneity and linear trend, therefore these tests do not reflect differences between NIC and the other dose categories. Estimated disease prevalence was also examined for combined exposure categories using this logistic model; these estimates are not shown in the tables. Few differences were seen across parental exposure or combined exposure

categories. Among tests for heterogeneity over paternal dose categories, only depression showed statistically significant differences in men. The tests for linear trend over paternal dose were significant for liver cirrhosis and depression in men and for insomnia in women. Tests for heterogeneity over maternal dose showed significant differences over dose for all disease, liver cirrhosis, asthma, and depression in males. Tests for heterogeneity over combined dose showed significant differences over dose for asthma in men and for exhaustion in women. Among tests for linear trend over combined dose groups, only exhaustion in women had significant results.

Women's health by city is not presented in the tables; it is briefly discussed here. Nagasaki residents reported current menstruation more often than did Hiroshima residents (59.3% and 51.9% of Nagasaki and Hiroshima residents, respectively). Nagasaki women currently menstruating also reported having a regular cycle more than did women from Hiroshima.

Table 4 shows estimated percentages and means, tests for heterogeneity, and tests for linear trend of women's health variables by parental dose categories. Tests for heterogeneity indicated that women born to fathers in different exposure categories reported current menstruation differentially; women born to fathers exposed to 1-99 mGy at the time of the bombing reported current menstruation less often than women born to fathers in other exposure categories. Tests for heterogeneity and tests for linear trend showed differences by maternal dose category; women were less likely to report current menstruation as maternal dose increased. This trend was also seen among women by combined dose category. Women reported regularity of cycle differentially by dose over both maternal dose and combined dose; the test for trend was significant for regular cycle over maternal dose and for slightly regular cycle over combined dose. The average number of pregnancies and deliveries across all women were 2.27 and 1.70, respectively. Average age at menarche, first delivery, and spontaneous menopause were 12.8, 26.1, and 49.9 years of age, respectively. These approximate means were largely consistent across cities and parental exposure categories.

Discussion

The overall response rate for this survey was 67.2% in Hiroshima and 62.5% in Nagasaki after multiple mailings. This rate is similar to that seen in other mail-based questionnaires in Japan (Hayashi et al., 1999; Nishikawa et al., 2015). A short analysis was run using Hiroshima city codes and response data to determine if participation bias was present; however, response rates did not appear to change by residential area. This same analysis is not currently possible in Nagasaki due to the way in which residential data is coded. Since little information is available on non-respondents regarding lifestyle factors, nonresponse by these factors cannot be assessed. Gender, prefecture in which one lives, and age are all known to impact the results of Japanese studies; these variables were considered (Kitamura et al., 2001; Saeki et al., 2005; Chitturi et al., 2007; Maruyama et al., 2012). Response

rates were higher among women and Hiroshima citizens than among men and Nagasaki citizens, respectively. Subjects born between 1946 and 1958 were more likely to respond than subjects born between 1959 and 1984. The analysis of each factor by gender and city and the age-adjusted results by dose are thought to have reduced the possible effects of these factors. As urbanity and various lifestyle factors are all known to influence disease incidence and prevalence in the Japanese population (Kitamura et al., 2001; Chitturi et al., 2007; Maruyama et al., 2012; Hatano et al., 2013), however, differential response could have impacted the results.

Reliability of the data is difficult to assess, since the possibility of socially desirable responding, that is, a respondent answering with what he or she believes is the socially "correct" choice, exists on any survey (Johnson et al., 2011; Van de Vijver and Matsumoto, 2011). The results of this survey were, however, compared to several sources in order to consider their validity.

Statistics from the Japanese National Health and Nutritional Survey were used for a comparison of the self-reported lifestyle factors recorded here to national averages (Ministry of Health Labour and Welfare, 2012). As several of the statistics in the national survey use male-only, age-adjusted data, the analyses of several factors in this study were rerun with only the male population for confirmation. While the population percentages of smokers and drinkers were different from the results reported here, Hiroshima males were found to smoke less and drink approximately the same amount as Nagasaki males, reflecting the present results. Likewise, trends for obesity among Hiroshima and Nagasaki males in the national survey reflected those for hypertension among males in the present study. Studies elsewhere have shown that regional dissimilarities, especially where urbanity differs, can account for such variations in menopause onset as seen in this study (Mohammad et al., 2004; Bernis and Reher, 2007).

The Japanese Collaborative Cohort (JACC) Study also provides some statistics on a national Japanese cohort. JACC collected information from a nationally representative population between the years of 1988 and 2009 (Ohno et al., 2001; Tamakoshi et al., 2013). A 2014 paper (Yaegashi et al., 2014) reported smoking and drinking tendencies for men of this cohort. They left out women, as, similarly to the present study, too few women smoked or drank for a meaningful analysis. Smoking and alcohol were self-reported, with 53.3% of men reporting current smoking, 26.2% reporting past smoking, 75.0% reporting current drinking, and 6.2% reporting former drinking (Yaegashi et al., 2014). In this present study, only 16.6% of women reported smoking and less than half reported drinking, numbers that encouraged past researchers to use a non-smoking, non-drinking baseline when discussing risk of disease. On the other hand, 51.1% of men reported smoking, 30.1% reported past smoking, 77.3% of men reported drinking, and 2.78% reported former drinking. These numbers are very similar to those seen in the JACC study.

A 2003 paper by Izumi, et al (Izumi et al., 2003) reports cancer incidence in children of atomic bomb

survivors between the years 1958 and 1997. Izumi reports 575 first solid cancers and 68 first primary hematopoietic cancers among 40,487 subjects: a cumulative incidence of 1.42% and 0.17%, respectively. In the present study, 470 of 16,183 subjects of both genders reported having had a first primary cancer, which is a prevalence of 2.9. While cumulative incidence is recorded in the cancer incidence paper and self-reported prevalence is described herein, both studies report only first primary cancers and therefore these numbers can be compared. Izumi only reported first primary cancers that occurred between the years of 1958 and 1997; this paper presents self-reported cancers occurring at any time in a subject's life until survey completion between 2000 and 2006. The additional follow-up time and bias from self-reported data may account for the higher number of patients with cancers seen here.

A 2013 paper (Tatsukawa et al., 2013) reports the results of the first round of the F1 Clinical Study. The F1 Clinical Study participants comprise a smaller group of mail survey recipients who volunteered after receiving the mail survey to participate in the clinical study. In the study, baseline rates of diseases and of disease end points were calculated for both males and females living in the a-bombed cities. Male baseline and female baseline curves took population dynamics into account—males were considered smokers and drinkers, while females were not, reflecting the risks of both genders appropriately. In the paper, at approximately age 48, roughly 3,200 of 10,000 (32%) males had hypercholesterolemia, 2,200 of 10,000 (22%) had hypertension, and 300 of 10,000 (3%) males had diabetes mellitus. At approximately age 48, about 3,600 of 10,000 (36%) pre-menopausal women had hypercholesterolemia, 4,700 of 10,000 (47%) post-menopausal women had hypercholesterolemia, 1,000 of 10,000 (10%) pre- and post-menopausal women had hypertension, and 100 of 10,000 (1%) pre- and post-menopausal women had diabetes mellitus. In the present study, percentages of subjects reporting disease categories were estimated from the analysis by parental dose in which age was mean-centered at 48 years. In this paper, at age 48, approximately 16-18% of men reported hyperlipidemia, 16-19% reported hypertension, and 7-9% reported diabetes mellitus. At age 48, approximately 10-13% of women reported hyperlipidemia, 8-9% reported hypertension, and 2-3% reported diabetes mellitus. The percentages for hypertension are similar between the studies. Differences in the other factors may have arisen because of the self-reported nature of our data; hyperlipidemia is difficult for subjects to measure themselves and may be reported more in a clinical setting, while subjects may report prediabetes as diabetes, overestimating the prevalence in the population.

Nonetheless, these differences should be considered in greater detail in the future.

As described in the methods section, a no information group exists for parental dose for subjects with parents who were only connected to the database after the birth of their child with an exposed parent. The F1 subject's "missing" parental exposure group was considered NIC for this study, as these parents were almost certainly not in

either city during the bombings. Due to the small number of these subjects, no impact is seen when looking at the NIC group as a whole; however, it is important to note that these subjects are approximately 15 years younger than respondents born to other NIC parents. Another age-related difference exists in the average ages of subjects in the various paternal and maternal dose groups. These age differences reflect the original F1 Mortality Cohort and are a result of the data collection methods described earlier. The logistic and linear regression models used in this study controlled for age; the reported results should therefore be largely accurate. Across combined dose exposure categories, the age-related difference is more pronounced: since the NIC category only includes subjects for whom both parents were NIC at the time of the bombing, no one under the age of 42 (at the time of survey completion) is in this group. Although the results are age-adjusted, residual confounding is likely and may account for some of the statistically significant results seen across dose categories, particularly where higher dose appeared protective. These results would then reflect the higher risk of illness in individuals over 50 years of age.

In this survey, Hiroshima residents appeared to have largely received a better education, have greater non-cancer disease prevalence, smoke less, and to comprise more postmenopausal women than Nagasaki residents. As the average age among both cities is the same, it is unlikely these differences are caused from age-related bias.

The gender differences seen in this study were largely in accordance with what would be expected of this population by looking at statistics from other Japanese lifestyle and cancer incidence studies. (National Institute of Health and Nutrition, 2006; National Institute of Health and Nutrition, 2007; Nishi et al., 2008; Hata et al., 2013; Tanaka et al., 2014; Yaegashi et al., 2014). According to the self-reported data in this survey, male respondents appeared more likely to have a university education (while women were more likely to have attended junior college), be heavier and taller, sleep more hours per night, report lifestyle-related diseases, smoke, and drink than women. They seemed less likely to report allergies, weight gain, and moderate levels of activity at work than women. As the difference in the percentage of men versus women claiming to be currently married was not large, this result may have arisen from chance. Men reported less cancer than women, an observation that is likely a reflection of the average age of the cohort. Although men are known to have a higher risk of cancer later in life, prior to the age of approximately 50, women have the higher risk. This statistic can be attributed to sex-specific cancer incidence in younger women.

Exposure categories seem, at the present, to have little if any correlation with the outcomes discussed in this report. Tests for heterogeneity and tests for linear trend revealed several potential differences in disease over exposure categories. However, with few exceptions, tests for heterogeneity and tests for linear trend were not significant for the same disease categories. This finding indicates that statistical significance in these instances may have been observed by chance. While this preliminary and descriptive analysis did not account for

multiple testing, by treating each outcome independently and conducting both heterogeneity and linear trend tests separately by gender and parental dose type, we would expect some seemingly positive results to be spurious, particularly where heterogeneity tests and tests of linear trend are not in agreement. Of the significant tests for heterogeneity, only depression in men over paternal dose and exhaustion in women over combined dose also had statistically significant tests for linear trend. Nonetheless, these as well as noted differences in lifestyle and general information, could have resulted from other factors, such as chance, residual age-related bias, or confounding. For example, children born to NIC parents (a group comprised of slightly older subjects) appeared to receive higher education in this report. Yet, due to overarching changes in the Japanese educational system after the war, those born earlier than 1950 were likely to have received less education than those born later. Although the results here were adjusted for age, remaining disparities could have had an impact, resulting in such differences as seen in this report.

In women's health, some differences by city were seen. Nagasaki residents reported menstruation and regular cycle descriptively more than did Hiroshima residents. As both age and smoking can impact the menstrual cycle, age due to menopause and smoking due to smoking-related illnesses such as endometriosis that can cause cycle irregularity, these factors were compared between cities. The average age at survey completion of the female respondents from each of these cities was approximately equal (48.0 years in Hiroshima and 47.1 in Nagasaki) and smoking trends did not seemingly differ in women by city (16.1% of women were current smokers in Hiroshima, 17.7% in Nagasaki). Therefore, the apparent differences seen in menstruation between the cities do not appear to be based on differences in age or smoking tendencies. Differences in women's health were also noted by exposure category. Tests for heterogeneity and tests for trend were each significant for current menstruation over maternal and combined dose; these tests also indicated that a cycle's regularity differed by dose groups. These differences are unlikely to have resulted from exposure, however, as unknown confounding factors and residual age-related bias are likely present here. It is possible that centering on average age in the logistic regression over-adjusted for this variable, creating the reverse trend between current menstruation and average age seen here. Furthermore, urban versus rural living can impact menstruation (Mohammad et al., 2004; Bernis and Reher, 2007). Although with the current data it is difficult to say which women are living in more urban locations, if urbanity and parental dose are related, this factor may have impacted the analysis. These results warrant further investigation in the future.

Overall, the regressions show little variation across variables, which is consistent with past studies conducted on this population (J. Neel and Schull, 1956; Kato et al., 1966; Neel et al., 1974; Neel et al., 1988; Otake et al., 1990; Yoshimoto et al., 1990; Yoshimoto et al., 1991; Little et al., 1994; Izumi et al., 2003; Kodaira et al., 2010). The aim of the F1 Mail Survey and F1 Clinical Study together

is to analyze this cohort over time and to determine if effects arise as a result of parental exposure. These initial results may not be predictive of later morbidity comparisons when more information at different time points is available. Further studies will be conducted in this regard. Special emphasis should be placed on physical and mental health, including both psycho-social health and cognitive function, as these are of particular interest to the public and to the scientific community.

This mail survey has produced a wealth of data gained from the 16,183 individuals who returned completed questionnaires to RERF. This study was designed to identify persons interested in participating in the F1 Clinical Study; this data combined with existing and forthcoming data from the clinical study will enable further analyses of genetic effects of radiation.

One factor that is both a strength and a limitation of this study is power. Given the number of cases for any individual outcome, the power to predict a difference or spot a trend across outcomes changes considerably. For instance, the power to detect, with a confidence level of 95%, a difference in hypertension prevalence between men with a paternal dose 1-99 mGy and men with a paternal dose 100+ mGy is 81.4%, while the power to detect a difference in stroke between these same categories is only 19.3% (DSS Research, 2014). As the subjects continue to age and more cases accumulate, the power to detect such differences will rise; yet, this limitation, when applicable, must be taken into account when viewing these results.

The response rate of 65.6% poses a potential threat to the study's validity. Although this rate is similar to other such surveys in a Japanese context (Hayashi et al., 1999; Nishikawa et al., 2015), it does present the possibility of bias. While up to four mailings were sent to recipients, a better approach may have been to telephone those who did not respond in order to better explain the goals of the survey and how it benefits them and society.

One further limitation is the difference in age across parental exposure categories, especially for combined dose. Although the results herein are age-adjusted, residual confounding may remain and should be taken into account in future studies.

In conclusion, The results reported in this manuscript are the first to illustrate the general health and lifestyle characteristics of the F1 Mortality respondents. The F1 Mail Survey Cohort was designed to be representative of the F1 Mortality Cohort at large, and differences across gender and city were as expected in the results. No conclusive results about trends over parental exposure can be drawn from this report; however, the cohort at baseline is described, paving the road for future studies. Confounding factors, such as age and gender, controlled in this study, should likewise be taken into account when conducting future studies and interpreting their results. Potential biases, such as the selection bias that may have occurred over health and lifestyle factors, could not be controlled in this paper for lack of information about subjects who did not respond. These should be duly considered in future studies, first by conducting bias analyses to determine whether participation bias was present, and then using the results of these analyses to

control for the true biases in the study. It was the aim of this paper to report the results of a mail survey designed to initiate studies with the capability of including lifestyle factors in their analyses. The results from this report should enable such analyses if researchers both control for the known confounders and take into account the possible biases reported herein.

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References

- Abouzeid Ali HE, Barber RC, Dubrova YE (2012). The effects of maternal irradiation during adulthood on mutation induction and transgenerational instability in mice. *Mutat Res*, **732**, 21-5.
- Barber R, Plumb MA, Boulton E, et al (2002). Elevated mutation rates in the germ line of first- and second-generation offspring of irradiated male mice. *Proc Natl Acad Sci USA*, **99**, 6877-82.
- Barber RC, Hardwick RJ, Shanks ME, et al (2009). The effects of in utero irradiation on mutation induction and transgenerational instability in mice. *Mutat Res*, **664**, 6-12.
- Barber RC, Hickenbotham P, Hatch T, et al (2006). Radiation-induced transgenerational alterations in genome stability and DNA damage. *Oncogene*, **25**, 7336-42.
- Bernis C, Reher DS (2007). Environmental contexts of menopause in Spain: Comparative results from recent research. *Menopause*, **14**, 777-87.
- Chitturi S, Farrell GC, Hashimoto E, et al (2007). Non-alcoholic fatty liver disease in the Asia-Pacific region: Definitions and overview of proposed guidelines. *J Gastroen Hepatol*, **22**, 778-87.
- Cullings HM, Fujita S, Funamoto S, et al (2006). Dose estimation for atomic bomb survivor studies: Its evolution and present status. *Radiat Res*, **166**, 219-54.
- DSS Research (2014). Calculators: Researcher's toolkit. <https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculator.aspx> (accessed October 2014)
- Fujiwara S, Suyama A, Cologne JB, et al (2008). Prevalence of adult-onset multifactorial disease among offspring of atomic bomb survivors. *Radiat Res*, **170**, 451-7.
- Grant EJ, Furukawa K, Sakata R, et al (2015). Risk of death among children of atomic bomb survivors after 62 years of follow-up: A cohort study. *Lancet Oncol*, **16**, 1316-23.
- Hata J, Ninomiya T, Hirakawa Y, et al (2013). Secular trends in cardiovascular disease and its risk factors in Japanese: Half-century data from the Hisayama Study (1961-2009). *Circulation*, **128**, 1198-205.
- Hatano Y, Matsumoto M, Inoue K, et al (2013). Rurality and participation in mass preventive health services: A nationwide descriptive study. *Hiroshima J Med Sci*, **62**, 43-8.
- Hayashi M, Iwanaga T, Mitoku K, et al (1999). Getting a high response rate of sexual behavior survey among the general population in Japan: Three different methods of survey on sexual behavior. *J Epidemiol*, **9**, 107-13.
- Izumi S, Koyama K, Soda M, et al (2003). Cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs. *Brit J Cancer*, **89**, 1709-13.
- Johnson TP, Shavitt S, Holbrook AL (2011). Survey response styles across cultures. In 'Cross-cultural research methods in psychology', Eds Matsumoto D., and Van de Vijver F. J. R. Cambridge University Press, New York, NY pp 130-75
- Joint US-Japan Working Group (2005). Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki. Eds Young RW and Kerr GD. In 'Dosimetry System 2002 DS02 Vol 2', INIS-JP--102, Japan.
- Kato H, Schull WJ (1960). Joint JNIIH-ABCC Life Span Study of children born of parents exposed to atomic bomb survivors, research plan. No. ABCC TR 4-60
- Kato H, Schull WJ, Neel JV (1966). A cohort-type study of survival in the children of parents exposed to atomic bombings. *Am J Hum Genet*, **18**, 339-73.
- Kitamura A, Sato S, Naito Y, et al (2001). [Trends in the incidence of cardiovascular diseases and risk factors among urban and rural Japanese males.] *Jpn J Public Health*, **48**, 378-94.
- Kodaira M, Ryo H, Kamada N, et al (2010). No evidence of increased mutation rates at microsatellite loci in offspring of A-bomb survivors. *Radiat Res*, **173**, 205-13.
- Koyama K, Suyama A, Grant E J, et al (2002). Health effects study of the children of a-bomb survivors: Mail survey. No. RERF RP 3-02
- Little M. P, Wakeford R, Charles MW (1994). An analysis of leukaemia, lymphoma and other malignancies together with certain categories of non-cancer mortality in the first generation offspring (F1) of the Japanese bomb survivors. *J Radiol Prot*, **14**, 203-18.
- Maruyama M, Ohira T, Imano H, et al (2012). Trends in sudden cardiac death and its risk factors in Japan from 1981 to 2005: The circulatory risk in communities study (CIRCS). *BMJ Open*, **2**, 573.
- Matsumoto D, Van de Vijver FJR (2011). Introduction to the methodological issues associated with cross-cultural research. In 'Cross-cultural research methods in psychology', Eds Matsumoto D. and Van de Vijver F. J. R. Cambridge University Press, New York, NY, 1-14.
- Ministry of Health, Labour, and Welfare (2012). Chapter 5: Results by prefecture, the National Health and Nutrition Survey in Japan, 2010. <http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h22-houkoku-11.pdf> (accessed September 2014)
- Mohammad K, Sadat Hashemi SM, Farahani FK (2004). Age at natural menopause in Iran. *Maturitas*, **49**, 321-6.
- National Institute of Health and Nutrition (2006). Summary results of the National Health and Nutrition Survey Japan, 2006. Tokyo, Japan.
- National Institute of Health and Nutrition (2007). Outline for the results of the National Health and Nutrition Survey Japan, 2007. Tokyo, Japan.
- Neel JV, Schull WJ (1956). The effect of exposure to the atomic bombs on pregnancy and termination in Hiroshima and Nagasaki. National Academy of Sciences, National Research Council, Washington 25, D.C.
- Neel JV, Kato H, Schull WJ (1974). Mortality in the children of atomic bomb survivors and controls. *Genetics*, **76**, 311-36.
- Neel JV, Satoh C, Goriki K, et al (1988). Search for mutations

- altering protein charge and/or function in children of atomic bomb survivors: Final report. *Am J Hum Genet*, **42**, 663-76.
- Nishi N, Sugiyama H, Hsu WL, et al (2008). Differences in mortality and incidence for major sites of cancer by education level in a Japanese population. *Ann Epidemiol*, **18**, 584-91.
- Nishikawa T, Okamura T, Nakayama H, et al (2015). Effects of a public education campaign on the association between knowledge of early stroke symptoms and intention to call an ambulance at stroke onset: The acquisition of stroke knowledge (ASK) study. *J Epidemiol*, 2016, [Epub ahead of print].
- Ohno Y, Tamakoshi A, JACC Study Group (2001). Japan collaborative cohort study for evaluation of cancer risk sponsored by Monbusho (JACC study). *J Epidemiol*, **11**, 144-50.
- Otake M, Schull WJ, Neel JV (1990). Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: A reanalysis. *Radiat Res*, **122**, 1-11.
- Rinchik EM, Russell LB, Copeland NG, et al. (1986). Molecular genetic analysis of the dilute- short ear (d-se) region of the mouse. *Genetics*, **112**, 321-42.
- Saeki H, Iizuka H, Mori Y, et al (2005). Prevalence of atopic dermatitis in Japanese elementary schoolchildren. *Brit J Dermatol*, **152**, 110-14.
- Shiraishi K, Shimura T, Taga M, et al (2002). Persistent induction of somatic reversions of the pink-eyed unstable mutation in F1 mice born to fathers irradiated at the spermatozoa stage. *Radiat Res*, **157**, 661-7.
- StataCorp LP (2013). Obtaining linear combinations of coefficients. In 'Stata user's guide: Release 13.' Stata Press, College Station, TX pp. 286-7
- Tamakoshi A, Ozasa K, Fujino Y, et al (2013). Cohort profile of the Japan collaborative cohort study at final follow-up. *J Epidemiol*, **23**, 227-32.
- Tanaka S, Tanaka S, Iimur, S, et al (2014). Cohort profile: The Japan diabetes complications study: A long-term follow-up of a randomised lifestyle intervention study of type 2 diabetes. *Int J Epidemiol*, **43**, 1054-62.
- Tatsukawa Y, Cologne JB, Hsu WL, et al (2013). Radiation risk of individual multifactorial diseases in offspring of the atomic-bomb survivors: A clinical health study. *J Radiol Prot*, **33**, 281-93.
- Yaegashi Y, Onoda T, Morioka S, et al (2014). Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. *Asian Pac J Cancer Prev*, **15**, 1023-9.
- Yoshimoto Y, Nee, JV, Schull WJ, et al (1990). Malignant tumors during the first 2 decades of life in the offspring of atomic bomb survivors. *Am J Hum Genet*, **46**, 1041-52.
- Yoshimoto Y, Schull WJ, Kato H, et al (1991). Mortality among the offspring (F1) of atomic bomb survivors, 1946-85. *J Radiat Res*, **32**, 327-51.